INFLAMMATION

Presented by
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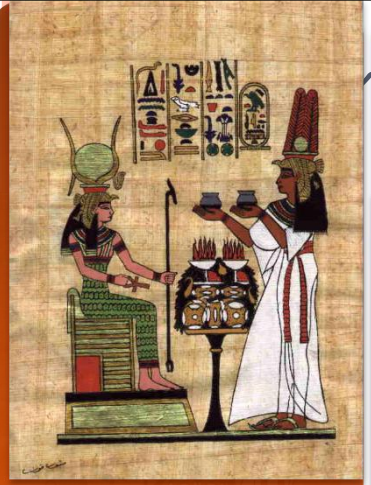
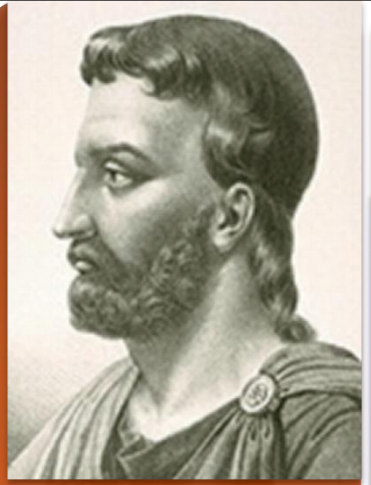
INTRODUCTION

Inflammatio" - to set on fire

Local response of living tissues to injury due to any agent

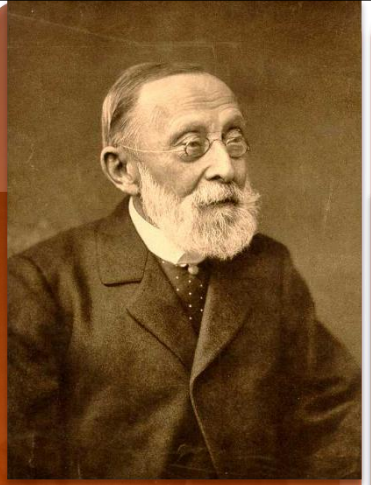


Egyptian Papyrus 3000 B.C



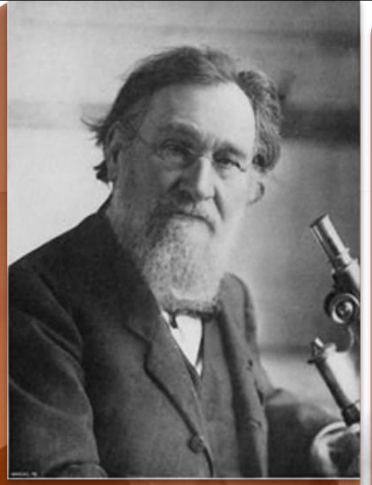
Celsus 1 a.D

4 cardinal signs.



Virchow

5th sign



Eli Metchnikoff

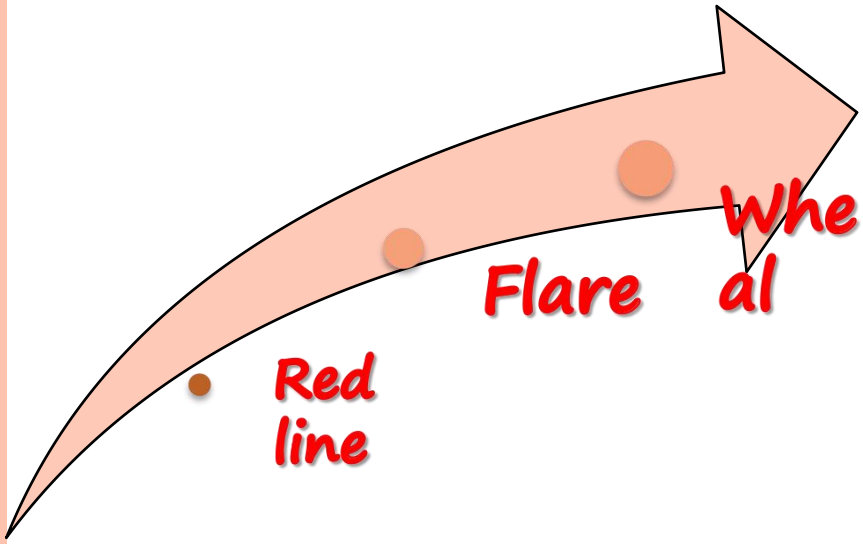
1880

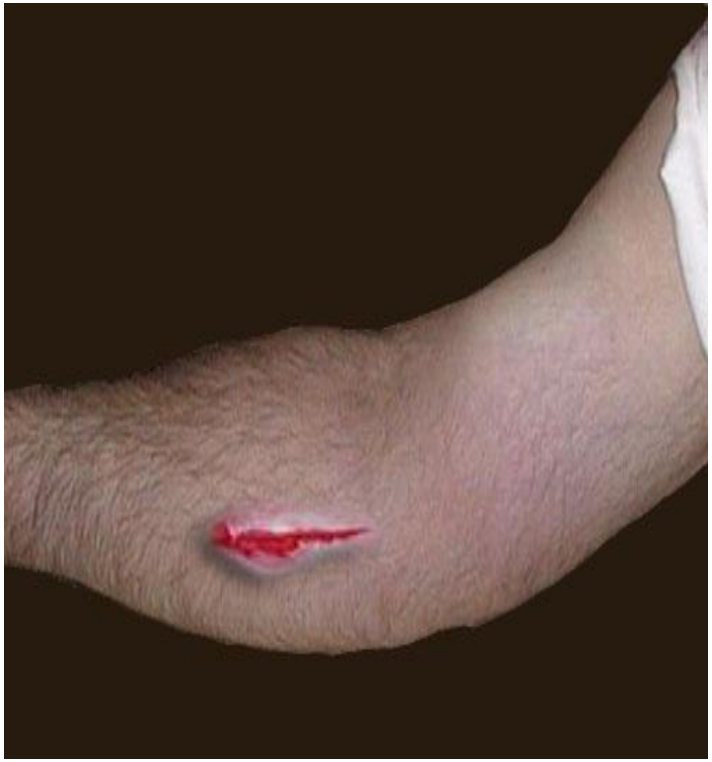
Phagocytosis

Sir Thomas Lewis

chemical substances, histamine mediate vascular changes in infl.

TRIPLE RESPONSE OR RED LINE RESPONSE – LEWIS EXPERIMENT





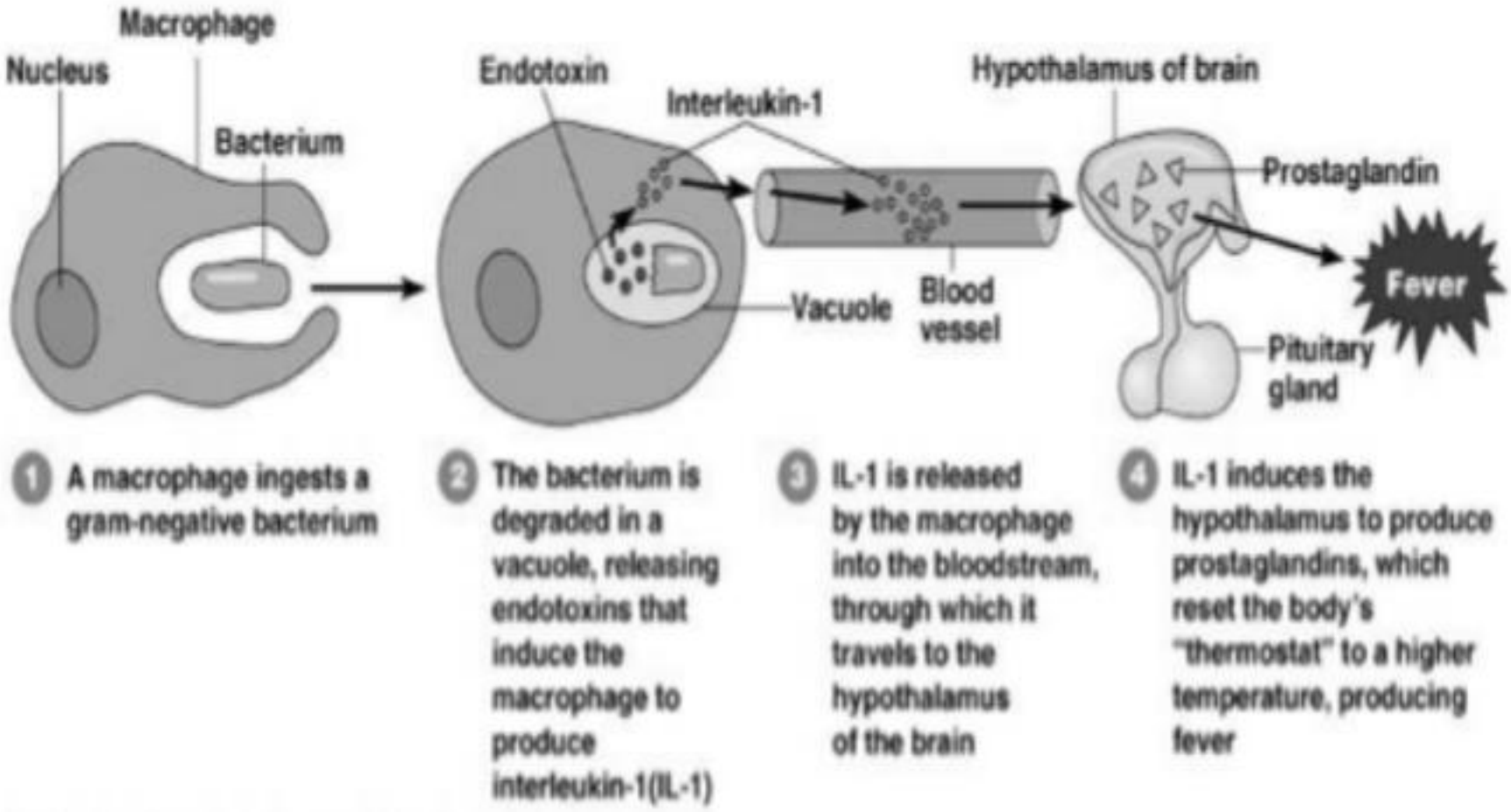
Cardinal Signs of Inflammation

ETIOLOGY

- Microbial Infection
- Hyper sensitivity /Immune reactions
- Physical agents,irritants,corrosive chemicals
- Tissue necrosis

