Pathophysiology-Inflammation

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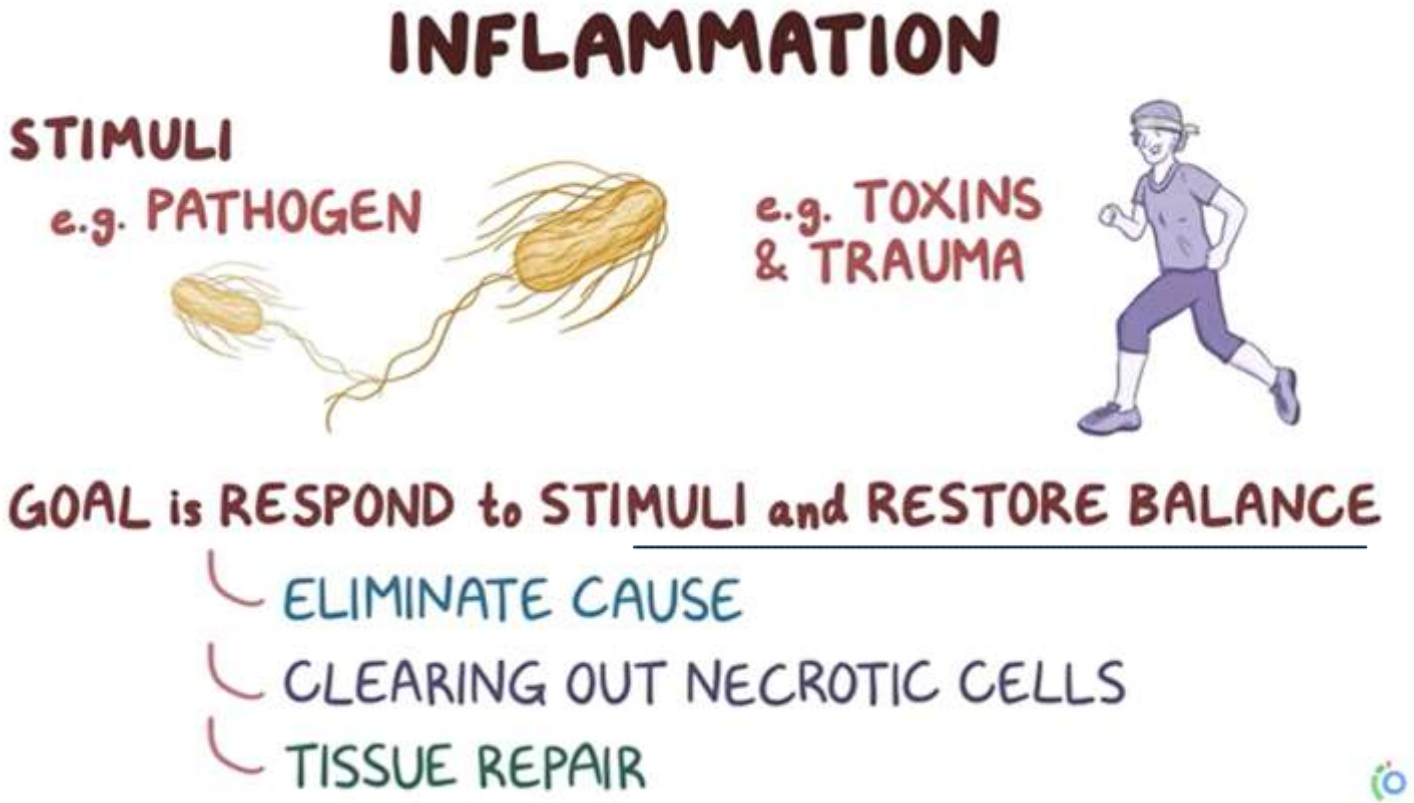
- **Inflammation** is a protective response of vascularized tissues to infections and tissue damage that brings cells and molecules of host defense from the circulation to the sites where they are needed, to eliminate the offending agents.



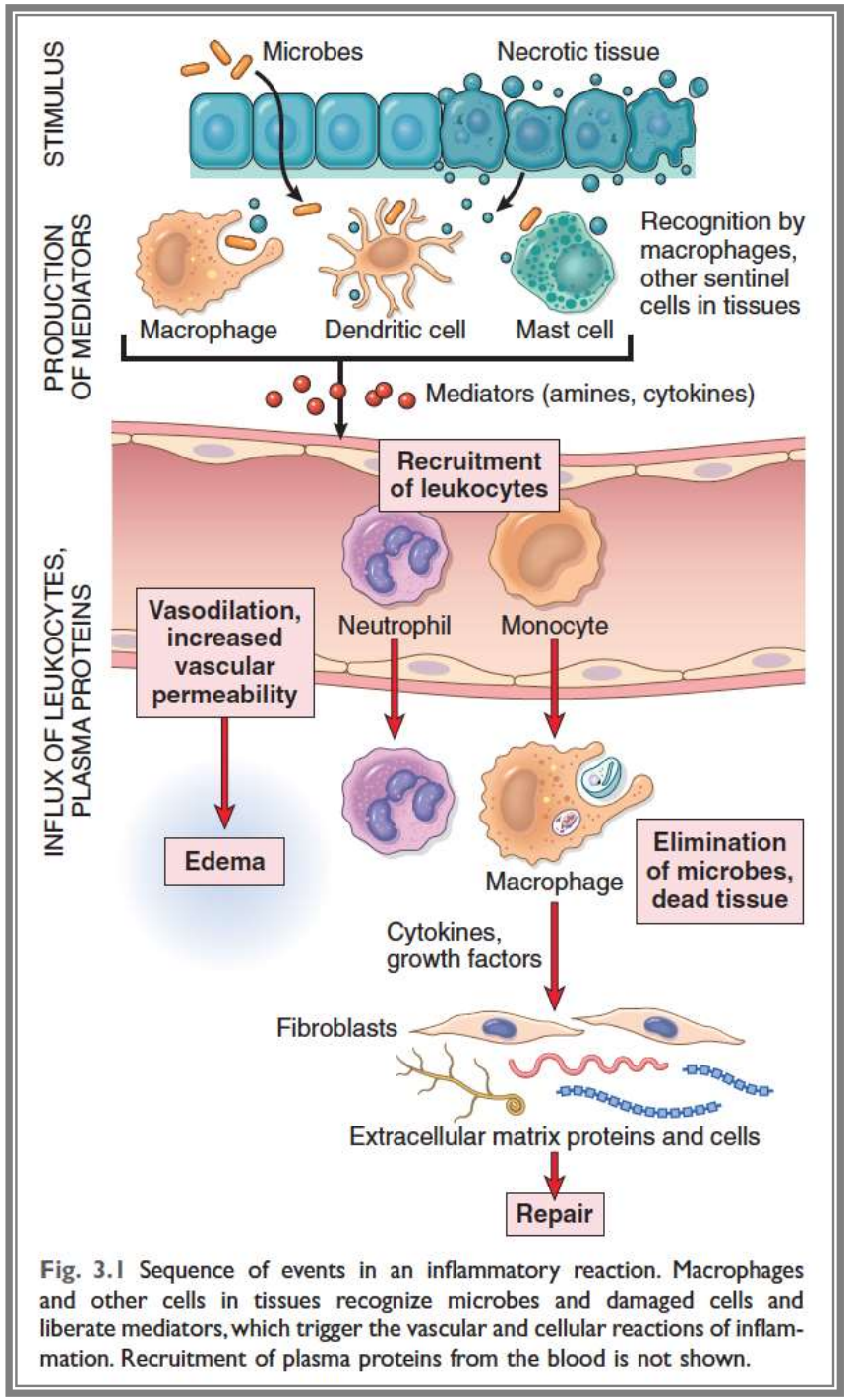


Fig. 3.1 Sequence of events in an inflammatory reaction. Macrophages and other cells in tissues recognize microbes and damaged cells and liberate mediators, which trigger the vascular and cellular reactions of inflammation. Recruitment of plasma proteins from the blood is not shown.

Causes of inflammation

Infections: (bacterial, viral, fungal, parasitic) are the ***most common*** medically important causes of inflammation.

Tissue necrosis: from any cause, including ischemia

Trauma: blunt & penetrating

Physical agents: thermal injuries-burns/frostbite; radiation

Chemicals: Agents as strong acids, alkalis

Foreign bodies: splinters, dirt, & sutures

Immune = hypersensitivity reactions: types I, II, III, & IV, against environmental substances or against self tissue

The typical inflammatory reaction develops through a series of sequential steps:

- **The offending agent, which is located in extravascular tissues**, is recognized by host cells and molecules.
- **Leukocytes and plasma proteins are recruited from the circulation to the site where the offending agent is located**.
- The leukocytes and proteins are activated and work together to destroy and eliminate the offending substance.
- The reaction is controlled and terminated.
- **The damaged tissue is repaired.**

LEUKOCYTES

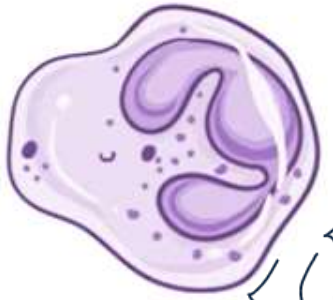
inflammatory mediators

بتحتوي على حبيبات عبارة عن

لاتحتوي على chemicles mediator

GRANULOCYTES

- NEUTROPHILS



- EOSINOPHILS

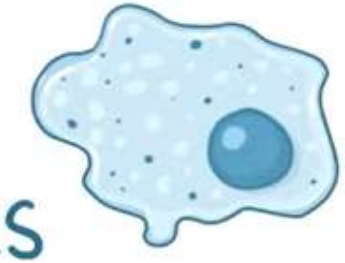
- BASOPHILS

- MAST CELLS

AGRANULOCYTES

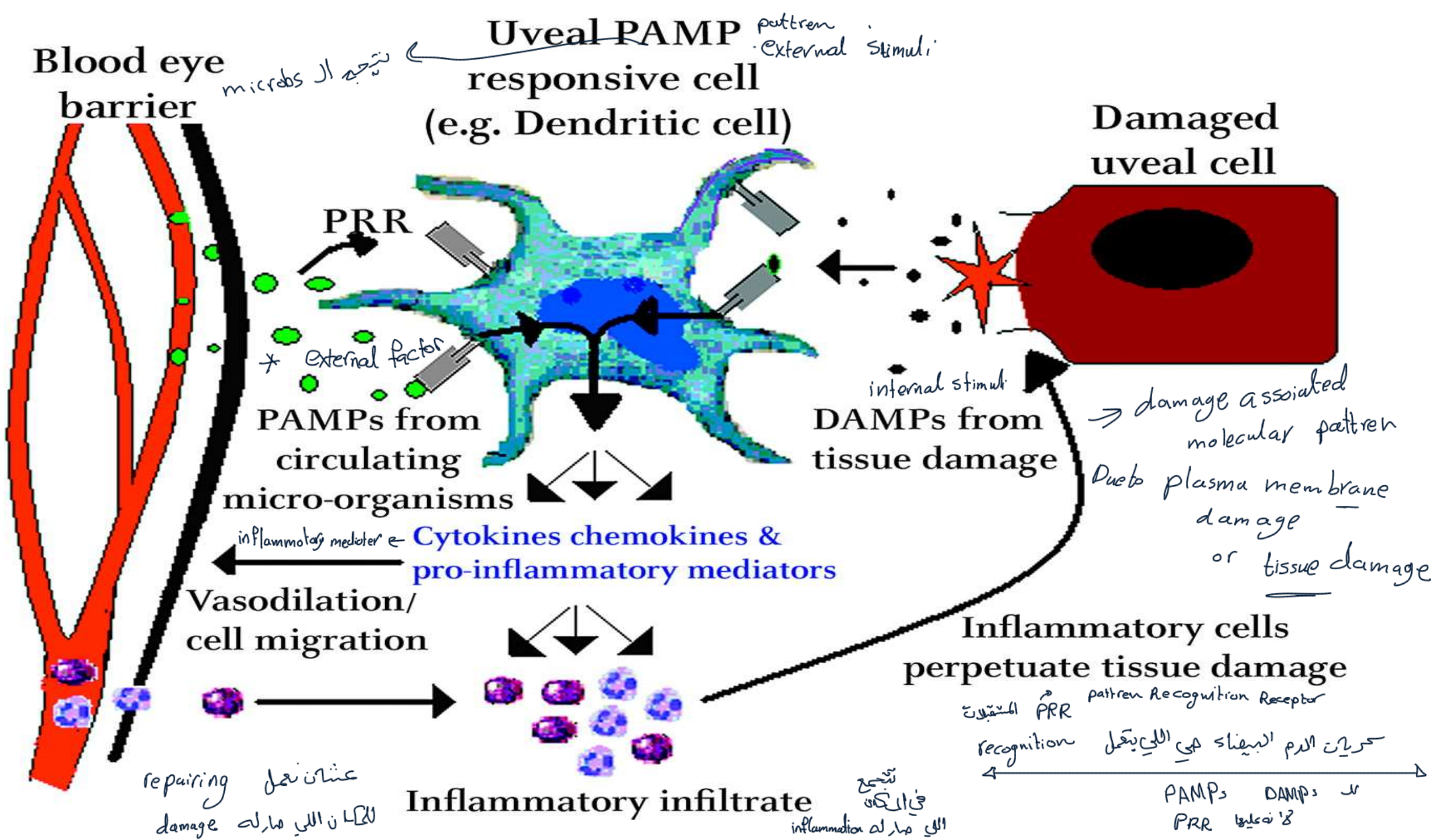
- LYMPHOCYTES

- MONOCYTES

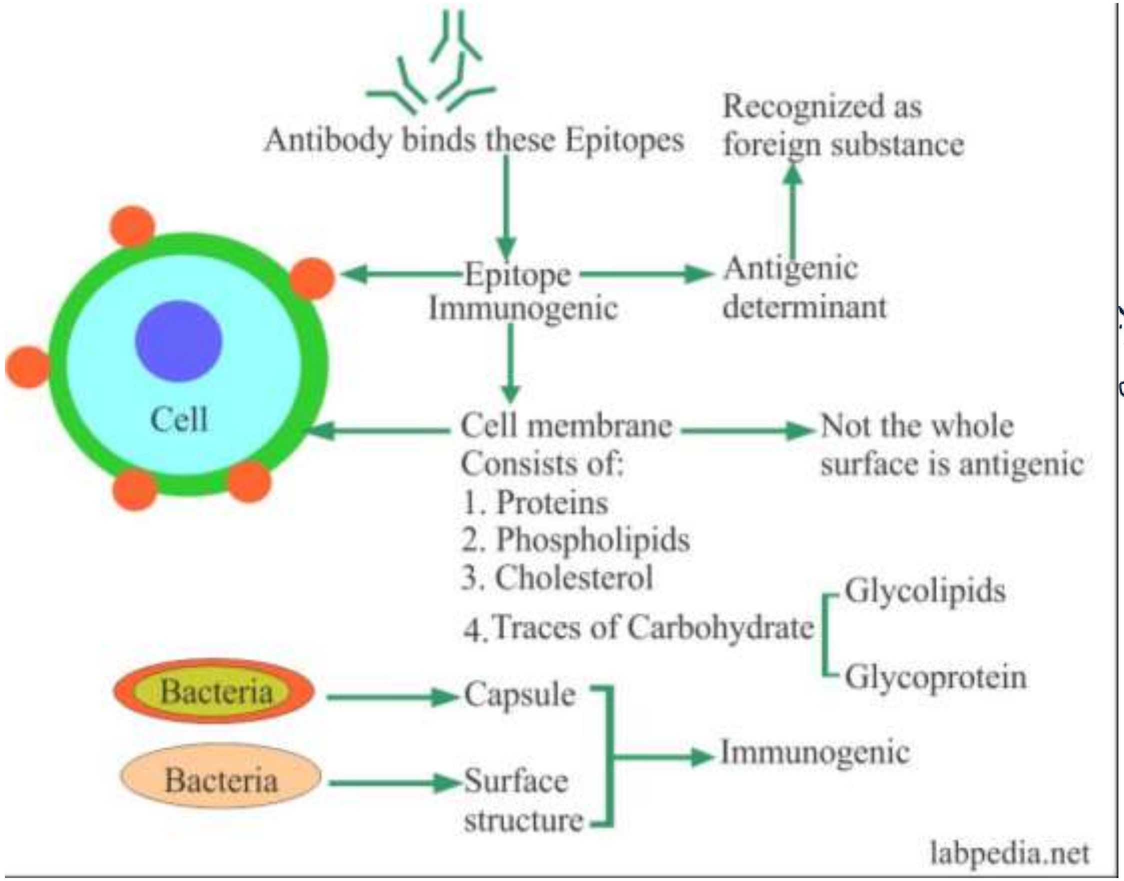


  - MACROPHAGES (تحاليز detrin tiations نبتعول)
  - DENDRITIC CELLS

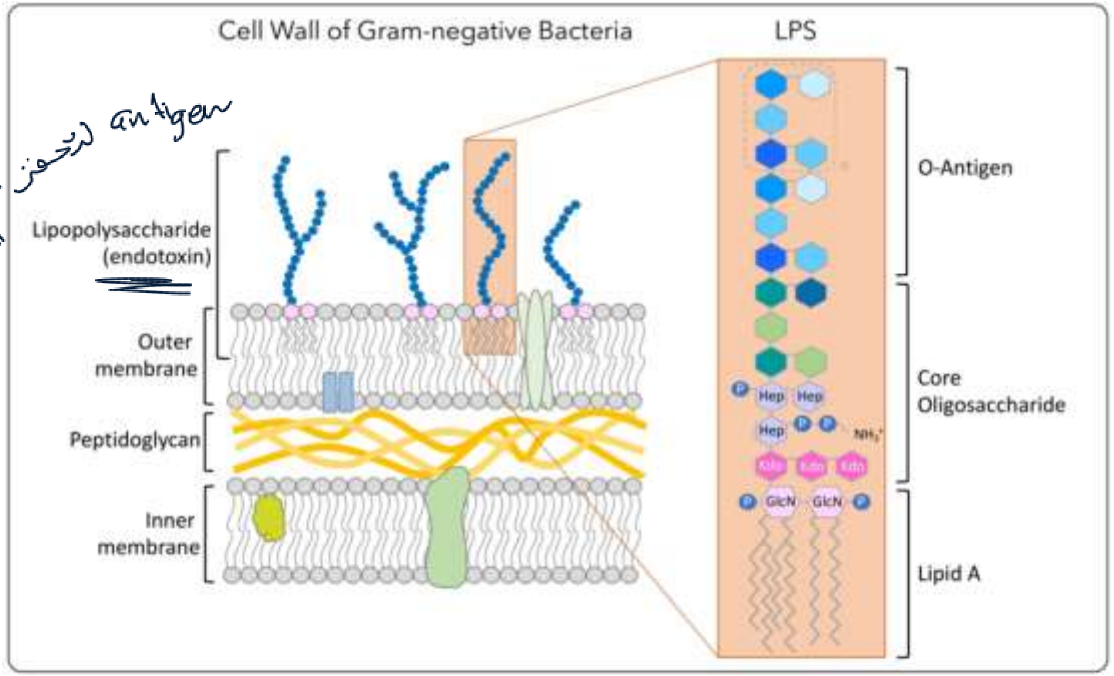
as phagocytosis


Uveal PAMP responsive cell (e.g. Dendritic cell)
pattren
External stimuli
Blood eye barrier
microbs
Damaged uveal cell
PRR
External factor
PAMPs from circulating micro-organisms
internal stimuli
DAMPs from tissue damage
damage assoiated molecular pattren
Due to plasma membrane damage or tissue damage
inflammatory mediater
Cytokines chemokines & pro-inflammatory mediators
Vasodilation/ cell migration
Inflammatory cells perpetuate tissue damage
PRR
pattren Recognition Receptor
recognition
PAMPs DAMPs
PRR
repairing
damage
Inflammatory infiltrate
inflammation

البكتيريا هاي بتعمل expression or express ل antigen هوعبارة عن ال endotoxin = polysaccharid هذا الي بيميزه
recognition بسوا طه ال mast cell



antigen لتحفز الجهاز المناعي



Gram negative Bacteria start to release endotoxins that attract mast cells having antibodies
Antigeng that are on the wall of Bacteria can be sugar, glycolipids or glycoproteins that attract the immune system by releasing antibodies.

