Inflammation

→Elimination of **foreign invaders** (infectious pathogens and damaged tissues) is mediated by a complex host response called "inflammation"

→Inflammation is a **protective** response intended to eliminate the initial cause of cell injury as well as the **damaged necrotic cells and tissues**. This is followed by healing and repair of the damaged tissues.

-Without inflammation, infections would **persist and wounds would never heal**.

-The inflammatory reaction and the subsequent repair process can cause **considerable harm.**

-The components of the inflammatory reaction that **destroy and eliminate microbes and dead tissues are capable of also injuring normal tissues**

-Many of human diseases are disorders in which the pathophysiologic basis is **inappropriate or exaggerated inflammation.**

→Five Cardinal signs of Inflammation:

a)Heat b)Erythema c)Pain d)Swelling(Edema) e)Loss of function.

→Types of Inflammations:

a)Acute Inflammation:

1-Short duration of action.
2-few minutes to a day.
3-Accumulation of plasma fluids.
4-Presence of Neutrophils.

b)Chronic Inflammation:

1-Long duration.
2-Accumulation of Macrophages &Lymphocytes.

C)Sub-acute:

-Between Acute & Chronic

→Steps of Inflammation (5Rs):

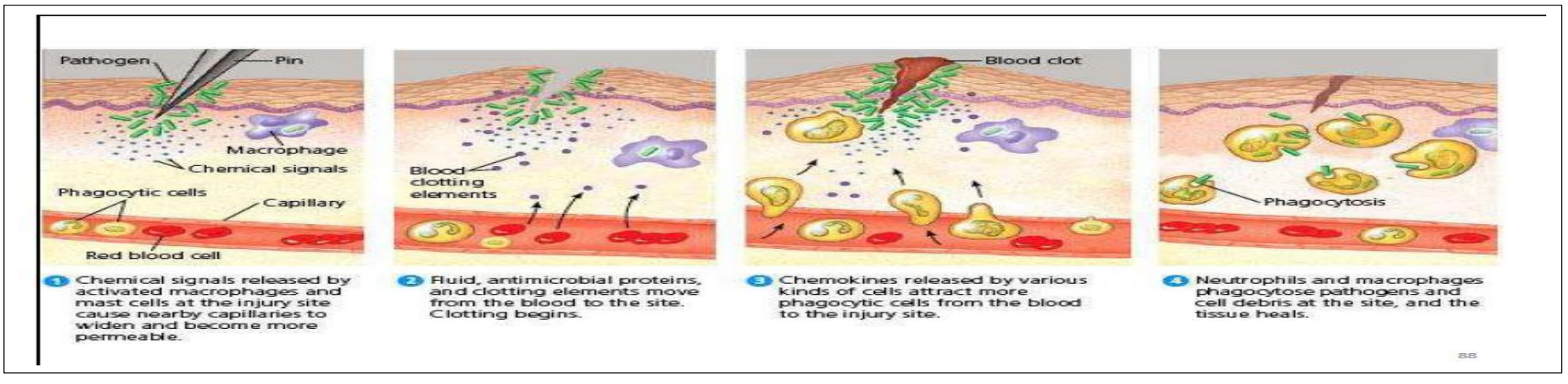
1-Recognition of Injurious agent.
2-Recruitment of Phagocytes.
3-Removal of the agent.
4-Regulation of Response.
5-Resolution (Repair).

Steps of inflammation

1. When a host encounters an injurious agent (e.g.] a microbe) or dead cells, **phagocytes** that reside in tissues try to eliminate these agents.
2. At the same time, phagocytes and other host cells liberate **chemical mediators** of inflammation.
3. Some of these mediators act on small blood vessels in the vicinity and promote the efflux of plasma and the **recruitment of circulating leukocytes** to the injury site.
4. The **recruited leukocytes** are activated by the injurious agent and by locally produced mediators and try to remove the offending agent by **phagocytosis .**

-An unfortunate side effect of the activation of **leukocytes may be damage to normal host tissues.**

5. The outcome of acute inflammation is either **elimination** of the injurious stimulus followed by decline of the reaction and repair of the damaged tissue] or persistent injury resulting in **chronic inflammation**.



Acute inflammation

→ *Acute inflammation* is a rapid response to injury or microbes and other foreign substances. It is designed to deliver leukocytes and plasma proteins to sites of injury. Once there, **leukocytes clear the invaders and begin the process at digesting and getting rid of necrotic tissues.**

→ Acute inflammation has two main features:

1-Vascular changes:

-**Increase** in vessel diameter resulting in increased blood flow (**vasodilation**) .

