INFLAMMATIONS III

EMAN MS MUHAMMAD

MORPHOLOGIC PATTERNS OF ACUTE INFLAMMATION

- The morphologic hallmarks of acute inflammation are:
- *dilation of small blood vessels,* and
- *accumulation of leukocytes,* and
- *accumulation of fluid in the extravascular tissue*.
- The vascular and cellular reactions account for the signs and symptoms of the inflammation.
- Increased blood flow to the injured area and ↑ vascular permeability → accumulation of extravascular fluid (*edema*) and account for the redness *(rubor)*, warmth *(calor)*, and swelling *(tumor)* that accompany acute inflammation.

- Leukocytes that are recruited and activated by the offending agent and by endogenous mediators may *release toxic metabolites* and *proteases extracellularly*.
- These metabolites and proteases cause tissue damage and loss of function (*functio laesa*).
- During the damage liberation of cytokines, prostaglandins, and neuropeptides → pain *(dolor).*

- Although these general features are characteristic of most acute inflammation, *special morphologic patterns* may superimposed on them, ***depending on:***
  1. *Severity of the reaction,*
  2. *Specific cause of inflammation, and*
  3. *The particular tissue and site involved.*
- Recognizing distinct gross and microscopic patterns of inflammation provide valuable clues about the underlying cause.

TYPES OF ACUTE INFLAMMATIONS

I. Suppurative inflammation:

1. **Localized inflammation:**
   - Abscess
   - Furuncle
   - Carbuncle
2. **Diffuse inflammation:**
   - Cellulitis

II. Non suppurative inflammation:

1. Catarrhal inflammation.
2. Membranous inflammation.
3. Sero-fibrinous inflammation.
4. Fibrinous inflammation.
5. Serous inflammation.
6. Hemorrhagic inflammation.
7. Necrotizing inflammation.
8. Allergic inflammation.

SUPPURATIVE INFLAMMATION (Pyogenic or Septic)

- ***Definition*:**
- Severe acute inflammation characterized by pus formation.
- ***Cause*:**
- Pyogenic microorganisms as *staph. aureus, strept. hemolyticus, pneumococcus, gonococcus and bacillus coli.*

- *Purulent inflammation* is characterized by production of pus.
- The most frequent cause of purulent inflammation ***(suppurative)*** is infection with bacteria that cause *liquefactive necrosis,* such as *staph.*
- These pathogens are referred to as *pyogenic (pus-producing)* bacteria.
- A common example of acute suppurative inflammation is acute appendicitis.

PUS

- **Pathogenesis of pus formation:**
- Pyogenic microorganisms cause marked tissue necrosis by its toxins.
- They exert strong chemotaxis on PML.
- Many PML are killed during their struggle with bacteria and are called pus cells.
- The dead leucocytes release proteolytic enzymes → rapid liquefaction of the necrotic tissue and the fibrin threads.
- The resulting fluid mix with other products of inflammation forming pus.

- **Composition of pus:**

1. Bacteria living and dead and their toxins.
2. Liquefied necrotic tissue mainly peptones.
3. Inflammatory *cellular exudate; PML, pus cells, macrophages and red cells.*
4. Inflammatory fluid exudate.

Characters of pus of staph. aureus infection:

1. Thick, turbid, yellow, odorless, and alkaline.
   - Thick consistency is due to high content of nucleic acid.
2. Yellow color is due to the presence of:
   - Many pus cells
   - Yellow pigments produced by staph. Aureus
   - Brown hemosiderin granules
3. Pus does not clot on standing because its fibrinogen content is destroyed by proteolytic enzymes.

Suppurative Inflammation

Abscess

- **Definition:**
- Localized suppurative inflammation resulting in formation of an irregular cavity containing pus.
- It is a defensive reaction of the tissue to prevent spread of infection to other parts of the body.

- **Cause:**
- Bacterial infection (commonly staph. aureus or parasites as amoebic abscess) or foreign materials (e.g. bullet wounds, or injecting needles).
- **Site:**
- Commonly the abscess occurs in the subcutaneous tissue.
- It may occur in any organ as the lung, brain, liver …… etc.

Pathology of an abscess:

1. Early the abscess shows two zones, a central necrotic zone surrounded by a zone of acute inflammation containing large number of PML.
2. Many PML die and their liberated proteolytic enzymes liquefy the margin of the necrotic area with the formation of pus, so the abscess shows three zones.

A. Central necrotic core which gradually diminishes in size by liquefaction of its margin until it disappears.
B. Mid-zone containing pus known as abscess cavity.
C. Peripheral zone of inflamed tissue called pyogenic membrane.

3. The abscess enlarges by further necrosis and liquefaction of the surrounding inflamed zone until the staph. produce the coagulase enzyme which helps fibrin formation that localizes the inflammation.
4. A subcutaneous abscess appears as a localized tender swelling covered by red edematous skin with opaque yellow center.

- The covering epidermis may undergo necrosis and the pus escapes.
- When the abscess cannot evacuate itself spontaneously, or when persistent or at critical locations such as the brain, abscesses have to be drained surgically as the body can absorb pus only very slowly.
- An internal abscess in the lung, liver or spleen opens in a hollow organ as the bronchi, and intestine.

5. Once the pus is evacuated healing by granulation tissue occurs.
6. With time the abscess may become walled-off and replaced by connective tissue.

- **Complications:**

1. Lymphatic spread of infection causes lymphangitis and lymphadenitis.
2. Blood spread of bacteria and its toxins causes bacteremia, septicemia or toxemia.
3. Septic thrombophlebitis and pyemia.
4. Inadequate drainage and treatment changes the abscess to chronic one.
5. Chronic abscess has a thick fibrous wall.
6. Complications of healing; chronic ulcer, sinus, fistula and keloid.

Ulcers

- Ulcer is a local defect, or excavation, of the surface of an organ or tissue that is produced by sloughing or shedding of inflamed necrotic tissue.
- Ulceration can occur only when tissue necrosis and resultant inflammation exist on or near a surface.