Inflammatory Cascade: *Pathogenesis and clinical findings*

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Note: *The Inflammatory Cascade is a non-specific response to all foreign pathogens and trauma.*

Abbreviations:
ILs: Interleukins
WBC's: White Blood Cells

Physical barrier and cell disruption (e.g. skin puncture) ← Stimuli

Activation of the immune response at site of injury

Mast cells at injured site release **histamine** + Chemical mediators releasing

Disrupted endothelial cells release **pro-inflammatory cytokines** (e.g IL's, TNFα) and chemokines

Disrupted endothelial cells release **leukocytosis-inducing factors**

↑ vessel permeability: extravasation of immune cells/mediators (e.g. WBC's, complement proteins, platelets)

Vasodilation: ↑ blood flow to injured site

Chemotaxis: immune cells migrate to injury site

↑ circulating WBC's

Cardinal signs of the inflammatory response

Redness (*rubor*) **Heat** (*calor*) **Pain** (*dolor*) + **Swelling** (*tumor*)

Continued Innate Immunity

Phagocytosis:
*(*main mechanism)*
neutrophils and macrophages engulf foreign pathogens and dead tissue

Pus

Complement System: opsonize pathogen (tag for destruction), promote inflammation

Natural Killer Cells: perforin-mediated wall breakdown (puncture holes), enzyme-mediated destruction

Acquired Immunity Recruitment

Humoral:
(B cell response)
production of antibodies, activation of complement system

Cell-mediated:
(T cell response)
↑ helper cell and cytotoxic cell activity

Note: *Dendritic cells at injury site aid in phagocytosis and antigen presentation to T cells.*

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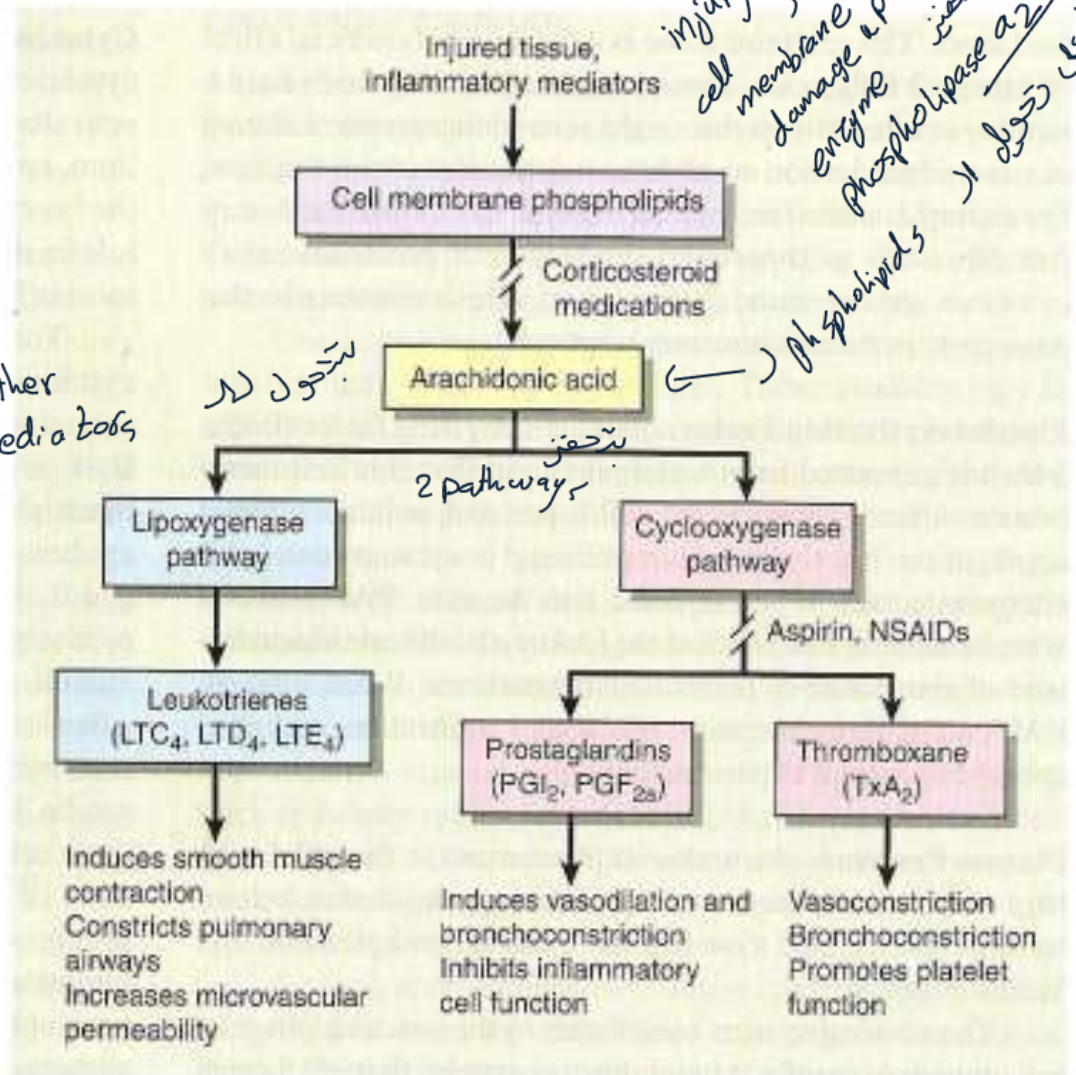
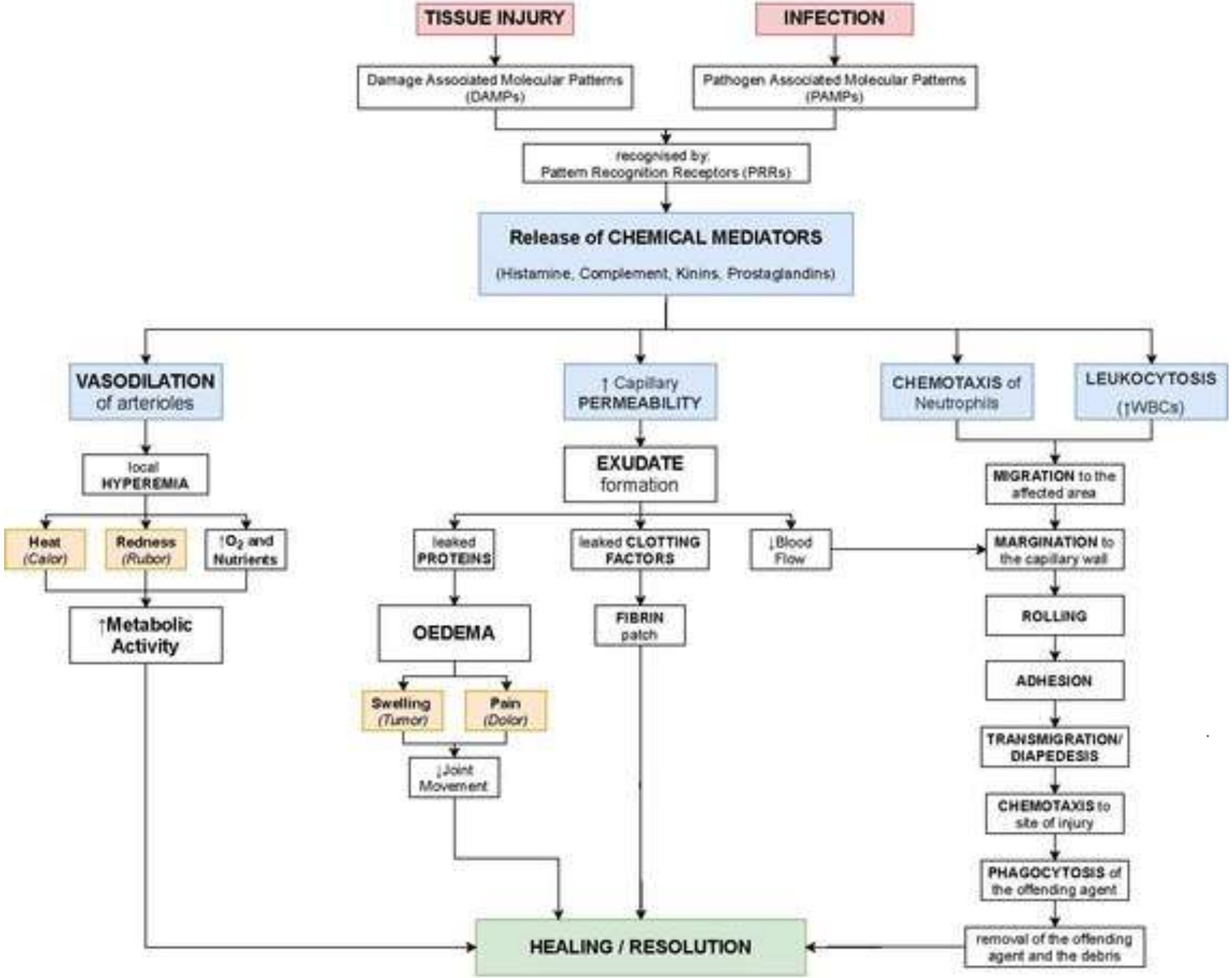
Arachinodic Acid Metabolites




TISSUE INJURY
INFECTION
Damage Associated Molecular Patterns (DAMPs)
Pathogen Associated Molecular Patterns (PAMPs)
recognised by: Pattern Recognition Receptors (PRRs)
Release of CHEMICAL MEDIATORS
(Histamine, Complement, Kinins, Prostaglandins)
VASODILATION of arterioles
↑ Capillary PERMEABILITY
CHEMOTAXIS of Neutrophils
LEUKOCYTOSIS (↑WBCs)
local HYPEREMIA
EXUDATE formation
MIGRATION to the affected area
Heat (Calor)
Redness (Rubor)
↑O_2 and Nutrients
leaked PROTEINS
leaked CLOTTING FACTORS
↓Blood Flow
MARGINATION to the capillary wall
↑Metabolic Activity
OEDEMA
FIBRIN patch
ROLLING
ADHESION
Swelling (Tumor)
Pain (Dolor)
TRANSMIGRATION/ DIAPEDESIS
↓Joint Movement
CHEMOTAXIS to site of injury
PHAGOCYTOSIS of the offending agent
HEALING / RESOLUTION
removal of the offending agent and the debris

تلخيص سريع لل inflammation بيصير نتيجة internal or external stimuli
damps أو pAmps
بيصير releasing
لل inflammatory mediators
mast cell → chemicle mediotrs

الهدف من ال inflammation انه بيصير تحفيز ال Host cell لحتى تعمل Defense
فبتحفز WBCs بأنواعها

تلخيص inflammatory cascade ←

بيصير injury لل cell نتيجة external stimuli مثال: microbs بكون عليه antigen هو عبارة عن ال endotoxin وبعمل لها recognition بواسطة ال receptors اللي على ال mast cell

فلما بصير عندنا activation لل receptor وبتعمل releasing لل inflammatory chemicals or mediators مثل ال Histammine + prostaglindens + ليكوترايينس.

وعندنا كمان ال clotting factors = XIIA و مسؤول عن الكينين pathway وهو المسؤول عن انتاج البرادي كينين

والهيستامين والبرادي كينين مسؤولين عن ال Vasodilation عشان يزيد ال Blood flow لل injury site

والهيستامين بزيد من vessels permeability فالسوائل بتخرج من الخلية يعني من الطبقات الداخلية لل (Lumen) وبتطلع لل interstitial fluid

وبصير عندنا accumlation في منطقة ال interstitial وبصير عندنا edema أو Swelling ولما يزيد تدفق الدم لل injury site بتظهر ال

inflammatory response signs عبارة عن Heat + redness + pain نتيجة ال edema تجمع السوائل بتضغط على nosireceptors

وهذه ال inflammatory chemicals نتيجة ال external stimuli = microbs

وصول ال chemical mediators بحتووا على ال inflammation بعملوا مناداة لل neutrophils وال monocyte عبارة عن granules Leuckcyte وبتوصل الخلايا ال neutro + mono لل site

اللي فيه injury رفي عندنا على ال endothelial cells نفترض انه صار ال injury على ال endothelial Layer وبتعمل expression لـ adhesive molecules or substances مواد قادرة على انها تعمل adhesion

فبترتبط ال neutro + mono على ال endothelial اللي صابها injury بتعمل expression لـ adhesion molecules مثال عليها ال selectins و بتيجي ال mono + neutro ال site of action

وبصير لها Differentiation لـ macrophages وبتلتصق بال endothelial cells عن طريق ال adhesive molecules اللي هم selectins وتفتش عندنا ال microb فبتلتصق الخلايا البيضاء مع ال endothelial

من جهة ومع ال microb من جهة اخرى وهون بتعمل Rolling يعني بتصير تتحرك وال endothelial cells عليها selectins فبترتبط ال macrophage عليها وتتمسك مع الثانية والثالثة
عشان تمنع ال microbs من انه يتفاعل مع ال Blood

موجودين على ال endothelial cells ال macrophages وعندنا بين ال endothelial cells ← (gaps) فبصير عملية

sequeezing زي انه بتحشر حالها الخلايا البيضاء في ال gaps لتمر وتخرج من ال another site وتعملهم تكسير تحولهم ل waste products
ويصير لهم excretion عن طريق ال urine

وما بيصير خروجها بشكل عشوائي وبترتبط بال VCAMs و بتخرج لل other site وبتسمي هذي العملية
تكون موجودة هذه ال molecules في ال gaps
Diapedesis

وهي العملية التي تهاجر فيها **خلايا الدم البيضاء** من الأوعية الدموية إلى الأنسجة المحيطة عن طريق المرور بين **الخلايا البطانية** في جدران الأوعية الدموية، خاصة أثناء الاستجابة الالتهابية.

عملية جذب الخلايا البيضاء مثل ال mono + neutro
لل Site of injury اسمها Chemotaxis positive
more activation for WBC's
neutro + macrophages
راحت لل mast cells

وهذه العمليات سريعة تكون وبعدما بتصير ابطأ وبدها بتاخذ ← longer time

عملية ال margination هي بداية عملية ← Diapedesis

لكن اذا كان ال stimuli ليس microb
اذا كان عندنا damage للplasma membrane وهو بيحتوي على phospholipids وبيتحول عن طريق phospholipase لـ Arachidonic acid
وبجهز عندنا 2 pathway

Neutrophils

infiltration

macro- + neutro phage

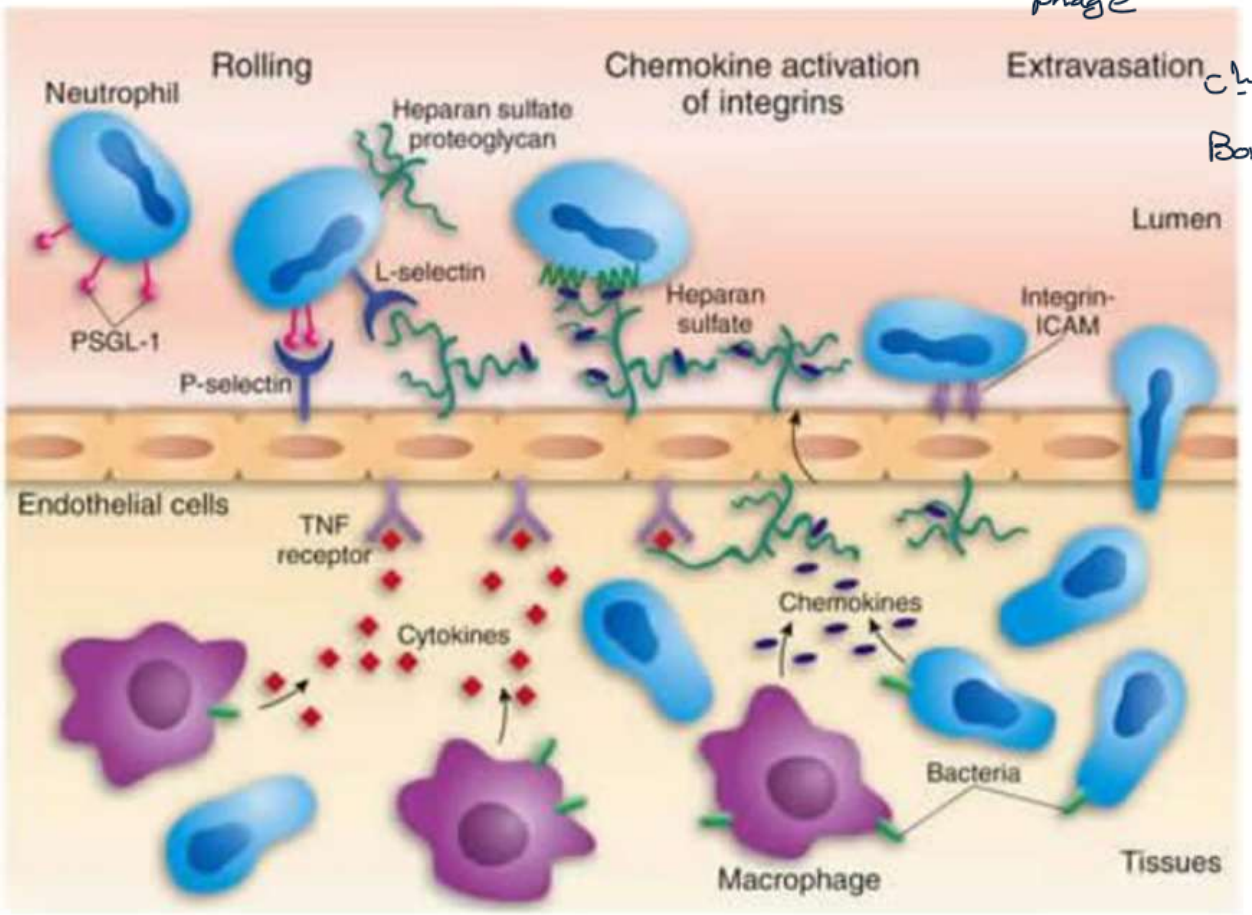
كمية كبيرة من ال

صار لها infiltration انتاجها بكميات

كبيرة من منطقة ال Bone marrow

استجابة الجسم لل

inflammation



The cardinal signs of inflammation

- Heat (Calor)
- Redness (Rubor)
- Swelling (Tumor)
- Pain (Dolor)
- Loss of function (Functio laesa)

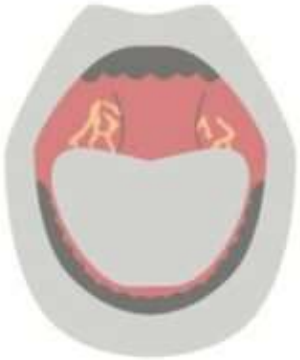
English	Latin	Cause
Heat	*Calor*	Vasodilation
Redness	*Rubor*	Vasodilation
Swelling	*Tumor*	Increased vascular permeability
		Increased granulation tissue
Pain	*Dolor*	Physical and chemical stimulation of nociceptors
Loss of function	*Functio laesa*	Pain
		Reflex muscle inhibition
		Disruption of tissue structure
		Fibroplasia and metaplasia

The cardinal signs of inflammation

Heat

Redness

Due to increased blood flow to site of inflammation



Swelling

Due to accumulation of fluid and cells

Pain

Due to stimulation of sensory neurons by inflammatory mediators

Loss of function

Due to tissue damage

Types of inflammation

Acute inflammation: Is the inflammatory response which is sudden in onset, of short duration, and is characterized by the classical ***cardinal signs*** of inflammation, in which the vascularized and exudative process predominates.

Chronic inflammation: Is an inflammation of a slow progress, marked chiefly by the formation of new connective tissue, it may be a continuation of an acute form or a prolonged low-grade form and usually causes permanent tissue damage.