-**Structural changes** that permit plasma proteins to leave the circulation **(increased vascular permeability) .**

2- Cellular events:

-Emigration of the leukocytes from the microcirculation and accumulation at the site of injury ***(cellular recruitment and activation)*** .

-The main leukocytes in acute inflammation are **neutrophils (polymorphonuclear leukocytes) .**

A- Vascular changes in acute inflammation

-Arteriolar **vasodilation** occurs, resulting in locally **increased blood flow and expansion of capillary beds.**

-This vascular expansion is the cause of the **redness (erythema) and warmth characteristic to inflammation .**

-As the capillary wall becomes more permeable, **plasma, moves into the extravascular tissues.**

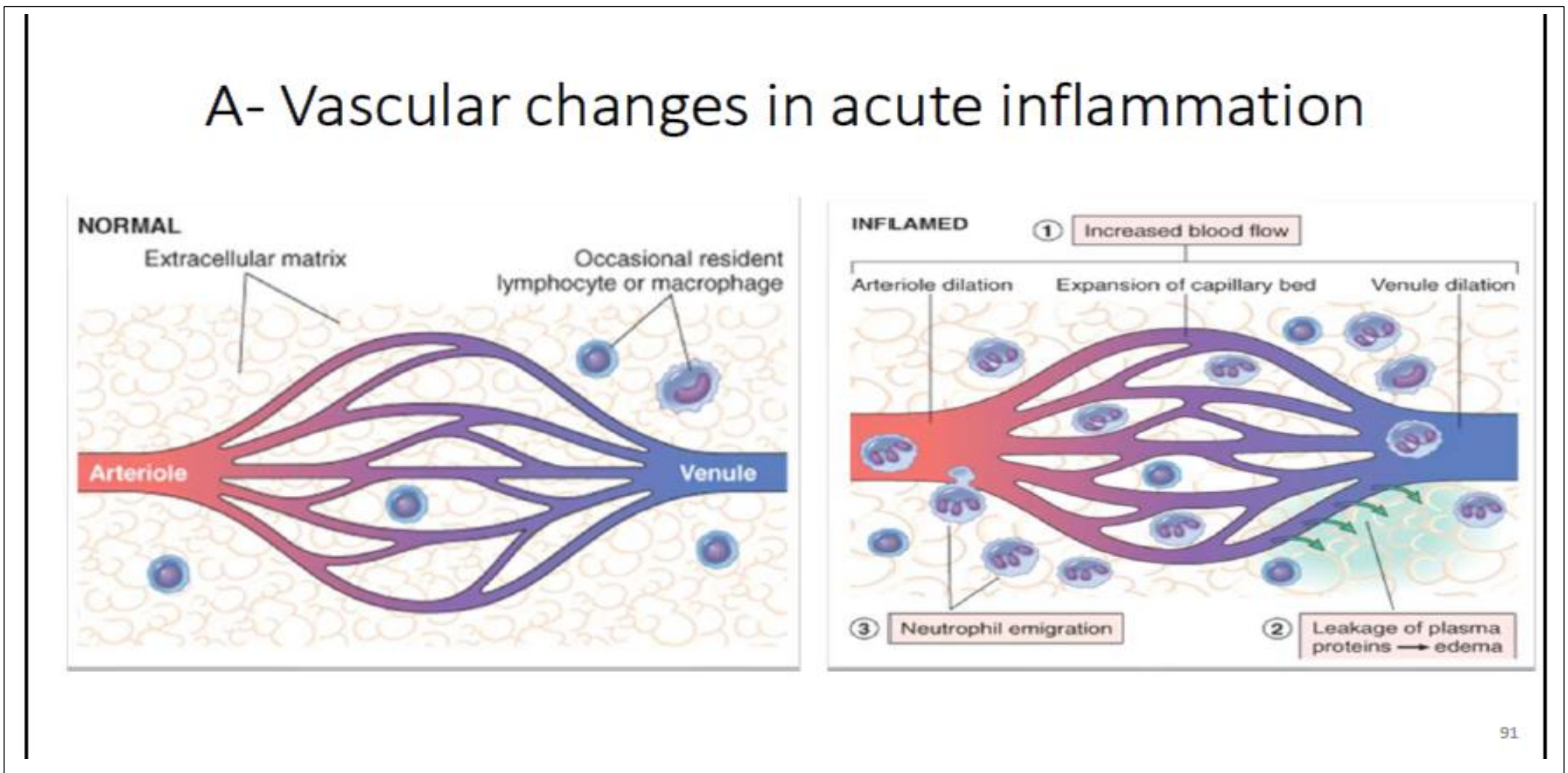
-This causes :

a)Red blood cells to become more **concentrated.**

b)Increasing **blood viscosity.** c)**Slowing** the circulation .

