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Arachidonic Acid Metabolites and Inflammation

Joseph Fantone, M.D.

Host Defense 2/12 10-11:00am

INFLAMMATORY MEDIATORS

PLASMA DERIVED

- COMPLEMENT CASCADE

C3a, C5a

- COAGULATION CASCADE

Thrombin, plasmin

CELL-DERIVED

- VASOACTIVE AMINES

histamine, serotonin

- OXYGEN METABOLITES

hydrogen peroxide (H_2O_2)

superoxide anion ($O_2^{\cdot-}$)

hypochlorous acid (HOCl)

- ARACHIDONIC ACID METABOLITES

cyclooxygenase-derived

lipoxygenase-derived

- CYTOKINES

Interleukins

Chemokines

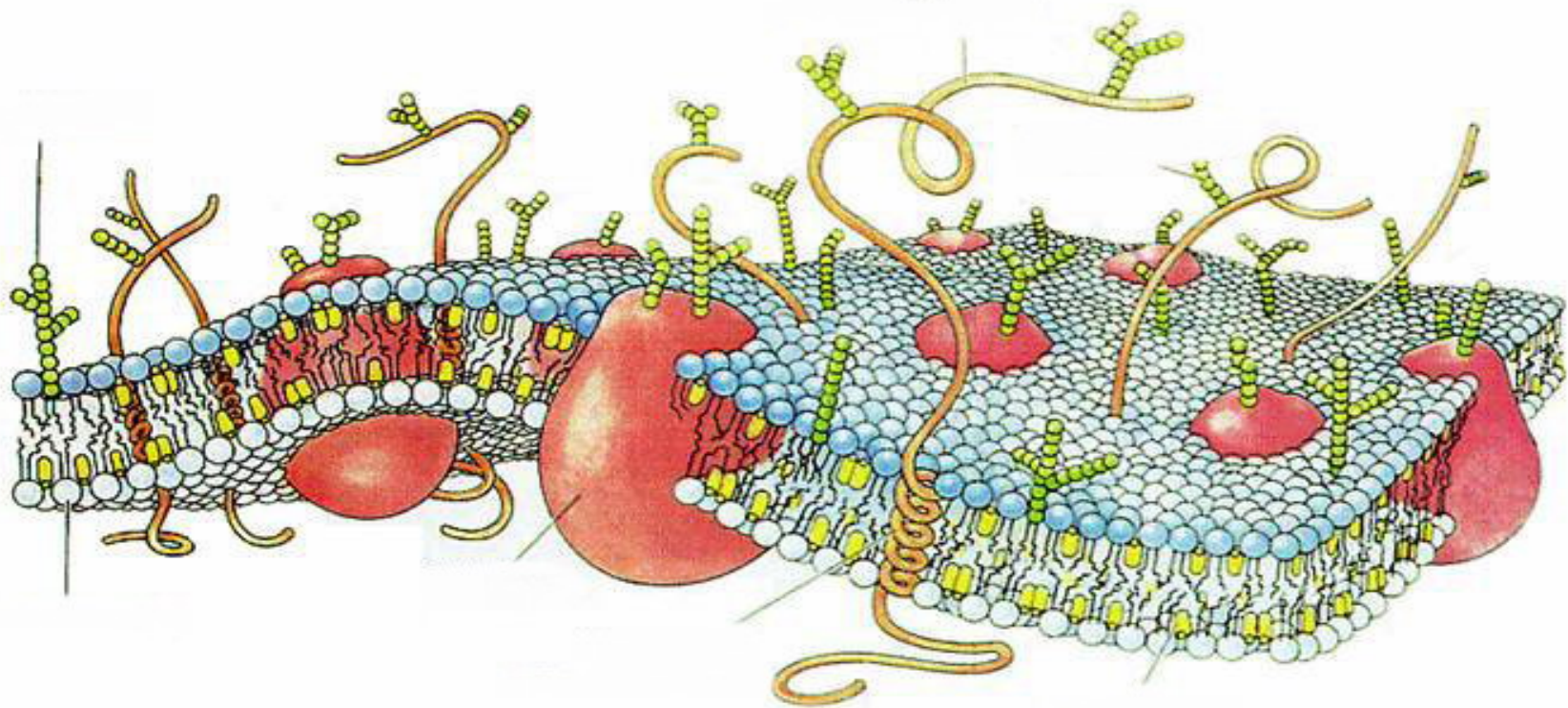
Interferons

Tumor Necrosis Factor

Growth Factors

Intended Learning Outcomes: To Understand The

- Primary inflammatory mediators derived from the metabolism of arachidonic acid including their primary cellular source and biological activity.
- Effects of nonsteroidal anti-inflammatory compounds on blocking the production of arachidonic acid metabolites during disease
- Mechanism of aspirin therapy and diets rich in fish containing high levels of omega 3 fatty acids as potentially important in lowering the incidence of cardiovascular disease.