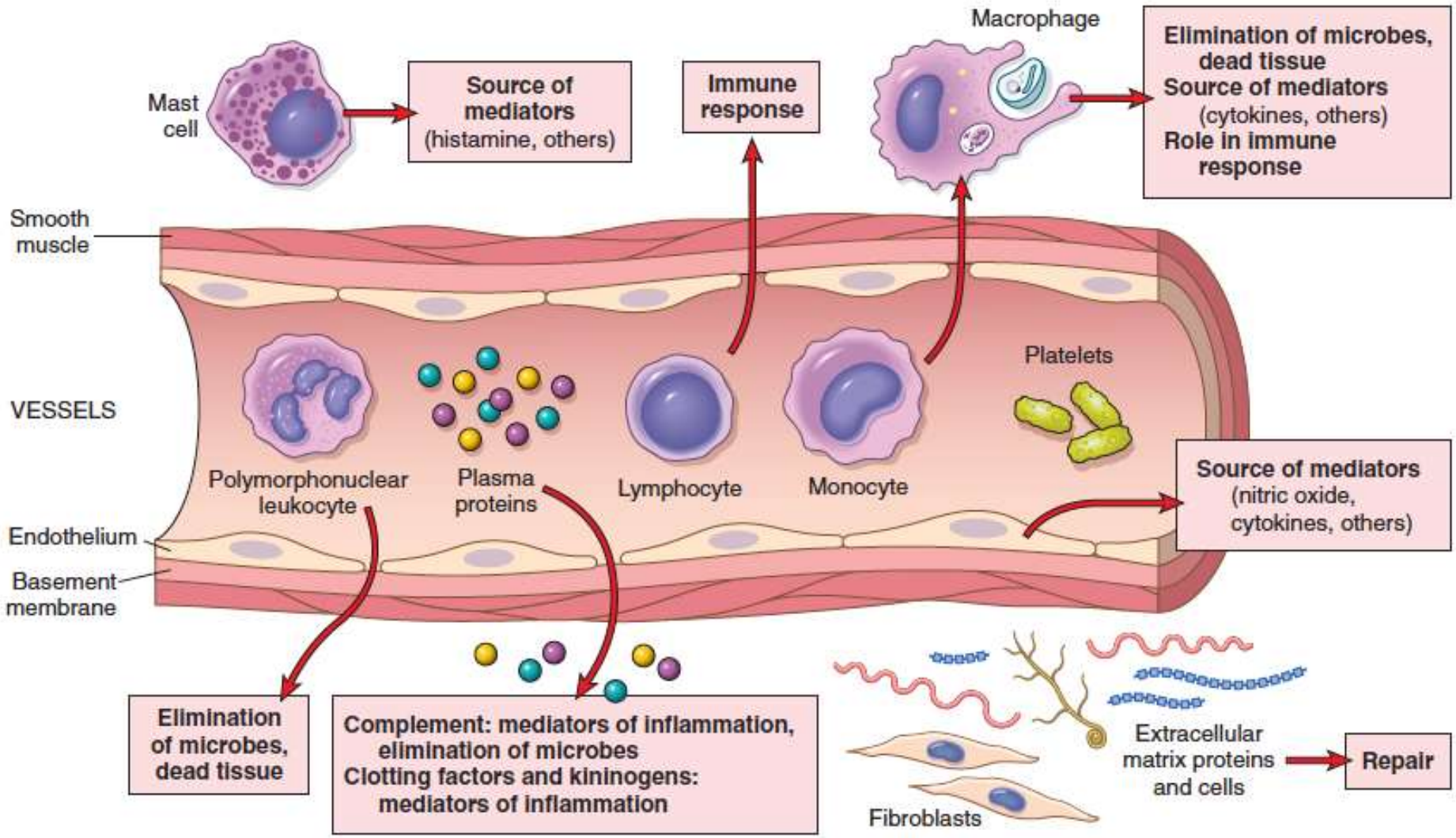
Table 3.1 Features of Acute and Chronic Inflammation

Feature	Acute	Chronic
Onset	Fast: minutes or hours	Slow: days
Cellular infiltrate	Mainly neutrophils	Monocytes/macrophages and lymphocytes
Tissue injury, fibrosis	Usually mild and self-limited	May be severe and progressive
Local and systemic signs	Prominent	Less

Characteristics of inflammations

	Acute	Chronic
Cause	Single injury	Permanent present of the causing agent /bacteria, etc./
Duration	Hours, days	Weeks, months, years; depending on the causing agent
Presentative symptom	↑ permeability, exudation	Proliferative fibroblasts No exudation
Main components in the process	Liquid Proteins /proteases and antiproteases/ PMN leukocytes Macrophages	Macrophage Lymphocytes Eosinophyl granulocytes Connective tissue hiperplasy
Connecting reactions	Thrombosis	Immune response

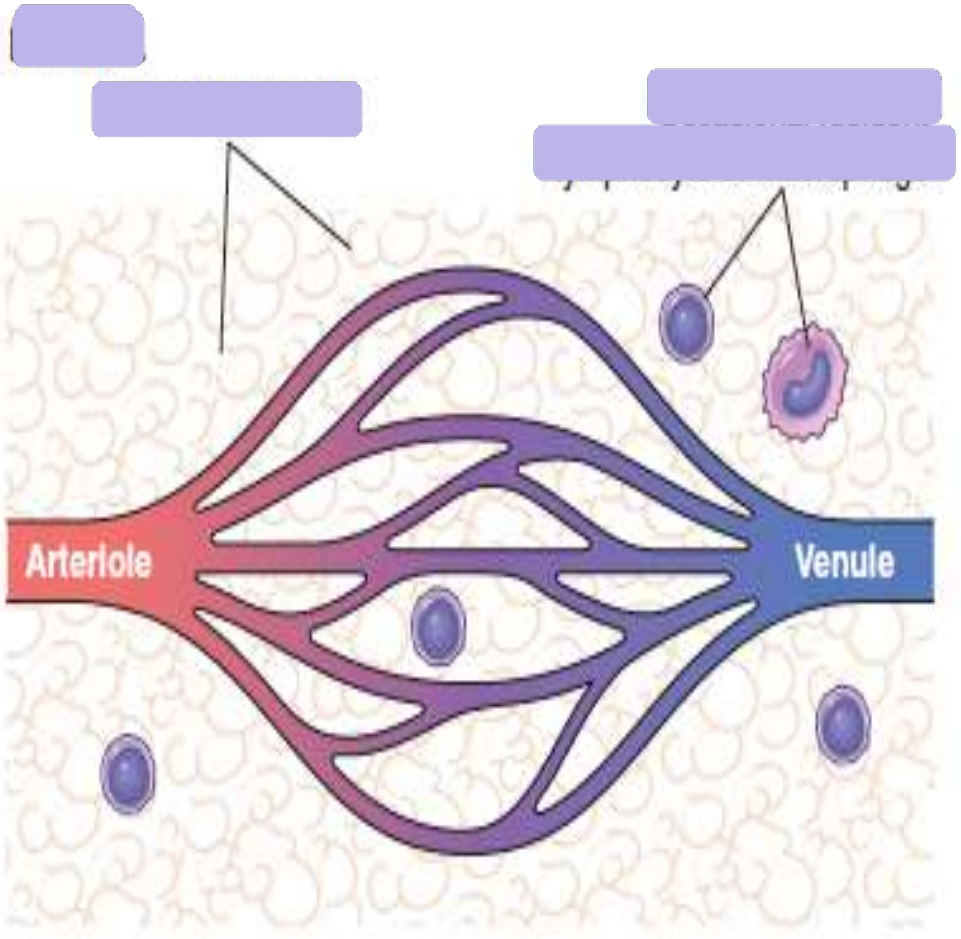
Components of Inflammatory Response

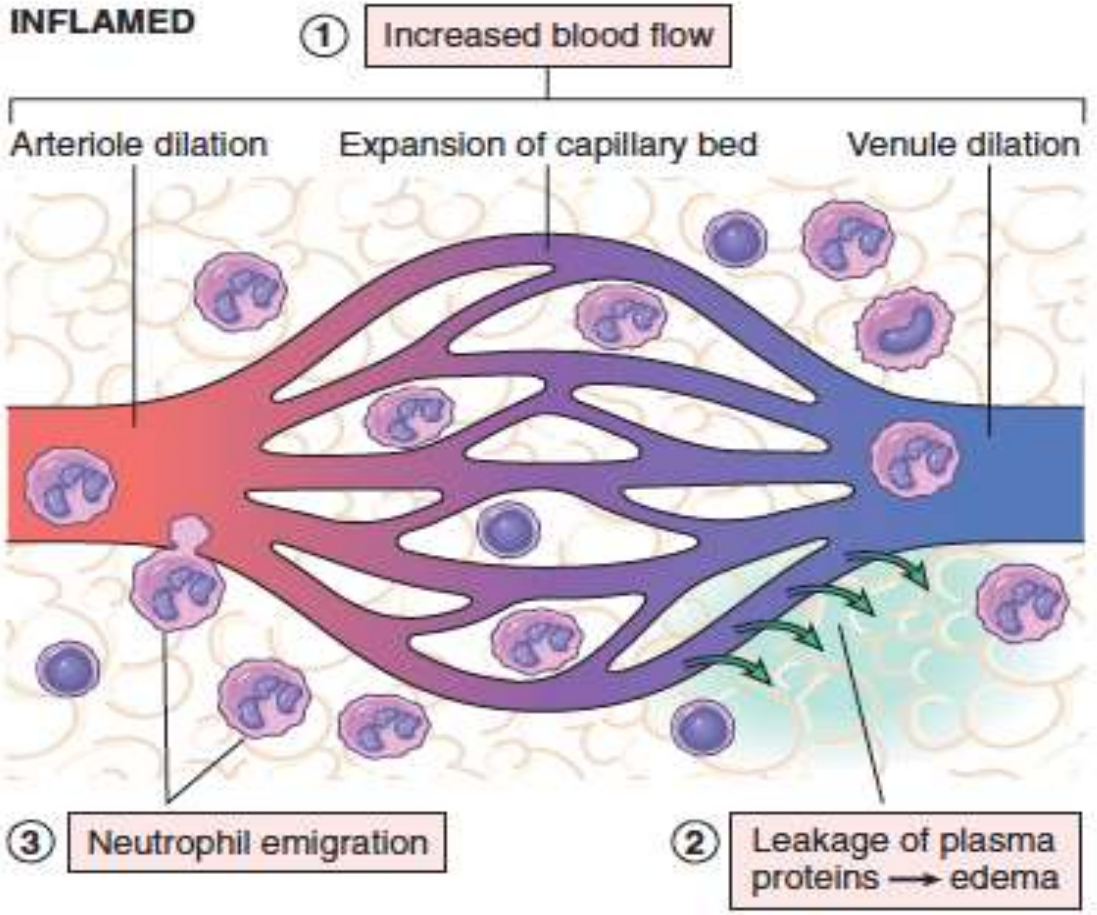


Components of Inflammatory Response

1. **Circulating bone marrow-derived cells**: include leukocytes, neutrophils, eosinophils, basophils, lymphocytes, monocytes, & platelets.
2. **Circulating proteins**: include clotting factors, kininogens, & complement components, all are synthesized by the liver.
3. **Vascular wall cells**: include endothelial cells (EC), and the underlying smooth muscle cells (SMC).
4. **Connective tissue cells**: include mast cells, macrophages & lymphocytes; to Phagocytose and the fibroblasts that synthesize the extracellular matrix (ECM).
5. **The extracellular matrix (ECM):** consist of fibrous structural proteins (e.g., collagen & elastin).

Acute Inflammation





Major Events In Inflammation

1. Vasodilation causing increased blood flow (warmth and erythema)

2. Extravasation and leakage of plasma fluids & proteins (edema)

3. Emigration of the leukocytes from and their accumulation at the site of injury

Vasodilation

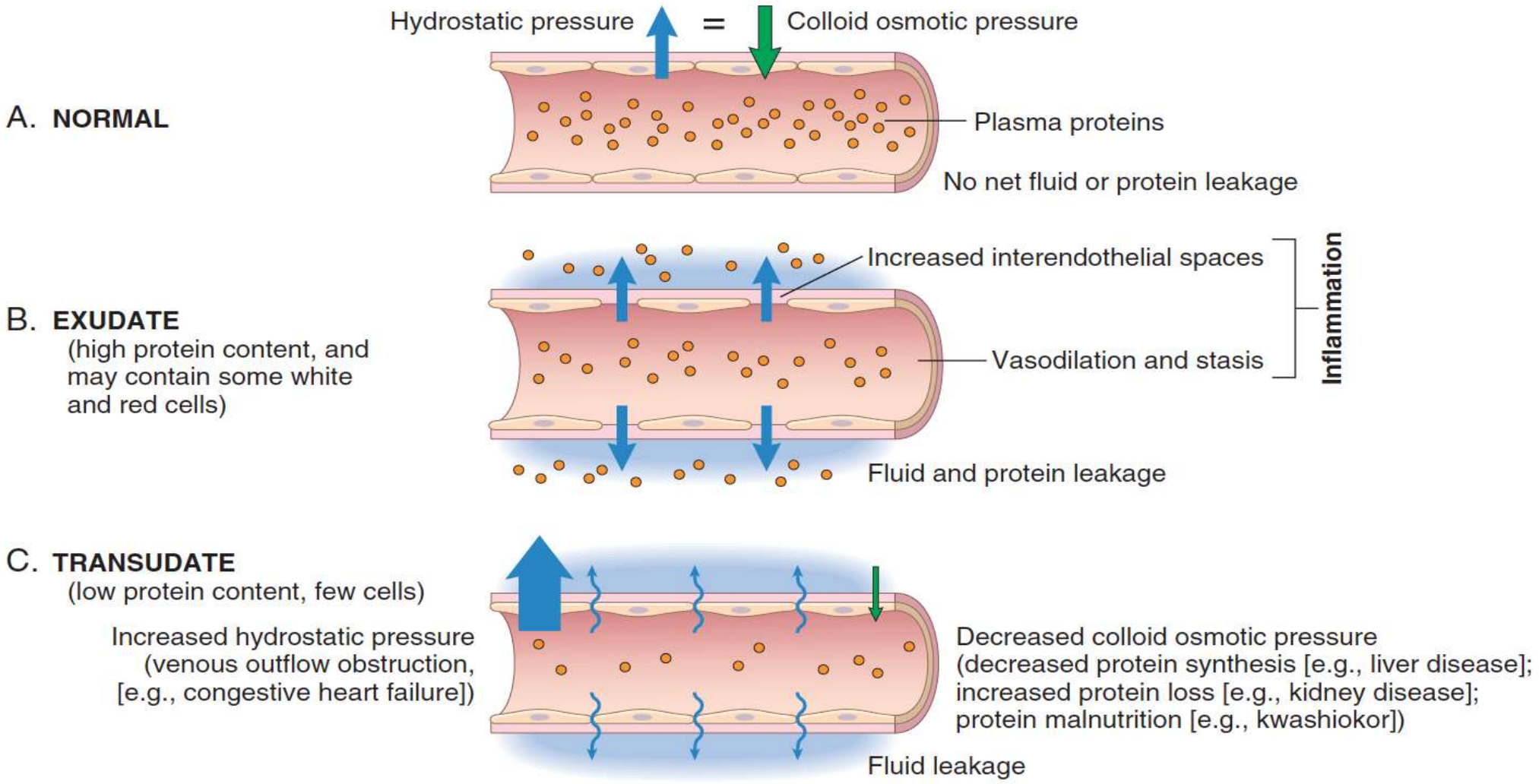


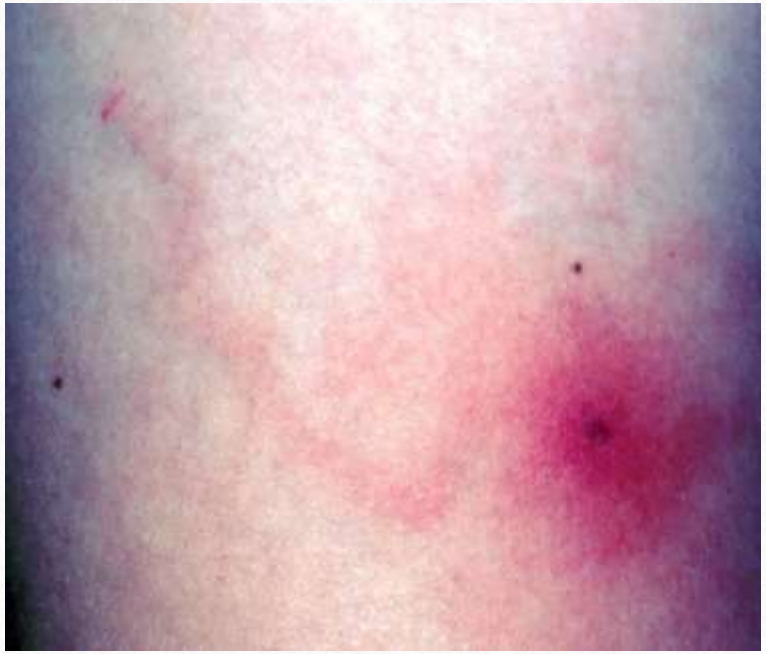
Fig. 3.2 Formation of exudates and transudates. (A) Normal hydrostatic pressure *(blue arrow)* is about 32 mm Hg at the arterial end of a capillary bed and 12 mm Hg at the venous end; the mean colloid osmotic pressure of tissues is approximately 25 mm Hg *(green arrow)*, which is equal to the mean capillary pressure. Therefore, the net flow of fluid across the vascular bed is almost nil. (B) An exudate is formed in inflammation because vascular permeability increases as a result of retraction of endothelial cells, creating spaces through which fluid and proteins can pass. (C) A transudate is formed when fluid leaks out because of increased hydrostatic pressure or decreased osmotic pressure.

Responses of Lymphatic Vessels

- In addition to blood vessels, lymphatic vessels also participate in the inflammatory response.

- In inflammation, lymph flow is ***increased and helps drain edema fluid***, leukocytes, and cell debris from the extravascular space.

- In severe inflammatory reactions, especially to microbes, the lymphatics may transport the offending agent, contributing to its dissemination. The lymphatics may become secondarily inflamed (***lymphangitis***), as may the draining lymph nodes (***lymphadenitis***).



Mechanisms of increased vascular permeability

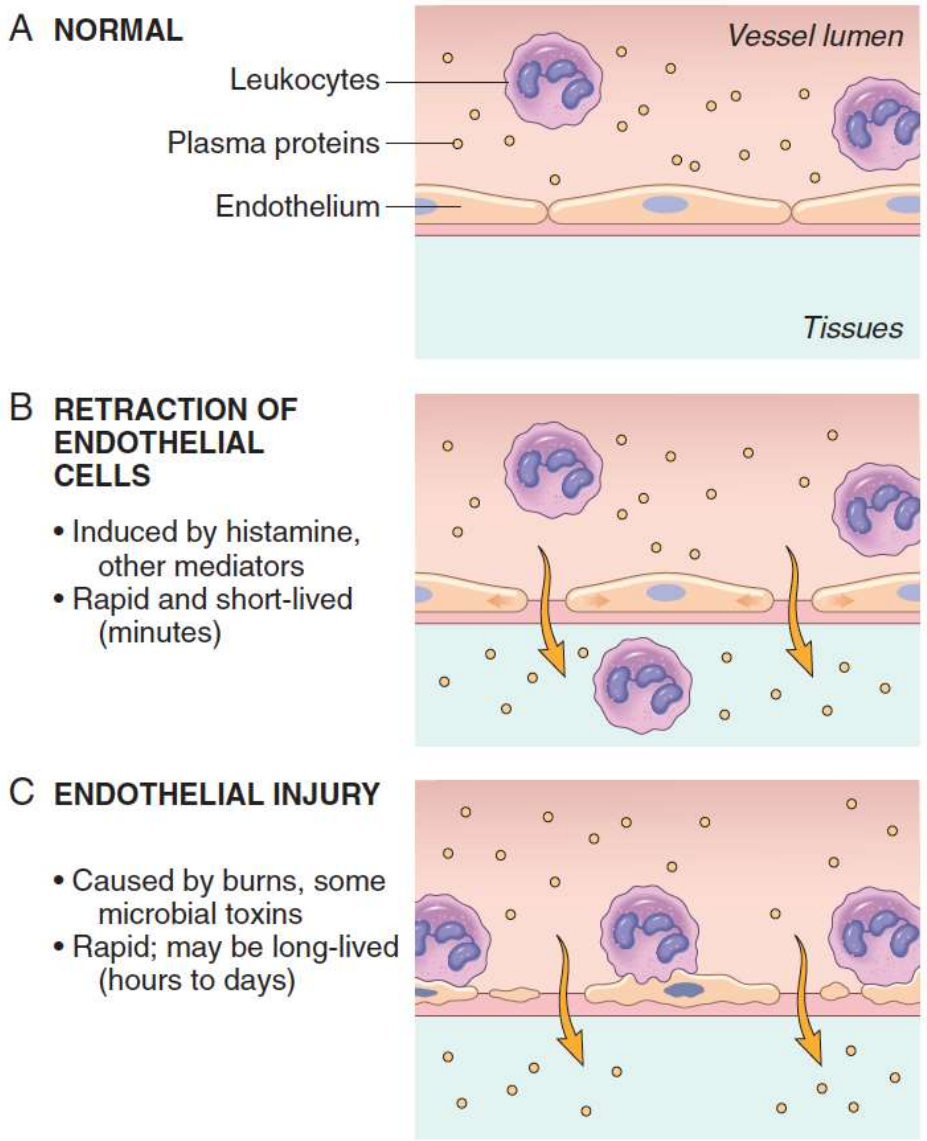


Fig. 3.3 Principal mechanisms of increased vascular permeability in inflammation and their features and underlying causes.

