جامعة الملك سعود
King Saud University

pathology
MED 439

MED439
KING SAUD UNIVERSITY

Inflammation and Repair L3

Objectives:

- **Chemical mediators of inflammation:**
  - **Definition**
  - **Know the general principles for chemical mediators**
  - **Know the cellular sources and major effects of the mediators**
  - **List the most likely mediators of each of the steps of inflammation**
- **Recognize the different patterns of inflammation**
- **List and describe the outcome of inflammation**

Color Index:
Girl's Slides
Important
Male's Notes
Female's Notes
Extra information

Chemical mediators of inflammation

Mediators

- Chemical mediators of inflammation are substances produced during inflammation inducing a specific events in acute inflammation.
- Play a major role in the early phase of acute inflammation and increases vascular permeability + vasodilation

The production of active mediators is triggered by:

- **Microbial products**
- **host proteins**, such as the proteins of the complement, kinin and coagulation systems (these are themselves activated by microbes and damaged tissues)

General principles for chemical mediators

Most mediators have the potential to cause harmful effects If they persist. Therefore, there should be a mechanism to checks and balances their action.

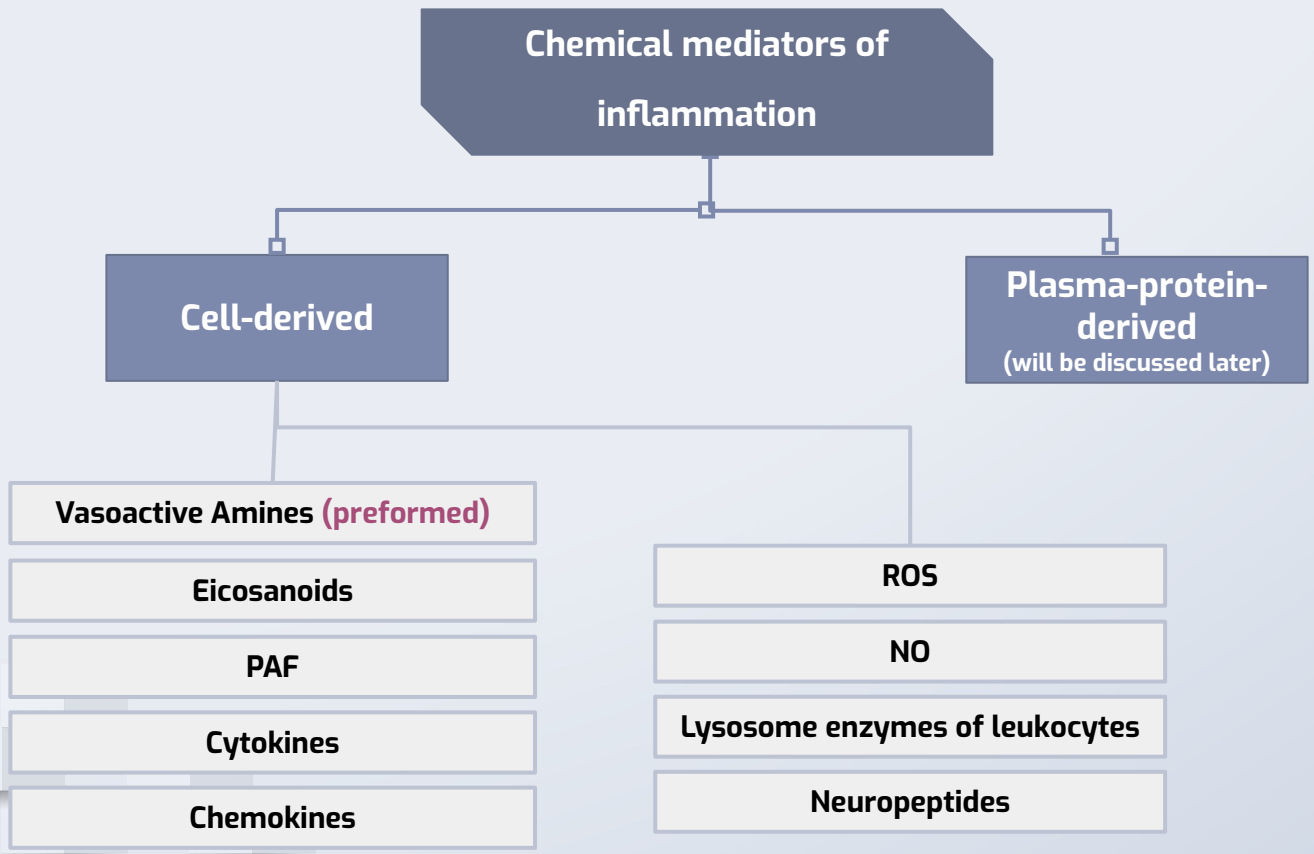
Mediators function is tightly regulated by:

- **Decay** (e.g. AA metabolites)
  AA: Arachidonic Acid
- **inactivated by enzymes** (e.g. kininase inactivates **bradykinin**)
- **eliminated** (e.g. antioxidants scavenge toxic oxygen metabolites)

Chemical mediators of inflammation

Source of chemical mediators

Cell-derived	Plasma-derived Formed in the blood in inactive form
1- **Synthesized as needed** (at the moment) (**prostaglandin**)	*1- **Complement***
2- **Preformed , sequestered and released** (mast cell histamine)	*2- **Kinins***
- Against offending agents in tissue	*3- Coagulation factors*
	***-Many in "pro-form"** requiring activation (enzymatic cleavage)*
	- Against circulation microbes