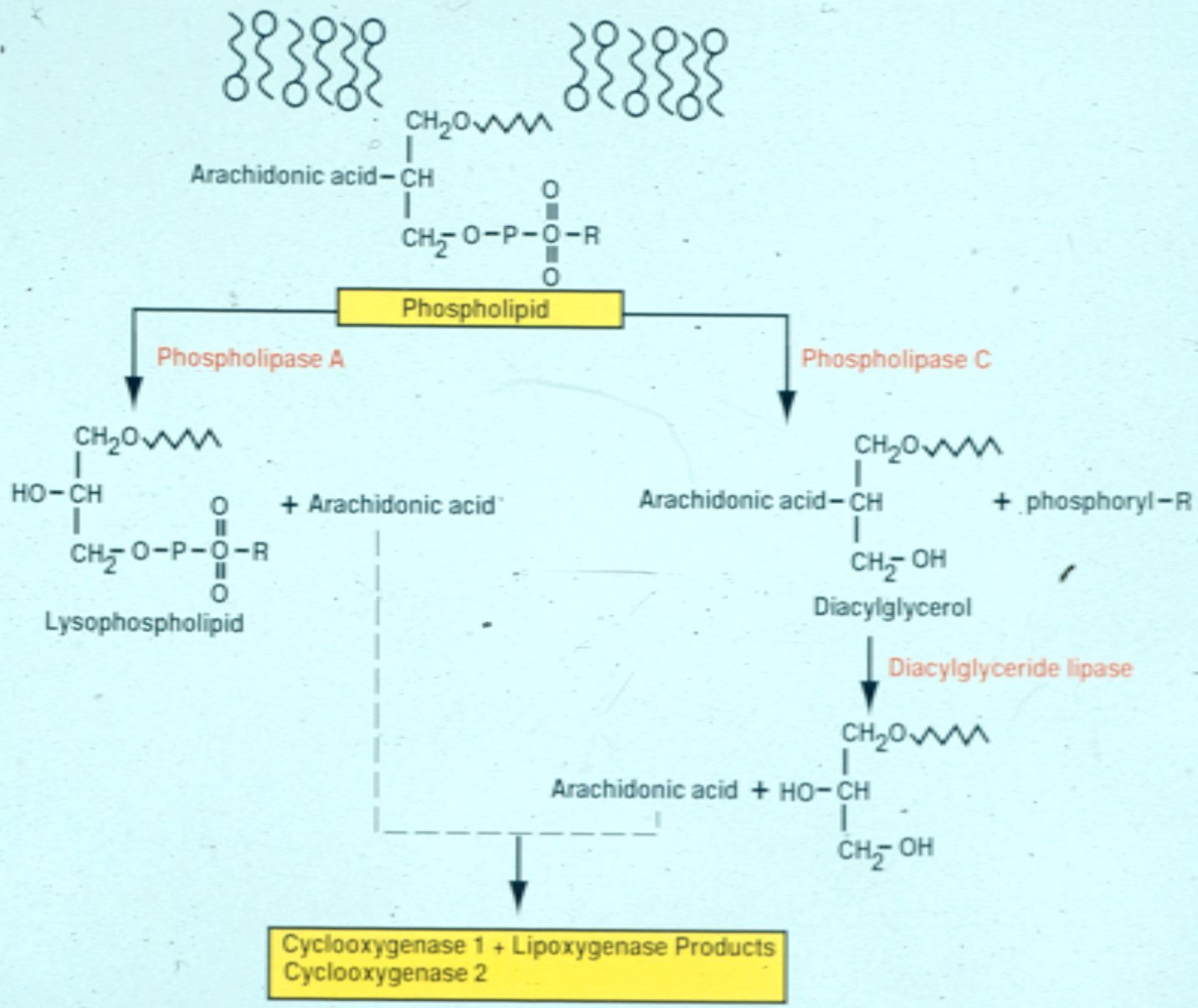


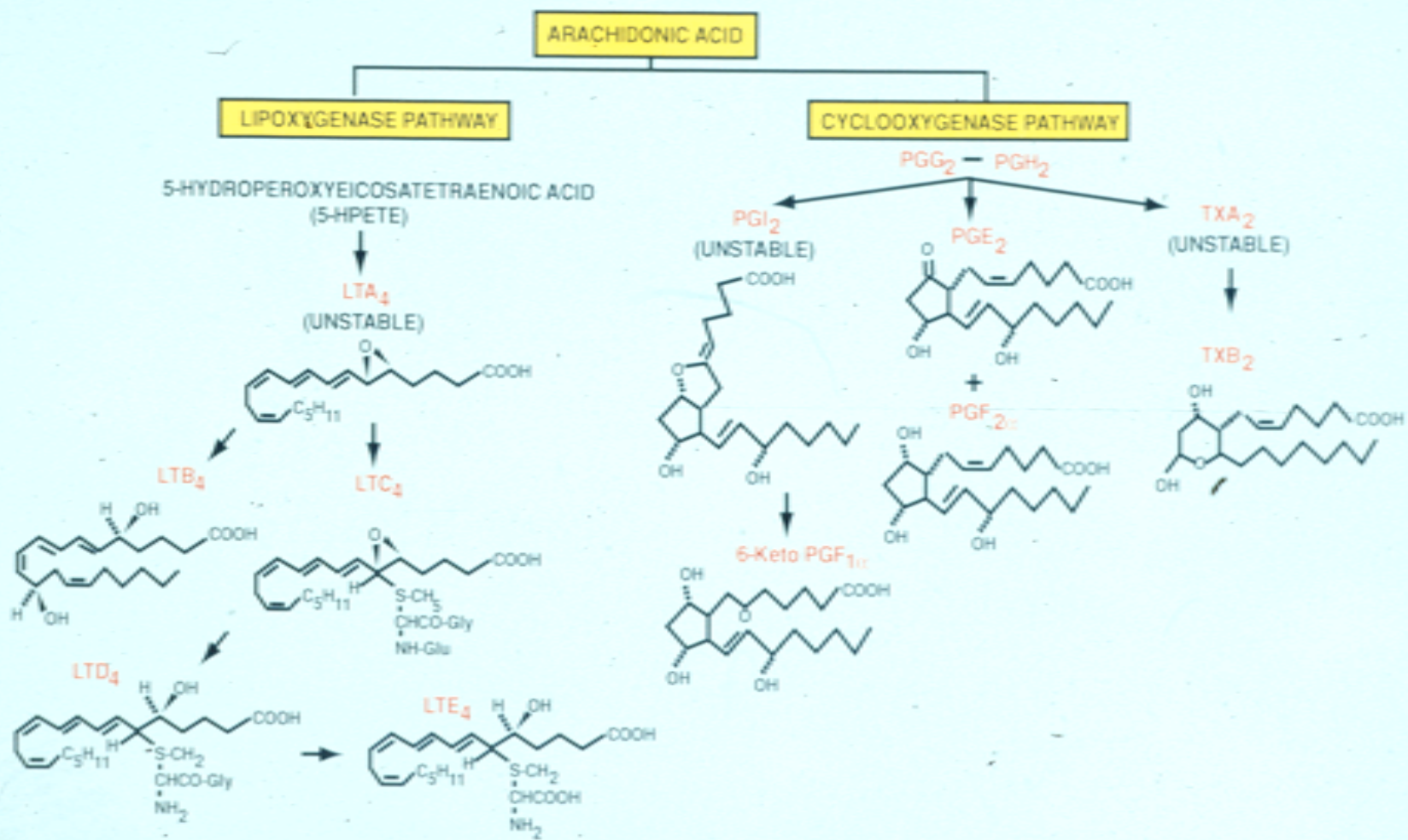
BY: Dana Burns

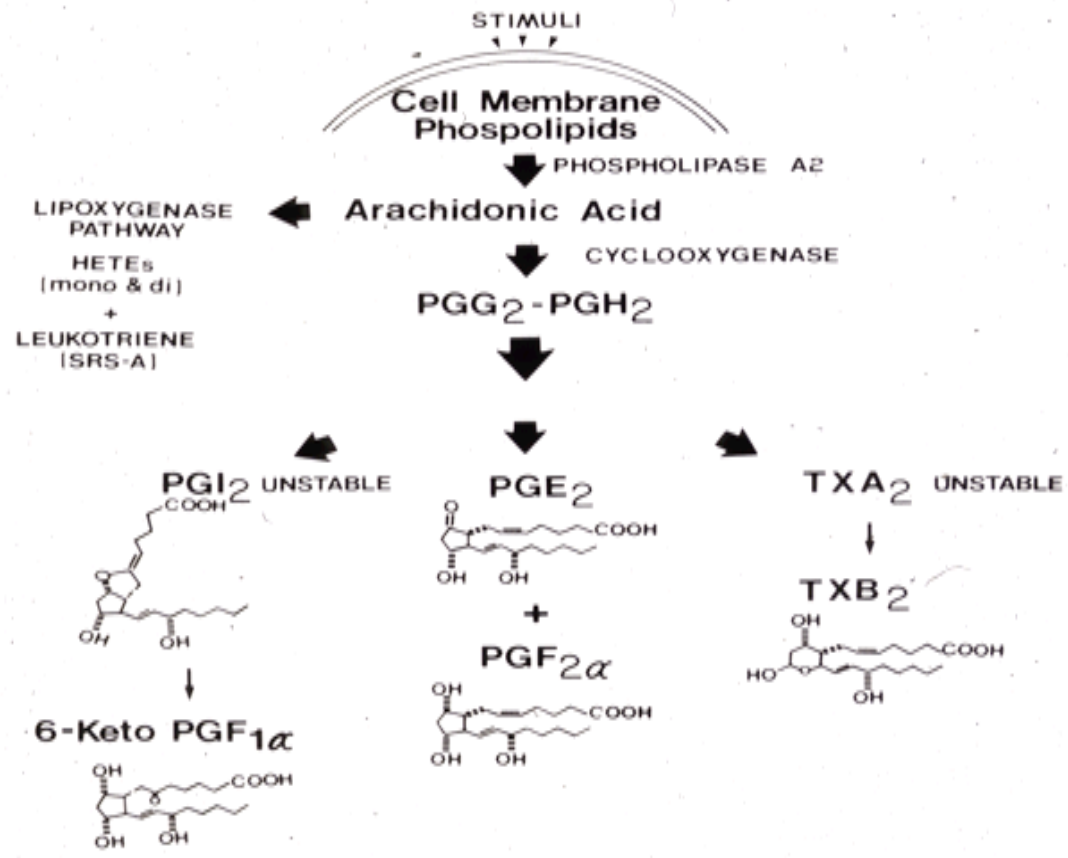
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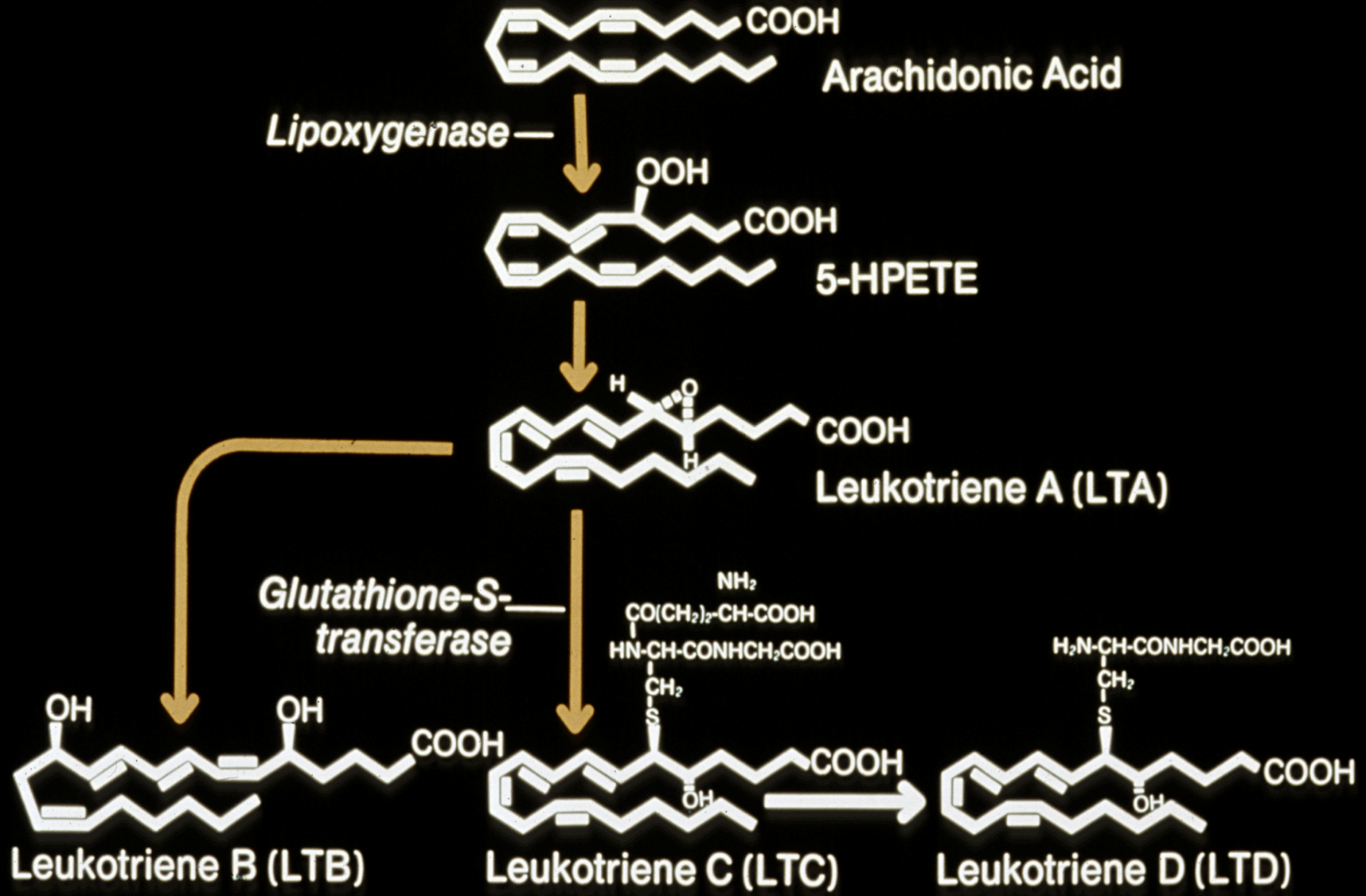
YOU ARE WHAT YOU EAT







Leukotriene Synthesis



CELL DEPENDENT END-PRODUCT SPECIFICITY OF ARACHIDONIC ACID-DERIVED PRODUCTS

CELL

Neutrophils

Macrophage/Monocyte

Platelets

Endothelial Cells

PRODUCT

Leukotrienes

**Prostaglandins +
Leukotrienes**

Thromboxane

Prostacyclin

Biological Function

Cyclooxygenase-derived Products:

Prostaglandin E₂/Prostacyclin

Immunoregulatory

•Inhibits Immune cell act

•Inhibits cytokine production

•Inhibits mast cell activation

Blocks platelet aggregation

Increases vasodilation

Stimulates adenylate cyclase

Thromboxane

Causes vasoconstriction

Induces platelet aggregation

Biological Function

Lipoxygenase-derived Products:

Leukotriene B₄

Neutrophil Activation

- degranulation

Mast cell activation

- degranulation

**Leukotriene C,D,E
(SRS-A)**

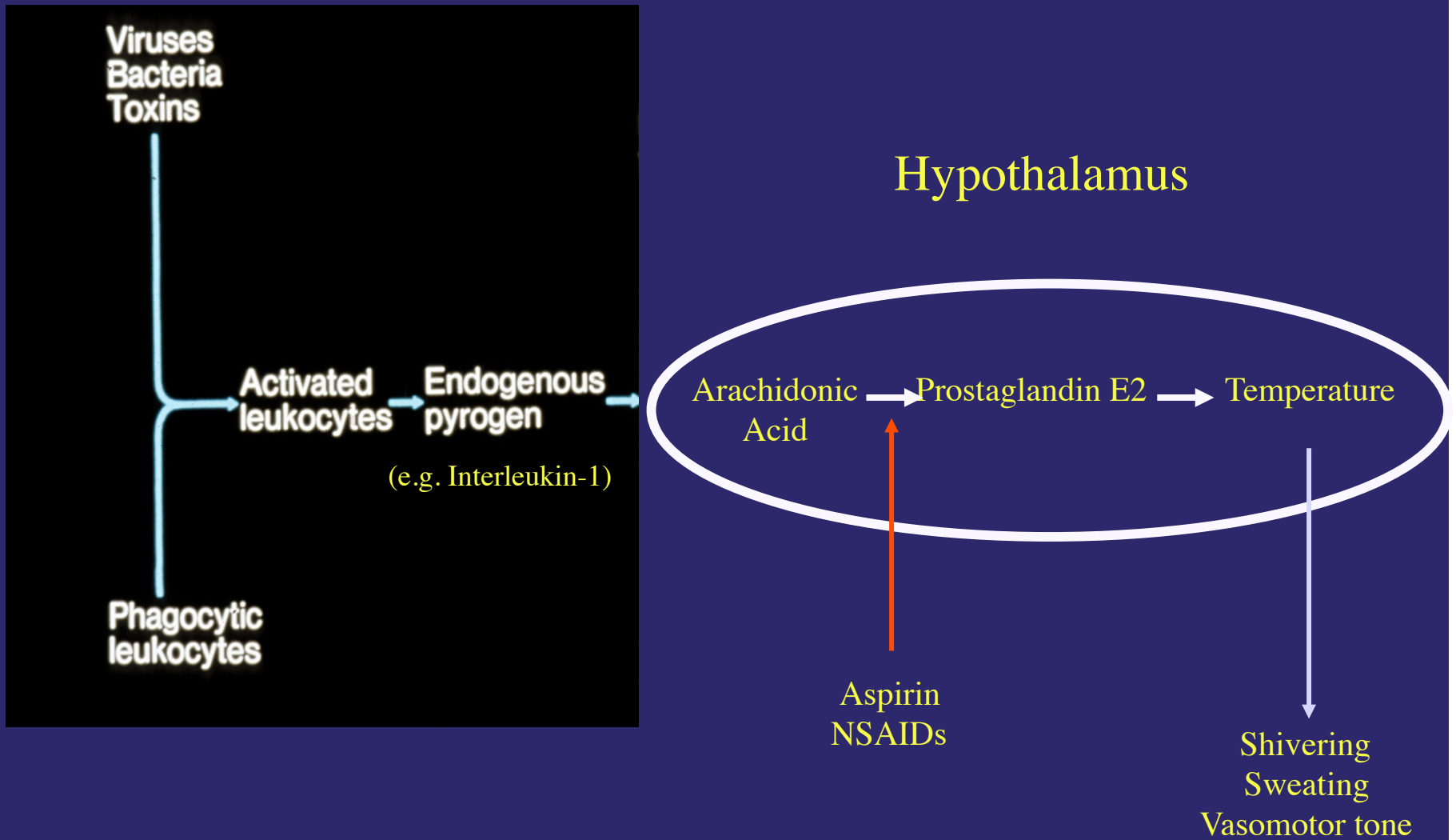
Causes smooth muscle contraction

Increases vascular permeability

In Vivo Effects of Arachidonic Acid Derived Products

- Regulates Thermostatic Set Point (Fever)
- Regulates Pain (Interacts with pain receptors)
- Regulates Blood Flow
- Regulates Leukocyte Activity