Increased Vascular Permeability

- **There are three basic patterns of increased permeability:**

- ***Immediate transient response***: Histamine-type.
- ***Immediate-sustained response***: which is seen in severe injury and is associated with damage to endothelial cells.
- ***Delayed prolonged response***: as in hypersensitivity type IV & exposure to ultraviolet light.

Leukocyte Recruitment to Sites of Inflammation

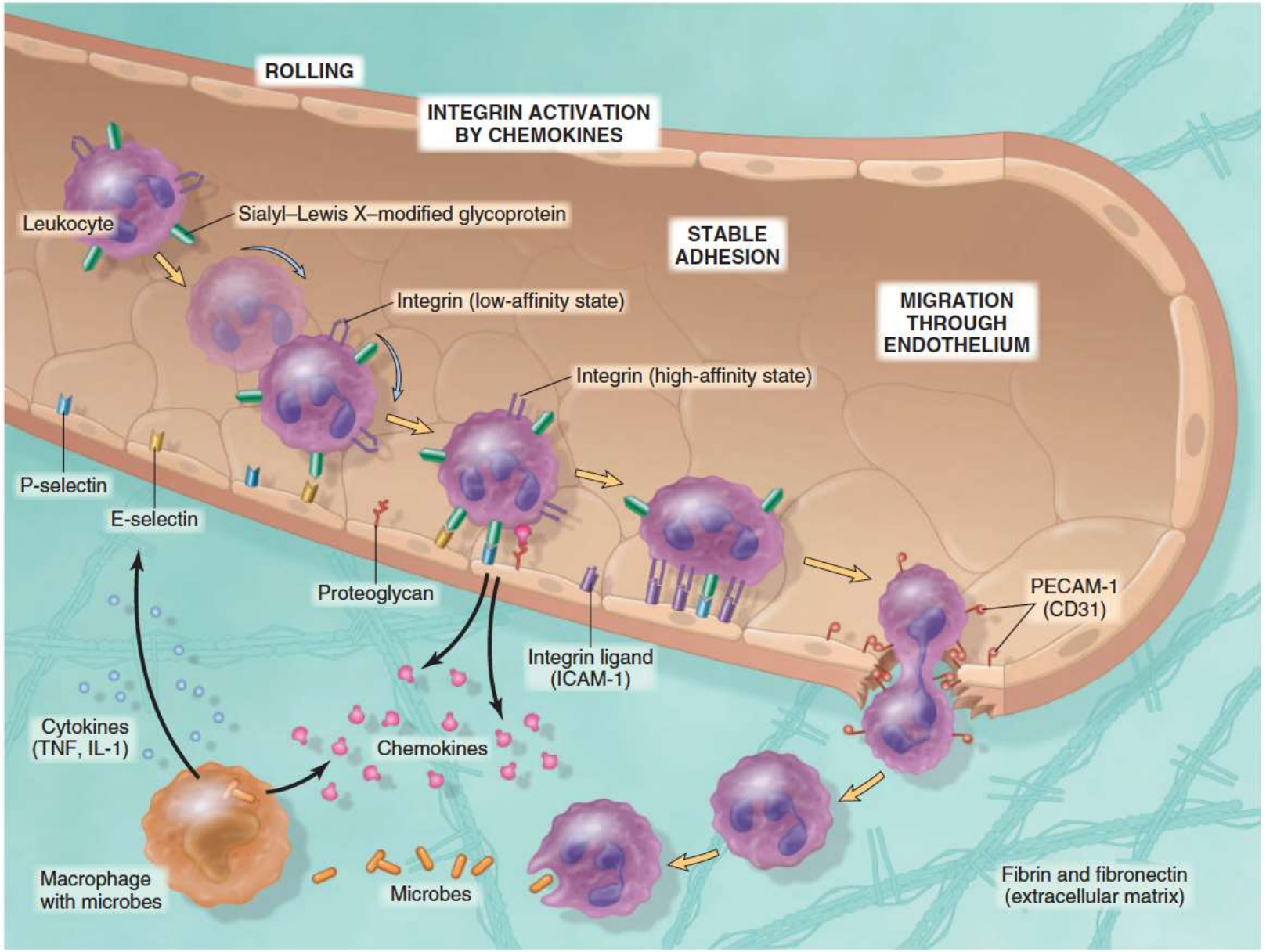
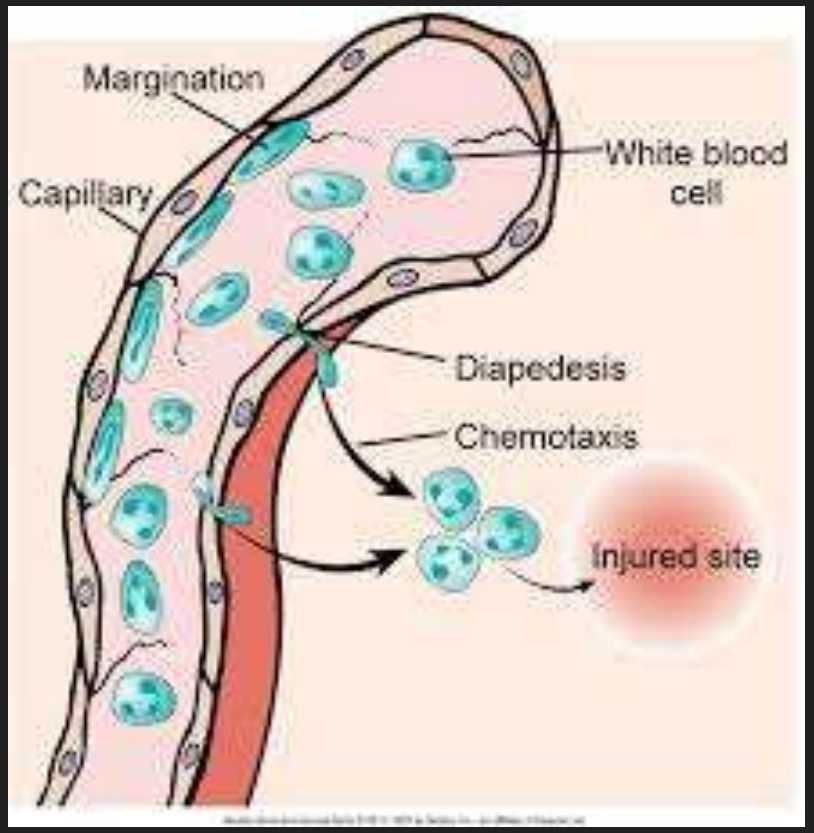


Fig. 3.4 The multistep process of leukocyte migration through blood vessels, shown here for neutrophils. The leukocytes first roll, then become activated and adhere to endothelium, then transmigrate across the endothelium, pierce the basement membrane, and move toward chemoattractants emanating from the source of injury. Different molecules play predominant roles at each step of this process: selectins in rolling; chemokines (usually displayed bound to proteoglycans) in activating the neutrophils to increase avidity of integrins; integrins in firm adhesion; and CD31 (PECAM-1) in transmigration. *ICAM-1,* Intercellular adhesion molecule-1; *PECAM-1 (CD31),* platelet endothelial cell adhesion molecule-1; *TNF,* tumor necrosis factor.

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

  - margination and rolling along the vessel wall;
  - firm adhesion to the endothelium;
  - transmigration between endothelial cells; and
  - migration in interstitial tissues toward a chemotactic stimulus

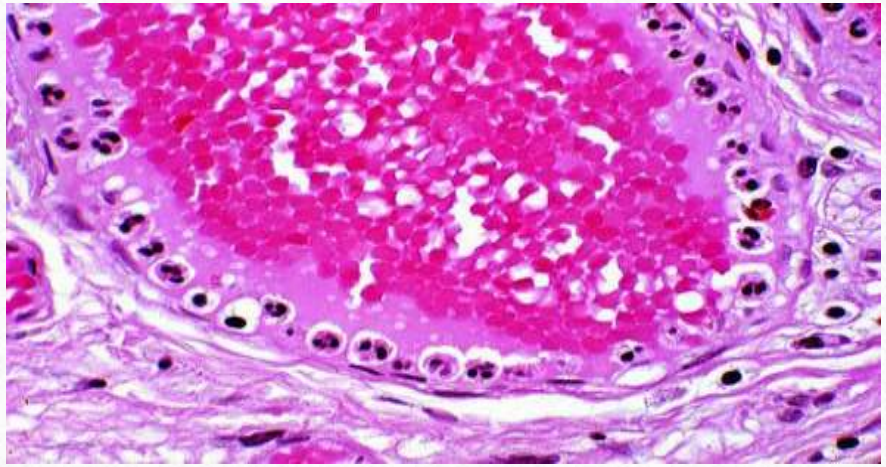


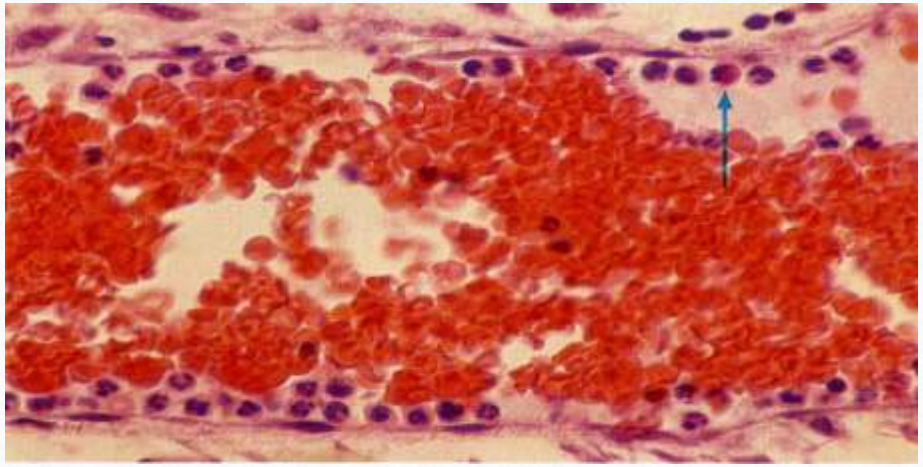
Mediators of cellular rolling and adhesion

- 1-The **selectins** which consist of
  - E-selectin is confined to the endothelial cells.
  - P-selectin is present on the platelets.
  - L-selectin is present on leukocytes, especially lymphocytes, it adheres lymphocytes to the endothelium.
- 2-The **immunoglobulin family molecules**: include two endothelial adhesion molecules:
  - An intercellular adhesion molecule 1 (ICAM-1) & Vascular cell adhesion molecule-1 (VCAM-1), both molecules interact with integrins found on leukocytes.
- 3-The **integrins & mucin-like glycoprotein**: are transmembrane-adhesive glycoproteins that also function as receptors for the extracellular matrix.

(1) Leukocyte Margination and Rolling

endothelium lined by WBC an appearance called ***pavementing*





(2) Adhesion

- The rolling leukocytes are able to sense changes in the endothelium that allows them to adhere firmly to endothelial surfaces, this process is mediated by integrins expressed on leukocyte cell surfaces interacting with their ligands (selectins) on endothelial cells.

(3) Transmigration (Diapedesis)

Squeezing
gaps
endothelial

- After being arrested on the endothelial surface, leukocytes migrate through the vessel wall primarily by squeezing between cells at intercellular junctions.

Phagocytosis

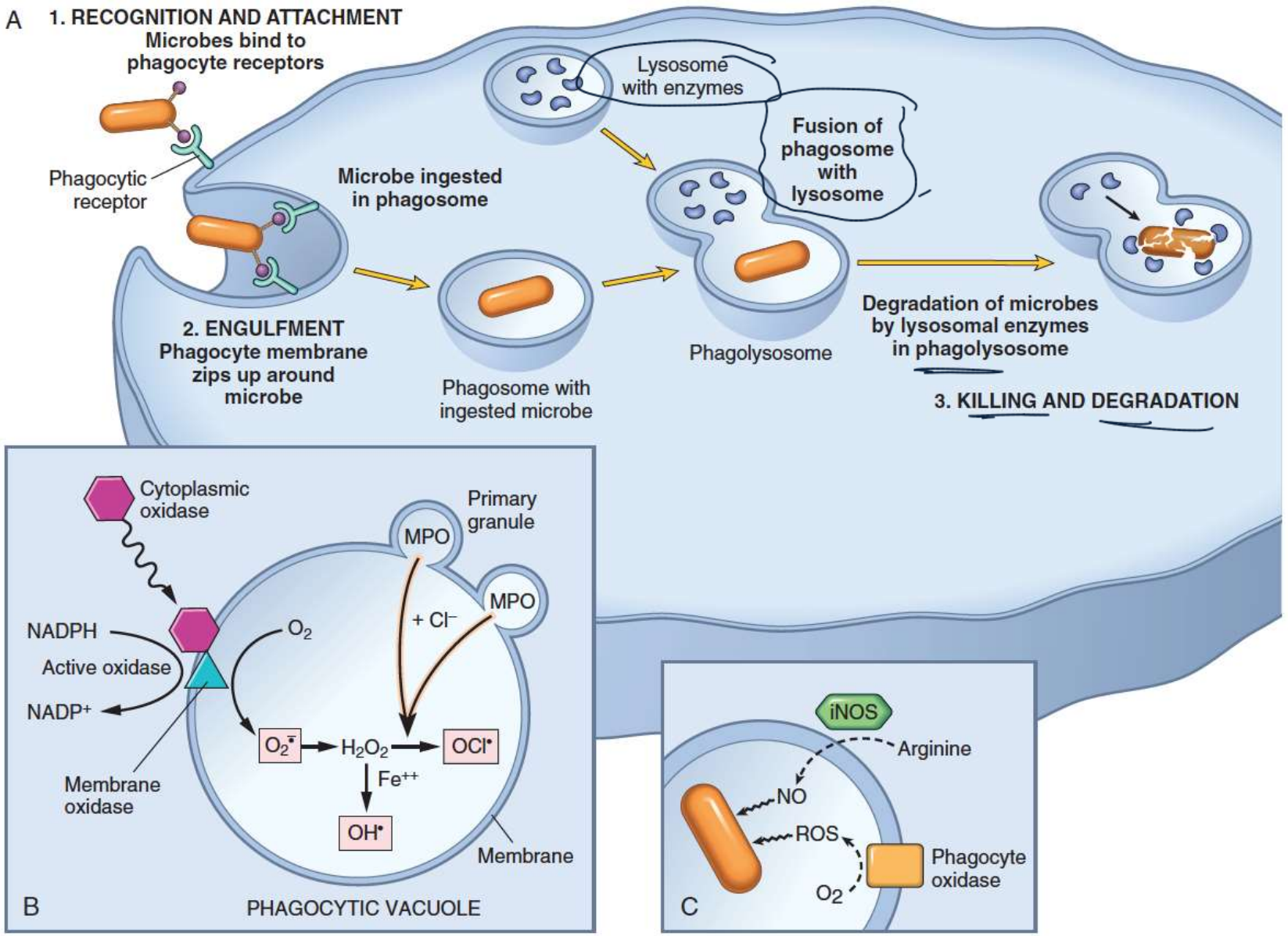


Fig. 3.7 Phagocytosis and intracellular destruction of microbes. (A) Phagocytosis of a particle (e.g., a bacterium) involves binding to receptors on the leukocyte membrane, engulfment, and fusion of the phagocytic vacuoles with lysosomes. This is followed by destruction of ingested particles within the phagolysosomes by lysosomal enzymes and by reactive oxygen and nitrogen species. (B) In activated phagocytes, cytoplasmic components of the phagocyte oxidase enzyme assemble in the membrane of the phagosome to form the active enzyme, which catalyzes the conversion of oxygen into superoxide (O_2^-) and H_2O_2. Myeloperoxidase, present in the granules of neutrophils, converts H_2O_2 to hypochlorite. (C) Microbicidal reactive oxygen species (ROS) and nitric oxide (NO) kill ingested microbes. During phagocytosis, granule contents may be released into extracellular tissues (not shown). *iNOS*, Inducible NO synthase; *MPO*, myeloperoxidase; *ROS*, reactive oxygen species.

Chemical Mediators

Chemical substances are derived from either ***plasma*** or the ***tissues***, they act as a link between the occurrence of injury and the onset of inflammation.

They are divided into two major categories :

- ***Plasma Derived-Mediators***, these include:

1. The kinin system.
2. The complement system.
3. The coagulation & fibrinolytic system.

- ***Cell derived mediators;*** these include:
- circulating platelets, basophils, endothelial cells monocyte/macrophages, tissue mast cells and the injured tissue itself are all potential cellular sources of vasoactive mediators.