EFFECTS OF INFLAMMATION

leucocytosis,fever endotoxemia



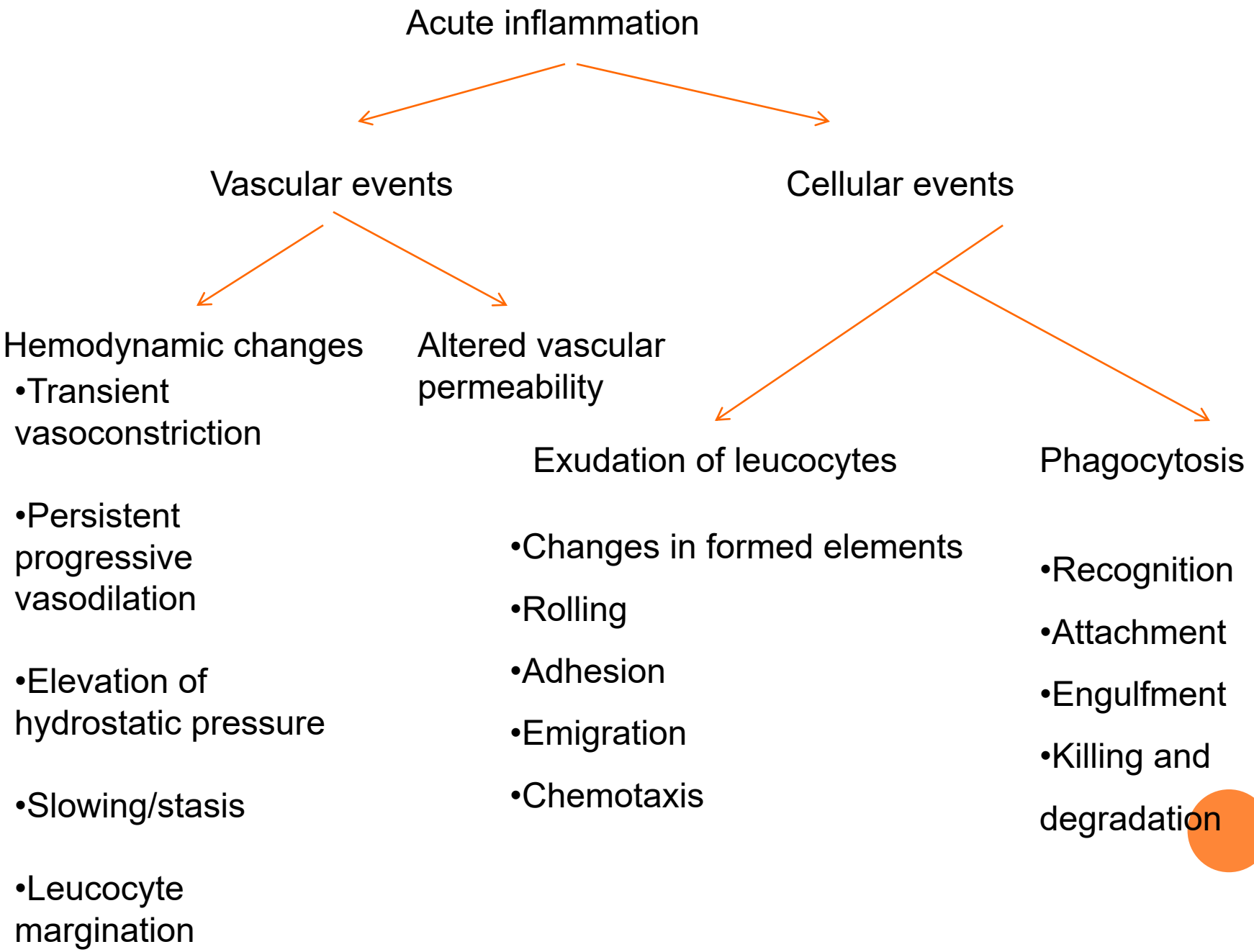
TYPES

Acute

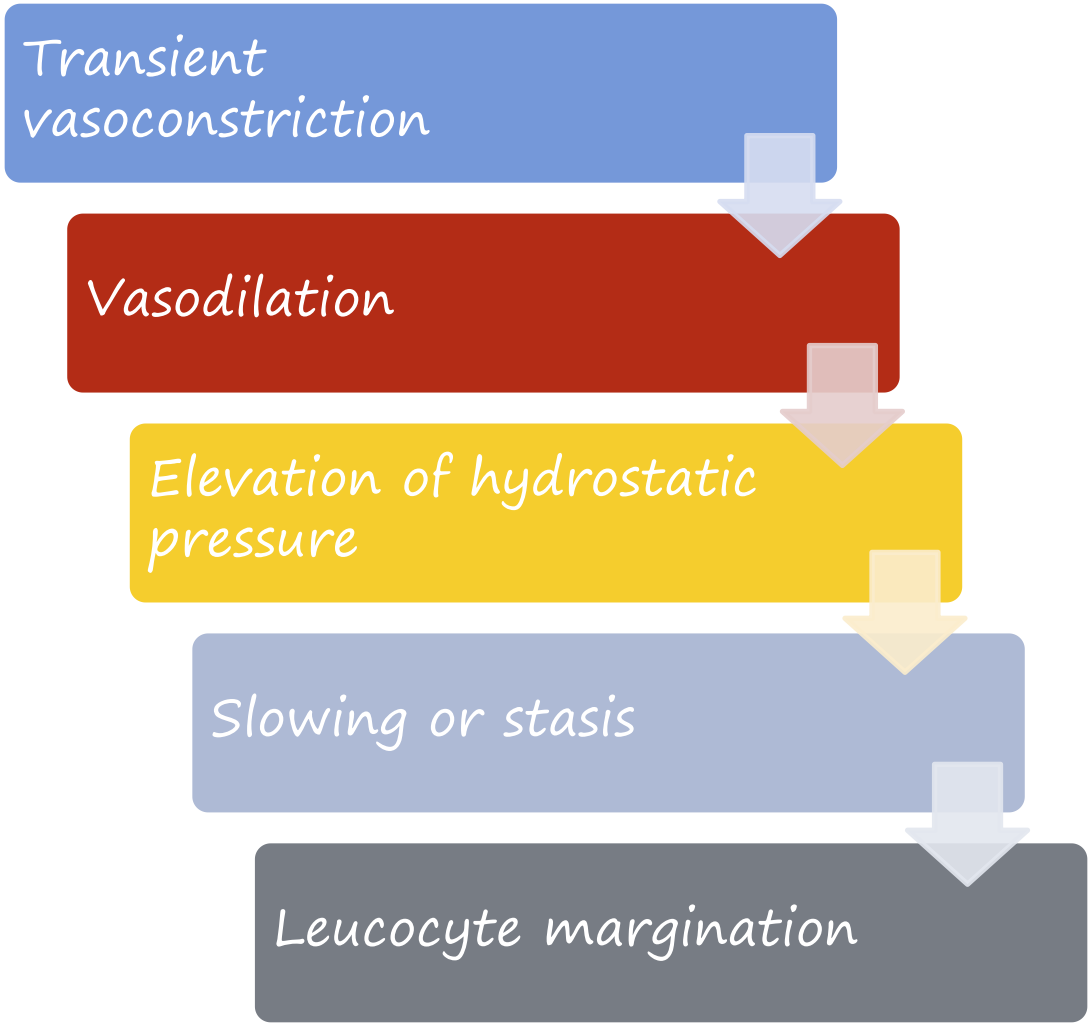
- Several hours
- PMNs, monocytes

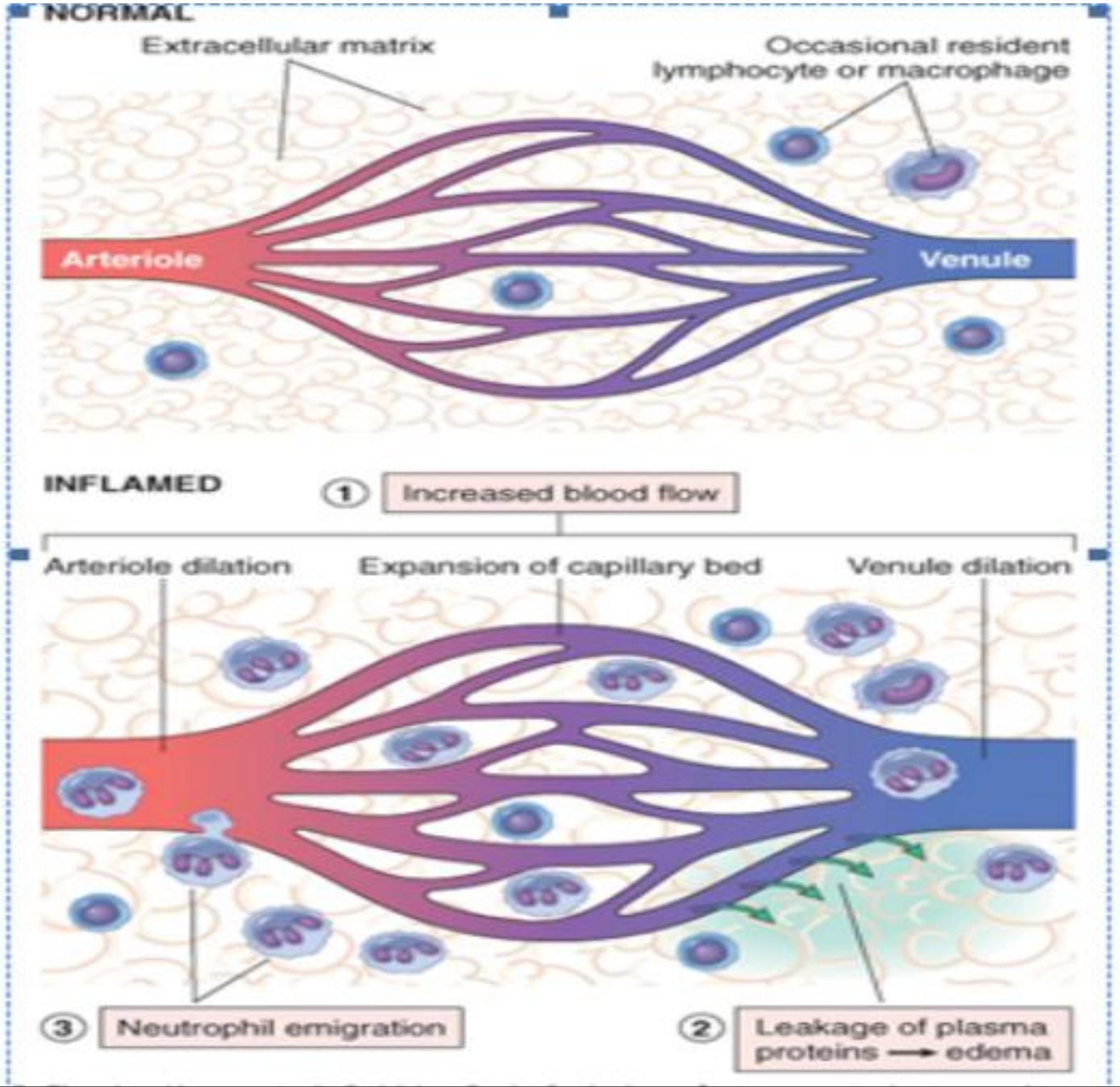
Chronic

- Acute ⇨ chronic, if stays for a longer time
- Lymphocytes, macrophages

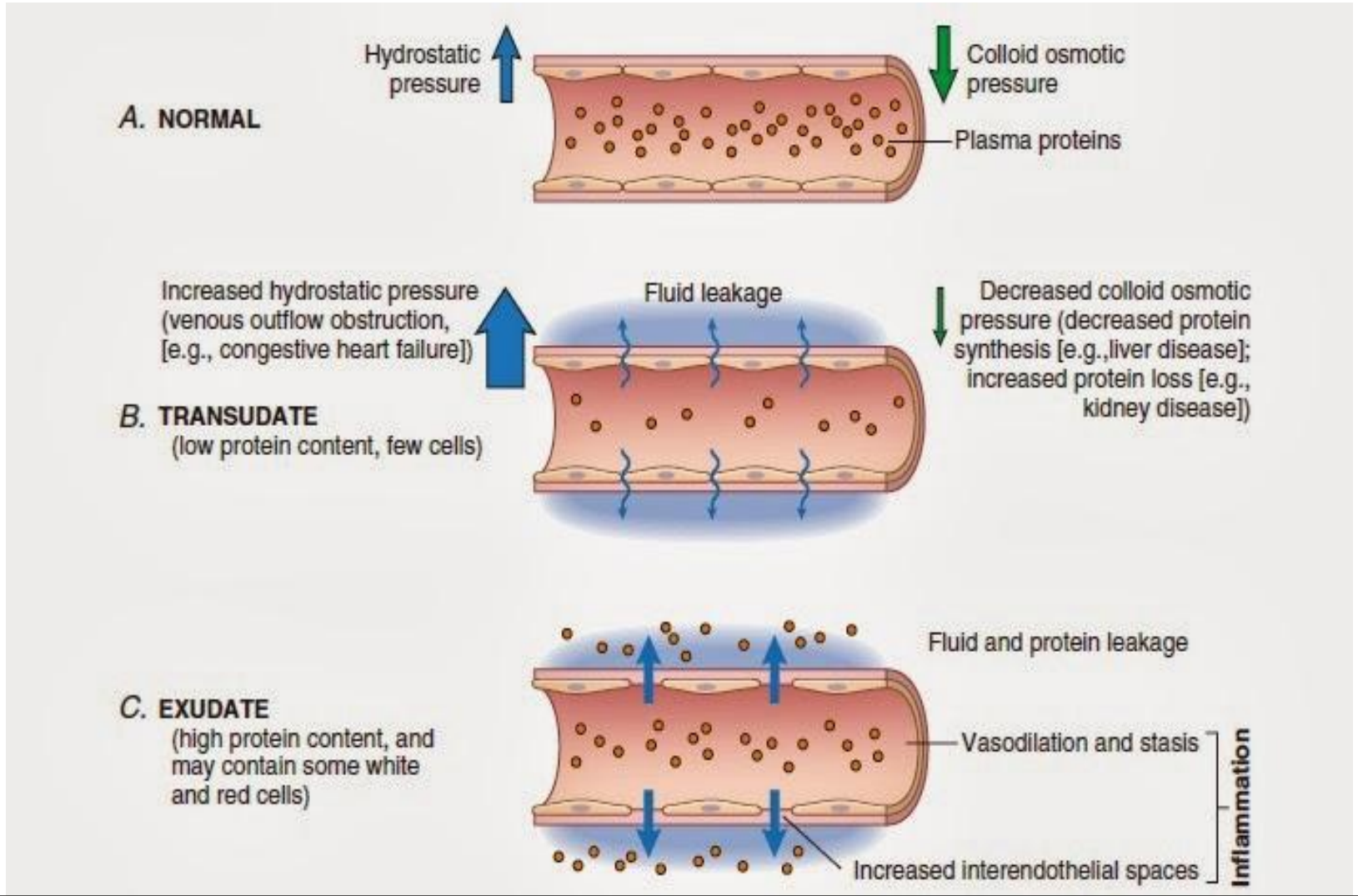

Acute inflammation
Vascular events
Cellular events
Hemodynamic changes
•Transient vasoconstriction
•Persistent progressive vasodilation
•Elevation of hydrostatic pressure
•Slowing/stasis
•Leucocyte margination
Altered vascular permeability
Exudation of leucocytes
•Changes in formed elements
•Rolling
•Adhesion
•Emigration
•Chemotaxis
Phagocytosis
•Recognition
•Attachment
•Engulfment
•Killing and degradation

Hemodynamic changes

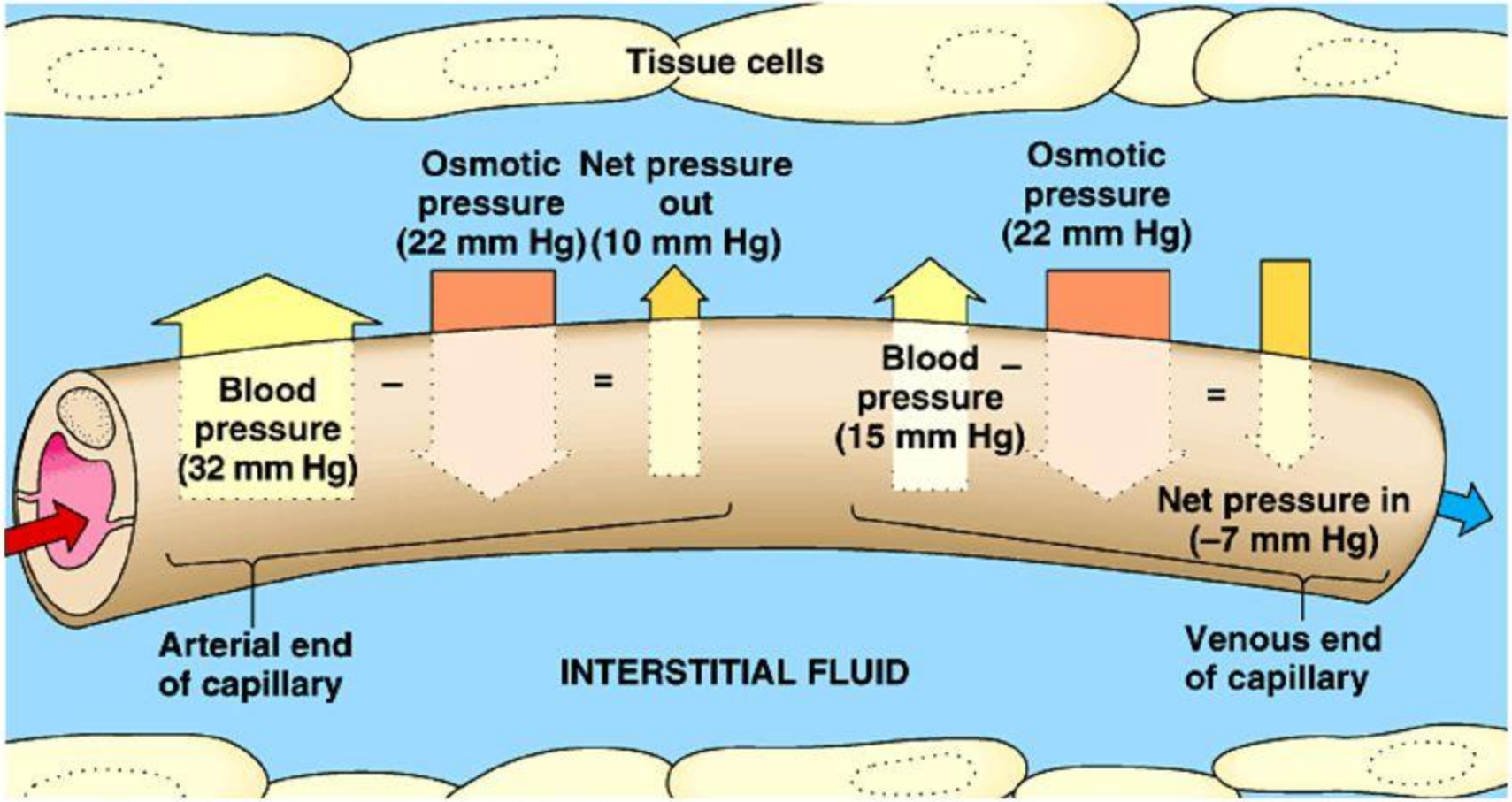



NORMAL
Extracellular matrix
Occasional resident lymphocyte or macrophage
Arteriole
Venule
INFLAMED
1
Increased blood flow
Arteriole dilation
Expansion of capillary bed
Venule dilation
3
Neutrophil emigration
2
Leakage of plasma proteins → edema

Altered vascular permeability



Starling Hypothesis



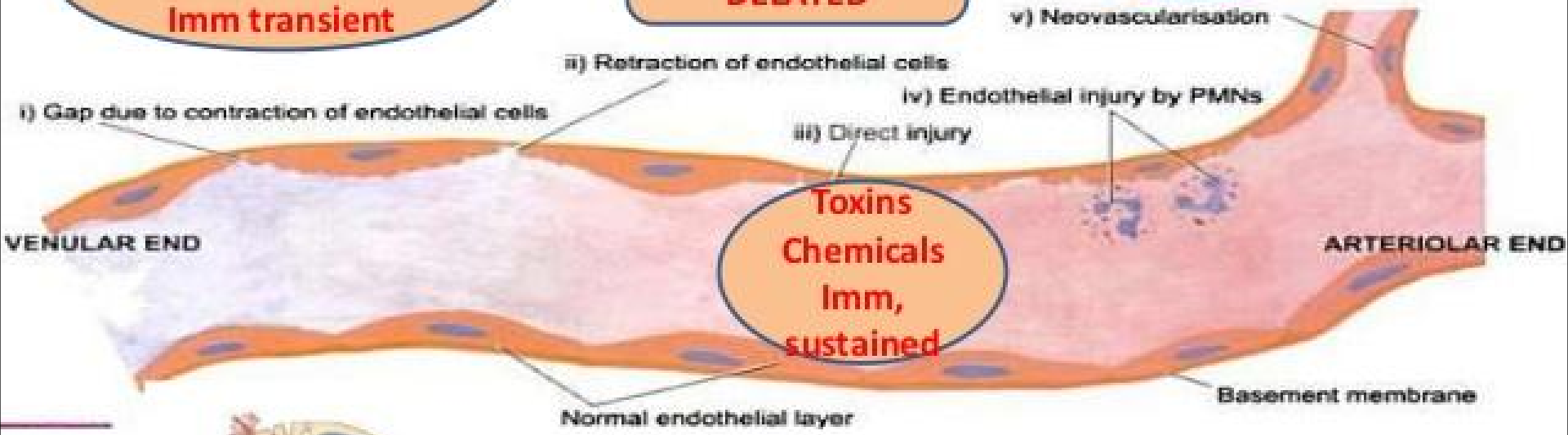
	Mechanism	Microvasculature	Response Type	Pathogenesis	Examples
1	***Endothelial cell contraction***	Venules	Immediate transient (15-30 min)	Histamine, bradykinin, others	Mild thermal injury
2	***Endothelial cell retraction***	Venules	Somewhat delayed (in 4-6 hrs) prolonged (for 24 hrs or more)	IL-1, TNF-α	*In vitro* only
3	***Direct endothelial cell injury***	Arterioles, venules, capillaries	Immediate prolonged (hrs to days), or delayed (2-12 hrs) prolonged (hrs to days)	Cell necrosis and detachment	Moderate to severe burns, severe bacterial infection, radiation injury
4	***Leukocyte-mediated endothelial injury***	Venules, capillaries	Delayed, prolonged	Leukocyte activation	Pulmonary venules and capillaries
5	***Neovascularisation***	All levels	Any type	Angiogenesis, VEGF (vascular endothelial growth factor)	Healing, tumors