Production of Fever

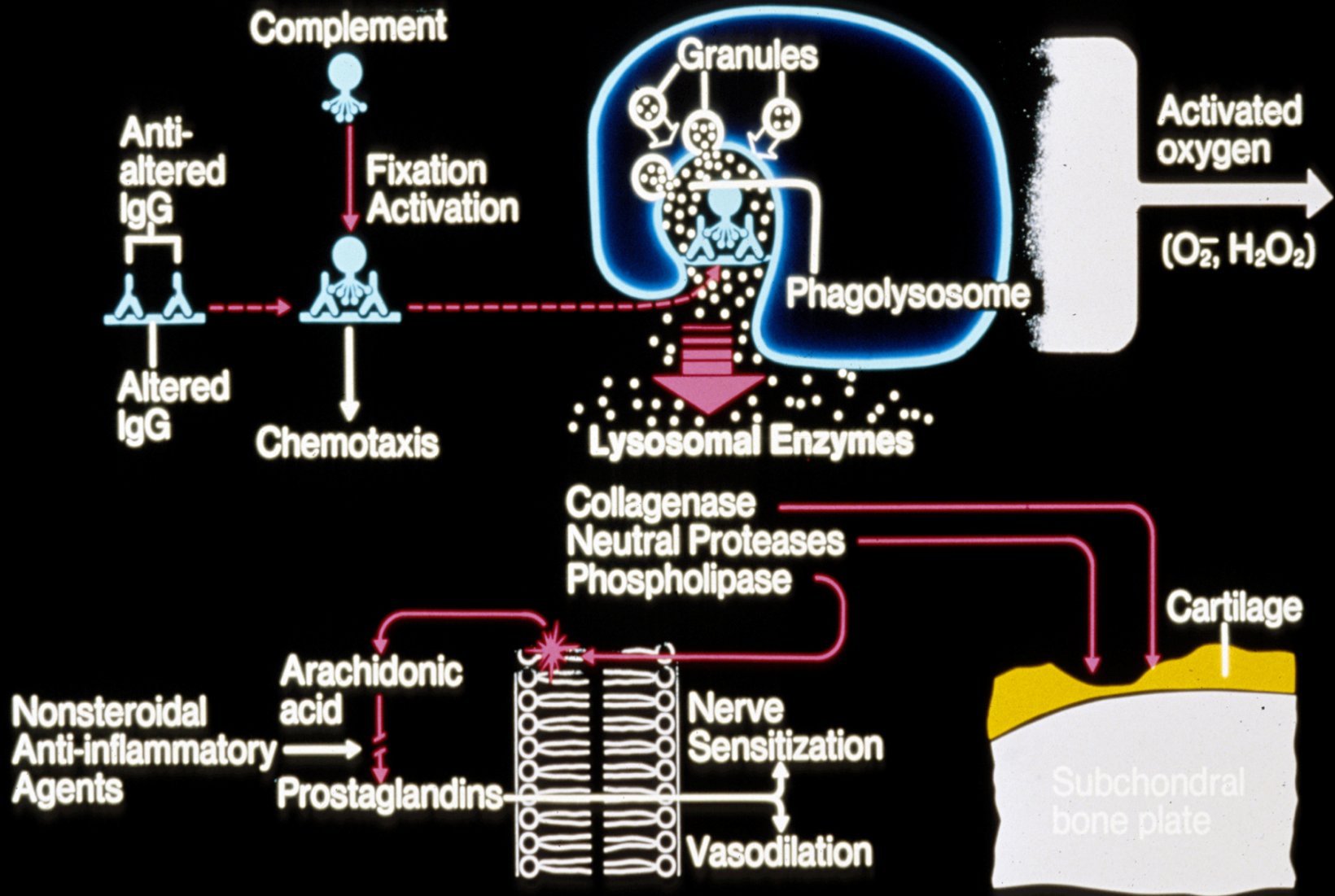


Rheumatoid Arthritis distorts joints

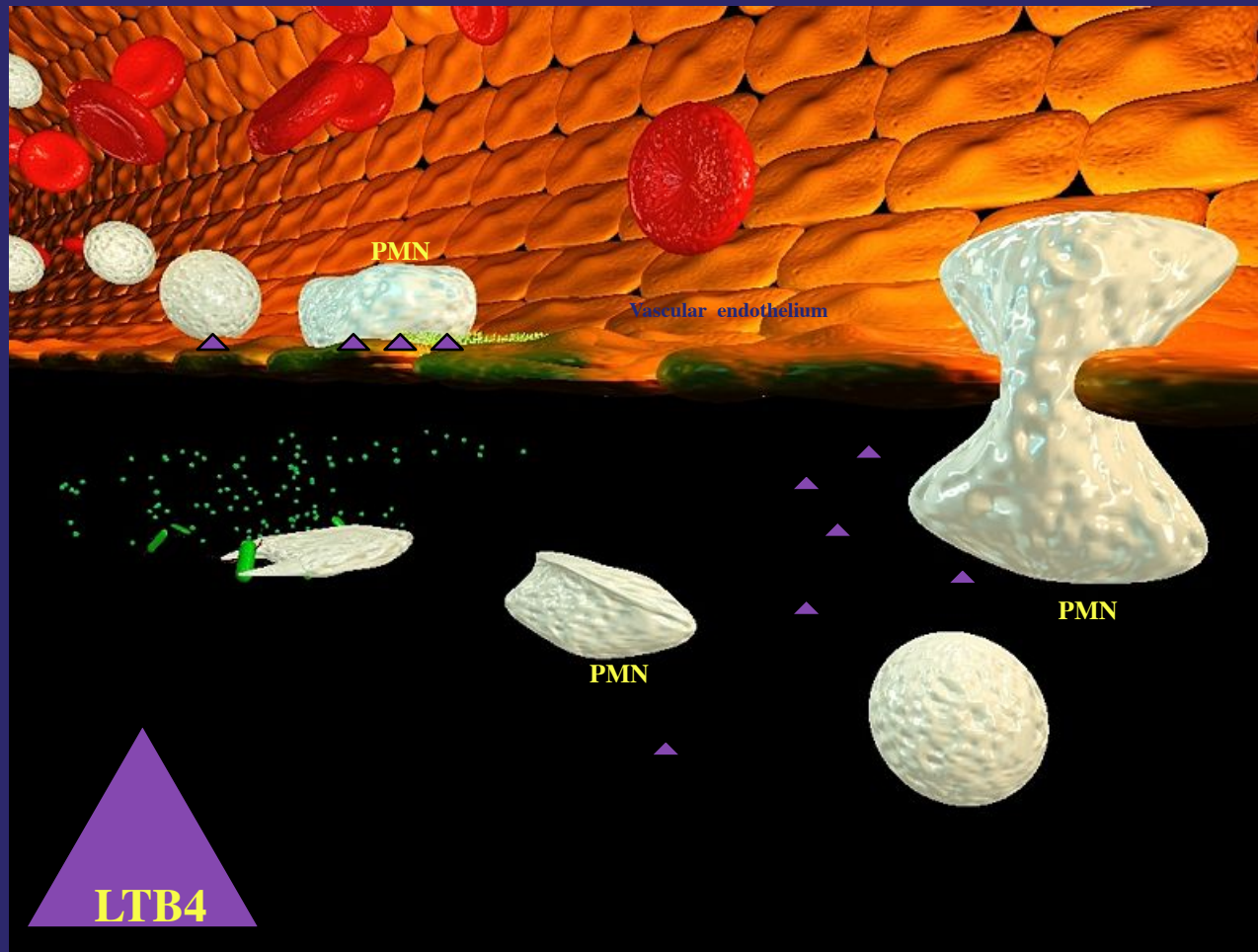


Source: <http://www.nih.gov/>

Immunopathology of Rheumatoid Arthritis



Chemotactic Activity of LTB₄



BY: Greg Luerman

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Pharmacologic Regulation of Arachidonic Acid-Derived Products

- **Modulate Phospholipase activity:**

- Suppress the release of arachidonic acid (no substrate available)
- Blocks both COX and LO-derived products

- **Modulate Cyclooxygenase Activity:**

- Blocks Cyclooxygenase-derived products
- COX-1 and COX-2 inhibitors

- **Modulate specific enzymes down-stream from COX:**

- Thromboxane synthetase inhibitors

- **Modulate lipoxygenase activity:**

- Block 5-lipoxygenase enzyme
- Small molecule receptor antagonists for cysteinyl leukotrienes

Non- Steroidal Anti-Inflammatory Compounds

- Aspirin (acetylsalicylic acid)
- Ibuprofen (propionic acid derivatives)
- Indomethacin (indole derivatives)
- Tylenol (Acetaminophen)
- COX-2 Inhibitors (Vioxx, celebrex, Bextra)

COX-2 Inhibitors

- CELEBREX (Celecoxib) Pfizer-(Pharmacia)
- BEXTRA (Valdecoxib) Pfizer
- VIOXX (Rofecoxib) Merck

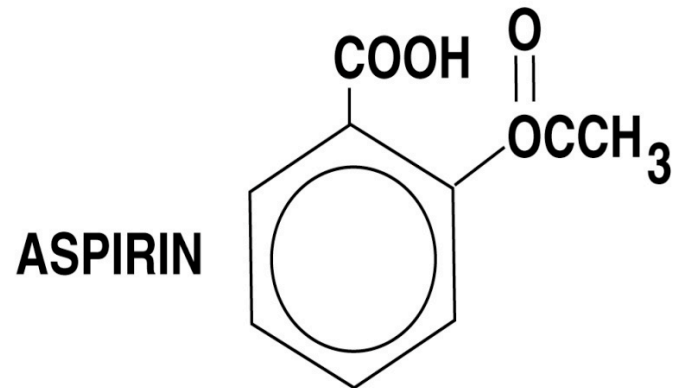
Osteoarthritis

Rheumatoid arthritis

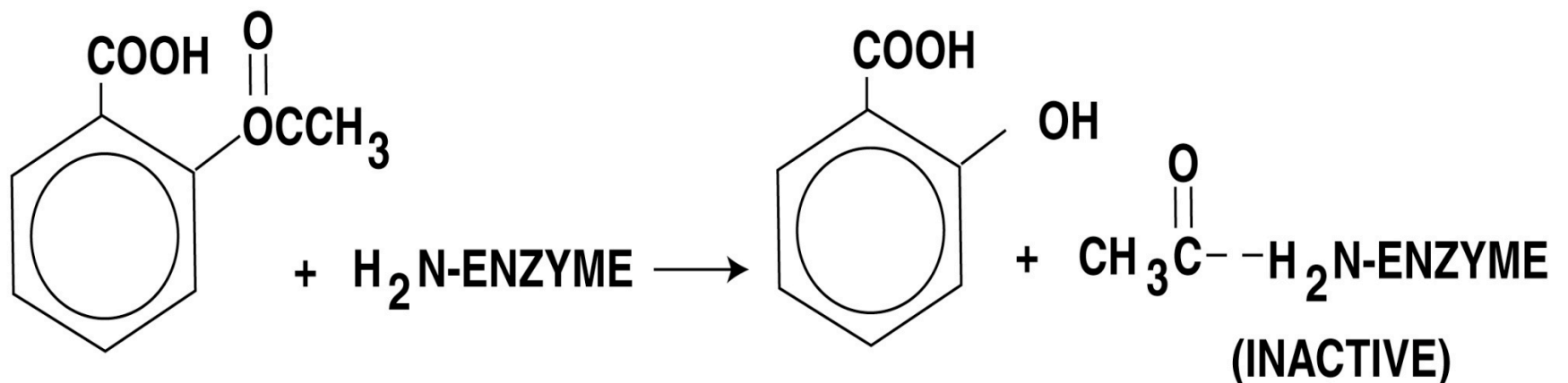
Primary dysmenorrhea

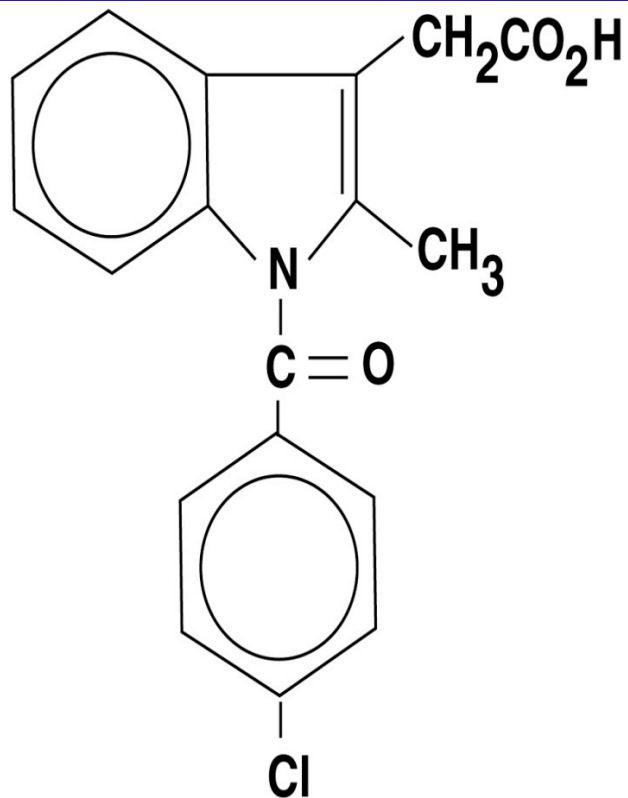
Pain management

Complications!!