Chemical mediators of inflammation:cell derived

Cell-derived mediators

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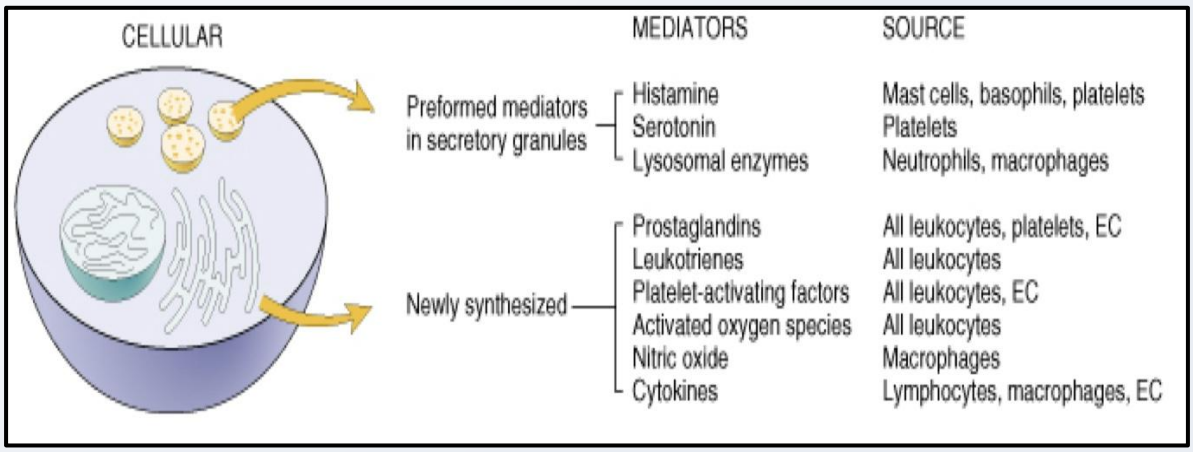
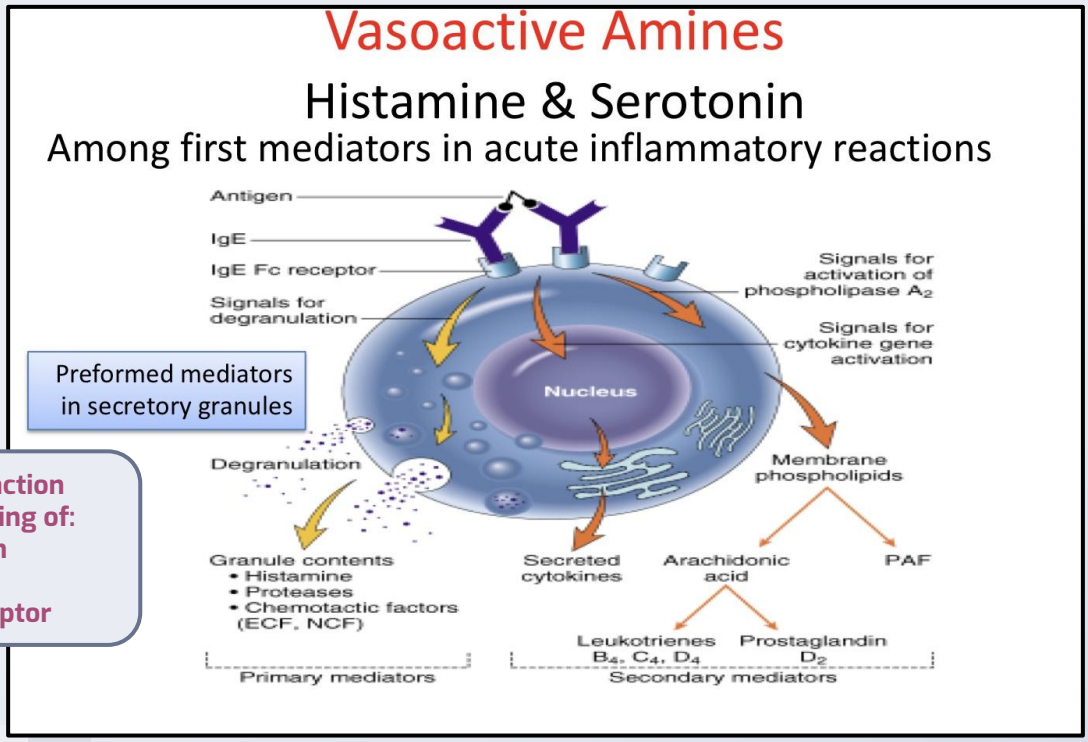
Producing cells



•Vasoactive Amines

-Histamine & serotonin
-Among first mediators in acute inflammation reactions



Immune reaction involves linking of:
Antigen
IgE
IgE Fc receptor

Chemical mediators of inflammation: cell derived-preformed

• Histamine

Secreted by Many cell types, esp. mast cells, circulating basophils, and platelets

Stimuli of release

- **Physical injury**
- **Immune reaction** (Binding of IgE to receptors of mast cells which causes secretion of histamine)
- **C3a and C5a fragments**
- **Cytokines** (e.g. IL-1 and IL-8)
- **Neuropeptides**

Action

1- **Arteriolar dilation**

2- **increased vascular permeability** (venular gaps)

3- **endothelial activation**

Short lived

Inactivated by : Histamin*ase*

Serotonin can work both as a vasoconstrictor and a vasodilator

• Serotonin (5-HT)

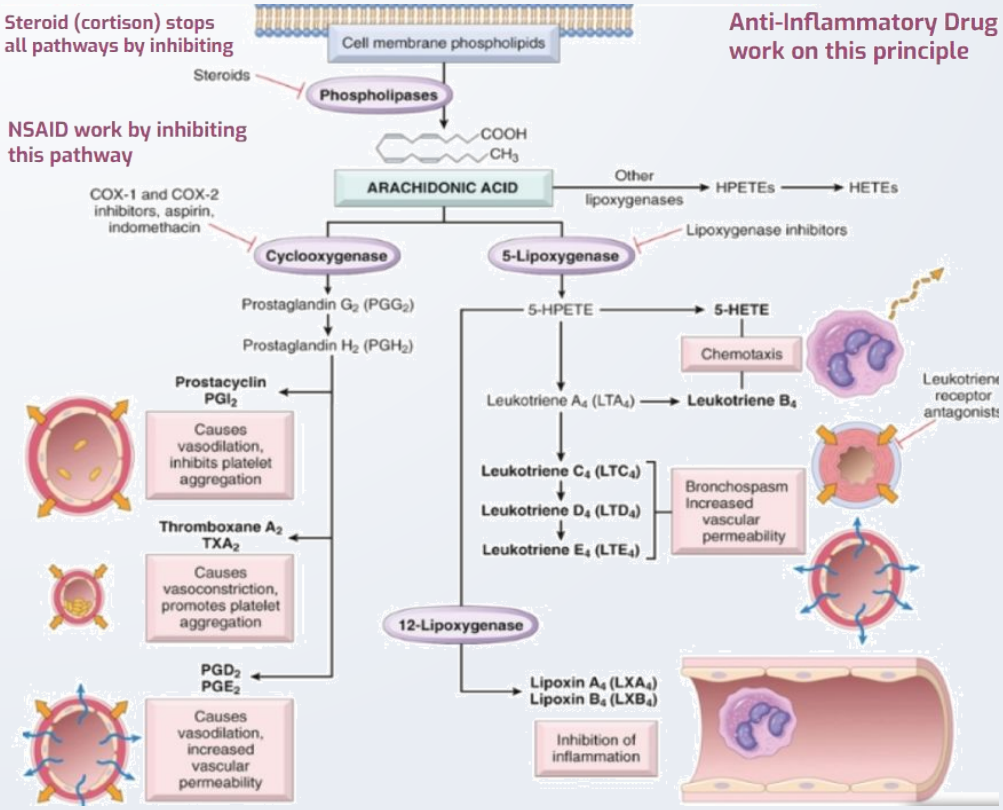
Source	Platelets only* (Composed of tryptophan)
Action	**Neurotransmitter** in the gastrointestinal tract. A **vasoconstrictor** (the importance of this action in inflammation is unclear. Could mediate termination of inflammation)
Stimulus	Platelet aggregation

5-HT is secreted by platelets. Platelets cause clotting and clotting causes vasoconstriction.

***It's important to know things that are only synthesized by one source**

Chemical mediators of inflammation: cell derived-newly synthesized

- **Arachidonic acid metabolites (eicosanoids)**



Source:
Leukocytes
Mast cells
Endothelial cells
Platelets

Most eicosanoids are produced from arachidonic acid, which is a polyunsaturated fatty acid that you get from eating foods like animal fats. They have many effects on your body, including inflammation, fever promotion, blood pressure regulation, and blood clotting.

-Arachidonic acid metabolites (eicosanoids)

Action	Eicosanoid
Vasodilation	Prostaglandins PGI2 (prostacyclin), PGE1, PGE2, PGD2
Vasoconstriction	Thromboxane A2 , leukotrienes C4,D4,E4
Increased vascular permeability	Leukotrienes C4,D4,E4
Chemotaxis, leukocyte adhesion	Leukotrienes B4
Smooth muscle contraction	Prostaglandins PGC4, PGD4, PGE4

Prostaglandins are very important because a lot of anti-inflammatory drugs of antipyretics and analgesics work on blocking prostaglandins pathway (anti-prostaglandins).

Chemical mediators of inflammation: cell derived-newly synthesized

Source :
Lymphocytes
Macrophages
Dendritic cells
Mast Cells
Endothelial cells
Epithelial cells

• Cytokines

-Polypeptides.

