Pathophysiology

BP305TT

CHEMICAL MEDIATORS OF INFLAMMATION

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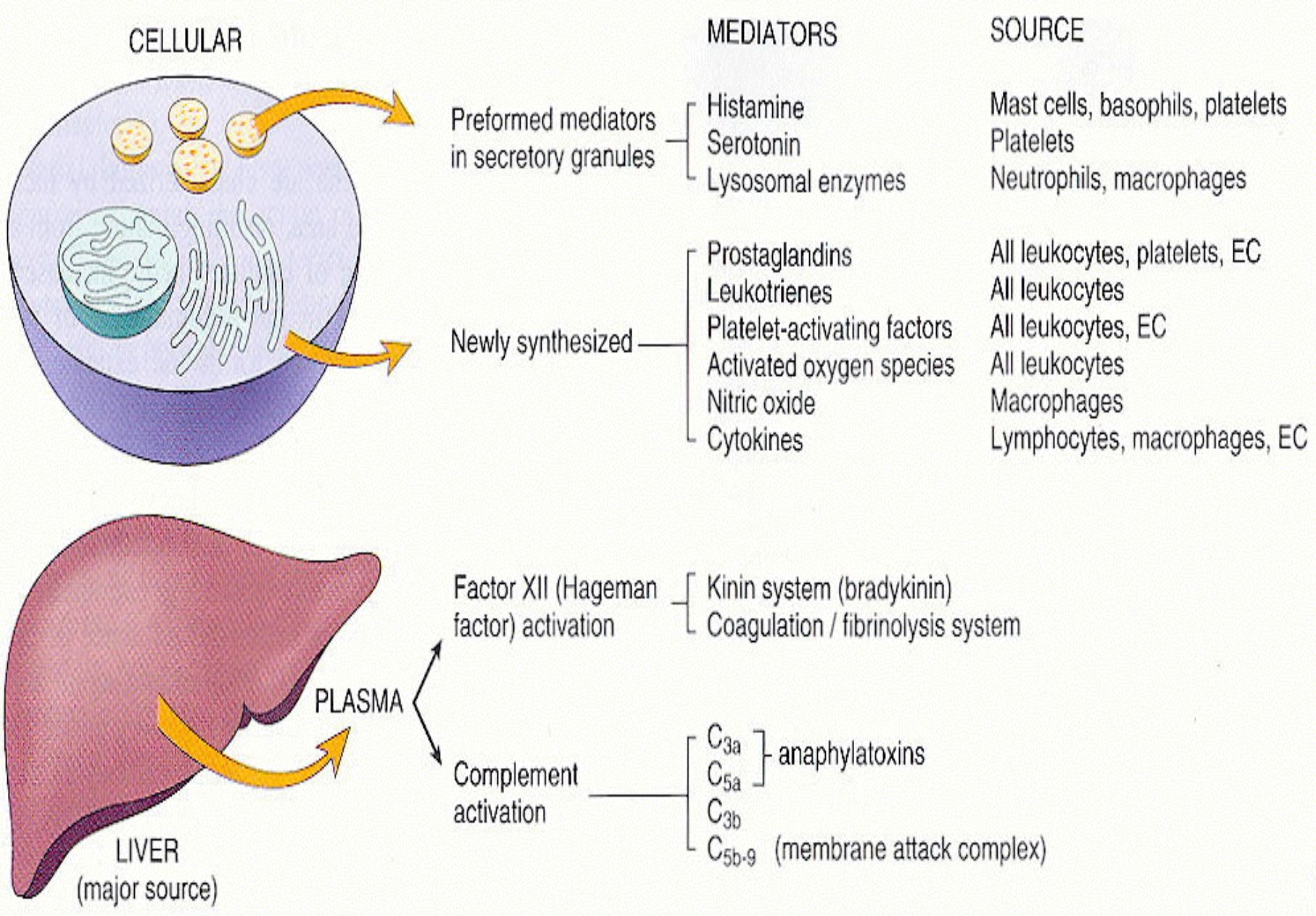
Professor

Definition

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


CELLULAR
MEDIATORS
SOURCE
Preformed mediators in secretory granules
Histamine
Serotonin
Lysosomal enzymes
Mast cells, basophils, platelets
Platelets
Neutrophils, macrophages
Newly synthesized
Prostaglandins
Leukotrienes
Platelet-activating factors
Activated oxygen species
Nitric oxide
Cytokines
All leukocytes, platelets, EC
All leukocytes
All leukocytes, EC
All leukocytes
Macrophages
Lymphocytes, macrophages, EC
PLASMA
Factor XII (Hageman factor) activation
Kinin system (bradykinin)
Coagulation / fibrinolysis system
Complement activation
C3a
C5a
anaphylatoxins
C3b
C5b-9
(membrane attack complex)
LIVER
(major source)

CHEMICAL MEDIATORS by EVENT

- **Vasodilation**

  Prostaglandins, Nitric Oxide, Histamine
- **Increased Vascular Permeability**

  Vasoactive amines (histamine, serotonin),C3a and C5a, Bradykinin, Leukotrienes, PAF
- **Chemotaxic Leukocyte Activation**

  C5a, LTB4, Chemokines (IL-1, IL-8, TNF-alpha), bacterial products (LPS)

CHEMICAL MEDIATORS by EVENT

- **Fever**

  IL-1, IL-6, TNF-alpha, Prostaglandins
- **Pain**

  Prostaglandins, Kinines (Bradykinin, Substance P)
- **Tissue Damage**

  Neutrophil and Macrophage products

  Lysosomal enzymes

  Oxygen metabolites

  Nitric Oxide

VASOACTIVE AMINES

- **Histamine**
  - Histamine mainly from mast cells
  - **Vasodilation and Increase Vascular Permeability**
  - Contraction of non-vascular smooth muscle (bronchi)
  - Stimulate cells to produce eotaxins(attract eosinophils)

VASOACTIVE AMINES

- Releasing Stimulators

  Direct physical or chemical injury

  Binding of IgE-Ag-complexes

  Fragments of C3a and C5a

  Cytokines (IL-1, IL-8)

  Neuropeptides (subs. P)