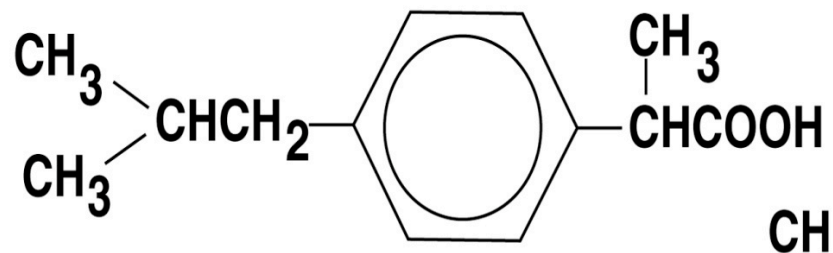


INHIBITS CYCLO-OXYGENASE ENZYME IRREVERSIBLY BY ACETYLATED THE ENZYME AT THE ACTIVE SITE, THUS THE PRODUCTION OF ENDOPEROXIDES AND THEIR DERIVATIVES, INCLUDING PROSTAGLANDINS, THROMBOXANES, AND PROSTACYCLINS WILL BE INHIBITED.





INDOMETHACIN



IBUPROFEN

BOTH INHIBIT CYCLO-OXYGENASE ACTIVITY BY BINDING REVERSIBLY TO THE ACTIVE SITE OF THE ENZYME, THUS BLOCKING THE FORMATION OF PROSTAGLANDINS, THROMBOXANES, AND PROSTACYCLINS.

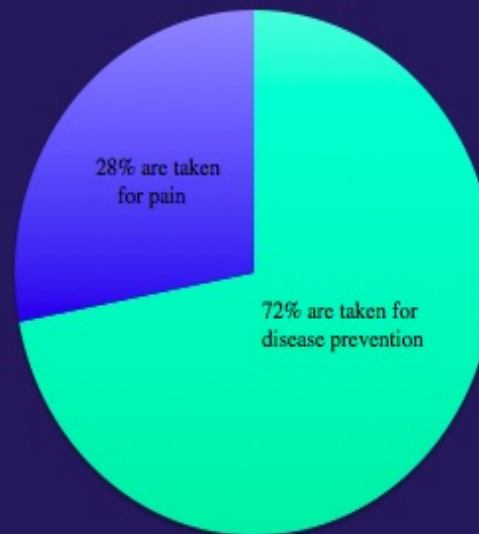
AN ASPIRIN A DAY

Roughly 80 million aspirin tablets are consumed daily in the USA

Of those:

72% are taken for disease prevention

28% are taken for pain



Reduce the risk of heart attack or
stroke with.....