Actions:

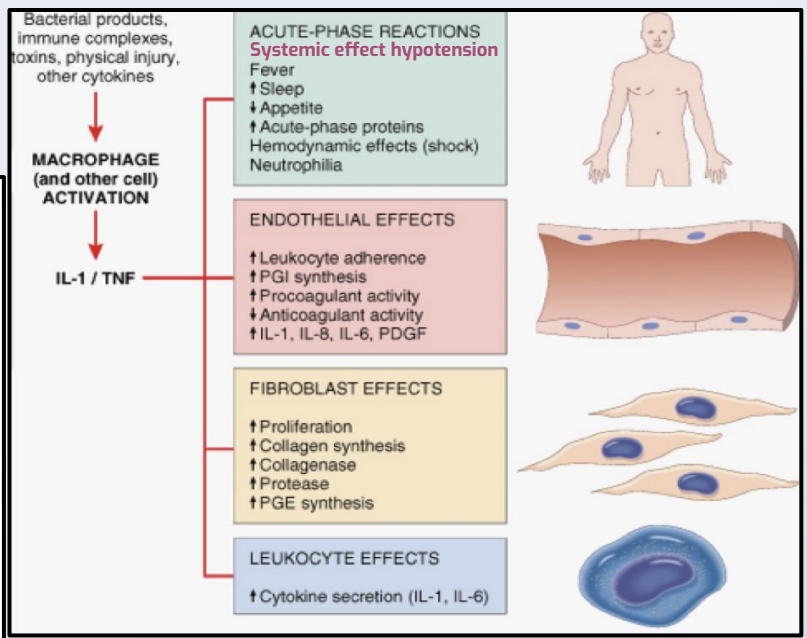
- Involved in early immune and inflammatory reactions
- Some stimulate bone marrow precursors to produce more leukocytes
- Have roles in *acute* and *chronic* inflammation

-Cytokines of *acute* inflammation

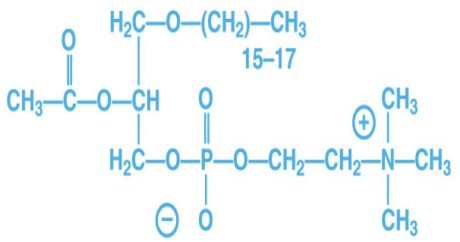
Actions:

Stimulates expression of endothelial adhesion molecules and secretion of other cytokines; systemic effect

Cytokine of *acute* inflammation: IL-1, IL-6 & TNF



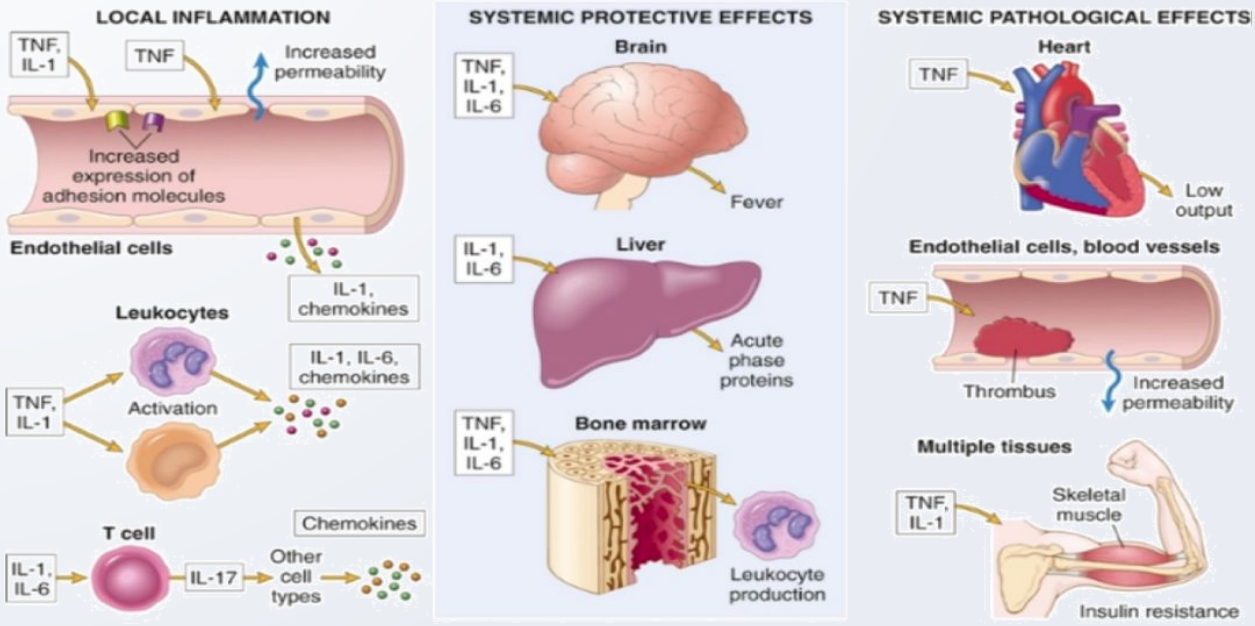
SOURCES	MAJOR INFLAMMATORY ACTIONS
Mast cells/basophils	Increased vascular permeability
Neutrophils	Leukocyte aggregation
Monocytes/macrophages	Leukocyte adhesion
Endothelium	Leukocyte priming/chemotaxis
Platelets	Platelet activation
Others	Stimulation of other mediators (LT, $O_2^{\cdot-}$)



PLATELET-ACTIVATING FACTOR **(PAF)**

Chemical mediators of inflammation: cell derived-newly synthesized

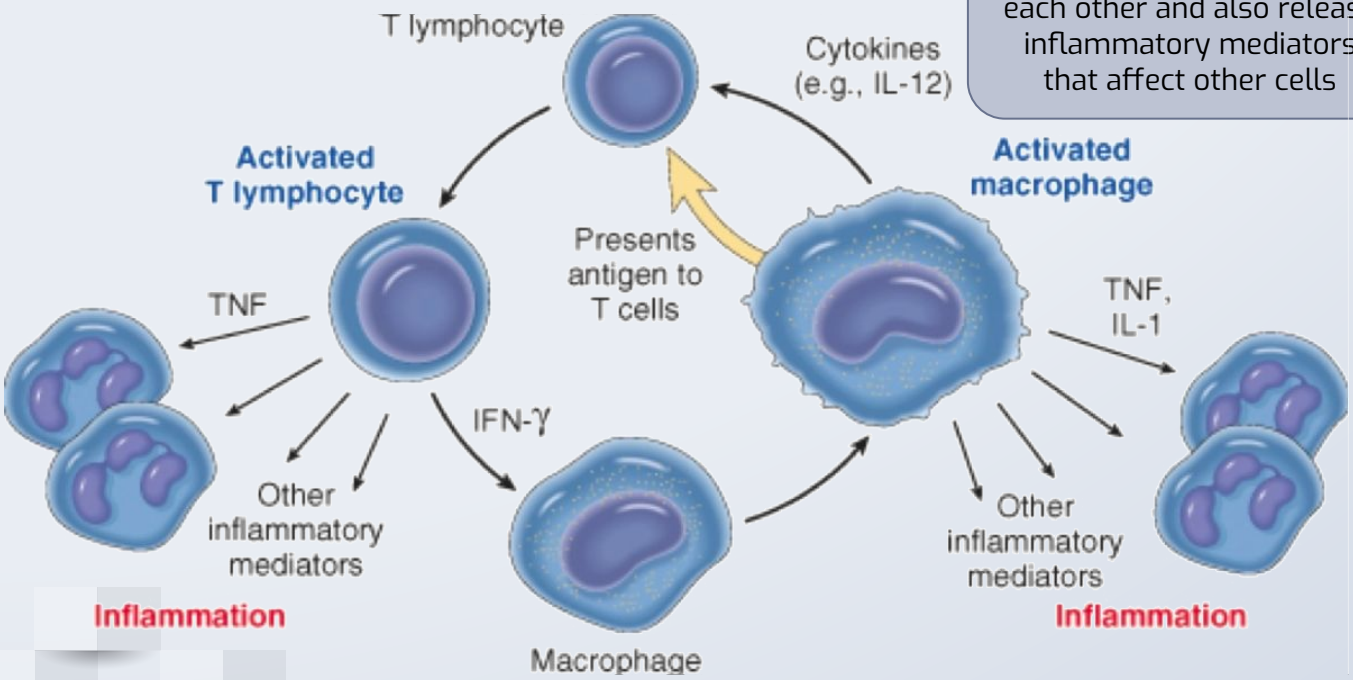
Major roles of cytokines in acute inflammation