- ***It is most commonly encountered in:***

(1) Mucosa of the *mouth, stomach, intestines, or genitourinary tract*; and

(2) *Skin and subcutaneous* tissue of the lower extremities in older persons who have circulatory disturbances that predispose to extensive ischemic necrosis.

(3) *Peptic ulcer of the stomach or duodenum*, in which ***acute and chronic inflammation may coexist.***

- During the ***acute stage*** there is intense PML infiltration and vascular dilation in the margins of the defect.
- *With **chronicity,** the margins and base of the ulcer develop fibroblastic proliferation, scarring, and accumulation of lymphocytes, macrophages, and plasma cells.*

Furuncle (boil)

- **Definition:**
- Localized suppuration inflammation formed of small abscess related to a hair follicle or sebaceous gland.
- It is caused by staph. aureus.
- Common sites are face and back of the neck in males and axilla in females.
- Multiple furuncles are called furunculosis.

Carbuncle

- **Definition:**
- Localized suppuration forming multiple communicating suppurative foci in the skin and subcutaneous fat discharging pus through several openings.
- **Cause:** Staph. aureus.
- Diabetes is a common predisposing factor.

- **Sites:**
- Areas where the skin and subcutaneous tissue are thick and tough as the back of the neck, scalp and buttocks.
- **Pathology:**
- Multiple communicating suppurative foci in the subcutaneous fat opening on the surface at multiple points particularly at the base of the hair follicles.

- Each suppurative focus develop in the same way as an abscess.
- Development of multiple suppurative foci in carbuncle is due to the presence of dense fibrous septa extending from the deep fascia up to the dermis dividing the area into several compartments.

Cellulitis (Phlegmonous inflammation)

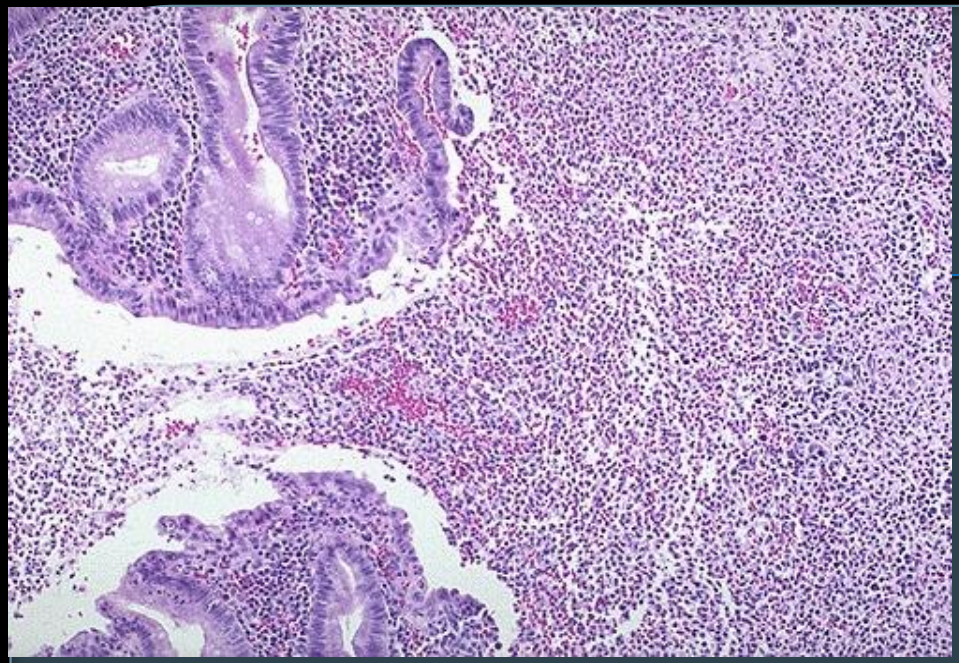
- **Definition:**
- Acute diffuse suppurative inflammation.
- **Cause:**
- Strept. hemolyticus.
- This organism produces two enzymes:
  1. Fibrinolysin (streptokinase): Dissolves fibrin.
  2. Hyaluronidase (spreading factor): Dissolves hyaluronic acid of ground substance helping spread of bacteria and its toxins.

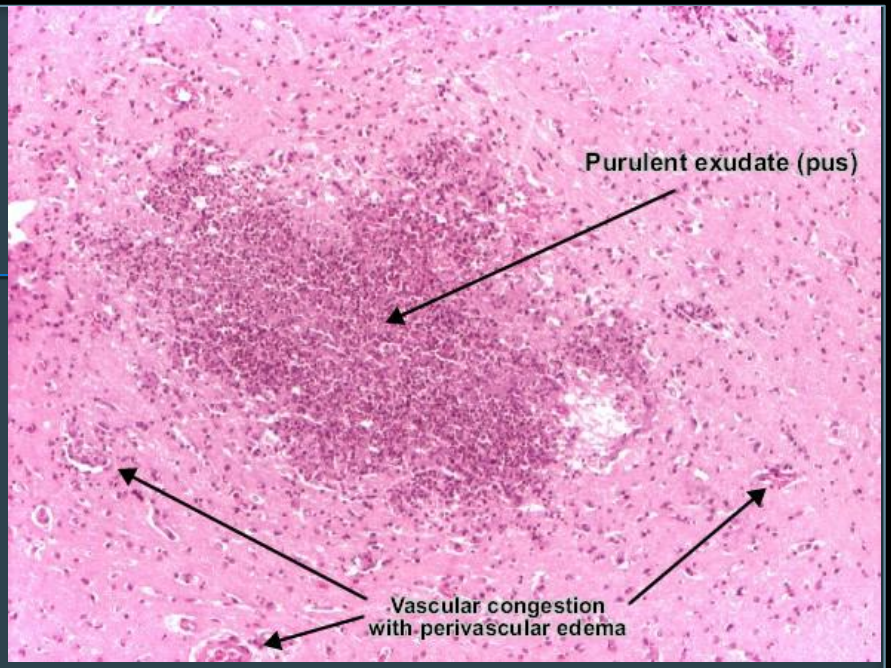
- **Sites:**
- Loose connective tissue as subcutaneous tissue, fascial planes, areolar tissue of the orbit, pelvis, scrotum and wall of the appendix.
- **Pathology:**
- The basic pathological changes are similar to those of abscess with the following differences:
  1. Failure of localization because of absence of fibrin.
  2. Necrosis is extensive and the separated dead masses are called roughs.
  3. Pus formation is slow.
- Pus is thin in consistency and may contain many red cells i.e. sanguinous.