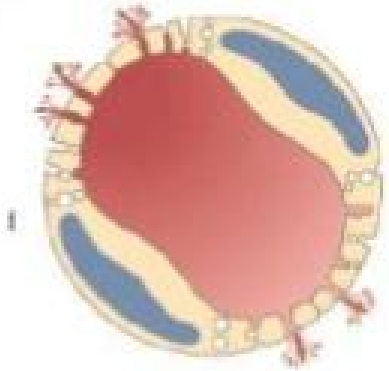
Five mechanisms of increased vascular permeability

Venules,vasoactiv mediators Imm transient

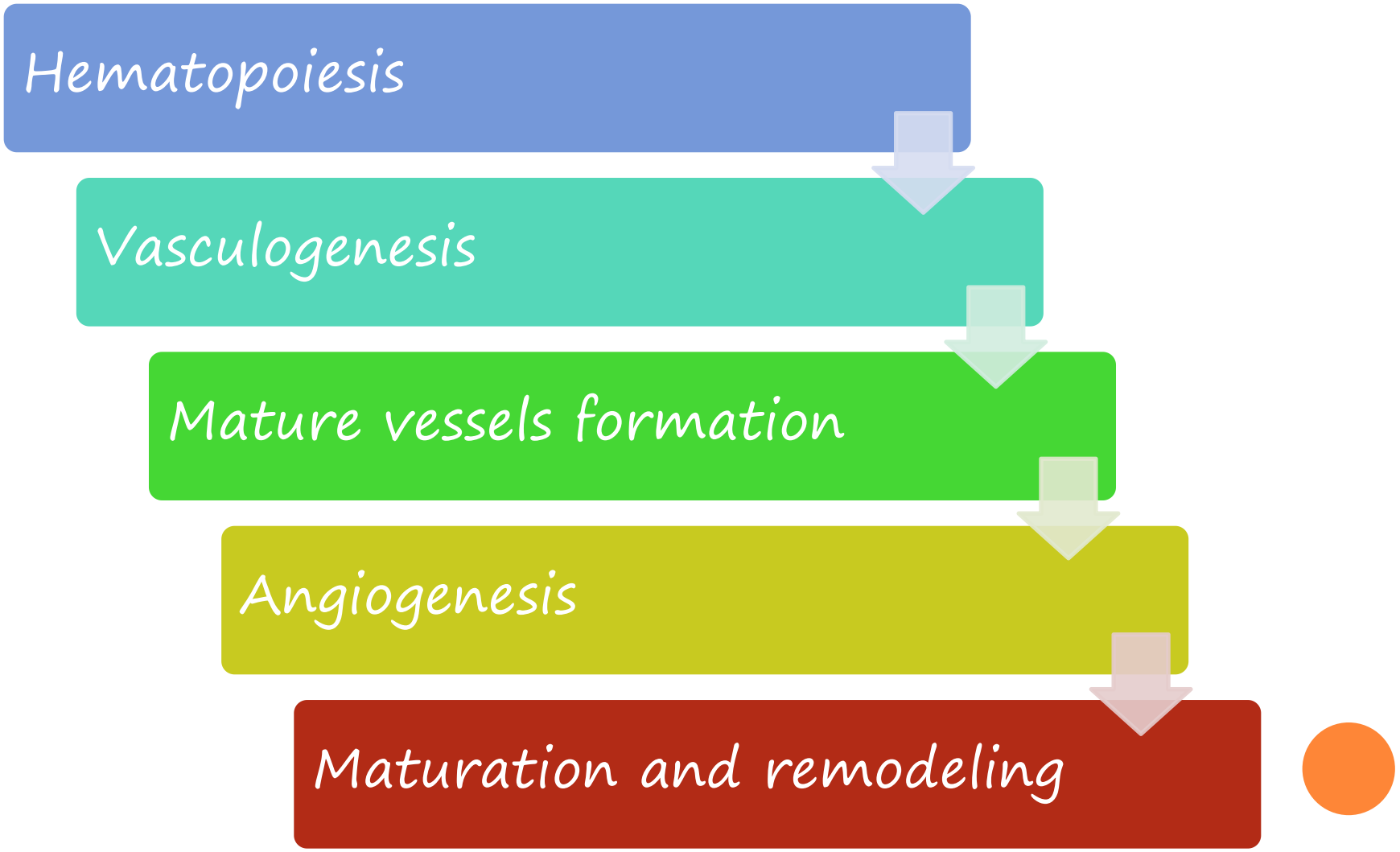
Venules IL-1, TNF DELAYED

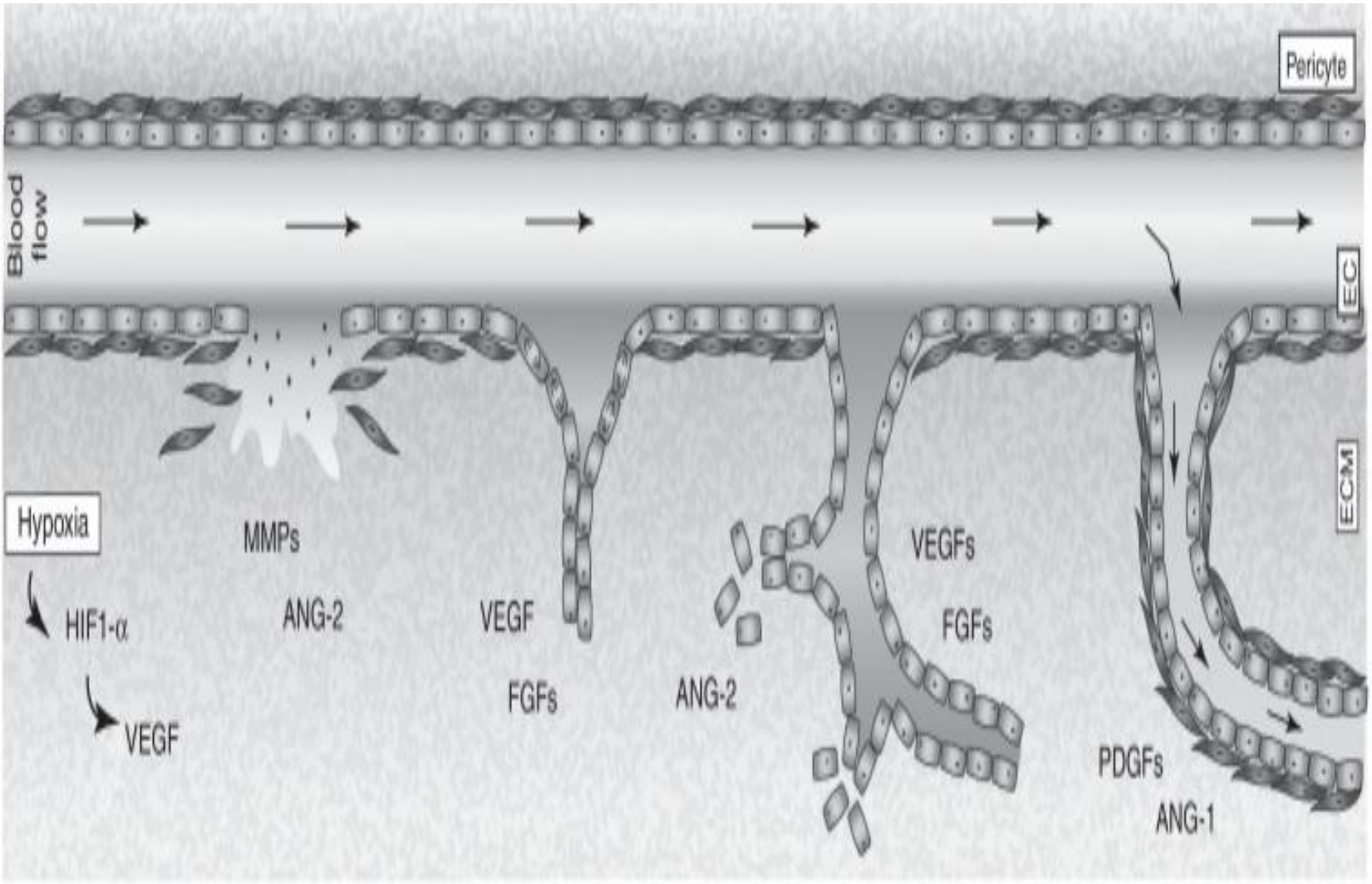
Persists till intercellular junction forms



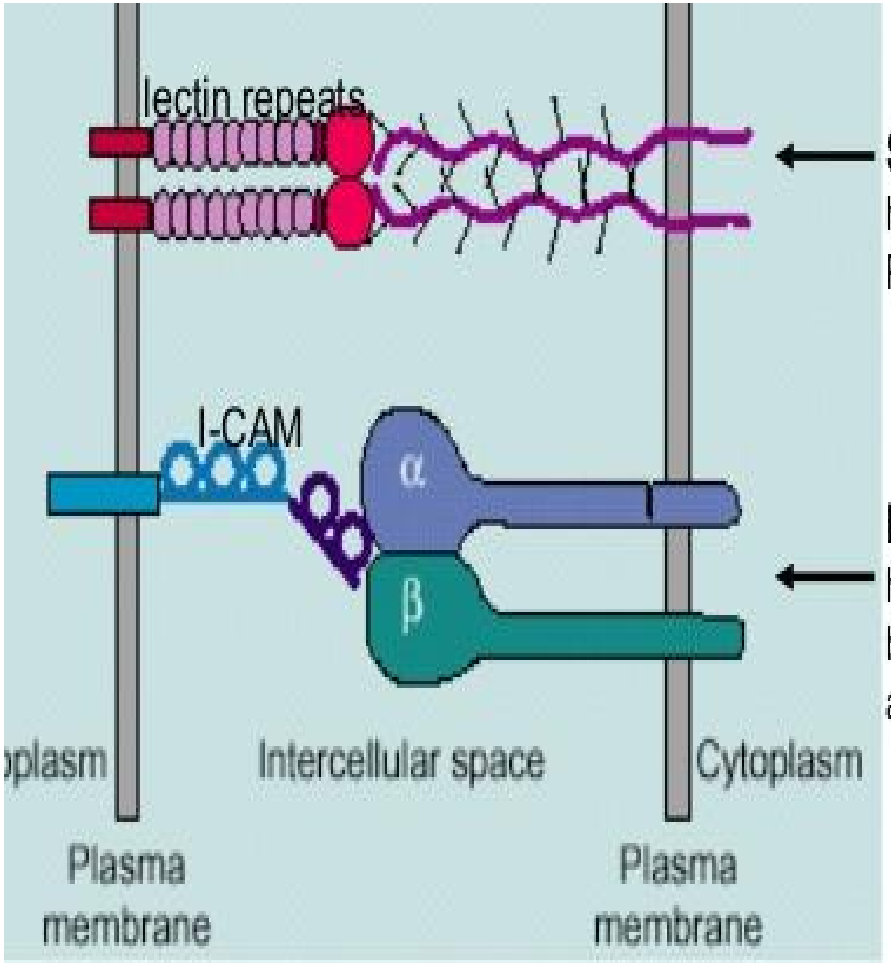


ANGIOGENESIS




Pericyte
Blood flow
EC
ECM
Hypoxia
HIF1-α
VEGF
MMPs
ANG-2
VEGF
FGFs
ANG-2
VEGFs
FGFs
PDGFs
ANG-1

SELECTINS AND INTEGRINS

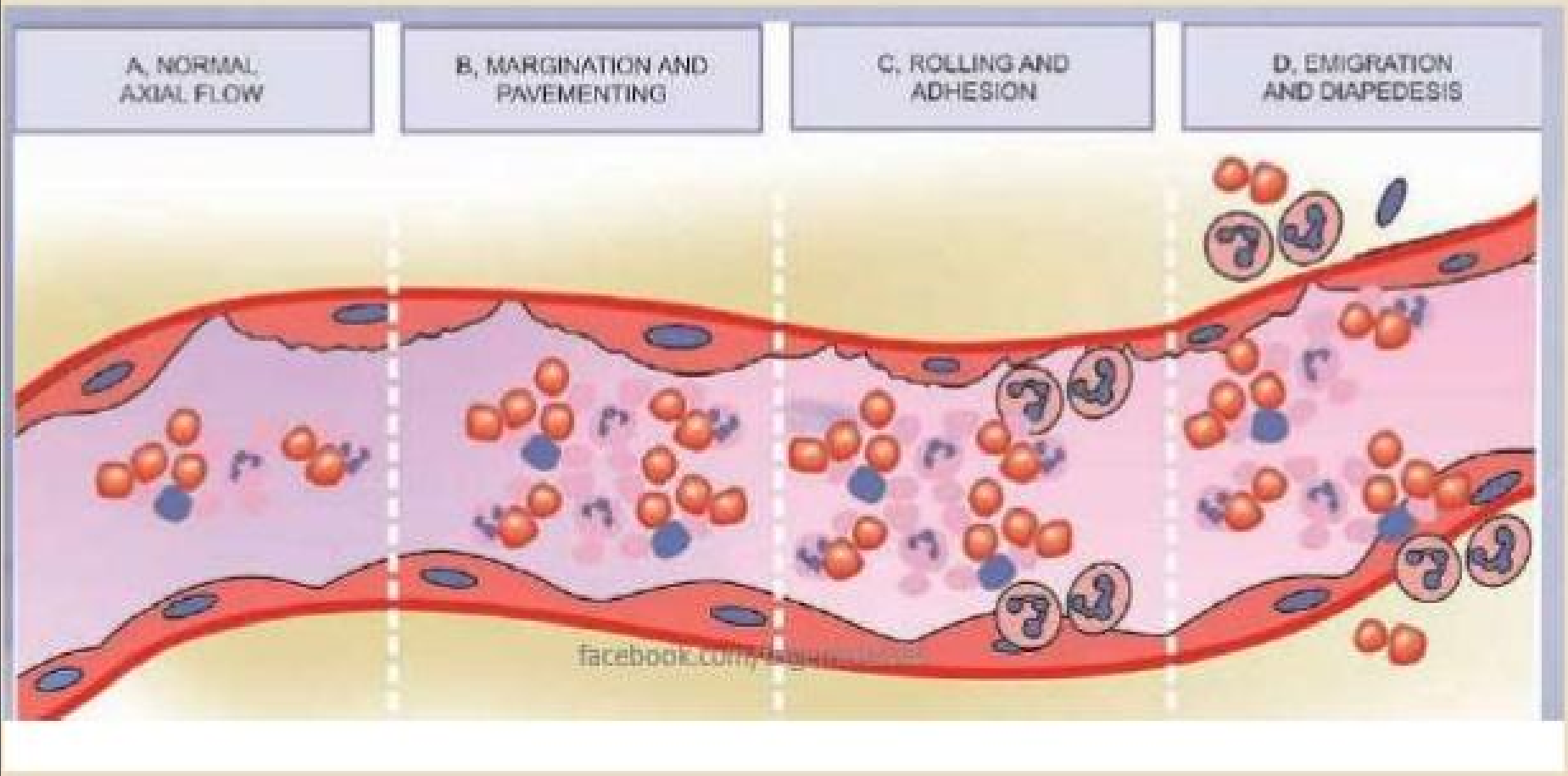


Selectins
heterophilic
P selectin + counter-receptor
PSGL-1, glycosylated

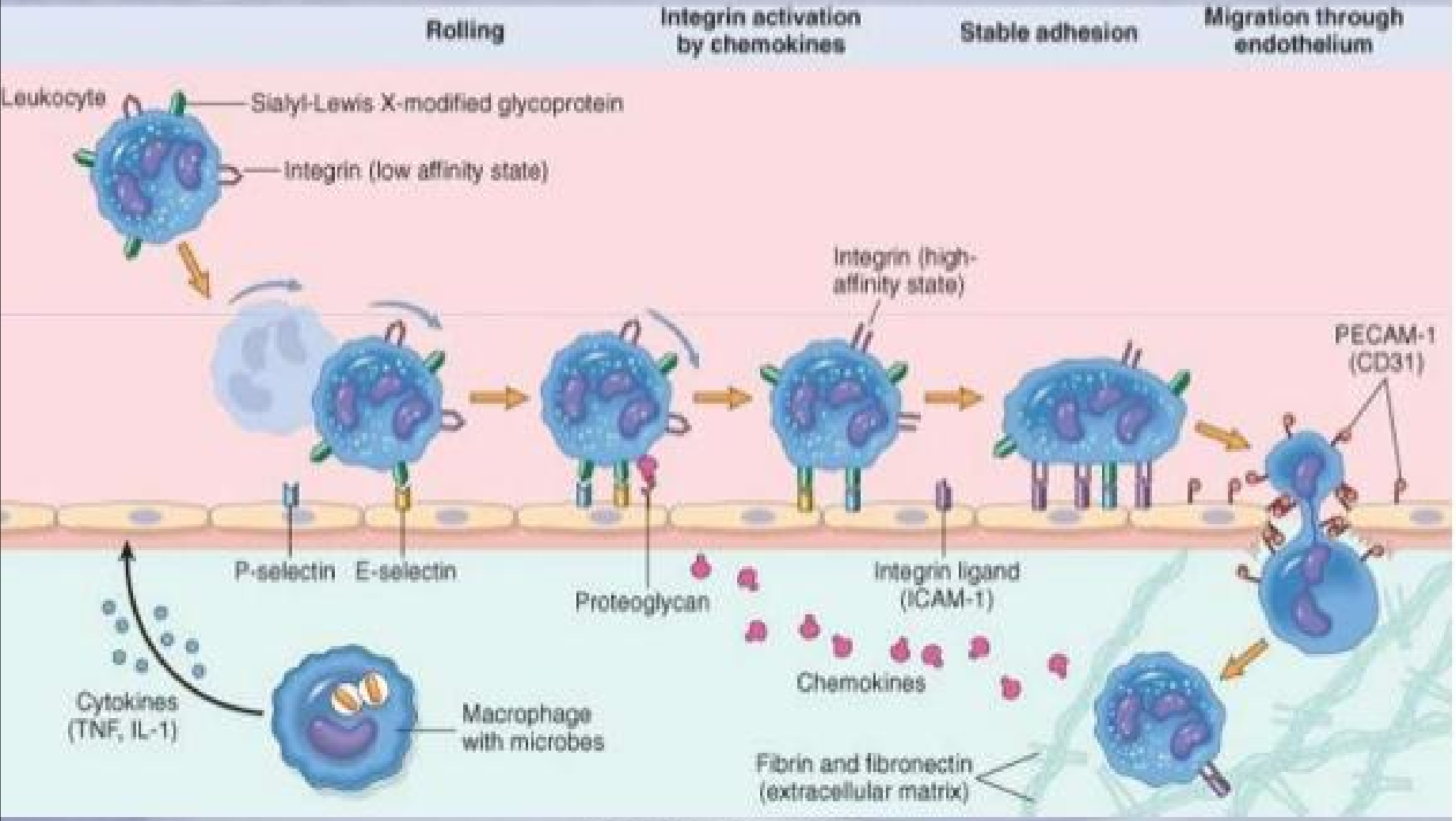
Integrins
heterodimers, heterophilic
bind to **ECM, Ig-CAMs, cadherins**
adhesion, polarity, migration

