INFLAMMATION

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Introduction

- Inflammation is defined as the local response of living mammalian tissues to injury due to any agent.
- Body defense reaction – eliminate or limit the spread of injurious agent

Cause of Inflammation

1. *Infective agents* like bacteria, viruses and their toxins, fungi, parasites.
2. *Immunological agents* like cell-mediated and antigen antibody reactions.
3. *Physical agents* like heat, cold, radiation, mechanical trauma.
4. *Chemical agents* like organic and inorganic poisons.
5. *Inert materials* such as foreign bodies

How Inflammation distinct from Infection ??

Inflammation

- Protective response by the body to variety of etiologic agents, while infection is invasion into the body by harmful microbes and their resultant ill-effects by toxins
- 2 basic processes with some overlapping
  - early *inflammatory response*
  - later followed by *healing*
- Sometimes it causes considerable harm to the body as well
    - anaphylaxis to bites by insects or reptiles, drugs, toxins,
    - atherosclerosis,
    - chronic rheumatoid arthritis,
    - fibrous bands
    - Adhesions in intestinal obstruction

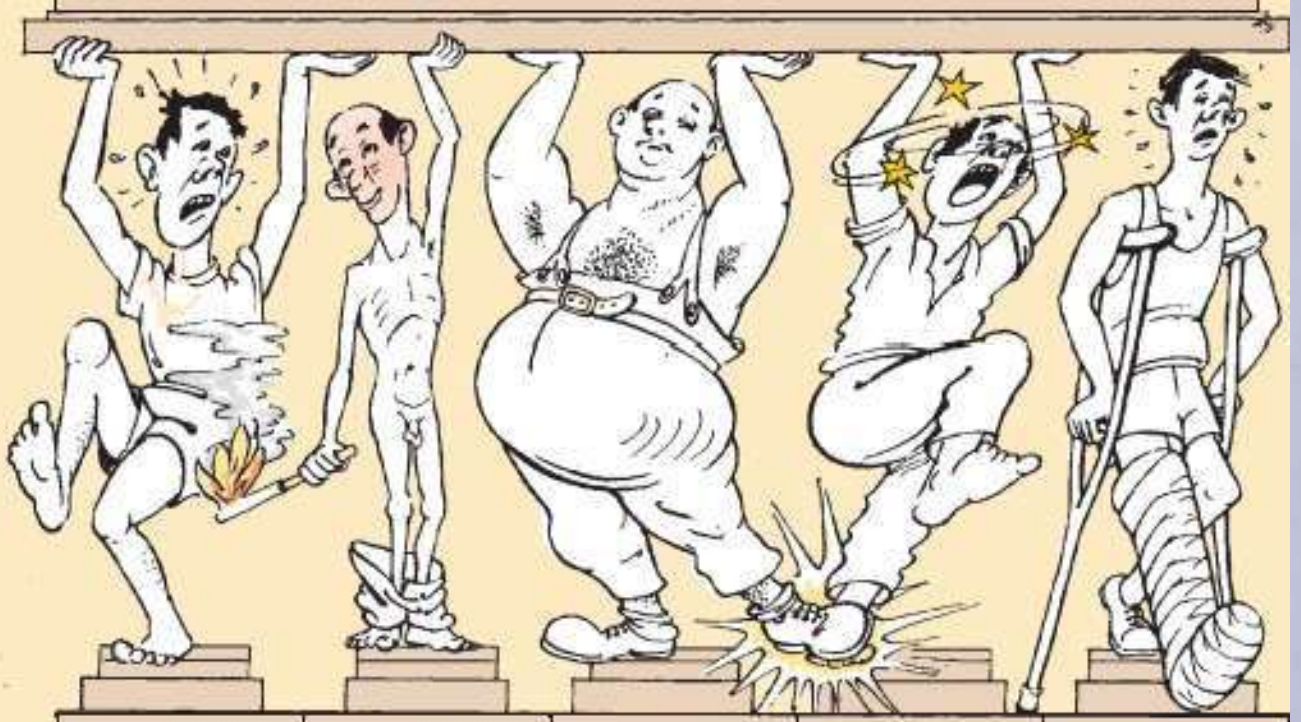
SIGNS OF INFLAMMATION

- 4 cardinal signs (Celsus)
  - rubor (redness);
  - tumor (swelling);
  - calor (heat);
  - dolor (pain)
- 5th sign functio laesa (loss of function) - Virchow


AC Celsus


R Virchow

INFLAMMATION

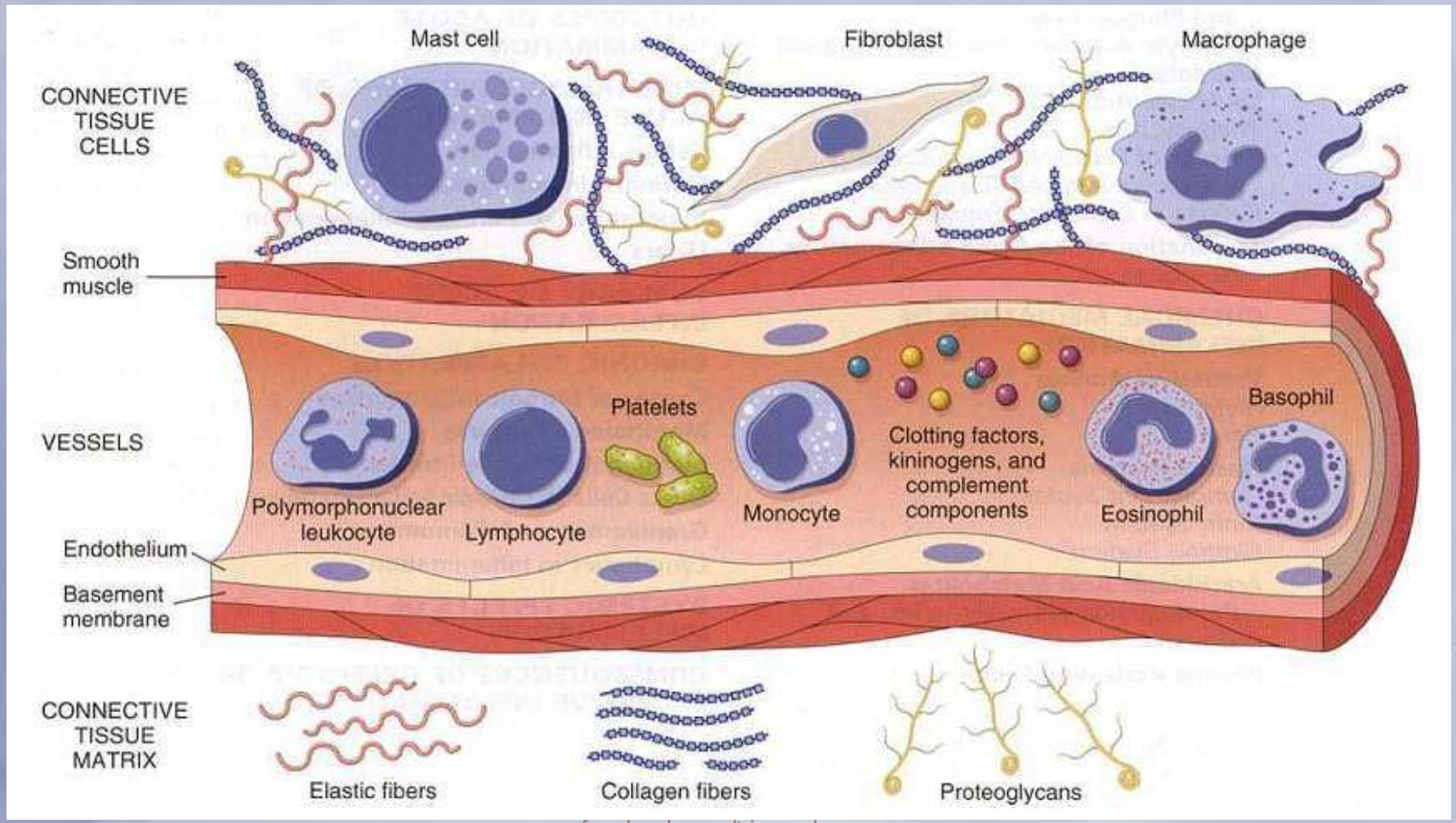


Calor	Rubor	Tumor	Dolor	Functio laesa
Local hypothermia, fever	Hyperemia (redness)	Tissue swelling (inflammatory tumor)	Burning pain	Functional impairment

TYPES OF INFLAMMATION

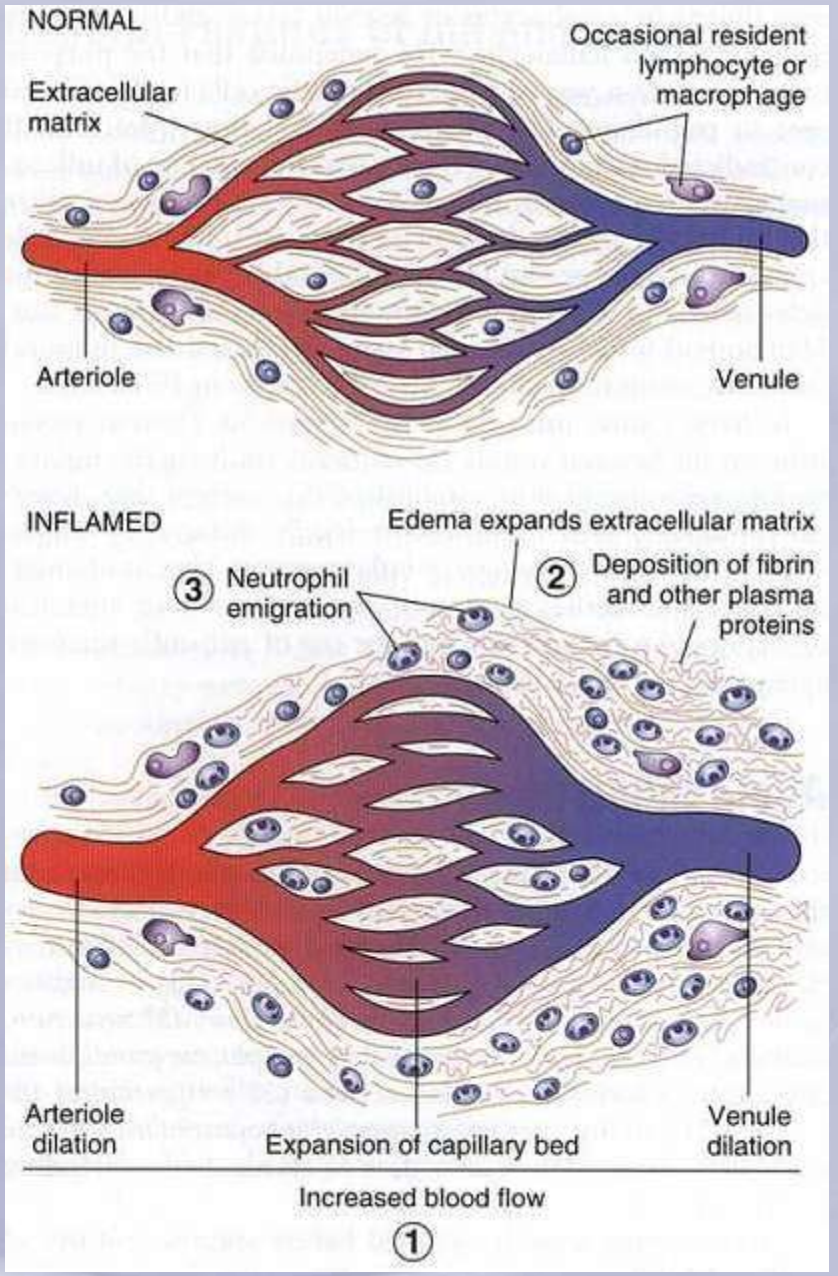
- Mainly of 2 types i.e. acute and chronic
- **Acute Inflammation**
  - short duration
  - represents the early body reaction- followed by healing
- **Chronic inflammation**
  - longer duration
  - causative agent of acute inflammation persists for a long time
- Another variant, **Chronic active inflammation**: stimulus is such that it induces chronic inflammation from the beginning

Components of Acute and Chronic Inflammatory responses



ACUTE INFLAMMATION

- The main features of acute inflammation are:
  - accumulation of fluid and plasma at the affected site;
  - intravascular activation of platelets;
  - polymorphonuclear neutrophils as inflammatory cells.



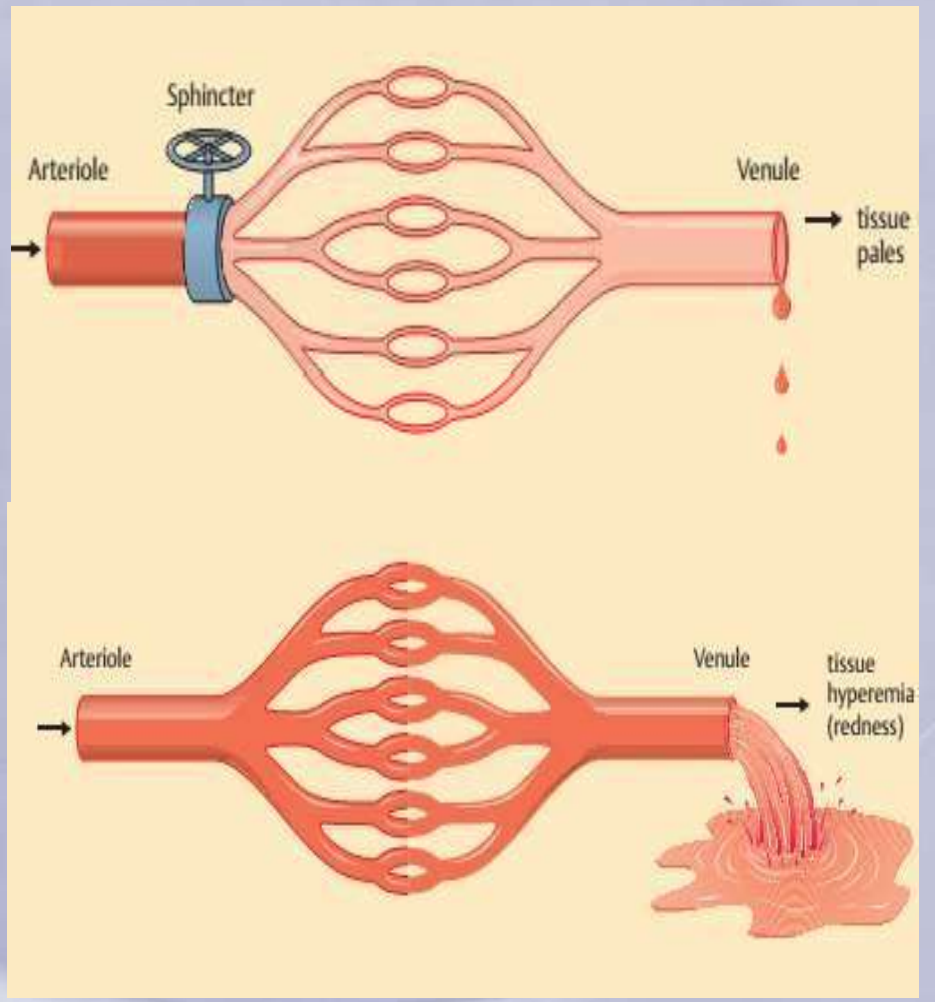
ACUTE INFLAMMATION

- Divided into following two events
  - Vascular events
  - Cellular events
- This 2 events are followed intermittently by release of mediators of acute inflammation.

