Inflammation

Lecture: 5-10

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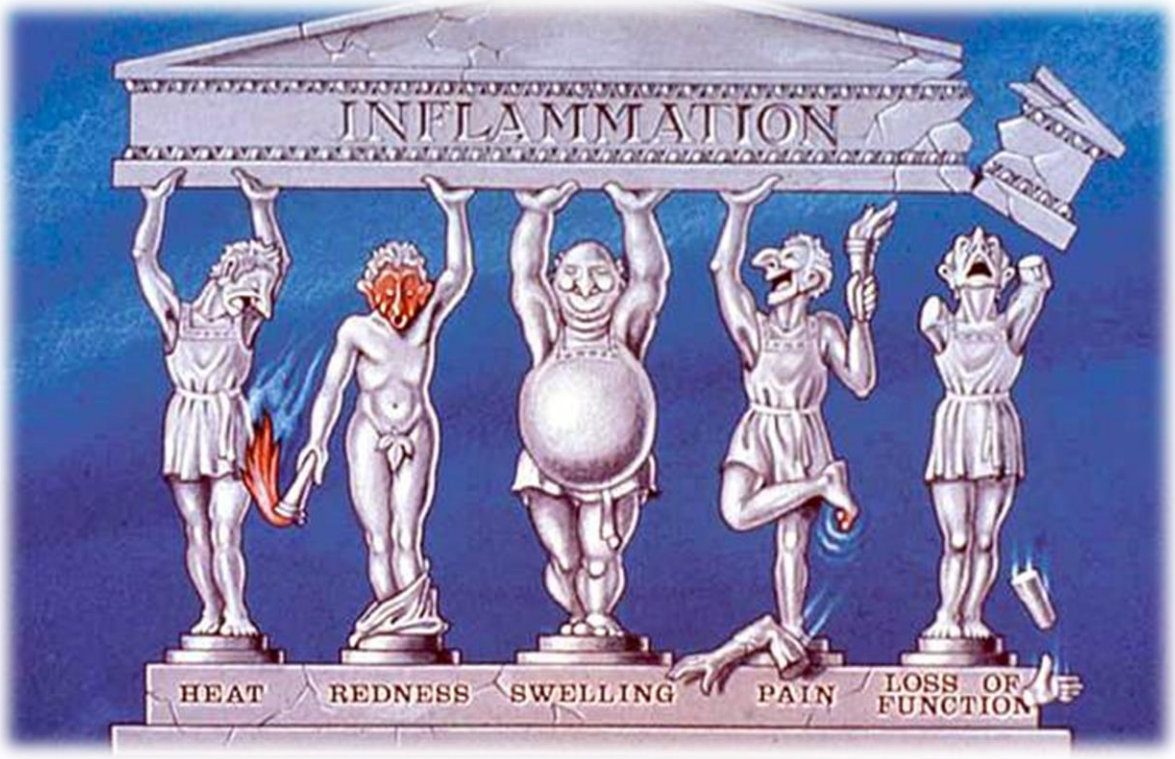


PATHOLOGY
TEAM 433

Red is definitions. Orange is listings. Green is examples.
Blue is hyperlinks. Purple is notes to remember.

Injury → Tissue damage → Tissue response → Eliminates the effect of injury → Repair

Inflammation

It is the local response of the vascularized living tissue to injury.
Inflammation is also a defensive host (Human) response to foreign invaders and necrotic tissue, but it is also capable of causing tissue damage.

Aim: **eliminate the initial cause of cell injury as well as the necrotic cells and tissues resulting from the original insult**

- **Protective response (innate immunity)**
- **Leads as far as possible to the healing and reconstitution of the damaged tissue.**

Inflammation can induce harm:
e.g. Anaphylactic reaction
Rheumatoid arthritis
Atherosclerosis

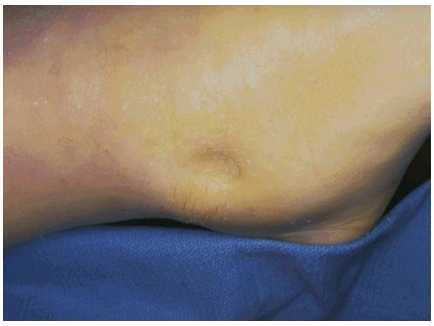
- **Inflammation is terminated when the offending agent is eliminated and the secreted mediators are broken down or dissipated.**
- **However, there are active anti-inflammatory mechanisms that serve to control the response and prevent it from causing excessive damage to the host.**

Features of inflammation:

- **The main components of inflammation are:**
  - **Vascular changes.**
  - **Cellular changes.**
  - **Chemical mediators.**

The cardinal signs of inflammation are rubor (redness), calor (heat), tumor (swelling), dolor (pain), and loss of function. Seen here is skin with erythema, compared to the more normal skin at the far right.

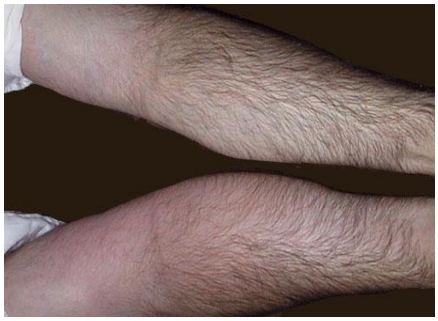
CAUSES OF INFLAMMATION:



1- **Infections.**
2- **Physical Trauma (e.g. burns & bites)**
3- **Drugs & Toxins.**
4- **Immunological Reaction**
5- **Foreign body insertion.**

CLINICAL FEATURES OF INFLAMMATION:

A- Local:



1. **Tumor (swelling / EDEMA)**
2. **Rubor (Redness)**
3. **Colar (Warmth / Heat)**
4. **Dolor (Pain)**
5. **Functio Lasea (loss of function)**

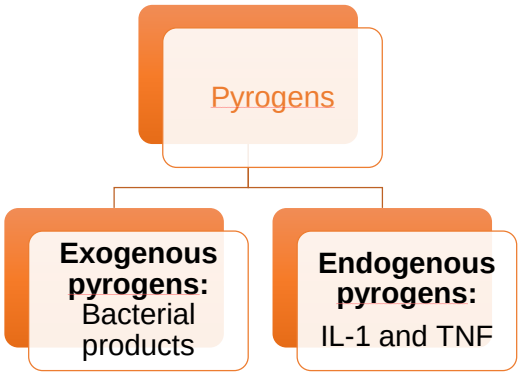
B- Systemic:

1. **Fever (Pyrexia).**
2. **Chills.**
3. **Vomiting.**
4. **General Weakness (malaise).**
5. **Leukocytosis.**
6. **Lymphocytosis.**
7. **Eosinophilia.**
8. **Leukopenia.**
9. **Elevated plasma levels.**

First: Fever

Fever is produced in response to <u>Pyrogens</u>

Pyrogens act by simulating prostaglandins in the vascular and perivascular cells of the hypothalamus.



NOTE : Bacterial products stimulate leukocytes to release cytokines such as IL-1 and TNF that increase the enzymes (cyclooxygenases) that convert AA into prostaglandins.

<u>Fever :</u>

- **In the hypothalamus, the prostaglandins, especially PGE_2, stimulate the production of neurotransmitters such as cyclic AMP, which function to reset the temperature set-point at a higher level.**
- **NSAIDs, including aspirin , reduce fever by inhibiting cyclooxygenase and thus blocking prostaglandin synthesis.**

Leukocytosis

- WBC count climbs to 15,000 or 20,000 cells/µl
- most bacterial infection (Neutrophil)

Lymphoytosis

- Most viral Infectious.
- examples: mononucleosis, mumps and German measles

Eosinophilia

- Most allergic reactions.
- examples bronchial asthma, hay fever, parasitic infestations

Leukopenia

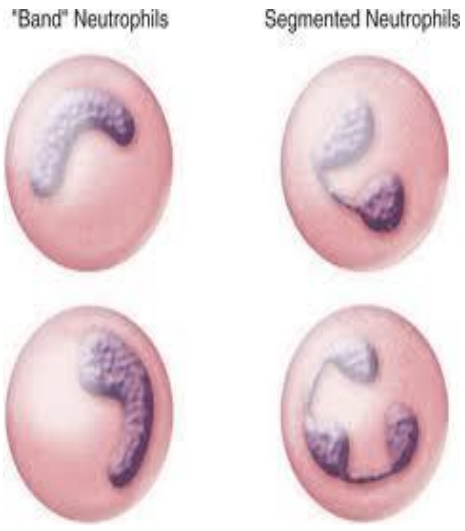
- Certain bacterial/Viral infectious
- examples typhoid fever, infection with rickettsiae/protozoa

Elevated plasma protein:

These plasma proteins are synthesized in the liver. And there are three of the best known of these proteins:

1- **C-reactive protein (CRP).**
2- **Fibrinogin.**
3- **Serum amyloid A (SAA).**
4- **Alpha-2-Macroglobulin.**
5- **Haptoglobin.**
6- **Ceruloplasmin.**
7- **Lipopolysacchride binding protein.**

The hepatocyte is stimulated by the cytokines, especially IL-6.



- Acute inflammation is marked by an increase in inflammatory cells. Perhaps the simplest indicator of acute inflammation is an increase in the white blood cell count in the peripheal blood, here marked by an increase in segmented neutrophils (PMN's). So, Band Neutrophils (immature neutrophils) are seen in acute inflammation (Left shift).

Types of cells can be found at peripheral blood and increase in blood at inflammation:

1- Neutrophils: phagocytize a foreign material, and then oxidize it and digest it through oxidase and protease (also increase in myocardial infarction).
2- Eosinophils: also phagocytic, they also can dispense antihistamine in an area of histamine release. (Found in allergic conditions and parasites. Found in both acute and chronic).
P.s. eosinophils can be found in peripheral blood and it can be found in local.

3- Lymphocytes: some of them are in T-cell system and produce various types of lymphokines, which have local effect. And some of them are in B-cell system, which produce Immunoglobulins and antibodies (usually chronic inflammation).
4- Plasma cells: produce antibodies.

Notes:

- **Monocytes and basophils can increase at acute inflammation, too.**
- **Basophil stores histamine, which cause allergic reaction.**
- **Plasma cells and macrophages are found in the tissues and they increase in chronic inflammation.**
- **Plasma cell has eccentric nucleus and plenty of Rough ER that produce immunoglobulin protein and it modified B-lymphocytes and T-lymphocytes**
- **Macrophage (chronic) is called histiocyte and it is active in phagocytosis (to engulf antigens) as well as it could increase in acute inflammation in last stages.**

The Laboratory changes which occur in inflammation effect:

1) **Number of inflammatory cells.**
2) **White blood cell count and differential count. If it was high, that means it is inflammation.**

Prolonged Erythrocytes sedimentation rate "ESR"
How to do an ESR? They will take a blood sample and put it in very fine glass tube, and they will measure time for the blood cells to come down, if the time is prolonged that means the blood is viscous. For normal erythrocytes sedimentation rate is from (1 - 2) minutes, more than this means Inflammation.

NOTE: More WBCs makes it more viscous

- **The rise in fibrinogen causes erythrocytes to form stacks (rouleaux) that sediment more rapidly at unit gravity than do individual erythrocytes.**

3) **C-reactive protein: is secreted by the liver and it "Acute phase protein" Is increased in inflammation.**

When a patient gets acute stress (inflammation or necrosis or cell damage), this protein is released.

4) **Complement protein.**

Types of inflammation:

1- **Acute inflammation. (Immediate and short duration)**
2- **Chronic Inflammation. (Protracted)**

NOTE: Most of the times, Inflammations start with acute and develop into chronic.

First: Acute inflammation:

A rapid response to an injurious x agent that serves to deliver mediators of host defense-leukocytes and plasma proteins-to the site of injury.
Systemically, acute inflammation maybe combined with fever.

The outcome of acute inflammation is either

1. **Elimination and resolution of the noxious stimulus, followed by decline of the reaction and repair of the damaged tissue.**
2. **Abscess formation and localized acute inflammatory exudate with pus formation in one area. (Complication.**
3. **Persistent injury resulting in chronic inflammation.**
4. **Healing by connective tissue replacement (fibrosis)**

- **Acute inflammation usually caused by:**
  1- **Bacterial infection. Most common of bacteria are streptococci and staphylococci.**
  2- **Tissue necrosis e.g. coagulative necrosis that occur in the heart, which lead to acute inflammation and increasing in acute inflammatory cells.**
- **Morphologic Patterns of Acute Inflammation:**

Several types of inflammation vary in their morphology and clinical correlates, because:

1- **The severity of the reaction.**
2- **Specific cause.**
3- **The particular tissue.**
4- **Site involved.**

Chemical Mediators:

Inflammation is mediated by chemical substances called Chemical Mediators.

Attraction of the interstitial leukocytes to the area of tissue injury occurs through chemotaxis

Any messenger that acts on blood vessels, inflammatory cells, or other cells to contribute to an inflammatory response.

- **The production of active mediators is triggered by:**
  1. **Microbial products.**
  2. **Host proteins, such as the proteins of the complement, kinin and coagulation systems.**

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

- **Mediator function is tightly regulated by:**
  1) **Decay (e.g. AA metabolites).**

2) **Inactivated by enzymes (kininase inactivates bradykinin).**
3) **Eliminated (antioxidants scavenge toxic oxygen metabolites).**

- **sources of chemical mediators :**

- **Plasma-derived:**
  1. **Complement**
  2. **kinins**
  3. **coagulation factors**
  4. **Many in "pro-form" requiring activation (enzymatic cleavage)**
- **Cell-derived:**
  1. ***Synthesized as needed (prostaglandin)***
  2. ***Preformed, sequestered and released (mast cell histamine)***

- **Chemical Mediators can be summarized in this table:**

1- **According to the source**

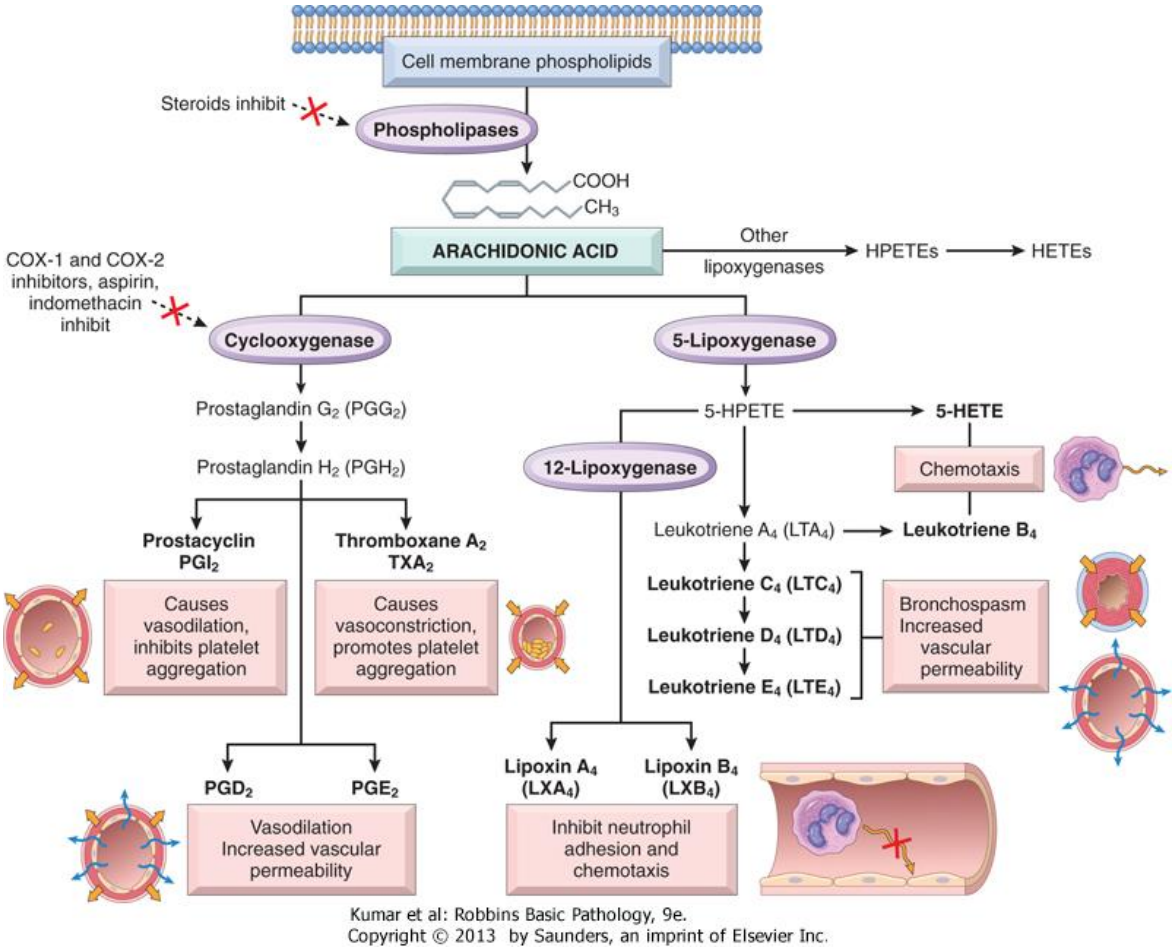
Mediator	Source	Action
Cell-derived		
Histamine	**Mast cells, platelets & basophils**	**Vasodilation, increase vascular permeability & endothelial activation**
Serotonin	**Tryptophan amino acid & platelets**	**Vasodilation & increase vascular permeability**
Prostaglandins	**Arachidonic acid, mast cells & leukocytes**	**Vasodilation, Pain & Fever**
Leukotrienes	**Arachidonic acid, mast Cells & leukocytes**	**Increase vascular permeability, chemotaxis & leukocyte adhesion & activation**
Platelet-activating factor	**Leukocytes & endothelial cells**	**Vasodilation, increase vascular permeability, chemotaxis, degranulation & oxidative burst**
Reactive oxygen species	**Leukocytes**	**Killing microbes & bacteria, Tissue damage**
Nitric oxide	**Endothelium & macrophages**	**Vascular smooth muscle relaxation & Killing microbes**
Cytokines (e.g. TNF, IL-1)	**T-lymphocytes, macrophages, endothelial cells & mast cells**	**Local endothelial activation (expression of adhesion molecules), systemic acute-phase response in severe infections & hypotension (septic) shock.**
Plasma protein-derived		
Compliment (e.g. C3a, C3b and C5a)	**Plasma (produce in the liver)**	**Vasodilation (mast cell stimulation, leukocyte chemotaxis and activation & opsonization**
Kinins	**Plasma (produce in the liver)**	**Vasodilation, increase vascular permeability, smooth muscle contraction & Pain**
Proteases activated during coagulation	**Plasma (produce in the liver)**	**Endothelial activation & leukocytes recruitment.**