ARACHIDONIC ACID METABOLITES

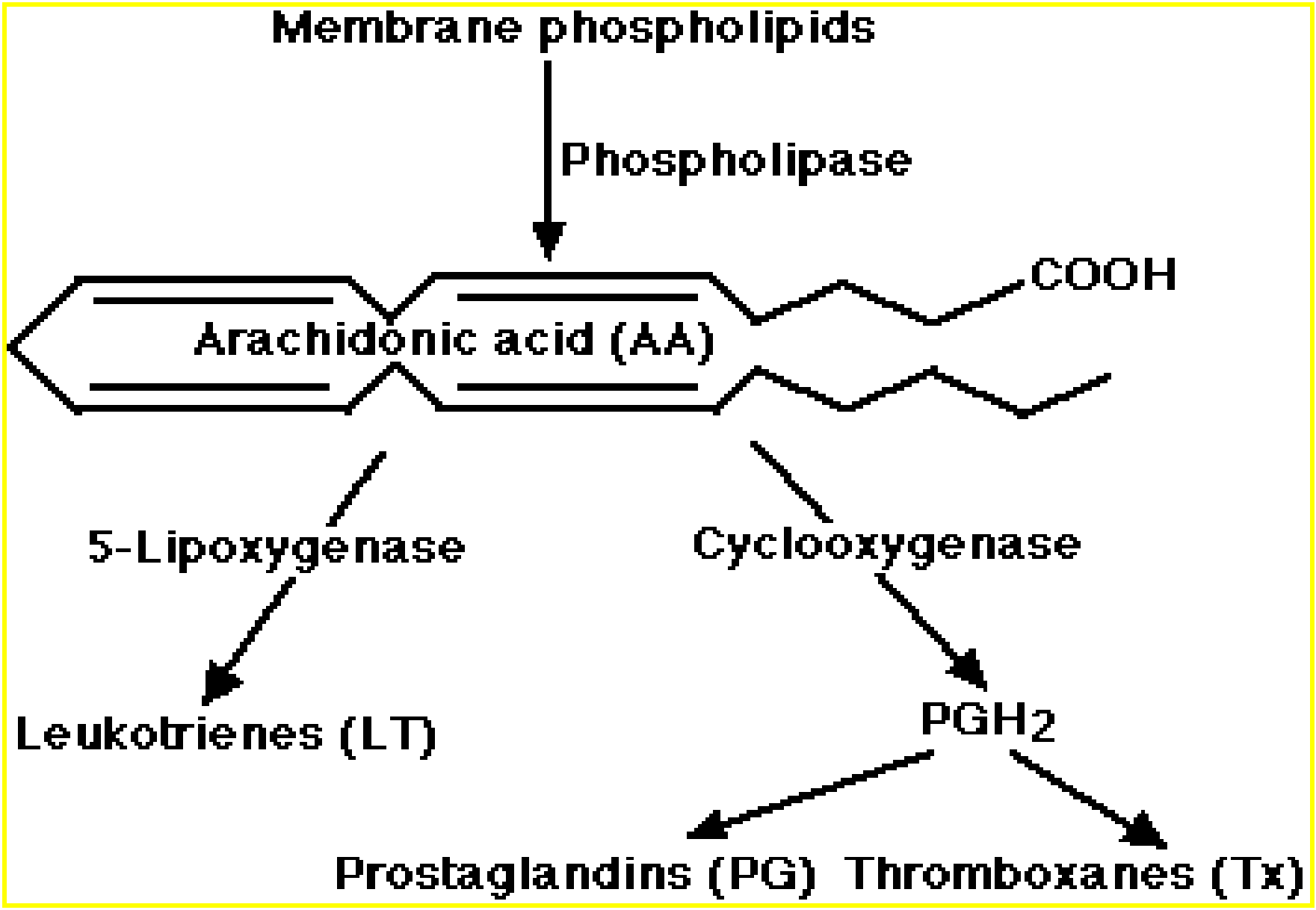
- Physiologic and pathologic processes (inflammation)
- Produced by endothelial cells, leukocytes and platelets
- Act on smooth muscle, endothelium and platelets

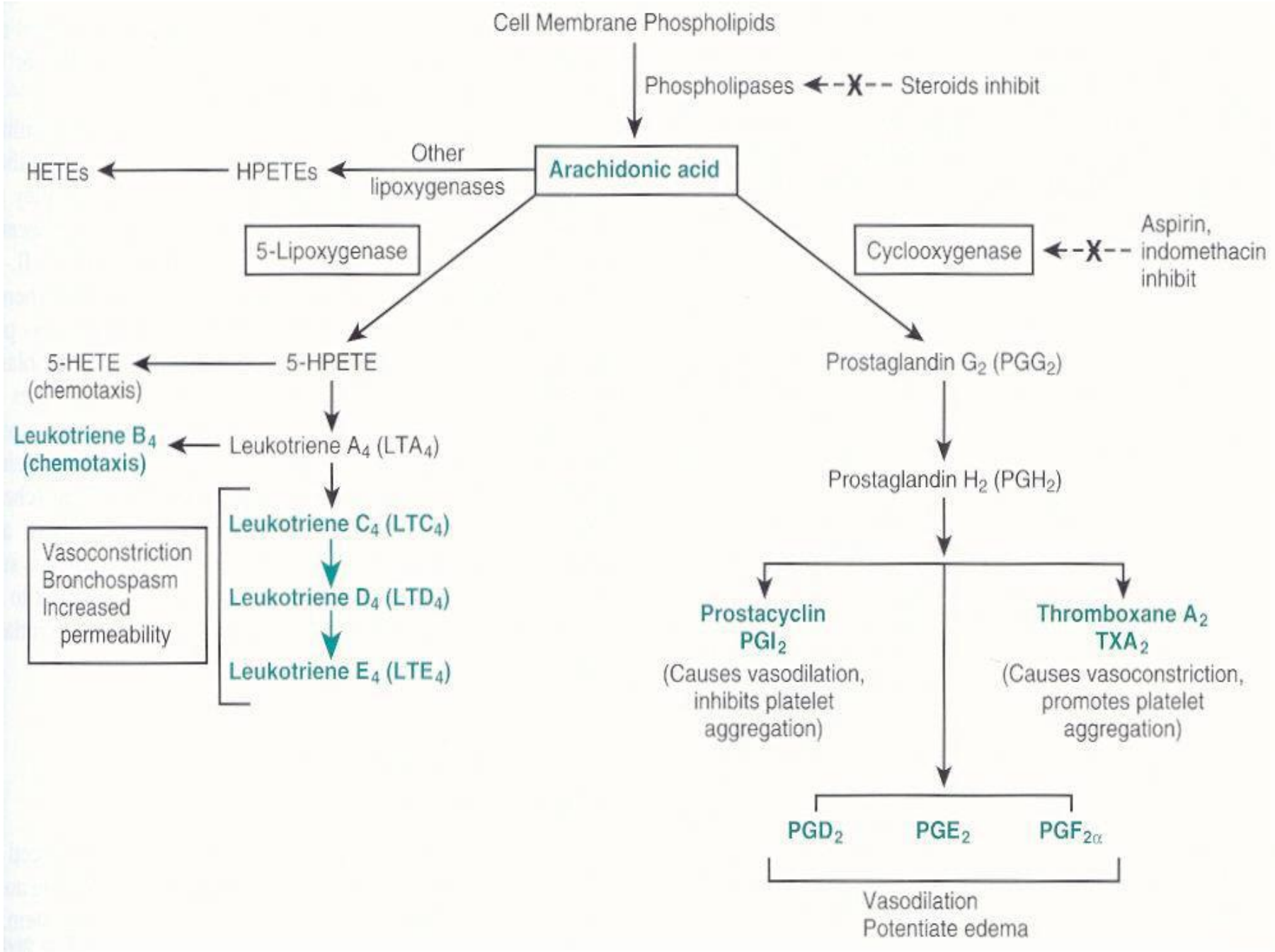
➢ **Origin:**

- ✓ **Arachidonic acid-derived from linoleic acid**
- ✓ Esterified in membrane phospholipids
- ✓ Must first be released from phospholipids by activated phospholipases