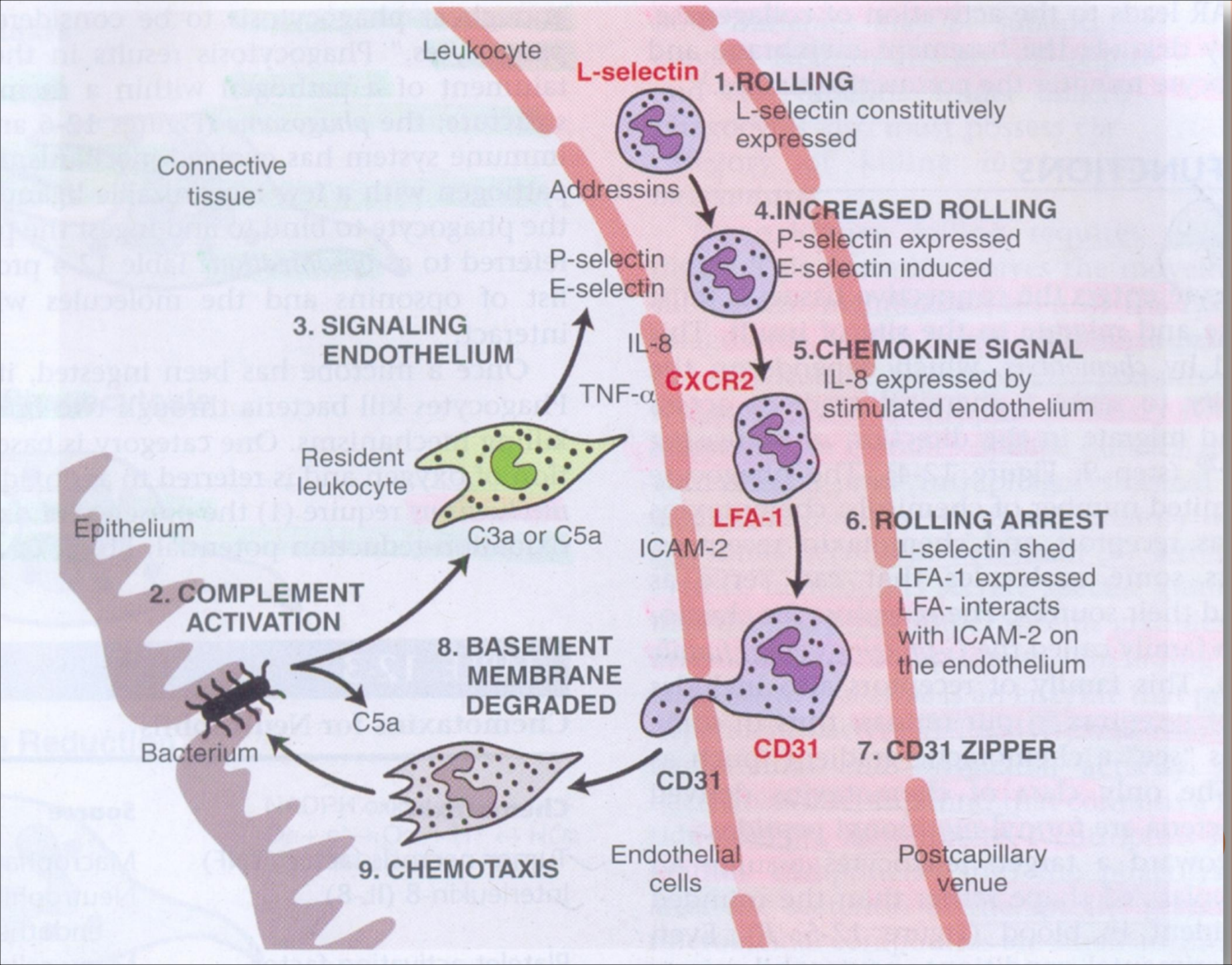
Hynes: TiCB: 9:M33 1999

CELLULAR EVENTS

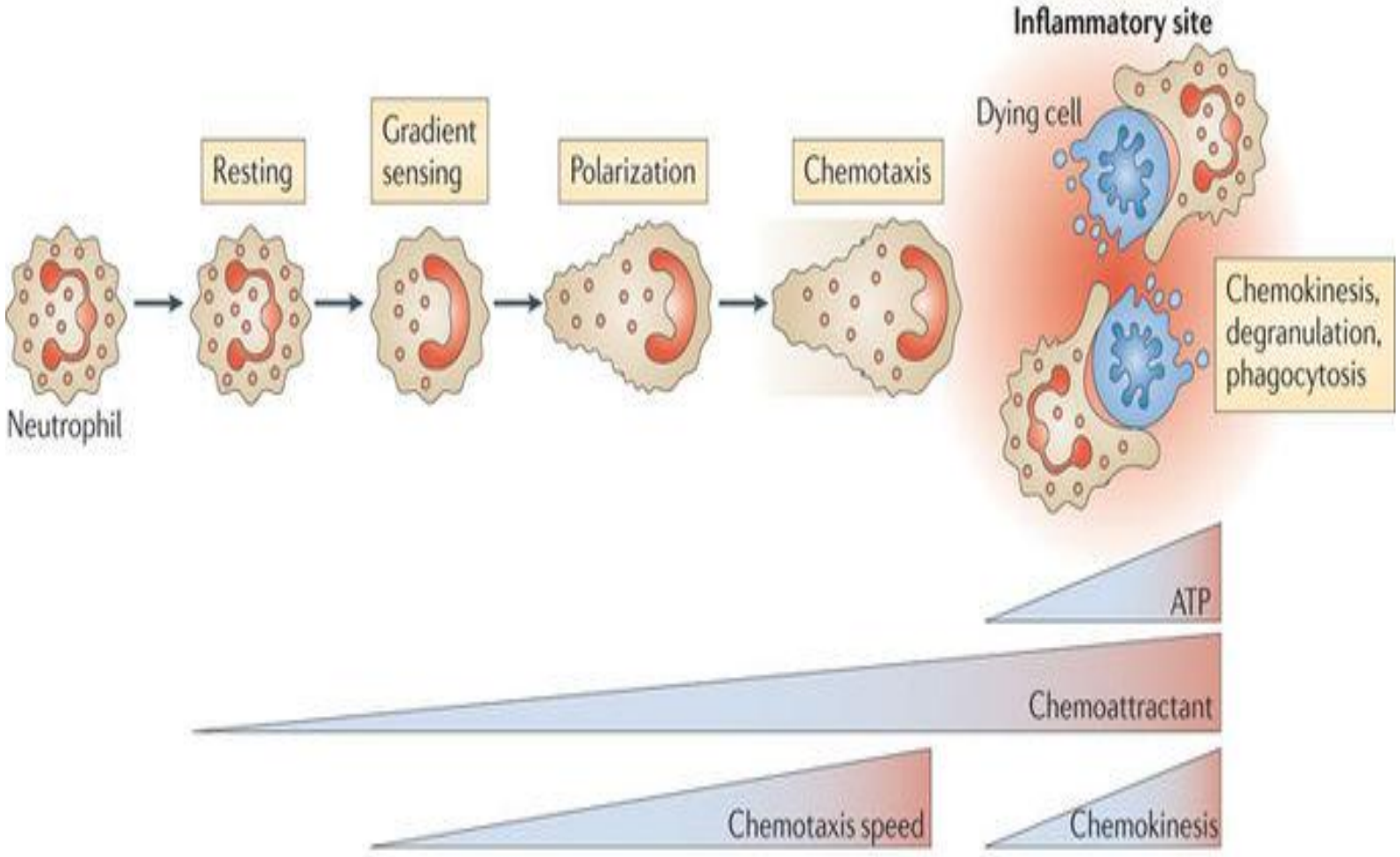


Events of Exudation of leucocytes



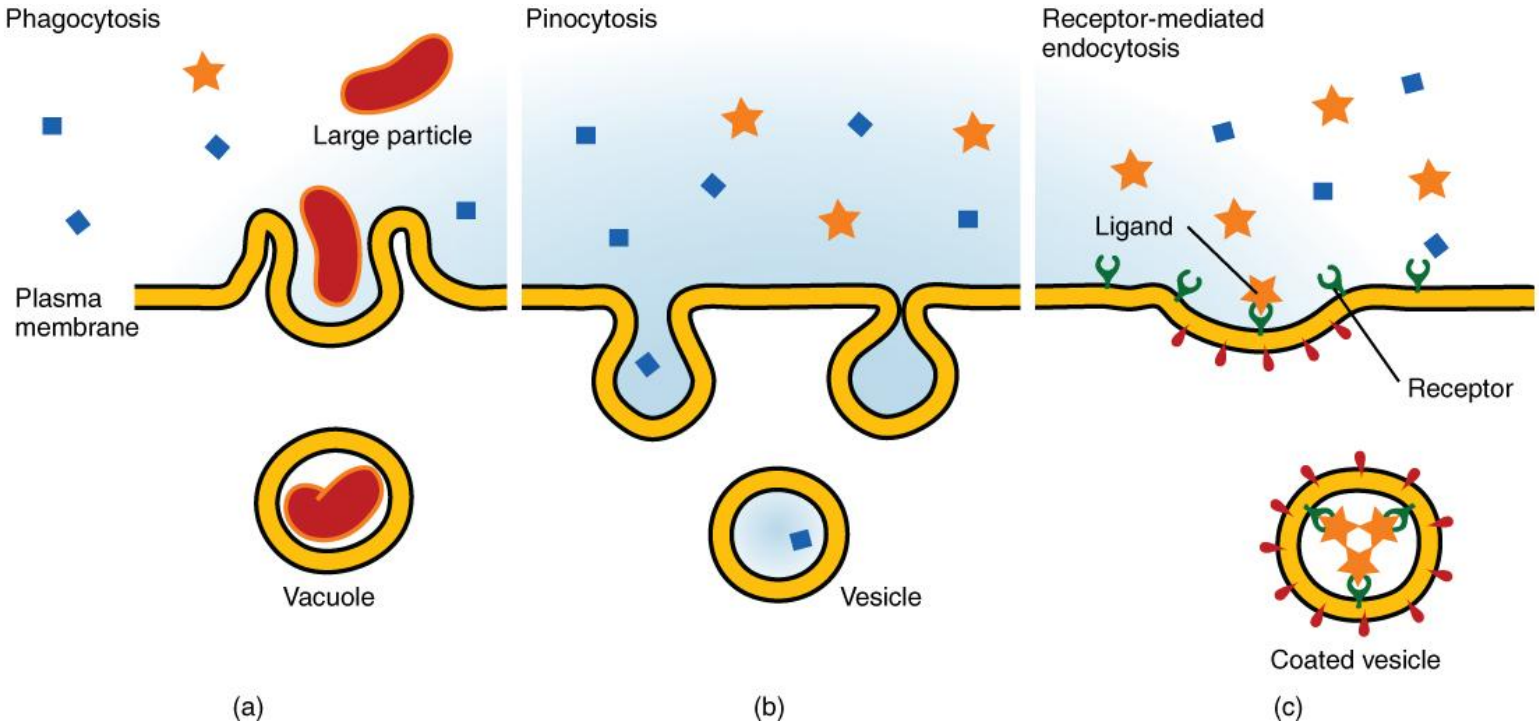

Leukocyte
L-selectin
1.ROLLING
L-selectin constitutively expressed
Connective tissue
Addressins
4.INCREASED ROLLING
P-selectin expressed
E-selectin induced
P-selectin
E-selectin
3. SIGNALING ENDOTHELIUM
IL-8
5.CHEMOKINE SIGNAL
IL-8 expressed by stimulated endothelium
TNF-α
CXCR2
Resident leukocyte
Epithelium
C3a or C5a
LFA-1
ICAM-2
6. ROLLING ARREST
L-selectin shed
LFA-1 expressed
LFA- interacts with ICAM-2 on the endothelium
2. COMPLEMENT ACTIVATION
8. BASEMENT MEMBRANE DEGRADED
C5a
Bacterium
CD31
7. CD31 ZIPPER
CD31
9. CHEMOTAXIS
Endothelial cells
Postcapillary venue

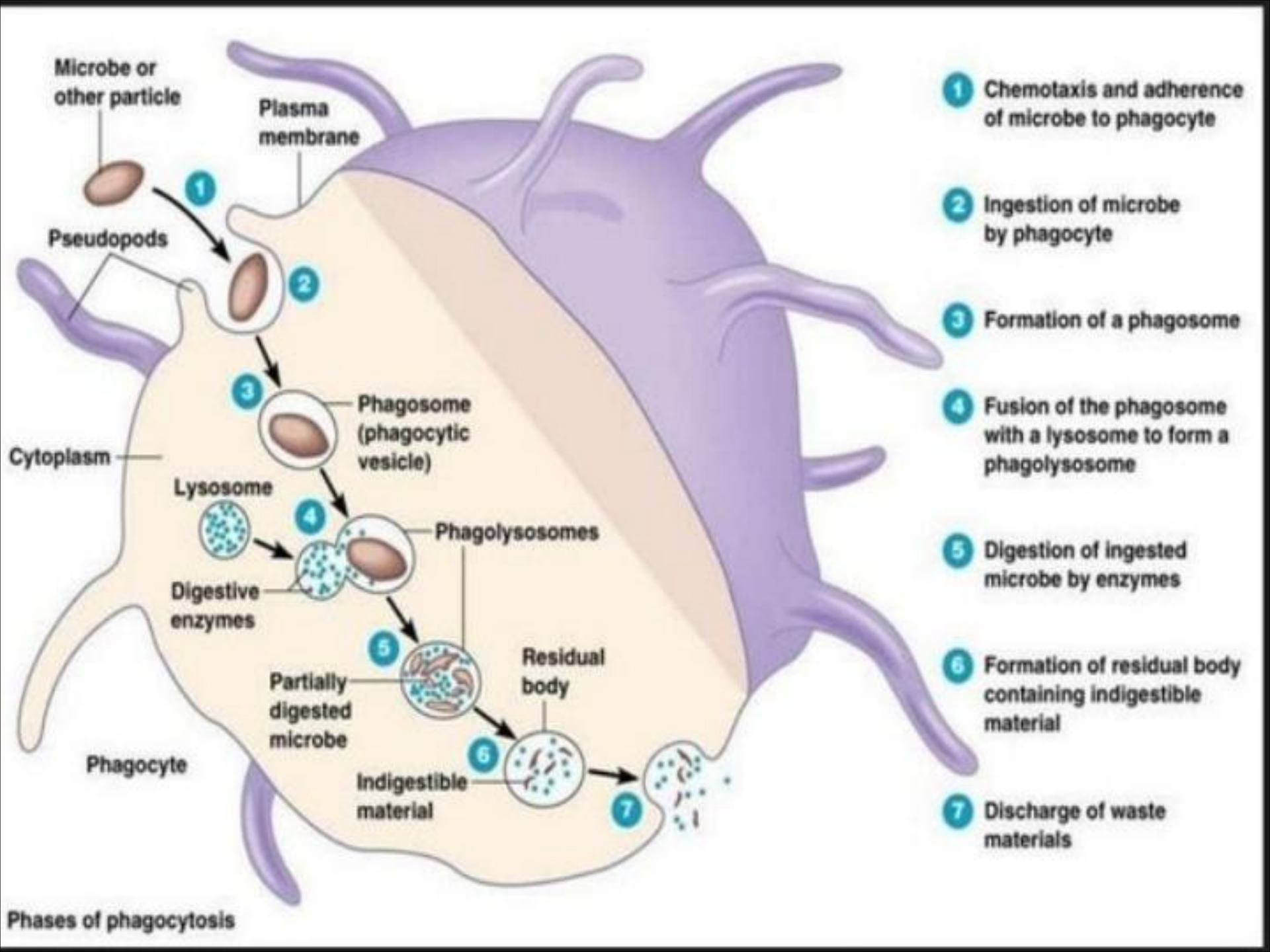
CHEMOTAXIS


Inflammatory site
Dying cell
Resting
Gradient sensing
Polarization
Chemotaxis
Neutrophil
Chemokinesis, degranulation, phagocytosis
ATP
Chemoattractant
Chemotaxis speed
Chemokinesis