2- According to the role of mediator in different reactions of inflammation

Role	Mediator
Vasodilation	**Histamine, [Prostaglandins PGI2 (prostacyclin), PGE1, PGE2, PGD2] & Nitric oxide**
Vasoconstriction	**Thromboxane A2, leukotrienes C_4, D_4, E_4**
Increase vascular permeability	**Histamine & Serotonin - C3a & C5a (by liberating vasoactive amine from mast cells, other cells) – Bradykinin – leukotrienes C_4, D_4 & E_4 – PAF – Substance P**
Leukocyte recruitment & activation	**TNF & IL-1 – Chemokines – C3a & C5a – Leukotriene B4 – Bacterial products (e.g. N-formyl methyl peptide)**
Fever	**TNF & IL-1 – Prostaglandins**
Pain	**Prostaglandins, Bradykinin & Neuropeptides**
Tissue damage	**Lysosomal enzymes of leukocyte, Reactive oxygen species & Nitric oxide**

Notes:

- **Serotonin is also called 5-Hydroxytryptamine (5-HT)**
- **Prostaglandins & leukotrienes derived from Arachidonic Acid, which is found in the lipoprotein of cell membrane.**
- **Aspirin, Ibuprofen and Panadol are anti-cyclooxygenase (look below). P.s. used for pain/fever**
- **Leukotriene B-4 is chemotactic to neutrophils.**
- **There is two Adhesion molecule: Integrin and Selectine.**
  Selectine main function is to roll and adhesion the cell while integrin is for adhesion only.
- **Reactive oxygen species is free-radicals.**
- **Anti-allergic drugs are anti-histamine.**
- **Kinins: Start as pre-kallikerin, then they transformed into kallikrein and as a final product, we have bradykrin.**
- **Hypotension (Septic) Shock is a serious condition that occurs when an overwhelming infection leads to life-threatening low blood pressure.**
  Bradykirin is the major cause of pain.
  The kinin systems are activated by the action of factor 12.
- **Neuropeptides are proteins secreted from nerve ending and create pain by acting on the thalamus.**
- **Substance P is a type of neuropeptide.**
- **TNF & IL-1 are types of cytokines. TNF stands for tumor necrosis factor. IL refers to interleukin.**



Kumar et al: Robbins Basic Pathology, 9e.

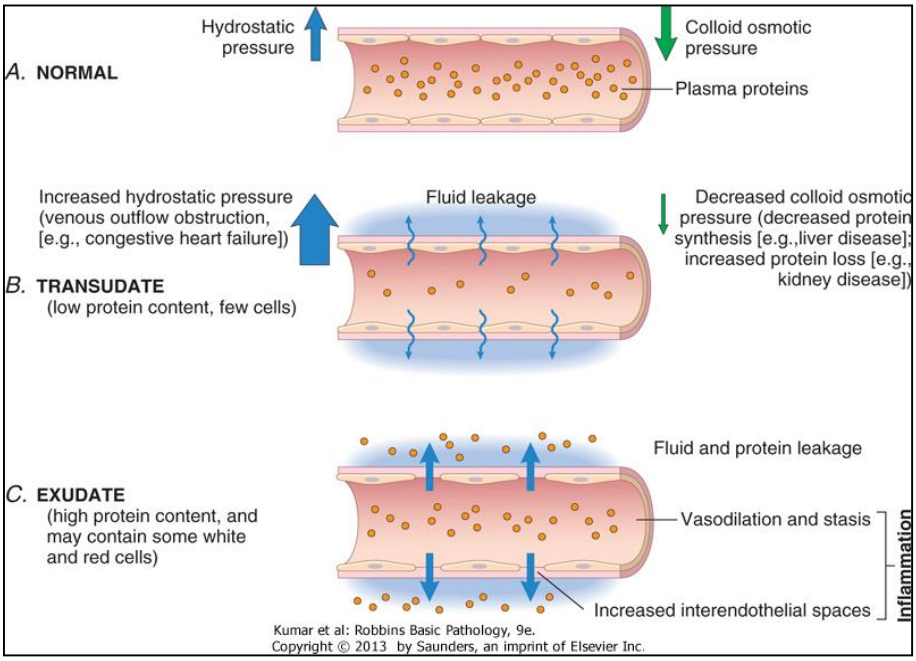
- The steps of inflammatory response are:
  1- **Recognition of the injurious agent.**
  2- **Recruitments of leukocytes.**
  3- **Removal of the agent.**
  4- **Regulation (Control) of the response.**
  5- **Resolution (Repair).**

Events of acute inflammation:

- ***Inflammation has vascular and cellular events to eliminate the cause.***

1- Vascular Changes: (Hemodynamic changes)

A- **Vascular contraction (Vasoconstriction): last few seconds to 5 minutes as a maximum.**
B- **Vascular dilation/dilatation (Vasodilation): is induced by chemical mediators such as histamine. It causes increasing in blood flow, which will cause warmth and redness. It is also causes erythema and stasis of blood flow.**
It lasts as long as acute inflammation persists.
C- **Increasing in vascular permeability (extravasation): Leads to the movement of protein-rich fluid & blood cell into extravascular tissue.**
- **Induced by histamine, kinins, and other mediators and It affects small & medium size venules, through gaps between endothelial cells**



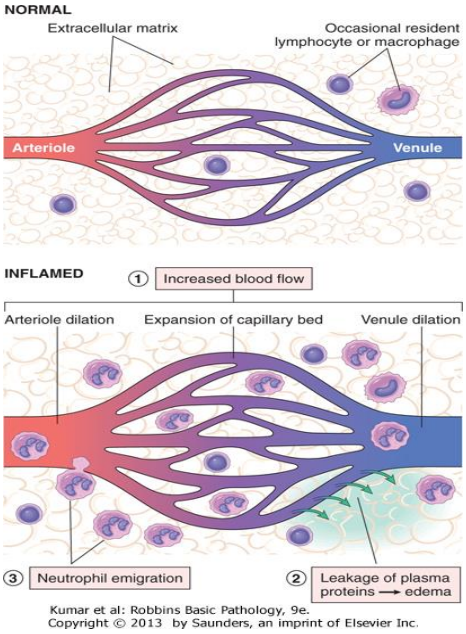
Stasis: slow circulation due to dilated small vessels packed with red cells

(A) Normal hydrostatic pressure and Colloid (Osmotic) pressure.

(B) A transudate is formed when fluid leaks out because of increased hydrostatic pressure or decreased osmotic pressure.

(C) An exudate is formed in inflammation because vascular permeability increases as a result of the increase in interendothelial spaces.

<u>Hydrostatic pressure</u>: The Pressure that the wall exerts on the blood vessels.



Vascular and cellular reactions of acute inflammation: The major local manifestations of acute inflammation, compared with normal, are (1) vascular dilation and increased blood flow (causing erythema and warmth), (2) extravasation of plasma fluid and proteins (edema), and (3) leukocyte (mainly neutrophil) emigration and accumulation.

Foundation block

Colloid pressure: **controls the quantity of protein in blood (e.g. albumin and globulin).**
When there is a drop in colloid pressure it causes edema and may cause ascites (accumulation of fluid in the abdominal cavity).

a. **Chronic liver disease also causing drop in colloid pressure because of the dysfunction in liver cell that manufacturing protein.**
b. **Renal problem is causing a drop in colloid pressure by excursion the proteins through urine.**

Osmatic pressure: controls electrolytes (K, Na,..)
-Abnormal osmatic pressure causes edema.
NOTE: Oncotic pressure is the same as colloid osmotic pressure.

Edema: **denotes an excess of fluid in the interstitial or serous cavities.**
The fluids that accumulate and make edema are two types:
Transudate and exudate.

Transudate is not related to inflammation but exudate is.

Heart failure will cause stasis in the blood which will cause hydrostatic pressure in this case, and because of this failure there is a stasis in the blood therefore the fluid goes out to the interstitial tissue which will cause edema. But this edema caused by heart failure not inflammation.

- **We study the fluid, by taking a sample of the fluid. They can tell if this fluid is exudate or transudate. And we can differentiate between them by:**

1- the cells, exudate depends on the type of inflammation but in all the types, exudate has a huge amount of inflammatory cells in the sample, but the transudate has a none or a small amount.
2- Measuring the protein, exudate rich in protein, but not transudate.
3-Measuring the specific gravity, the normal value is 1.012, if it gets higher then it is an exudate fluid, while the transudate is less than the normal value.

Transudate	Exudate
is a fluid with low protein content	**An inflammatory extravascular fluid that has a high protein concentration, cellular debris**
specific gravity of less than 1.012	**a specific gravity above 1.020**
It is essentially an ultrafiltrate of blood plasma that results from osmotic or hydrostatic imbalance across the vessel wall without an increase in vascular permeability	**It implies significant alteration in the normal permeability of small blood vessels in the area of injury**

NOTE: PUS IS CONSEDERED AS AN EXUDATE BUT WITH A HIGHER PROTEIN LEVEL

NOTE: The Lymphatic vessels admit the escaped fluid into the lymphatic system and after several days, the swelling subsides.

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

2- Cellular Changes:

A critical function of inflammation is to deliver leukocytes to the site of injury and to activate the leukocytes to perform their normal functions in host defense. (Cell will move from the blood circulation to the site of injury)

Functions of leukocytes:

- **A- Ingest offending agents, kill bacteria and other microbes, and get rid of necrotic tissue and foreign substances.**
- **B- Induce tissue damage and prolong inflammation, since the leukocyte products that destroy microbes and necrotic tissues can also injure normal host tissues.**

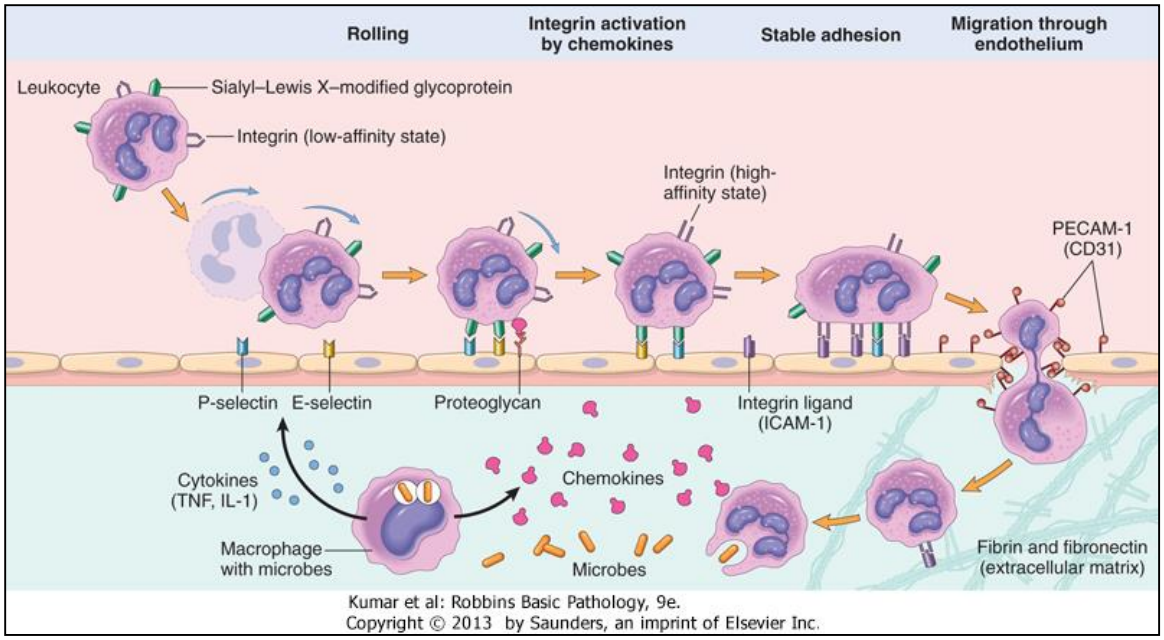
NOTE: Cellular events begin soon after vasodilation.

- **Leukocytes Recruitment (Emigration / Extravasation):**
  - **I- In the lumen:**
    1. **Margination (Pavementing).**
    2. **Rolling.**
    3. **Adhesion to endothelium.**
  - **II- Transmigration (Diapedesis) across the endothelium.**
  - **III- Migration in interstitial tissues toward a chemotactic stimulus.**

First: Margination.

Because the blood flow slows early in inflammation (stasis), the endothelium can be lined by white cells.

Resident tissue macrophages, mast cells, and endothelial cells respond to injury by secreting the cytokines TNF, IL-1, and chemokines.



*** LEUKOCYTE INFILTRATION AND PHAGOCYTOSIS**

The next phase, which we will now examine, is the migration of WBC from the circulation to the site of injury.

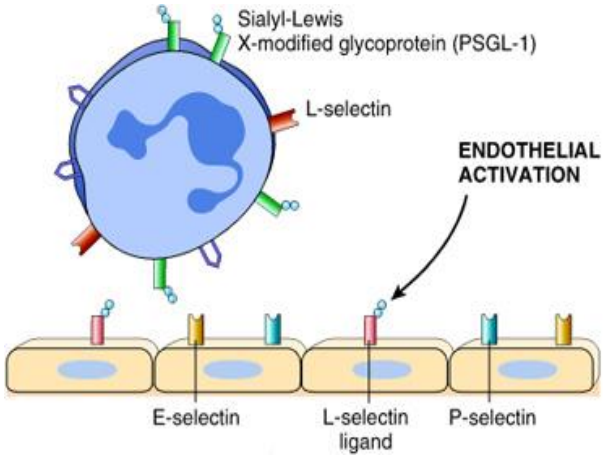
Leukocyte Exudation

The most striking finding in inflammation under the microscope - what we call a "pathognomonic" feature - is the presence of leukocytes. The sequence events in leukocyte infiltration (SLIDE) can be divided into (1) margination, (2) sticking, (3) emigration and (4) phagocytosis.

In a typical course of inflammatory events, vasodilation, transudation, and then slowing of circulation occurs as the blood viscosity increases. As stasis develops, one begins to see the peripheral orientation of leukocytes, principally neutrophils, along the vascular endothelium (margination). Leukocytes first stick transiently and then more avidly (sticking). Soon after they migrate through the vascular wall into the interstitial tissue (emigration).

Second: Adhesion Molecules and Receptors.