- Alteration in the microvasculature
- This is again divide in 2 phases
  - Hemodynamic changes
  - Changes in the vascular permeablity

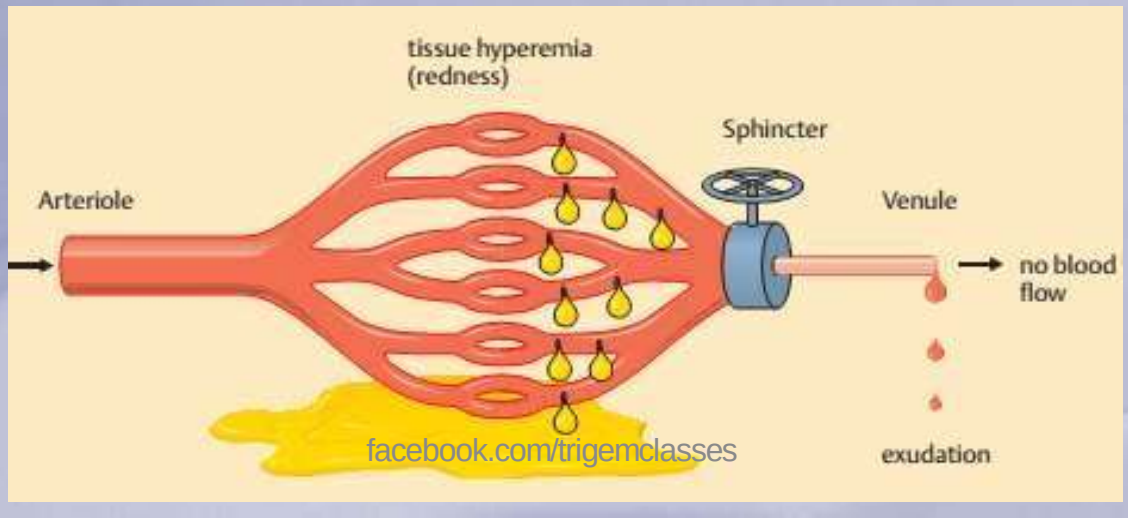
Hemodynamic changes

1. **Transient vasoconstriction :** immediate vascular response irrespective of the type of injury, mainly arterioles
   - **Mild injury -** 3-5 seconds
   - **Severe injury -** 5 minutes
2. **Persistent progressive vasodilatation :** mainly arterioles, others to a lesser extent.
   - obvious within half an hour of injury
   - increased blood volume in microvascular bed of the area
   - redness and warmth



Hemodynamic changes

3. **Progressive vasodilatation** elevate the local hydrostatic pressure
   - transudation of fluid into the extracellular space
   - swelling
4. **Slowing or stasis** increased concentration of red cells, and thus, raised blood viscosity

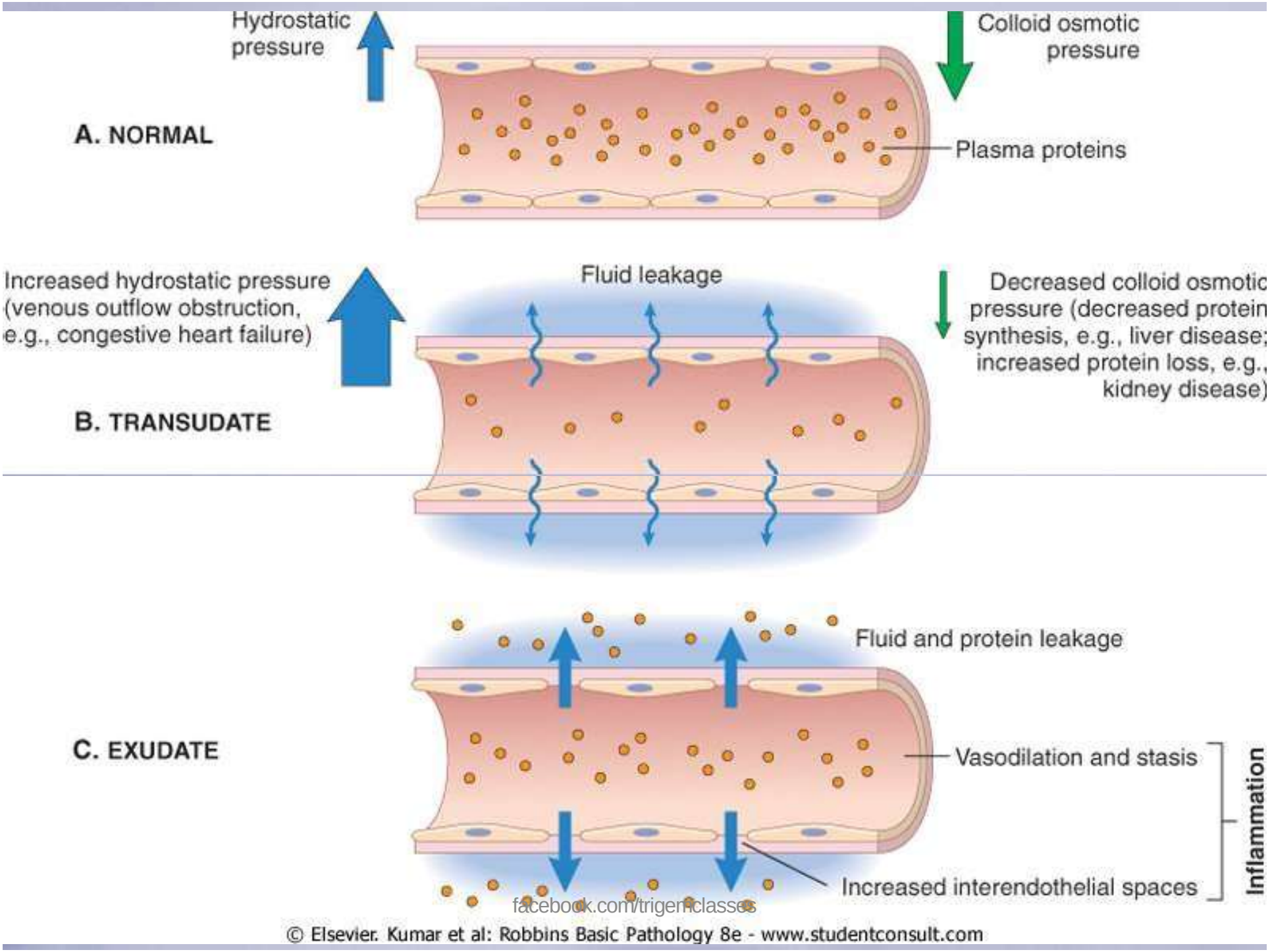


Hemodynamic changes

5. **Leucocytic Margination** peripheral orientation of leucocytes (mainly neutrophils) along the vascular endothelium
   - stick to the vascular endothelium briefly
   - move and migrate through the gaps between the endothelial cells - extravascular space
   - This is known is *emigration*

Altered Vascular Permeability

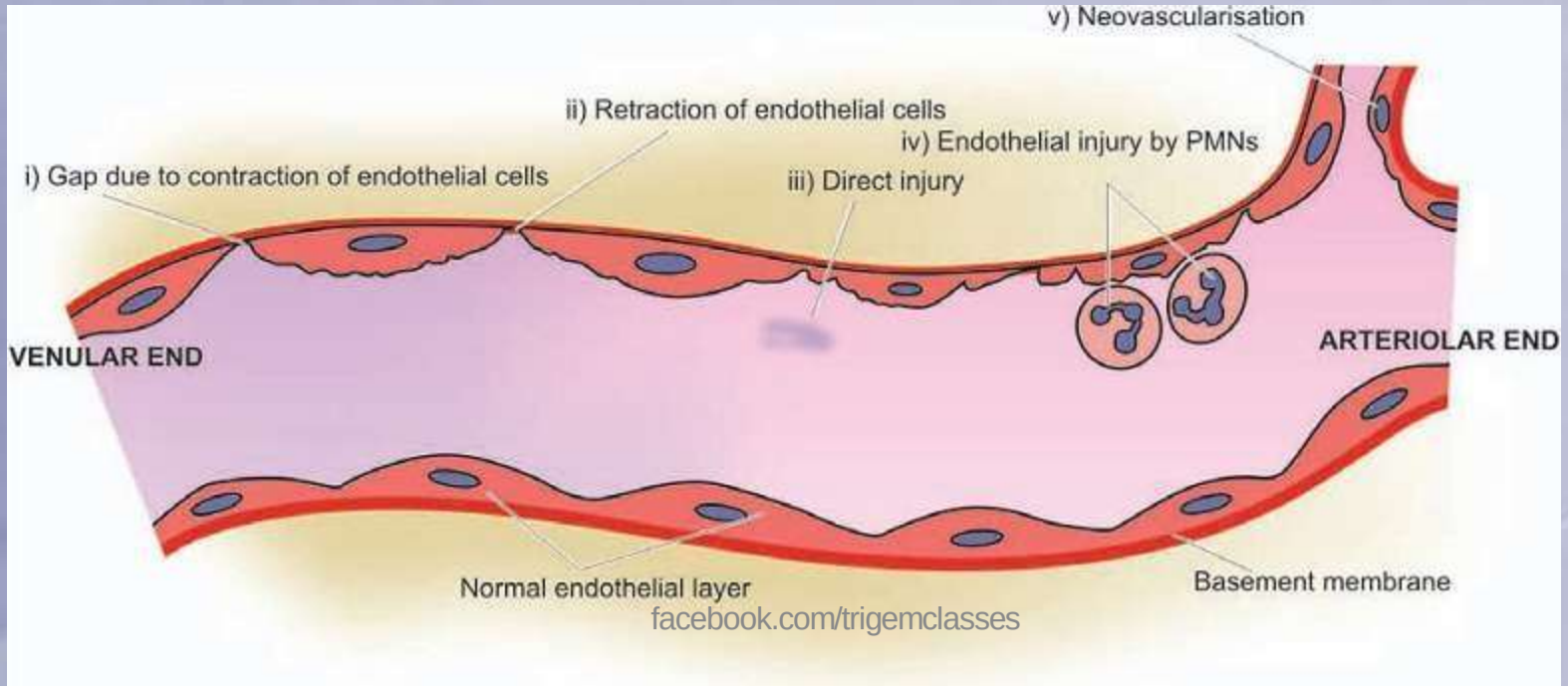
- Accumulation of oedema fluid - interstitial compartment which comes from blood plasma by its escape through the endothelial wall of peripheral vascular bed.
- Escape of fluid is due to vasodilatation and consequent elevation in hydrostatic pressure - **transudate**.
- Subsequently, the characteristic inflammatory oedema, appears by increased vascular permeability of microcirculation – **exudate**.



Any one fluid that is both exudate and transudate in Oral Cavity ?

MECHANISMS OF INCREASED VASCULAR PERMEABILITY

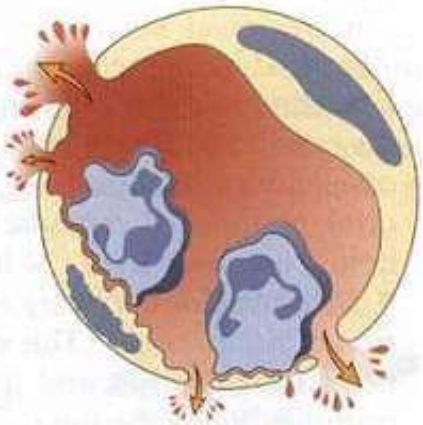
1. Contraction of endothelial cells.
2. Retraction of endothelial cells
3. Direct injury to endothelial cells
4. Endothelial injury mediated by leucocytes
5. Leakiness and neo-vascularisation



MECHANISMS OF INCREASED VASCULAR PERMEABILITY

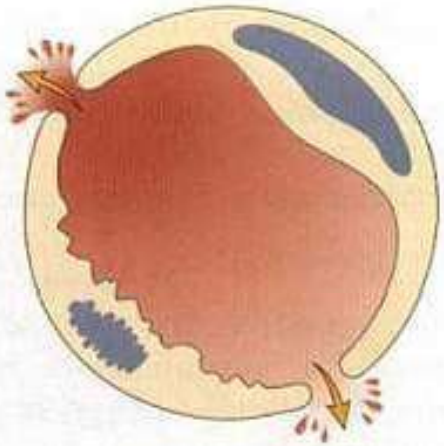
Leukocyte-dependent injury

- Mostly venules
- Pulmonary capillaries
- Late response
- Long-lived (hours)



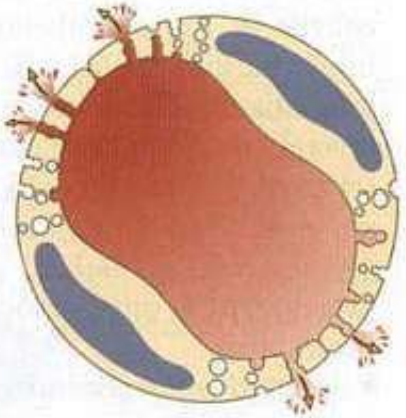
Gaps due to endothelial contraction

- Venules
- Vasoactive mediators (histamine, leukotrienes, etc.)
- Most common
- Fast and short-lived (minutes)



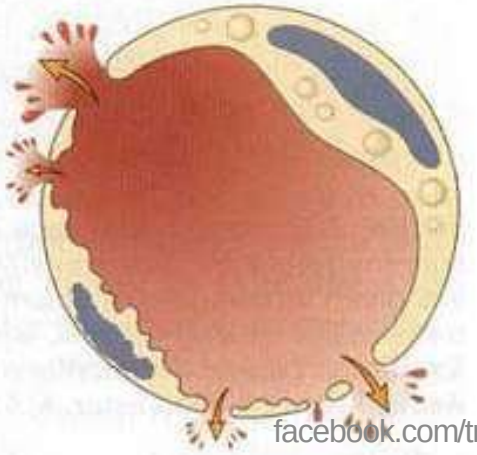
Increased transcytosis

- Venules
- Vascular endothelium–derived growth factor



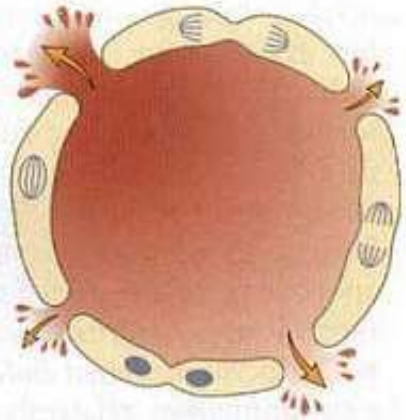
Direct injury

- Arterioles, capillaries, and venules
- Toxins, burns, chemicals
- Fast and may be long-lived (hours to days)



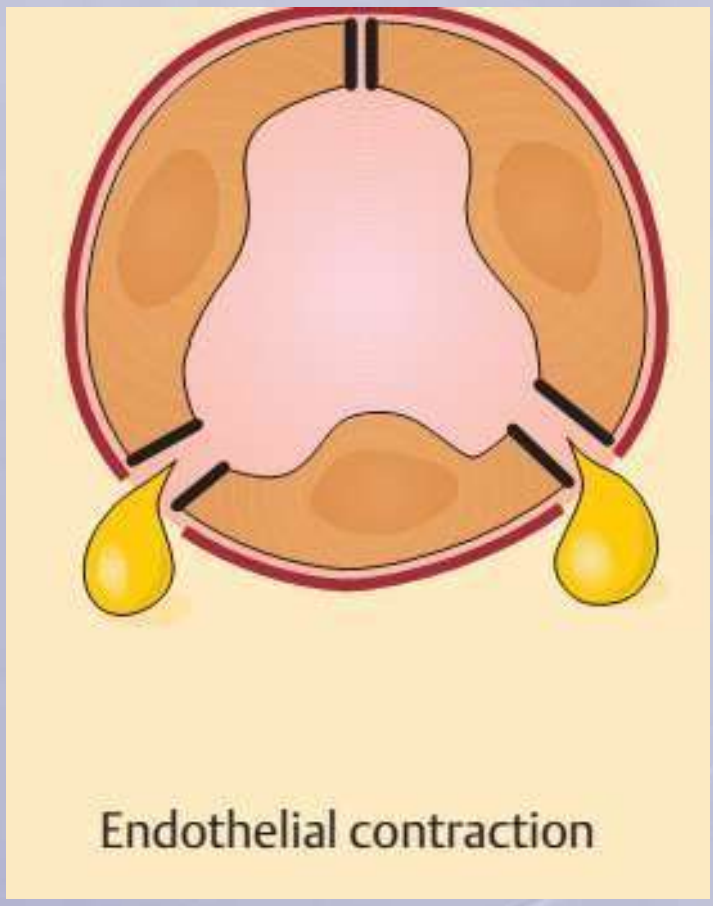
New blood vessel formation

- Sites of angiogenesis
- Persists until intercellular junctions form



Contraction of endothelial cells

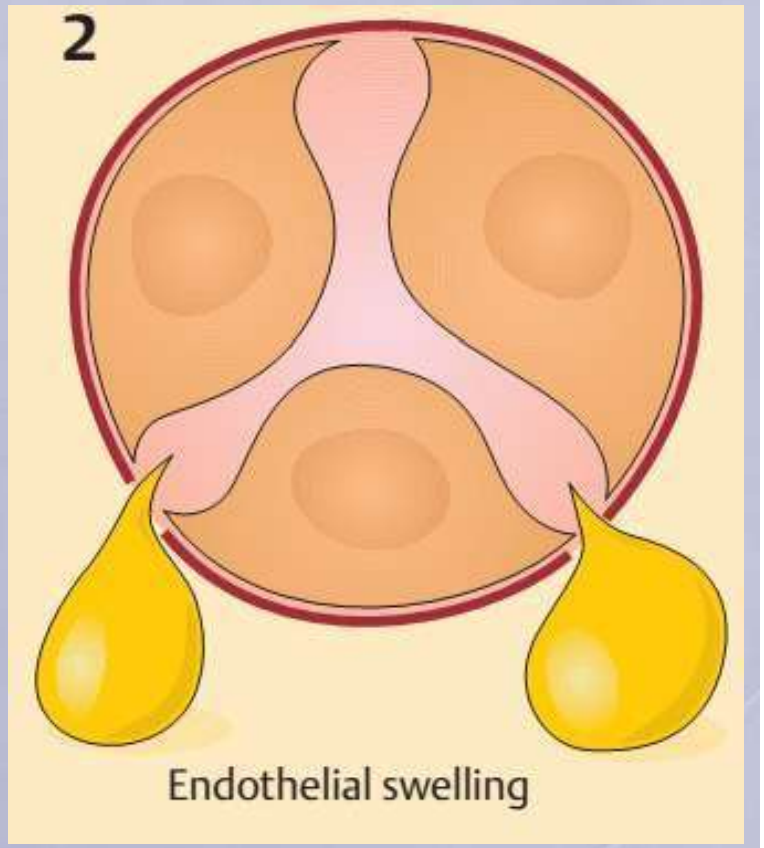
- Affects venules exclusively.
- Endothelial cells develop temporary gaps
- Contraction resulting in vascular leakiness.
- Mediated by the release of **histamine**, **bradykinin** and **other chemical mediators.**
- Short duration (15-30 minutes) - immediately after injury.