Chemical Mediators

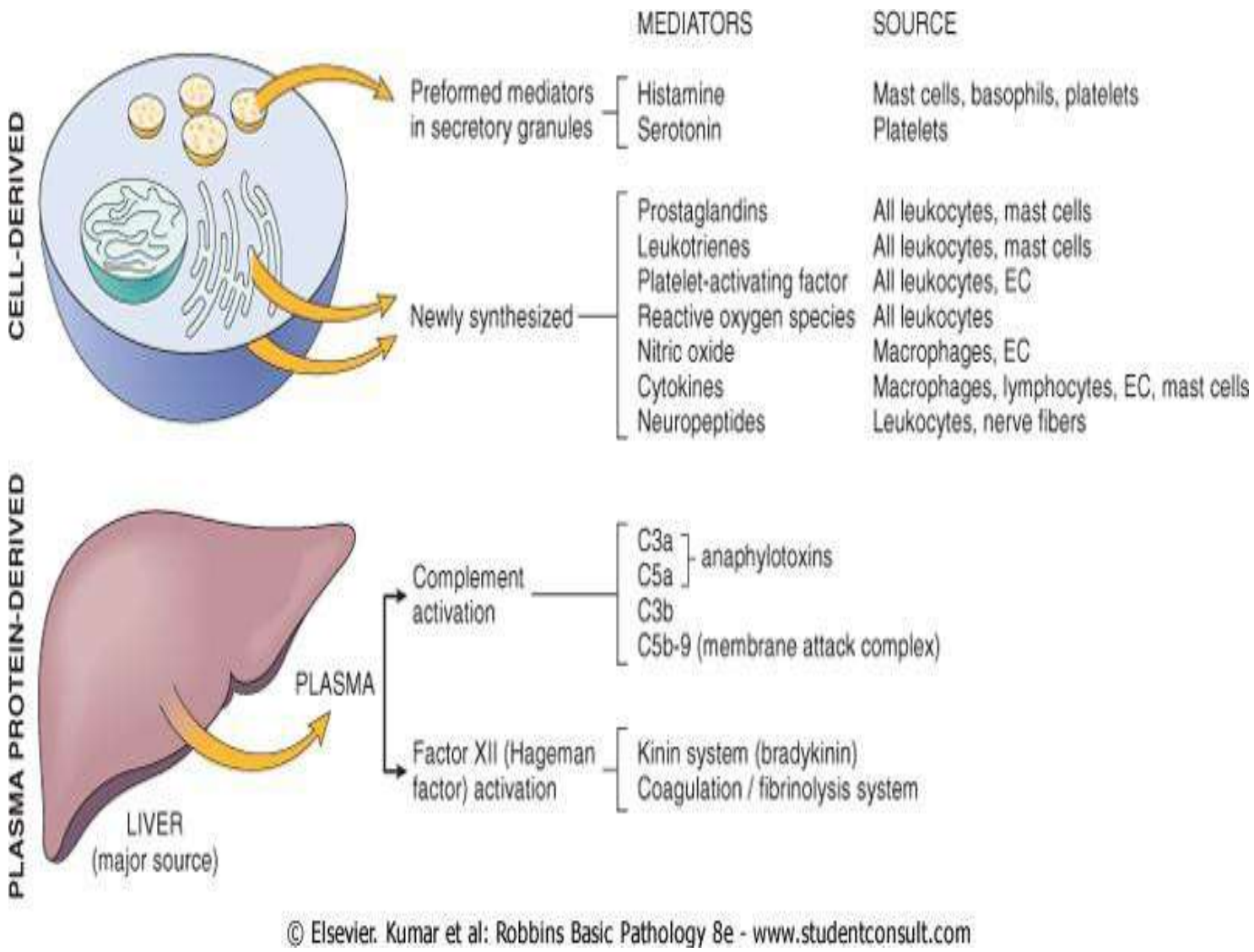


Table 3.5 Principal Mediators of Inflammation

Mediator	Source	Action
Histamine	Mast cells, basophils, platelets	Vasodilation, increased vascular permeability, endothelial activation
Prostaglandins	Mast cells, leukocytes	Vasodilation, pain, fever
Leukotrienes	Mast cells, leukocytes	Increased vascular permeability, chemotaxis, leukocyte adhesion, and activation
Cytokines (TNF, IL-1, IL-6)	Macrophages, endothelial cells, mast cells	Local: endothelial activation (expression of adhesion molecules). Systemic: fever, metabolic abnormalities, hypotension (shock)
Chemokines	Leukocytes, activated macrophages	Chemotaxis, leukocyte activation
Platelet-activating factor	Leukocytes, mast cells	Vasodilation, increased vascular permeability, leukocyte adhesion, chemotaxis, degranulation, oxidative burst
Complement	Plasma (produced in liver)	Leukocyte chemotaxis and activation, direct target killing (membrane attack complex), vasodilation (mast cell stimulation)
Kinins	Plasma (produced in liver)	Increased vascular permeability, smooth muscle contraction, vasodilation, pain

Major roles of cytokines in acute inflammation

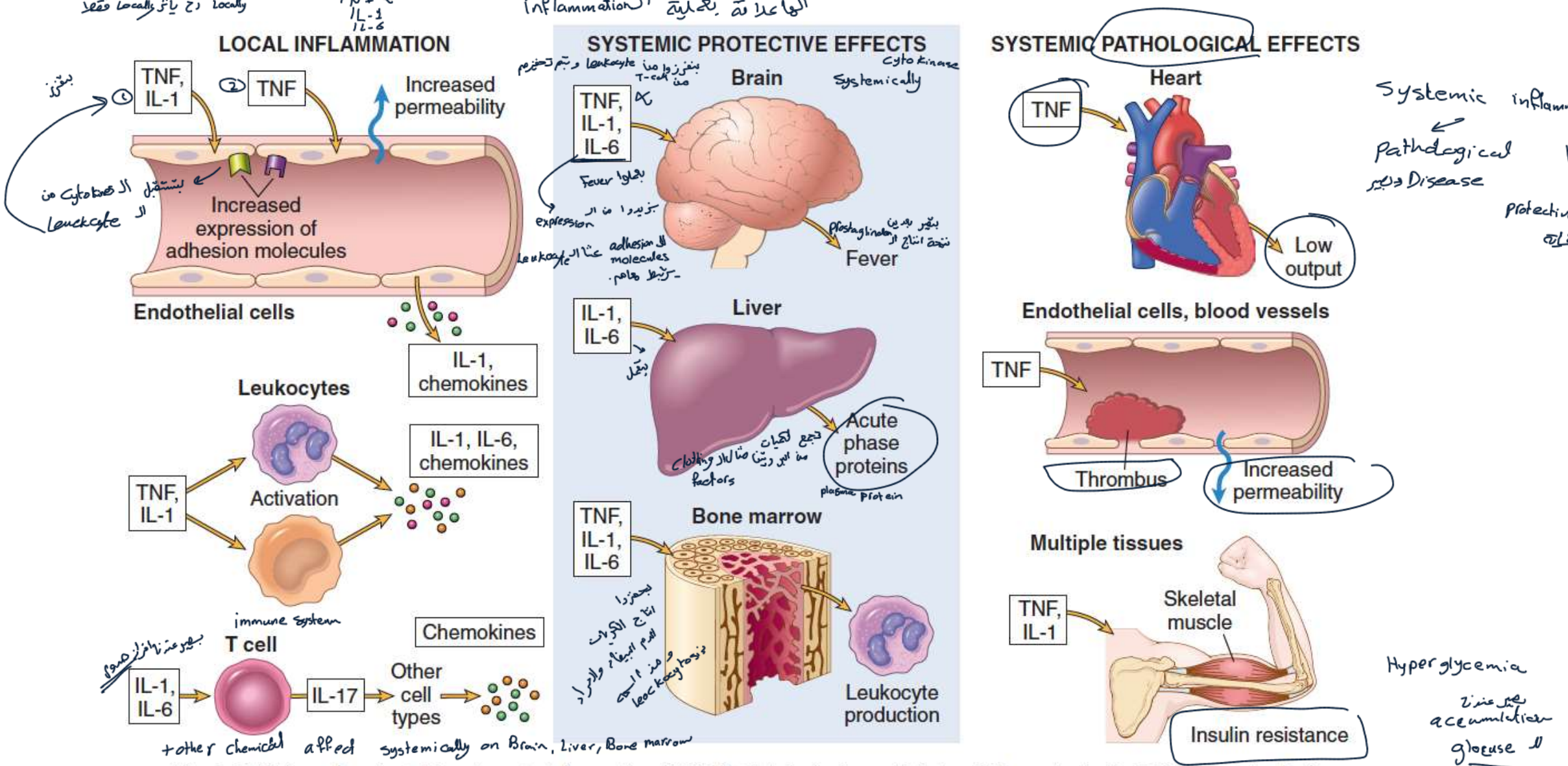


Fig. 3.10 Major roles of cytokines in acute inflammation. *PDGF*, Platelet-derived growth factor; *PGE*, prostaglandin E; *PGI*, prostaglandin I.

The complement system

in general

C3 C4 C5

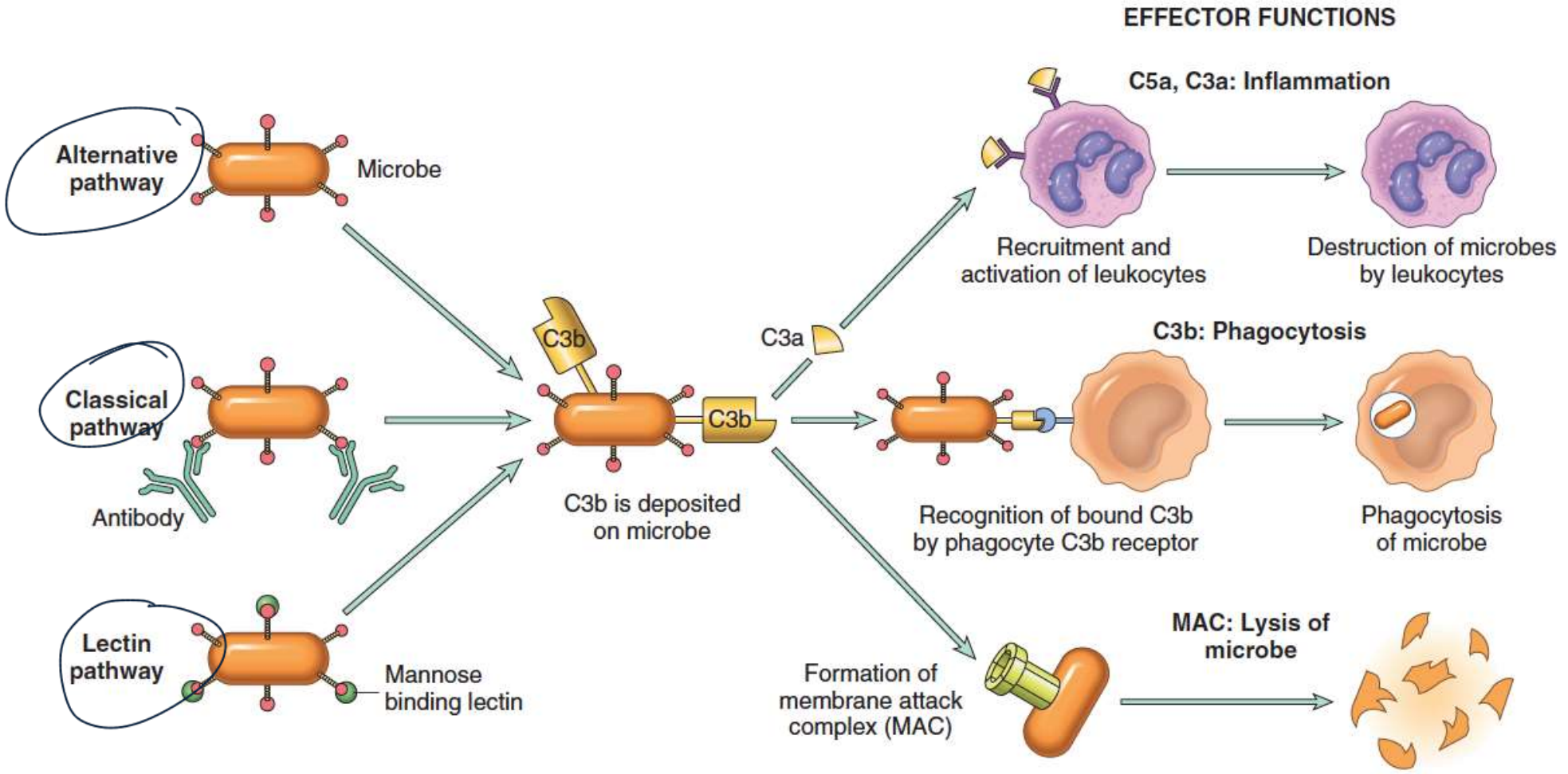
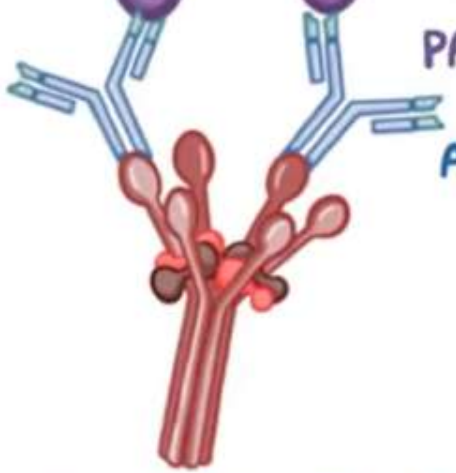


Fig. 3.11 The activation and functions of the complement system. Activation of complement by different pathways leads to cleavage of C3. The functions of the complement system are mediated by breakdown products of C3 and other complement proteins, and by the membrane attack complex (MAC).

CLASSICAL PATHWAY

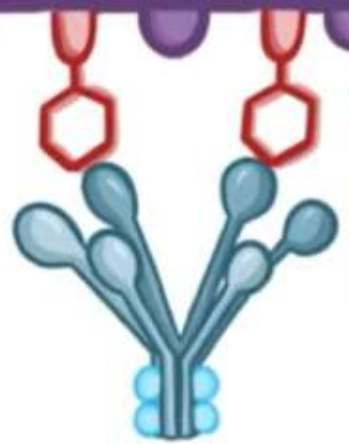
LECTIN BINDING PATHWAY

ALTERNATIVE PATHWAY



PATHOGEN

ANTIBODY



MANNOSE

MANNOSE BINDING LECTIN PROTEIN

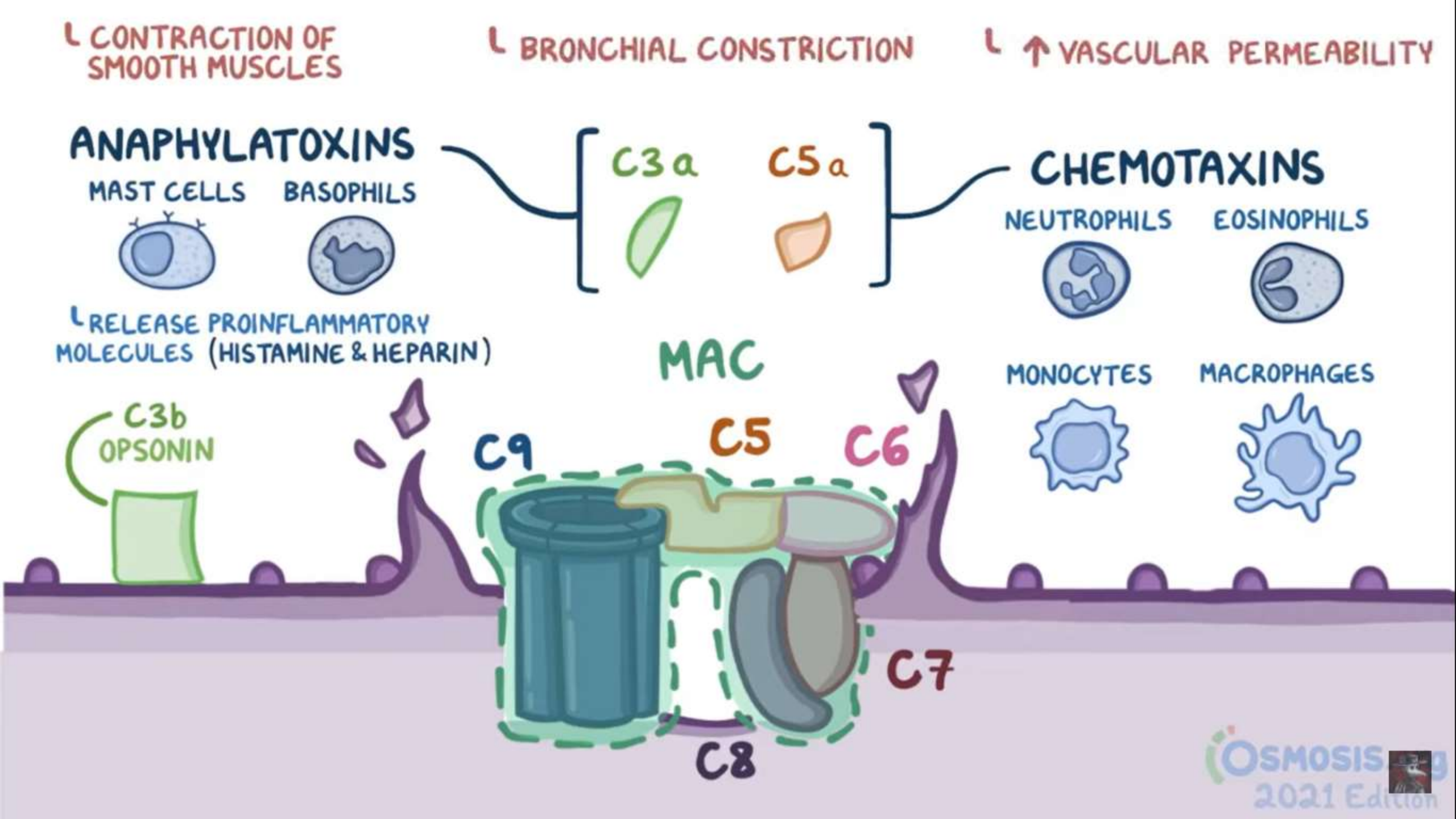
C3 b

C3 a

* ALONG THE WAY

- C5 a + C3 a → CHEMOTAXIN
  → ANAPHYLATOXINS
- C3 b → OPSONIN

HELP DESTROY PATHOGEN


CONTRACTION OF SMOOTH MUSCLES
BRONCHIAL CONSTRICTION
↑ VASCULAR PERMEABILITY
ANAPHYLATOXINS
MAST CELLS
BASOPHILS
C3a
C5a
CHEMOTAXINS
NEUTROPHILS
EOSINOPHILS
RELEASE PROINFLAMMATORY MOLECULES (HISTAMINE & HEPARIN)
MAC
MONOCYTES
MACROPHAGES
C3b OPSONIN
C9
C5
C6
C7
C8
OSMOSIS
2021 Edition

Effects of the complement system

(1) Vascular effects: ***C3a & C5a (anaphylatoxins)*** increase vascular permeability & cause vasodilation.

(2) WBC activation, adhesion, & chemotaxis: ***C5a*** activates WBC, increases their adhesion to EC (integrins), & is a potent chemotactic agent for all WBC (except lymphocytes).

(3) Phagocytosis: When fixed to a microbial surface, ***C3b*** & its inactive proteolytic product C3b act as ***opsonins***, augmenting phagocytosis by neutrophils & macrophages, which express receptors for these complement products.

(2) Kinin system activation

- In which factor XIIa convert plasma prekallikrein into kallkrein, which act on the circulating HMWK (***high molecular weight kininigen***) that leads finally to the formation of ***bradykinin***.

- ***Bradykinin***, *like Histamine* causes arteriolar dilatation, increases vascular permeability, & bronchial smooth muscle contraction.

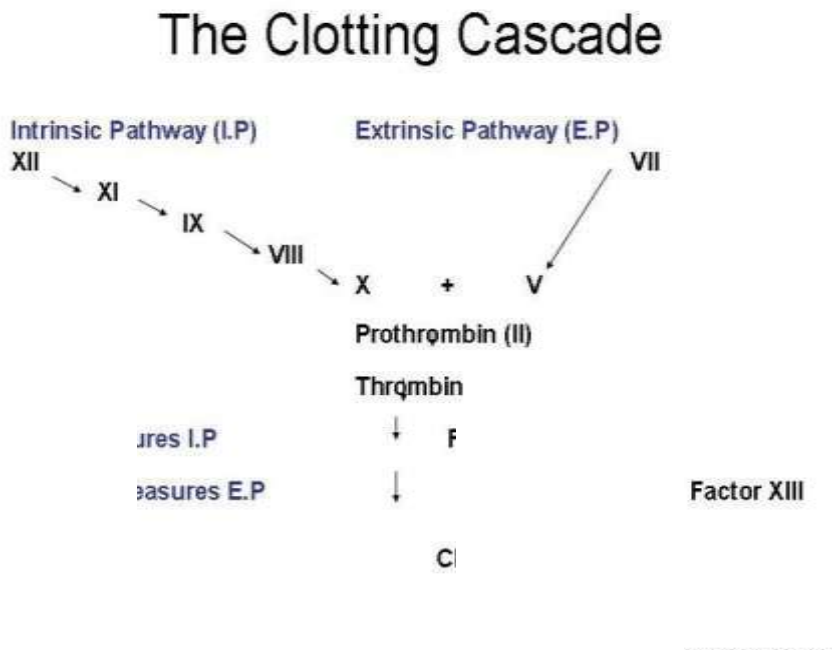
(3) The clotting system:

The clotting system & inflammation are intimately connected processes.

The clotting system is divided into two pathways that play a role in the activation of thrombin and formation of fibrin.

I- The intrinsic clotting pathway

II- The extrinsic pathway



Clotting factors and inflammation

(1) Factor Xa increases vascular permeability & WBC emigration.

(2) Thrombin enhances WBC adhesion to EC.

(3) Fibrinogen cleavage results in the generation of fibrinopeptides that increases vascular permeability & are chemotactic for WBC.

Cell-derived mediators

1. **Preformed mediators in secretory granules of cells**: e.g.

Histamine is secreted by mast cells, basophils & platelets.

Serotonin is secreted by platelets.

Lysosomal enzymes are secreted by neutrophils & macrophages.

2. **Newly-synthesized mediators**: e.g.

Prostaglandins (PG) are secreted by all WBC, platelets, and endothelial cells.

Leukotriens (LT) are secreted by all leukocytes.

Platelets-activating factor (PAF) is secreted by leukocytes & endothelial cells.

Cytokines such as lymphokines are secreted by T-lymphocytes also by macrophages & mast cells.

Nitric oxide is secreted by macrophages.

Activated oxygen radicals (ROS) are released by all Leukocytes.

Other Cell-derived mediators

- Reactive Oxygen Species (ROS):

Released by neutrophils & macrophages during inflammation, have a role in microbial killing & tissue injury.

- Nitric oxide (NO):

A short-lived free radical gas produced by many cells, causing vasodilation & microbial killing.