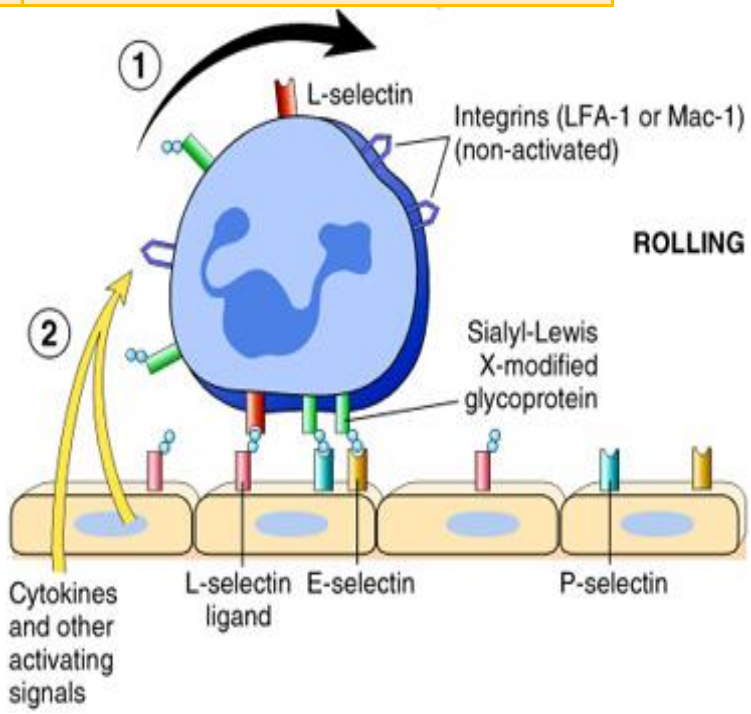
Mediators such as histamine, thrombin, and platelet activating factor (PAF) stimulate the redistribution of P-selectin from its normal intracellular stores in granules (Weibel-Palade bodies) to the cell surface. (Histamine will work on arterioles to increase vascular permeability).



1- Selectins:

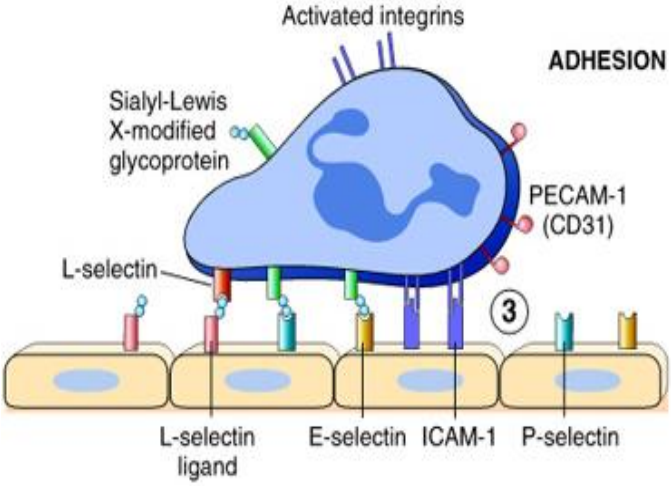
Type	Site
E-selectin	**Confined to endothelium**
P-selectin	**Present in endothelium and platelets**
L-selectin	**Expressed on most leukocyte and endothelium**

NOTE: selectin means any of a family of sugar-binding lectins that are found on the surface of cells and that promote their adhesion to other cells and mediate their migration to sites of inflammation.



2- Integrins:

Are transmembrane heterodimeric glycoproteins, made up of α and β chains expressed on many cell types and bind to ligands on endothelial cells, other leukocytes, and the extracellular matrix



3- The immunoglobulin family molecules:

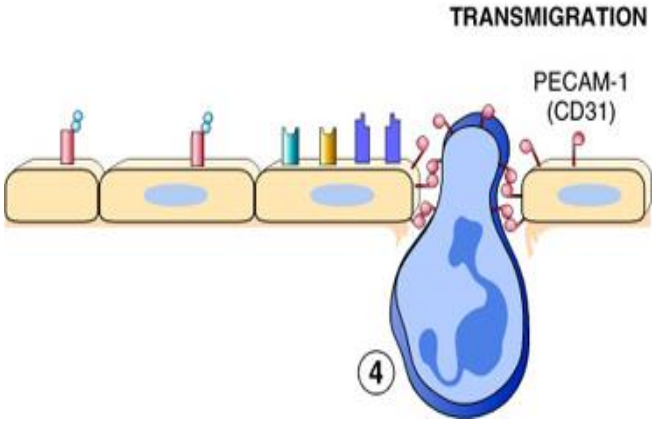
- ICAM-1 (intercellular adhesion molecule 1).
- VCAM-1 (vascular cell adhesion molecule 1).
- Induced by TNF and IL-1.

4- Mucin-like glycoproteins:

- These glycoproteins are found in the extracellular matrix and on cell surfaces.

NOTE: Neutrophils, monocytes, lymphocytes, eosinophils, and basophils all use the same pathway to migrate from the blood into tissues.

Third: Transmigration.



Migration of the leukocytes through the endothelium is called Transmigration or Diapedesis. Diapedesis occurs predominantly in the venules. Chemokines act on the adherent leukocytes and stimulate the cells to migrate toward the site of injury or infection.

In most forms of <u>acute inflammation</u>: neutrophils predominate in the inflammatory infiltrate during the first 6 to 24 hours, then are replaced by monocytes in 24 to 48 hours (because neutrophils are more numerous in the blood, they respond more rapidly to chemokines, but are short-lived; they undergo apoptosis and disappear after 24 to 48 hours, whereas monocytes survive longer).

<u>In Chronic inflammation</u>: macrophages, lymphocytes and plasma cell are found.

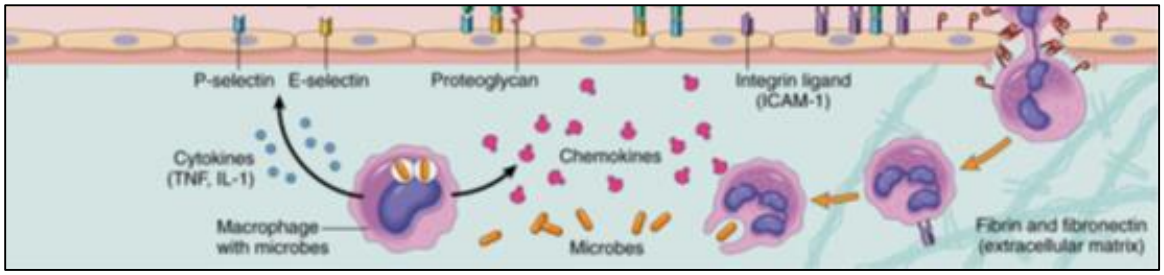
<u>The type of emigrating leukocyte varies with the type of stimulus</u>:

- **In viral infections, lymphocytes may be the first cells to arrive.**
- **In some hypersensitivity reactions and parasitic infection, eosinophil may be the main cell type.**

<u>NOTE</u>: The type of emigrating leukocyte (in general not in chronic) <u>varies with the age of the inflammatory response</u>.

Fourth: Chemotaxis.

After extravasation, leukocytes emigrate in tissues toward the site of injury by a process called chemotaxis, defined as locomotion oriented along a chemical gradient. (Chemoattractants)



There are two types of Chemotaxis (chemoattractants):

<u>Exogenous</u> and <u>Endogenous</u> substances

The most common exogenous agents are <u>bacterial products.</u>

Endogenous chemoattractants include several chemical mediators:

1- **Components of the complement system, particularly C5a**
2- **products of the lipoxygenase pathway, mainly leukotriene B_4 (LTB_4)**
3- **Cytokines, particularly those of the chemokine family (e.g., IL-8).**

NOTE : All these chemotactic agents bind to specific seven-transmembrane G-protein-coupled receptors (GPCRs) on the surface of leukocytes.

Leukocytes activation:

It results in:

1- **Phagocytosis.**
2- **Intracellular destruction.**
3- **Liberation of substances that destroy extracellular microbes and dead tissues.**
4- **Production of mediators**

Phagocytosis:

Involved three distinct and interrelated (مترابطة) steps:

A- **Opsonization.**
B- **Engulfment.**
C- **Killing or degradation of the ingested material.**

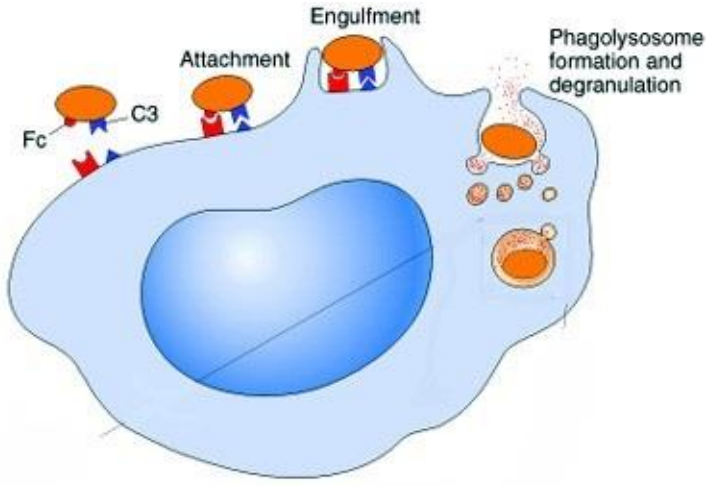
- **Opsonization:**

  Recognition and Attachment of the particle to be ingested by the leukocyte.
  The substances that do this are opsonins.

  - **These substances include:**
    - **antibodies (IgG)**
    - **complement proteins (C3)**
    - **And others: lectins (mannose-binding lectin (MBL), collectins, fibronectin, fibrinogen, and C-reactive protein**
  - **These can coat microbes and are recognized by receptors on phagocytes (Fc and C3b receptors).**

- **Engulfment:**

Extensions of the cytoplasm (pseudopods) flow around the particle to be engulfed, eventually resulting in complete enclosure of the particle within a phagosome. The phagocytic vacuole then fuses with a lysosomal granule, resulting in phagolysosome



- **Killing and degradation of microbes:**

There are two mechanisms of microbial killing:

1- **Oxygen-dependent mechanisms.**

(The H_2O_2-MPO-halide system is the most efficient bactericidal system in neutrophils).

2. **Oxygen-independent mechanisms.**

These include:

- bactericidal permeability increasing protein (BPI)
- lysozyme
- lactoferrin
- major basic protein
- defensins

❖ In addition, neutrophil granules contain many enzymes, such as elastase, that also contribute to microbial killing

Defects in Leukocyte Function:

- Defects in leukocyte adhesion , both genetic and acquired, lead to increased vulnerability to infections: Leukocyte adhesion deficiency 1and 2 ,Defects in microbicidal activity ,Chronic granulomatous disease ,Decreased oxidative burst. 2 types:
  A. X-linked: NADPH oxidase (membrane component)
  B. Autosomal recessive:
     - NADPH oxidase (cytoplasmic components)
     - Myeloperoxidase deficiency (absent MPO-H_2O_2 system)

- Defects in phagolysosome function

Chédiak-Higashi syndrome
Protein involved in organelle membrane fusion (no phagolysosomes)

Rare patients with defective host defenses have been shown to carry mutations in TLR signaling pathways.

Gain-of-function mutations in genes encoding some components of the inflammasome, one of which is called cryopyrin

Second: Chronic inflammation.

CHRONIC INFLAMMATION : Inflammation of prolonged duration (weeks to years) in which continuing inflammation, tissue injury, and healing. It is slow evolving (weeks to months) resulting into fibrosis.

Chronic inflammation may arise in :

1-persistance infectious microbes that are difficult to eradicate these includes mycobacterium tuberculosis , and certain viruses and fungi all which tend to establish persistence infection and elicit a t lymphocyte-mediated immune response delayed-type hyper sensitively

2-immuno -mediated inflammatory diseases

Diseases that are caused by excessing and inappropriate activation of immune system are increasingly recognized as being a health problem.

Autoimmune:

Immune reaction developed against defected person's own tissues leading to autoimmune diseases,

In such diseases, autoantigents evoke a self-perpetuating immune reaction that result in tissue damage and persistent inflammatory disease, such as rheumatoid arthritis inflammatory bowel diseases and psoriasis

Immune response against comment environmental substance are the cause of allergic diseases such as bronchial asthma

immune-mediated diseases shows morphological patterns of mixed acute and chronic inflammation because they are characterized by repeated bouts of inflammation in most cases this diseases tend to be chronic and intractable .

3- Prolonged exposure to potentially toxic agents

nondegradeble exoguns materials such as inhaled particulate silica which can cause chronic inflammatory response in the lungs

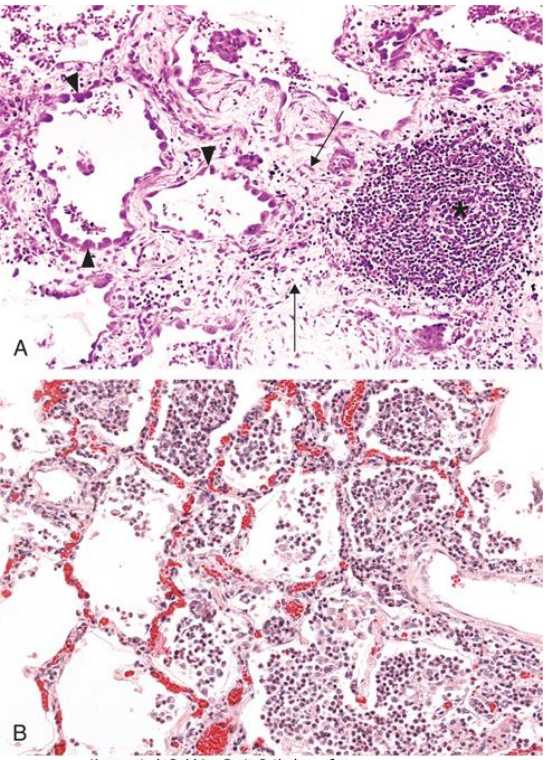
endogenous agents such as cholesterol crystals which may contribute to atherosclerosis

4- mild forms of chronic inflammation may be important in the pathogeneses of many diseases that are not conventionally thought of as inflammatory disorders such disease include neurodegenerative disorders such as alzhaymars diseases , atherosclerosis metabolic syndromes and the associated type 2 diabetes and some form of cancer in which inflammatory reaction promote tumor development

- **In chronic inflammation 3 mechanisms happens together "reactions":**
    a. **Infiltration with mononuclear cells, including:**
        i. **Macrophages**
        ii. **Lymphocytes**
        iii. **Plasma cells**
    b. **Tissue destruction, largely induced by the products of the inflammatory cells.**
    c. **Repair, involving new vessel proliferation (angiogenesis) and fibrosis**
        i. **The repair mechanism :the macrophages comes and eat up the necrotic tissue leaving holes that are later filled with**

proliferation of new blood vessels& fibroblast that buries down collagen fibers and close the injured area (formation of a scar).

- **Fibrosis : Why is there a fibrosis in chronic inflammation?**
  Because macrophages secrete a cytokine TGF β which induce fibrosis.
  *** Fibrosis causes a massive pain .**
  NOTE:
  - **Angiogenesis: Is the physiological process through which new blood vessels form from pre-existing vessels.**
  - **Acute inflammation is distinguished by vascular changes, edema, and a predominantly neutrophilic infiltrate.**



Kumar et al: Robbins Basic Pathology, 9e.

A, Chronic inflammation in the lung, showing the characteristic histologic features: collection of chronic inflammatory cells (*asterisk*); destruction of parenchyma, in which normal alveoli are replaced by spaces lined by cuboidal epithelium (*arrowheads*); and replacement by connective tissue, resulting in fibrosis (*arrows*).

B, by contrast, in acute inflammation of the lung (acute bronchopneumonia), neutrophils fill the alveolar spaces and blood vessels are congested.

Cells in chronic inflammation:

- **Complex interactions between several cell populations and their secreted mediators.**
- **Mediated by the interaction of monocyte macrophages with T and B lymphocyte, plasma cells and others**
- **Chronic inflammation existence of macrophages, plasma cells and eosinophils**

NOTE: Eosinophils response to (parasites & allergic reaction).