TNF antagonists is effective in the treatment of rheumatoid arthritis

-Cytokines of chronic inflammation: Interferon-gamma (INF-γ)& interleukin (IL-12)

Activated lymphocytes and macrophages influences each other and also release inflammatory mediators that affect other cells



Chemical mediators of inflammation: cell derived-newly synthesized

·Chemokines

Small protein
They are chemoattractants for leukocytes

Main function:-
-Leukocytes recruitment & activation in inflammation
-normal anatomic organization of cells in lymphoid and other tissue (Chemotaxis of leukocytes)
Secreted by leukocytes and activated macrophages

• Reactivate oxygen species (ROS)

Synthesized via: NADPH oxidase pathway.
Source: Neutrophils and Macrophages.
Stimuli of release: microbes, immune complexes, cytokines.
Action: microbicidal (cytotoxic) agent, causes tissue damage.

• Nitric oxide (NO)

Short-lived
Soluble free-radical gas

Functions:-

- **Vasodilation.**

- **Antagonism of platelet activation** (adhesion, aggregation, & degranulation).

- **Reductive of leukocytes recruitment**.

- **Microbicidal (cytotoxic) agent** (with or without ROS) in activated macrophages (Reduces number but strengthen macrophage).

Chemical mediators of inflammation: cell derived-newly synthesized

• Lysosomal enzymes of leukocytes

Neutrophils & monocytes

- Enzymes:

Acid proteases

Neutral proteases

(e.g. elastase , collagenase , cathepsin)

- Their action is checked by:

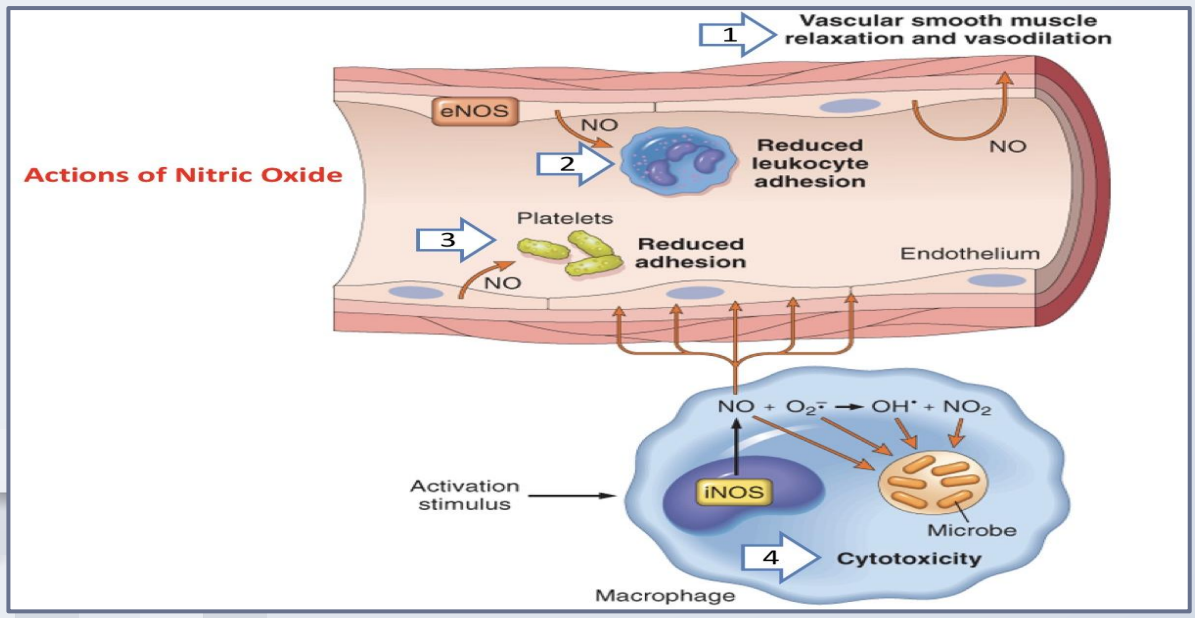
Serum antiproteases (e.g. alpha1-antitrypsin)

·Neuropeptides

- **Small proteins**
- **Secreted by nerve fibers** minaly in lung & GIT
- **Initiate inflammatory response**

E.g. substance P:

- Transmits pain signals
- Regulates vessel tone
- Modulates vascular permeability



Chemical mediators of inflammation :

Cell derived mediators (discussed earlier)

Plasma-protein derived mediators

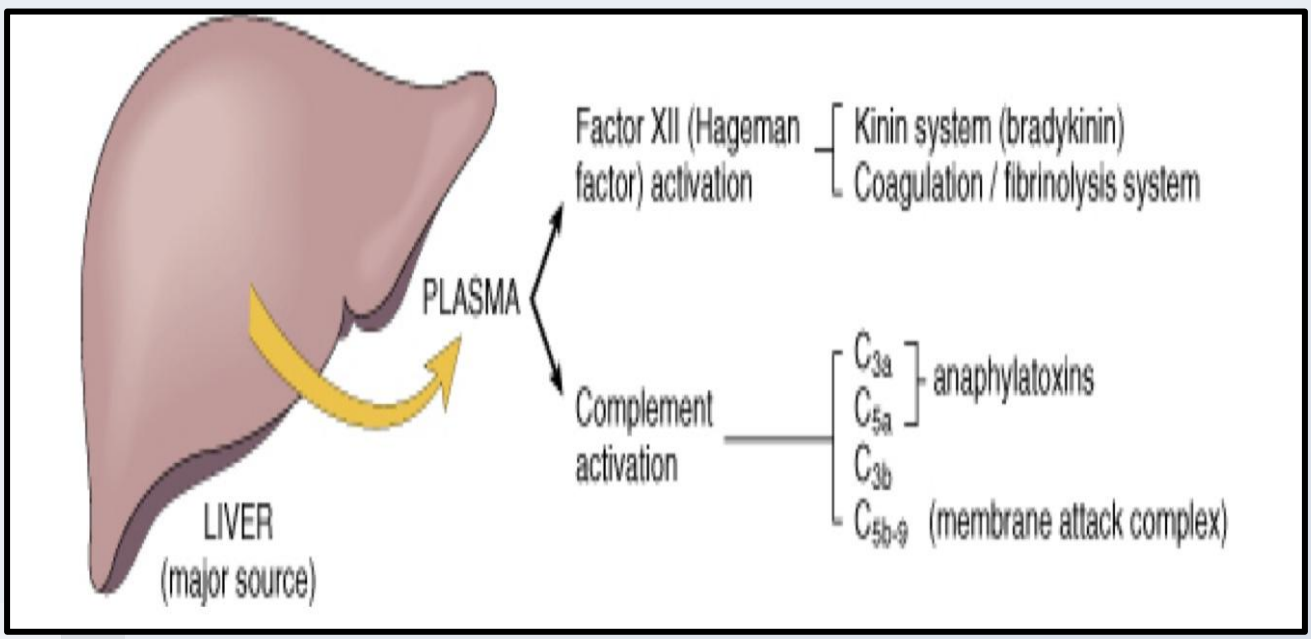
Plasma protein derived includes:

- Complement system
- Coagulation & Kinin system

1- clotting systems
2- kinin
3-complement

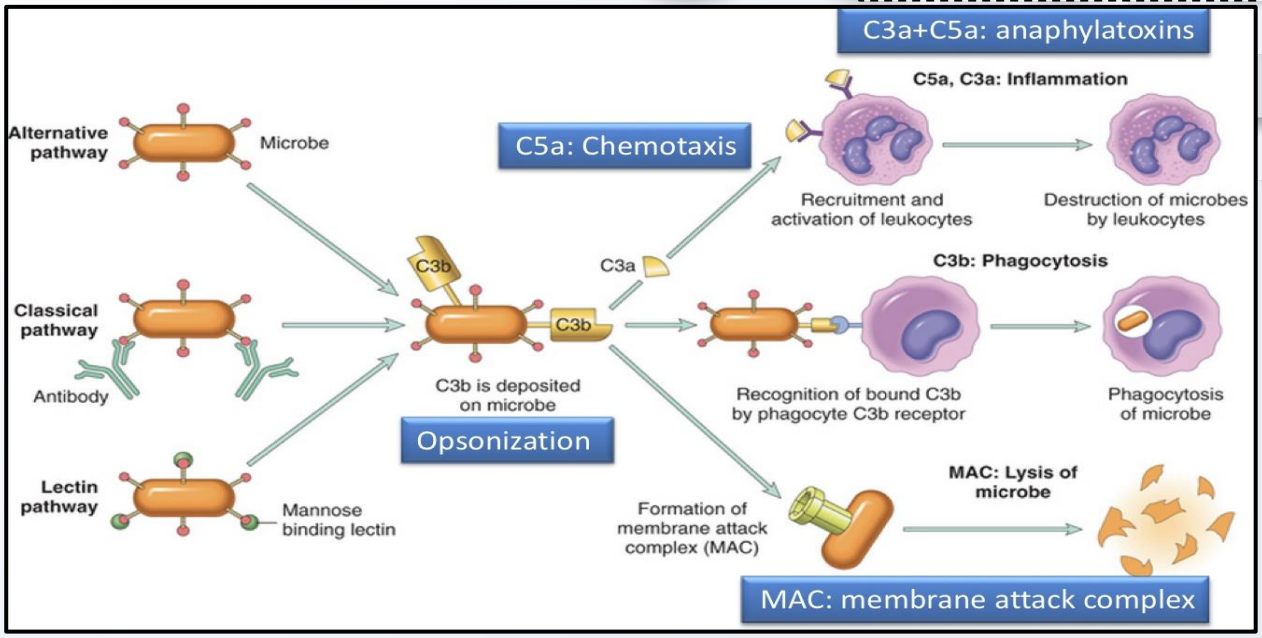
A) complement system:

Proteins secreted by the liver and they are inactive, they get *activated by*:
1- Classical pathway: c1,c4,c2
2- Alternative pathway: c3
3- Mannose binding lectin (MBL) pathway
4- Lytic pathway: : C5b-9 membrane attack complex (MAC) attacks cytoplasmic membrane during anaphylactic shock



Complement system

Increase vasodilation + increased vascular permeability → hypotension

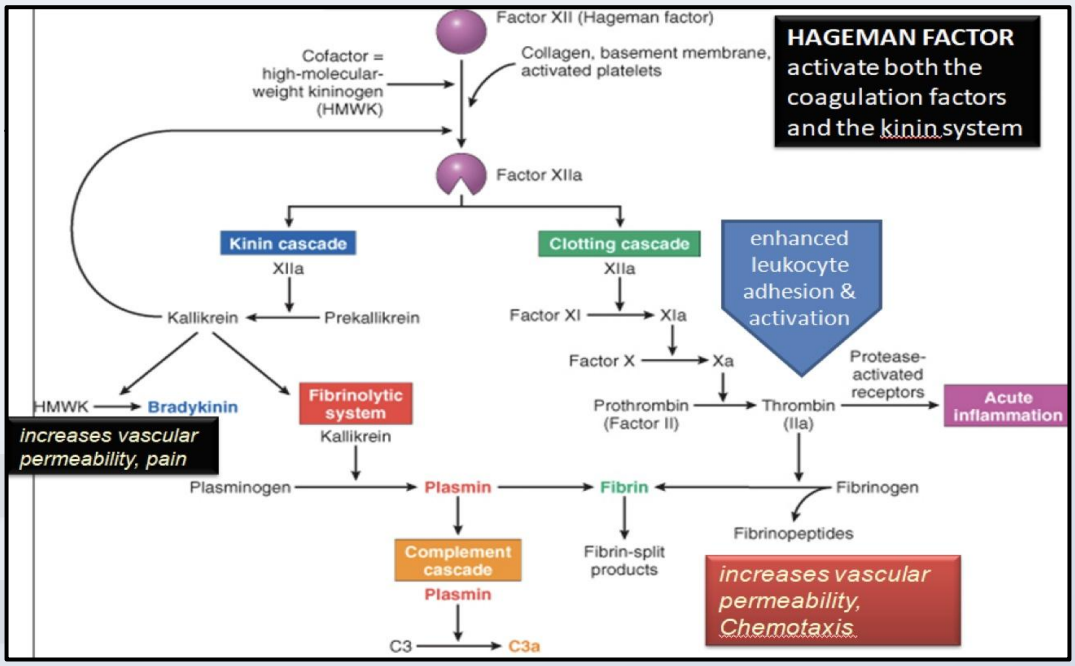


Notes:

Anaphylactic shock is type I hypersensitivity
- C3a and C5a are chemotactic: induce chemotaxis
- C5a is more important than C3a
- Opsonins include immunoglobulins and c3b (C3b is more important)

B) Kinin system:

- it gets activated when coagulation cascade is activated (factor 12 especially)
- coagulation protein produce thrombosis
- factor 12 is called Hageman factor
- bradykinins are plasma proteins that come for kinins and it increase the vascular permeability and cause pain
- activation of hageman factor lead to activation of prekallikrein and it get converted to kallikrein
- kallikrein metabolism will lead to bradykinin formation



Chemical mediators of inflammation: cell plasma protein derived

Complement protein: action

C3a & C5a → increase vascular system permeability (anaphylatoxins)
C5a → chemotaxis
C3b → opsonization
C5-9 → membrane attack complex , lead to bacterial lysis

⋆Role of mediators in different reactions of inflammation:

Vasodilation	Prostaglandins, histamine, nitric oxide
Increased vascular permeability	Vasoactive amines (Histamine and serotonin) bradykinin leukotrienes C4,D4,E4 PAF Substance P
Chemotaxis, leukocytes recruitment and activation	C3a , C5a Leukotrienes B4 Chemokines IL-1 , TNF
Fever	IL-1 , TNF Prostaglandins E
Pain	Prostaglandins E Bradykinin
Tissue damage	Neutrophils and macrophages lysosomal enzymes Oxygen metabolites Nitric oxide

EXTRA SLIDE (HELPFUL).