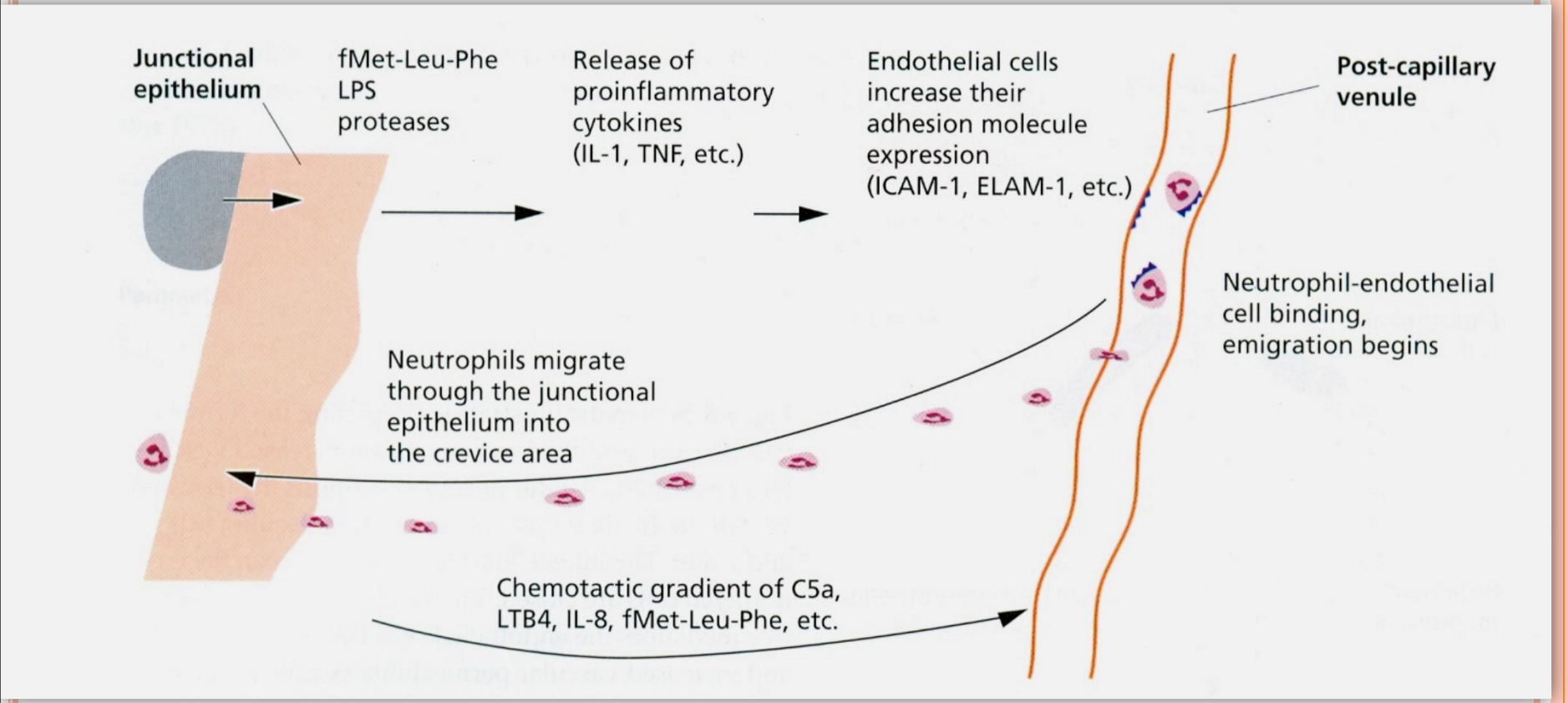
CHEMOTAXIN	SOURCE
TNF	Macrophages/Monocytes
IL 8	Neutrophils, Endothelium
Platelet AF	Many cells
Leukotriene B4	Many cells
C5a	Serum/Plasma
Neutrophil Chemotactic F	Mast Cells
IL 1	B Cells, Macrophage
IFN γ	Activated T cells
N- f-mp	Bacteria

MARGINATION

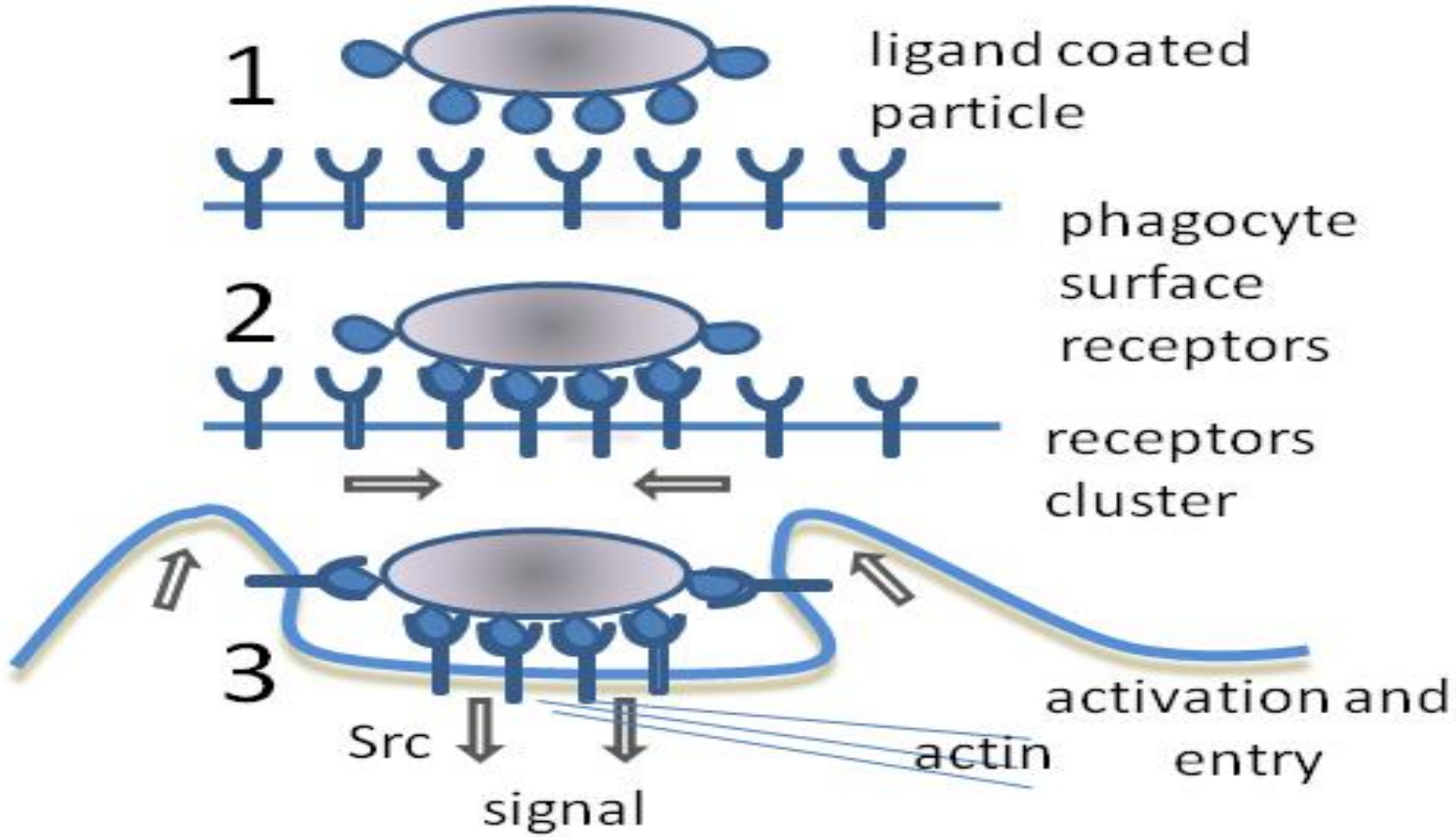

Phagocytosis
Large particle
Plasma membrane
Vacuole
(a)
Pinocytosis
Vesicle
(b)
Receptor-mediated endocytosis
Ligand
Receptor
Coated vesicle
(c)



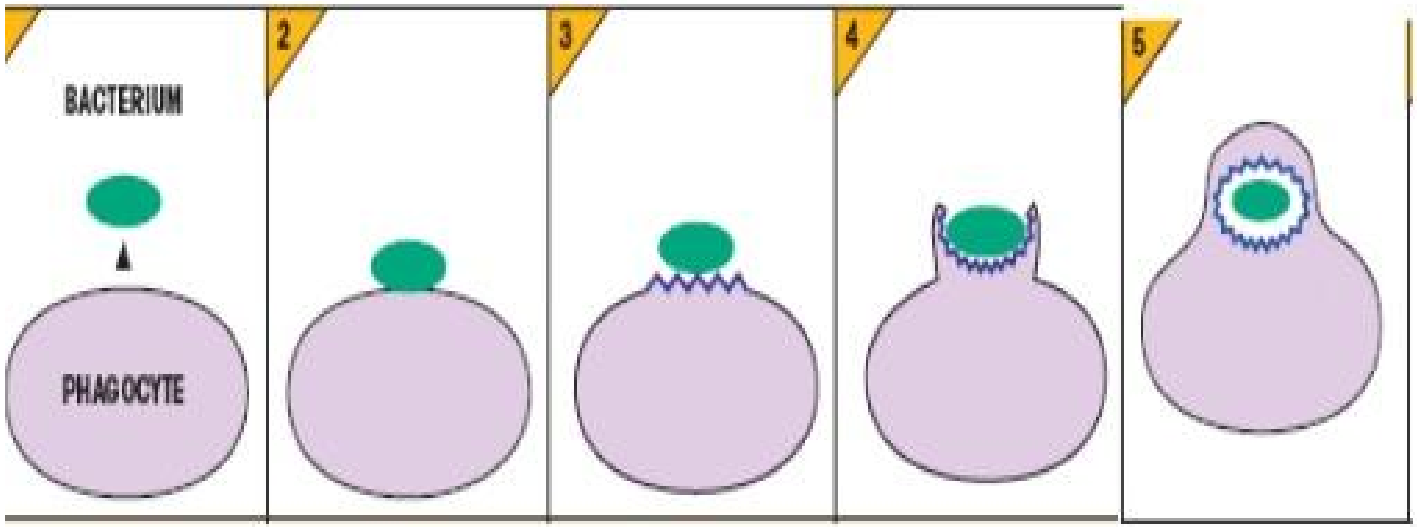
Phases of phagocytosis


Junctional epithelium
fMet-Leu-Phe
LPS
proteases
Release of proinflammatory cytokines (IL-1, TNF, etc.)
Endothelial cells increase their adhesion molecule expression (ICAM-1, ELAM-1, etc.)
Post-capillary venule
Neutrophil-endothelial cell binding, emigration begins
Neutrophils migrate through the junctional epithelium into the crevice area
Chemotactic gradient of C5a, LTB4, IL-8, fMet-Leu-Phe, etc.

PARTICLE RECOGNITION



Zipper theory



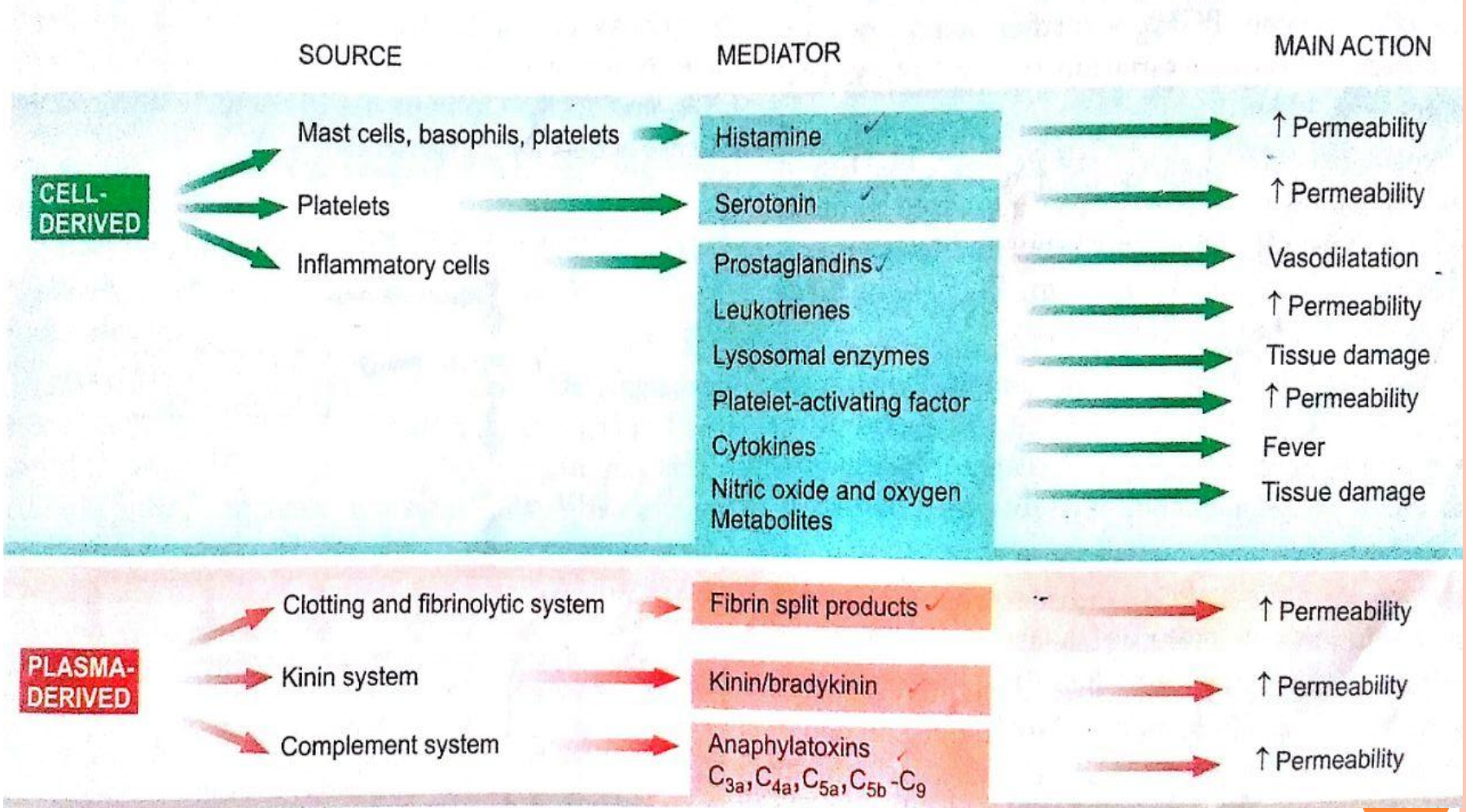
According to the zipper mechanism, ingestion occurs by sequential engagement of a phagocyte's membrane against the particle surface, and pseudopod advance proceeds no further than receptor-ligand interactions permit.