Macrophages	
In tissue:	**In blood which is called monocytes**
The liver (Kupffer cells)	**Under the influence of adhesion molecules and chemokines ,** *** monocytes begin to emigrate into extravascular tissues quite early in acute inflammation and within 48 hours they may constitute the predominant cell type**
Spleen and lymph nodes (sinus histiocytes)	
Central nervous system (microglial cells)	
Lungs (alveolar macrophages)	

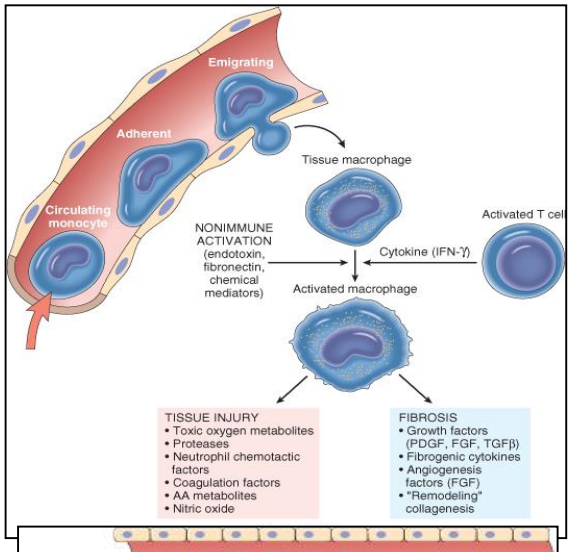
MONONUCLEAR CELL INFILTRATION:

1 : Macrophages: **Macrophages may be activated by a variety of stimuli, including:**

- **cytokines (e.g., IFN-γ) secreted by sensitized T lymphocytes and by NK cells**
- **bacterial endotoxins**
- **other chemical mediators**

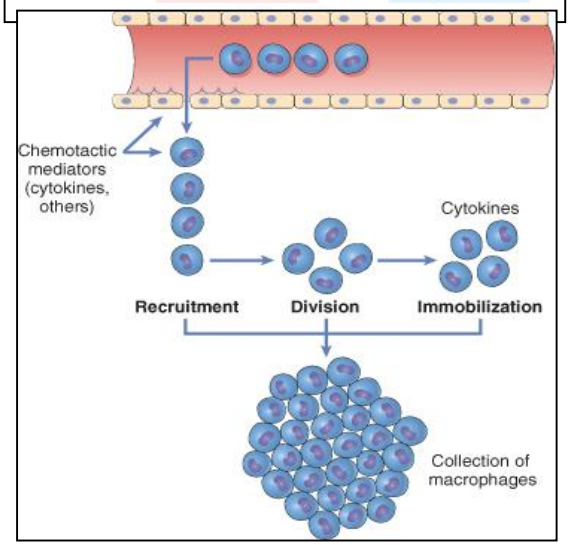
The roles of activated macrophages in chronic inflammation (Products of macrophages):

1. **Eliminate injurious agents such as microbes**
2. **Initiate the process of repair .**
3. **It is responsible for much of the tissue injury in chronic inflammation**



The roles of macrophages in host defense and the inflammatory response :

1. **Ingest and eliminate microbes and dead tissues.**
2. **Initiate the process of tissue repair and are involved in scar formation and fibrosis.**
3. **Secrete mediators of inflammation, such as cytokines (TNF, IL-1, chemokines, and others) and eicosanoids.**
4. **Display antigens to T lymphocytes and respond to signals from T cells, thus setting up a feedback loop.**



In chronic inflammation, macrophage accumulation persists, this is mediated by different mechanisms:

1. **Recruitment of monocytes from the circulation.**
2. **Local proliferation of macrophages.**
3. **Immobilization of macrophages.**

NOTE: Collection of activated macrophages (GRANULOMA)

(Granulomatous inflammations):

A form of granulomatous inflammation characterized by the formation of granulomas.

- **The term granulation tissue was used by ancient surgeons for the red, granular tissue filling the non-healing wounds.**

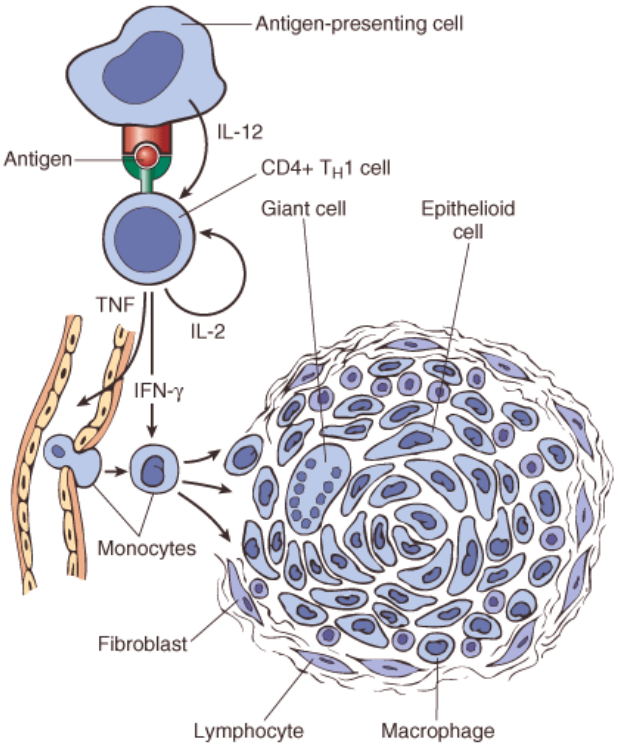
- **With the advent of microscopy, it was discovered that granulation tissue occurs in all wounds during healing, and it may occur in chronic inflammation**

Features of Granulomatous inflammation:

- **Aggregation of epithelioid microphages which form 0.5 to 2.0 mm surrounded by a rim of lymphocytes.**
- **Inflammatory vascular granulation tissue: is associated with chronic inflammation and fibroblasts. It represent a healing phase, endothelial (vascular) proliferation and chronic inflammatory cells are prominent.**
- **Giant cells: Sometimes the microphages join with each other which create a multinucleated giant cell.**
- **Giant cells arise in response to infections or foreign body insertion.**
- **A variation of multinucleated or foreign body giant cells is the Langhan's giant cell, which has nuclei arranged peripherally.**

Formation of granuloma:

The antigens that cause chronic inflammation are different; some of them are degradable by inflammatory cells. But others or certain bacteria (e.g. Mycobacterium tuberculosis) is non-degradable by inflammatory cells, this bacteria also can live inside macrophages.



The mechanism:

When an antigen, which is non-degradable, enters the body, it stimulates microphages and inflammatory cells. Then, the microphages engulf this antigen by phagocytosis.

- **The macrophage secretes its enzymes and proteases (protein catabolism enzymes).**
- **The macrophage tries to degrade the antigen inside phagosomes, which will make the macrophage secreting interleukin 12.**
- **Interleukin 12 activates T-lymphocytes.**

- **T-lymphocytes transformed into TH1 cells.**
- **TH1 cells secret interferon gamma (*IFN*-γ) & IL-2 by *CD4+ T cells***
- **(*IFN*-γ) acts on the macrophage to transfer it into epithelioid macrophages.**
- **Epithelioid macrophages (histiocytes/cells) collection is called granuloma.**
  NOTE: The most important characteristic feature of granulomatous inflammation is the existence of Epithelioid macrophages.

- **Epithelioid macrophages*: squamous cell-like appearance.* It *is a type of macrophages (modified macrophages).***
- ***Granulomas are encountered in certain specific pathologic states.***
- ***Neutrophils ordinarily remove agents that incite an acute inflammatory response. However, there are circumstances in which reactive neutrophils cannot digest the substances that provoke acute inflammation.***

Q) Why Granulomatous inflammation is important to know?

Recognition of the granulomatous pattern is important because of the limited number of conditions (some life-threatening) that cause it.

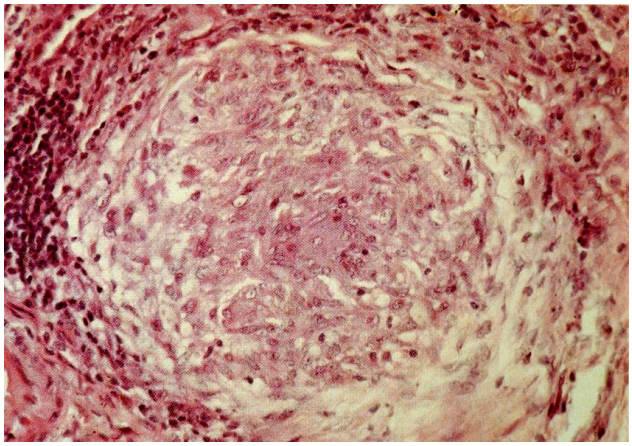
Types and causes of granulomas:

	Foreign body granuloma (non-Immune) * Out of the body .	Immune granuloma * From the body itself .
Types	**Are incited by relatively inert foreign bodies. (Can't digest)** **Foreign body granulomas formed when material such suture are large enough to preclude phagocytosis by a single macrophage.** **These material do not incite any specific inflammatory immune response.** **The foreign material can usually be identified in the center of the granuloma which means the granuloma surrounds the foreign body.**	**Are caused by insoluble particles, typically microbes(infection), which are capable of inducing a cell-mediated immune response.** **(e.g. Type 4 hypersensitivity)**
Causes	***Suture*** ***Graft material*** ***talc (associated with intravenous drug abuse)***	***Bacteria*** ***Tuberculosis*** ***Leprosy*** ***Actinomycosis*** ***Cat-scratch disease*** ***Parasites*** ***Schistosomiasis*** ***Leishmaniasis*** ***Fungi*** ***Histoplasmosis*** ***Blastomycosis*** ***Metal/Dust*** ***Berylliosis***

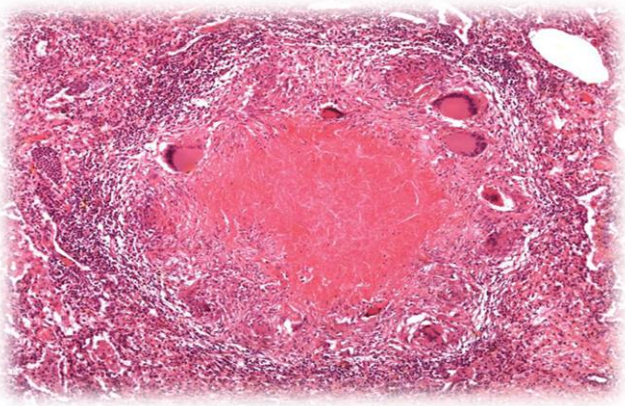
NOTES:

1. **The types of granuloma under microscope are: Caseous or Non-caseous**
2. **In general, most of granulomatous caused by Parasites and Fungi. However, certain bacteria can also cause granuloma.**
3. **There are unknown causes for granuloma (both are non-caseous)**

- **Sarcoidosis.**
- **Chron's disease.**



Non-casous granuloma of Sarcoidosis

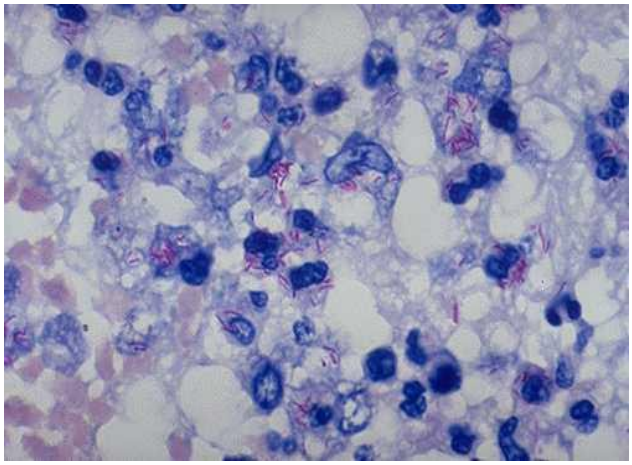


A typical granuloma resulting from infection with mycobacterium tuberculosis showing central caseous necrosis, activated epithelioid macrophages (histiocytes), many giant cells and a peripheral accumulation of lymphocytes.

High-power histology of a granuloma: a collection of epithelioid histiocytes

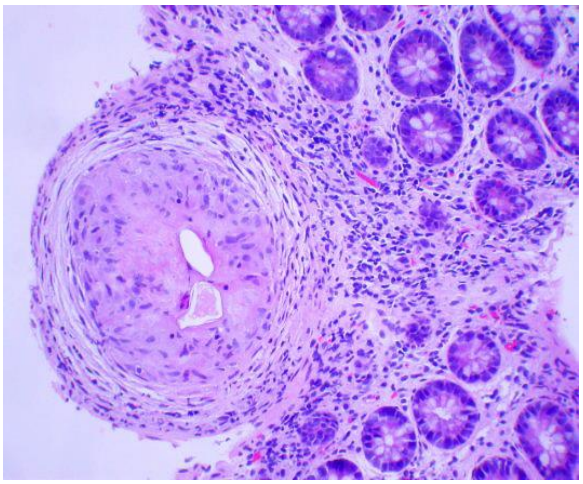
[Tuberculosis (disease of the lung)]

Primary Tuberculosis is the first infection
Secondary Tuberculosis when the immunity decreases and the bactiria is activating
And miliary Tuberculosis



[Sputum , tuberculosis]

Shows a special stain that is AFB (ACID FAST BACILI) which is used to high light the macrophages .

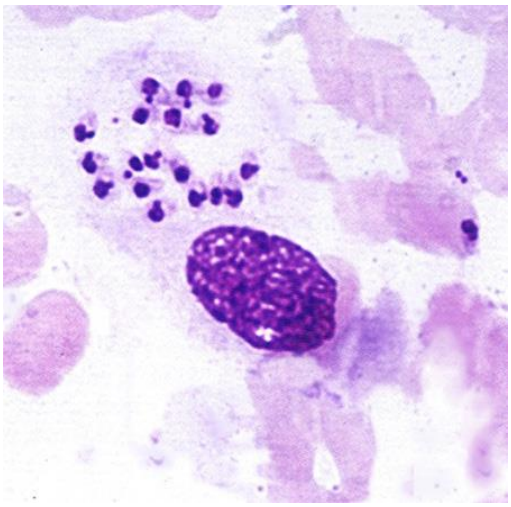


[Schistosomiasis] **is a disease affecting many people in developing countries like Africa .in the form of acute Schistosomiasis its sometimes referred to as snail fever which is caused and cutaneous Schistosomiasis .**

Each causes of Schistosomiasis have different symptoms.

May travel to different parts of the body and its localization determines ……

Intestine has eggs of Schistosomiasis



Leishmaniasis

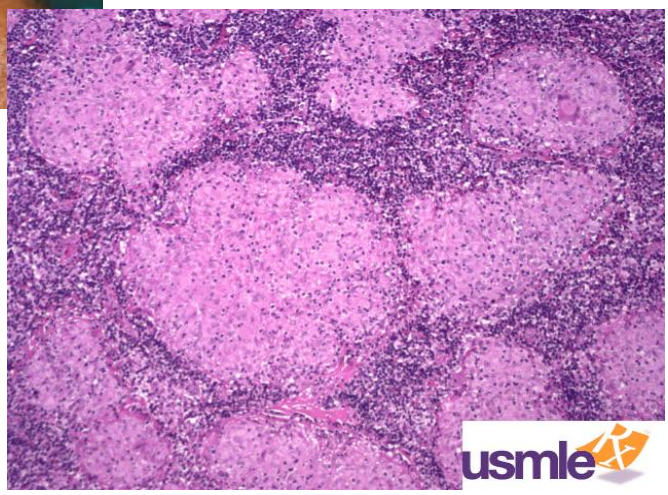
Leprosy:

Its spreading from person to another

Sarcoidosis :

The etiology in this case is unkown .

Non-caseating granuloma



NOTE: Staphylococcus infection does not cause granulomatous inflammation.

Other cells in chronic inflammation :

2 : Lymphocytes

- ***Both T & B Lymphocytes migrates into inflammation site***
- **B lymphocytes may develop into *plasma cells,* which secrete antibodies**
- **T lymphocytes are activated to secrete cytokines:**
  - ***CD4+ T lymphocytes promote inflammation and influence the nature of the inflammatory reaction***

3 :Plasma cells

- **Lymphoid cell (Mature B cells)**
- **Common cell in chronic inflammation**
- **Primary source of antibodies**
- **Antibodies are important to neutralize antigen and for clearance of foreign Ag**

4 :Eosinophils

- **are abundant in immune reactions mediated by IgE and in parasitic infections**
- **respond to chemotactic agents derived largely from mast cells**
- **Granules contain major basic protein: toxic to parasites and lead to lysis of mammalian epithelial cells**

5 :Mast Cells

- **are widely distributed in connective tissues**
- **express on their surface the receptor that binds the Fc portion of IgE antibody ,**
  - **the cells degranulate and release mediators, such as histamine and products of AA oxidation**

According to lymphocytes: CD4+ helper T cells:

1 : TH1 cells produce the cytokine IFN-γ,

Function: activates macrophages in the classical pathway.

2 : TH2 cells secrete IL-4, IL-5, and IL-13

Function: recruit and activate eosinophils and are responsible for macrophage activation.

3 : TH17 cells secrete IL-17 and other cytokines

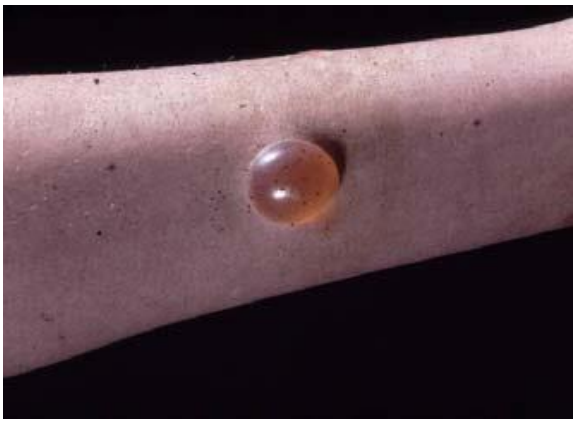
Function: induce the secretion of chemokines responsible for recruiting neutrophils and monocytes into the reaction.