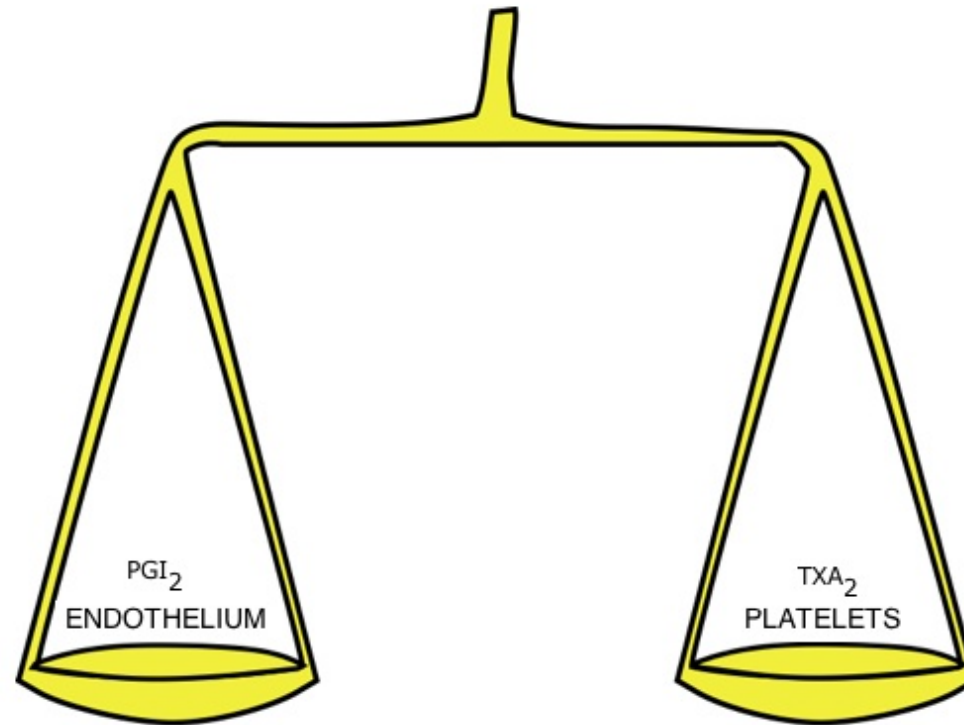


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THE HOMEOSTATIC BALANCE

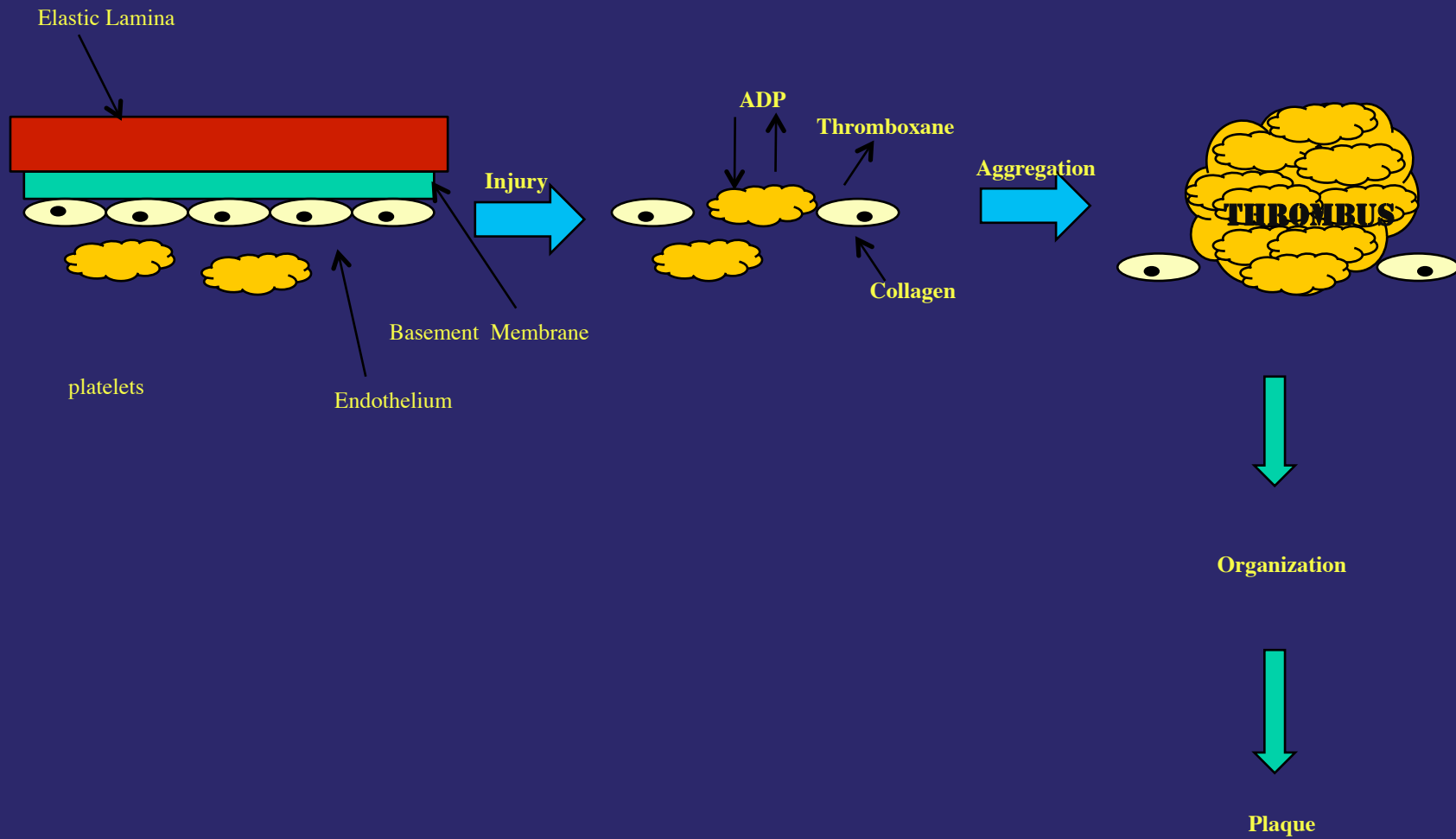


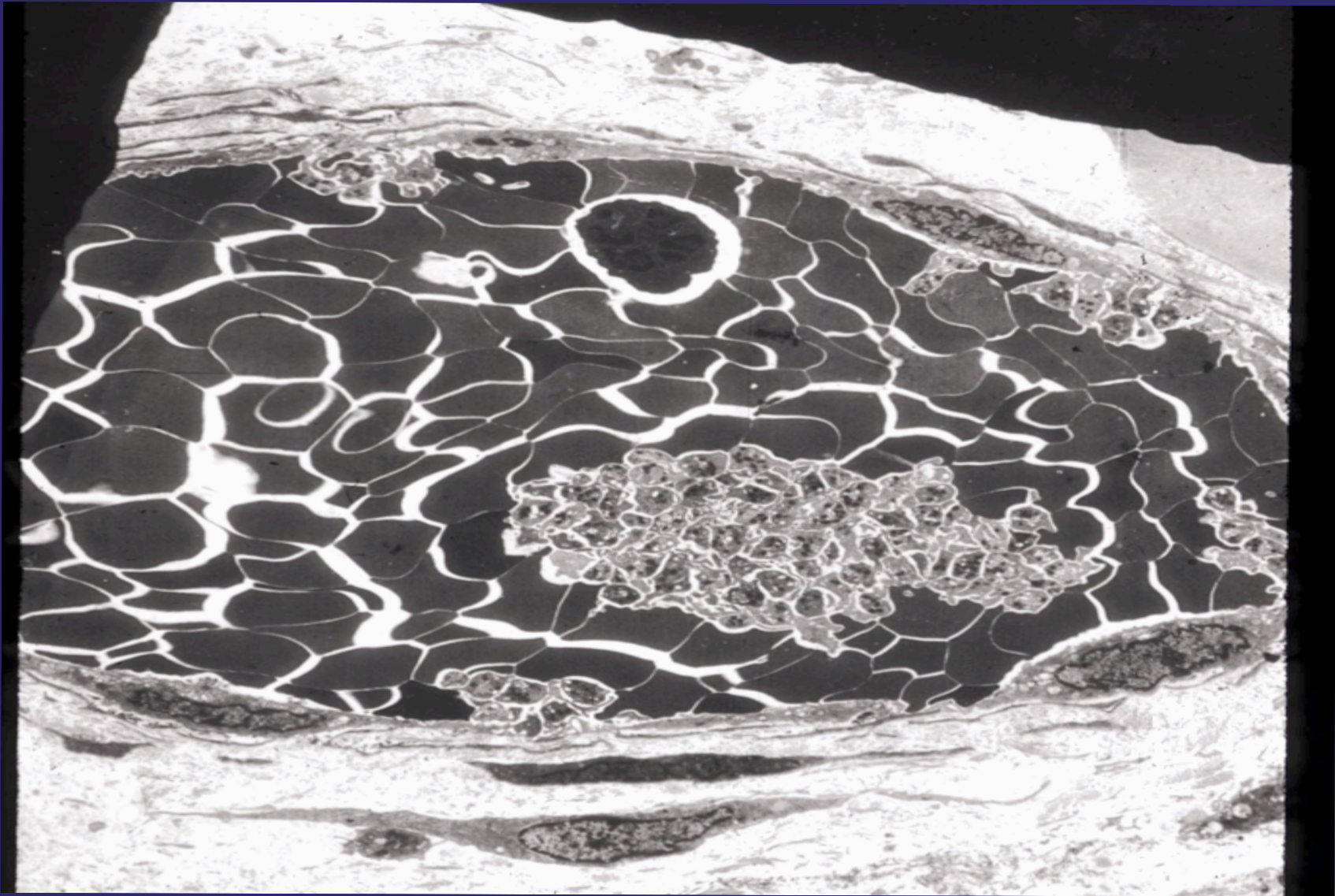
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Thrombus Formation