- Lysosomal enzymes:

Granules in neutrophils & monocytes, cause microbial killing and tissue injury.

Table 3.8 Role of Mediators in Different Reactions of Inflammation

Reaction of Inflammation	Principal Mediators
Vasodilation	Histamine Prostaglandins
Increased vascular permeability	Histamine C3a and C5a (by liberating vasoactive amines from mast cells, other cells) Leukotrienes C_4, D_4, E_4
Chemotaxis, leukocyte recruitment and activation	TNF, IL-1 Chemokines C3a, C5a Leukotriene B_4
Fever	IL-1, TNF Prostaglandins
Pain	Prostaglandins Bradykinin
Tissue damage	Lysosomal enzymes of leukocytes Reactive oxygen species

MORPHOLOGIC PATTERNS OF ACUTE INFLAMMATION:

The

- causative agents.
- severity of injury.
- the type of tissue involved,

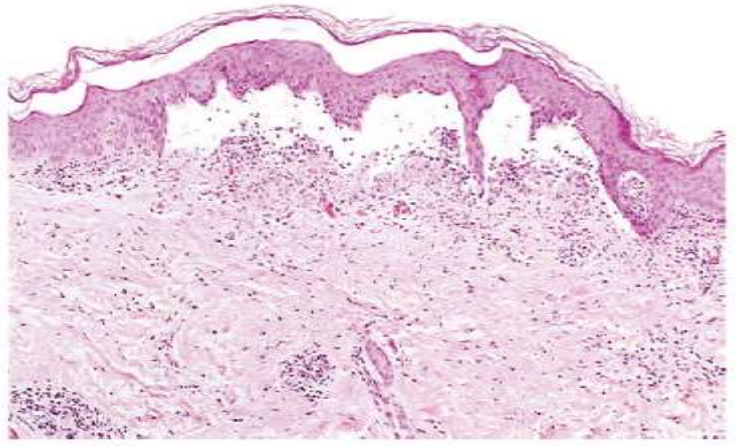
Can all modify the basic morphologic patterns of acute inflammation, producing distinctive appearances.

Serous inflammation

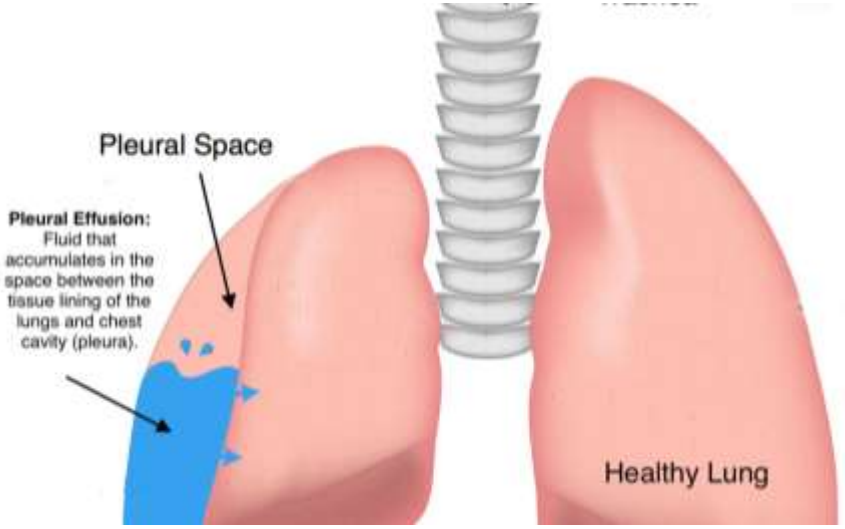
This is characterized by the outpouring of thin fluid that is either derived from the blood (serum) or the secretion of serous mesothelial cells of the pleura, peritoneum, pericardium, or the synovial cells lining the joint spaces.

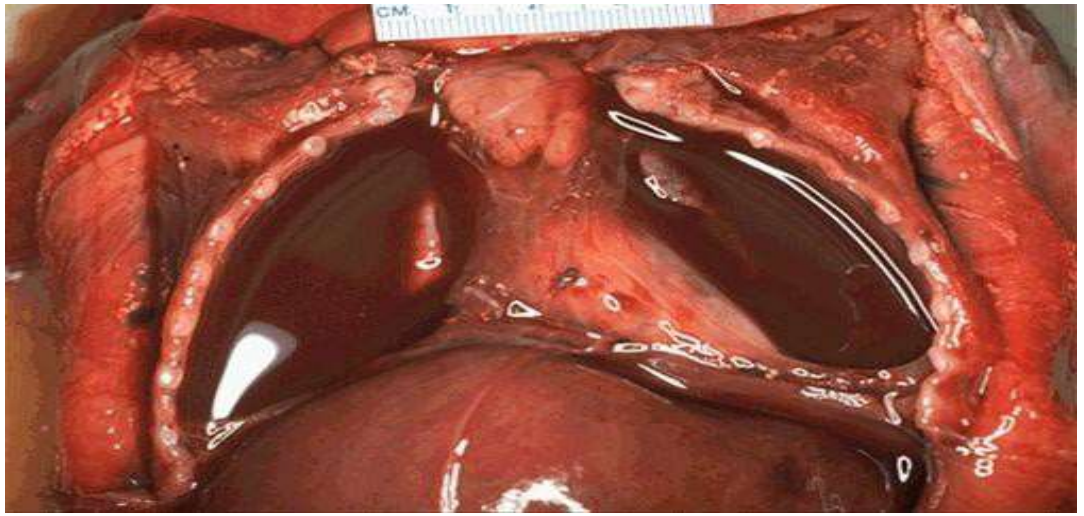
- Fluid accumulating in serous cavities is called ***effusions***, as seen in Tuberculosis.

- ***Skin blister*** that results from a burn or viral infection is also an example of serous inflammation.



Serous inflammation





- Photographic appearance of serous inflammation, (TB) showing collection of a clear watery fluid in both pleural cavities compressing both lungs.

Fibrinous Inflammation

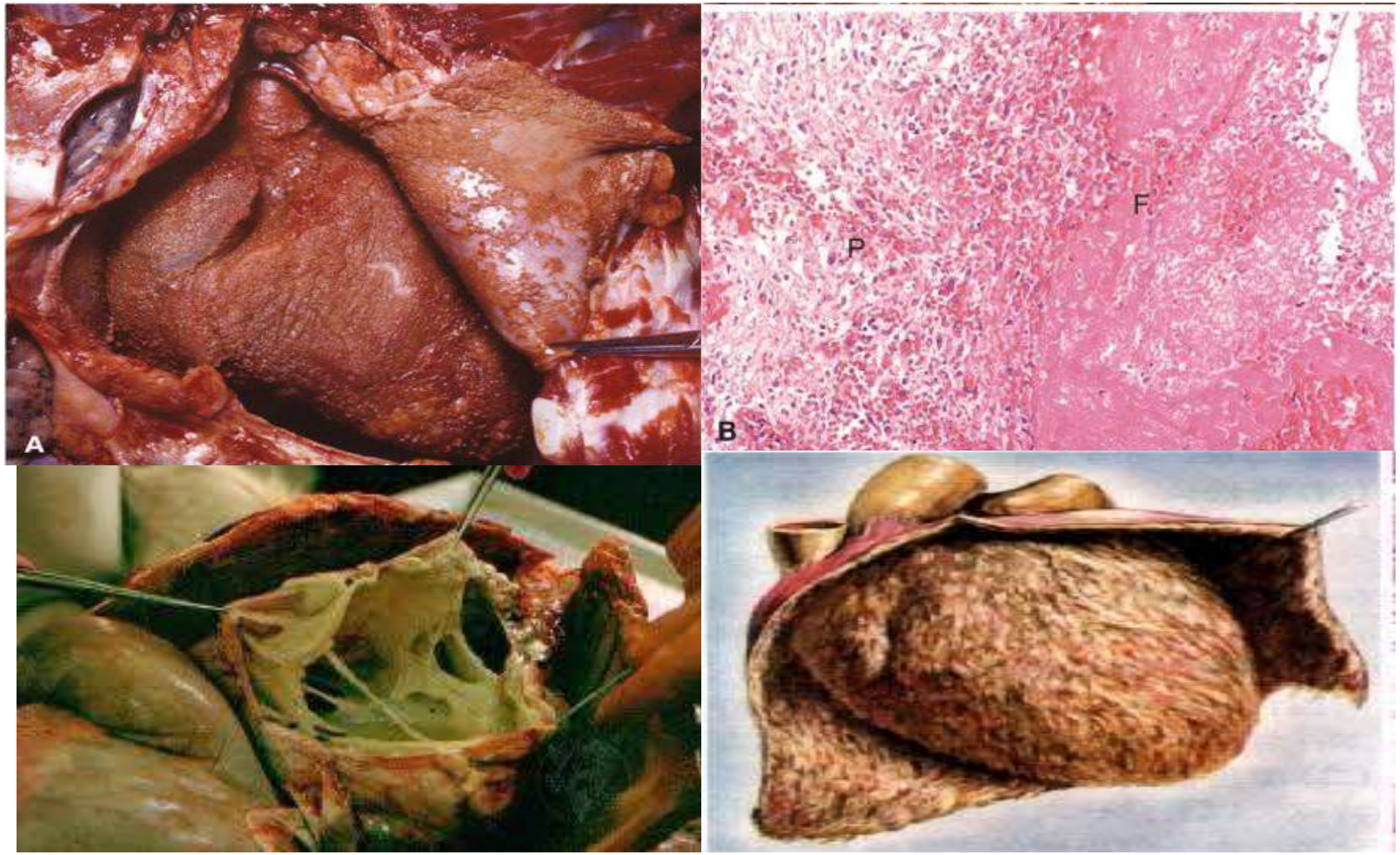
In this type of inflammation, there is the exudation of a large number of plasma proteins including fibrinogen with subsequent precipitation of masses of fibrin. This is characteristic of certain severe inflammatory responses.

In ***rheumatic pericarditis***, the pericardial space may become filled with large masses of fibrin, when the epicardium is stripped from the pericardium, the rubbery adherent fibrin coats both surfaces and simulating the appearance of bread and butter.

The organization of fibrinous exudates by the formation of new capillaries with fibroblasts obliterates the cavity.

Alternatively, there is fibrinolysis & resolution.

Fibrinous Inflammation

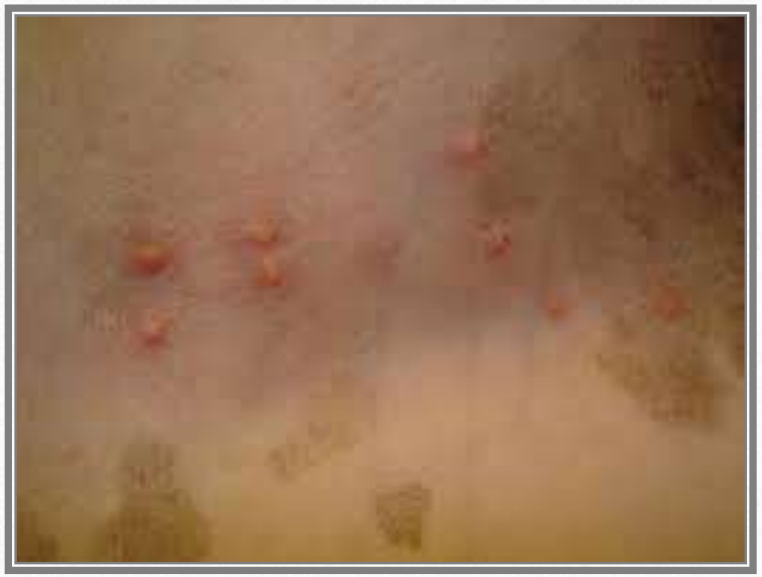


Top left- Gross appearance of fibrinous pericarditis, pericardium opened to show fine precipitates of fibrinous material.

Top right- microscopic view of same case showing homogenous pinkish–colored fibrinous material (F).

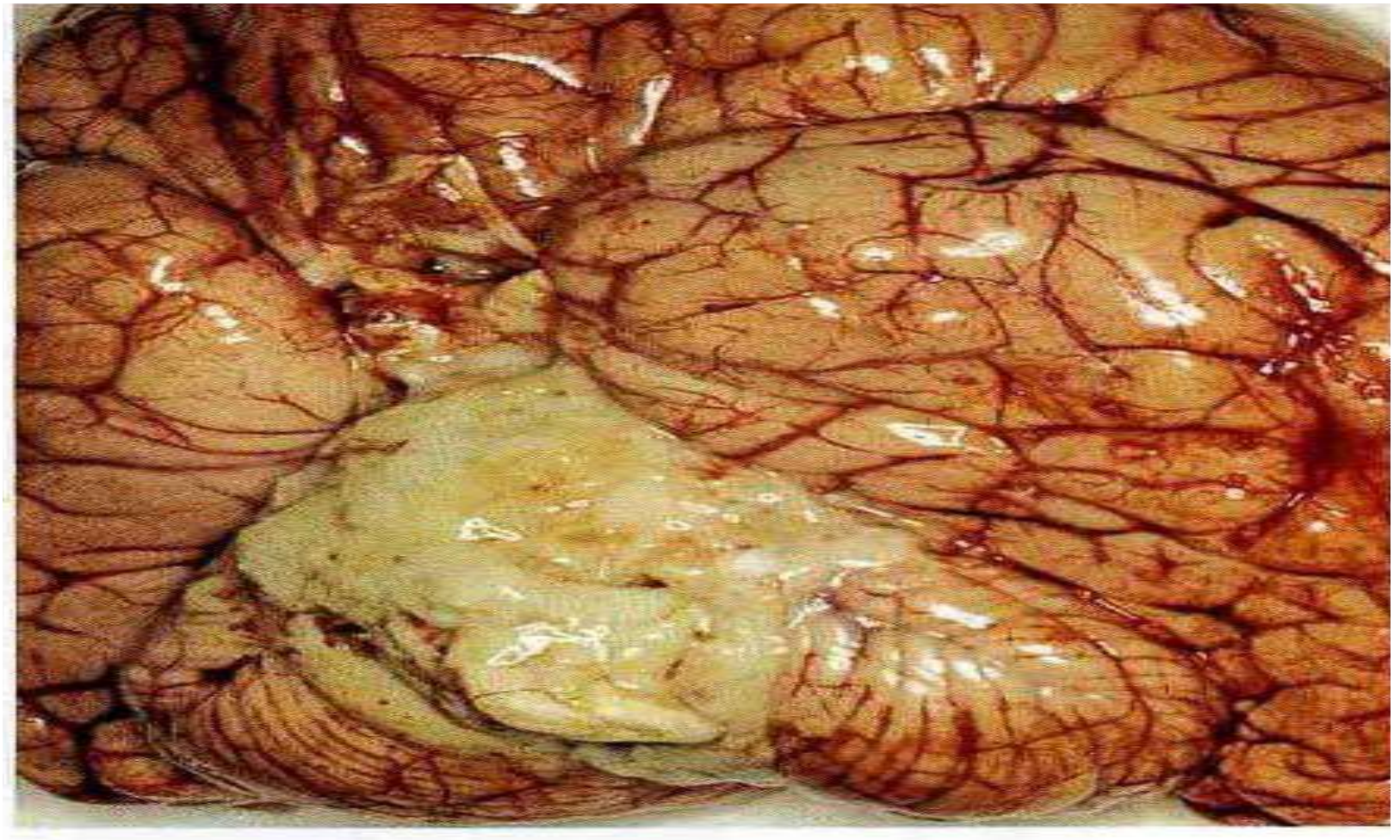
The bottom-Gross appearance of chronic fibrinous inflammation in rheumatic pericarditis showing thick bread & butter appearance of fibrinoid material.

Suppurative inflammation



- This is characterized by the production of a large amount of ***pus*** (or ***purulent exudate***).
- Infection with Staphylococci produces localized suppuration as the skin pustule.
- In suppurative appendicitis, there is pus within the lumen and an intensive infiltration of polymorph neutrophils that are present in the mucosa, submucosa, muscularis & serosa of the appendix.

Suppurative inflammation

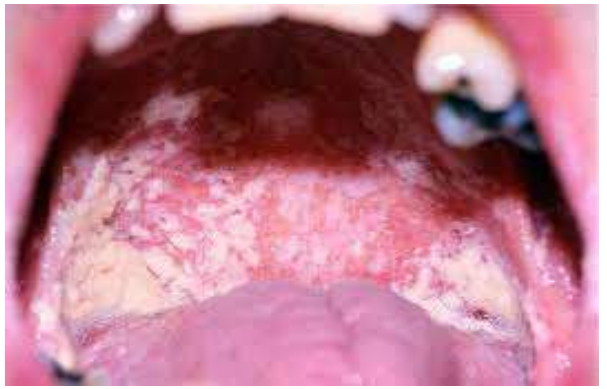


- Gross appearance of the lower surface of the brain showing suppurative inflammation of meninges.

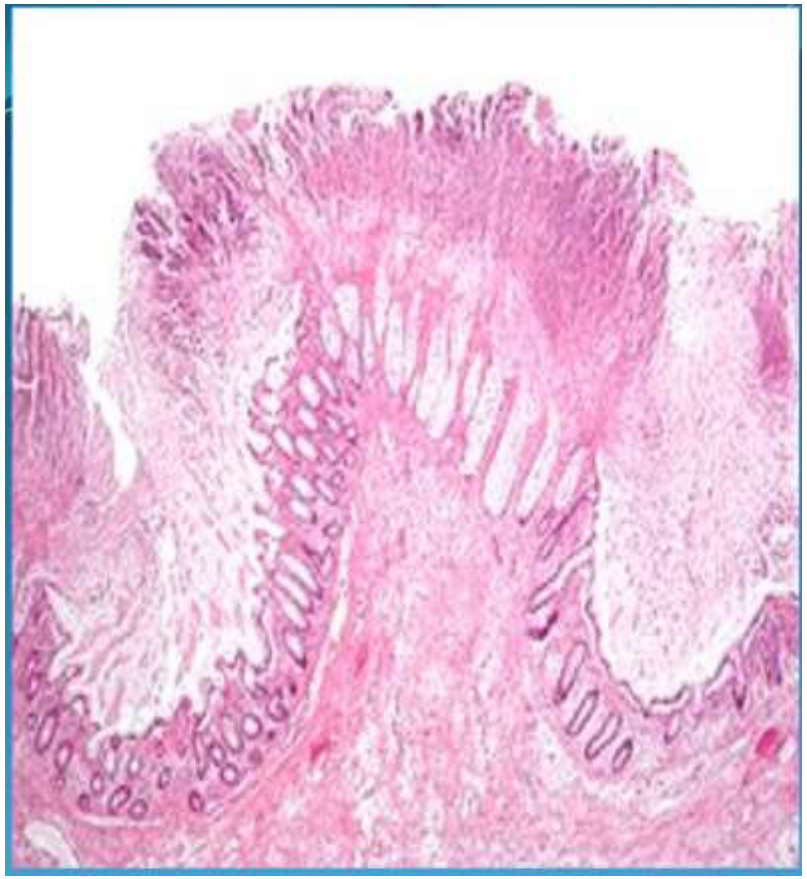
Membranous or pseudomembranous inflammation

- This is a form of inflammatory reaction that is characterized by the formation of a membrane or more correctly a pseudomembrane because it is a non–viable structure.
- It is usually made up of precipitated fibrin, necrotic epithelium & inflammatory leukocytes including polymorph neutrophils, red cells, bacteria & debris of dead tissue producing a false membrane over the inflamed surfaces looking like a bursting volcano.
- This occurs when the inflammation is so severe as to cause epithelial necrosis and sloughing.

An example of this pattern is seen with Diphtheria affecting the larynx & pharynx. It may also affect the large bowel causing pseudomembranous colitis. The latter is caused by Clostridium difficile infection.