Endothelial contraction

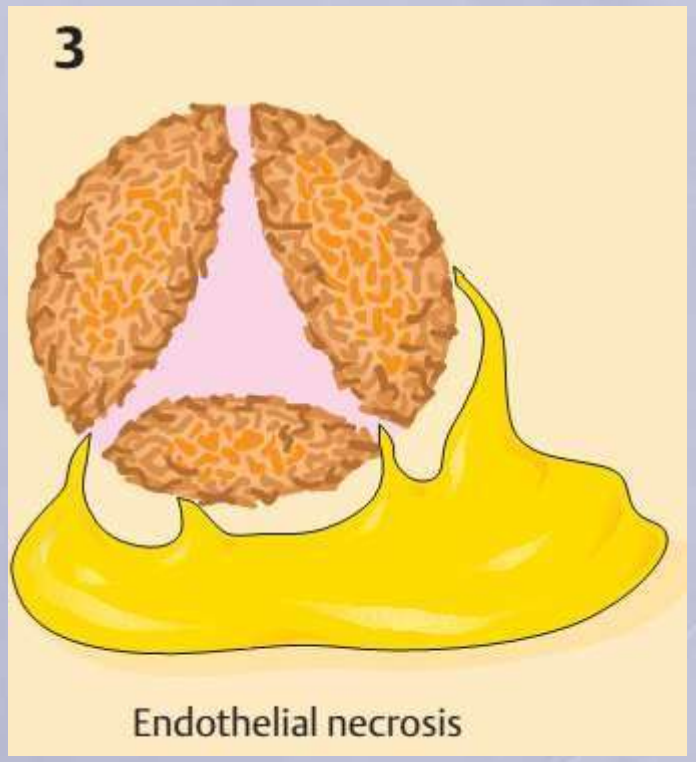
Retraction of endothelial cells

- Structural re-organisation of the cytoskeleton of endothelial cells - Reversible retraction at the intercellular junctions.
- Mediated by cytokines such as interleukin-1 (IL-1) and tumour necrosis factor (TNF)-α.



Direct injury to endothelial cells

- Causes cell necrosis and appearance of physical gaps.
- Process of thrombosis is initiated at the site of damaged endothelial cells.
- Affects all levels of microvasculature.
- Either appear **immediately** after injury and last for several hours or days – severe bacterial infections
- Or **delay of 2-12 hours** and last for hours or days - moderate thermal injury and radiation injury



Endothelial necrosis

Endothelial injury mediated by leucocytes

- Adherence of leucocytes to the endothelium at the site of inflammation.
- Activation of leucocytes - release proteolytic enzymes and toxic oxygen.
- Cause endothelial injury and increased vascular leakiness.
- Affects mostly venules and is a *late response*.

Leakiness and neovascularisation

- Newly formed capillaries under the influence of **vascular endothelial growth factor** (VEGF).
- Process of repair and in tumours are excessively leaky

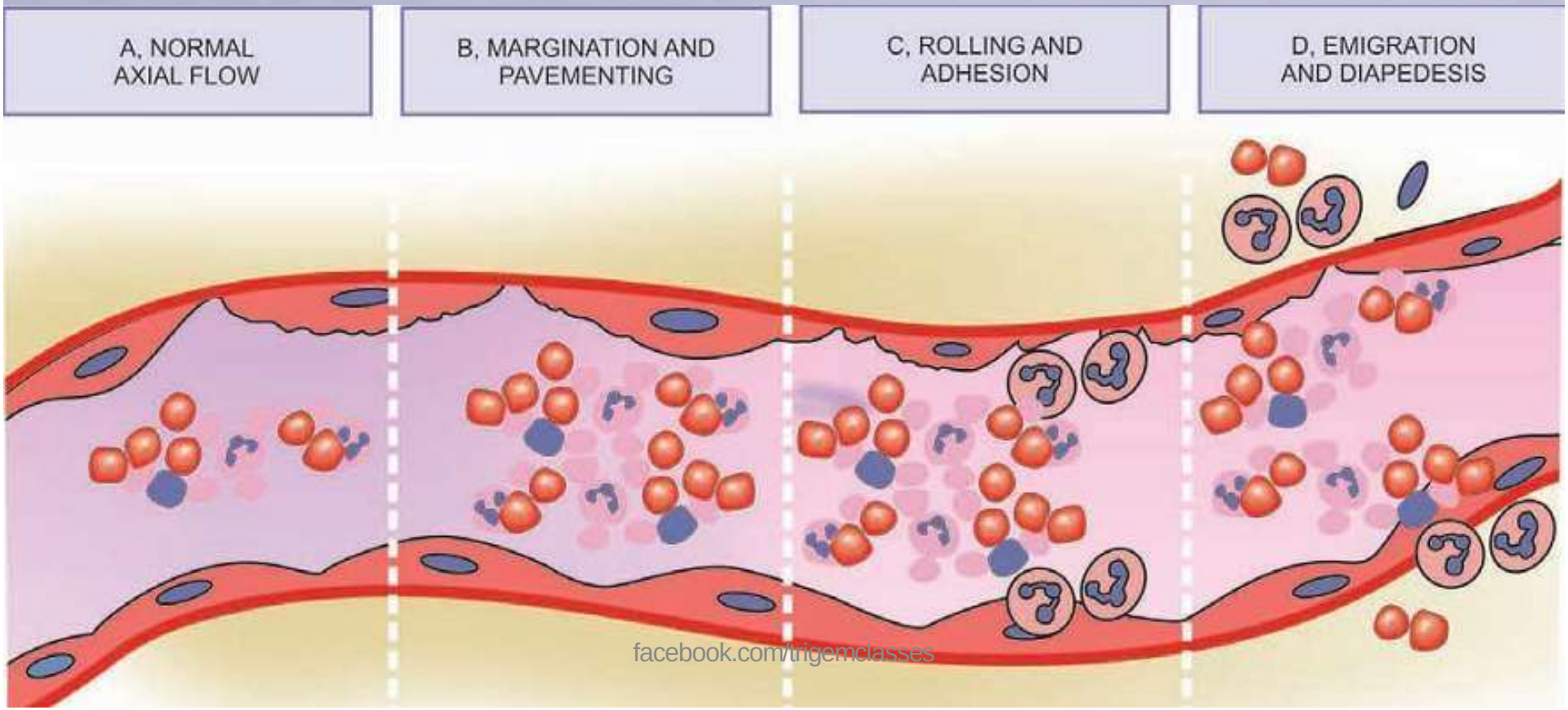
CELLULAR EVENTS

- Cellular phase of inflammation consists of 2 processes

1. Exudation of leucocytes
2. Phagocytosis.

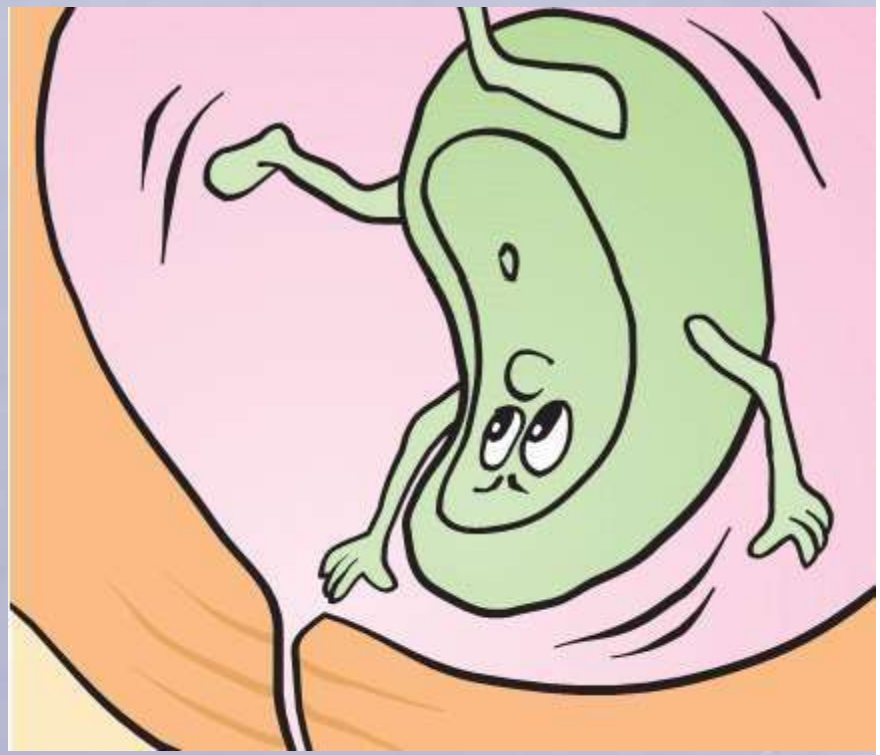
Exudation of leucocytes

1. Changes in the formed elements of blood.
2. Rolling and adhesion
3. Emigration
4. Chemotaxis



CHANGES IN THE FORMED ELEMENTS OF BLOOD

- Central stream of cells comprised by leucocytes and RBCsand peripheral cell **free layer** of plasma close to vessel wall.
- Later, central stream of cells widens and peripheral plasma zone becomes narrower because of loss of plasma by exudation.
- This phenomenon is known as ***margination.***
- Neutrophils of the central column come close to the vessel wall - ***pavementing***

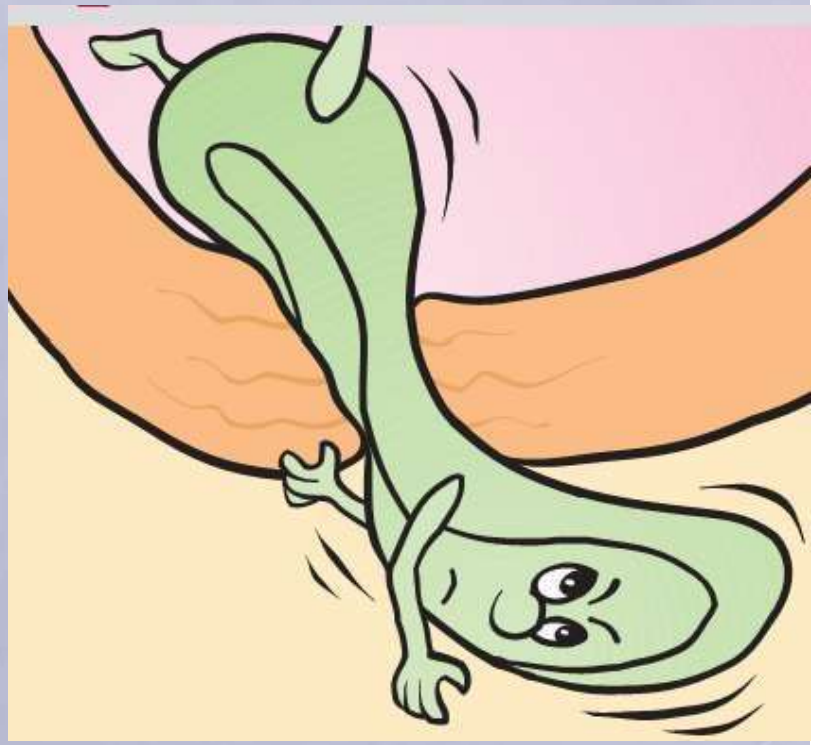


ROLLING AND ADHESION

- Peripherally marginated and pavemented neutrophils slowly roll over the endothelial cells lining the vessel wall ***(rolling phase)***.
- Transient bond between the leucocytes and endothelial cells becoming firmer ***(adhesion phase)***.
- The following molecules bring about rolling and adhesion phases
  - **Selectins**
  - **Integrins**
  - **Immunoglobulin gene superfamily adhesion molecule**

EMIGRATION

- After sticking of neutrophils to endothelium,
- The former move along the endothelial surface till a suitable site between the endothelial cells is found where the neutrophils throw out cytoplasmic pseudopods.
- Cross the basement membrane by damaging it locally – collagenases and escape out into the extravascular space - ***emigration***



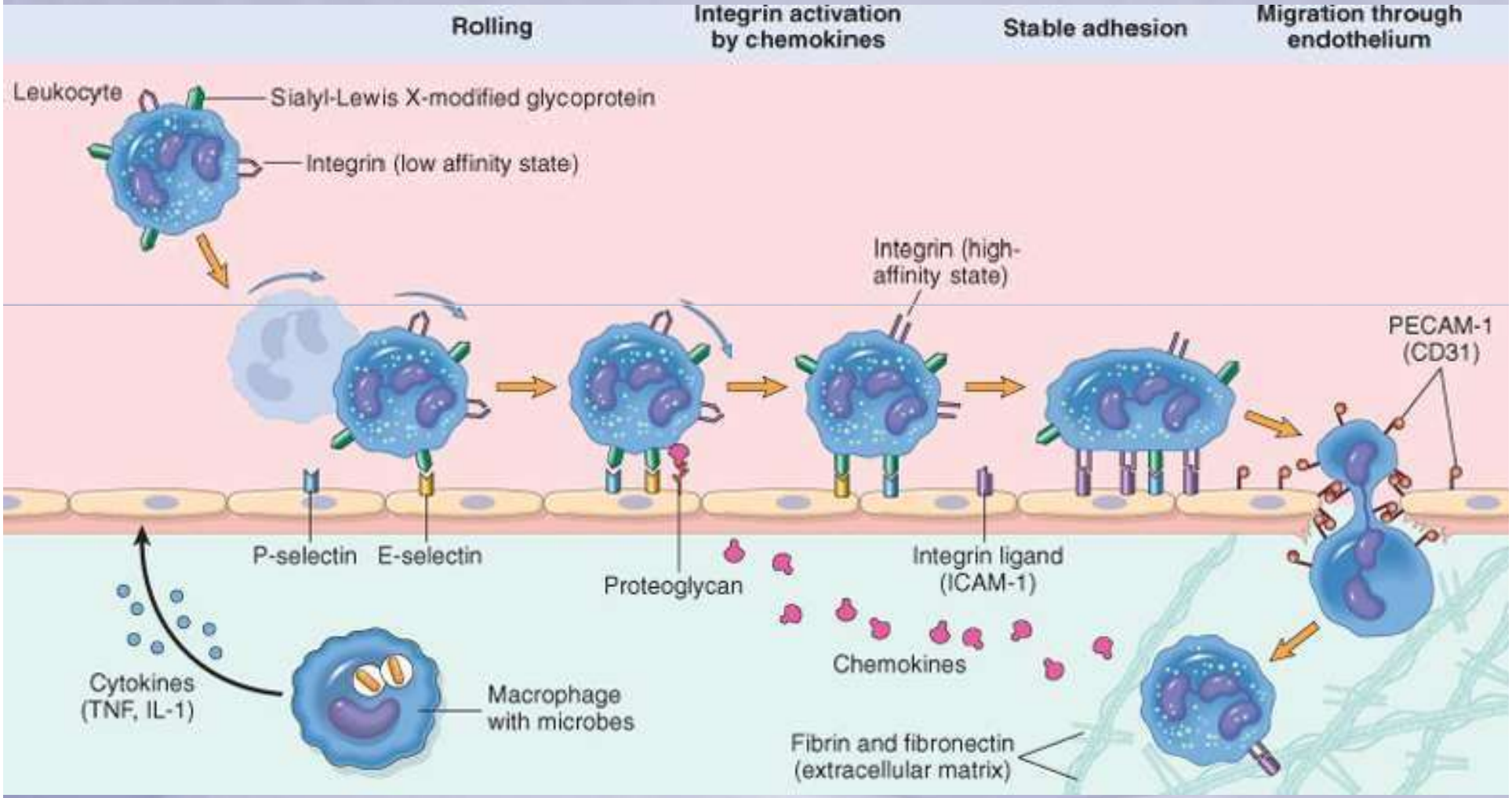
EMIGRATION

- ***Diapedesis*** - escape of red cells through gaps between the endothelial cells
  - passive phenomenon.
  - raised hydrostatic pressure
  - haemorrhagic appearance to the inflammatory exudate

CHEMOTAXIS

- After extravasating from the blood, Leukocytes migrate toward sites of infection or injury along a chemical gradient by a process called ***chemotaxis***
- They have to cross several barriers - endothelium, basement membrane, perivascular myofibroblasts and matrix.
- Potent **chemotactic substances** or ***chemokines*** for neutophils.
  - Leukotriene B4 (LT-B4) - arachidonic acid metabolites.
  - Components of complement system - C5a and C3a in particular.
  - Cytokines
  - Interleukins, in particular IL-8