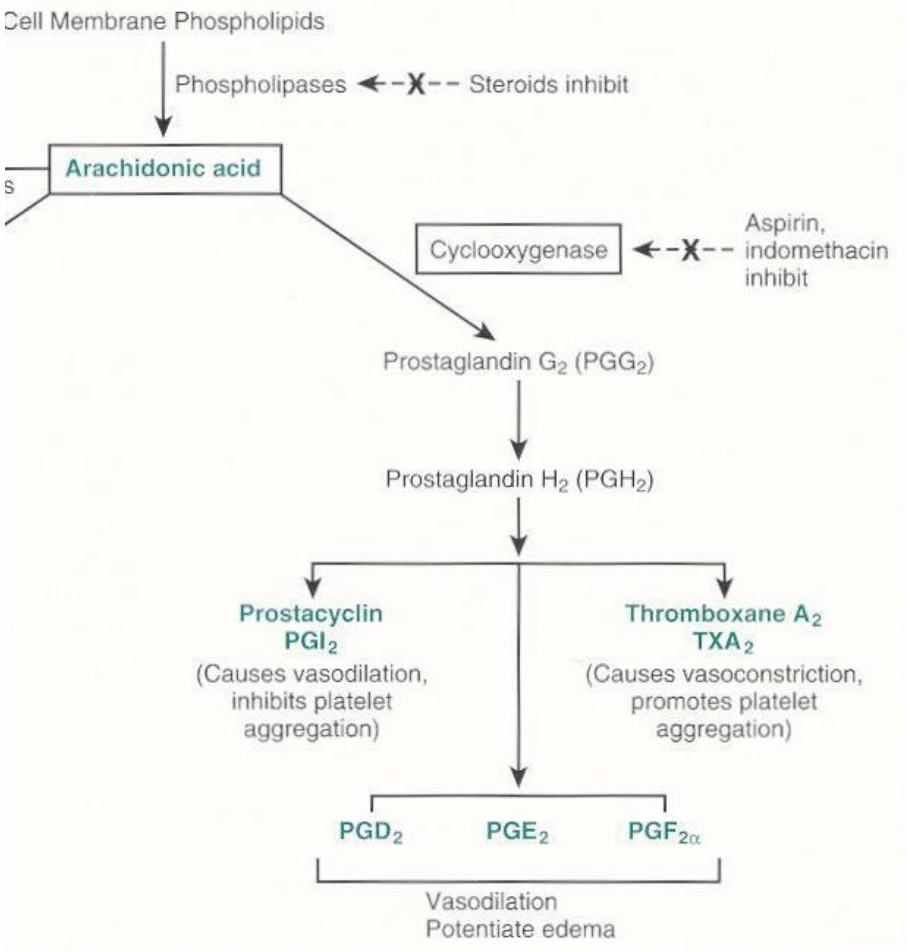
➢ Two pathways:

- ✓ Cyclooxygenase (COX)
- ✓ Lipoxygenase


Membrane phospholipids
Phospholipase
COOH
Arachidonic acid (AA)
5-Lipoxygenase
Cyclooxygenase
Leukotrienes (LT)
PGH2
Prostaglandins (PG)
Thromboxanes (Tx)


Cell Membrane Phospholipids
Phospholipases
Steroids inhibit
Arachidonic acid
Other lipoxygenases
HPETEs
HETEs
5-Lipoxygenase
Cyclooxygenase
Aspirin, indomethacin inhibit
5-HPETE
5-HETE (chemotaxis)
Leukotriene A4 (LTA4)
Leukotriene B4 (chemotaxis)
Leukotriene C4 (LTC4)
Leukotriene D4 (LTD4)
Leukotriene E4 (LTE4)
Vasoconstriction
Bronchospasm
Increased permeability
Prostaglandin G2 (PGG2)
Prostaglandin H2 (PGH2)
Prostacyclin PGI2
(Causes vasodilation, inhibits platelet aggregation)
Thromboxane A2 TXA2
(Causes vasoconstriction, promotes platelet aggregation)
PGD2
PGE2
PGF2α
Vasodilation
Potentiate edema