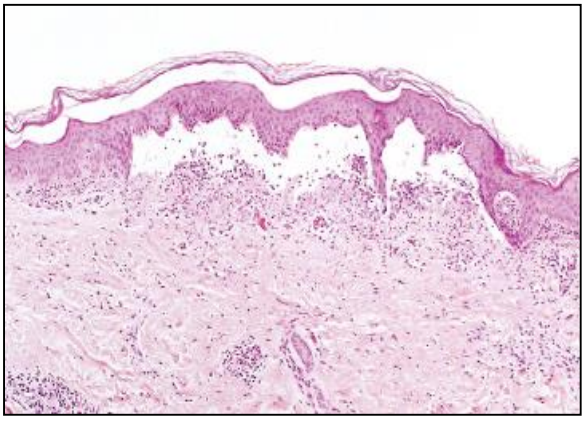
Extra information: CD4 cells are cells that contain glycoprotein called CD4 on their surface.

Morphologic Inflammation :

SEROUS INFLAMMATION:

Marked by the outpouring of a thin fluid. It has low amount of inflammatory cells. Usually occurs in the skin and creates vesicles.

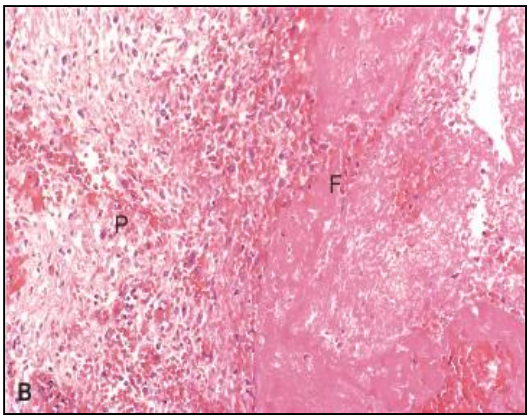


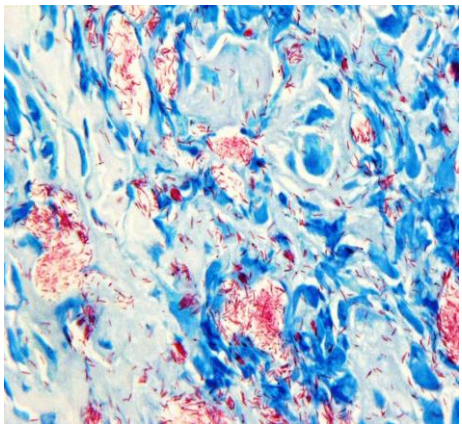


FIBRINOUS INFLAMMATION:

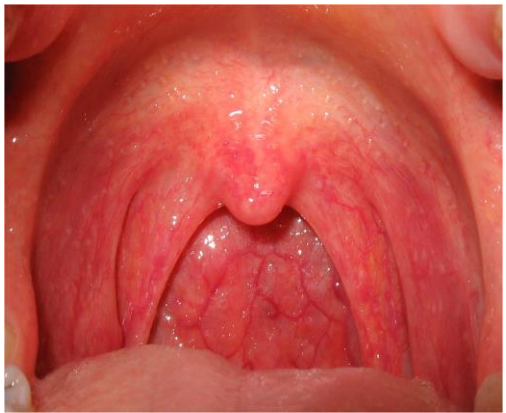
Rich of neutrophils and fibrin that is involved in the clotting of blood. It is formed from fibrinogen by the protease thrombin.

A fibrinous exudate is characteristic of inflammation in the lining of body cavities, such as the meninges, pericardium and pleura.
Fibrinous exudates may be removed by fibrinolysis, if not: it may stimulate the ingrowth of granulation tissue (organization)





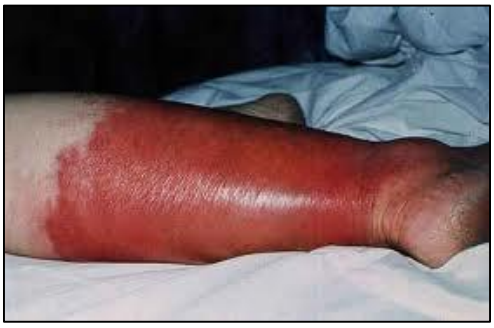
Catarrhal inflammation:



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

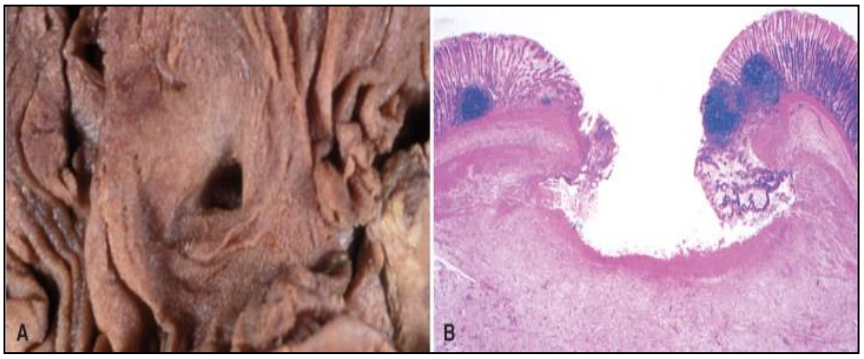
CELLULITIS:

Denotes a spreading acute inflammation through interstitial tissues.



ULCERS:

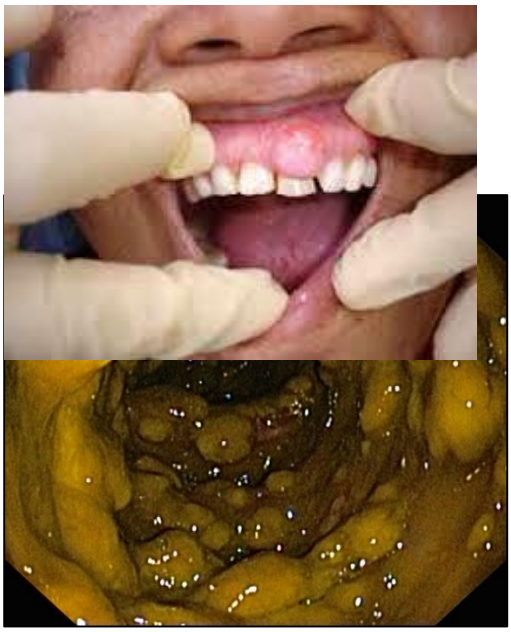
An ulcer is a local defect of the surface of an organ or tissue that is produced by the sloughing (shedding) of inflammatory necrotic tissue.
Usually occur in GIT tract and skin.



(CHRONIC INFLAMMATION)It beings acute then becomes chronic.

Pseudomembranous colitis:

Occurs in the colon due to excessive antibiotics intake. These antibiotics will kill the bacteria (normal flora) which are necessary for the body and replace it with bacteria, which resist the antibiotics. Eventually it will create yellowish pseudo-membrane that consists of fibrin and neutrophils.



SUPPURATIVE OR PURULENT INFLAMMATION

Suppurative abscess.

- **An enclosed collection of pus consists of a mixture of neutrophils and necrotic debris.**

Note: * Fistula / A tract between two surfaces.
But A sinus is a track leading from a focus of suppuration to a cutaneous or mucous surface.

Healing and repairing:

The goal of the repairing : is to restore the tissue to its original state. But Healing is usually a tissue response .

- Some tissues can be completely reconstituted after injury, such as the repair of bone after a fracture or the regeneration of the surface epithelium in a cutaneous wound.

- For tissues that are incapable of regeneration, repair is accomplished by connective tissue deposition, producing a scar.

The cells in the body are divided into three groups depending on their capability to heal and repair itself:

3- **Labile cells**
4- **Stable cells**
5- **Permanent cells**

1- Labile cells:
Are cells which are capable of multiplying and regenerating themselves all the time (they always enter into the cell cycle) even if there is no injury. And always multiplying, regenerating themselves, replacing their dead cells, repairing their own damage and always capable of mitosis. Therefore, if there is a tissue injury in organs, which have the labile cells the repair of the injury, is quicker, more effective and it can restore the organ or the tissue to almost its previous normal status.

Examples of labile cells:
- **Epithelial cells in the skin.**
- **Epithelium of the gastrointestinal system (formed by glandular cells, which they are labile cells)**
- **Epithelium of the genitourinary system (urinary bladder, ureter and renal pelvis).**
- **Hematopoietic cells in the bone marrow (bone marrow cells).**

2- Stable cells:
Are cells which are capable of regenerating themselves but only if there was an injury.

Examples of stable cells:
- Hepatocyte, if there is an injury in liver cells like an infection by a virus, which caused inflammation only in the cells (not the connective tissue or the matrix) those cells can regenerate and repair themselves. For example, if a person drinks alcohol he will have fatty change, which will lead to cell injury. Then he stopped drinking, the cells regenerate and they go back to normal.
However, sometimes if a person has an inflammation, which affects the matrix of the liver so here, the person may get fibrosis in the liver.
- Cells in renal tubules, acute renal failure cause damage in renal tubules, the renal tubules

which are damaged regenerate and the renal function goes back to normal.
- Smooth muscle cells BUT the myocardial fibers are an exception.

3- Permanent cells:
Are the cells that never regenerate and they cannot be replaced and the damage is permanent.

Examples of permanent cells:
- Neurons, if there is disease in the blood vessels that supply the brain (atherosclerosis, thrombus, etc.) which stop the blood supply and will cause ischemia, it will affect the neurons. If a person can't swallow, can't move hands and feet and can't talk:

- **Can't swallow because the neurons which supply the nerve fibers to the Vagus nerve are damaged or dead.**
- **Can't move hands and feet because of the cells, which supply the motor neuron orders to right arm and leg are also damaged.**
- **Can't talk because the neurons, which are responsible for talking, have been damaged so he cannot speak (aphasia).**

- Myocardial fibers

NOTE:
- **Healing in myocardium called myocardial fibrosis.**
- **Healing in brain called gliosis.**

Stem cells
Are multipotent, embryogenic cells (before differentiation) which can replace permanent cells, but it is still a research area and has not yet been approved.

NOTE: Labile cells have stem cells in the basal cell layer help in replication.

Growth Factors:

Most growth factors are proteins that stimulate the survival and proliferation of particular cells, and may also promote migration, differentiation, and other cellular responses.

Growth Factor	Sources	Functions
Epidermal growth factor (EGF)	**Activated macrophages, salivary glands, keratinocytes, and many other cells**	**Mitogenic for keratinocytes and fibroblasts; stimulates keratinocyte migration; stimulates formation of granulation tissue**
Transforming growth factor-α (TGF-α)	**Activated macrophages, keratinocytes, many other cell types**	**Stimulates proliferation of hepatocytes and many other epithelial cells**
Hepatocyte growth factor (HGF) (scatter factor)	**Fibroblasts, stromal cells in the liver, endothelial cells**	**Enhances proliferation of hepatocytes and other epithelial cells; increases cell motility**
Vascular endothelial growth factor (VEGF)	**Mesenchymal cells**	**Stimulates proliferation of endothelial cells; increases vascular permeability**
Platelet-derived growth factor (PDGF)	**Platelets, macrophages, endothelial cells, smooth muscle cells, keratinocytes**	**Chemotactic for neutrophils, macrophages, fibroblasts, and smooth muscle cells; activates and stimulates proliferation of fibroblasts, endothelial, and other cells; stimulates ECM protein synthesis**
Fibroblast growth factors (FGFs), including acidic (FGF-1) and basic (FGF-2)	**Macrophages, mast cells, endothelial cells, many other cell types**	**Chemotactic and mitogenic for fibroblasts; stimulates angiogenesis and ECM protein synthesis**
Transforming growth factor-β (TGF-β)	**Platelets, T lymphocytes, macrophages, endothelial cells, keratinocytes, smooth muscle cells, fibroblasts**	**Chemotactic for leukocytes and fibroblasts; stimulates ECM protein synthesis; suppresses acute inflammation**
Keratinocyte growth factor (KGF) (i.e., FGF-7)	**Fibroblasts**	**Stimulates keratinocyte migration, proliferation, and differentiation**

Mechanism of repair:

- **Repair begins early in inflammation.**
- **At site of inflammation, fibroblasts and vascular endothelial cells begin proliferating to form a specialized type of tissue (hallmark of healing) called: Granulation tissue**
- **The process is called organization**

Repair by connective tissue (granulation tissue):

It consists of:

1. **fibroblasts surrounded by abundant extracellular matrix**

Fibroblast Migration and Proliferation

- **Migration of fibroblasts to the site of injury and their subsequent proliferation are triggered by multiple growth factors, including TGF-β, PDGF, EGF, FGF, and the cytokines IL-1 and TNF This leads to:**

I. **increased synthesis of collagen and fibronectin**

II. **decreased degradation of extracellular matrix (ECM) by metalloproteinases**

2. **Newly formed blood vessels: (*NOTE: Angiogenesis*: The formation and differentiation of blood vessels. Angiogenesis from Endothelial Precursor Cells EPCs.)**
3. **Scattered macrophages and some other inflammatory cells.**

- **New granulation tissue is often edematous.**
- **Histologically: granulation tissue is composed of:**

Proliferation of new small blood vessels and proliferation of fibroblasts

Note: After the injury the epithelium returns to its normal state .

- **Liver cells have the power to return to its normal state.**
- **Any wound doesn't have the power to return to its full strength, just 80% of its strength.**

Healing

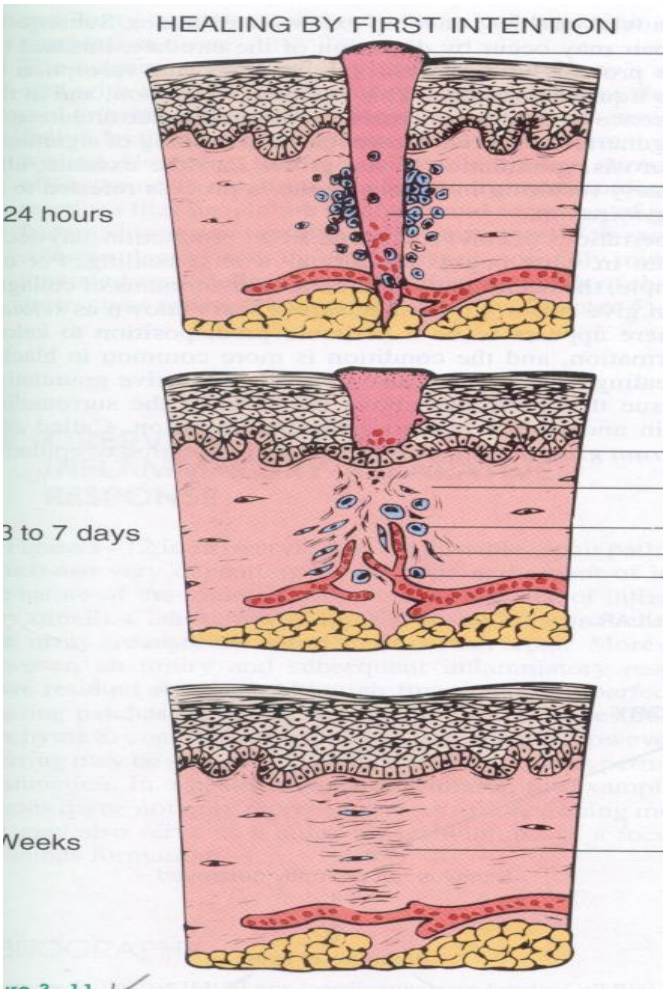
Healing is usually a tissue response

1. **to a wound (commonly in the skin)**
2. **to inflammatory processes in internal organs**
3. **to cell necrosis in organs incapable of regeneration**

Healing of Wounds:

1- **Healing by First intention (primary union): usually occur in clean and linear wounds especially surgical wounds. Or any wound but there won't be any major (big) damage, and the edges of the wound most are regular and sharp. Primary union (healing by first intention)**

- **24 hr.:** hematoma & neutrophils, mitotic activity of basal layer, thin epithelial layer
- **Day 3:** macrophages, granulation tissue
- **Day 5:** collagen bridges the incision, epidermis thickens
- **2nd week:** continued collagen and fibroblasts, blanching
- **End of 1st month:** scar (cellular connective tissue, intact epidermis, lost appendages).
- **Later:** collagen type III is slowly replaced by collagen type I and the wound acquires tensile strength.
- **By the end of third month:** the tissue has approximately 80% of its original strength.