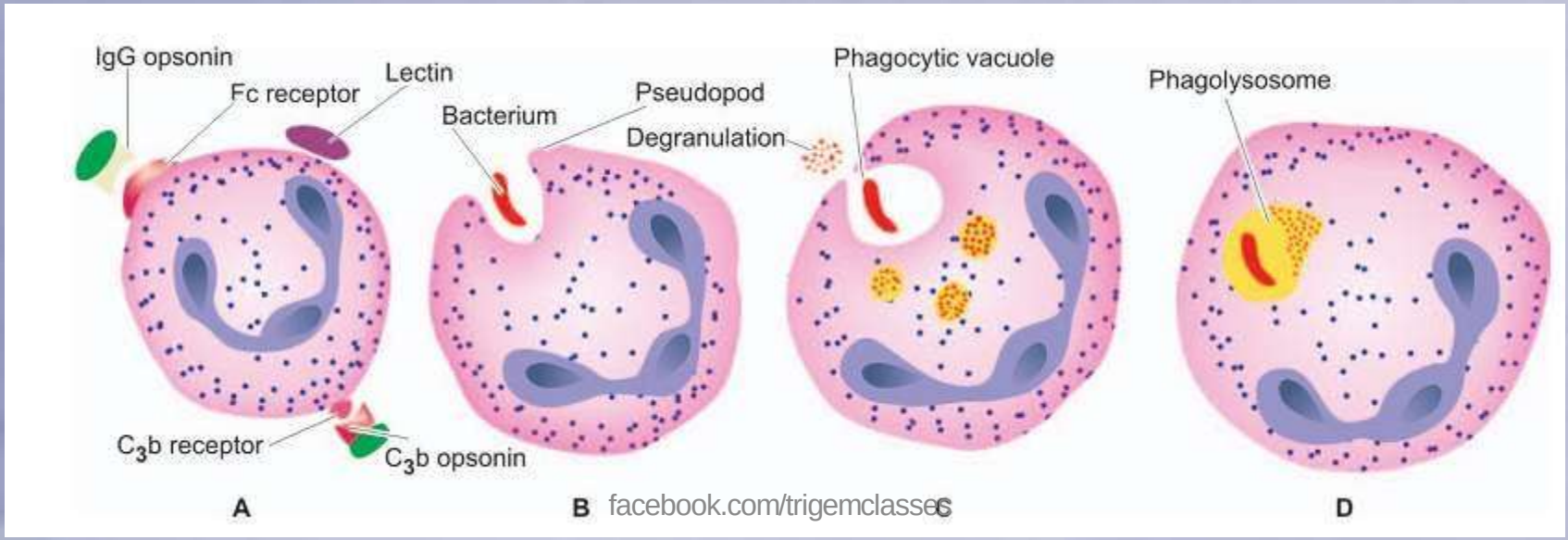
Events of Exudation of leucocytes



PHAGOCYTOSIS

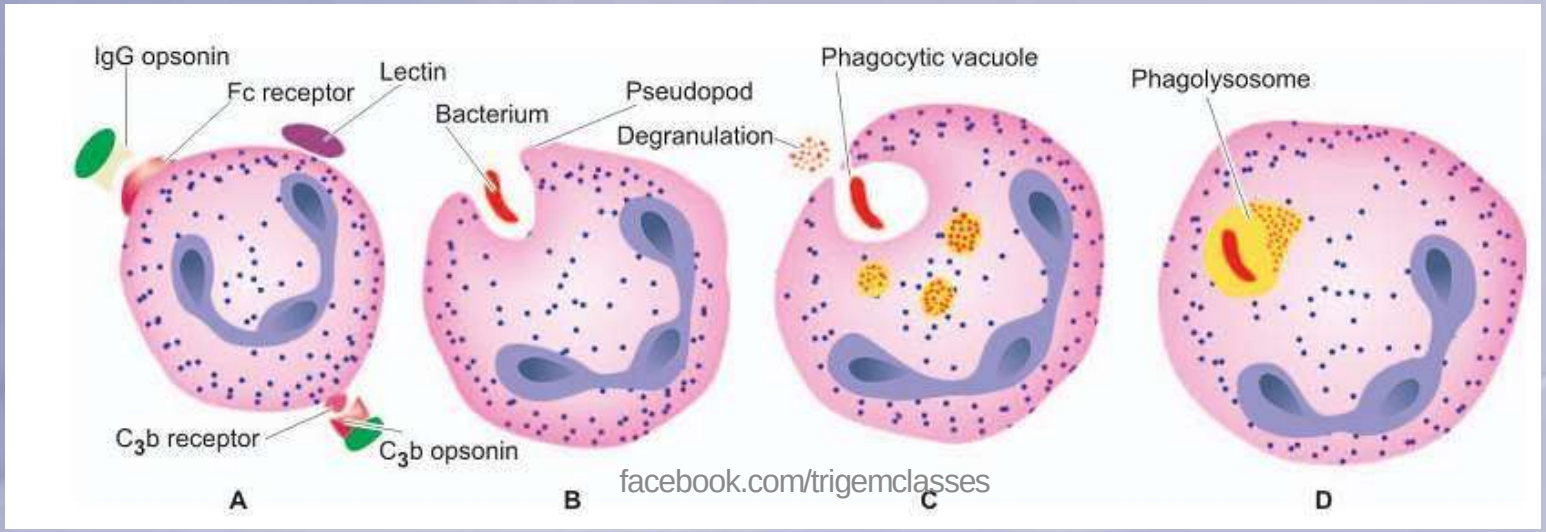
- The process of engulfment of solid particulate material by the cells.
- 2 main types of phagocytic cells
  - **Polymorphonuclear neutrophils (PMNs)** : early in acute inflammatory response, also known as *microphages*
  - ***Macrophages*** **:** Circulating monocytes and fixed tissue mononuclear phagocytes
- This phagocytic cells releases proteolytic enzymes - lysozyme, protease, collagenase, elastase, lipase, proteinase, gelatinase and acid hydrolases

- The microbe undergoes the process of phagocytosis in following 3 steps :
  - Recognition and attachment
  - Engulfment
  - Killing and degradation



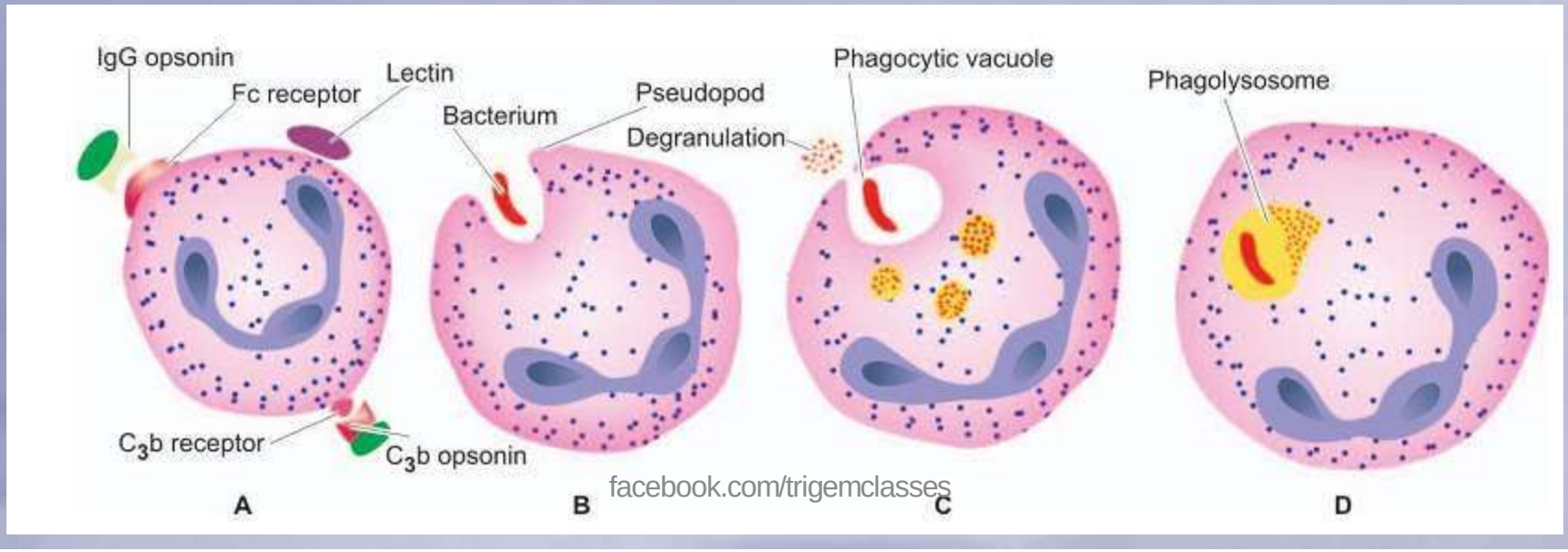
RECOGNITION AND ATTACHMENT

- Phagocytosis is initiated by the **expression of surface receptors** on macrophages.
- Its further enhanced when the microorganisms are **coated with specific proteins, *opsonins*.**
  - Establish a bond between bacteria and the cell membrane of phagocytic cell.
  - Major opsonins are
    - *IgG opsonin .*
    - *C3b opsonin*
    - *Lectins*



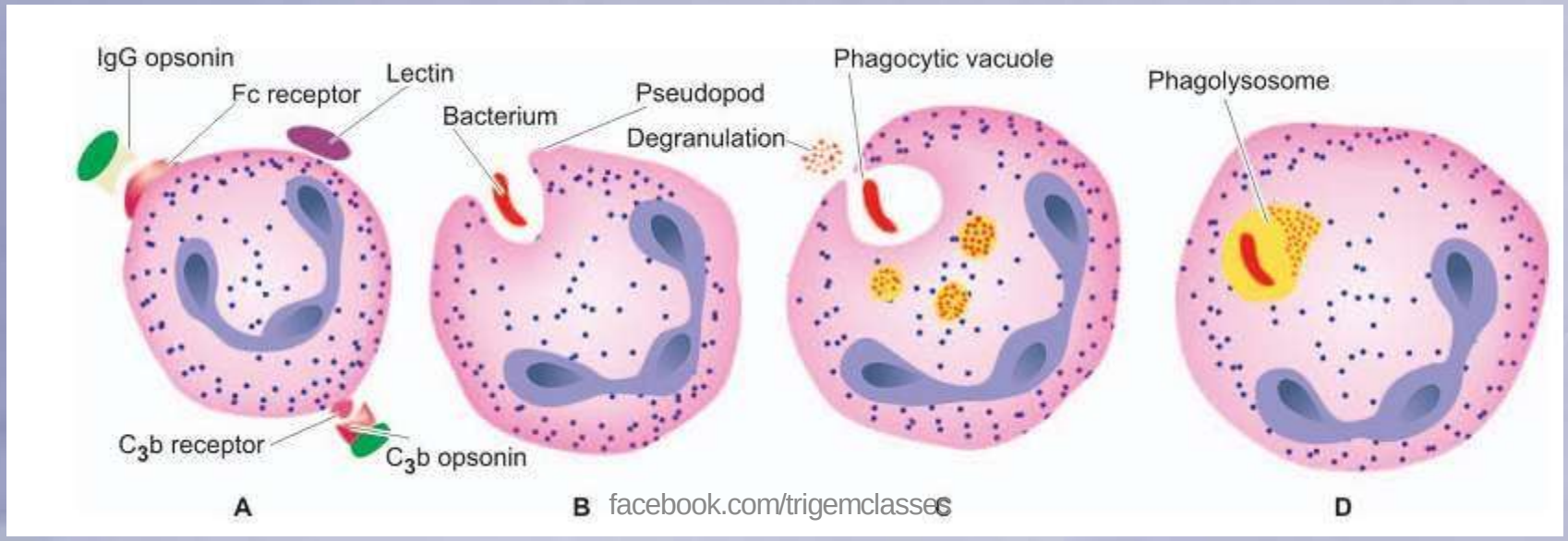
Engulfment

- Formation of cytoplasmic pseudopods around the particle due to activation of actin filaments around cell wall.
- Eventually plasma membrane gets lysed and fuses with nearby lysosomes – phagolysosome.



KILLING AND DEGRADATION

- Killing of MCO take place by Antibacterial substances further degraded by hydrolytic enzymes
- Sometimes this process fails to kill and degrade some bacteria like tubercle bacilli.



Disposal of microorganisms

- **Intracellular mechanisms**
  - Oxidative bactericidal mechanism by **oxygen free radicals**
    - MPO-dependent
    - MPO-independent
  - Oxidative bactericidal mechanism by **lysosomal granules**
  - Non-oxidative bactericidal mechanism
- **Extracellular mechanisms**
  - Granules
  - Immune mechanisms

INTRACELLULAR MECHANISMS

- Kill microbes by oxidative mechanism and less often non-oxidative pathways
- **Oxidative bactericidal mechanism by oxygen free radicals.**
  - production of reactive oxygen metabolites (O'_2 H_2O_2, OH', HOCl, HOI, HOBr)
  - activated phagocytic leucocytes requires the essential presence of NADPH oxidase
  - present in the cell membrane of phagosome reduces oxygen to superoxide ion (O'_2)

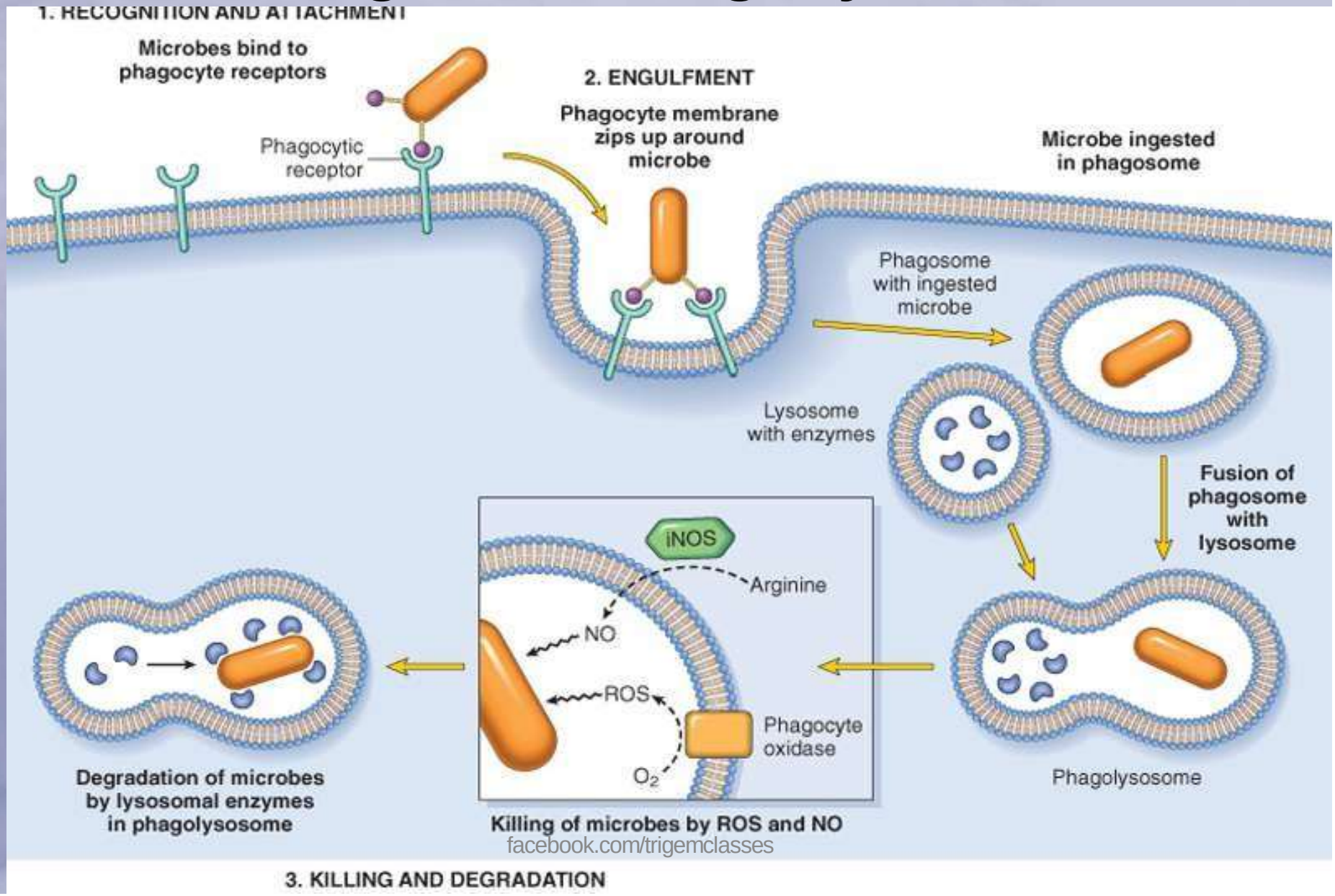
- Superoxide is subsequently converted into H_2O_2.
- Bactericidal activity is carried out either via enzyme myeloperoxidase (MPO) or MPO independent.
- **MPO dependent killings**
  - MPO acts on H_2O_2 in the presence of halides - form hypohalous acid (HOCl, HOI, HOBr)
- **MPO independent killings**
  - Mature macrophages lack the enzyme MPO.
  - bactericidal activity by producing OH– ions and superoxide singlet oxygen (O')
  - H_2O_2 in the presence of O'_2 (**Haber-Weiss reaction**) or in the presence of Fe++ (**Fenton reaction**)

- **Oxidative bactericidal mechanism by lysosomal granules**
  - preformed granule-stored products of neutrophils and macrophages.
  - secreted into the phagosome and the extracellular environment.
- **Non-oxidative bactericidal mechanism**
  - Some agents released from the granules of phagocytic cells do not require oxygen for bactericidal activity
    - ***Granules :*** cause lysis of within phagosome, ex: lysosomal hydrolases, permeability increasing factors, cationic proteins (defensins), lipases, ptoteases, DNAases.
    - ***Nitric oxide :*** reactive free radicals similar to oxygen free radicals
      - potent mechanism of microbial killing
      - produced by endothelial cells as well as by activated macrophages