PHAGOCYTOSIS KILLING

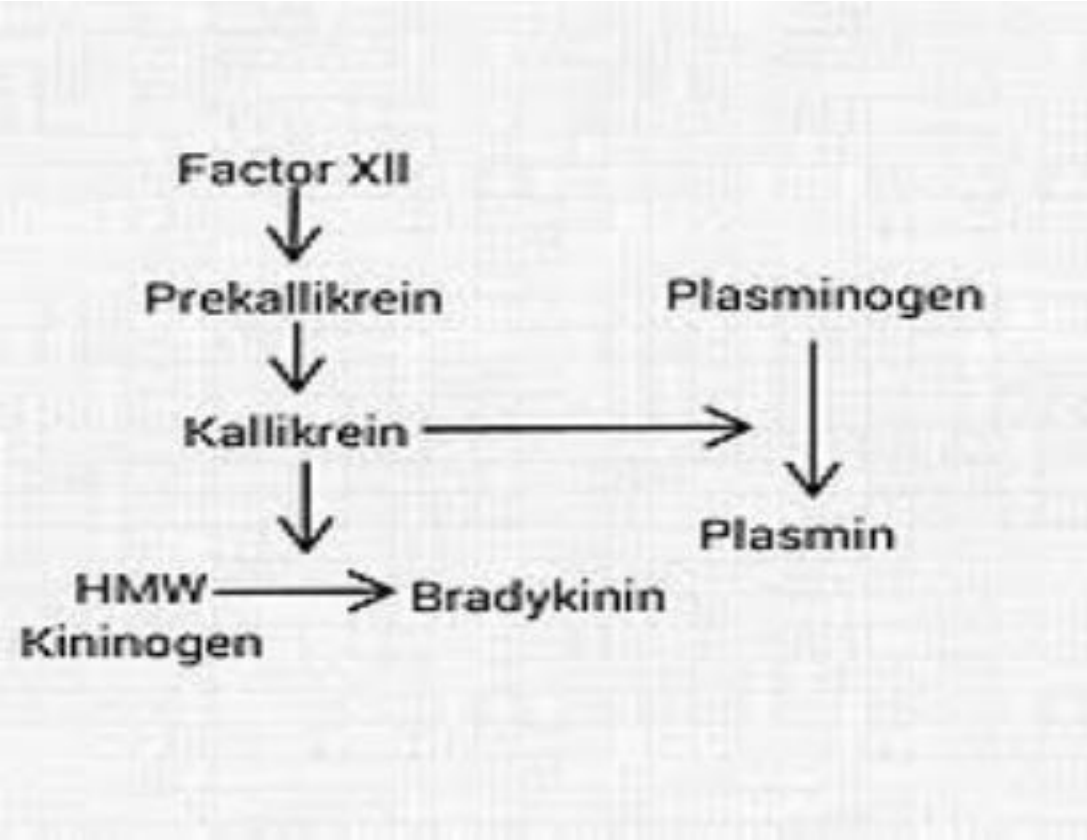
OXIDATIVE MECHANISM	NON-OXIDATIVE MECHANISM
NADPH stimulated ⇨ O_2 prodn	Mediated by defensins, TNF, Lysozyme, Hydrolytic enzymes
$2H^+ + 2O_2^-$ —SOD→ $H_2O_2 + O_2$ —CATALASE→	Mechanism – requires phagosome – lysosome fusion. PHAGOLYSOSOME
$H_2O_2^-$ → $H_2O + O_2$	2 specific granules – specific & Azurophil
H_2O_2 ⇨ OH^0 ⇨ DNA damage —MYELOPEROXIDASE→	Specific Granule – extracellular & intraphagolysosome secretion
Cl^-, Br^-, I^- → HOCl, HOBr	Azurophilic granule – intraphagolysosomal secretion

CELLS	FUNCTIONS	MEDIATORS
MAST CELL	Anaphylactic effects to C3a & C5a Ag recognised by IgE (Boyce JA, 2003) Toll like receptors (Marshall et al, 2003)	Histamine Leukotriene C4 TNFα IL6 SRS-A
DERMAL DENDROCYTES	Periodontal tissue destruction (Maldonado et al, 2004) Receptors for C3a & MHC ClassII molecules	MMPs
PERIPHERAL DENDRITIC CELLS(DCs)	Ag processing &presentation	ICAM-1, LFA-3, CO-STIMULATORY FACTORS(B7-1, B7-2)
NEUTROPHILS	Phagocytic killing of microorganisms Receptors like CR1, CR2, CR3, CR4, C5aR & for IgG	1 granules (MPO, lysozyme, cationic proteins, acid hydrolases, elastase) 2 granules (lysozyme, alk. Phosp, collagenase, lactoferrin) 3 granules (gelatinase, catheosin) Reactive O_2 metabolites
MONOCYTE	Differentiate to macrophages >20 Phagocytosis Ag processing & presentation	Prostaglandins, leukotrienes IL 1 Hydrolases phospolipase
BASOPHIL	Bacterial & parasitic infections	Platelet activating Factor
EOSINOPHIL	Antihelminthic & antiparasitic activity mediated IgE	PGE2 synthesis Lysosomal(neurotoxin, peroxidase)
LYMPHOCYTES CD4+ CD8+ B cell NK	Humoral & cell mediated immune response Chronic inflammatory cell Regulates macrophage response TCR, BCR, KIR, KAR Ag processing and presentation	B cells- Ab production T cells – delayed hypersensitvity , cytotoxitv

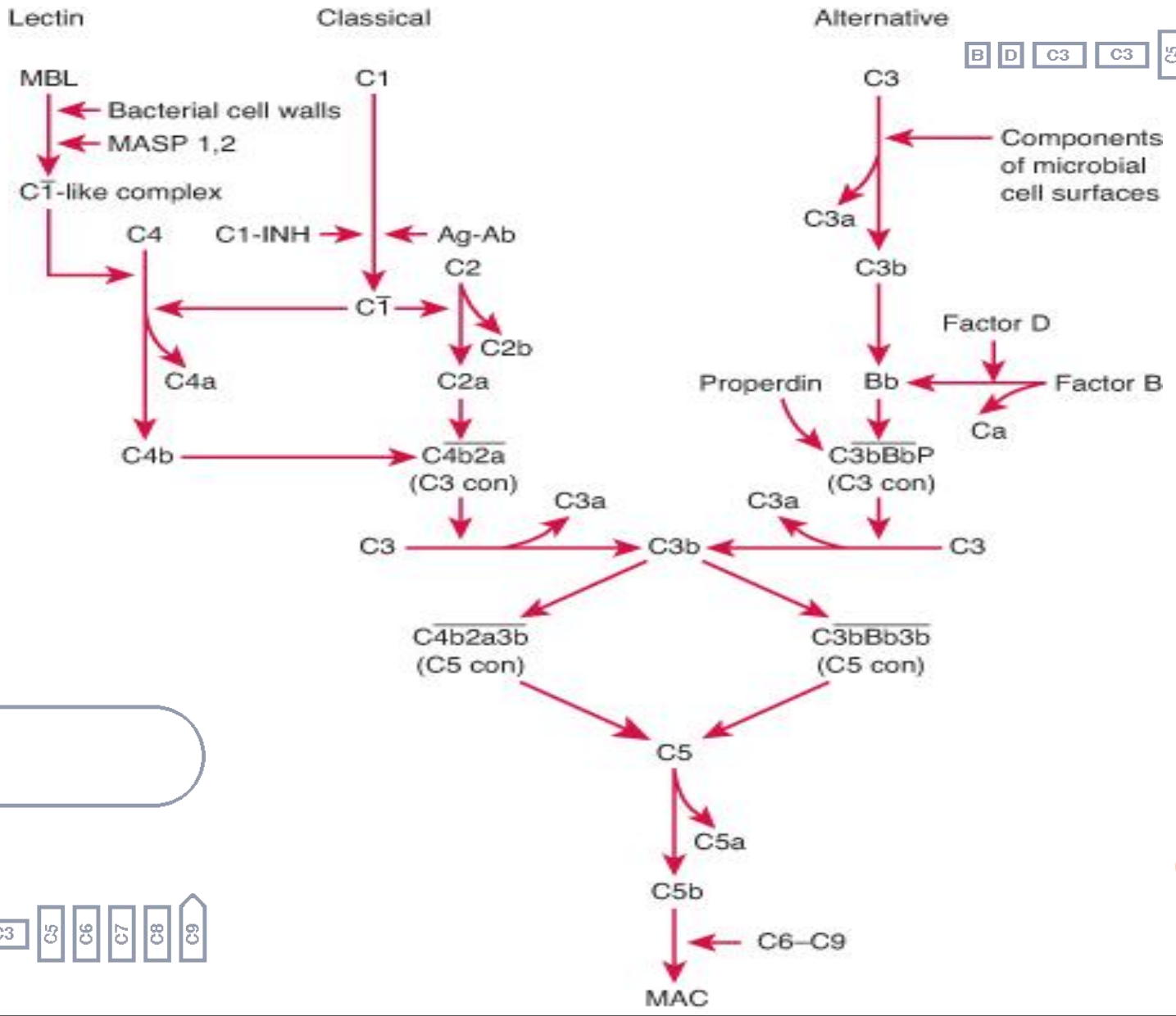
Chemical mediators



FIBRINOLYTIC PATHWAY



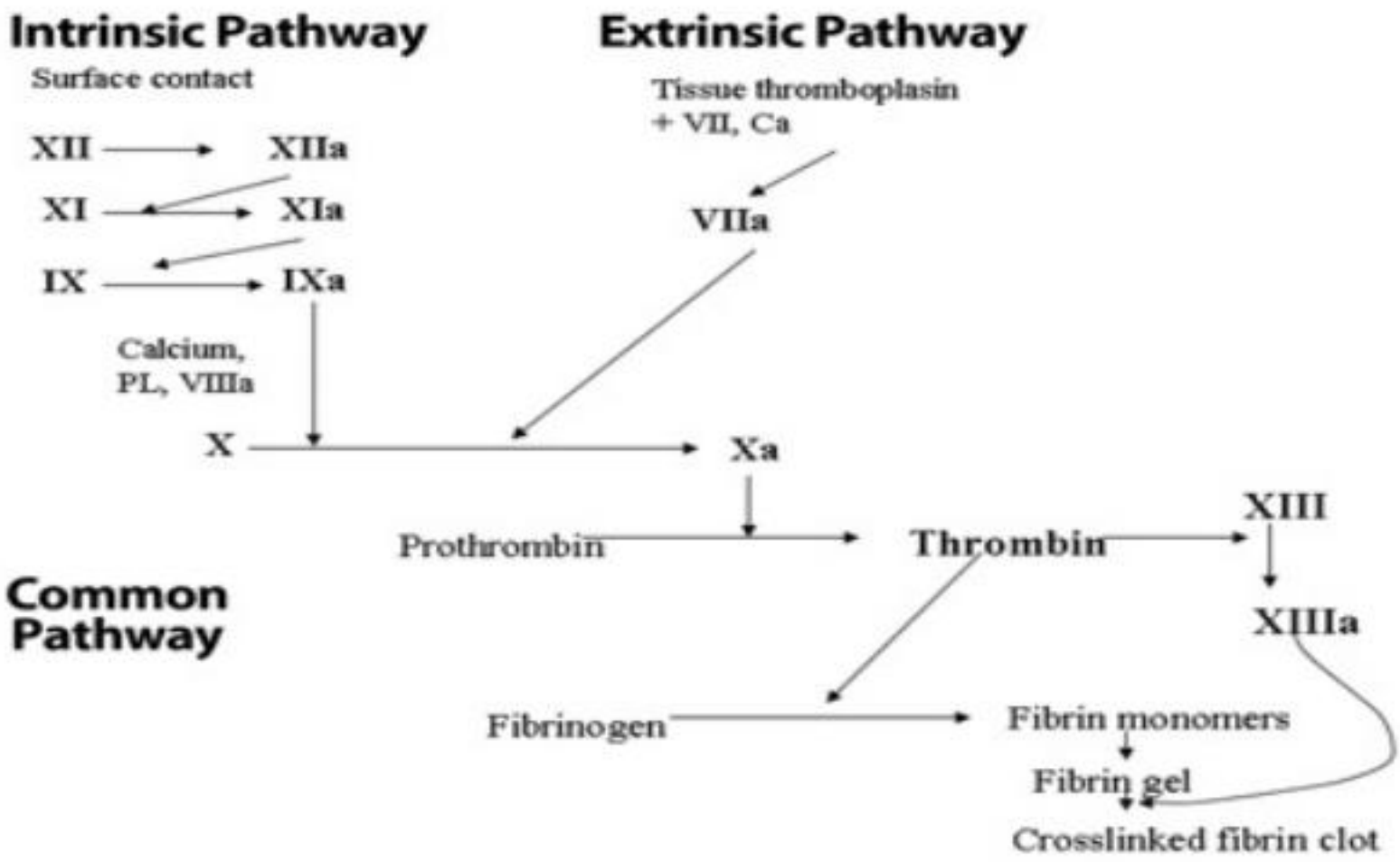
COMPLEMENT

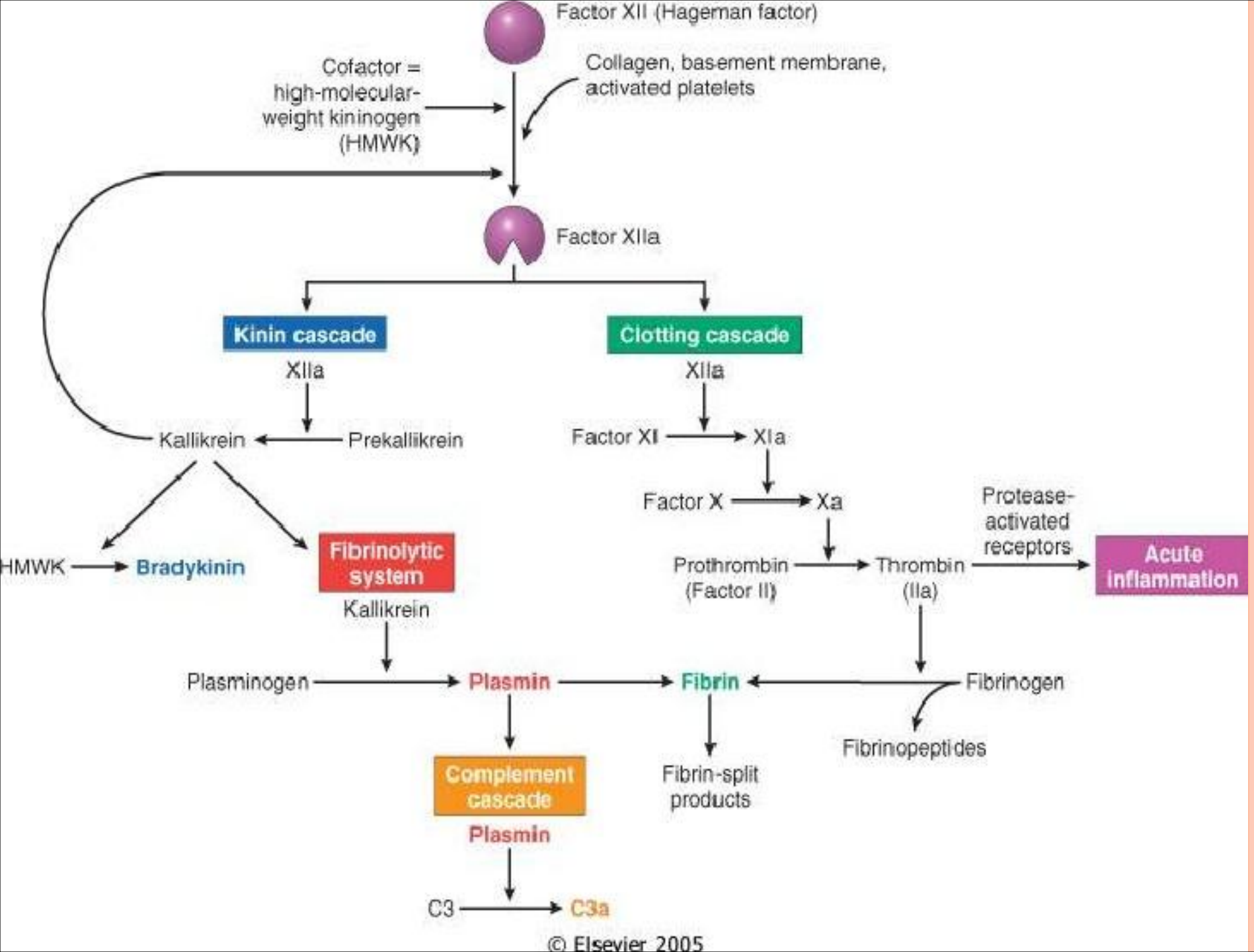

Lectin
Classical
Alternative
MBL
Bacterial cell walls
MASP 1,2
C1-like complex
C1
C4
C1-INH
Ag-Ab
C2
C1
C2b
C4a
C2a
C4b
C4b2a
(C3 con)
C3
C3a
C3b
C4b2a3b
(C5 con)
C3bBb3b
(C5 con)
C5
C5a
C5b
C6–C9
MAC
C3
Components
of microbial
cell surfaces
C3a
C3b
Factor D
Properdin
Bb
Factor B
Ca
C3bBbP
(C3 con)
C3a
C3
B
D
C3
C3
C5
C6
C7
C8
C9
C1q
C4
C2
C3
C5
C6
C7
C8
C9