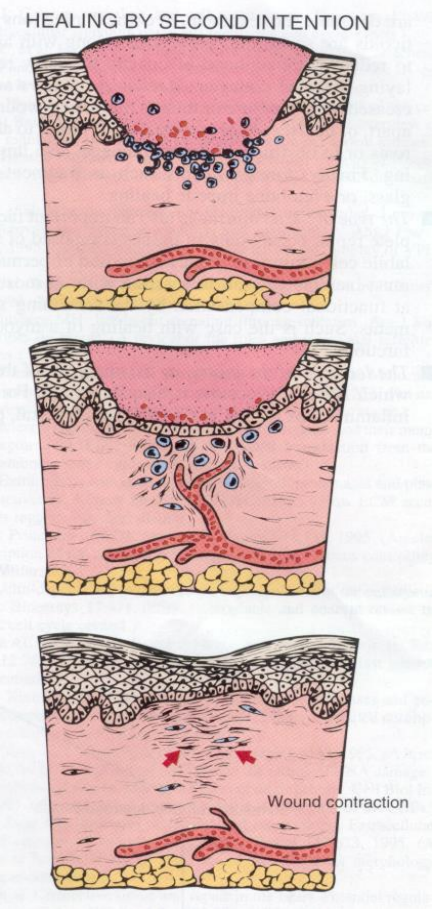
The Mechanism:

Healing by first intention occurs when wounds edges are approximated and the wound is quickly covered with epithelium and bound together by collagen. Epithelial regeneration is the principle mechanism of repair.

I. **Migration of capillaries, neutrophils, macrophages & fibrocytes into the clot within the first 24 hours.**
II. **Falling of the scab (patch of dried, clotted blood), revealing re-epithelialization.**
III. **The blood clot in the apposed tissues is removed by the macrophages.**
IV. **Producing granulation tissues.**
V. **Decrease in numbers of neutrophils and increase of macrophages.**
VI. **Increase of collagen in the gaps, decrease in number of blood vessels.**
VII. **The scar begin to contract.**

Note: If the collagen fibers are increase, the fibroblast and blood vessels will decrease.

Healing by first intention is best exemplified by the healing of an apposed surgical incision.



2- Healing by Second intention (secondary union):

Edges of the wound cannot be opposed in healing by second intention, leaving a defect containing blood clot and debris. The process of second intention is the same as the first BUT it takes much longer AND the granulation tissue is much more pronounced.

It occurs in large, gaping wounds, as well those that are infected or contain foreign material.

NOTE: In both types of healing, the wound contracts in the later stages due to the presence of the myofibroblast, this is a contractile cell that has proprieties of both fibroblasts and smooth muscle cells.

Three main phases of cutaneous wound healing:

(1) Inflammation.

(2) Formation of granulation tissue.

(3) ECM deposition and remodeling.

Healing by primary intention occur in surgical clean wound and healing by secondary intention occur when excessive tissue damage is present.

❖ **Difference between primary intention and secondary intention**

The basic process of healing is the same in all wounds. In contrast to healing by primary intention, wounds healing by secondary intention Require more time to close because the edges are far apart Show a more prominent inflammatory reaction in and around the wound Contain more copious granulation tissue inside the tissue defect Wound contraction (5 to 10%), myofibroblasts

❖ **Delaying of wound healing:**

Variables that modify healing may be extrinsic (e.g., infection) or intrinsic to the injured tissue. Particularly important are infections and diabetes. The most common cause of delayed

wound healing Infections. (the most important cause of delay in healing; it prolongs inflammation and potentially increases the local tissue injury)

1. **Presence of foreign body.**
2. **Poor perfusion (due either to arteriosclerosis and diabetes or to obstructed venous drainage)**
3. **Excess corticosteroid / Chronic diseases (e.g. diabetes mellitus, which increases the chances of infections and delaying healing of the wound).**
4. **Tumors (cancers)**
5. **Nutritional deficiencies (protein deficiency and vitamin C deficiency inhibit collagen synthesis and retard healing)**
6. **Mechanical factors.**

NOTE: Excess corticosteroid: Have well-documented anti-inflammatory effects, and their administration may result in weakness of the scar. However, the anti-inflammatory effects of glucocorticoids are sometime desirable. For example in corneal infections.

○ What is the role of macrophages in wound healing?

- **Cleanup of debris, fibrin, and other foreign material at the site of repair.**
- **Macrophages recruit other cells: fibroblasts and angioblasts**
- **Stimulation of matrix production, interleukins that stimulate fibroblasts and angioblasts to produce the extracellular matrix.**
- **Remodeling of the scar. They secrete collagenases**

Remodeling: is the process which the macrophages eat up the extra collagen fiber.

Debris: the dirty things on the injury .

○ Complication that occur due to repair or healing:

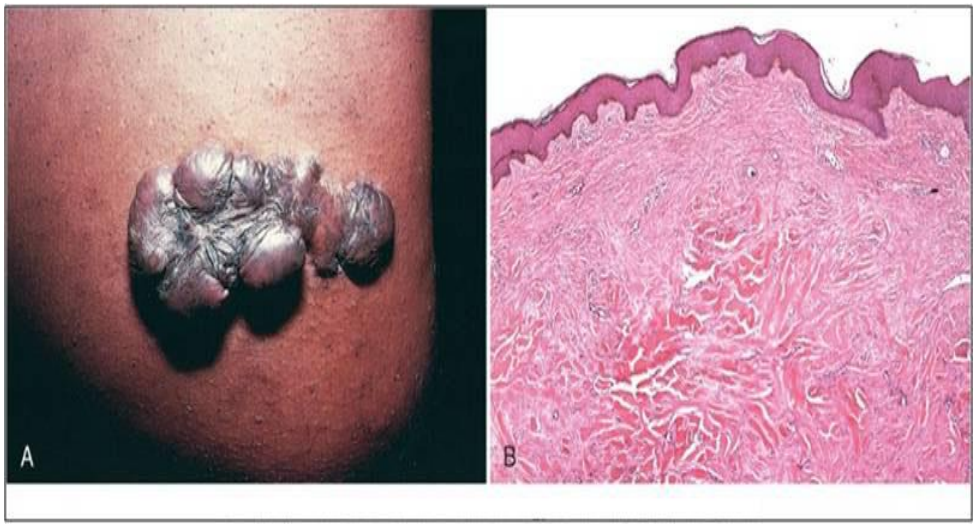
Complications in wound healing can arise from abnormalities in any of the basic components of the repair process. These aberrations can be grouped into three general categories:

1) **Deficient scar formation**
2) **Excessive formation of the repair components**
3) **Formation of contractures**

Examples :

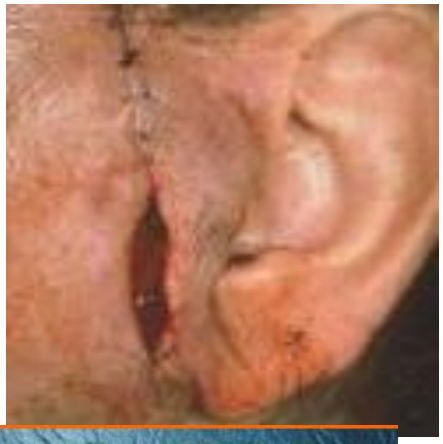
1- **Fibrous adhesion:**
In the last stages of healing, attraction of fibroblast occurs because of secretion of growth factors.
This fibrosis can cause Fibrous bands in the gap, which may cause obstruction. (Ischemia)
It occurs especially in intra-abdominal organs, as a following of previous surgery.

2- **Keloid:** **Is a type of hypertrophic scar, composed of irregularly deposited collagen. They may appear as bulging masses and occurs in certain wounds and burns especially in people who have dark skin (e.g. Africans).It happens as a following of minor or major injury. Note: Dark people have more possibility to get the keloid .**

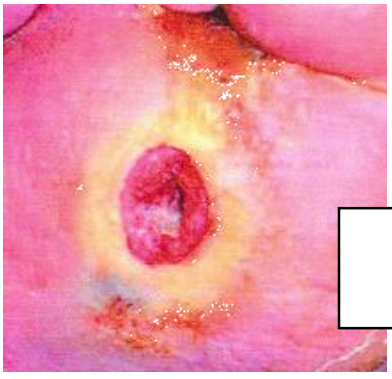


A. Excess collagen deposition in the skin forming a raised scar known as a keloid.
B. Thick connective tissue deposition in the dermis.

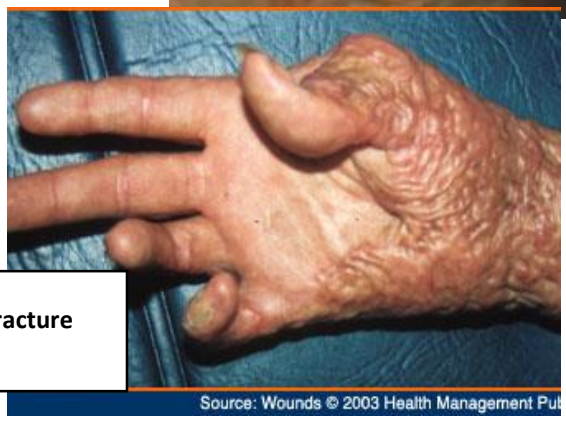
3- **Wounds dehiscence:**
Is a surgical complication in which a wound rapture along with surgical suture. (E.g. incisional hernia)



4- **Extra:**



Wound ulceration



Contracture

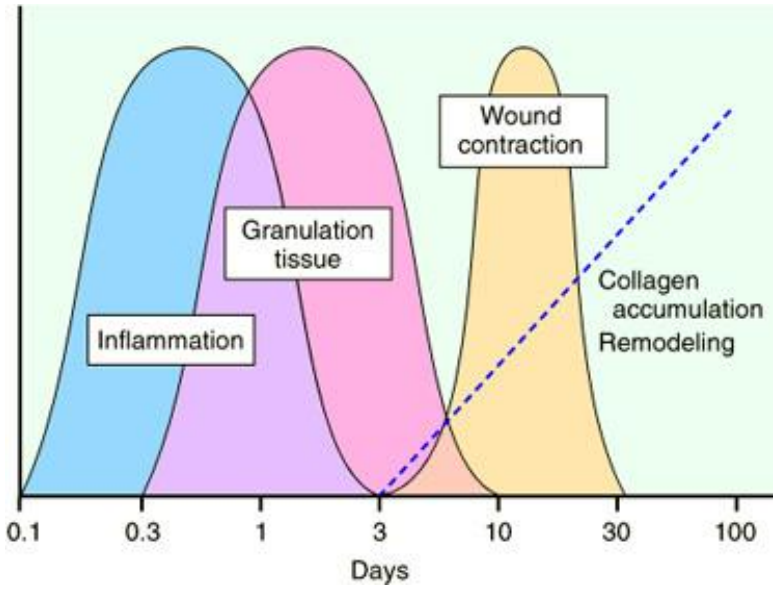
Foundation block

SCAR FORMATION:

Scar is a large amount of collagen fibers.

- **Further healing: increased collagen, decreased active fibroblasts and new vessels (thrombosis and degeneration)**
- **At the end: scar (inactive fibroblasts, dense collagen, fragments of elastic tissue, extracellular matrix, few vessels)**

- **Three processes that participate in the formation of a scar:**
  1) **Emigration and proliferation of fibroblasts in the site of injury.**
  2) **Deposition of ECM.**
  3) **Tissue remodeling.**

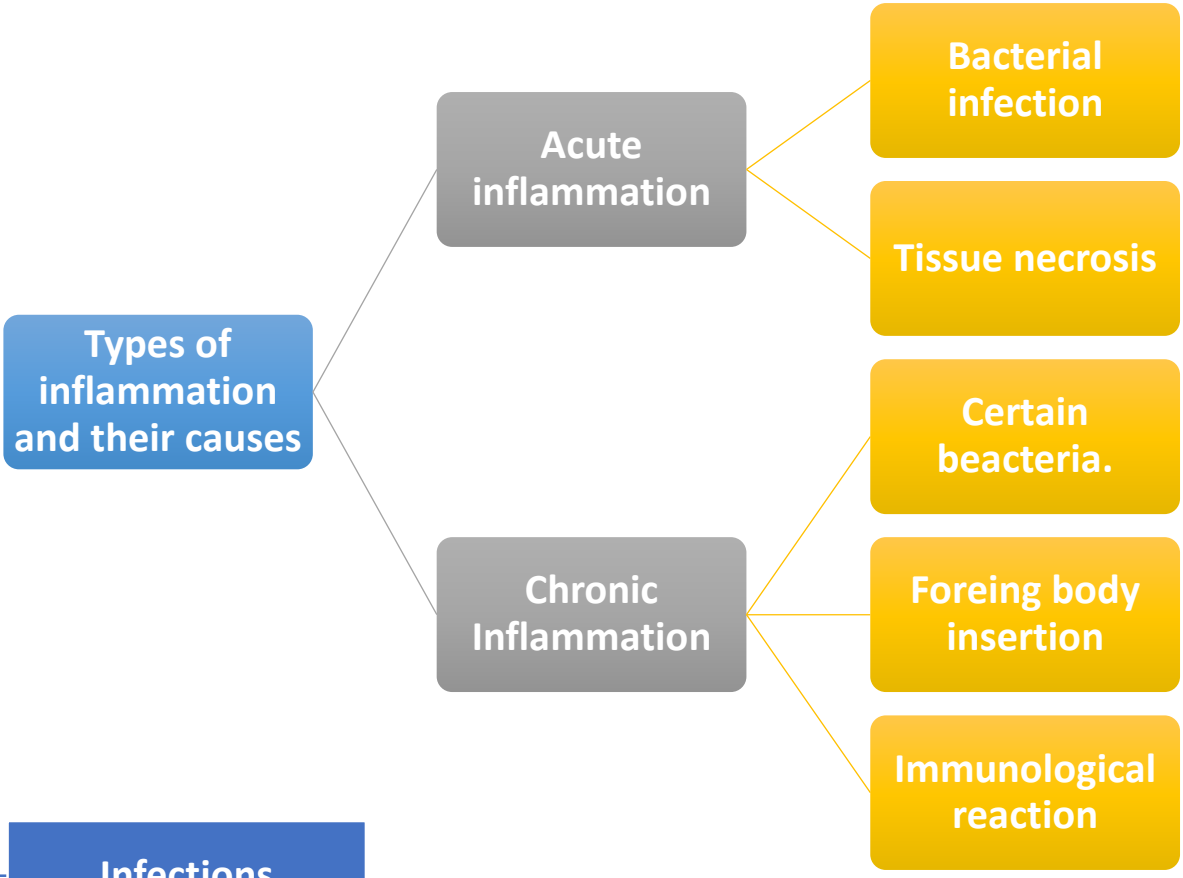


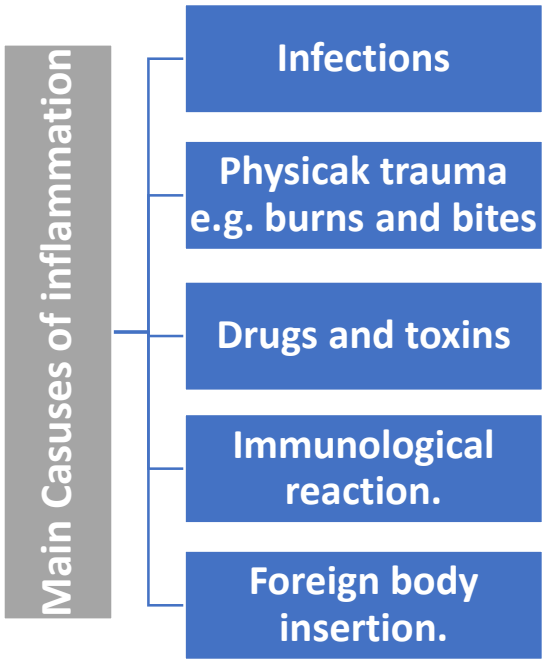
- **ECM Deposition and Scar Formation:**
  - **As repair continues, the number of proliferating endothelial cells and fibroblasts decreases.**
  - **Net collagen accumulation, however, depends not only on increased collagen synthesis but also on decreased degradation.**
- **Functions of the Extracellular Matrix**

The ECM is much more than space filler around cells. Its various functions:

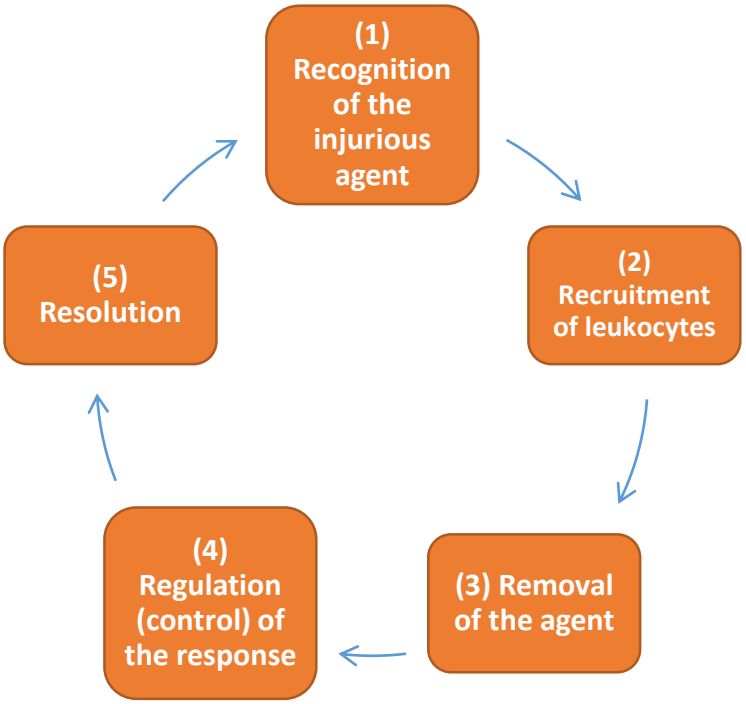
- **Mechanical support**
- **Control of cell proliferation**
- **Scaffolding for tissue renewal**
- **Establishment of tissue microenvironments.**

Summary:


Types of inflammation and their causes
Acute inflammation
Bacterial infection
Tissue necrosis
Chronic Inflammation
Certain beacteria.
Foreing body insertion
Immunological reaction


Main Casuses of inflammation
Infections
Physicak trauma e.g. burns and bites
Drugs and toxins
Immunological reaction.
Foreign body insertion.