List summary of chemical mediators

Mediator	Principal Sources	Actions
Cell-Derived		
Histamines	Mast cells, basophils, platelets	Vasodilation, increased vascular permeability, endothelial activation
Serotonin	Platelets	Vasodilation, increased vascular permeability
Prostaglandins	Mast cells, leukocytes	Vasodilation, pain, fever
Leukotrienes	Mast cells, leukocytes	Increased vascular permeability, chemotaxis, leukocyte adhesion and activation
Platelet-activating factor	Leukocytes, mast cells	Vasodilation, increased vascular permeability, leukocyte adhesion, chemotaxis, degranulation, oxidative burst
Reactive oxygen species	Leukocytes	Killing of microbes, tissue damage
Nitric oxide	Endothelium, macrophages	Vascular smooth muscle relaxation, killing of microbes
Cytokines (tumor necrosis factor [TNF], interleukin 1 [IL-1])	Macrophages, endothelial cells, mast cells	Local endothelial activation (expression of adhesion molecules), fever/pain/anorexia/hypotension, decreased vascular resistance (shock)
Chemokines	Leukocytes, activated macrophages	Chemotaxis, leukocyte activation
Plasma Protein-Derived		
Complement products (C5a, C3a, C4a)	Plasma (produced in liver)	Leukocyte chemotaxis and activation, vasodilation (mast cell stimulation)
Kinins	Plasma (produced in liver)	Increased vascular permeability, smooth muscle contraction, vasodilation, pain
Proteases activated during coagulation	Plasma (produced in liver)	Endothelial activation, leukocyte recruitment

Morphologic of Acute Inflammation

· inflammation vary in their morphology and clinical correlates. Why?

Depends on

- The severity of the reaction
- specific cause e.g: pyogenic bacteria produced abscess
- the particular tissue
- site involved

Acute inflammation may be caused by:

- **Infarctions**
- **Drugs**
- **Trauma**

Healing can be associated with formation of scars

Morphologic Patterns of Acute Inflammation

- **Serous Inflammation**
- **Fibrinous Inflammation**
- **Catarrhal Inflammation**
- **Suppurative Or Purulent Inflammation**
- **Ulcers**
- Others

1- Serous Inflammation

A

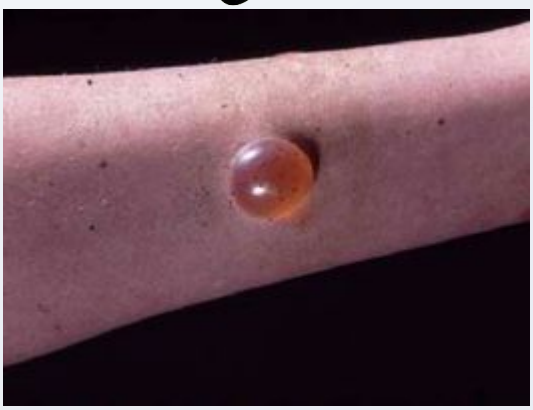
Marked by the outpouring of a thin fluid this fluid occurs immediately and has less amount of inflammatory cells, it's also poor in fibrin .

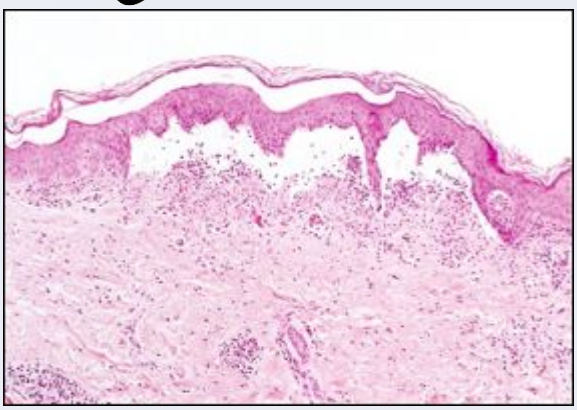
B

Happens with tuberculosis usually as a vesicle.

C

Pleural effusion is caused by inflammation





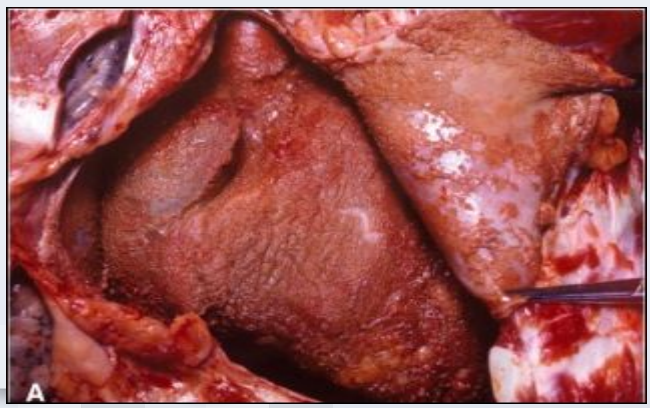
2- Fibrinous Inflammation

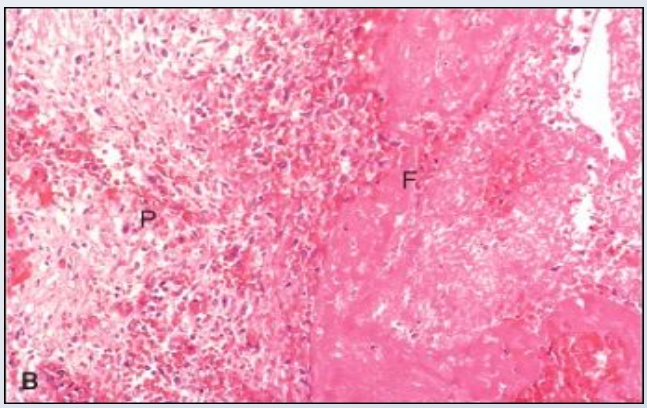
– **A fibrinous exudate** (fluid accumulation) **is a characteristic** of inflammation in the **lining of body cavities**, such as the meninges, pericardium and pleura (larger molecules such as fibrinogen pass the vascular barrier)

– **Fibrinous exudates may be removed by fibrinolysis**.

– **If not:** it may stimulate the ingrowth of granulation tissue (*organization*)

will be explained in details in lec 5

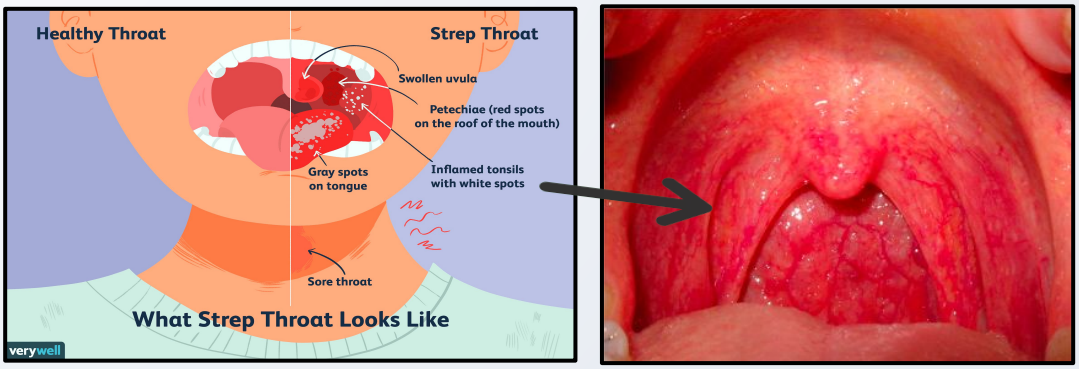




3-Catarrhal inflammation

Inflammation **affects** **mucosa-lined** surfaces with the outpouring of watery mucus

E.g. Common cold which might include: Sore throat and increase of mucus secretion



4- Suppurative or Purulent Inflammation

Characterized by the production of large amounts of pus or purulent exudate consisting of neutrophils, necrotic cells, and edema fluid caused by pyogenic (pus-producing) bacteria. E.g. staphylococci, staphylococcus aureus and streptococci.