-This process is called Stasis.

-As stasis develops ,leukocytes (Principally neutrophils) begin to accumulate along the endothelial surface ,this process is called margination.



Transudate & exudate

-The **vasodilation and increased volume** of blood flow lead to an increase↑ in intravascular **hydrostatic pressure**, resulting in **movement of fluid from capillaries into the tissues.**

-This fluid, called a **transudate**, is an ultrafiltrate of **blood plasma and contains little protein**, sometimes due **to decrease in colloidal pressure due to liver or kidney disease** .

-Transudation is soon followed by **increasing vascular permeability** that allows the movement of **protein-rich fluid** and cells (called an **exudate**) into the perivascular space, This REDUCES ↓, the intravascular osmotic pressure.

-**Generally**: **- Fluid accumulation** in extravascular spaces is called **edema.**

-Fluid may be a transudate or exudate.

-**Exudates** are **typical of inflammation** .

-Transudates accumulate in various non-inflammatory conditions:

1- **Liver disease** (decrease in protein synthesis leading to decreased Colloidal pressure).

2-**Kidney disease** (Increase in protein loss leading to decreased Colloidal pressure).

3-**Congestive heart failure** (Decrease in outflow as in case of venous congestion leading to increase in Hydrostatic pressure) .

B- Cellular events in acute inflammation

(Leukocyte Recruitment and Activation)

-The sequence of events in the recruitment of leukocytes from the vascular lumen to extravascular space consists of:

(1) **Margination**, adhesion to endothelium, and **rolling** along the vessel wall ,**this step is mediated by a protein called Selectin on the endothelial wall of the blood vessels binds to Carbohydrate receptors on the Leukocytes**.

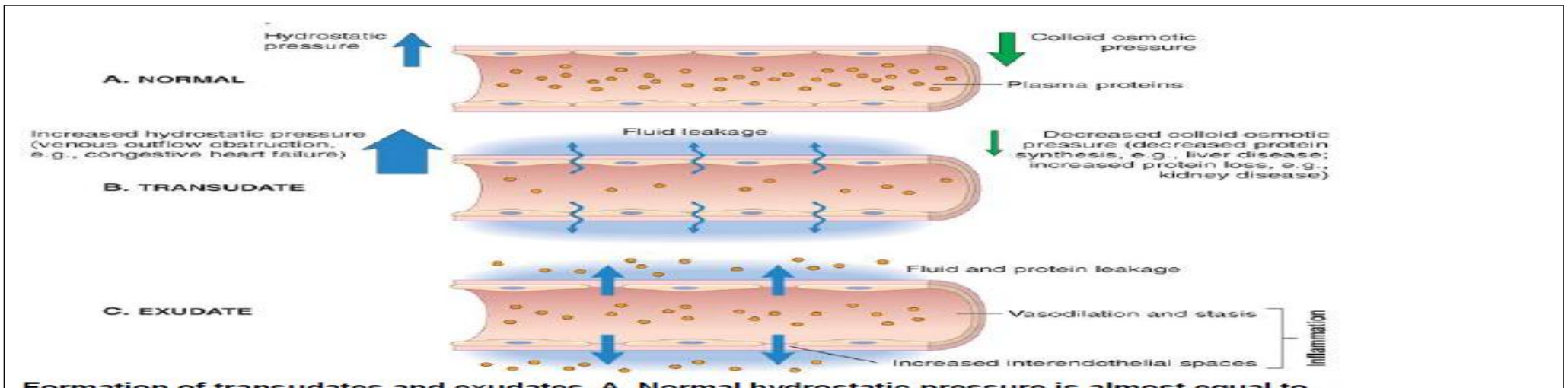
(2) **Firm adhesion** to the endothelium ,this step is mediated by a protein called integrin on the Neutrophils binds to ICAMI & VCAM II on the endothelial layer of the blood vessel.

(3) **Transmigration** between endothelial cells

(4) **Migration in interstitial tissues** toward a chemotactic stimulus Rolling, adhesion, and transmigration are mediated by binding of adhesion molecules on leukocytes and endothelial surfaces.