Membranous or pseudomembranous inflammation



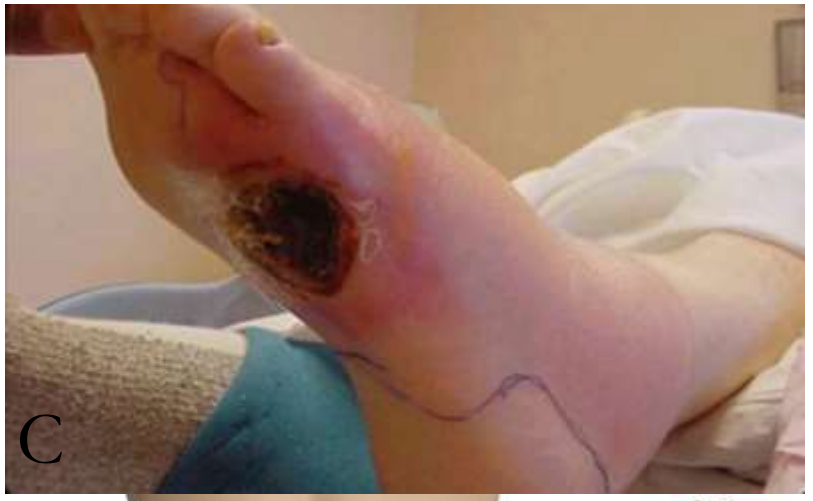
Left: Gross appearance of the colon showing pseudomembranous colitis showing numerous soft yellow pseudomembranes on the colonic mucosal surface.

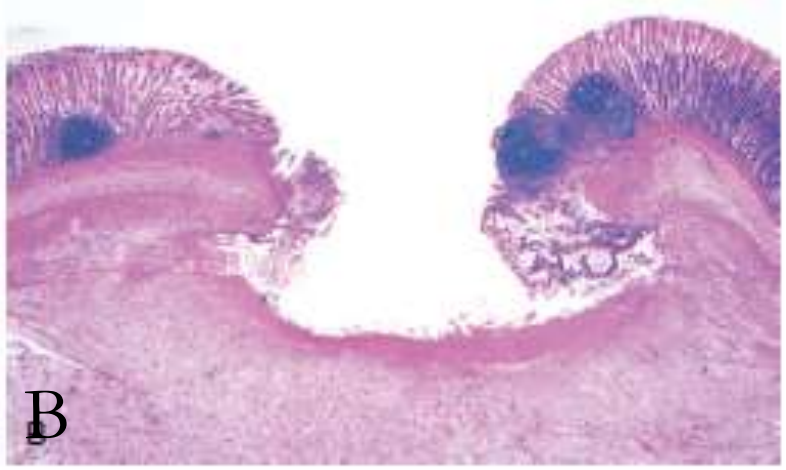
Right: microscopic appearance of pseudomembranous colitis showing a bursting volcano–like precipitate of necrotic slough on colonic mucosa.

Ulcerative inflammation

- An ulcer is a local defect, or excavation, of the surface of an organ or tissue that is produced by necrosis of cells and sloughing (shedding) of necrotic and inflammatory tissue.
- Ulcers are most encountered in
  (1) the mucosa of the GIT and
  (2) the subcutaneous tissues of the lower extremities in older persons who have circulatory disturbances
- Ulcerations are best exemplified by peptic ulcers of the stomach or duodenum, in which *acute and chronic inflammation coexist*.
  - During the acute stage, there is intense polymorphonuclear infiltration and vascular dilation in the margins of the defect. As it develops into a chronic stage, the margins and base of the ulcer develop scarring with an accumulation of lymphocytes, macrophages, and plasma cells.

Ulcerative inflammation





نتيجة ال diabetes

A. Mouth Ulcer

B. Histological appearance of an ulcer

C. Diabetic foot ulcer

D. Decubitus Ulcer/Pressure Ulcer/Bedsores: occurs at sites with little fat and muscle over bony prominences. Ulceration occurs due to the breakdown and ulceration of tissue due to a combination of the weight of the body on the surface of the skin and the friction of a resistant surface such as a bed.

Outcomes of acute inflammation

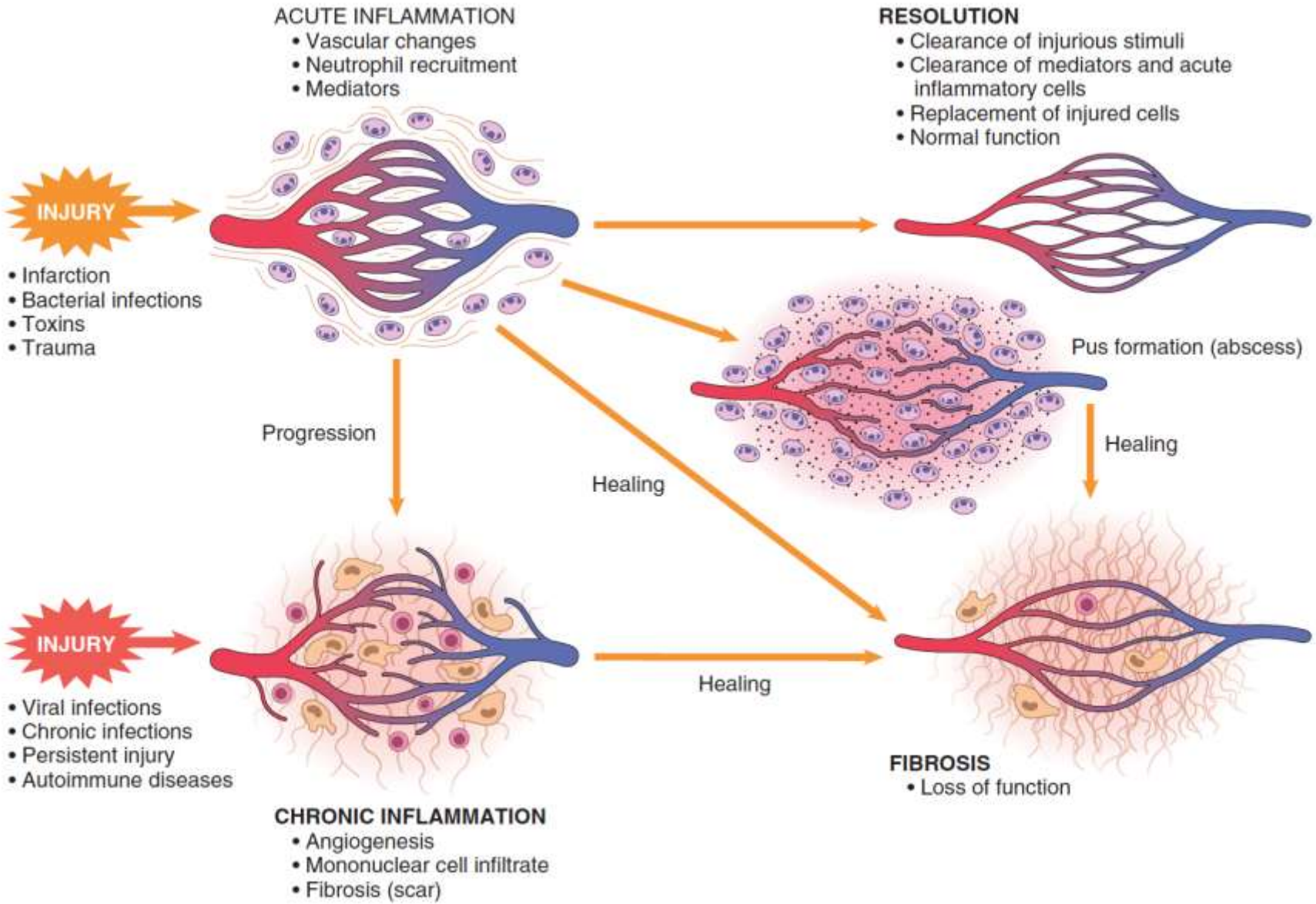


Fig. 3.16 Outcomes of acute inflammation: resolution, healing by fibrosis, or chronic inflammation. The components of the various reactions and their functional outcomes are listed.

acute اذا لم تتم معالجة ال
بتتحول
chronic

Chronic Inflammation

Types of Chronic Inflammatory Cells
Effects of Inflammation

Chronic Inflammation

Inflammation of prolonged duration (weeks, months to years) in which active inflammation, tissue injury, & healing proceed simultaneously.

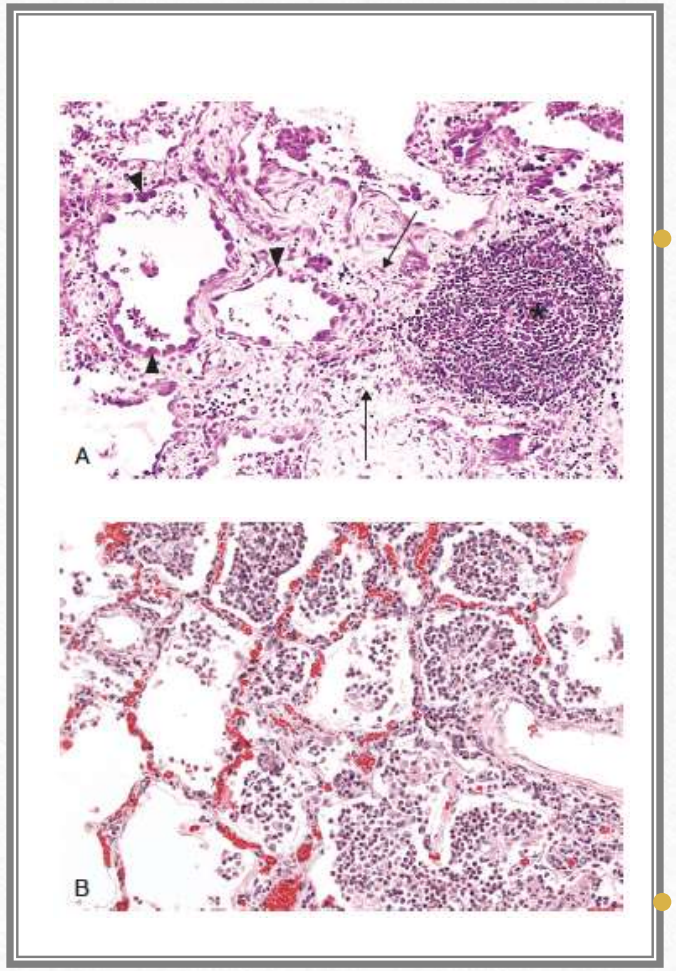
In contrast to acute inflammation, which is distinguished by vascular changes, edema, & neutrophilic infiltrate, chronic inflammation is characterized by chronic ***inflammatory cells infiltration*** together with ***connective tissue deposition & scarring***.

Characteristics of Chronic Inflammation

1. ***Mononuclear chronic inflammatory cells infiltration***, including macrophages, lymphocytes and plasma cells.
2. ***Tissue destruction***, largely directed by the inflammatory cells.
3. ***Repair***, involving new vessel proliferation (angiogenesis) & fibrosis.

fibroblast

Chronic Vs Acute inflammation in the lungs



Chronic inflammation in the lung, showing the characteristic histologic features:

- * collection of chronic inflammatory cells;
- ⏏ destruction of parenchyma (normal alveoli replaced by spaces lined by cuboidal epithelium); and
- ↑ replacement by connective tissue, resulting in fibrosis.

Acute inflammation of the lung (acute bronchopneumonia), neutrophils fill the alveolar spaces and blood vessels are congested.

Nature of leukocyte infiltrates in inflammatory reactions

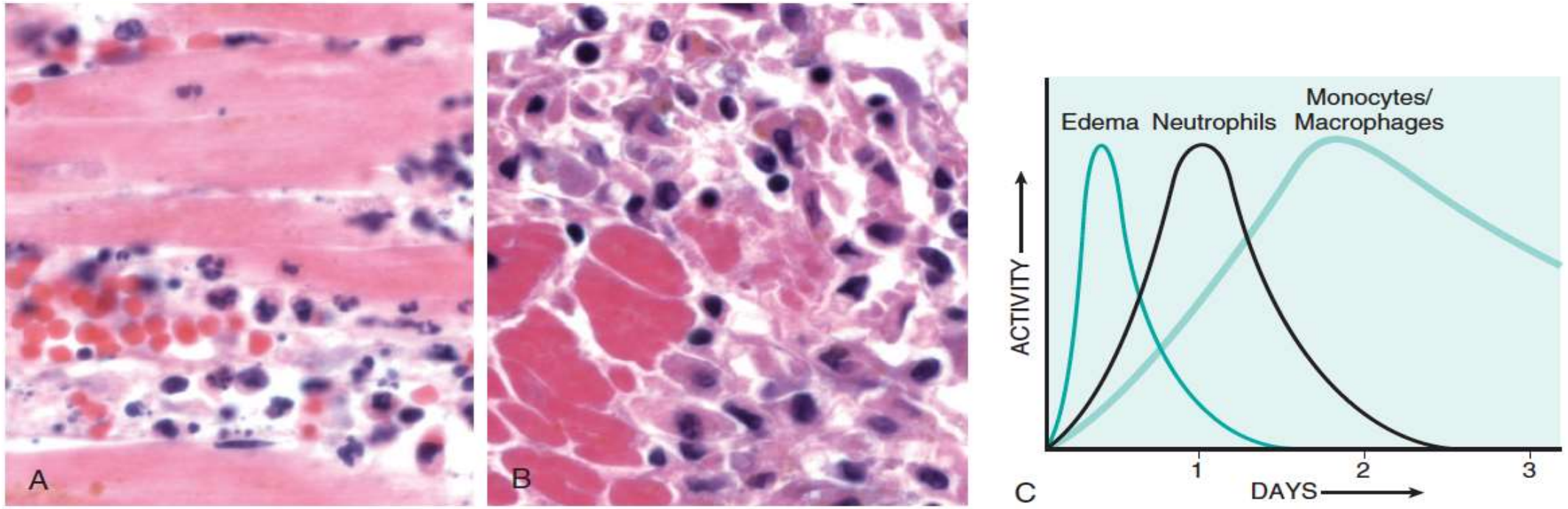


Fig. 3.5 Nature of leukocyte infiltrates in inflammatory reactions. The photomicrographs show an inflammatory reaction in the myocardium after ischemic necrosis (infarction). (A) Early (neutrophilic) infiltrates and congested blood vessels. (B) Later (mononuclear) cellular infiltrates. (C) The approximate kinetics of edema and cellular infiltration. For simplicity, edema is shown as an acute transient response, although secondary waves of delayed edema and neutrophil infiltration also can occur.

Causes of chronic inflammation

1. Progression of acute to chronic inflammation
2. Viral infections = *Most viral infections elicit chronic inflammation*
3. Persistent infections= *microbes that are difficult to eradicate e.g., tubercle bacilli of T.B*
4. Immune-mediated inflammatory diseases, or hypersensitivity diseases = *Rheumatoid arthritis (RA) & inflammatory bowel syndrome (IBS) + bronchial asthma*
5. Prolonged exposure to potentially toxic agents=

- *Exogenous eg. inhaled silica & asbestos*
- *Endogenous eg. plasma lipid components, which may contribute to atherosclerosis*

Chronic Inflammatory cells and Mediators

- Macrophages
- Lymphocytes
- Plasma cells
- Eosinophils
- Mast cells
- Neutrophils

(1) Macrophages

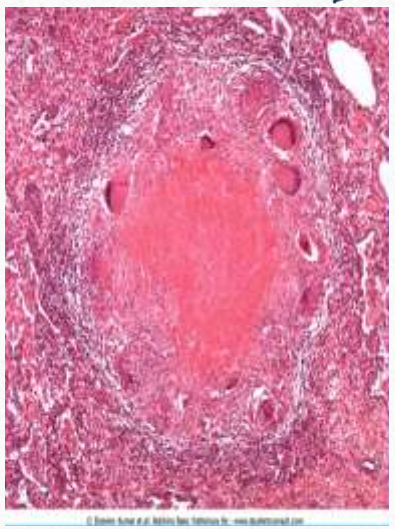
The ***most important*** cell of chronic inflammation, are tissue cells that are derived from circulating blood monocytes.

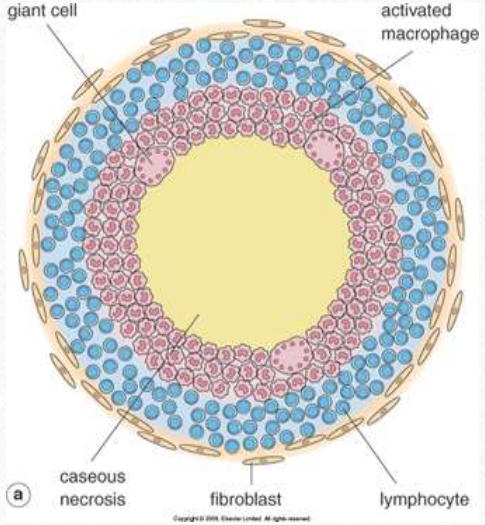
Macrophages, scattered diffusely in most connective tissues normally, but found in increased numbers in certain organs (*mononuclear phagocyte system*):

- liver (Kupffer cells),
- CNS (microglial cells),
- Lungs (alveolar macrophages),
- Spleen & lymph nodes (sinus histiocytes).

Activated macrophages

The activated macrophages appear large, flat pink, this appearance is similar to that of squamous cells & therefore, these cells are called ***epithelioid macrophages*** (epithelial-like). Focal aggregates of these cells are called a ***granuloma***.





Macrophage Products

1. Acid & neutral proteases, plasminogen activator.
2. ROS & NO.
3. (Arachidonic Acid) AA metabolites.
4. Cytokines, e.g., IL-1 & TNF.
5. GFs (PDGF, FGF, TGF-β) that influence the proliferation of fibroblasts, SMC, & the production of ECM.

Fate of macrophages

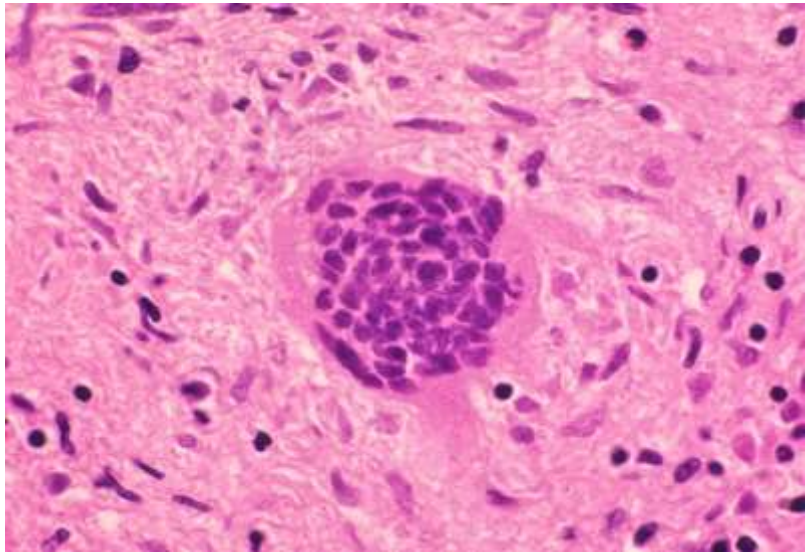
- At sites of acute inflammation where the irritant is cleared & the process is resolved, macrophages die, or pass into lymphatics.

- However, in chronic inflammatory sites, macrophage accumulation persists, & proliferates.

- Steady release of lymphocyte-derived chemokines & other cytokines (e.g., IFN-γ) is an important mechanism by which macrophages are recruited to, or immobilized, in inflammatory sites.

Giant cell:

IFN-γ can also induce macrophages to fuse into large, multinucleated cells called giant cells, a cell contains two or more (up to hundreds) nuclei.

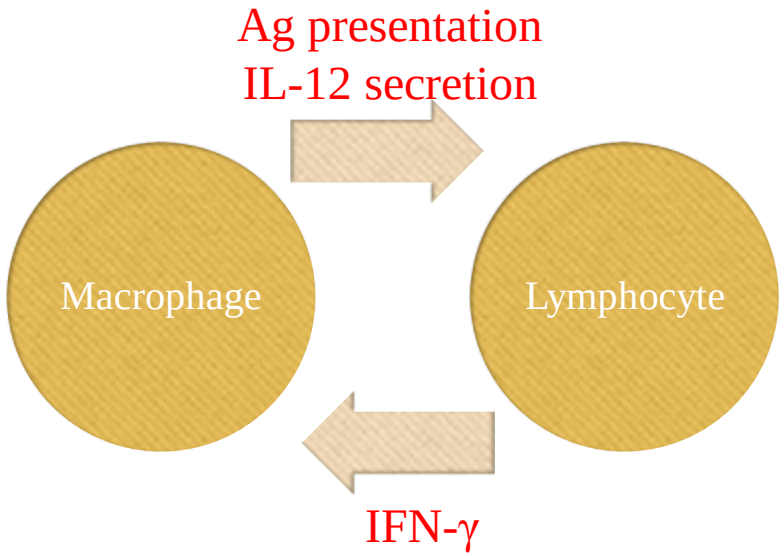


(2) Lymphocytes

Both T & B lymphocytes migrate into inflammatory sites using some of the same adhesion molecule pairs & chemokines that recruit monocytes.