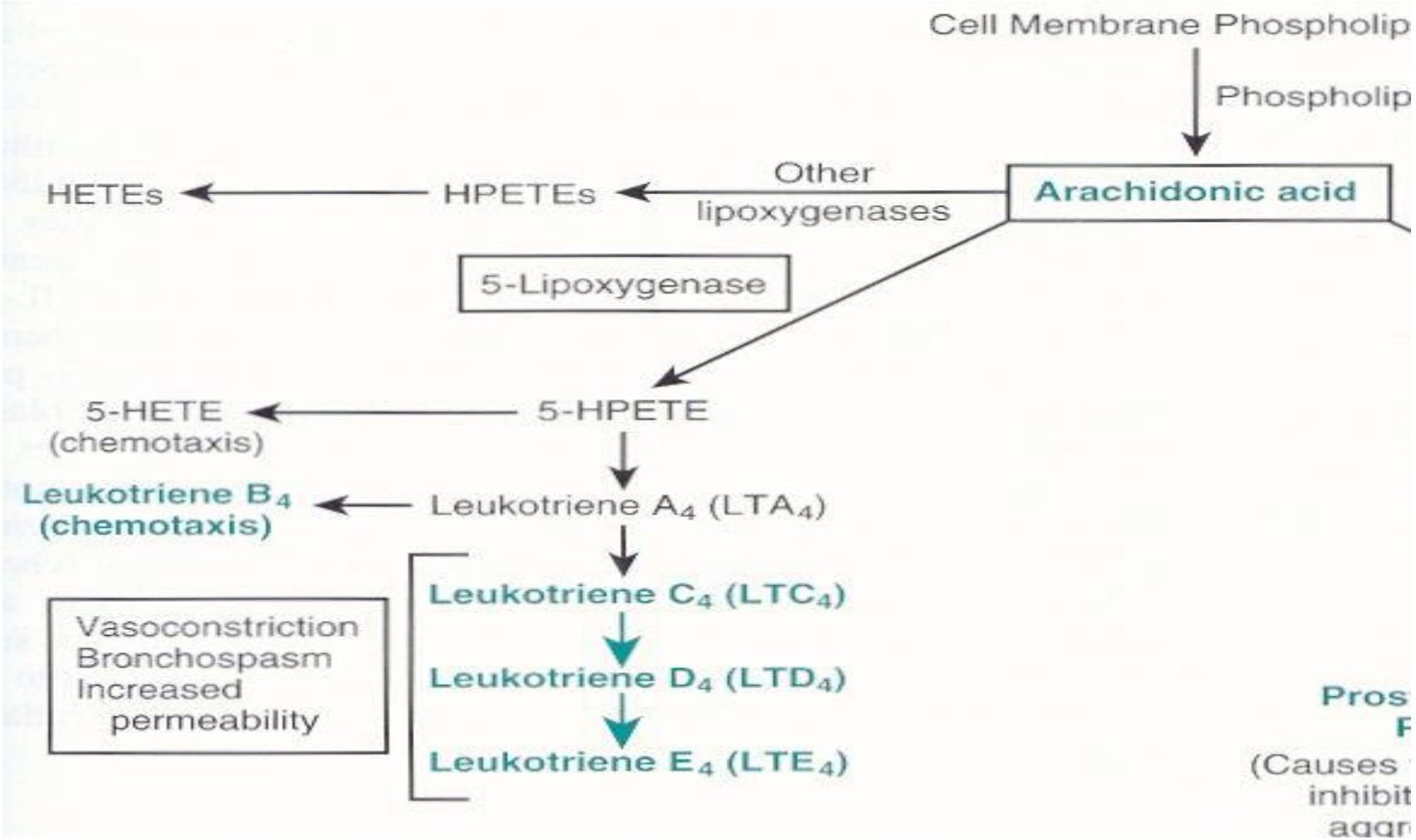
CYCLOOXYGENASE PATHWAY



CYCLOOXYGENASE PATHWAY

- 2 cyclooxygenase enzymes
  - COX-1
  - COX-2
- 3 important products
  - Thromboxane A2
  - Aggregates platelets and causes vasoconstriction
  - Prostacyclin (PGI_2)
  - Endothelial cells inhibits platelet aggregation and causes vasodilation
  - Prostaglandins PGE_2, PGF_2 and PGD_2
  - Variety of actions on vascular tone and permeability

LIPOXYGENASE PATHWAY



LIPOXYGENASE PATHWAY

- Leukotrienes
- Leukotriene B4 is a potent chemotactic agent
- Leukotrienes C4, D4, E4
  - Potent vasoconstrictors
  - Potent mediators of increased vascular permeability on venules only
  - Up to 1000 times as potent as histamine in producing increased vascular permeability

LYSOSOMAL CONSTITUENTS:

Granules of neutrophils, macrophages, lymphocytes, eosinophils and mast cells

Purpose

- **Increase vascular permeability**

–Histamine

- **Chemotaxis**

–Histamine

- **Degradation of ECM**

–Collagenase, hydrolase, protease (trypsin), elastase

- **Kill infected cells and/or infectious organisms**

–Lactoferrin, lysozyme, myeloperoxidase, major basic protein, granzyme/perforin (T Lymphocytes)

–Oxygen-independent mechanisms

PLATELET ACTIVATING FACTOR

- Produced by platelets, endothelial cells, leukocytes
- Functions:
  - –Platelet aggregation and release
  - –Bronchoconstriction
  - –Vasodilation and vascular permeability
  - –Increase leukocyte adhesion
  - –Leukocyte chemotaxis, oxydative burst

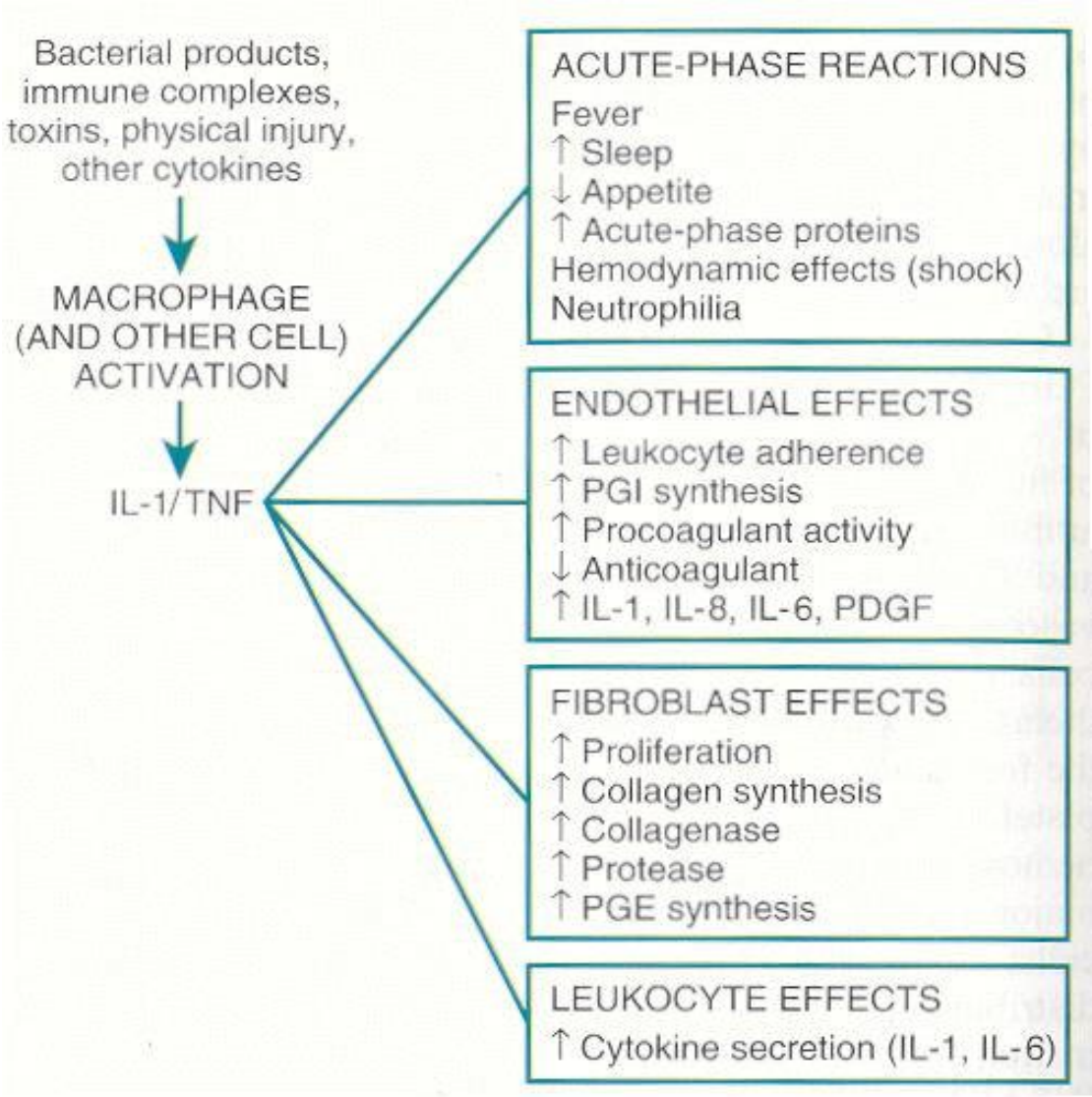
CYTOKINES

- Transmitters for cell-to-cell chatting
  - Modulate cell function
- Primarily from activated macrophages and lymphocytes
- IL-1, IL-8, TNF