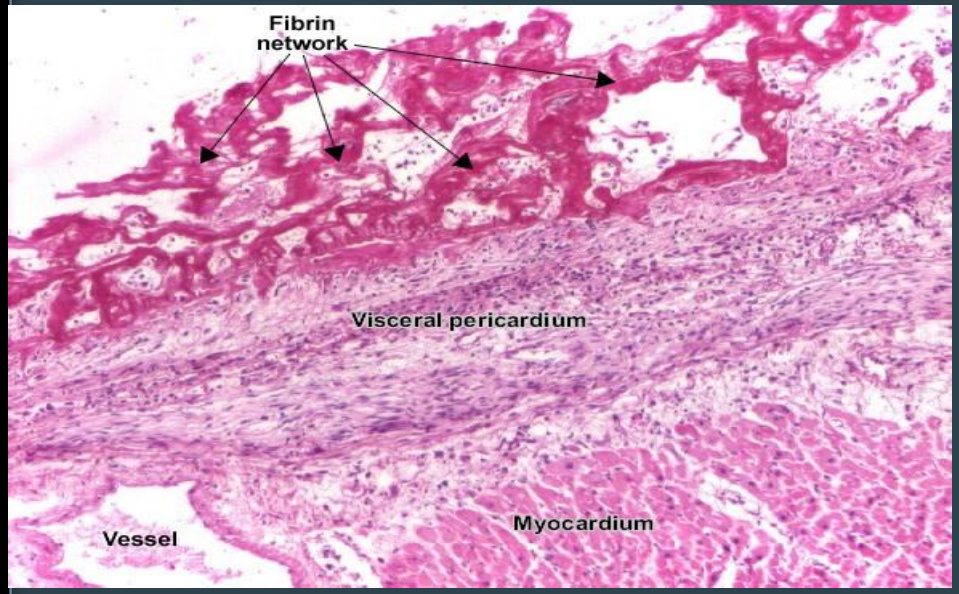
- **Complications**:

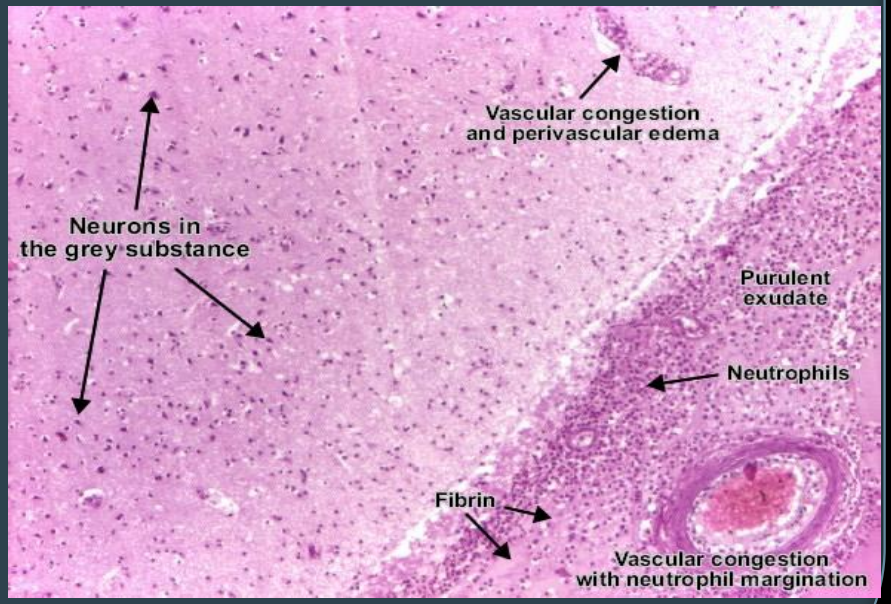
1. Acute lymphangitis and lymphadenitis.
2. Septic thrombophlebitis causing pyemia.
3. Septicemia.