EXTRACELLULAR MECHANISMS

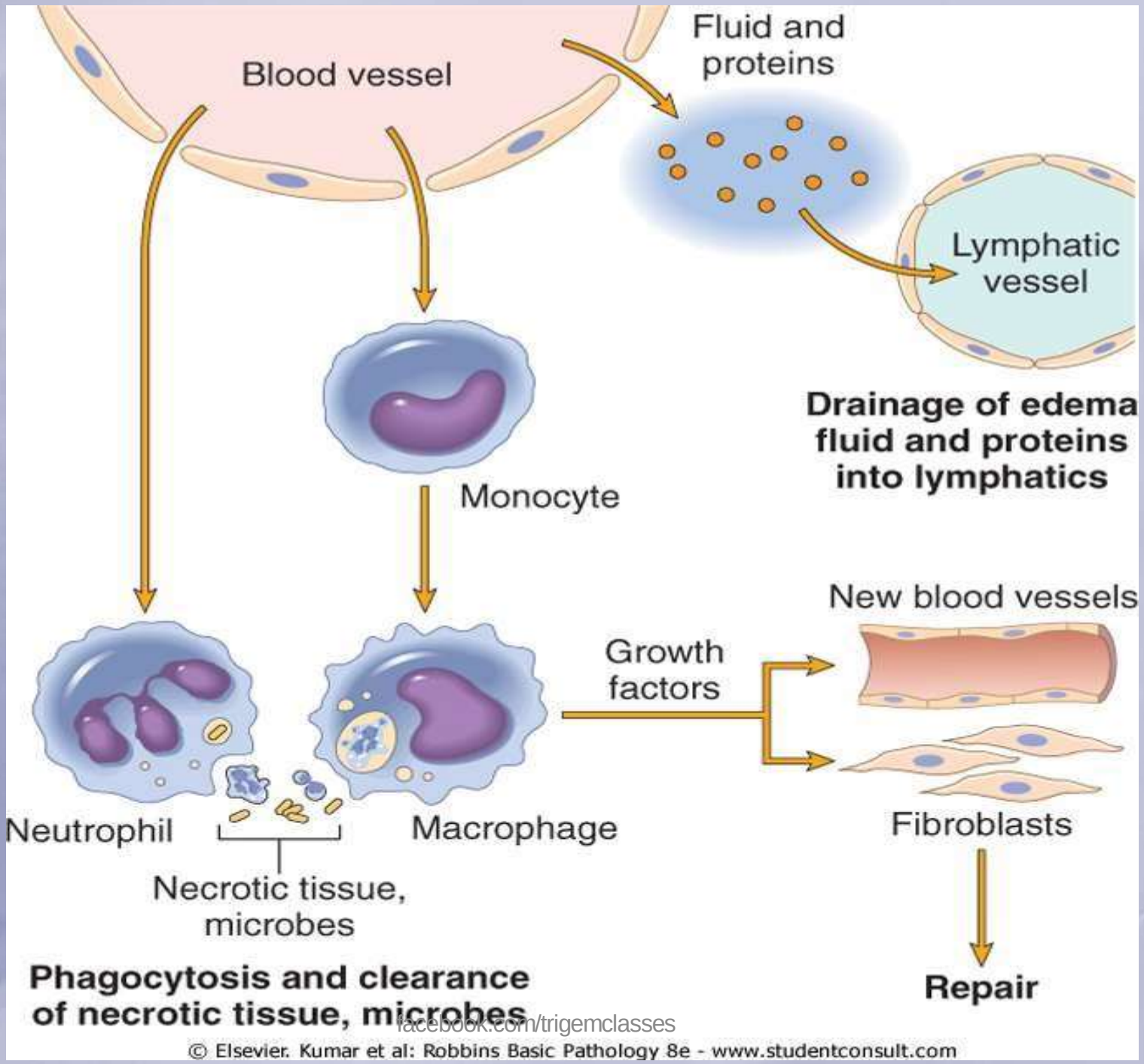
- **Granules**
  - Degranulation of macrophages and neutrophils
- **Immune mechanisms**
  - immune-mediated lysis of microbes
  - takes place outside the cells
  - by mechanisms of cytolysis, antibody-mediated lysis and by cell-mediated cytotoxicity

Stages of Phagocytosis



Outcomes of acute inflammation

1. resolution - restoration to normal, limited injury
   - chemical substances neutralization
   - normalization of vasc. permeability
   - apoptosis of inflammatory cells
   - lymphatic drainage
2. healing by scar
   - tissue destruction
   - fibrinous inflammtion
   - purulent infl. → abscess formation (pus, pyogenic membrane, resorption - pseudoxanthoma cells - weeks to months)
3. progression into chronic inflammation


Blood vessel
Fluid and proteins
Lymphatic vessel
Drainage of edema fluid and proteins into lymphatics
Monocyte
New blood vessels
Growth factors
Neutrophil
Macrophage
Fibroblasts
Necrotic tissue, microbes
Phagocytosis and clearance of necrotic tissue, microbes
Repair
facebook.com/trigemclasses
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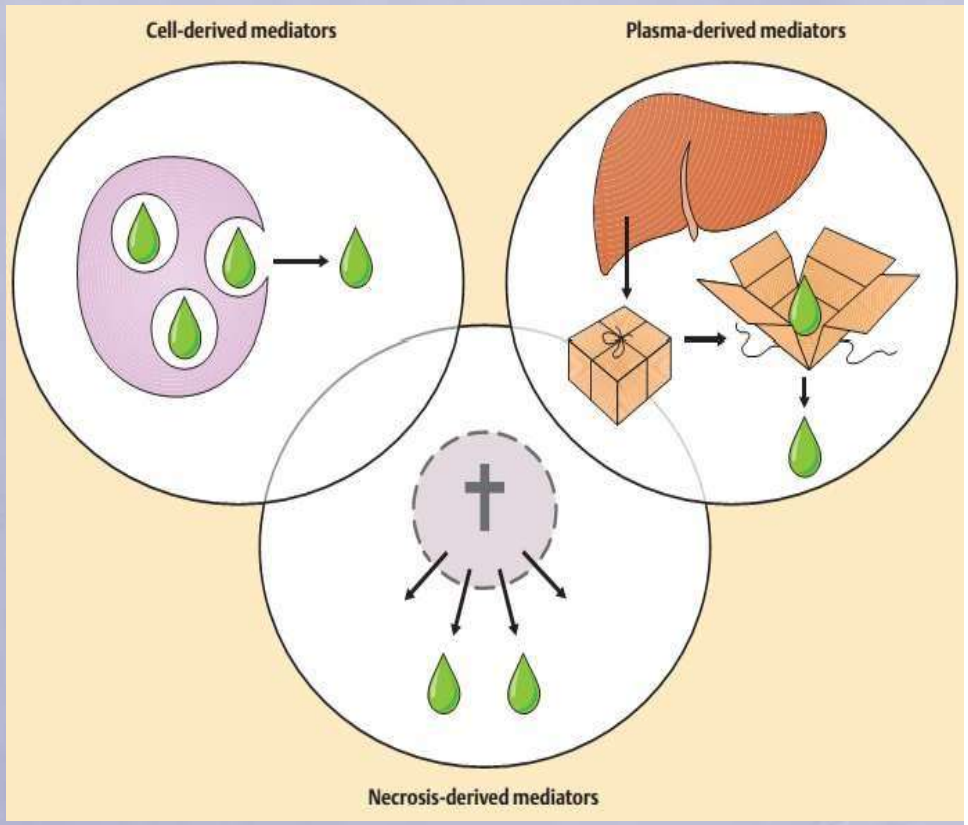
Clinical Examples of Leukocyte-Induced Injury: **Inflammatory Disorders**

Disorders	Cells and Molecules Involved in Injury
Acute	
Acute respiratory distress syndrome	Neutrophils
Acute transplant rejection	Lymphocytes; antibodies and complement
Asthma	Eosinophils; IgE antibodies
Glomerulonephritis	Antibodies and complement; neutrophils, monocytes
Septic shock	Cytokines
Vasculitis	Antibodies and complement; neutrophils
Chronic	
Arthritis	Lymphocytes, macrophages; antibodies
Asthma	Eosinophils, other leukocytes; IgE antibodies
Atherosclerosis	Macrophages; lymphocytes?
Chronic transplant rejection	Lymphocytes; cytokines
Pulmonary fibrosis	Macrophages; fibroblasts

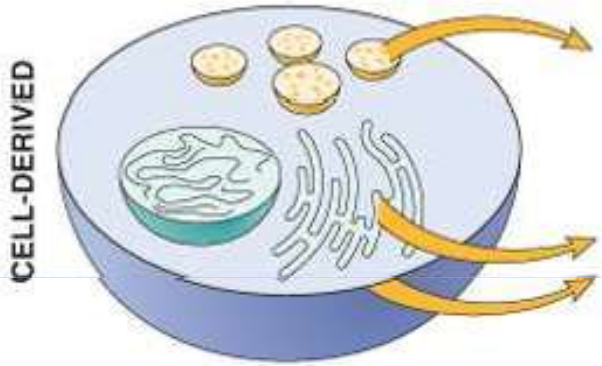
Chemical Mediators of Inflammation

Chemical Mediators of Inflammation

- Chemical mediators that are responsible for vascular and cellular events.
- Knowledge of this mediators – basis of anti-inflammatory drugs.
- It may either of two types,
  - **Cell Derived** - produced locally by cells at the site of inflammation
  - **Plasma derived** – mainly from liver
- Some mediators are derived from Necrotic cells

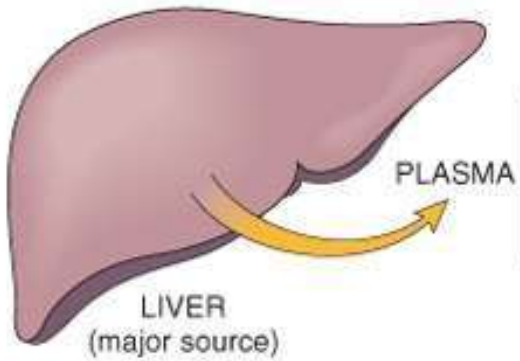


Chemical Mediators of Inflammation



CELL-DERIVED

PLASMA PROTEIN-DERIVED



	MEDIATORS	SOURCE
Preformed mediators in secretory granules	Histamine	Mast cells, basophils, platelets
	Serotonin	Platelets
Newly synthesized	Prostaglandins	All leukocytes, mast cells
	Leukotrienes	All leukocytes, mast cells
	Platelet-activating factor	All leukocytes, EC
	Reactive oxygen species	All leukocytes
	Nitric oxide	Macrophages, EC
	Cytokines	Macrophages, lymphocytes, EC, mast cells
	Neuropeptides	Leukocytes, nerve fibers
Complement activation	C3a (anaphylotoxins)	
	C5a (anaphylotoxins)	
	C3b	
	C5b-9 (membrane attack complex)	
Factor XII (Hageman factor) activation	Kinin system (bradykinin)	
	Coagulation / fibrinolysis system	

- Induce their effects by binding to specific receptors on **target cells -** it may be one or a very few targets, or multiple
- Some may have direct enzymatic and/or toxic activities. Ex: **lysosomal proteases**
- Some may stimulate target cells to release **secondary effector molecules**
- Control the response and tightly regulated
  - amplify a particular response
  - opposing effects
- Once activated and released from the cell, mediators either
  - quickly decay. Ex**: arachidonic acid metabolites**
  - inactivated by enzymes ex: **kininase inactivates bradykinin**
  - eliminated Ex: **antioxidants scavenge toxic oxygen metabolites**
  - Inhibited. **Complement-inhibitory proteins**

Cell-derived mediators

- Sequestered in intracellular granules
  - Rapidly secreted upon cellular activation. Ex: **histamine** in mast cells
  - synthesized from beginning in response to a stimulus. Ex: **Prostaglandins and cytokines**
- Tissue macrophages, mast cells, and endothelial cells – capable of producing different mediators.
- Various cell derived mediators
  1. Vasoactive amines
  2. Arachidonic acid metabolites
  3. Lysosomal component
  4. Platelet activating factors (PAF)
  5. Cytokines
  6. Reactive Oxygen Species (ROS) and nitrogen oxide (NO)
  7. Neuropeptides

Vasoactive Amines

- Stored as preformed molecules in **mast cells** or early inflammatory cells.
- **Histamine**
  - many cell types, particularly **mast cells** adjacent to vessels, circulating **basophils** and **platelets**
  - variety of stimuli
    - physical injury
    - immune reactions involving binding of IgE antibodies to Fc receptors on mast cells
    - C3a and C5a fragments of complement – ***anaphylatoxins***
    - Leukocyte-derived histamine-releasing proteins
    - Neuropeptides e.g., **substance P**
    - Certain cytokines e.g., **IL-1** and **IL-8**
  - arteriolar dilation & increased vascular permeability : **endothelial contraction** and **interendothelial gaps**
  - itching and pain
  - inactivated by histaminase

- **Serotonin**
  - 5-hydroxytryptamine
  - preformed vasoactive mediator - effects similar to those of histamine but less potent
  - Released from **platelet** dense body granules during platelet aggregation

ARACHIDONIC ACID (AA) METABOLITES

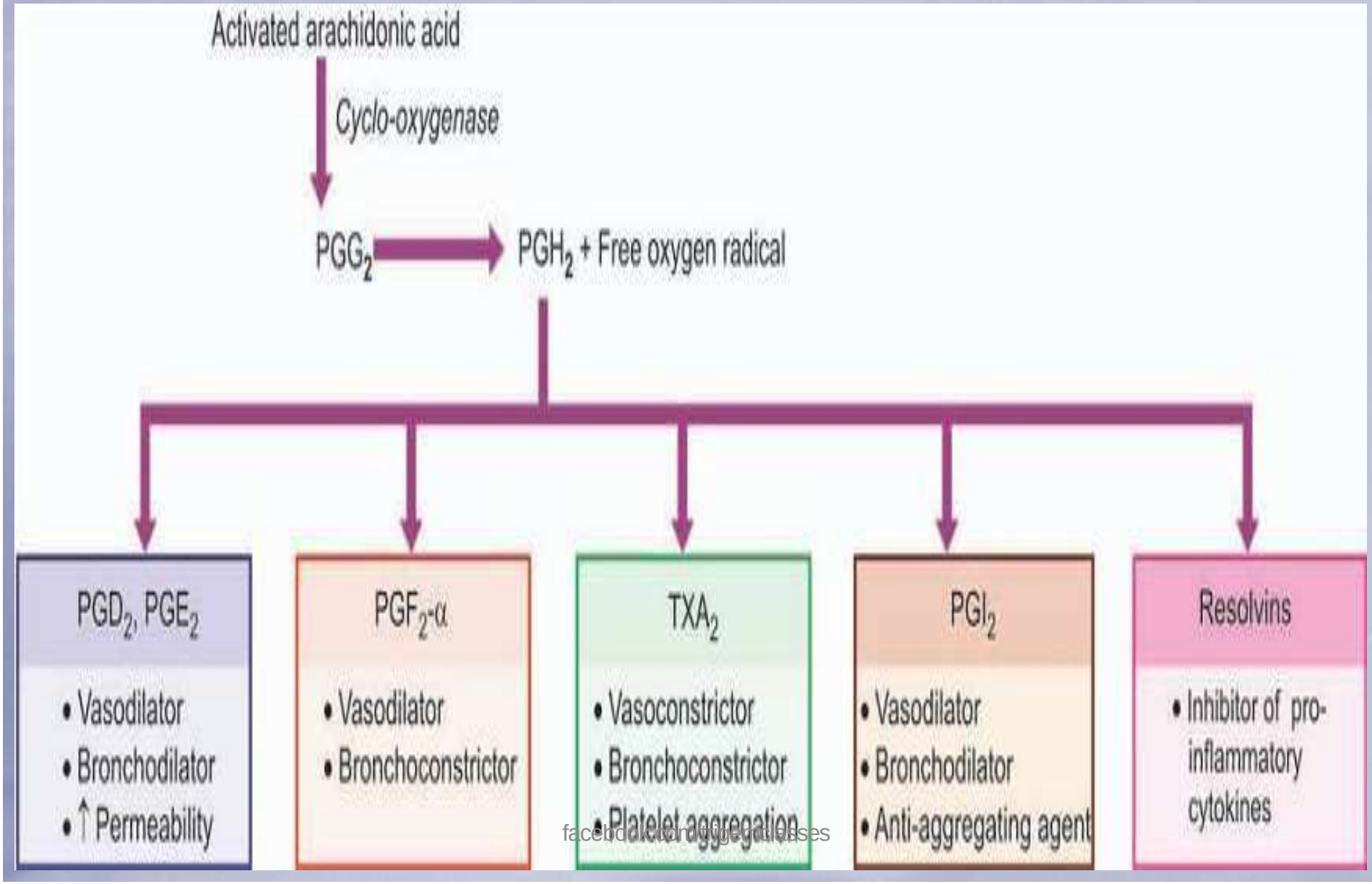
- Also known as *eicosanoids*.
- Variety of biologic processes, including inflammation and hemostasis - virtually every step of inflammation.
- short-range hormones that act locally at the site of generation and then decay spontaneously or are enzymatically destroyed
- Derived from : Leukocytes, mast cells, endothelial cells, and platelets
- Dietary linoleic acid

- Component of cell membrane phospholipids.
- AA is released from these phospholipids via cellular phospholipases
  - that have been activated by mechanical, chemical, or physical stimuli, or by inflammatory mediators such as C5a.
- Metabolism proceeds along either of this two major enzymatic pathways
  - ***Cyclooxygenase*** **:** prostaglandins and thromboxanes - **AUTOCOIDS**
  - ***Lipoxygenase*** **:** leukotrienes and lipoxins

Cyclooxygenase Pathway

- **Cyclooxygenase -** a fatty acid enzyme present as COX-1 and COX-2,
- Metabolizes AA to following derivative
  - Prostaglandins (PGD2, PGE2 and PGF2-α)
  - Thromboxane A2 (TXA2)
  - Prostacyclin (PGI2)
  - Resolvins
- Major anti-inflammatory drugs act by inhibiting activity of the enzyme COX– NSAIDs & COX-2 inhibitors