IL-I and TNF

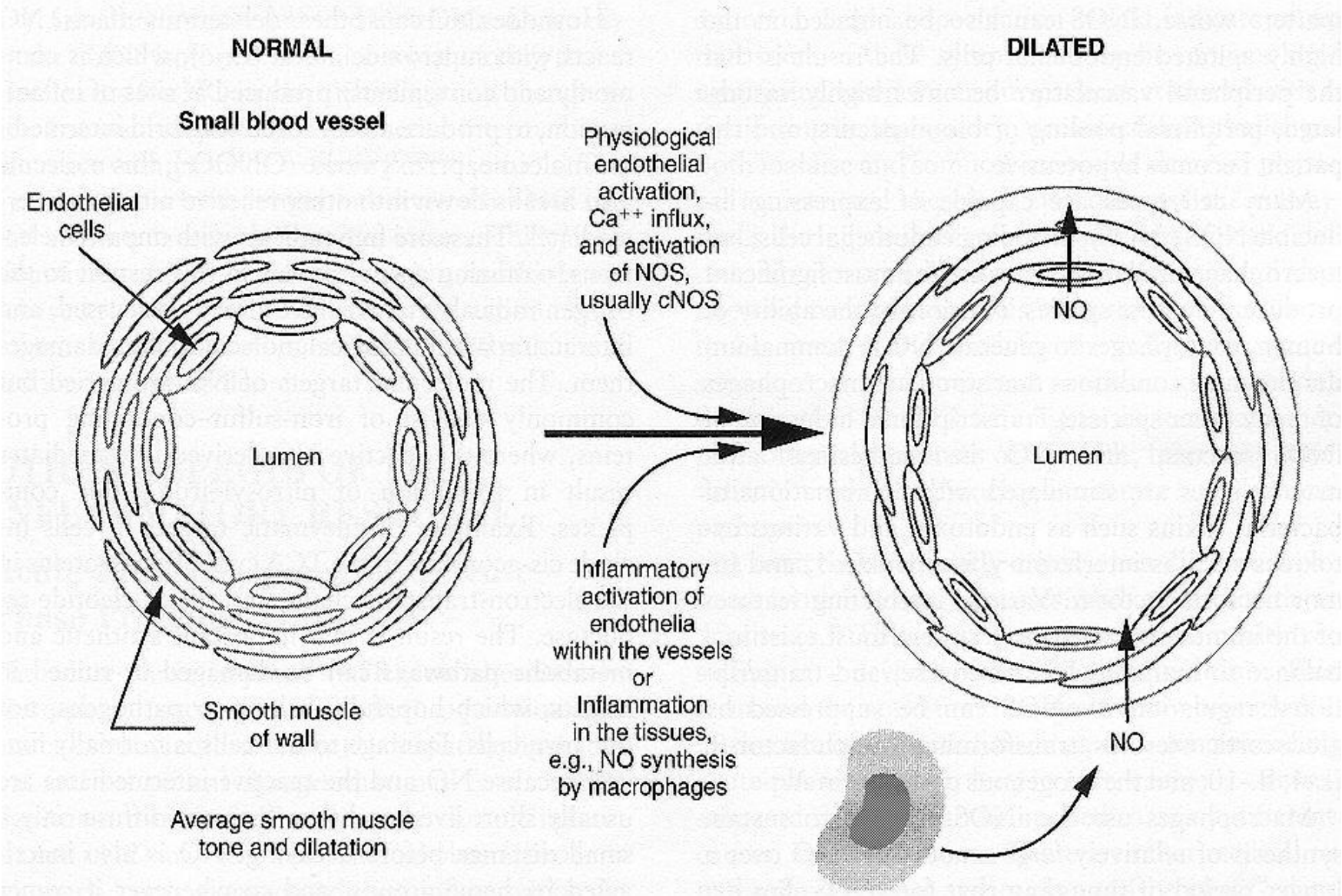
Master Cytokines”

- Origin
  - –Monocytes
  - –Macrophages
- Similar in action
- Effects:
  - –Systemic
  - –Endothelium
  - –Fibroblasts
  - –Leukocytes



NITRIC OXIDE (NO)

- Nitric oxide is synthesized from L-arginine by NOS
- Effects:
  - –Smooth muscle relaxation -VASODILATION
  - –Bactericidal
  - –Reduce platelet aggregation and adhesion