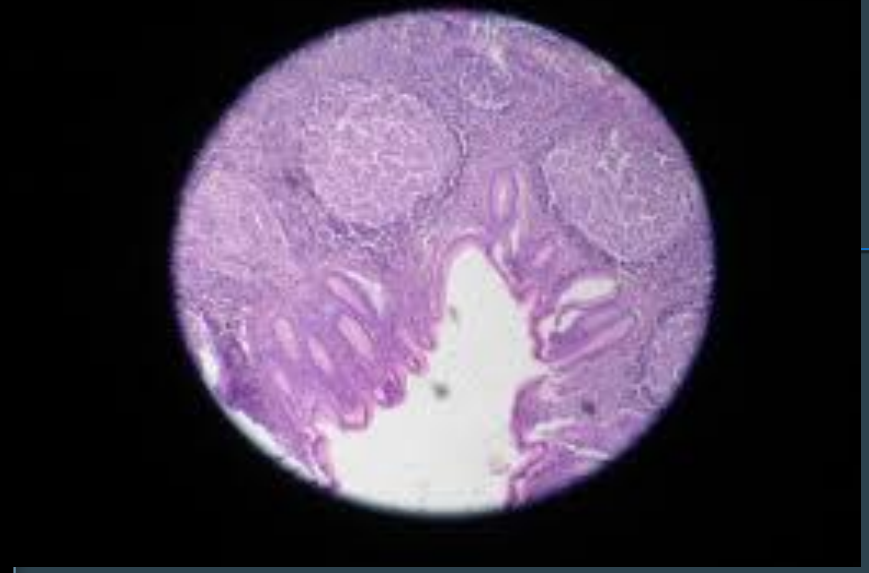
NON-SUPPURATIVE INFLAMMATION

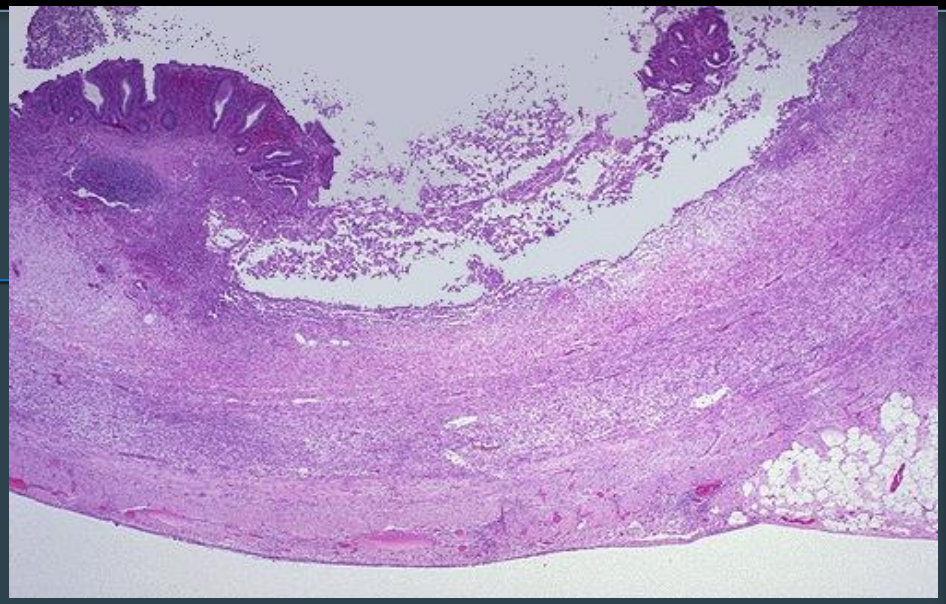


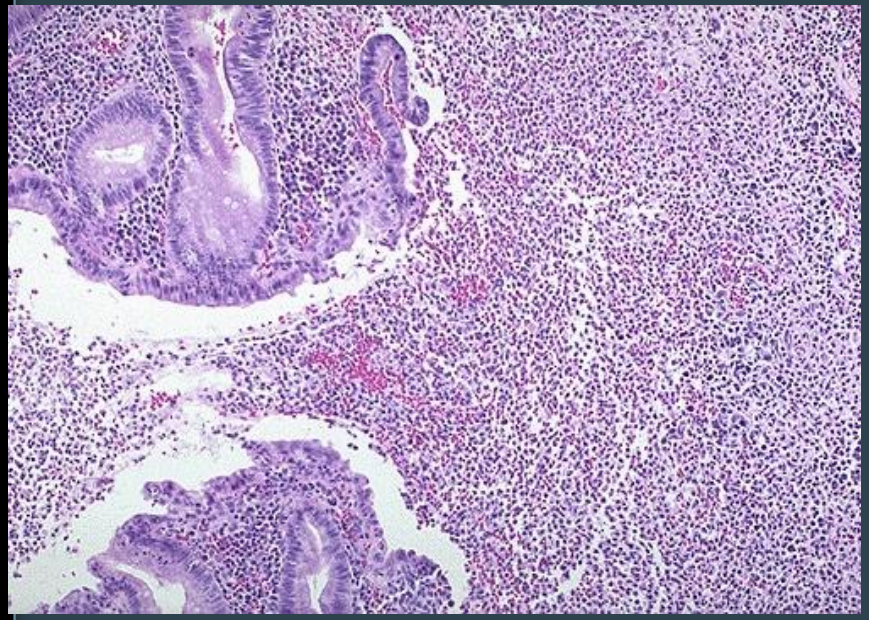

Purulent exudate (pus)
Vascular congestion
with perivascular edema

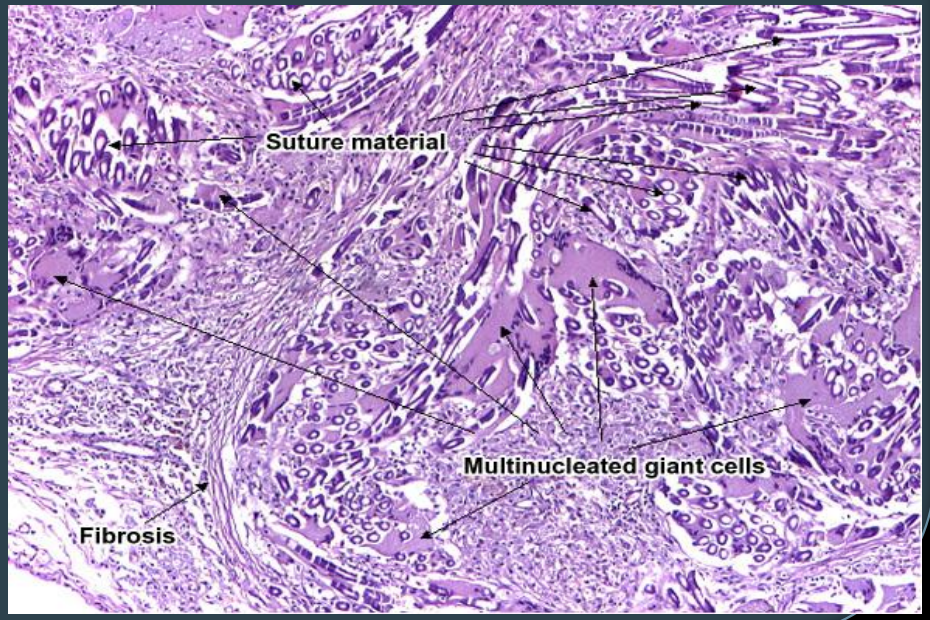

Fibrin
network
Visceral pericardium
Vessel
Myocardium


Vascular congestion
and perivascular edema
Neurons in
the grey substance
Purulent
exudate
Neutrophils
Fibrin
Vascular congestion
with neutrophil margination








Suture material
Multinucleated giant cells
Fibrosis

Catarrhal inflammation

- **Definition:**
- Mild acute non suppurative inflammation of the mucous membranes characterized by excess mucus secretion e.g. catarrhal rhinitis, bronchitis, appendicitis.