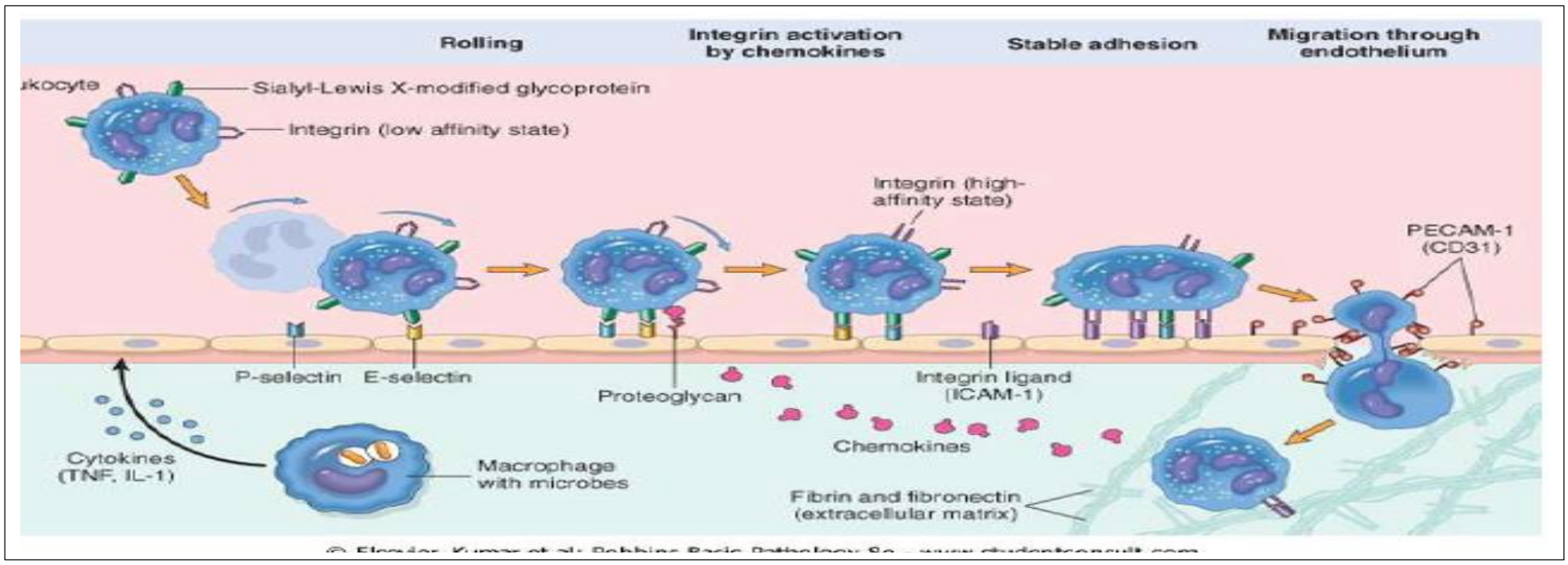
-**Bradykinnin is an immune mediator which binds to Mast cells leading to the release of Histamine which increases permeability & Prostaglandin which irritates the nerve producing the pain.**

- **Chemical mediators**, **chemo attractants** and certain cytokines affect these processes.



Formation of transudates and exudates. A, Normal hydrostatic pressure is almost equal to the mean colloid osmotic pressure. Therefore, the net flow of fluid across the vascular bed is almost nil. B, 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 increased interendothelial spaces.

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→Migration in interstitial tissue & chemotaxis:

-After escaping from the blood, leukocytes migrate **toward sites of infection** or injury along a chemical gradient by a process called **chemotaxis.**

-Both **exogenous and endogenous** substances can be chemotactic for leukocytes,

including:

(1) Bacterial products **(exogenous**).

(2) Cytokines (**endogenous**).

(3) Components of the complement system (**endogenous**) .

-The type of emigrating leukocyte varies with the age of inflammation:

-In most forms of acute inflammation, ***neutrophils*** predominate in the inflammatory infiltrate during the first 6 to 24 hours and are replaced by ***monocytes*** in 24 to 48 hours .

Exception

-There are exceptions to this pattern:

1- In infections caused by ***Pseudomonas*** organisms, the cellular infiltrate is dominated by continuously recruited neutrophils for several days .

2- In **viral infections** lymphocytes may be the first cells to arrive .

Leukocyte-Induced Tissue Injury

-leukocytes ingest offending agents, **kill bacteria and other microbes**, and eliminate necrotic tissue and foreign substances

-**A price that is paid** for the **defensive potency of leukocytes** is that, once activated, they may induce **tissue damage and prolong inflammation**, since the leukocyte products can also injure normal host tissues.