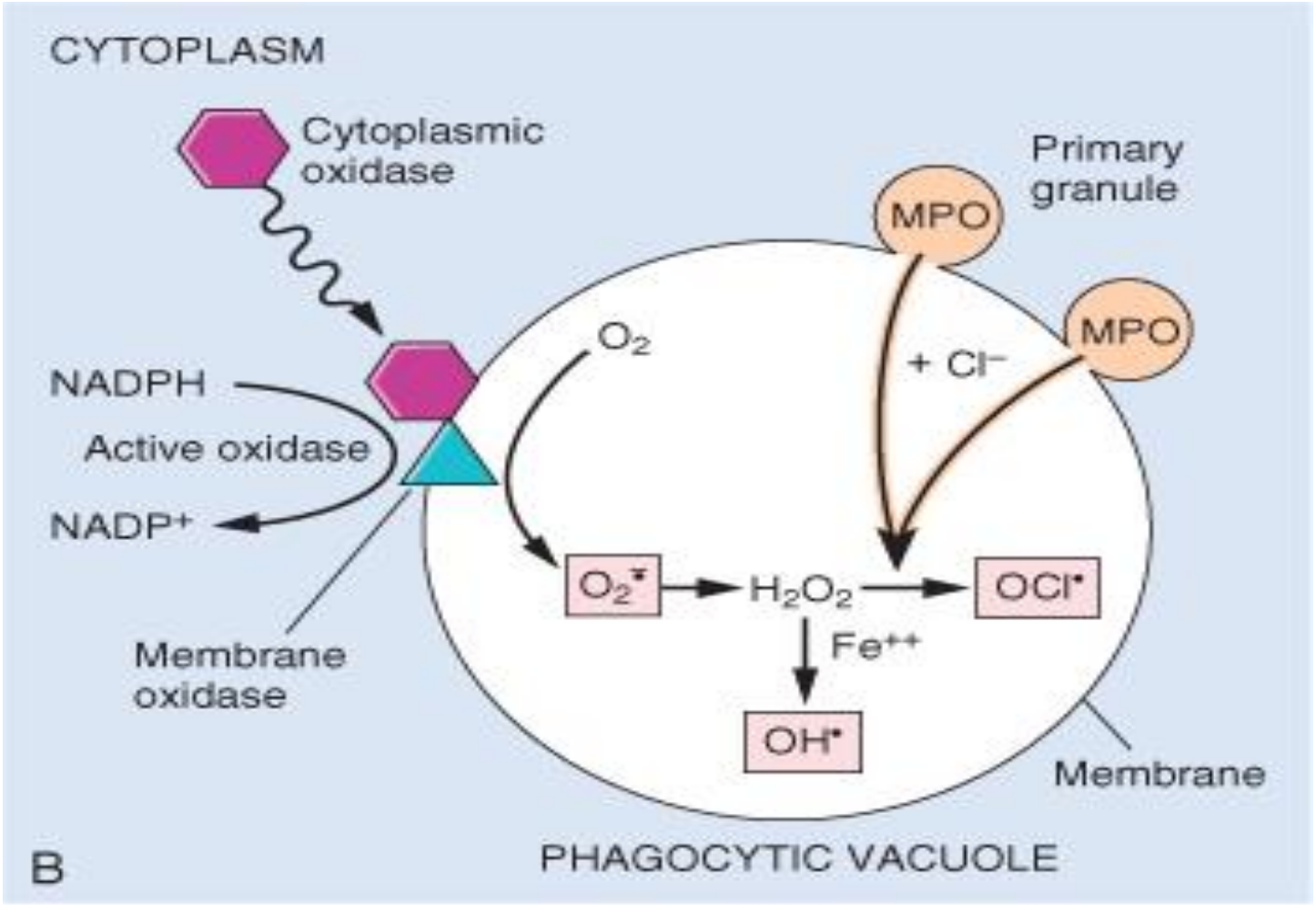

NORMAL
DILATED
Small blood vessel
Endothelial cells
Lumen
Smooth muscle of wall
Average smooth muscle tone and dilatation
Physiological endothelial activation, Ca++ influx, and activation of NOS, usually cNOS
Inflammatory activation of endothelia within the vessels or Inflammation in the tissues, e.g., NO synthesis by macrophages
NO
Lumen
NO

OXYGEN-DERIVED FREE RADICALS

- Include:

–hydrogen peroxide (H2O2), superoxide anion (O2-) and hydroxyl radicals (OH●)

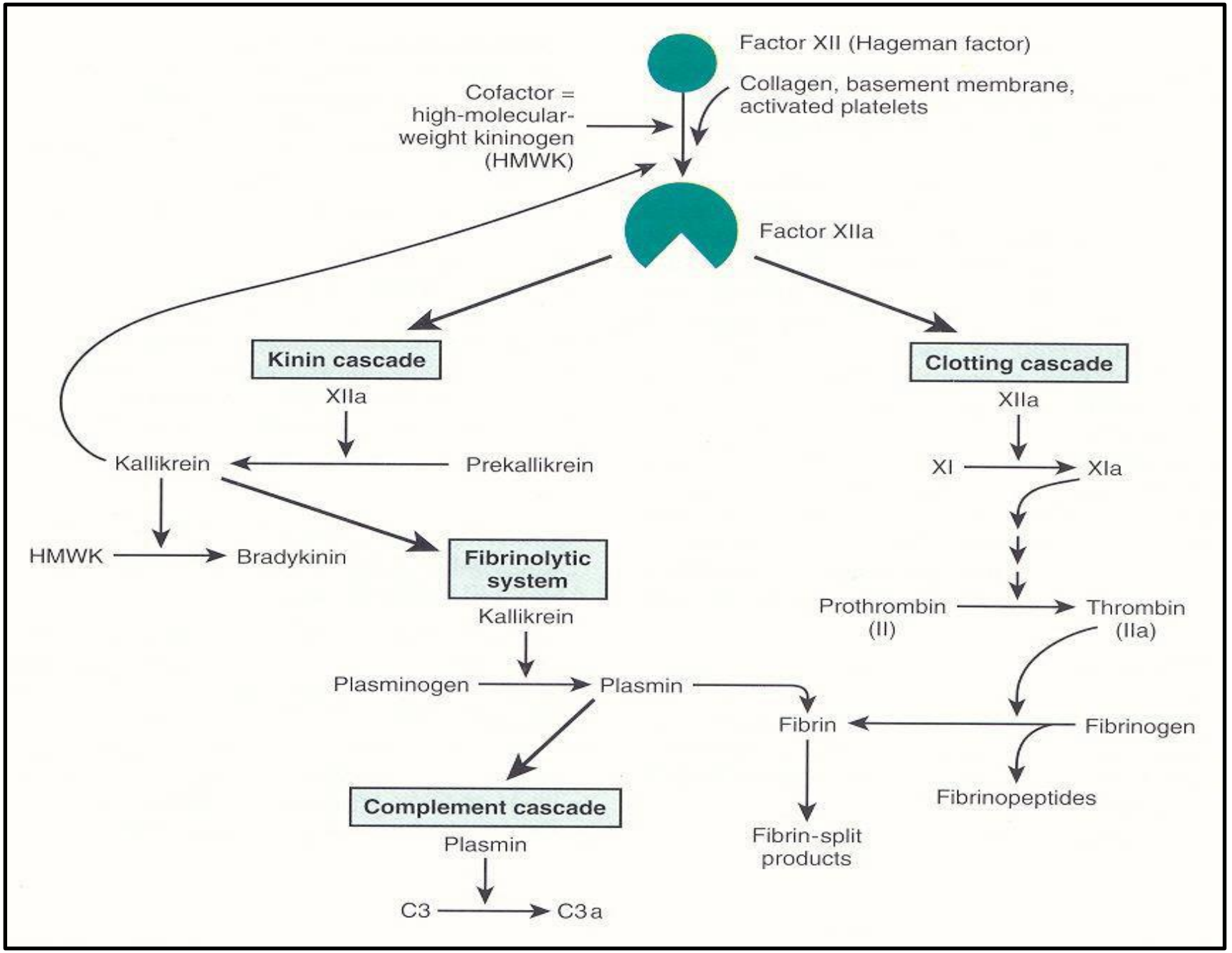
- Cause endothelial damage –increased vascular permeability
- Inhibite antiproteases –damage to ECM
- Injury to variety of cells



PLASMA PROTEASES

- 3 interrelated systems are active within this category

1. Kinin system
    - » Highly vasoactive
2. Complement system
    - – Vasoactive
    - – Chemotactic
3. Clotting system
    - – Vasoactive
    - – Cleaves C3


Factor XII (Hageman factor)
Collagen, basement membrane, activated platelets
Cofactor = high-molecular-weight kininogen (HMWK)
Factor XIIa
Kinin cascade
XIIa
Kallikrein
Prekallikrein
HMWK
Bradykinin
Fibrinolytic system
Kallikrein
Plasminogen
Plasmin
Complement cascade
Plasmin
C3
C3a
Clotting cascade
XIIa
XI
XIa
Prothrombin (II)
Thrombin (IIa)
Fibrin
Fibrinogen
Fibrinopeptides
Fibrin-split products