- **Gross Picture:**
- Early the mucous membrane appears red, hot, swollen and dry.
- Dryness is due to temporary cessation of mucus secretion.
- Then excess watery mucoid discharge appears, composed of inflammatory fluid exudate, mucus, small number of PML and sheded epithelial cells.
- When the PML ↑ the discharge becomes thick and yellowish.

- **Microscopic Picture:**
- Mucosal cells appear swollen and rounded due to mucus accumulation (mucoid change) and may rupture or desquamate.
- *The submucosa shows hyperemia, inflammatory edema and mild PML infiltration.*

Membranous inflammation (Pseudomembranous e.g. Diphtheritic)

- **Definition:**
- Severe acute non suppurative inflammation characterized by the formation of pseudo-membrane on the affected surface e.g. diphtheria and bacillary dysentery.

- **Pathogenesis:**
- The bacteria remain on the mucosal surface and produce powerful exotoxin which causes patchy mucosal necrosis.
- The exotoxin diffuses through the necrotic mucosa to the submucosa causing acute inflammation.
- The exotoxin is absorbed in the blood stream causing severe toxemia.

- **Gross Picture:**
- Early the mucosa is congested and shows small grayish yellow patches of necrosis.
- Next a yellowish white slightly elevated pseudo-membrane is formed on the surface.
- The membrane is adherent and its removal leaves a bleeding surface with the formation of another membrane.

- **Microscopic Picture:**
- The pseudo-membrane is formed of necrotic mucosal cells, bacteria and acute inflammatory cells held together by a fibrin network.
- The submucosa shows hyperemia, inflammatory edema, fibrin network and PML, pus cells, macrophages and red cells.

Sero-fibrinous inflammation

- **Definition:**
- Acute non suppurative inflammation characterized by formation of excess fluid exudate rich in fibrinogen e.g. inflammation in serous sacs (pleura, pericardium and peritoneum).
- Next the visceral and parietal layers become thickened, opaque, grayish yellow and reticulated due to fibrin deposition.

- If excess fibrin deposition occurs, inflammation is of the dry type.
- The inflammatory serous fluid collects in the serous sac.
- If excess serous fluid collects in the sac, inflammation is of the wet type.

- **Microscopic Picture:**
- The serosal cells lining the visceral and parietal layers swell due to degeneration and desquamate leaving bare surfaces.
- An inflammatory fluid exudate rich in fibrinogen pours from the bare surfaces.
- The fibrinogen changes to fibrin forming a network on both the visceral and parietal layers entangling the acute inflammatory cells.
- The subserosa shows hyperemia, inflammatory edema, fibrin network and acute inflammatory cells.

Fibrinous inflammation

- **Definition:**
- Acute non suppurative inflammation characterized by an exudate rich in fibrinogen e.g. lobar pneumonia.

- **Fibrinous exudate develops when:**
  1. The vascular leaks are large or
  2. There is a local procoagulant stimulus.
- With large ↑ in vascular permeability, fibrinogen pass out of the blood, and fibrin is formed and deposited in the extracellular space.
- The fibrinous exudate is characteristic of inflammation in the lining of body cavities, such as the meninges, pericardium, and pleura.

- **Histologically,** fibrin appears as an eosinophilic meshwork of threads or sometimes as an amorphous coagulum.
- Fibrinous exudates may be dissolved by *fibrinolysis* and cleared by macrophages.
- If the fibrin is not removed, with time, it may stimulate the ingrowth of fibroblasts and blood vessels and thus lead to *scarring*.

- Conversion of the fibrinous exudate to scar tissue ***(organization)*** within the pericardial sac leads to:

1. *Opaque fibrous thickening of the pericardium and epicardium in the area of exudation and,*
2. *If the fibrosis is extensive → obliteration of the pericardial space.*

Serous inflammation

- **Definition:**
- Acute non suppurative inflammation characterized by excess serous exudate e.g. mild buns and herpes simplex which show epidermal vesicles full of serous fluid containing few inflammatory cells.

- Serous inflammation is characterrized by *exudation of cell poor fluid into spaces created by injury to surface epithelia* or into the peritoneum, pleura, or pericardium.
- Typically, the fluid in serous inflammation is not infected by destructive organisms and does not contain large numbers of leukocytes.

- **In body cavities the fluid may be derived from:**
  1. Plasma as a result of ↑ vascular permeability or
  2. Secretions of mesothelial cells due to local irritation.
- Accumulation of fluid in these cavities is called an ***effusion*****.**

- Effusions consisting of ***transudates*** also occur in non-inflammatory conditions e.g.,
  1. Reduced blood outflow in heart failure, or
  2. Reduced plasma protein levels in some kidney and liver diseases.
- The skin blister resulting from a burn or viral infection represents a serous inflammation.

Hemorrhagic inflammation

- **Definition:**
- Acute non suppurative inflammation characterized by cellular exudate rich in RBCs due to vascular damage e.g. smallpox and hemolytic strept. infection.

Necrotizing inflammation

- **Definition:**
- Acute non suppurative inflammation characterized by marked tissue necrosis e.g. cancrum oris and Vincent-angina.

Allergic inflammation

- **Definition:**
- Acute non suppurative inflammation **characterized by:**

A. Tissue necrosis
B. Vascular dilatation, thrombosis, and destruction.
C. Cellular exudate formed mainly of PML and eosinophils.
D. Contraction of smooth muscles e.g. bronchi and intestine.
E. Increased mucous secretion by mucous glands.

Bacterial Infection of the Blood

Bacteremia

- ***Definition:***
- ***Bacteremia*** is a transient presence of small number of bacteria in the blood stream which do not multiply significantly, and without toxic manifestations.
- They are commonly not detected by direct microscopy.
- Blood culture is done for their detection e.g. infection with *Salmonella typhi, E. coli, Strept. viridans*.

- ***Pathogenesis:***
- Bacteria enter the blood stream from septic focus in the body e.g. tonsillitis, sinusitis, cholecystitis, salpingitis.
- A common example of bacteremia is that occurring after tooth extraction.