BIOLOGIC EFFECTS OF COMPLEMENT

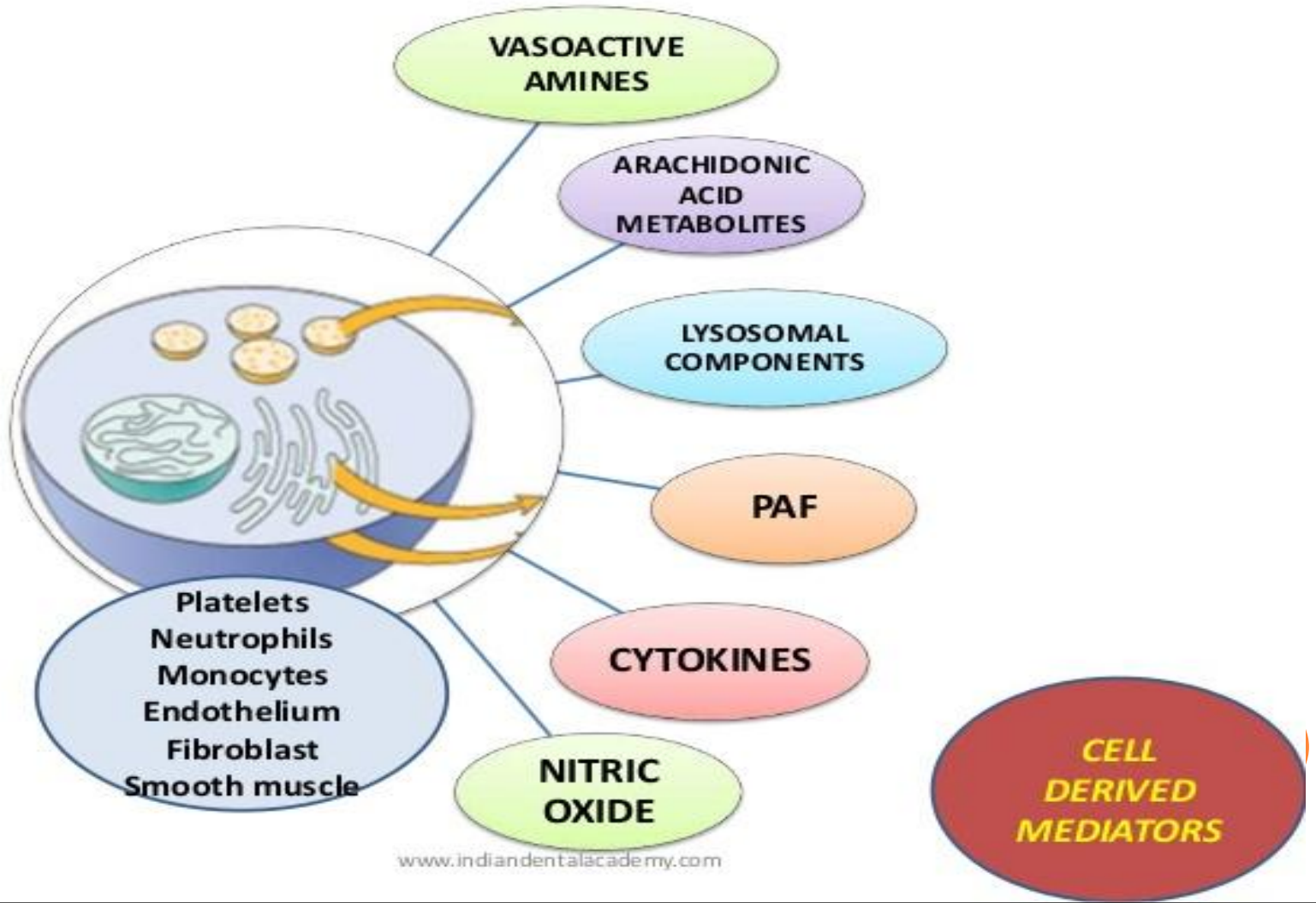
ACTIVITY	*COMPONENTS*
Cytolytic & cytotoxic damage	C 1-9
Leukocytic chemotactic activity	C3a, C5a, C 567
Mast cell histamine release	C3a, C5a
Increased vascular permeability	C3a, C5a
Kinin activity	C2, C3a
Leukocyte lysosomal release	C5a
Promotion of phagocytosis	C3, C5
Enhancement of coagulation	C6
Promotion of clot lysis	C3, C4
Inactivation of bacterial LPS	C5, C6

CLOTTING CASCADE

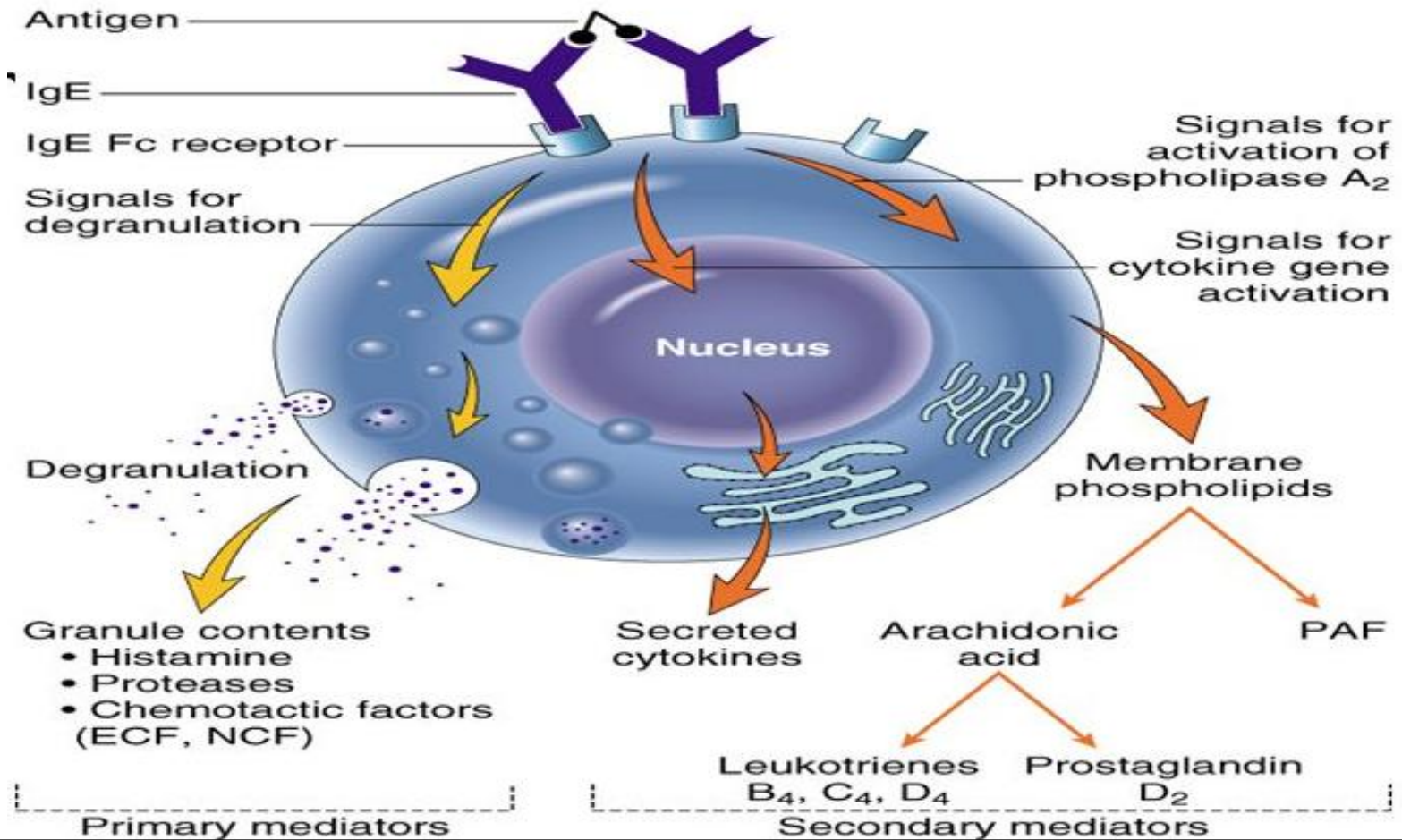




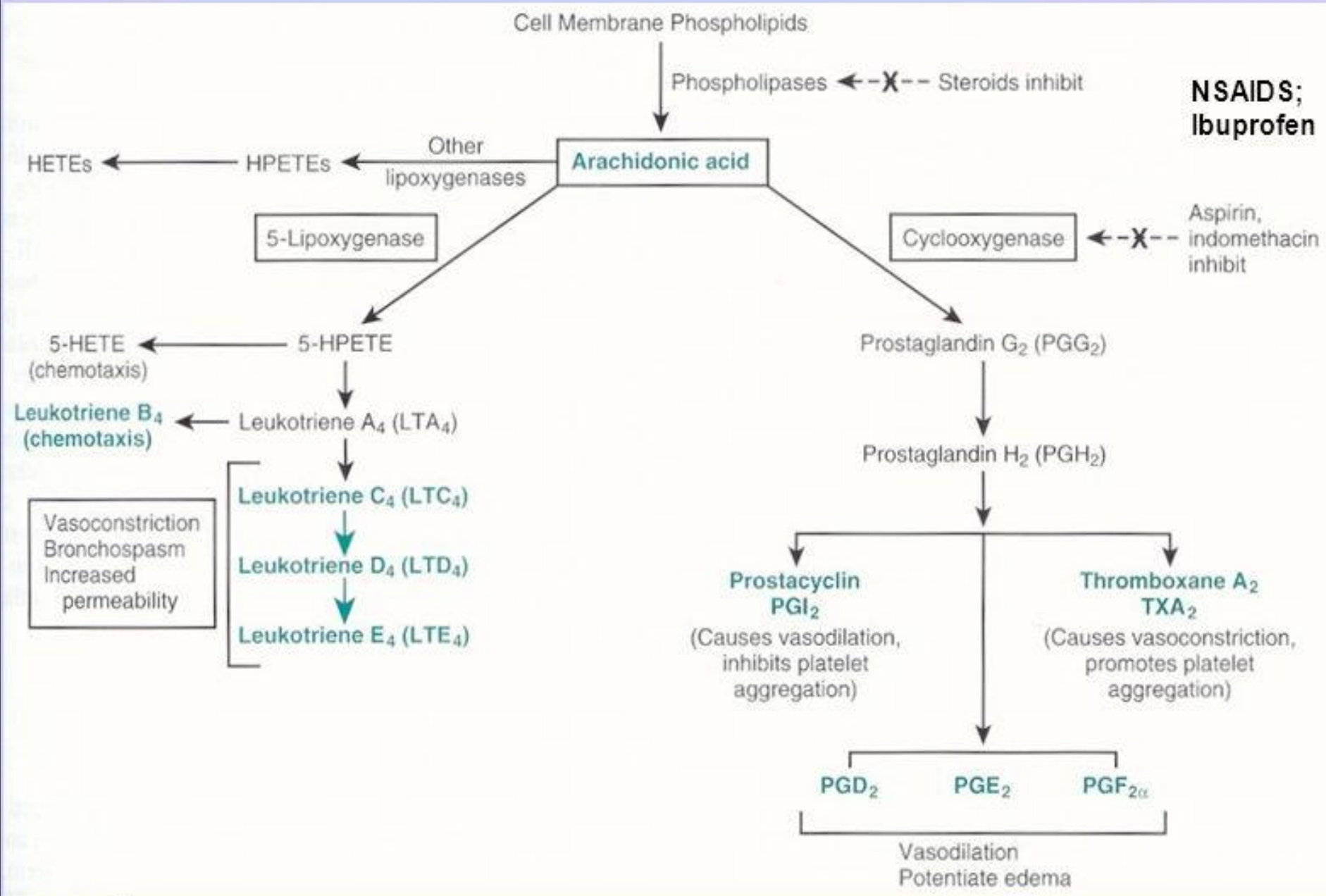
CELL DERIVED MEDIATORS



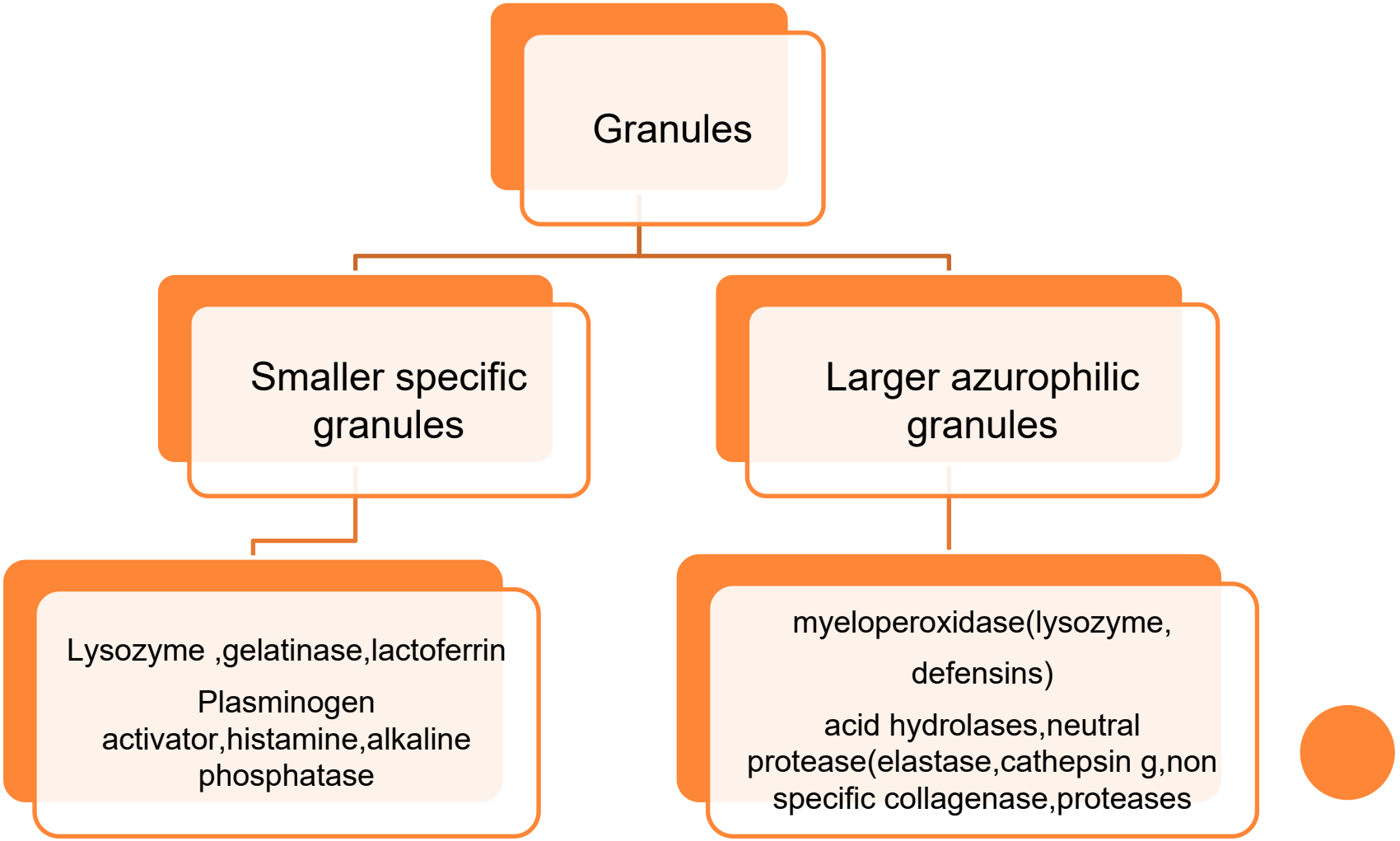
Vasoactive amines



Arachidonic Acid Derivatives



LYSOSOMAL CONSTITUENTS OF LEUCOCYTES



CHEMOKINES

C-X-C/ ALPHA

- One aminoacid residue separate the first two conserved cysteine residues.
- Act primarily on neutrophils,less on monocytes and esinophils
- IL-8
- Secreted by activated macrophages,endothelial cells

C-C/ BETA

- Include monocyte chemoattractant protein(MCP-1),eotaxin,macrophage inflammatory protein,(MIP-1$^{\alpha}$) and RANTES(regulated and normal T cell expresed and secreted)
- Attract monocytes ,esinophils ,basophils but not neutrophils.