KININ SYSTEM

- Activated by Hageman factor (XIIa)
- Bradykinin
  - –Generated from the plasma
  - –Potent vasodilator
  - –Contraction of smooth muscle
  - –Produces pain
  - –Stimulates release of histamine
    - •Increased vascular permeability
  - –Activates the arachidonic acid cascade

COAGULATION SYSTEM

Plasma proteins (inactive)

- –Intrinsic pathway -Hageman factor(XII)
- –Extrinsic pathway

Thrombin converts fibrinogen to fibrin

- –Fibrinopeptides are formed
- –**RESULT: Increase vascular permeability and chemotaxis for leukocytes**

Plasmin(mainly lyses fibrin clots):

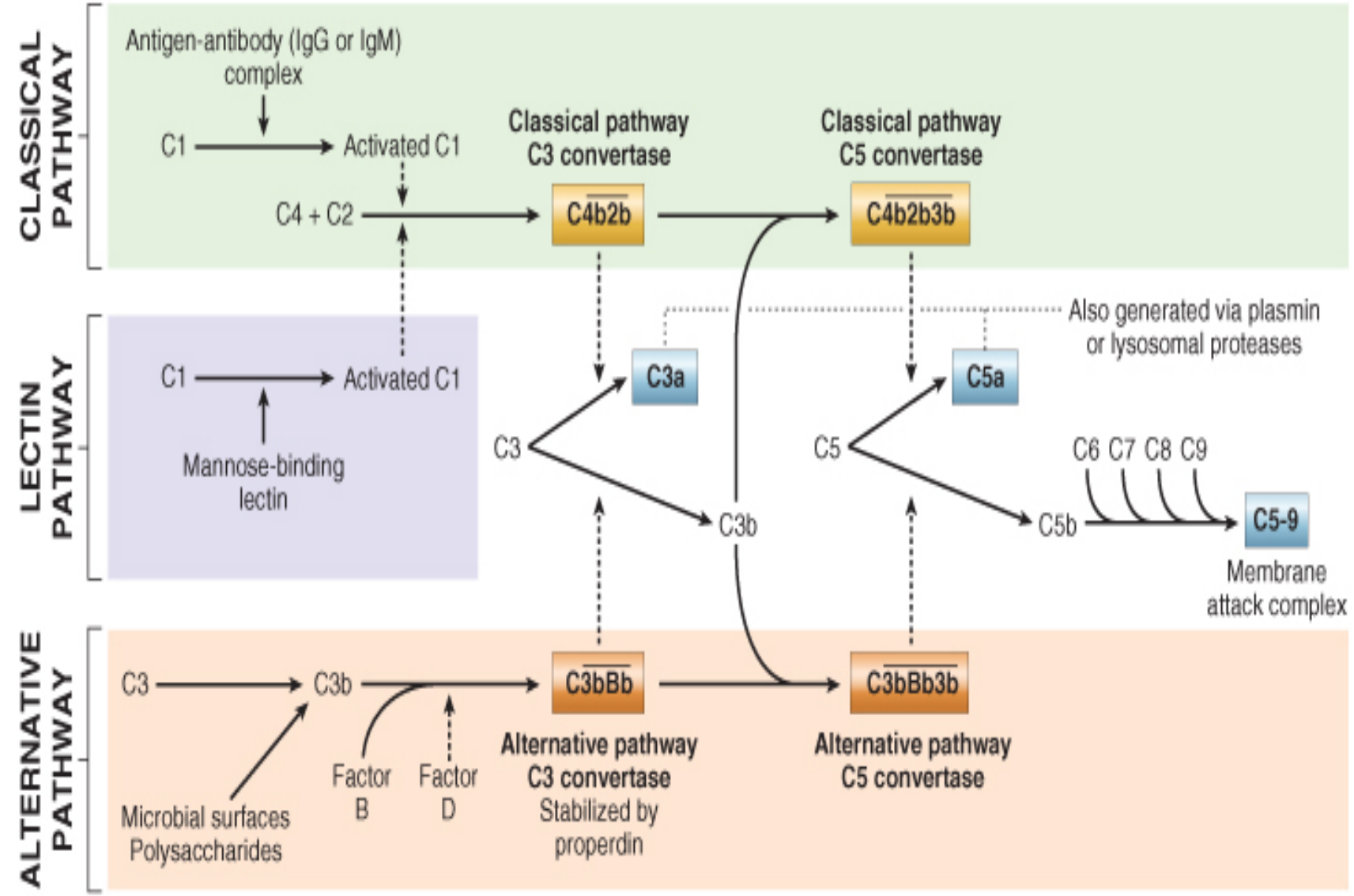
- –Activates Hageman factor (XII) ⇨bradykinin
- –Cleaves C3 into C3a (active)
- –"fibrin-split products" formed from fibrin breakdown
- –**RESULT: Increase vascular permeability**

COMPLEMENT SYSTEM

- Plasma proteins - act against microbial agents
- Products of activated complement
  - Vascular permeability
  - Chemotaxis
  - Opsonization
  - Lysis

COMPLEMENT SYSTEM

- Classical pathway
- Alternate pathway
- Common pathway
- Important inflammatory mediators
  - C3a and C5a (anaphylatoxins)
  - Cause release of histamine from mast cells
  - Lysosomal enzyme release in inflammatory cells
  - C5a
  - Activates lipoxygenase pathway
  - Chemotactic many inflammatory cells
  - Increases adhesion of leukocytes


CLASSICAL PATHWAY
Antigen-antibody (IgG or IgM) complex
C1
Activated C1
C4 + C2
Classical pathway C3 convertase
C4b2b
Classical pathway C5 convertase
C4b2b3b
LECTIN PATHWAY
C1
Activated C1
Mannose-binding lectin
Also generated via plasmin or lysosomal proteases
C3a
C5a
C3
C5
C6 C7 C8 C9
C3b
C5b
C5-9
Membrane attack complex
ALTERNATIVE PATHWAY
C3
C3b
C3bBb
C3bBb3b
Factor B
Factor D
Alternative pathway C3 convertase
Stabilized by properdin
Alternative pathway C5 convertase
Microbial surfaces
Polysaccharides

INFLAMMATORY CELLS

- Polymorphonuclear neutrophils
- Eosinophils
- Basophils
- Lymphocytes
- Plasma cells
- Mononuclear-Phagocyte System

POLYMORPHONUCLEAR NEUTROPHILS

- Granulocytes
- Granules contain:
  - Proteases,
  - Myeloperoxidase,
  - Lysozyme, Esterase,
  - Aryl sulfate,
  - Cationic proteins,
  - Acid and Alkaline phospatase
- **Function**:
  - Initial phagocytosis
  - Engulfment