- ***Effects of Bacteremia:***
- The bacteria are usually phagocytosed and destroyed by cells of the reticulo-endothelial system specially when the number is small.
- Sometimes bacteria localize in the tissues causing a pathological lesion e.g. staph. bacteremia may cause a renal carbuncle or acute osteomyelitis, and strept. viridans bacteremia may cause subacute bacterial endocarditis.

Septicemia

- ***Definition:***
- ***Septicemia*** means presence of rapidly multiplying, highly pathogenic bacteria in the blood e.g. pyogenic cocci, bacilli of plague, or
- The circulation and multiplication of large number of virulent bacteria and their toxins in the blood stream.
- The condition is highly fatal.

- Septicemia is accompanied by systemic effects like toxemia, multiple small hemorrhages, neutrophilic leucocytosis and DIC.
- ***Etiology:***
- ***Causative organisms:***

1. Pyogenic bacteria as strept., staph., pneumococci and gonococci.
   - The commonest is strept. hemolyticus.
2. Bacilli as bacillus proteus, bacillus anthrax and bacillus pestis.

- ***Sources:***
- Important sources are infected pin prick, septic wounds, puerperal sepsis and acute osteomyelitis.
- Bacteria invade the blood especially in cases with low body resistance.

Pathology of Strept. Hemolyticus Septicemia:

1. Red cell hemolysis by hemolysin → anemia and red staining of the intima of the vessels by the liberated hemoglobin.
2. Petechial hemorrhage in the skin, mucous and serous membranes due to capillary destruction by the streptococcal toxins.
3. Cloudy swelling, fatty change and focal necrosis in the heart, liver and kidney.
4. Serofibrinous or suppurative inflammation in the serous sacs.

5. ***Acute splenic swelling:***

- ***Macroscopically:***
- The spleen is enlarged, soft and friable.
- Cut surface shows dark red semi-fluid red pulp easily scraped by knife or washed under the tap water.
- ***Microscopically:***
- The sinuses are dilated, congested and contain excess neutrophils and macrophages.
- Littoral cells lining the sinuses show active phagocytosis.

- The lymph follicles show hyperplasia and leucocytic infiltration.
- Later on they show necrosis and atrophy.

6. Acute bacterial endocarditis may occur.

Pyaemia

- ***Definition:***
- ***Pyaemia*** is the circulation of septic emboli in the blood stream and their arrest in different organs causing multiple small abscesses, or
- It is the dissemination of small septic thrombi in the blood which cause their effects at the site where they are lodged.

- This can result in pyaemic abscesses or septic infarcts.
- Pyaemia has a high mortality rate.

- ***Pathogenesis of pyaemia:***
- When septic focus involves a vein, septic thrombophlebitis occurs.
- Proteolytic enzymes in the inflamed area break down fragments from the septic thrombus.
- These fragments circulate in the blood stream as septic emboli.
- Next the septic emboli get impacted in the small vessels of different organs producing multiple small pyaemic abscesses.
- Bacteria are pyogenic types specially staph aureus.

- ***Types:***
- ***Systemic pyaemia:***
- Septic emboli circulate in the systemic venous blood.
- They are derived from acute osteomyelitis, puerperal sepsis, suppurative otitis media, cellulitis and acute bacterial endocarditis.
- They get arrested in the lung forming multiple pyaemic abscesses.
- Smaller emboli from the lung reach the kidney, liver, brain … etc.

- ***Pathological Picture:***
- The affected organ shows multiple small abscesses.
- The abscesses are nearly of the same size, peripheral in position, rounded in shape, yellow in color and surrounded by dark red zone of congestion.
- Cloudy swelling and fatty change in the parenchymatous organs caused by toxemia.
- Leucocytosis may occur in pyaemia as it is a pyogenic infection, however leucopenia is more common due to bone marrow depression by the associated toxemia.

- ***Portal pyaemia:***
- The septic emboli circulate in the portal venous blood.
- They are derived from acute suppurative appendicitis, infected piles, acute cholecystitis, diverticulitis and septic lesions in the colon.
- The emboli get arrested in the liver forming multiple pyaemic abscesses.

Pyaemic abscesses

- ***Definition:***
- ***Pyaemic abscesses*** are multiple small abscesses, nearly of the same size, surrounded by zone of congestion.
- ***Sites:*** Various organs e.g., cerebral cortex, myocardium, lungs and renal cortex, resulting from very small emboli fragmented from septic thrombus.

- **Microscopy:** Pyaemic abscess shows central zone of necrosis containing numerous bacteria, surrounded by zone of suppuration and an outer zone of acute inflammation.

Septic Infarcts

- ***Septic infarcts*** result from lodgment of larger fragments of septic thrombi in the arteries with relatively larger foci of necrosis, suppuration and acute inflammation e.g. septic infarcts of the lungs, liver, brain, and kidneys from septic thrombi of leg veins or from acute bacterial endocarditis.

Toxemia

- ***Definition:***
- ***Toxemia*** is a circulation of *bacterial toxins* in the blood causing pathological and clinical manifestations.

- **Bacterial toxins are of two types:**

1. ***Exotoxins:*** Produced by gram positive bacteria as diphtheria bacilli, shigella organisms and some types of strept. and staph.
2. ***Endotoxins:*** Released from the bodies of dead gram negative bacteria as typhoid bacilli.

- **Types:**

1. ***Acute toxemia:*** Occurs in acute infections as diphtheria.
2. ***Chronic toxemia:*** Occurs in chronic infections as TB.

- ***Manifestations of Toxemia:***

1. ***Constitutional signs and symptoms:*** Fever, rigor, headache, weakness and ↑ rate of tissue metabolism.
2. ***Degeneration:*** Mainly in the heart, kidney and liver in the form of cloudy swelling and fatty change.

- Severe toxemia causes acute heart failure.
- Chronic toxemia may cause amyloid degeneration.

3. ***Necrosis and hemorrhage of the adrenal cortex:*** May be fatal due to acute adrenal cortical insufficiency.
4. ***Anemia:*** Due to bone marrow depression by the toxins.