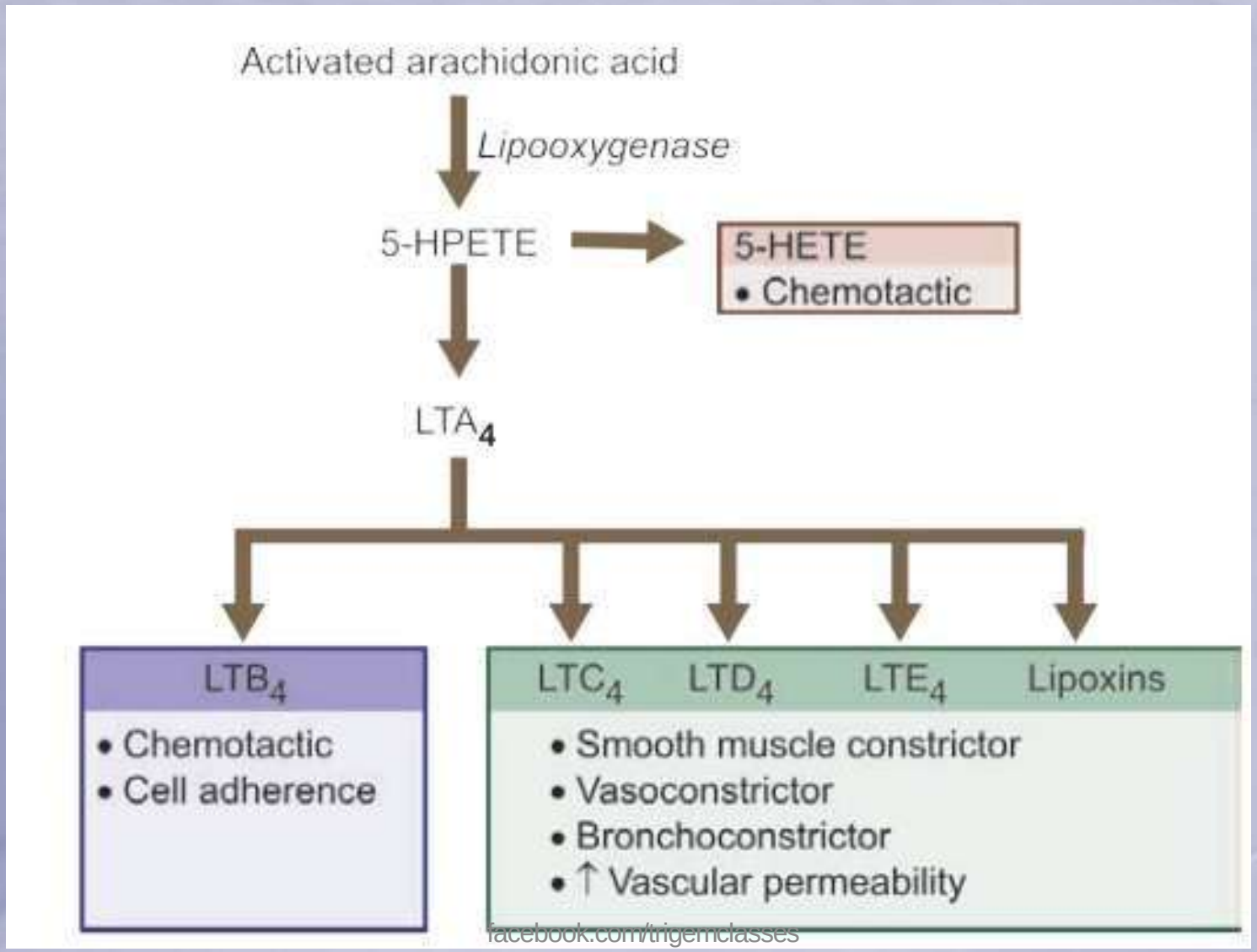
Cyclooxygenase Pathway

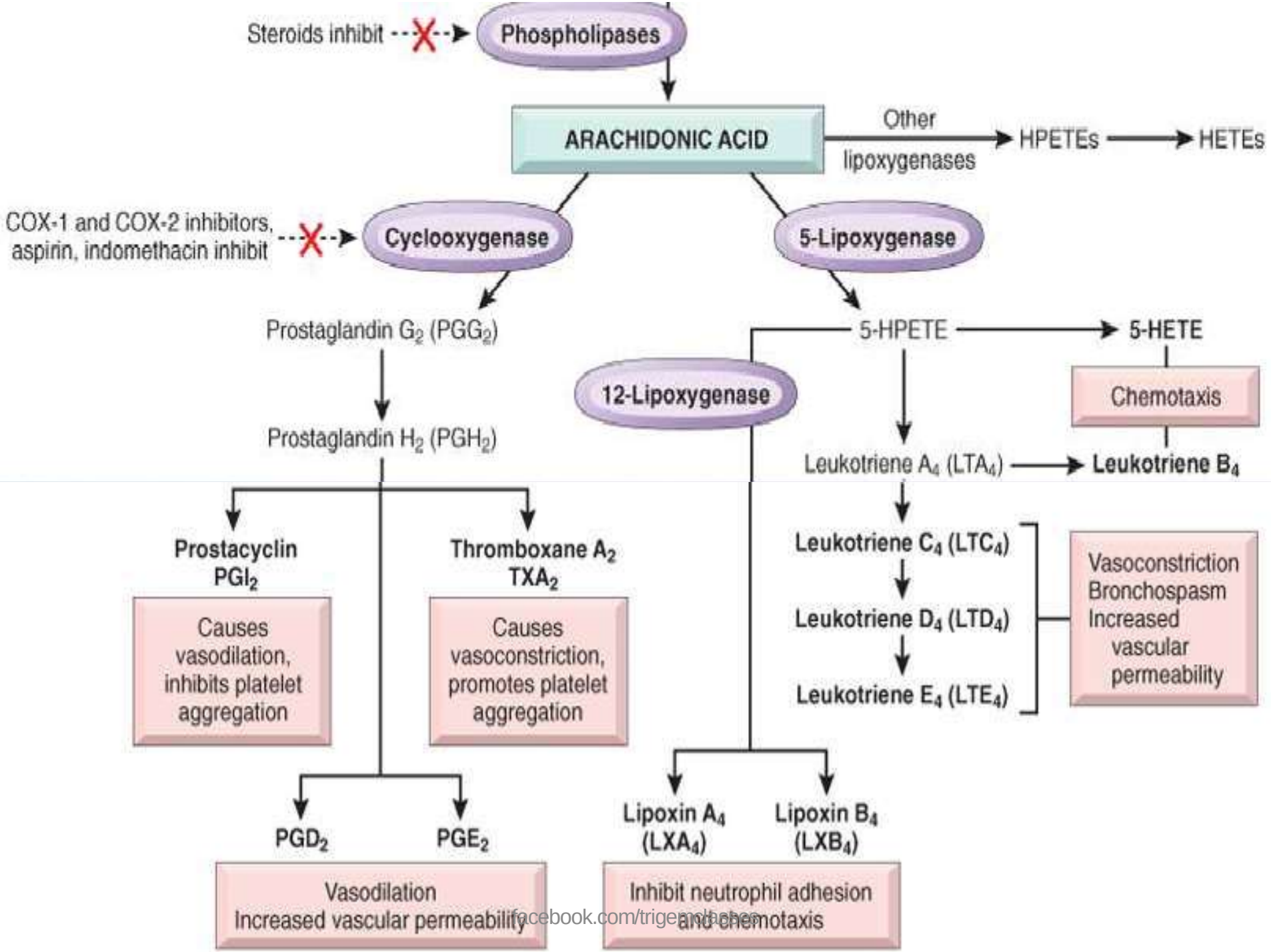


Lipoxygenase Pathway

- **Lipo-oxygenase** - predominant enzyme in neutrophils.
- Acts on activated AA to form hydroperoxy eicosatetraenoic acid (5-HPETE).
- Further peroxidation forms following metabolites
  - *5-HETE* (hydroxy compound) - intermediate
  - *Leukotrienes* (LT)
  - *Lipoxins* (LX)

Lipoxygenase Pathway





LYSOSOMAL COMPONENTS

- Inflammatory cells like neutrophils and monocytes– lysosomal granules. Its of 2 types:
- **Granules of neutrophils**
  - **Primary or azurophil** : myeloperoxidase, acid hydrolases, acid phosphatase, lysozyme, defensin (cationic protein), phospholipase, cathepsin G, elastase, and protease
  - **Secondary or specific**: alkaline phosphatase, lactoferrin, gelatinase, collagenase, lysozyme, vitamin-B12 binding proteins, plasminogen activator
  - **Tertiary**: gelatinase and acid hydrolases
- **Granules of monocytes and tissue macrophages**
  - acid proteases, collagenase, elastase and plasminogen activator
  - more active in chronic inflammation

PLATELET ACTIVATING FACTOR (PAF)

- **Phospholipid** (membrane) -derived mediator with a broad spectrum of inflammatory effects.
- Membrane of neutrophils, monocytes, basophils, endothelial cells, and platelets (and other cells) by the action of **phospholipase A_2.**
- Functions of PAF
  - Stimulating platelets,
  - vasoconstriction and bronchoconstriction
  - inducing **vasodilation and increased vascular permeability**
    - low conc. 100-1000 times potent than HISTAMINE
  - enhanced **leukocyte adhesion**, **chemotaxis, leukocyte degranulation, and the oxidative burst**
  - **stimulates** the synthesis of **other mediators**, particularly eicosanoids

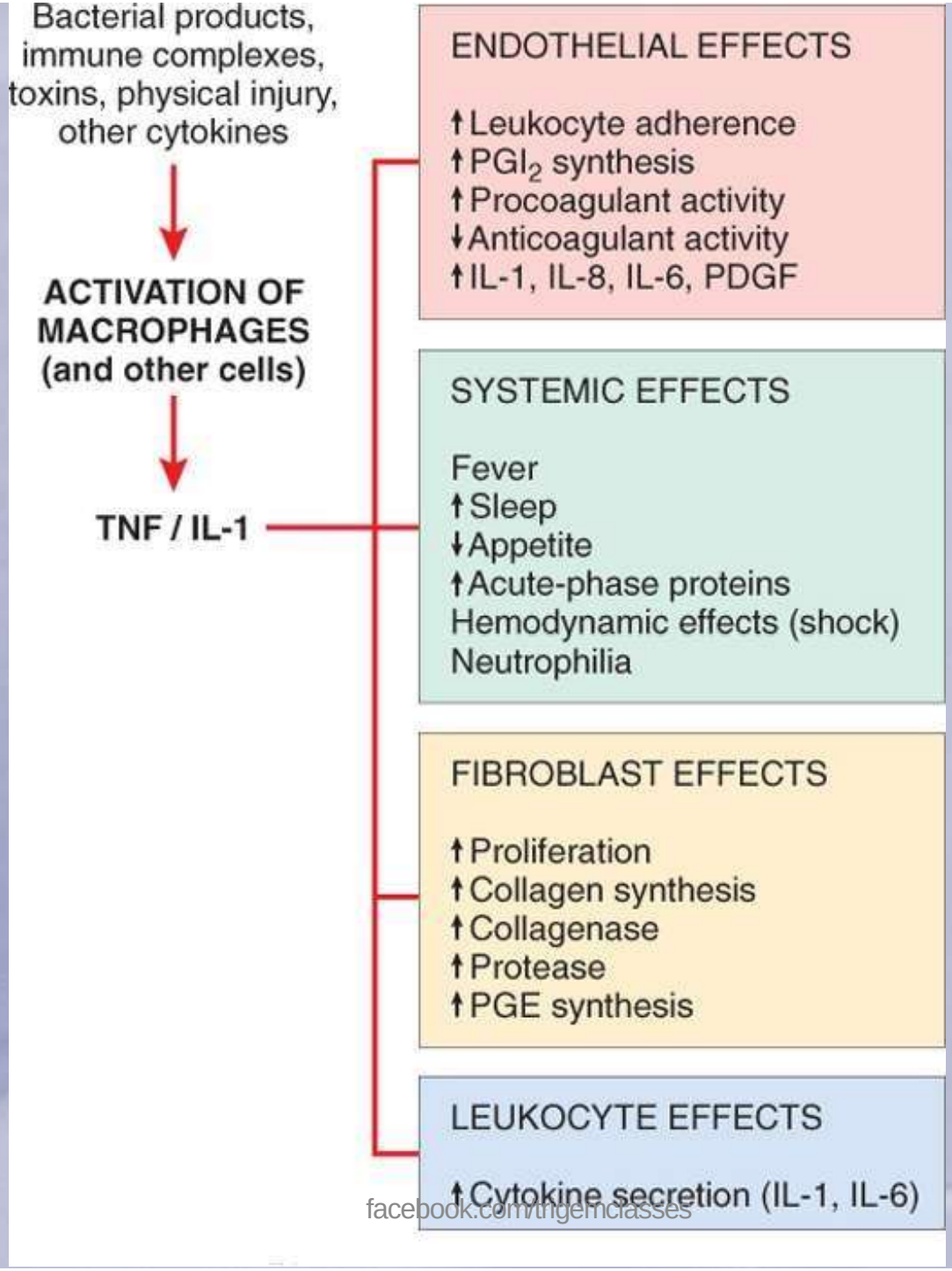
CYTOKINES

- polypeptide substances produced by activated **lymphocytes *(lymphokines)*** and activated **monocytes *(monokines).***
- Major cytokines in acute inflammation
  - TNF and IL-1,
  - Chemokines - a group of chemoattractant cytokines
- Chronic inflammation : interferon-γ (IFN-γ) and IL-12

Tumor Necrosis Factor and Interleukin-1

- Produced by activated macrophages, as well as mast cells, endothelial cells, and some other cell types
- Stimulated by microbial products, such as bacterial endotoxin, immune complexes, and products of T lymphocytes
- Principal role in inflammation - **endothelial activation**
  - expression of adhesion molecules on endothelial cells- increased leukocyte binding and recruitment,
  - enhance the production of additional cytokines (notably chemokines) and eicosanoids

- **TNF** – increases **thrombogenicity** of endothelium and causes **aggregation and activation** of neutrophils
- **IL-1** - fibroblasts, resulting in **increased proliferation and production** of extracellular matrix
- May enter the circulation - **systemic acute-phase reaction**
  - Fever & lethargy
  - hepatic synthesis of various acute-phase proteins,
  - metabolic wasting (*cachexia*),
  - neutrophil release into the circulation,
  - release of adrenocorticotropic hormone (inducing corticosteroid synthesis and release).



Chemokine

- act primarily as chemoattractants for different subsets of leukocytes
- Also activate leukocytes
- Chemokines are classified into four groups out of which 2 are the major group
  - CXC chemokines: IL-8
  - CC chemokines : MCP-1

Reactive Oxygen Species

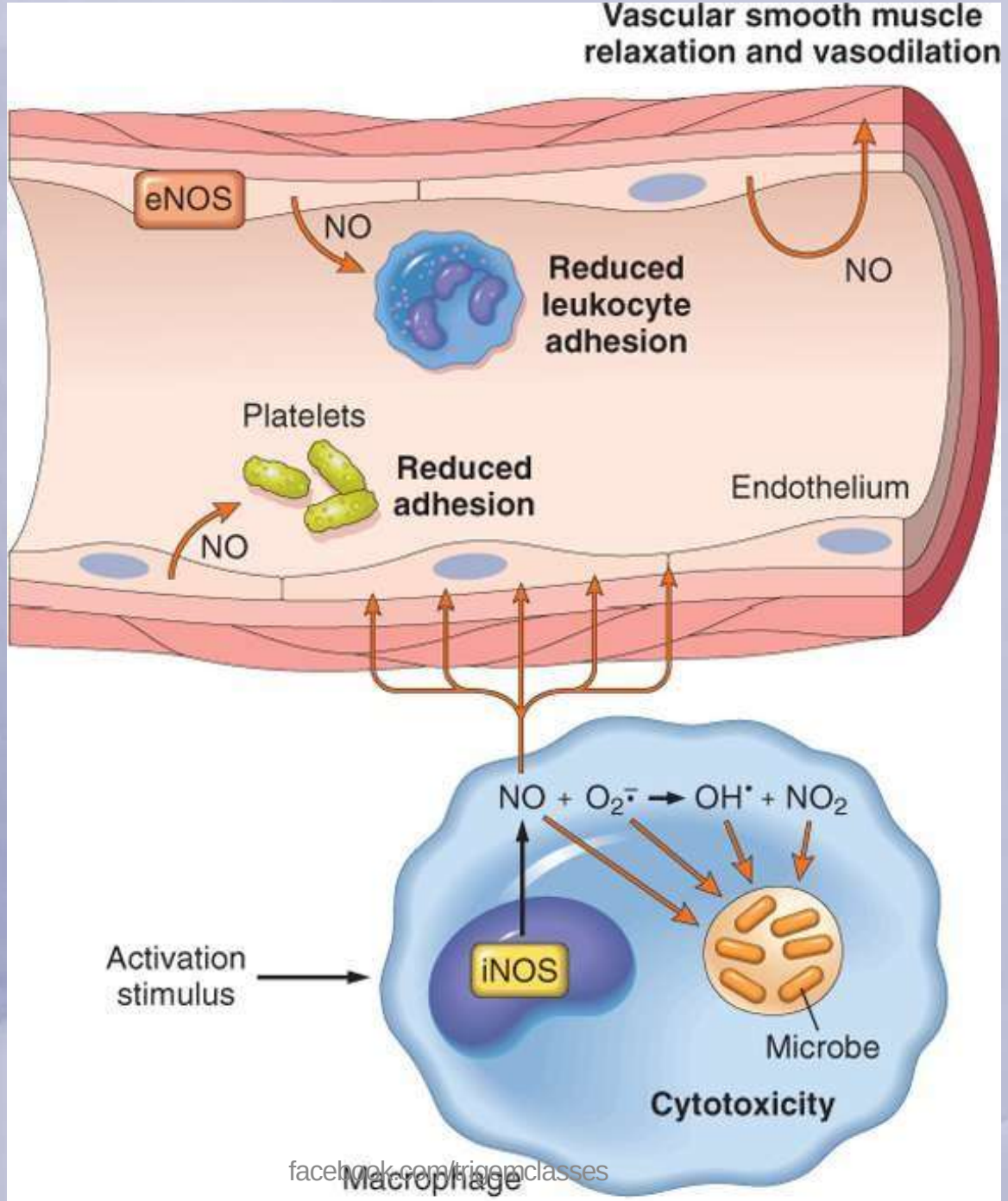
- synthesized via the NADPH oxidase – from neutrophils and macrophages
- by microbes, immune complexes, cytokines, and a variety of other inflammatory stimuli
- Within lysosomes - destroy phagocytosed microbes and necrotic cells
- **low levels**
  - increase chemokine, cytokine, and adhesion molecule expression
  - amplifying the cascade of inflammatory mediators

- High levels - tissue injury by several mechanisms
  1. endothelial damage, with thrombosis and increased permeability;
  2. protease activation and antiprotease inactivation, with a net increase in breakdown of the ECM;
  3. direct injury to other cell types
- Various antioxidant - protective mechanisms against this ROS
  – catalase, superoxide dismutase, and glutathione

Nitric Oxide

- short-lived, soluble, free-radical gas
- formed by activated macrophages during the oxidation of arginine by the action of enzyme, NO synthase (NOS).
- Three isoforms of NOS
  - Type I (nNOS) – neuronal, no role in i/m
  - Type II (iNOS) – induced by chemical mediators, macrophages and endothelial cells
  - Type III (eNOS) - primarily (but not exclusively) within endothelium

- NO plays many roles in inflammation including
  - relaxation of vascular smooth muscle (vasodilation),
  - antagonism of all stages of platelet activation (adhesion, aggregation, and degranulation)
  - reduction of leukocyte recruitment at inflammatory sites
  - action as a microbicidal (cytotoxic) agent (with or without superoxide radicals) in activated macrophages.