EOSINOPHILS

- Larger than Neutrophils,
- Similar in function and Structure
- Granules
  - Richer in Myeloperoxidase
  - Lack in lysozyme
- Give Inflammatory response in following condition
  - Allergic condition
  - Parasitic infestations
  - Skin diseases

BASOPHILS

- Morphological and Pharmacological similar to Mast cell
- Coarse granules
- Receptors for IgE
- Degranulated when crosslinked with antigen
- Role:
  - Immediate and delayed type of hypersensitivity reaction
  - Release of Histamine

LYMPHOCYTES

- Present in Blood, Spleen, Thymus, lymph nodes
- Give following type of inflammatory reaction
  - In tissue, they are dominant cells in chronic inflammation and late stage of acute inflammation
  - In Blood, there number increased in chronic infections like Tuberculosis

PLASMA CELLS

- Larger than Lymphocytes with more abundant cytoplasm
- Rich in RNA and γ-globulin in their cytoplasm
- There number increased in following conditions
  - Prolonged infection with immunological response
  - Hypersensitivity states
  - Multiple myeloma

CHRONIC INFLAMMATION

Defined as a prolonged process in which tissue destruction and inflammation occur at the same time.

CHRONIC INFLAMMATION

- Caused by 3 ways:

1. Chronic inflammation following acute inflammation
2. Recurrent attack of acute inflammation
3. Chronic inflammation starting:

   when the infection with organisms of low pathogenicity is chronic from the beginning. E.g. Tuberculosis

TYPE OF CHRONIC INFLAMMATION

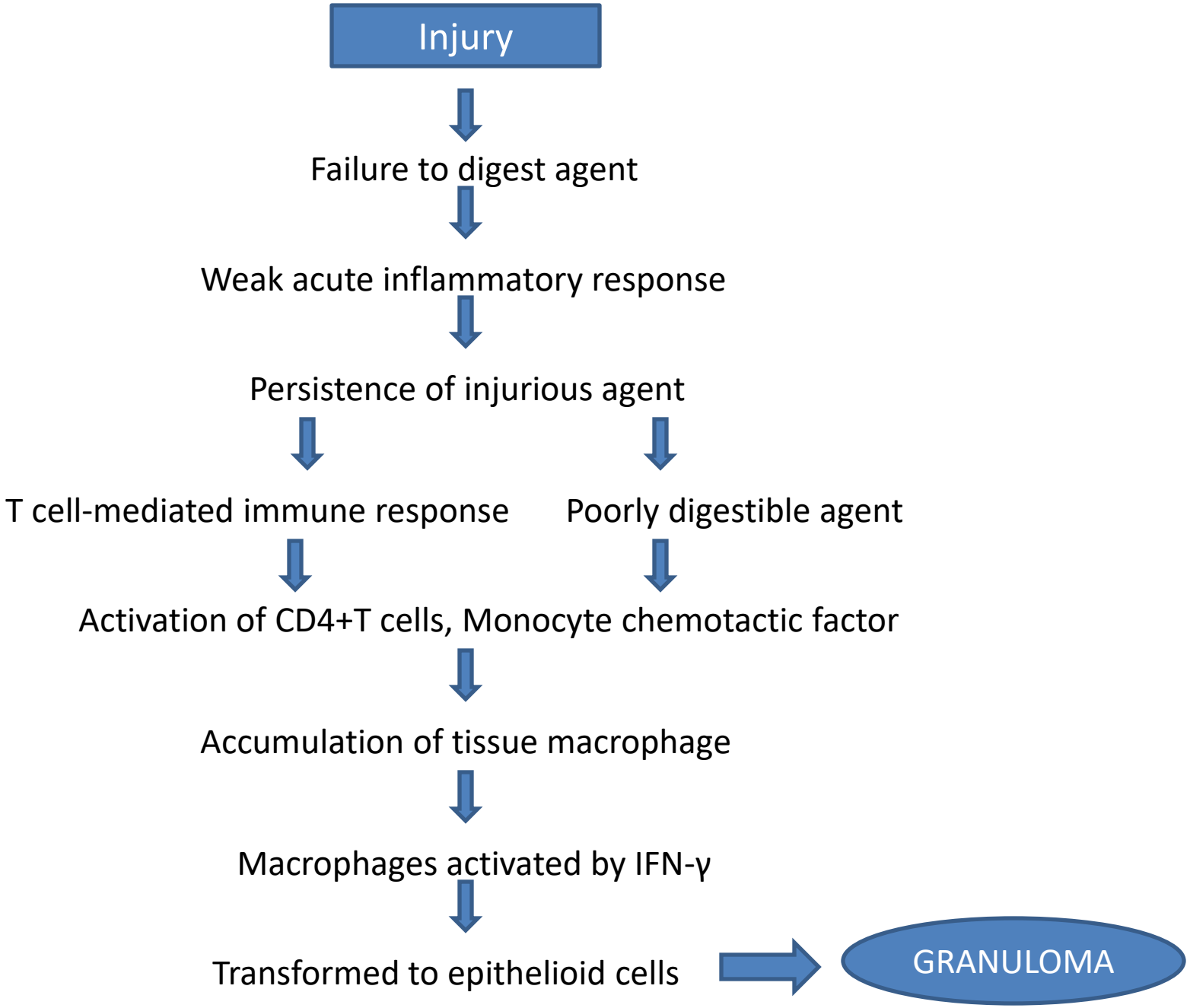
- Divided into 2 types

1. **Non-specific**: When the irritant substance produces a non-specific chronic inflammatory reaction with formation of granulation tissue and healing by fibrosis. e.g. Chronic ulcer
2. **Specific**: When the injurious agent causes a characteristic histologic tissue response e.g. tuberculosis, Leprosy

GRANULOMATOUS INFLAMMATION

- **Granuloma** defined as a circumscribed, tiny lesion, about 1 mm in diameter, composed predominantly of collection of modified macrophages called **epithelioid cells** and rimmed at the periphery by lymphoid cells.
- **Epithelioid cells** called because of their epithelial cell-like appearance, are modified macrophages, having pale staining abundant cytoplasm, vesicular and lightly staining sliper-shaped nucleus, weakly phagocytic.

- Giant cells:
  - Formed by fusion of adjacent epithelioid cells and have 20 or more nuclei.
  - Weakly Phagocytic but produce secretory products which help in removing the invading agents.
- Necrosis:
  - May be feature of some Granulomatous conditions
- Fibrosis:
  - Due to proliferation of fibroblasts at the periphery of granuloma.


Injury
Failure to digest agent
Weak acute inflammatory response
Persistence of injurious agent
T cell-mediated immune response
Poorly digestible agent
Activation of CD4+T cells, Monocyte chemotactic factor
Accumulation of tissue macrophage
Macrophages activated by IFN-γ
Transformed to epithelioid cells
GRANULOMA