C/γ GAMMA

- Lack first two cysteine residues of the four conserved cysteines.
- Specific for lymphocytes

CX3C

- Recently described fourth class of cytokines

CYTOKINES

Cytokines that regulate lymphocyte function

- IL-1 and IL-2 favour lymphocyte growth,IL-10 and TGF-β negative regulators of immune responses.

Natural immunity

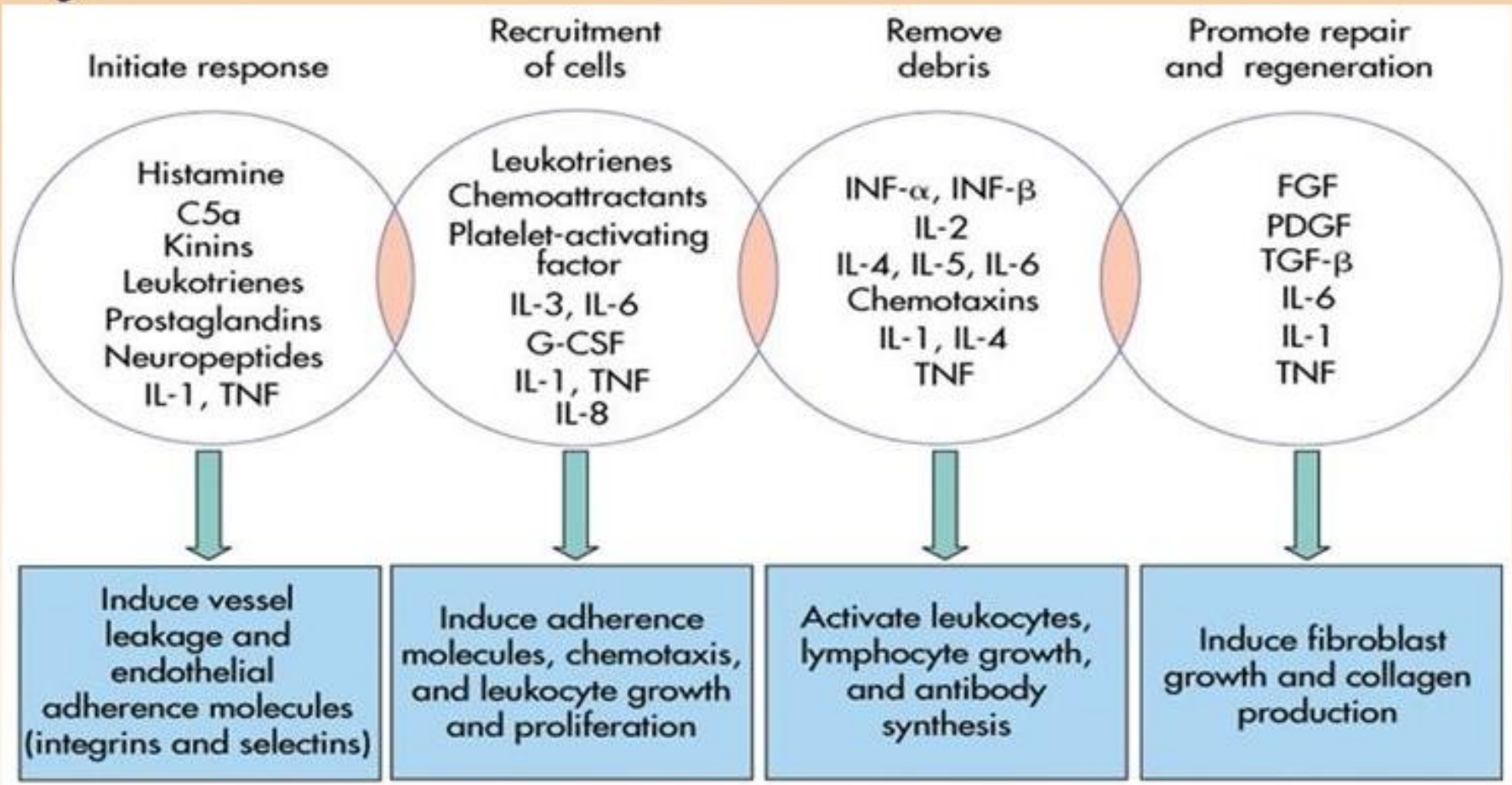
- TNF-α and IL-β

Cytokines that stimulate hematopoiesis

Mediate immature leucocyte growth and sifferentiation

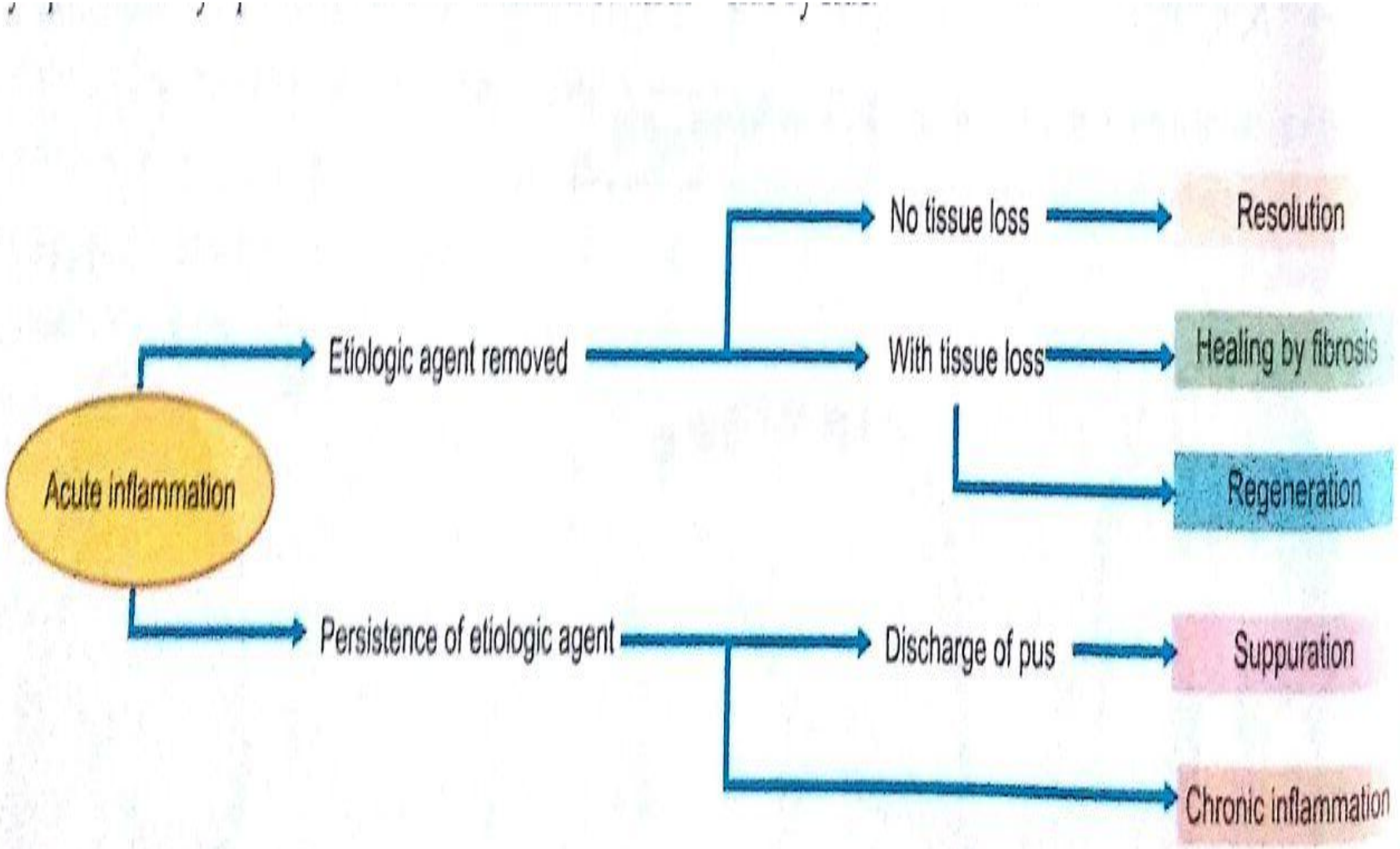
Cytokines that activate inflammatory cells

Activate macrophages , IFN-γ,TNF-α,IL-10,IL-12

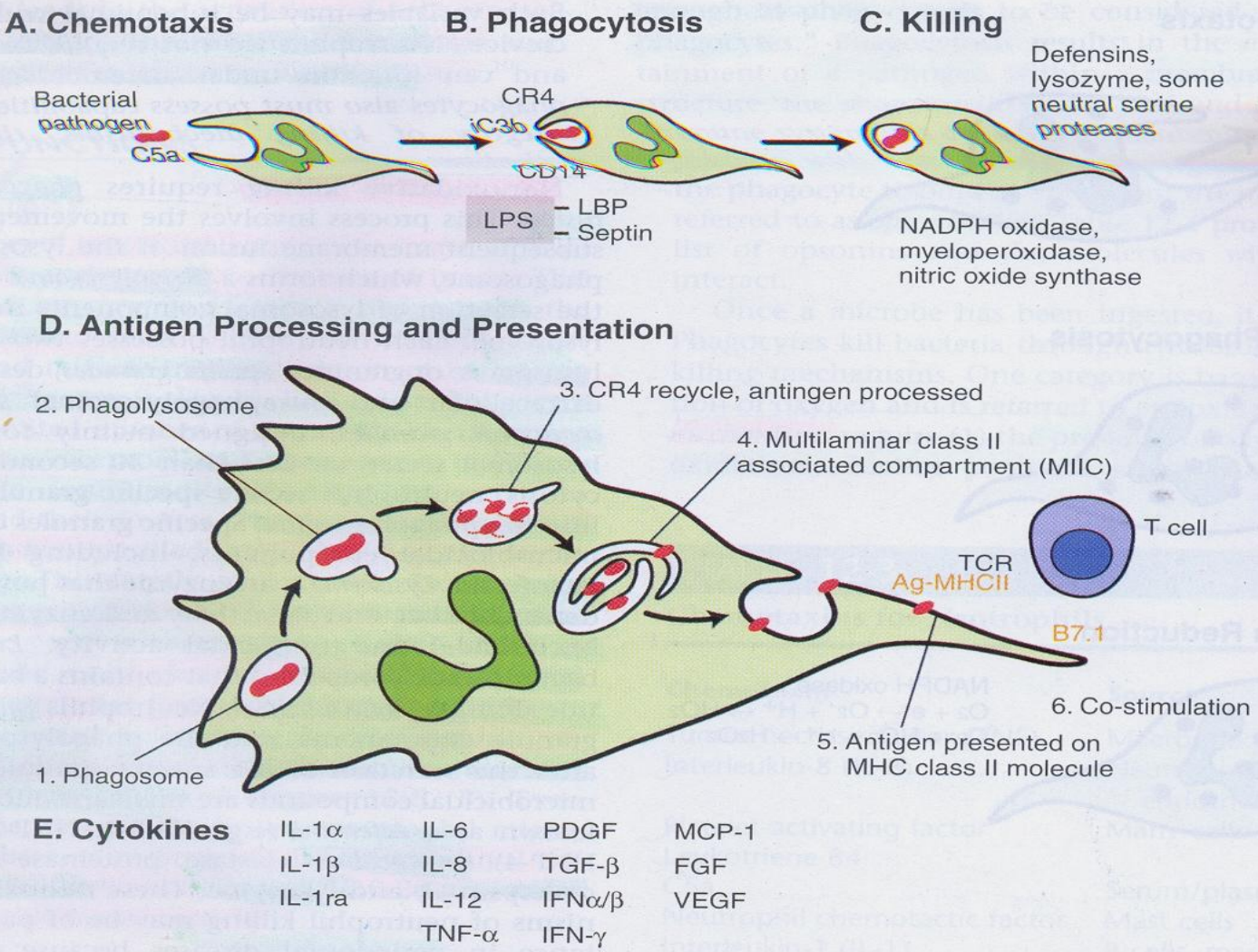


G-CSF = Granulocyte colony-stimulating factor
IL = Interleukin
TNF = Tumor necrosis factor
INF = Interferon
FGF = Fibroblast growth factor
PDGF = Platelet-derived growth factor
TGF-β = Transforming growth factor-beta

FATE OF ACUTE INFLAMMATION



CHRONIC INFLAMMATION



GRANULOMATOUS INFLAMMATION

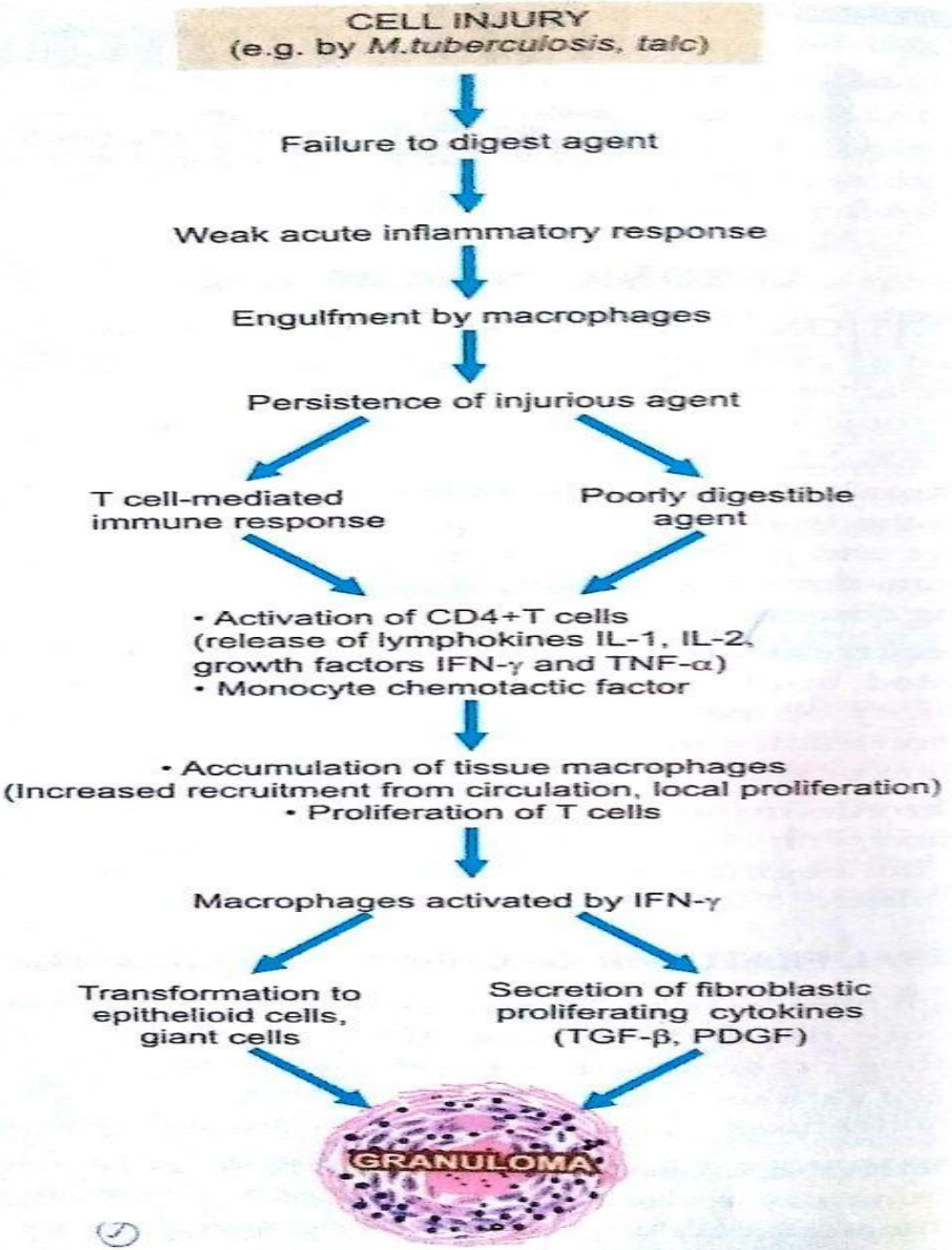


Figure 11.1 Mechanism of evolution of a granuloma (IL=interleukin; IFN= interferon; TNF = tumour necrosis factor).

GINGIVAL INFLAMMATION:

The sequence of events in the development of gingivitis is analyzed in three different stages

Stage one gingivitis:

The initial lesion, first manifestation of gingival inflammation are

vascular changes,dilation of capillaries and increased blood flow.

Stage two gingivitis :

The early lesion, after 4-7 days clinical signs of erythema may appear,prominent cells are lymphocytes.

Stage three gingivitis:

The established lesion, in chronic gingivitis the blood vessels become

engorged and congested, venous return is impaired, and the blood flow becomes sluggish,

results in localized gingival anoxemia, which superimposes a some what bluish hue on the

reddened gingiva

THANK

YOU