Neuropeptides

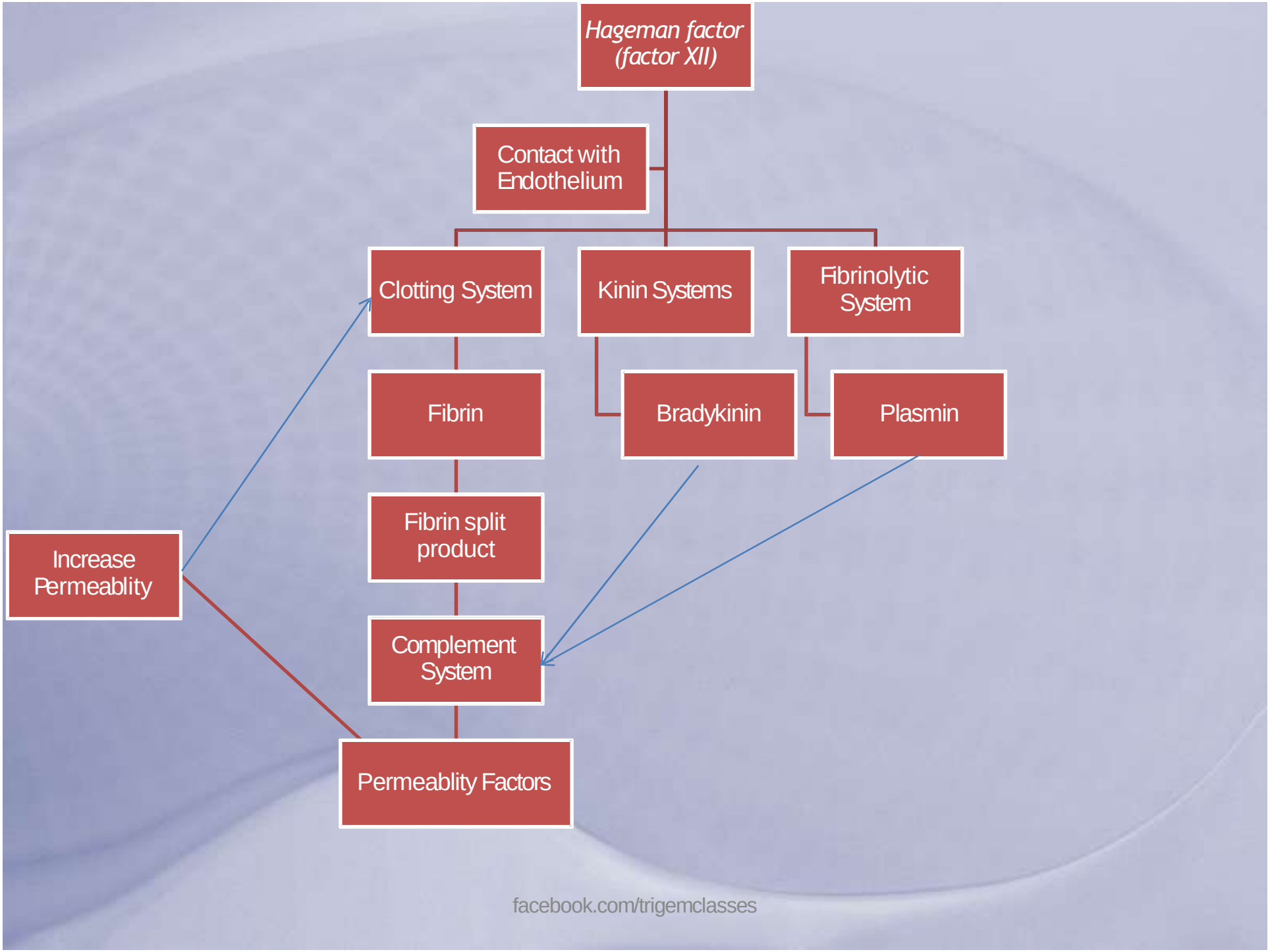
- initiate inflammatory responses
- small proteins, such as *substance P*
- transmit pain signals, regulate vessel tone, and modulate vascular permeability
- prominent in the lung and gastrointestinal tract

Plasma-protein-derived mediators

- Circulating proteins of three interrelated systems- the **complement, kinin, clotting and fibrinolytic** systems
- **Inactive precursors** that are activated at the site of inflammation – action of enzyme.
- Each of these systems has its **inhibitors and accelerators** in plasma - **negative and positive** feedback mechanisms respectively.
- **Hageman factor (factor XII)** of clotting system - a key role in interactions of the four systems.

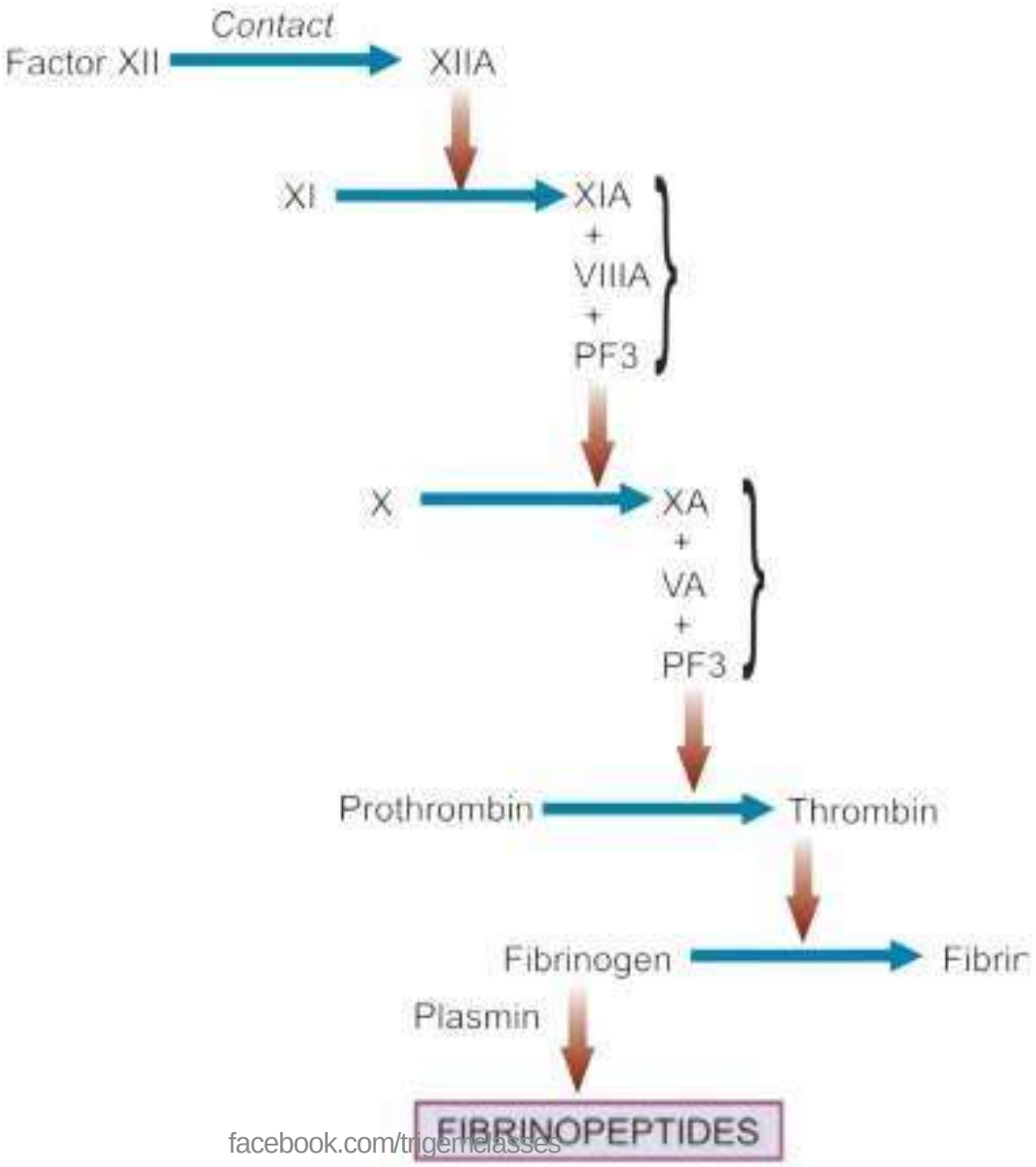
Hageman factor (factor XII)

- protein synthesized by the liver.
- initiates four systems involved in the inflammatory response
  - **Kinin system** - vasoactive kinins;
  - **Clotting system** - inducing the activation of thrombin, fibrinopeptides, and factor X,
  - **Fibrinolytic system** - plasmin and inactivating thrombin;
  - **Complement system** - anaphylatoxins C3a and C5a
- Gets activated - collagen, basement membrane, or activated platelets.



Clotting system

- factor XIIa-driven proteolytic cascade leads to activation of **thrombin.**
- Functions of thrombin
  - cleaves circulating soluble **fibrinogen** to generate an insoluble ***fibrin clot***
    - ***Fibrinopeptides*** - increase vascular permeability & chemotactic for leukocytes.
  - In i/m, Binding of thrombin to the receptors on endothelial cells - activation and enhanced **leukocyte adhesion**

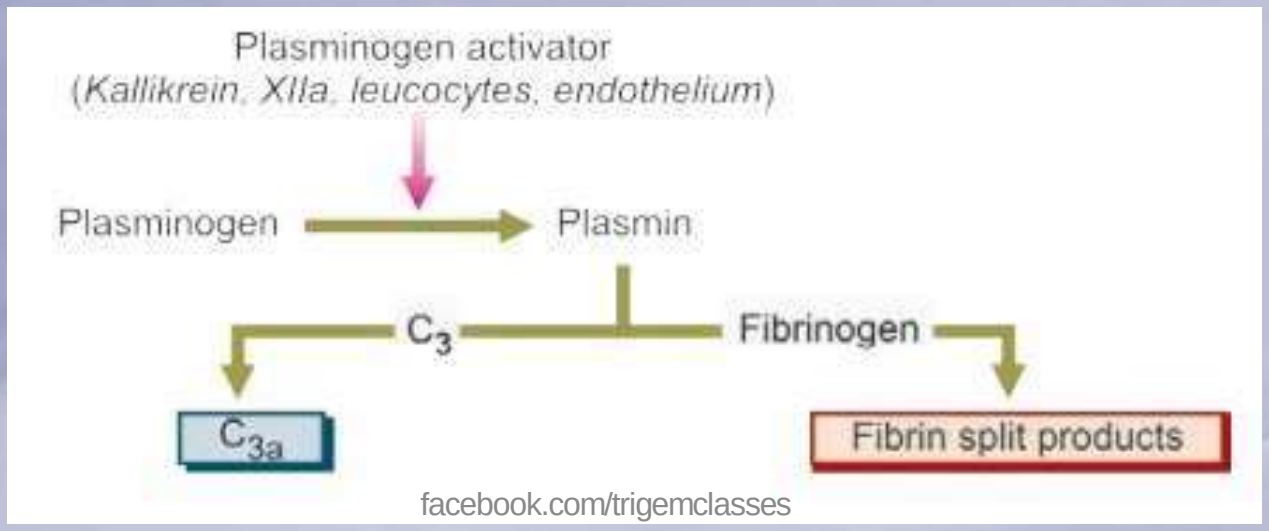


Fibrinolytic System

- Hageman factor induces clotting system and fibrinolytic system **concurrently** – control over the 2 system
- Limit clotting by cleaving fibrin - **solubilizing** the fibrin clot.
- In absence of this – even **minor injury** could lead to coagulation of **entire vasculature**.
- ***Plasminogen activator*** **-** released from endothelium, leukocytes, and other tissues) and **kallikrein** from kinin system
  - Cleave *plasminogen,* a plasma protein – further forms **PLASMIN**

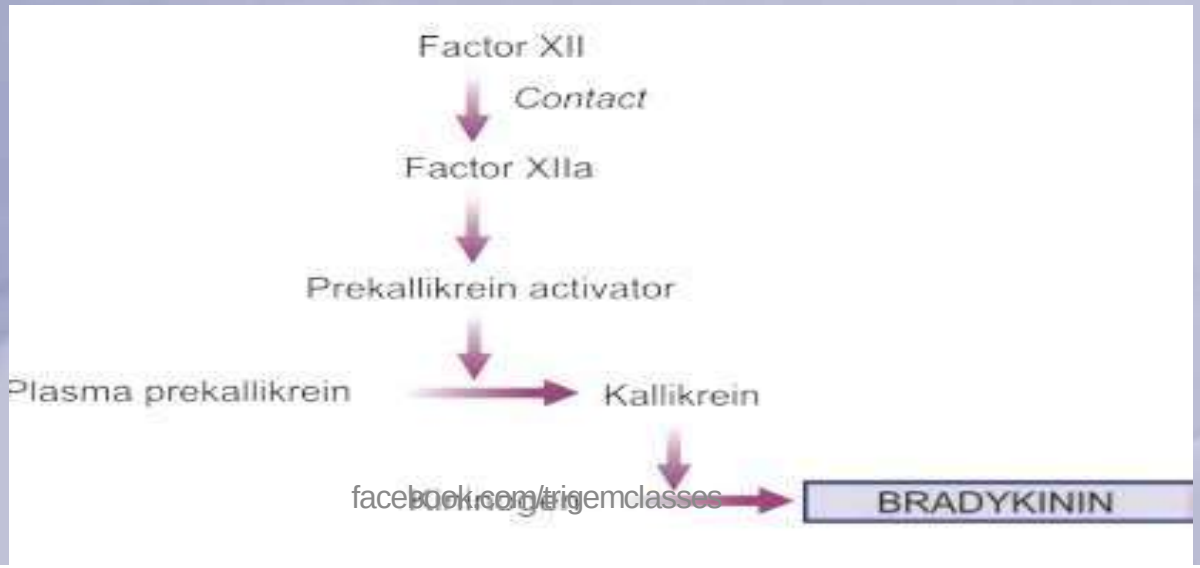
Fibrinolytic System : Plasmin

- Multifunctional protease that cleaves fibrin.
- **Cleaves** the C3 complement protein - production of C3a
- **Activate Hageman factor -** amplify the entire set of responses



Kinin System

- **Haegman Factor** activates **Prekallikrein activator** - acts on plasma **prekallikrein** to give kallikrein.
- **Kallikrein** acts on **kininogen** (HMW) to give **Bradykinin**.
- Bradykinin are **short-lived** - rapidly degraded by **kininases** present in plasma and tissues



Kinin System : Bradykinin

- Slow contraction of smooth muscle
- Bradykinin acts in the early stage of i/m :
  - vasodilatation;
  - increased vascular permeability
  - pain