Sapremia

- **Definition:**
- **Sapremia** is the presence of toxic metabolites in the blood stream derived from the action of saprophytic bacteria on necrotic tissue.
- The condition occurs mainly in gangrene.

Outcomes (course) of acute inflammation

- Although, many variables may modify the process of inflammation, including the nature and intensity of the injury, the site and tissue affected, and the responsiveness of the host, ***acute inflammatory reactions typically have one of five outcomes:***

I. **Complete resolution:**

- All inflammatory reactions, after they have succeeded in eliminating the offending agent, should end with restoration of the site of acute inflammation to normal.
- This is called ***resolution*** and is the usual outcome:

A. *when the injury is limited or short-lived or*
B. *when there is little destruction and*
C. *when the damaged parenchymal cells can regenerate.*

- Vasodilation, chemical production, and leukocyte infiltration cease.
- Resolution involves removal of cellular debris and microbes by macrophages, and resorption of edema fluid by lymphatics.
- Damaged parenchymal cells regenerate.

II. Healing by scarring or fibrosis:

- This occurs after l tissue destruction, when:

A. *there is large amounts of tissue destruction,*
B. *the injury involves tissues that are incapable of regeneration,*
C. *there is abundant fibrin exudation, or*
D. *in serous cavities (pleura, peritoneum) that cannot be adequately cleared.*

- Fibrous scarring composed primarily of collagen occurs in these areas of damage.
- The scar does not contain any specialized structures, such as parenchymal cells, hence functional impairment may occur.

III. **Abscess Formation:**

- A cavity is formed containing pus; an opaque liquid containing dead PML and bacteria with debris from destroyed cells.

IV. **Progression and spread:**

- The bacteria overcome the defense mechanism of the immune system and inflammation spreads directly, by lymphatics, and by blood causing fatal septicemia.

v. Progression to chronic inflammation:

- This occurs when *acute inflammatory response cannot be resolved,* as a result of:
  A. *persistence of the injurious agent or*
  B. *interference with the normal process of healing.*
- This process lasting many days, months or even years and may → formation of chronic wound.
- Chronic inflammation is characterized by the dominating presence of macrophages in the injured tissue.

- Macrophages are powerful defensive agents of the body, but the toxins they release (including ROS) are injurious to the tissues as well as invading agents.
- Chronic inflammation is almost always accompanied by ***tissue destruction.***

Outcomes of acute inflammation

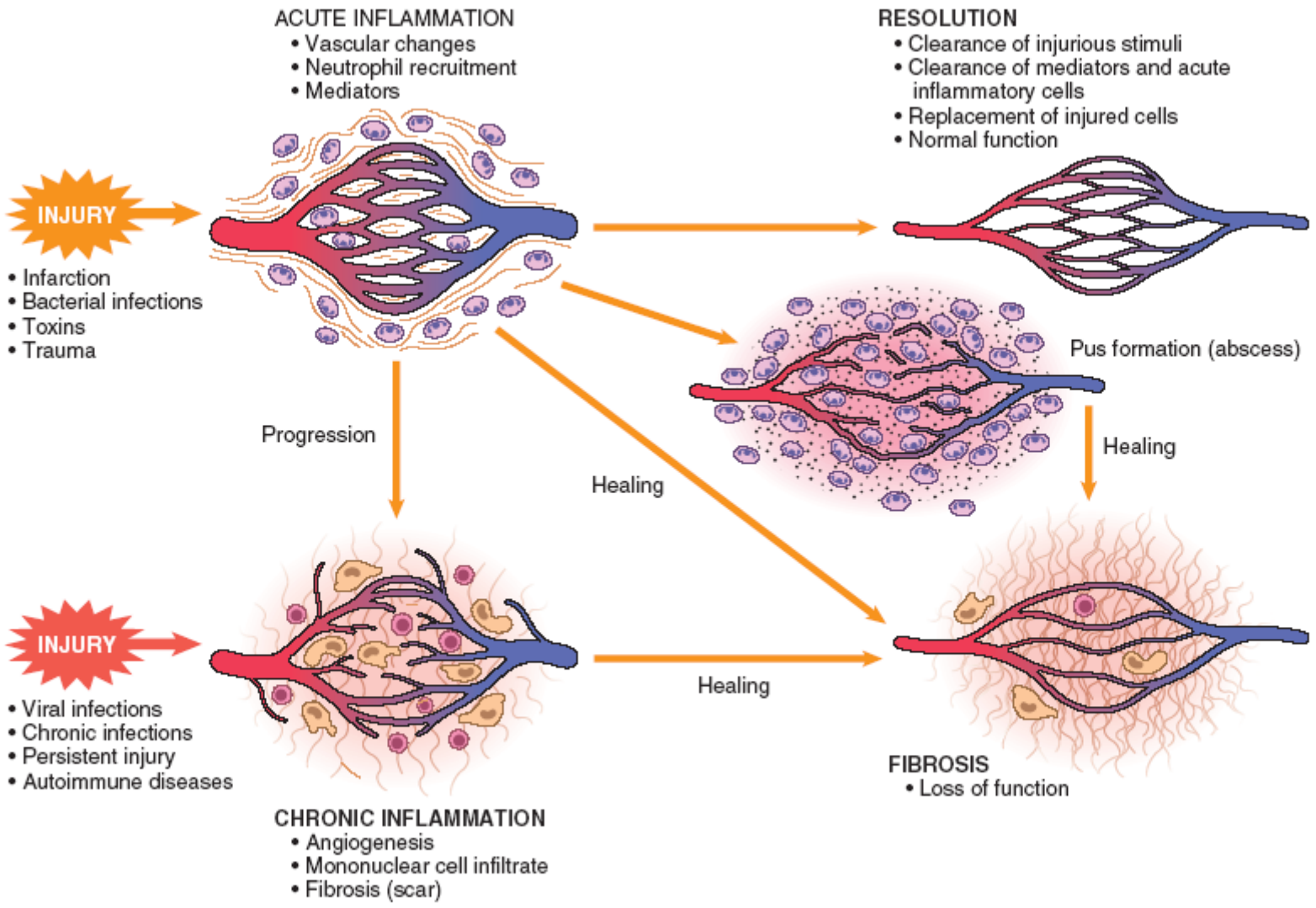


Fig. 3.16 Outcomes of acute inflammation: resolution, healing by fibrosis, or chronic inflammation. The components of the various reactions and their functional outcomes are listed.