Lymphocytes are mobilized in the setting of:

1. any specific immune stimulus (infections).
2. in non-immune-mediated inflammation (e.g. due to infarction or tissue trauma).



(3) Plasma cells

Are the terminally differentiated end-product of B-cell activation; they can ***produce antibodies*** directed either against

(1) Persistent Ags in the inflammatory site, or

(2) Altered tissue components.

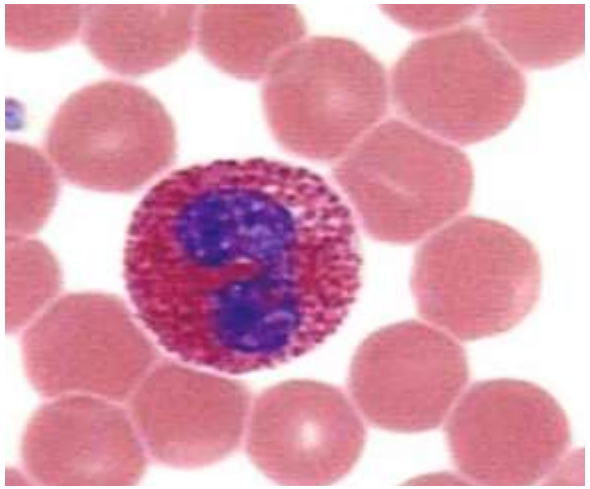
(4) Eosinophils

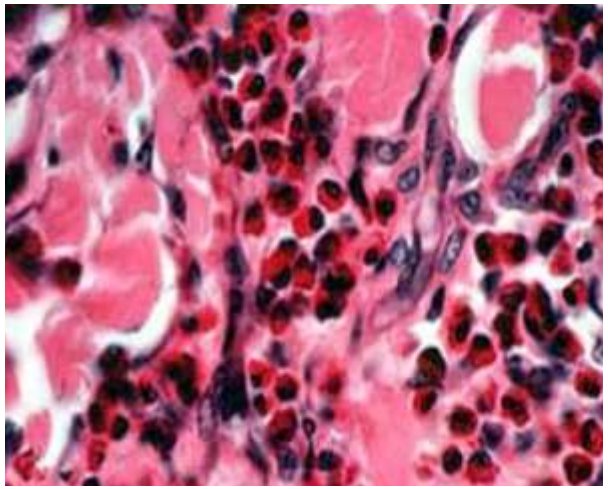
Characteristically found in inflammatory sites around:

(1)***Parasitic infection***, eosinophil-specific granules contain a major basic protein, a highly charged cationic protein that is toxic to parasites.

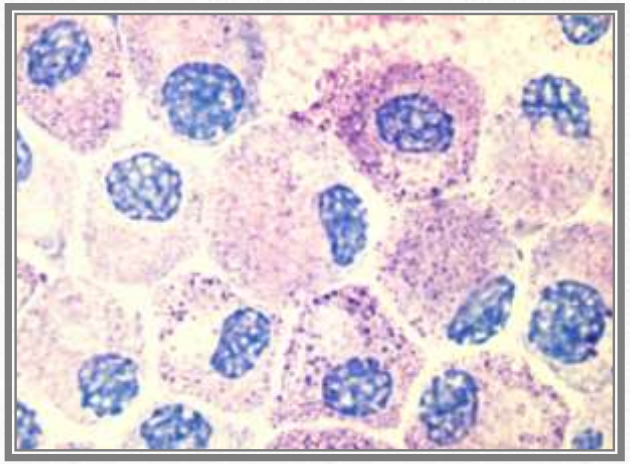
(2)***Part of Allergic immune reactions***.

The emigration of eosinophils is driven by adhesion molecules similar to those used by neutrophils, & by specific chemokines derived from WBC or epithelial cells.

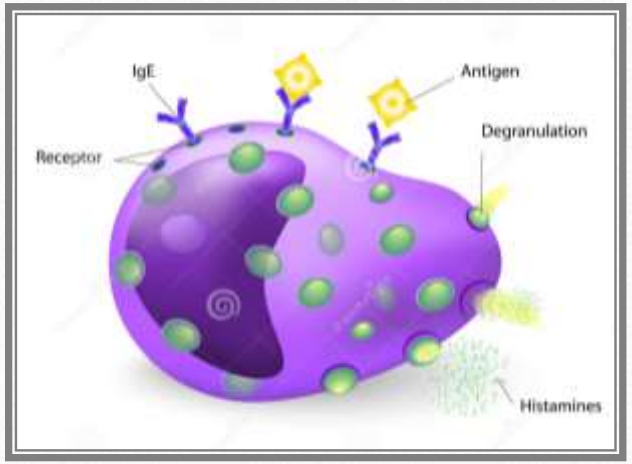




(5) Mast cells



- Are sentinel (guard) cells, widely distributed in connective tissues throughout the body & can participate in both acute & chronic responses.
- In atopic individuals, mast cells are “armed” with IgE Antibodies (Ab) specific for certain Antigens (Ag).
- When these Ags are subsequently encountered, the prearmed mast cells are triggered to release histamine that elicits the vascular dilation & increased permeability of acute inflammation.
- IgE-armed mast cells are central players in allergic reactions including anaphylactic shock & can elaborate cytokines such as TNF & chemokines.



What is a MAST CELL?

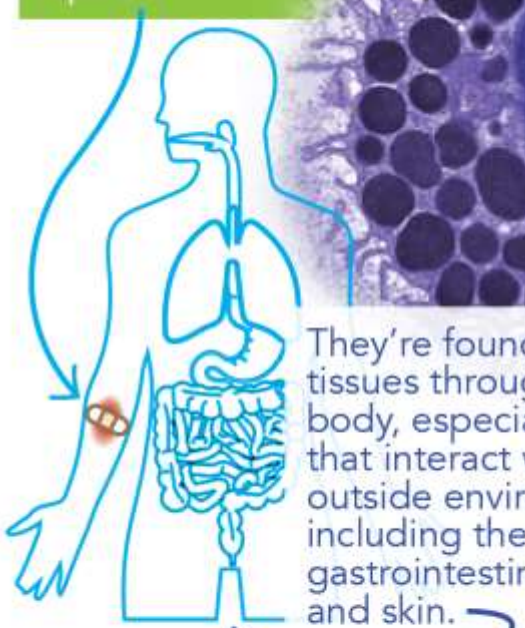
Mast cells are a part of the **immune system**.

Mast cells are well-known for releasing histamine during allergic reactions, such as in pollen or insect sting allergies.

They play an important role in **anaphylaxis!**

Mast cells play a role in inflammation, help defend against pathogens and are involved in wound healing and tissue repair.

They can detect and respond to foreign substances.



They're found in most tissues throughout the body, especially those that interact with the outside environment, including the lungs, gastrointestinal tract and skin.

When a mast cell is activated by a trigger, these granules release many mediators (chemicals that mediate reactions leading to symptoms).

histamine is a mediator

MAST CELL DISEASE happens when these cells aren't behaving normally.

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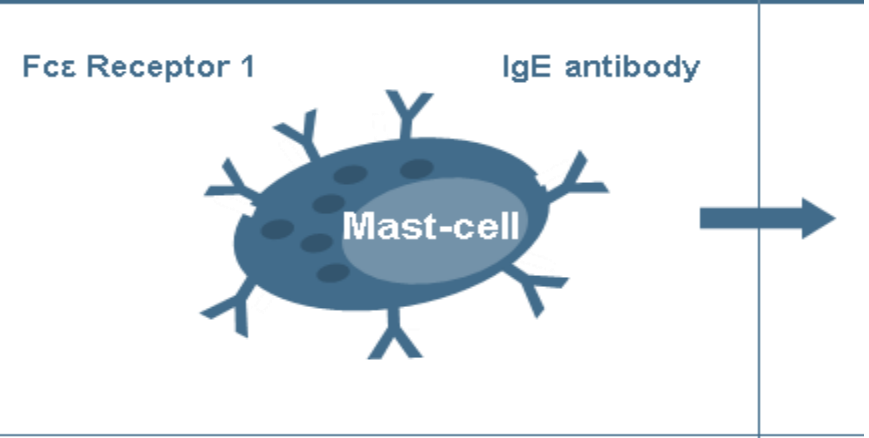
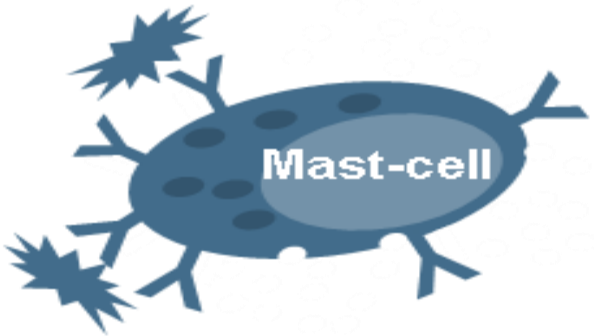
tmsforacure.org

Resting Mast Cell

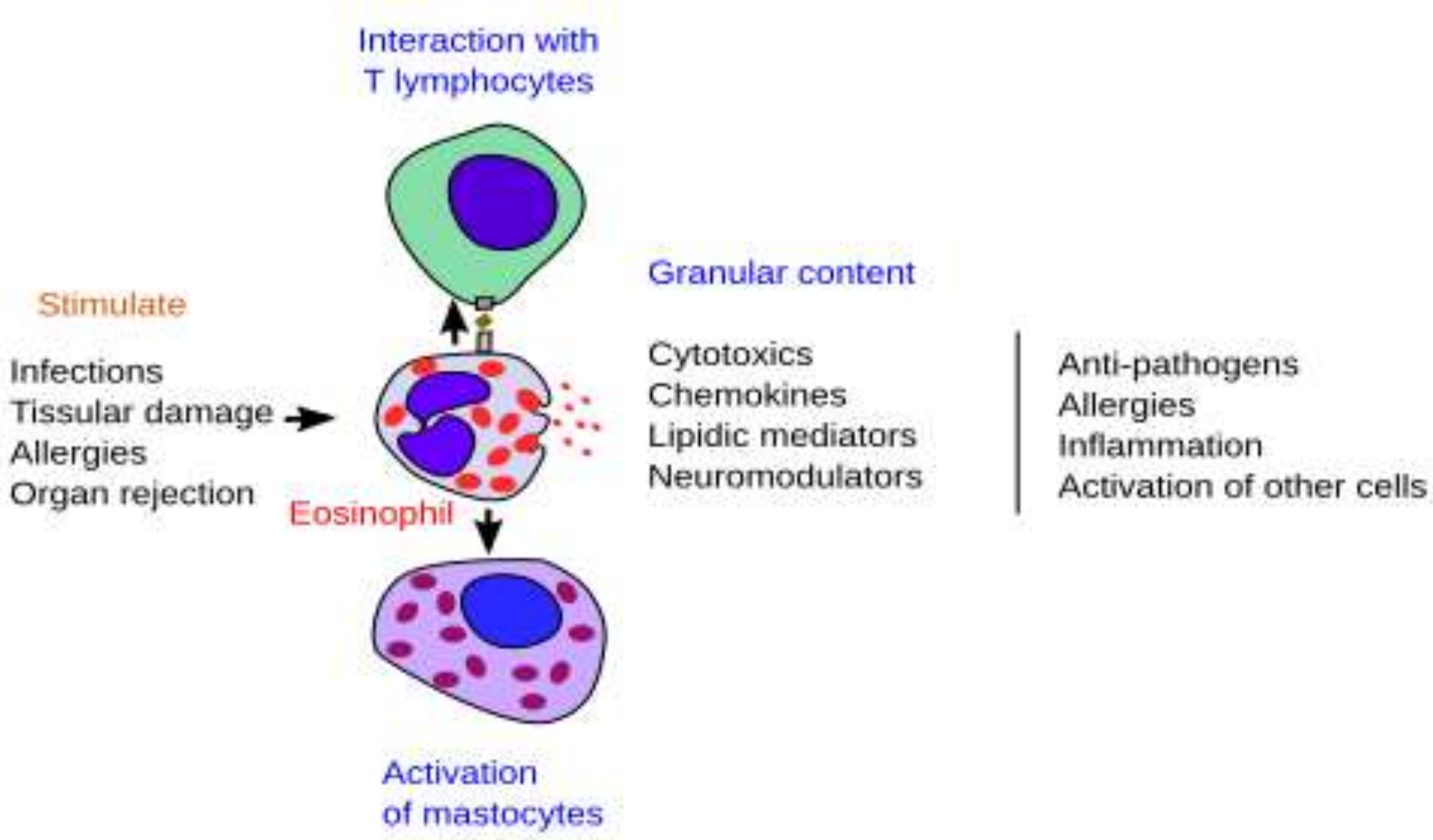


Resting mast cell contains granules containing histamine and other inflammatory mediators

Activated Mast Cell



Multivalent antigen cross-links bound IgE antibody, causing release of granule contents


Interaction with
T lymphocytes
Granular content
Stimulate
Infections
Tissular damage
Allergies
Organ rejection
Cytotoxics
Chemokines
Lipidic mediators
Neuromodulators
Anti-pathogens
Allergies
Inflammation
Activation of other cells
Eosinophil
Activation
of mastocytes

(6) Neutrophils

- Although neutrophils are the classic hallmarks of acute inflammation, many forms of chronic inflammation may continue to s[redacted] due either to persistent of
  (1) [redacted], or
  (2) [redacted], or
  (3) to mediators elaborated by macrophages.

Effects of inflammation

A- Beneficial effects:

- These act partly through the flow of exudates into the tissue & partly by the phagocytic & microbial effects of migrated WBC:
  - **Dilution of toxins.**
  - **Protective antibodies.**
  - **Fibrin formation.**
  - **Promotion of immunity.**

B-Harmful effects:

- **Swelling:** of acutely inflamed tissue may have serious mechanical effects e.g in acute laryngitis suffocation in children.
- **Rise in tissue pressure**

Beneficial effects of inflammation

(1) Dilution of toxins:

Exudates dilute chemical and bacterial toxins & enhance their carriage by lymphatics.

(2) Protective antibodies:

The proteins present in the exudates include antibodies, which have been already present in the plasma as a result of previous infection or immunization. These antibodies attack injurious agents in an attempt to destroy them immunologically.

Beneficial effects of inflammation

(3) Fibrin formation :

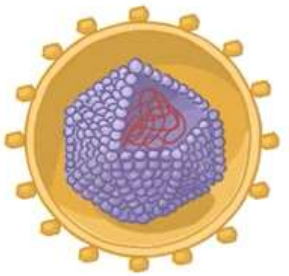
Fibrinogen of the blood is included in the exudates. In the extravascular space, it is converted into solid fibrin. A network of the deposited fibrin is seen in the inflamed tissue forming a mechanical barrier that precludes the movement & spread of bacteria, it may also aid in their phagocytosis.

(4) Promotion of immunity:

Bacteria in the inflammatory exudates, whether free or phagocytosed, are carried to the lymph nodes by lymphatics. There they mount an immune response, which provides antibodies & cellular mechanisms that may appear after a few days and may remain for years. These immunological mechanisms help destroy microbial agents.

INFLAMMATION

COMPLEX RESPONSE to HARMFUL STIMULI



- PATHOGEN
- TRAUMA or TOXINS

BLOOD VESSELS DILATE → PERMEABLE

→ ATTRACT IMMUNE CELLS & FLUID

HEAT

REDNESS

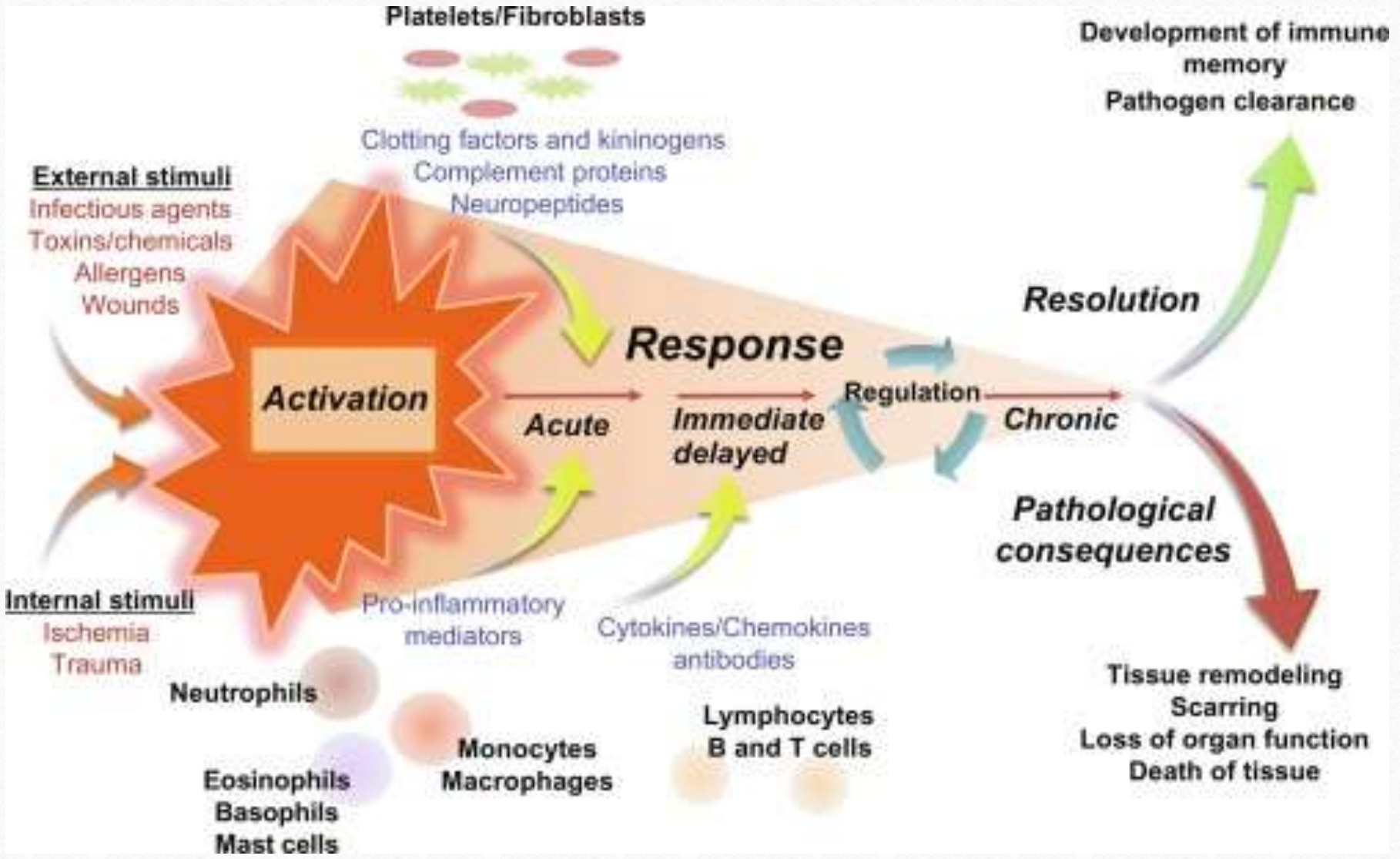
PAIN

SWELLING

LOSS OF FUNCTION

WOUND REPAIR & RESOLUTION

- INITIAL TISSUE INTEGRITY
- FIBROUS SCAR


Platelets/Fibroblasts
Clotting factors and kininogens
Complement proteins
Neuropeptides
External stimuli
Infectious agents
Toxins/chemicals
Allergens
Wounds
Activation
Response
Acute
Immediate
delayed
Regulation
Chronic
Resolution
Development of immune memory
Pathogen clearance
Pathological consequences
Tissue remodeling
Scarring
Loss of organ function
Death of tissue
Internal stimuli
Ischemia
Trauma
Pro-inflammatory mediators
Cytokines/Chemokines antibodies
Neutrophils
Monocytes
Macrophages
Lymphocytes
B and T cells
Eosinophils
Basophils
Mast cells

Thank You