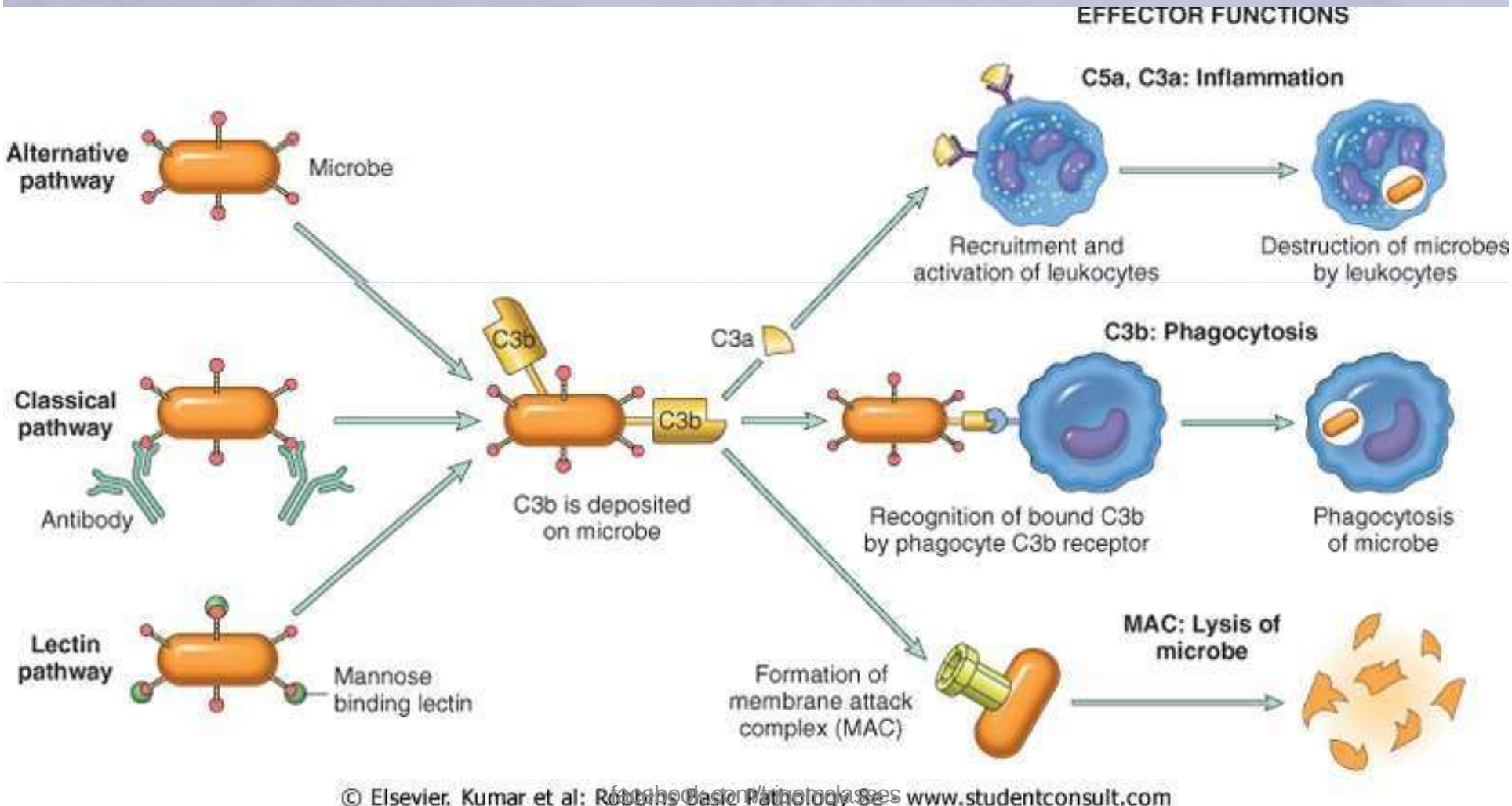
Complement System

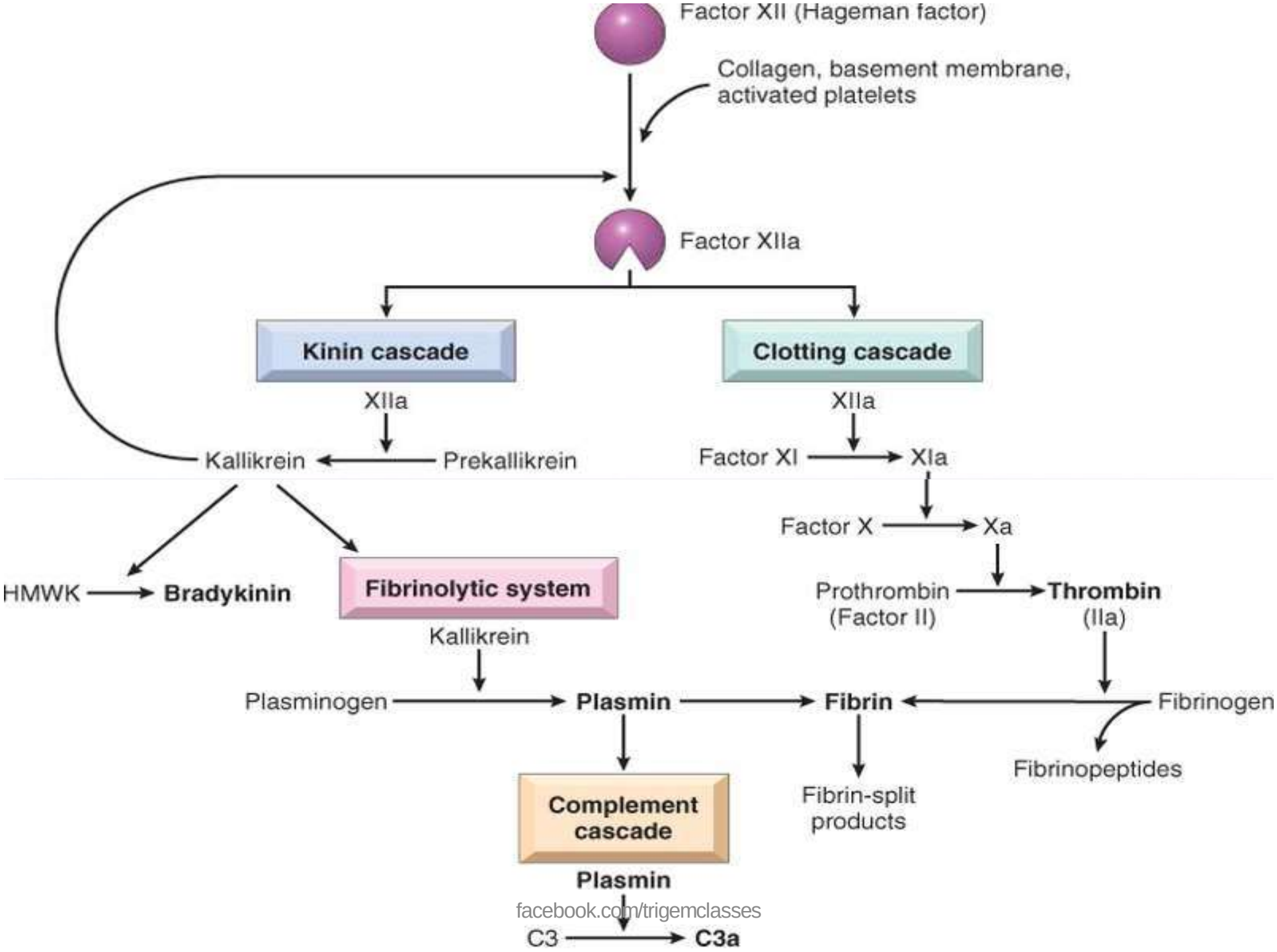
- Important role in host defense (immunity) and inflammation
- Consists of plasma proteins (C1 – C9) – activated at the sites of i/m
- Contribute to the inflammatory response by **increasing vascular permeability** and leukocyte chemotaxis.
- The activation of complement - tightly controlled by cell-associated and circulating ***regulatory proteins***
- **Inappropriate or excessive** complement activation (e.g., in antibody-mediated diseases) - serious tissue injury in a variety of **immunologic disorders**

- The critical step in the activation of biologically active complement products is the activation of the third component, C3 – C3a.
- This occurs in 3 steps :
  1. **Classical Pathway** : antigen-antibody complexes
  2. **Alternative pathway :** triggered by bacterial polysaccharides - microbial cell-wall components
  3. **Lectin pathway :** plasma lectin binds to mannose residues on microbes – activates early component of the classical pathway
- As C3 activated – further activation of other complement proteins takes place i.e C1 – C9

- The actions of activated complement system in inflammation are as under:
  - **C3a, C5a, C4a (anaphylatoxins)** - activate mast cells and basophils to release of histamine
  - **C3b** - an opsonin.
  - **C5a** - chemotactic for leucocytes.
  - **Membrane attack complex (MAC) (C5b-C9)** - a lipid dissolving agent and causes holes in the phospholipid membrane of the cell

Complement System





Vasodilation	Prostaglandins
	Nitric oxide
	Histamine
Increased vascular permeability	Histamine and serotonin C3a and C5a (by liberating vasoactive amines from mast cells, other cells) Bradykinin Leukotrienes C_4, D_4, E_4 PAF Substance P
Leukocyte recruitment and activation	TNF, IL-1 Chemokines C3a, C5a Leukotriene B_4 (Bacterial products, e.g., *N*-formyl methyl peptides)
Fever	IL-1, TNF
	Prostaglandins
Pain	Prostaglandins
	Bradykinin
	Neuropeptides
Tissue damage	Lysosomal enzymes of leukocytes
	Reactive oxygen species
	Nitric oxide

Chronic Inflammation

- Inflammation of prolonged duration (weeks to months to years) in which active inflammation, tissue injury, and healing proceed simultaneously.
- It involves mainly following events
  - Angiogenesis
  - Mononuclear cell infilterate - macrophages, lymphocytes, and plasma cells
  - Fibrosis - Scar

Causes of Chronic Inflammation

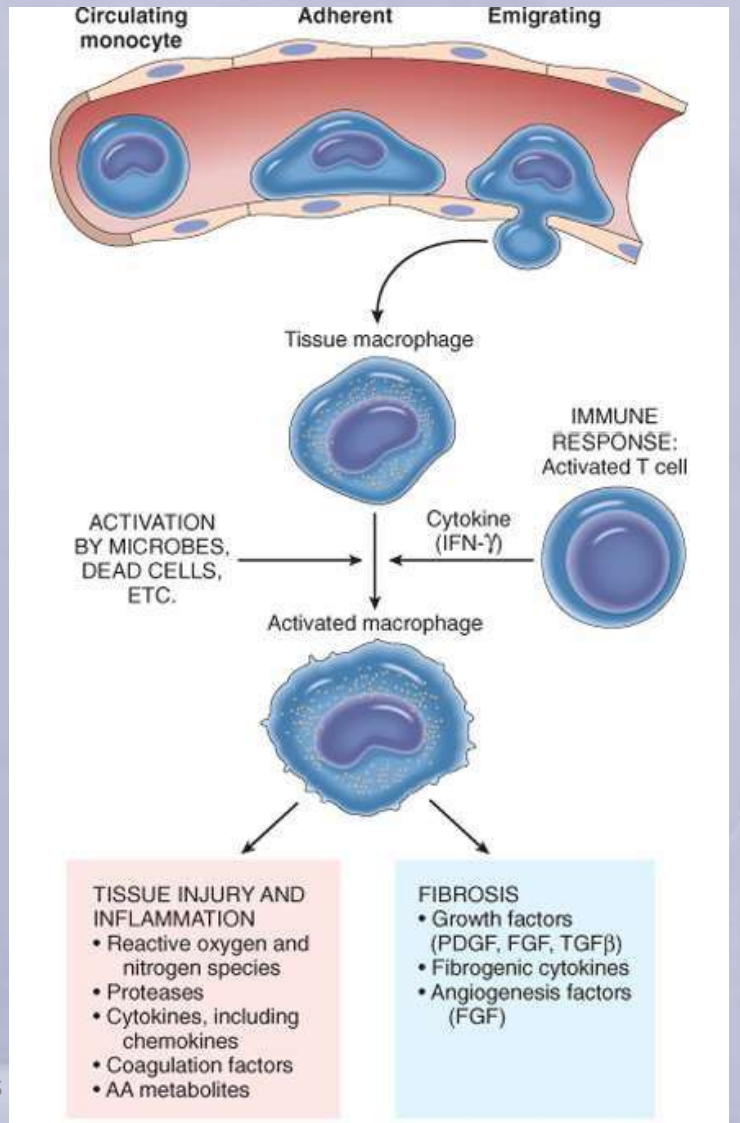
- **Following acute inflammation**
  - persistence of the injurious agent or because of interference with the normal process of healing
  - e.g. in **osteomyelitis, pneumonia** terminating in **lung abscess**
- **Recurrent attacks of acute inflammation**
  - repeated bouts of acute inflammation culminate in chronicity of the process
  - **Ex: R**ecurrent *urinary tract infection* - **chronic pyelonephritis**, Repeated acute infection of gall bladder - **chronic cholecystitis**
- **Chronic inflammation starting *de novo***
  - low pathogenicity is chronic from the beginning
  - Ex: infection with ***Mycobacterium tuberculosis, Treponema pallidum***

Chronic Inflammatory Cells and Mediators

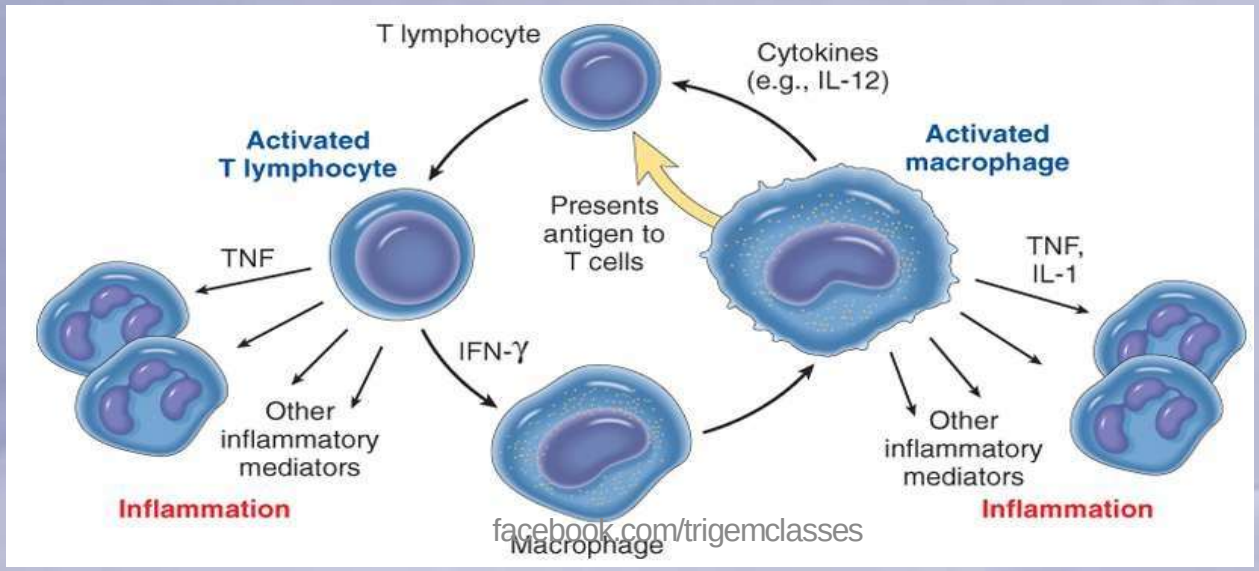
- Macrophages
- Lymphocytes,
- Plasma Cells,
- Eosinophils,
- Mast Cells

Macrophages

- Dominant cells of chronic inflammation
- Derived from circulating blood *monocytes*
- **Reticulo-endothelial system**
  - Also known as *Mononuclear-phagocyte system*.
  - Macrophage present in
    - liver - ***Kupffer cells***
    - spleen
    - lymph nodes - ***sinus histiocytes***
    - central nervous system - ***microglial cells***
    - lungs - ***alveolar macrophages***



- Tand Blymphocytes migrate - inflammatory sites – chemokines.
- Lymphocytes and macrophages interact in a bidirectional way
- important role in chronic inflammation



- inflammatory sites around **parasitic infections** or as part of **immune reactions mediated by IgE**
- Associated with *allergies*
- Induced by specific chemokines – eotaxin
- Granules contain major basic protein - highly charged cationic protein
  - toxic to parasites
  - also causes epithelial cell necrosis

- Sentinel (watch) cells widely distributed in connective tissues throughout the body
- Both acute and chronic inflammatory responses.
- Elaborate cytokines such as TNF and chemokines
- **atopic** individuals - individuals prone to allergic reactions
  - Mast cells Armed with IgE antibody
  - As the environmental antigens enters
  - It releases histamines and AA metabolites
  - ***anaphylactic shock***

- **Fever :** infectious form of inflammation
- **Anaemia :** accompanied by anaemia of varying degree
- **Leucocytosis :** leucocytosis but generally there is relative lymphocytosis in these cases.
- **ESR :** elevated
- **Amyloidosis :** develop secondary systemic (AA) amyloidosis.

- Also known as *acute-phase reaction*.
- Cytokines TNF, IL-1, and IL-6.
- The acute-phase response consists of several clinical and pathologic changes
  - Fever
  - Elevated plasma levels of **acute-phase proteins**
    - C-reactive protein (CRP),
    - Fibrinogen,
    - Serum amyloid A (SAA) protein
  - Leukocytosis
  - septic shock

- Especially when inflammation is caused by infection
- ***Pyrogens*** - Prostaglandin (PG) synthesis in the vascular and perivascular cells of the hypothalamus – NEUROTRANSMITTER- temp. reset.
- Lipopolysaccharide (LPS) from bacterial cell wall (**Exogenous Pyrogens**) – Leukocytes – cytokines like IL1 & TNF (**Endogenous Pyrogens**) – COX (AA-PG)