Systemic Effects of Acute Inflammation

- ***Inflammation, even if it is localized, is associated with cytokine-induced systemic reactions that are collectively called the acute-phase response (APR).***
- Anyone who has suffered severe bout of bacterial or viral illness (e.g., pneumonia or influenza) has experienced the systemic manifestations of acute inflammation.

- Systemic changes are reactions to cytokines whose production is stimulated by bacterial products such as LPS, viral double stranded RNA and by other inflammatory stimuli.
- TNF, IL-1, and IL-6 are important mediators of the APR.
- Other cytokines, especially type I interferon, also contribute to the reaction.

- ***The APR consists of several clinical and pathologic changes:***

1. ***Fever,*** ↑ of body temperature, by 1° to 4°C, is one of the most prominent manifestations of APR, especially in inflammation associated with infection.

- Substances that induce fever are called ***pyrogens,*** e.g., prostaglandins that are produced in the vascular and perivascular cells of the hypothalamus.

- Bacterial products, such as LPS ***(exogenous pyrogens)***, stimulate leukocytes to release cytokines such as IL-1 and TNF ***(endogenous pyrogens)*** that ↑ ***COX*** enzymes that convert arachadonic acid into prostaglandins.
- In the hypothalamus, ***PGE2,*** stimulate the production of ***neurotransmitters*** that reset the temperature set point at a higher level.
- NSAIDs, including ***aspirin,*** reduce fever by inhibiting prostaglandin synthesis.
- *How, and even if, fever contributes to the protective host response remains unclear.*

2. ***Acute-phase proteins*** are plasma proteins, mostly synthesized in the liver in response to *cytokines.*

- Their plasma concentrations may ↑ several hundred-fold in response to inflammatory stimuli.
- *Three of the best-known of these proteins are:*
  A. *C-reactive protein (CRP),*
  B. *fibrinogen, and*
  C. *serum amyloid A (SAA) protein.*
- *CRP and SAA, may bind to microbial cell walls, and act as opsonins and/or fix complement.*

- ***Fibrinogen*** binds to RBCs → formation of ***rouleaux*** that *sediment more rapidly than do individual red cells.*
- This is the basis for measuring ***ESR*** for an inflammatory response caused by any stimulus.
- Acute-phase proteins have beneficial effects during acute inflammation, but prolonged production of these proteins especially SAA in chronic inflammation can, in some cases, cause ***secondary amyloidosis***.

- *Elevated serum levels of CRP* serve as a marker for ↑ risk of myocardial infarction in patients with coronary artery disease.
- It is postulated *that inflammation involving atherosclerotic plaques* in coronary arteries predisposes to thrombosis and infarction.
- Another peptide whose production is ↑ in the APR is the *iron-regulating peptide* ***hepcidin.***
- *Chronically elevated plasma hepcidin reduces the availability of iron and are responsible for* ***anemia*** associated with ***chronic inflammation.***

3. ***Leukocytosis:*** It is a common feature of inflammation, especially induced by bacterial infection.

- The leukocyte count usually climbs to 15,000 or 20,000 cells/mL, but sometimes it may reach extraordinarily high levels of 40,000 to 100,000 cells/mL.
- These extreme elevations are referred to as ***leukemoid reactions,*** because they are similar to (and must be distinguished from) the white cell counts observed in leukemia.

- Leukocytosis occurs initially because of *accelerated release of cells from the bone marrow caused by cytokines, including TNF and IL-1* and is therefore associated with a *rise in the number of more immature neutrophils in the blood,* referred to as a ***shift to the left*** of myeloid cells.

- Prolonged infection also *induces proliferation of precursors in the bone marrow, caused by ↑ production of* ***colony-stimulating factors (CSFs).***
- If inflammation is sustained bone marrow output of leukocytes ↑, more than compensates for the loss of these cells in the inflammatory reaction.
- Most bacterial infections induce an ↑ in the blood neutrophil count, called ***neutrophilia.***

- ***Viral infections,*** such as infectious mononucleosis, mumps, and German measles, *cause an* ***absolute*** ↑ *in the number of lymphocytes* ***(lymphocytosis).***
- In some allergies and parasitic infestations, there is an ↑ *in the number of blood eosinophils,* called ***eosinophilia.***
- Certain infections *(typhoid fever and some viruses, rickettsiae, protozoa)* are associated with *decreased number of circulating white cells* ***(leukopenia),*** with relative lymphocytosis.

- **Other manifestations of the APR include:**
- ↑ *heart rate and blood pressure; decreased sweating,* mainly because of redirection of blood flow from cutaneous to deep vascular beds, to minimize heat loss through the skin.
- *There are also rigors (shivering), chills (search for warmth), anorexia, somnolence, and malaise,* probably because of the actions of cytokines on brain cells.

- In ***sepsis,*** the large amounts of bacteria and their products in blood stimulate production of large quantities of TNF and IL-1.
- High blood levels of cytokines cause widespread clinical and pathologic abnormalities such as:
  A. *DIC,*
  B. *hypotensive shock, and*
  C. *metabolic disturbances including insulin resistance and hyperglycemia.*

- This clinical triad is known as ***septic shock.***
- A syndrome similar to septic shock may occur as a complication of non-infectious disorders, such as *severe burns, trauma, pancreatitis*.
- *Collectively these reactions are called* ***systemic inflammatory response syndrome (SIRS).***

4. ***Lymphangitis-lymphadenitis:***

- The lymphatics and lymph nodes draining the inflamed tissue show reactive inflammatory changes in the form of lymphangitis and lymphadenitis.
- This response represents *either*
  1. *A nonspecific reaction to mediators released from inflamed tissue* or
  2. *A specific immunologic response to foreign antigen.*
- The affected lymph nodes y show ***follicular hyperplasia*** and proliferation of mononuclear phagocytic cells in the sinuses of lymph node ***(sinus histiocytosis).***


Thank You