→Examples:

I-Infections that are difficult to eradicate, such as **tuberculosis (Acid fast),** the host response contributes more to the pathology than does the microbe itself.

2- When the inflammatory response is inappropriately directed against host tissues, as in **autoimmune diseases .**

3- When the host reacts excessively against non-toxic environmental substances, such as **allergic diseases** that induce asthma.

Leukocyte-induced Tissue injury (on Cellular level)

-The injury is initiated by release of contents of lysosome of the leukocyte to surrounding tissue by:

1. If the phagocytic vacuole remains **transiently open** to the outside before complete closure of the phagolysosome.

2-If cells encounter materials **that cannot be easily ingested**, such as immune complexes, the attempt to phagocytose these substances ***(frustrated phagocytosis)*** triggers release of lysosomal enzymes into the surrounding tissue or lumen.

3-Following phagocytosis of **potentially injurious substances**, such as **urate crystals**, which damage the membrane of the phagolysosome.

Morphological patterns of acute Inflammation

a)Non Suppurative Inflammation

-**Morphology of acute inflammation differs according to the cause, the response and the tissue involved.**

1. Serous inflammation:

-Characterized by the presence of **watery, protein-poor** fluid derived from serum.

-**Purpose:** Immediate **dilution of the harmful agent** at the site of inflammation

.e.gSkin blister from burn or viral infection .

.e.g**Inflammation of serous membranes** such as the pleura, pericardium, peritoneum .

2.Fibrinous inflammation :

-Due to more **severe injuries .**

-**Greater vascular permeability** resulting of the **passage of large molecules as fibrinogen which appear as meshwork of threads .**

-Could happen in linings of body cavities such as **meninges, pericardium and pleura** .

-May be removed by **macrophages** with **restoration of normal structure (resolution).**

- Or failure to **completely remove the fibrin** resulting of growth of fibroblasts leading to **scarring .**

Fibrinous pleuritis and fibrinous pericarditis

-**Bread and butter Pericarditis** : Pericardium, which is regularly smooth and bright, becomes **opaque and granular**, and macroscopically resembles two pieces of buttered bread pressed together then pulled apart .

3- Ulcer

-**Local defect** of **the surface of the organ or tissue** due to **necrosis of the cells** .

-Most inflammatory necrosis found in : a)Stomach. b)Intestine. c)Urogenital .

d)Ulcers in lower extremities of old persons due to circulatory disorders.

4- Membranous inflammation:

-**Severe acute inflammation** characterized by the formation of **pseudo membrane** on the affected surface .

-Observed with certain bacteria :

a)Diphtheria.

b)Bacillary Dysentery.

c)Clostridium difficile.

5- Hemorrhagic inflammation:

-***Acute inflammation characterized by cellular exudate rich in red blood cells due to vascular damage Seen in :***

a) Plague.

b)Smallpox.

c)Hemolytic streptococcal infections .

d)Anthrax.

6-Catarrhal inflammation

-**Mild acute inflammation** of the mucous membranes with **excess mucin** secretion as in common cold.

b)Suppurative inflammation

1-Localized suppurative inflammation Abscess, furuncle, carbuncle:

-Characterized by presence of **purulent exudate** (pus)consisting of : Neutrophils ,Necrotic cells & edema fluids .

-Caused by: Staph ,Strepto that's why **they are Pyogenic**.

→Furuncle and carbuncle:

a)Furuncle(Boil)	b)Carbuncle
It is an **abscess** in relation of **hair follicles or sebaceous** gland. -It is caused by staphylococci e.g. acne	This is a **large suppurative** lesion which develops usually in diabetic patients because of their **low resistance** to infection. The most common site is the back of **the neck, scalp**.

2-Diffuse suppurative inflammation :

-Cellulitis :

-Cellulitis is a bacterial infection of the skin that involves the skin's deeper layers : the dermis and subcutaneous tissue.

-Might be caused by staph., and streptococci.

3-Empyema

-Suppurative inflammation in a body cavity.

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

Examples : Pericardial, peritoneal, and pleural empyema.

-Gallbladder and appendiceal empyema.

4-Phlegmon:

-Diffuse suppurative inflammation that spreads in connective tissues **without sharp demarcation**.

-Examples :Erysipelas inflammation in connective tissues of skin usually caused by

Beta –hemolytic Streptococci involving Erythema & Swelling.