An **abscess** is a cavity lined by granulation tissue and containing:-

1- inflammatory cells (neutrophils)
2- necrotic cells (Dead cells)
3- bacteria (staphylococcus aureus and streptococci)
4- fibrinous material

Abscesses: A localized collections of purulent inflammatory tissue caused by suppuration buried in a tissue, an organ, or a confined space

Abscess: inside the body, **Pus**: outside the body

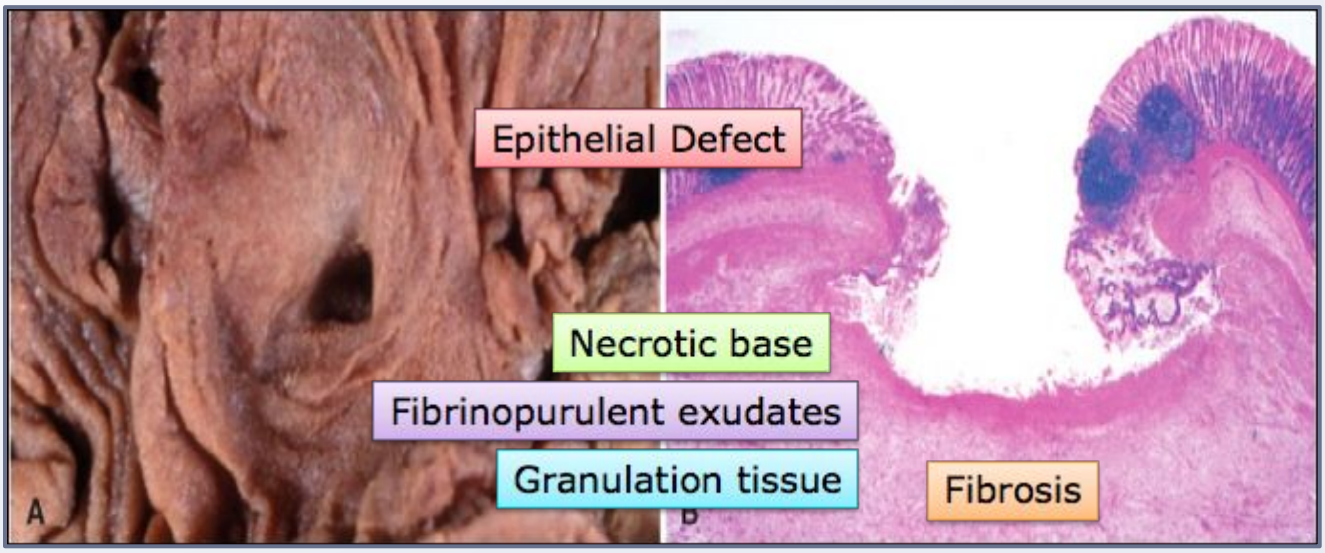
notes :

pus sample is sent to: culturing and sensitivity microbiology department.

Empyema of gallbladder has pyogenic inflammation: (pus +bile).

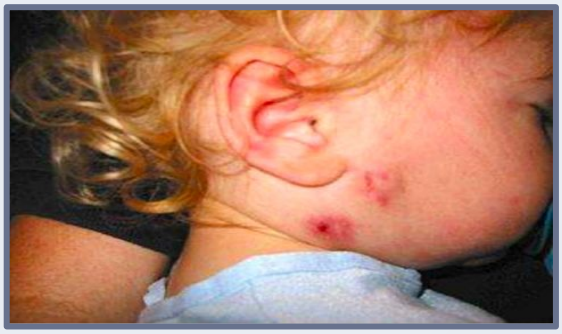
5- Ulcers

An ulcer is a local defect of the surface of an organ or tissue that is produced by the sloughing (shedding) of inflammatory necrotic tissue



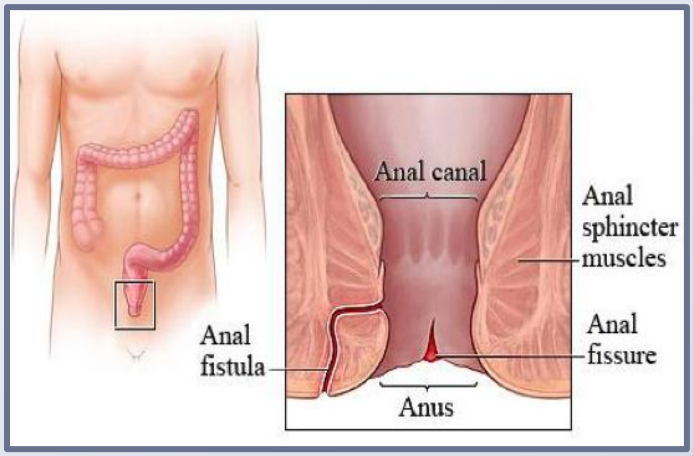
6- Sinus

A tract between the abscess and a surface (skin).
has one channel, and drains outside



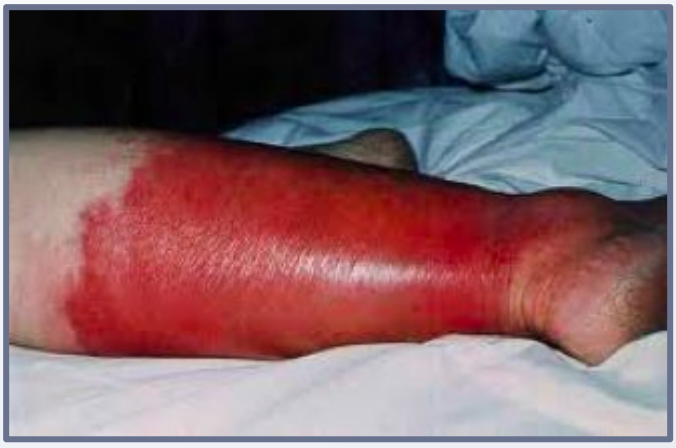
7-Fistula

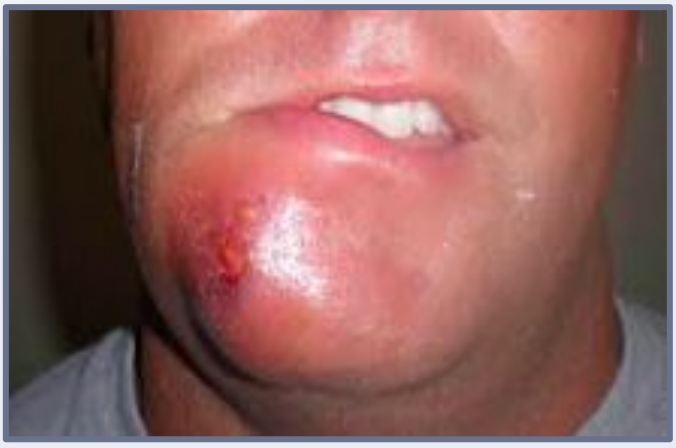
A tract between two surfaces.
has two channels (to the skin & to the closest mucosa)
Common in anus



8- cellulitis

a spreading of acute inflammation through interstitial tissues.
(not limited to one spot)