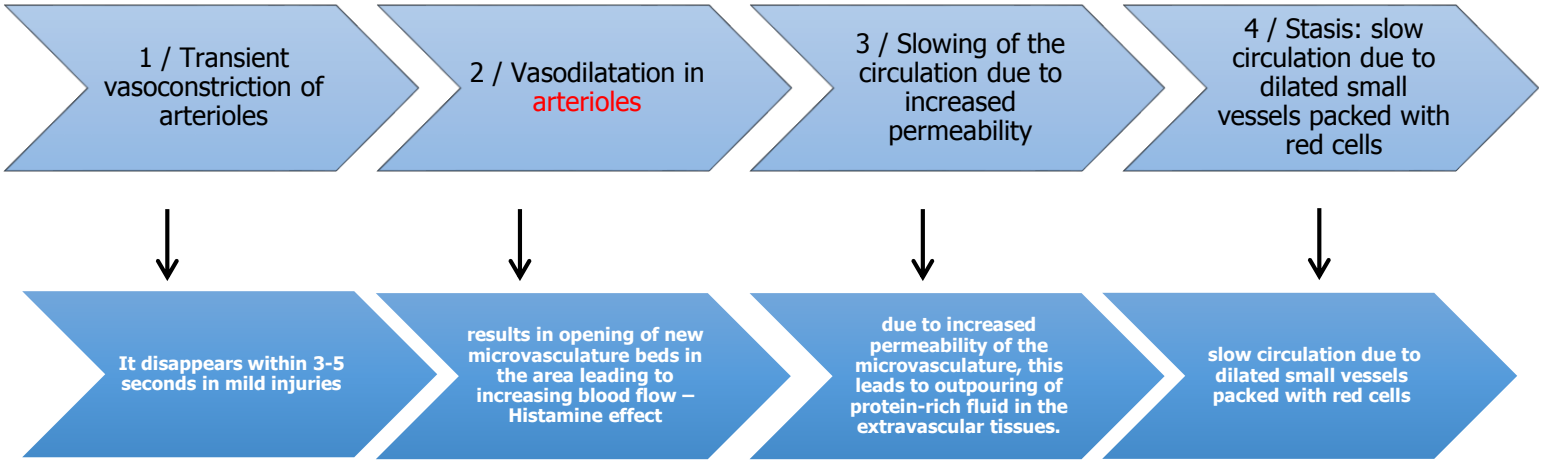
Steps of the inflammatory response:



OVERVIEW OF INFLAMMATION AND TISSUE REPAIR (FROM ROBBIN'S):

Cells of Inflammation			
Cell	**Activity**	**Phagocytosis**	**Inflammation**
Neutrophil	Proteases, oxidases	+	Acute
Eosinophil	Antihistamine	+	Acute, chronic
Macrophage (modified monocytes)	Antigen processing and digestion	+	Late acute, chronic
Lymphocyte	Lymphokines	-	Chronic
Plasma cell	Antibody production	-	Chronic

○ Phases of changes in Vascular Caliber and Flow:



	Acute	Chronic
Causative agent	**Bacterial pathogens, injured tissues**	**Persistent acute inflammation due to non-degradable pathogens, viral infection, persistent foreign bodies, or autoimmune reactions**
Major cells involved	**neutrophils (primarily), basophils (inflammatory response), and eosinophil's (response to helminth worms and parasites), mononuclear cells (monocytes, macrophages)**	**Mononuclear cells (monocytes, macrophages, lymphocytes, plasma cells), fibroblasts**
Primary mediators	**Vasoactive amines, eicosanoids**	**IFN-γ and other cytokines, growth factors, reactive oxygen species, hydrolytic enzymes**
Onset	**Immediate**	**Delayed**
Duration	**Few days**	**Up to many months, or years**
Outcomes	**Resolution, abscess formation, chronic inflammation**	**Tissue destruction, fibrosis, necrosis**
Local & systemic signs	**Prominent**	**Less prominent, may be subtle**

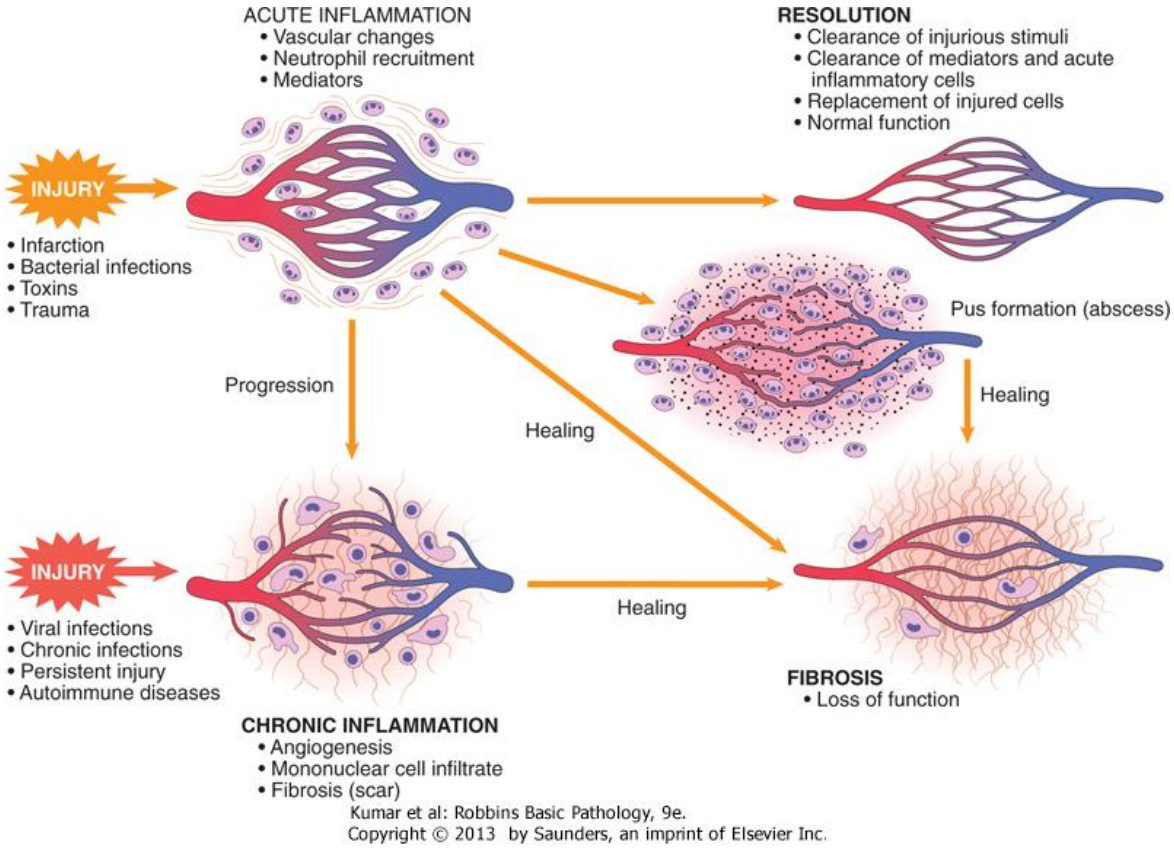
Transudate vs exudate		
	Transudate	**Exudate**
Main causes	**Increased hydrostatic pressure,** **Decreased in colloid and osmotic pressure**	**Inflammation**
Specific gravity **http://en.wikipedia.org/wiki/Specific_gravity**	**< 1.012**	**> 1.020**

http://www.youtube.com/watch?v=suCKm97yvyk

○ Leukocyte Recruitment to Sites of Inflammation:

Leukocytes are recruited from the blood into the extravascular tissue, where infectious pathogens or damaged tissues may be located, and are activated to perform their functions.
Leukocyte recruitment is a multi-step process consisting of loose attachment to and rolling on endothelium (mediated by selectins); firm attachment to endothelium (mediated by integrins); and migration through interendothelial spaces.
Various cytokines promote expression of selectins and integrin ligands on endothelium (TNF, IL-1), increase the avidity of integrins for their ligands (chemokines), and promote directional migration of leukocytes (also chemokine's); many of these cytokines are produced by tissue macrophages and other cells responding to pathogens or damaged tissues.
Neutrophils predominate in the early inflammatory infiltrate and are later replaced by macrophages.

Defects in Leukocyte Functions	
Disease	**Defect**
Acquired	
Bone marrow suppression: tumors (including leukemias), radiation, and chemotherapy	**Production of leukocytes**
Diabetes, malignancy, sepsis, chronic dialysis	**Adhesion and chemotaxis**
Anemia, sepsis, diabetes, malnutrition	**Phagocytosis and microbicidal activity**
Genetic	
Leukocyte adhesion deficiency 1	**Defective leukocyte adhesion because of mutations in β chain of CD11/CD18 integrins**
Leukocyte adhesion deficiency 2	**Defective leukocyte adhesion because of mutations in fucosyl transferase required for synthesis of sialylated oligosaccharide (receptor for selectins)**
Chronic granulomatous disease	**Decreased oxidative burst**
X-linked	**Phagocyte oxidase (membrane component)**
Autosomal recessive	**Phagocyte oxidase (cytoplasmic components)**
Myeloperoxidase deficiency	**Decreased microbial killing because of defective MPO-H2O2 system**
Chédiak-Higashi syndrome	**Decreased leukocyte functions because of mutations affecting protein involved in lysosomal membrane traffic**



○ Sequence of Events in Acute Inflammation:

The vascular changes in acute inflammation are characterized by increased blood flow secondary to arteriolar and capillary bed dilation (erythema and warmth).
Increased vascular permeability, as a consequence of either widening of interendothelial cell junctions of the venules or direct endothelial cell injury, results in an exudate of protein-rich extravascular fluid (tissue edema).
The leukocytes, initially predominantly neutrophils, adhere to the endothelium via adhesion molecules and then leave the microvasculature and migrate to the site of injury under the influence of chemotactic agents.
Phagocytosis, killing, and degradation of the offending agent follow.
Genetic or acquired defects in leukocyte functions give rise to recurrent infections.
The outcome of acute inflammation may be removal of the exudate with restoration of normal tissue architecture (resolution); transition to chronic inflammation; or extensive destruction of the tissue resulting in scarring.

○ CHRONIC INFLAMMATION:

Inflammation of prolonged duration (weeks to years) in which continuing inflammation, tissue injury, and healing. It is slow evolving (weeks to months) resulting into fibrosis.

- **It occurs in two major:**
  - **Chronic nonspecific inflammation: (no granuloma) e.g. after tuberculosis.**
  - **Chronic specific inflammation: formation of granuloma) e.g. chronic viral hepatitis.**

○ The causes of chronic inflammation are either:

1- **As an outcome of acute inflammation.**
2- **Another causes :**

A. **Most of viral infections are chronic inflammation (e.g. TB).**
B. **Persistent infection by microbes.**
   These include :
   I. **-*Mycobacterium tuberculosis***
   II. **-*Treponema pallidum* (the causative organism of syphilis)**
   III. **-Certain viruses and fungi**
C. **Immune diseases especially autoimmune, which occur when the body is unable to identify what itself and not self. Therefore, it might create antibodies against DNA, RNA, synovial membranes, liver or blood vessels.**
   I. **e.g.**
   II. **Rheumatoid arthritis, inflammatory bowel disease and psoriasis**
   III. **OR *allergic diseases,* such as bronchial asthma.**
D. **Bacterial infection ((e.g. Brucellosis بكتيريا تسبب الحمّى المالطيّة)**
E. ***Prolonged exposure to potentially toxic agents.***
   Examples:
   I. **Non-degradable exogenous materials such as inhaled particulate silica, which can induce a chronic inflammatory response in the lungs (silicosis)**
   II. **Endogenous agents such as cholesterol crystals, which may contribute to atherosclerosis**
F. **Mild forms of chronic inflammation can cause many diseases such as :**
   i. **neurodegenerative disorders such as Alzheimer disease**
   ii. **atherosclerosis**
   iii. **metabolic syndrome and the associated type 2 diabetes,**
   iv. **and some forms of cancer in which inflammatory reactions promote tumor development**

○ Granulomatous inflammation:

is distinctive pattern of chronic inflammation characterized by aggregates of activated microphages with scattered lymphocytes . Granulomas are characteristic of certain specific pathological state , A granuloma is a cellular attempt to contain an offending agent that is difficult to eradicate. It's caused by limited conditions and some of them are life-threating

Epitheloid macrophages:

They're activated macrophages have squamous cell-like appearance

granulomas can form under 4 settings:

1. **with persistent T-cell responses to certain microbes**
2. **In some immune-mediated inflammatory diseases**
3. **In response to relatively inert foreign bodies**
4. **In a disease of unknown etiology**

A. persistent T-cell responses to certain microbes:

Immune granuloma mechanism:-

Initiating events:

1- **indigestible antigenic material in macrophages**
2- **Antigen presentation on cell membrane**
3- **CD4+TH1 lymphocytes activation , the responding T cells produce cytokines, such as IL-2, and IFN-γ.**

Examples:

1- **Mycobacterium tuberculosis**
2- **Tuberculosis is the prototype of a granulomatous disease caused by infection and should always be excluded as the cause when granulomas are identified**
3- **Schistosomiasis**
4- **Leishmaniasis**
5- **Leprosy**

B. immune-mediated inflammatory diseases

Example:

Crohn's disease: type of inflammatory bowel disease and an important cause of granulomatous inflammation

- **Caused by: Immune reaction against intestinal bacteria or self antigens**
- **Occasional noncaseating granulomas in the wall of the intestine, with dense chronic inflammatory infiltrate**

C. In response to relatively inert foreign bodies

- **Examples for foreign bodies:**

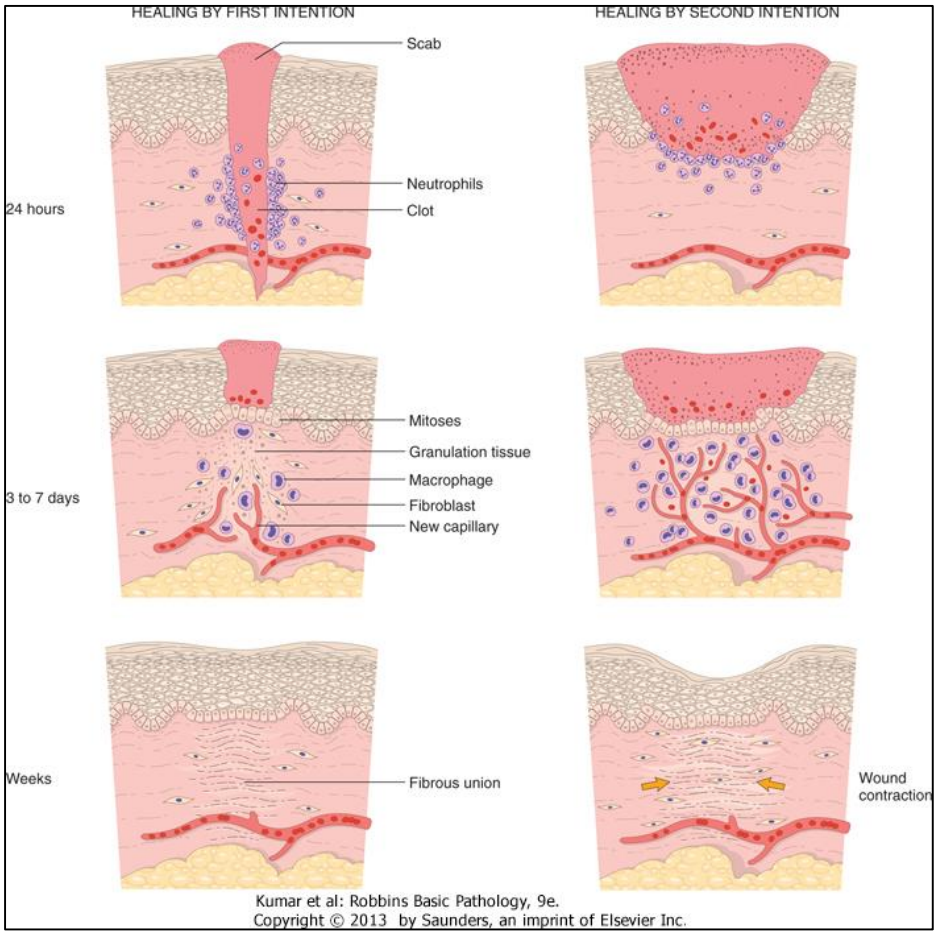
1- **Suture**
2- **Graft materials**
3- **Talc " associated with intravenous drug abuse**