Outcomes of acute inflammation

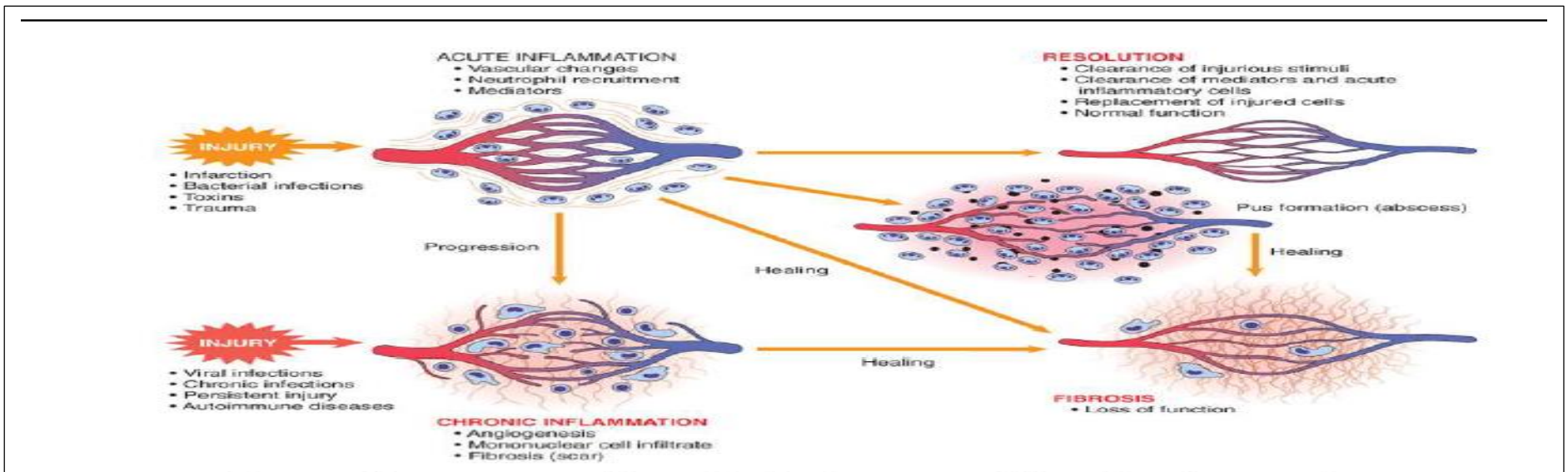
→Acute inflammation generally has one of three outcomes :

1- Resolution: When the injury is **limited or short**, when there has been **no or minimal tissue damage,** the usual outcome is resolution.

2-Progression to chronic inflammation may follow acute inflammation if **the offending agent is not removed.**

3-Scarring or fibrosis results after :

1- Massive tissue **destruction.**
2- Inflammation occurring in tissues that **do not regenerate.**
3- **Extensive exudates** (due to increased vascular permeability) may **not be completely absorbed** with resultant fibrosis.
4- **Abscesses** formed in case of **bacterial or fungal infections** (these organisms are then said to be pyogenic, or "pus forming).



Outcomes of acute inflammation: resolution, healing by scarring (fibrosis), or chronic inflammation

Tissue repair

→Restoration of tissue architecture or function after injury occurs by 2 ways (Tissue Repair):

a)Regeneration : **New tissue** replace damaged components and return to **normal state**.

b)Healing (Scar formation or Fibrosis) :

-Tissues are **incapable of complete restoration** or the damage is severe, Laying down of **connective (fibrous**) tissue occurs& **scar formation**.

-**Fibrosis** (**extensive deposition of collagen** in lungs, liver, kidney or heart after ischemic necrosis).

→**Repair** involves the **proliferation of various cells,** and close interactions between **cells and the extracellular matrix (ECM).**

Physiologic cell proliferation

-Cell numbers can be changed by **increased or decreased rates** of stem cell input, **cell death by apoptosis**, or changes in the rates of **proliferation or differentiation**.

-Proliferative Capacities of Tissues :

1-Continuously dividing Tissues : (labile tissues) :
-Are continuously being lost and replaced by maturation from stem cells.
-Include cells in the bone marrow and the majority of surface epithelia, such as **surfaces of the skin, oral cavity, vagina, and cervix; the epithelium of the ducts (e.g., salivary glands, pancreas, biliary tract); the epithelium of the gastrointestinal tract, uterus.**
→These tissues can readily **regenerate** after injury as long as the pool of stem cells is **preserved as it has high proliferative capacity (100% regenerated).**