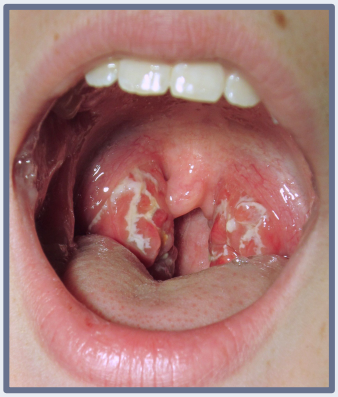




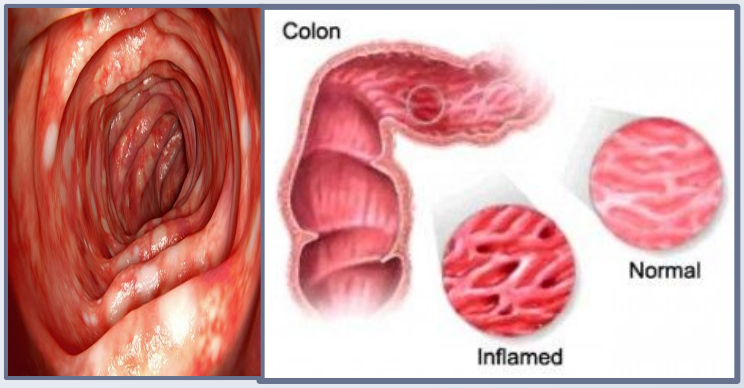
9- pseudomembranous inflammation

It refers to swelling or inflammation of the **colon (colitis) or tonsils (tonsillitis)** due to an overgrowth of some bacteria.

This infection is a common cause of diarrhea , it happens after extreme use of antibiotics.



Tonsillitis



Colitis

Outcomes of Acute Inflammation

it may have one of the four outcomes:

01 **Complete resolution**

Events in the resolution of inflammation:

1- **Neutralization, decay, or enzymatic degradation** of the various chemical mediators; normalization of vascular permeability; and cessation of leukocyte emigration and apoptosis.

2- The necrotic debris, edema fluid, and inflammatory cells are **cleared by phagocytes** and lymphatic drainage.

3- **Lymph node become enlarged and inflamed.**

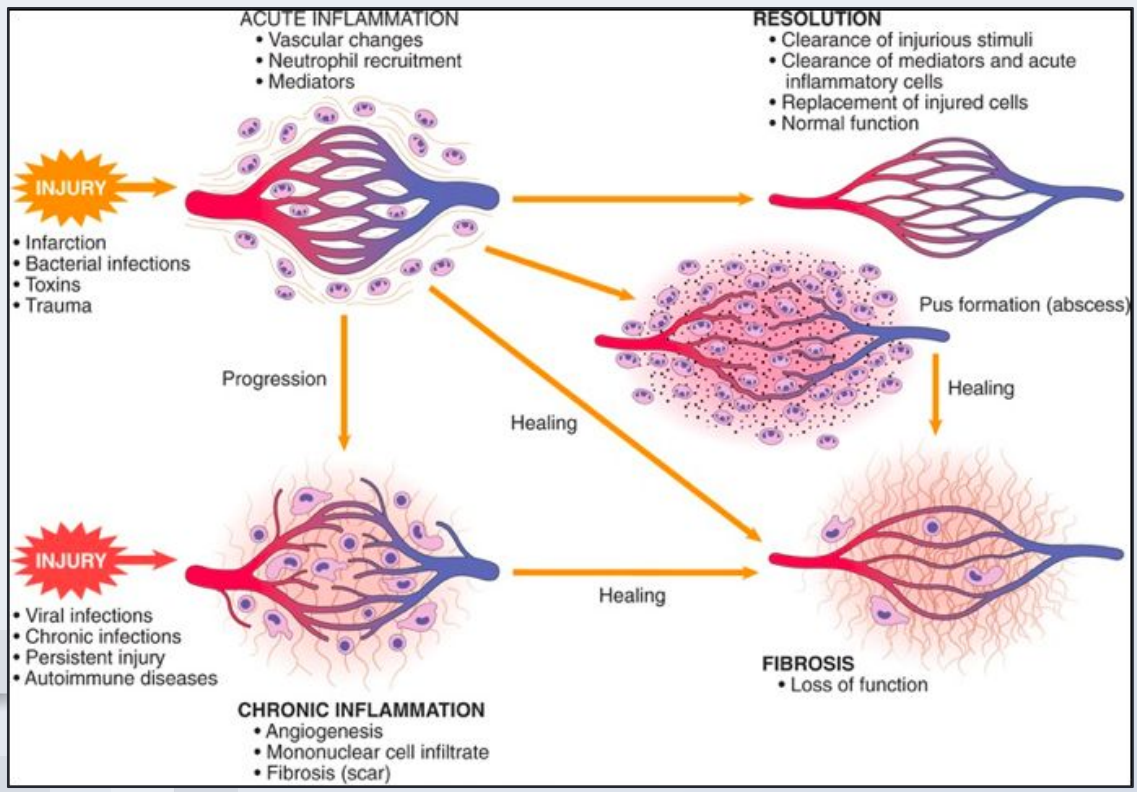
02 **Progression of the tissue response to chronic inflammation**

03 **Fibrosis:** Healing by connective tissue replacement.

04 **Abscess formation**

Outcomes of Acute Inflammation

SUMMARY



MCQs

1-Which one of the following is NOT a cell-derived chemical mediator?			
a- PAF	B- Kinins	C- Chemokines	D- ROS
2- Immunoglobulin responsible for allergic reactions			
A- IgE	B- IgA	C- IgG	D-IgM
3-Which of these is NOT associated with serous inflammation?			
A- Marked by the outpouring of a thin fluid	B- Happens with tuberculosis usually as a vesicle.	C- Pleural effusion is caused by inflammation	D-production of large amounts of pus
4- Acute inflammation can be caused by:			
A-Infarction	B- Drugs	C- Trauma	D- All of them
5-A fibrinous exudate (fluid accumulation) is a characteristic of inflammation in the lining of			
A- Stroma	B- Endothelial cells	C- Body cavity	D- Interstitial tissue
6-A tract between two surfaces.			
A- Sinus	B- Fistula	C- Sinusoid	D- None of the above

SAQs

Q1: It refers to swelling or inflammation of the colon (colitis) or tonsils (tonsillitis) due to an overgrowth of some bacteria

Q2: shedding of inflammatory necrotic tissue is a symptom of?

1- B 2- A
3- D 4- D
5- C 6- B

1 -Pseudomembranous inflammation
2- Ulcer

- غادة العثمان
- البندري العنزي
- بنان القاضي
- رغد خالد سويعد
- رغد العسيري
- روان باقادر
- ريناد الحميدي
- سارة العبيد
- سارة القحطاني
- ساره المقاطي
- سديم آل زايد
- سمو عبدالرحمن
- شذى الدوسري
- شعاع خضري
- غادة العبدي
- غيداء العسيري
- غيداء المرشود
- فاطمة المعيذر
- فرح السيد
- منال التويم
- مها فهد
- نورة بامرعي

- ماجد العسكر
- هادي الحمصي
- أحمد الخواشكي
- بدر الريس
- حمد الربيعه
- حمود القاضب
- سالم الشهري
- عبد العزيز الكريدا
- عبد اللطيف الشريمي
- فراس القايدي
- فيصل الفضل
- يزيد القحطاني
- أسامة العقل
- بندر الحربي
- حمد الموسى
- سعد الدحيم
- عبد الرحمن الروقي
- عبد الرحمن المبكي
- عبد العزيز العمري
- علي الماطري
- محمد السنيدي
- محمد السياري
- محمد القهيدان
- محمد الوهيبي
- مشعل الثنيان
- نايف آل الشيخ

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