D. In a disease of unknown etiology

- Example: Sarcoidosis
- It's non caseating with abdundant activated macrophages

o Healing and repair:

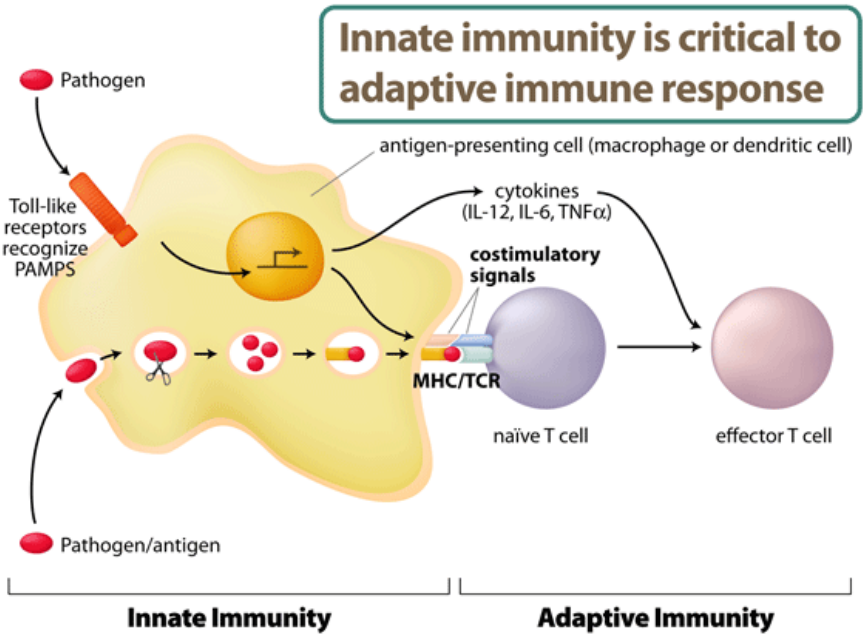
Cells are classified into 3 depending on capability of healing:
Labile cells: Regenerate all the time (e.g. epithelial cells in the skin).
Stable cells: regenerate only when there is an injury (e.g. hepatocytes).
Permanent cells: Never regenerate (e.g. neurons).
Healing in myocardium called myocardial fibrosis.
Healing in brain called gliosis.
Stem cell are embryogenic cells can replace permanent cell but it still under researches.
Growth factors are proteins promote migration of particular cells.
Two types of healing: 1- First intention. 2- Second intention.
The most known cause of delaying wound healing is infections.
Three complications may occur due to wound healing:
Fibrous adhesion (causes ischemia).
Keloid (causes disfiguration تشوه).
Wound dehiscence (causes incisional hernia)



https://www.youtube.com/watch?v=zZpMQ_7qiRg

Cutaneous Wound healing:

Primary union (Healing by 1st intention)	Secondary union (Healing by 2nd intention)
Clean surgical incision	**More extensive loss of cells and tissue:** **-Infarction** **-Inflammatory ulceration** **-Abscess formation**
No significant bacterial contamination	**Surface wound with large defect**
Minimal loss of tissue	**Large tissue defect that must be filled**
Clot, scab formation	


Innate immunity is critical to adaptive immune response
Pathogen
antigen-presenting cell (macrophage or dendritic cell)
Toll-like receptors recognize PAMPS
cytokines (IL-12, IL-6, TNFα)
costimulatory signals
MHC/TCR
naïve T cell
effector T cell
Pathogen/antigen
Innate Immunity
Adaptive Immunity


Inflammation
Types
Acute inflammation
Causes
Tissue necrosis
Bacterial Infections
Outcomes
Complication
Resolution
Chronic Inflammation
Cells
Macrophages
Lymphocytes
Plasma cells
Arise in
1- Persistence infectious microbes
2- immune-mediated inflammatory diseases
3- Prolonged exposure to potentially toxic agents
4- mild forms of chronic inflammation
Mechanism
a. Infiltration with mononuclear cells
b. Tissue destruction
c. Repair
Granulomatous inflammation
Features
Inflammatory vascular granulation tissue
Giant cells
Epithetioid macrophages
Cause
Deposition of a indigestible antigenic material
Types under microscope
Caseous
Non-caseous
Types
Immune granuloma
Foreign body granuloma
Mechanism
1- Margination
2- Adhesion
3- Transmigration
4- Chemotaxis
Cellular changes
Leukocytes recruitment & activation
Caused by
3- Liberation of some substances
4- Production of mediators
1- Phagocytosis.
2- Intracellular destruction.
Mechanism
A- Opsonization.
B- Engulfment.
C- Killing or degradation of the ingested material.
Features
Vascular changes
Abscess (exudate or pus)
Vasodilation
Vasoconstriction
Increase vascular permeability
Clinical features
Systemic
General Weakness (malaise).
Chills.
Fever (Pyrexia).
Vomiting.
Elevated plasma levels.
Tumor
Local
Rubor
Color
Dolor (Pain)
Functio Lasea
Action
Pain
Fever
Tissue damage
Chemical Mediators
Source
Cell-derived
Plasma-derived
Activated by
Microbial products.
Host proteins
Healing and repair
Types
Primary intention
Secondary intention
Complications
Formation of contractures
Excessive formation of the repair components
Response to
Inflammatory process
Wound
Deficient scar formation
Cell necrosis in organs
Cells
Labile cells
Stable cells
Permanent cells
Mechanism
1- Margination
2- Falling
3- Removing the clot
4- Producing granulation tissue
5- Decreasing of neutrophils & blood vessels
6- Increasing in collagen & macrophages

MCQ'S:

1- Regarding acute inflammation

a) Initial vasoconstriction is the result of histamine and nitric oxide
b) Stasis occurs due to vasodilatation and the larger caliber of vessels
c) Increased permeability leads to protein depleted plasma leaking into the tissue
d) Initial formation of endothelial gaps lasts for only 15-30 minutes
e) Cytokines (IL-1 and TNF) are responsible for the early permeability

2- Histamine is involved in acute inflammatory responses and is released from mast cells. Which of the following statements is incorrect?

a) It is found in blood basophils, platelets and mast cells
b) It causes increased permeability of arterioles
c) It may be released by physical trauma
d) It causes constriction of large vessels
e) It acts on the microcirculation via H1 receptors

3- Chronic inflammation is characterized by all of the below except:

a) Tissue destruction
b) Angiogenesis
c) Infiltration with neutrophils
d) Fibrosis
e) Increased tissue concentration of lymphocytes.

4- Which of the following diseases does not cause granulomatous inflammation?

a) Cat-scratch disease
b) Actinomycosis
c) Sarcoidosis
d) Leishmaniasis
e) Staphylococcus infection

5- In an experiment, Enterobacter cloacae organisms are added to a solution containing leukocytes. Engulfment and phagocytosis of the microbes is observed to occur. Next a substance is added which enhances engulfment.
Which of the following substances is most likely to produce this effect?

a) Complement C3b
b) Glutathione peroxidase
c) Immunoglobulin M
d) P-selectin
e) NADPH oxidase

6- What are the Chemical mediators involved in raising temperature?

a) interleukin-1 and LPS

7- What always precedes chronic inflammation?

It can be preceded by recurrent or unresolved acute inflammation or it can be a primary response itself.

8- What cell types are characteristic of chronic inflammation?

Lymphocytes, plasma cells, macrophages, proliferating endothelial cells and fibroblasts.

9- What is a granuloma?

A circumscribed collection of epithelial macrophages.

10- What is the role of macrophages in chronic inflammation?

They proliferate in the inflammatory site , phagocytize debris , activate lymphocytes and stimulate plasma cell production.

11- Where do the eosinophil's usually increase?

1- In Allergic reactions.
2- In Parasitic Infections.

12- What are the outcomes of acute inflammation?

I. Complete resolution.
II. Complication and formation of abscess.
III. Chronic inflammation.

13- What is the source of serotonin?

Tryptophan acid and platelets.

***14*- inflammatory process?**

Killing microbes.

***15*- Define neuropeptide and give an example for it?**

Proteins, which secreted from nerve ending and create pain by acting on the thalamus.
Ex: Substance P.

16- Define colloid (osmotic) pressure?

The pressure controls the amount of proteins in the blood.

17- What type of edema is related to inflammation?

Exudate.

18- How long does the vasodilation phase last?

It lasts as long as acute inflammation persist.

19- What is the cause of stasis?

Increase vascular permeability.

20- What does stasis cause?

Pavementing of WBCs.

21- What happens to neutrophils after 24 hours?

Replaced by monocytes.

22- Define opsonization, and what type of chemical mediators are involved in it?

Recognition and Attachment of the particle to be ingested by the leukocyte.
Complement proteins (C3b).

23- What are the two mechanisms of killing microbes?

I- Oxygen-dependent mechanisms.
II- Oxygen-independent mechanisms.

24- Where does chronic inflammation arise in?

I- persistence infectious microbes.
II- immune-mediated inflammatory diseases.
III- Prolonged exposure to potentially toxic agents.
IV- mild forms of chronic inflammation.

25- What are the anaphylatoxins ?

C3a and C5a

26- What are they called that?

They mediated release of histamine via basophil and mast cell degranulation .

27- What cells release histamine?

Basophils , mast cells and platelets .

28- What systemic inflammatory effects do cytokines have ?

Fever , leukocytosis and synthesis and release of acute phase proteins.

29- What is the role of macrophages in chronic inflammation?

Macrophages are long lived they proliferate in the inflammatory site,phagocytize debris ,activate lymphocyte via cytokines ,and stimulate plasma cell production .

30- What is a granuloma?

A circumscribed collection of epithelial macrophages , usually surrounded by a rim of lymphocytes with multi-nucleated giant cells.

31- What is the correct sequence of leukocyte response in acute inflammation?

Margination> pavementing > adhesion > emigration > chemotaxis > phagocytosis .

32- What are the endogenous pyrogens ?

IL-1 and TNF.

33- What cells are found in a granuloma?

epithelioid macrophages , multinucleated giant cells , and lymphocytes .

34- Define Angiogenesis?

The physiological process through which new blood vessels form from pre-existing vessels.

35- What is the most important cell in granulomatous inflammation?

Epithelioid histiocytes.

36- What is the cytokines that is important in activating macrophages and transforming them into epithelioid cells?

IFN-γ

37- What does the multinucleated cell in TB?

Langhan's cell.

38- An example for a particle, which is capable of inducing a cell-mediated immune response?

Type 4 hypersensitivity.

39- What are the types of granulomas under the microscope?

Caseous or Non-caseous.

40- What is the difference between healing and repairing?

Repairing is to restore the tissue to its original state. But Healing is usually a tissue response.

41- In healing and repairing types of cells, in what kind myocardium fibers is classified to?

Permanent cells.

42- Healing in the brain, what does it called?

Gliosis.

43- What is the function of growth factors?

Stimulate the survival and proliferation of particular cells, and may also promote migration

44- Define stem cells?

Multipotent, embryogenic cells (before differentiation) which can replace permanent cells.

45- What causes delaying in wound healing?

- **Infections.**
- **Presence of foreign body.**
- **Poor perfusion.**
- **Excess corticosteroid /Chronic diseases.**
- **Tumors (cancers)**
- **Nutritional deficiencies.**
- **Mechanical factors.**

46- Healing occurs in two types, what are they?

A) Healing by first intention.
B) Healing by second intention.

47- What is the difference between the first and the second intention?

The second intention takes longer than the first.

48- What is the role of macrophages in wound healing?

- **Cleanup of debris, fibrin, and other foreign material at the site of repair.**
- **Macrophages recruit other cells: fibroblasts and angioblasts**
- **Stimulation of matrix production**
- **Remodeling of the scar.**

49- What are the complication of healings?

- **Deficient scar formation.**
- **Excessive formation of the repair components.**
- **Formation of contractures.**

CASES:

- **40-year-old woman had bilateral silicone breast implants placed two years ago. Since that time, she has noted increased firmness with slight deformity of the breast on the left. The implants are removed, and there is evidence for leakage of the implant contents on the left.**

Which of the following cell types is most likely to be most characteristic of the inflammatory response in this situation?

A. **Mast cell**
B. **Eosinophil**
C. **Giant cell**
D. **Neutrophil**
E. **Plasma cell**

Because the silicone is a foreign material and produces a foreign body reaction.

- **A clinical study is performed of patients with pharyngeal infections. The most typical clinical course averages 3 days from the time of onset until the patient sees the physician. Most of these patients experienced fever and chills. On physical examination, the most common finding is a pharyngeal purulent exudate.**

Which of the following types of inflammation did these patients most likely have?

A. **Granulomatous inflammation**
B. **Acute inflammation**
C. **Abscess formation**
D. **Resolution of inflammation**
E. **Chronic inflammation**

- **A 40-year-old woman has had a chronic cough with fever and weight loss for the past month. A chest radiograph reveals multiple nodules from 1 to 4 cm in size, some of which demonstrate cavitation in the upper lobes. A sputum sample reveals the presence of acid fast bacilli.**

Which of the following cells is the most important in the development her lung lesions?

A. **Macrophage**
B. **Fibroblast**
C. **Neutrophil**
D. **Mast cell**
E. **Platelet**

Because Epithelioid cells and giant cells are derived from macrophages and are important in the development of granulomatous inflammation.

- **A 90-year-old woman has developed a fever and cough over the past 2 days. Staphylococcus aureus is cultured from her sputum. She receives a course of antibiotic therapy. Two weeks later she no longer has a productive cough, but she still has a fever. A chest radiograph reveals a 3 cm rounded density in the right lower lobe whose liquefied contents form a central air-fluid level. There are no surrounding infiltrates. Which of the following is the best description for this outcome of her pneumonia?**

A. **Hypertrophic scar**
B. **Abscess formation**
C. **Regeneration**
D. **Bronchogenic carcinoma**
E. **Progression to chronic inflammation**

- **A 37-year-old man has had nausea and vomiting for 5 weeks. He experienced an episode of hematemesis yesterday. On physical examination he has no abnormal findings. Upper GI endoscopy is performed, and there is a 1.5 cm diameter lesion in the gastric antrum which appears to be an area with loss of the epithelial surface. These findings are most typical for which of the following pathologic processes?**

A. **Abscess**
B. **Serositis**
C. **Granuloma**
D. **Gangrene**
E. **Ulcer**

- **A 15-year-old girl has had episodes of sneezing with watery eyes and runny nose for the past 2 weeks. On physical examination she has red, swollen nasal mucosal surfaces. She has had similar episodes each Spring and Summer when the amount of ragweed pollen in the air is high.**

Her symptoms are most likely to be mediated by the release of which of the following chemical mediators?

A. **Complement C3b**
B. **Platelet activating factor (PAF)**
C. **Tumor necrosis factor (TNF)**
D. **Histamine**
E. **Immunoglobulin G**

Histamine, mainly released from mast cells in perivascular locations, leads to vasodilation and fluid exudation. That is why people with allergies take antihistamines.

- **We suspect that a patient has a myocardium infarction, what is the procedure we follow?**

  A. **We do WBCs count, and we count the inflammatory cells. And we will find it increased. Thus he has acute inflammation.**

- **A child, who has a fever, vomiting, chills and sore throat. We took a blood sample and we found out that his lymphocytes is around 70% of WBCs. What kind of inflammation he has? And caused by what?**

  A. **He most likely has viral infection, which cause chronic inflammation**

- **A patient has a renal problem, he is losing lots of protein in his urine, therefore his colloid pressure becomes low.**
  What is the result of decreasing in colloid pressure in this situation?

  A. **The fluid comes out from blood vessels causing edema.**

- **A patient came with pleural effusion "pleural cavity is the potential space between the two pleural (visceral and parietal) of the lungs. 3-5 milliliters is the normal value of the fluid in this cavity, but after taking x-ray for this patient (or taking a sample by a needle), it appears that he has 2 liters of fluid. What possibly could be the causes of this accumulation?**

  A. **This accumulation it could be by heart failure, or kidney problem, or liver problem or inflammation.**

  Serous cavities: synovial cavity, peritoneum cavity (abdominal) and pleural cavity.

- **A person who has a bronchopneumonia, after taking the antibiotics all of his signs disappear, but after x-raying him we found a lesion on his lungs.**
  What kind of acute inflammation outcome is this?

  A. **This is a complication of the acute inflammation that can be removed by surgery.**