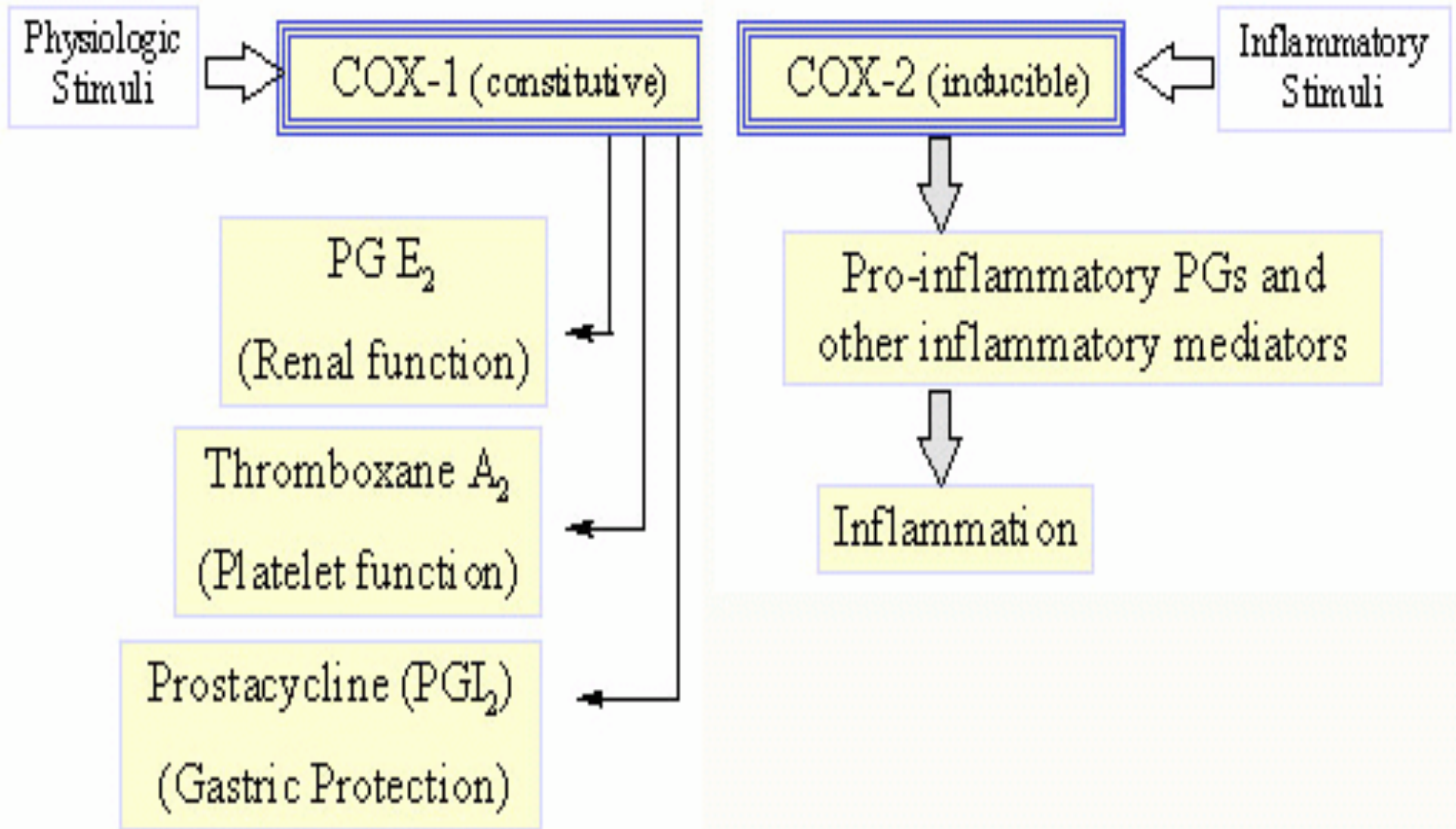


Source: Undetermined

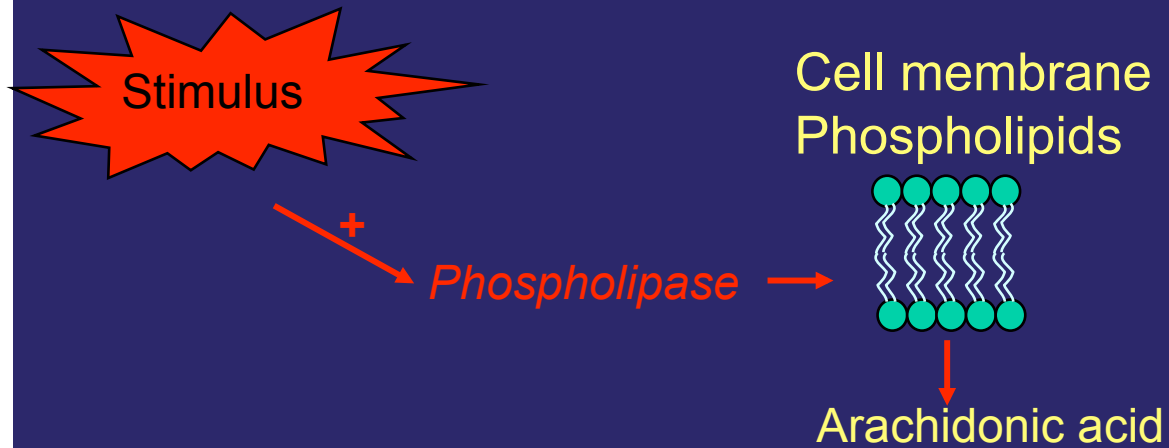
Can Aspirin Act As An Anti-thrombogenic Agent?

- Inhibits platelet aggregation by blocking platelet-derived thromboxane production
- Blocks platelet cyclooxygenase for the life of the platelet, as no new protein synthesis occurs
- Blocks endothelial cell-derived prostacyclin
- Suppression of endothelial cell-derived prostacyclin is short lived as endothelial cells can generate new cyclooxygenase enzyme
- Platelet activity is blocked more than endothelial cell activity

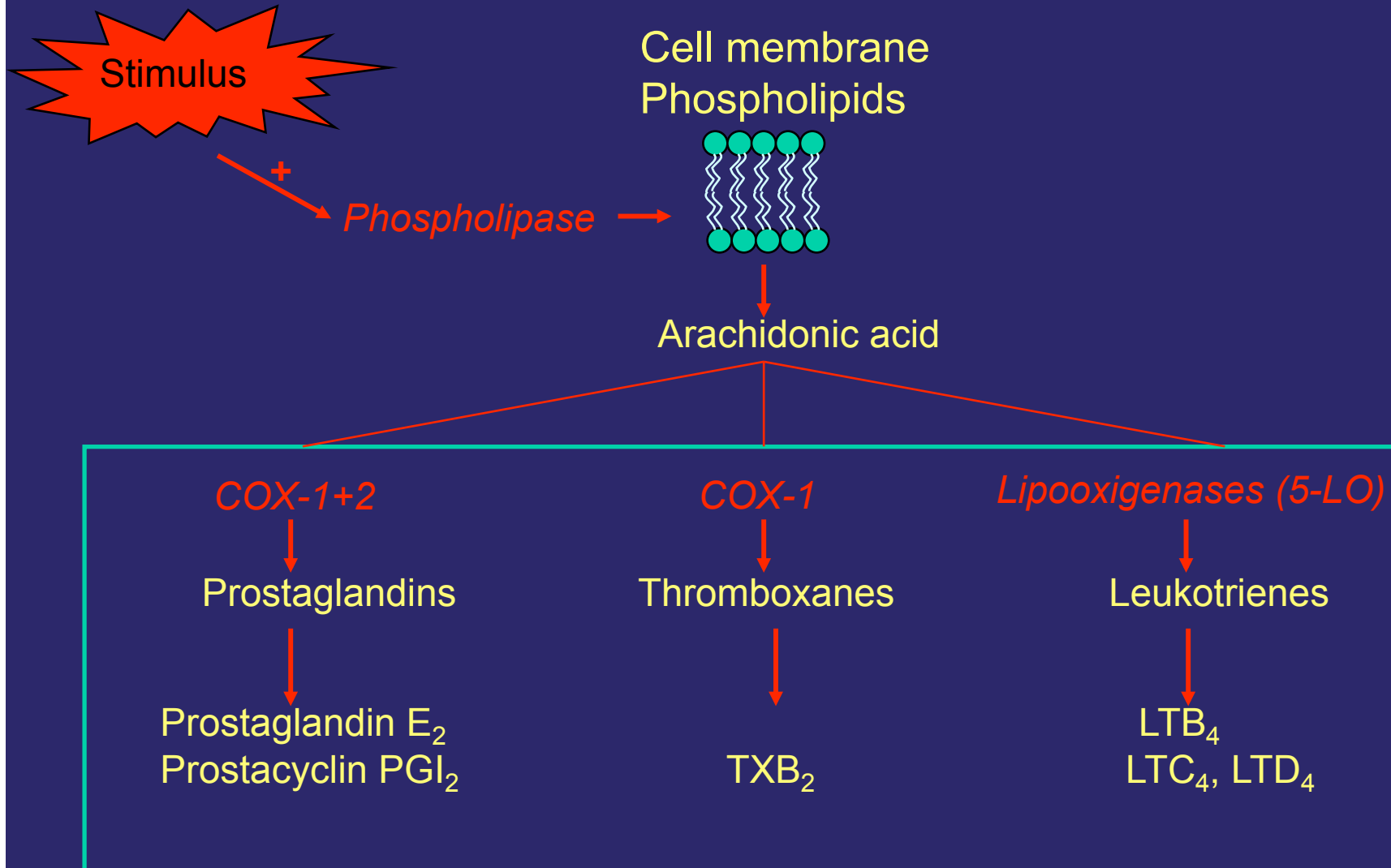
COX-2 inhibitors work by blocking COX-2 enzyme which is involved in the inflammation pathway. By sparing COX-1 gastrointestinal toxicity is reduced



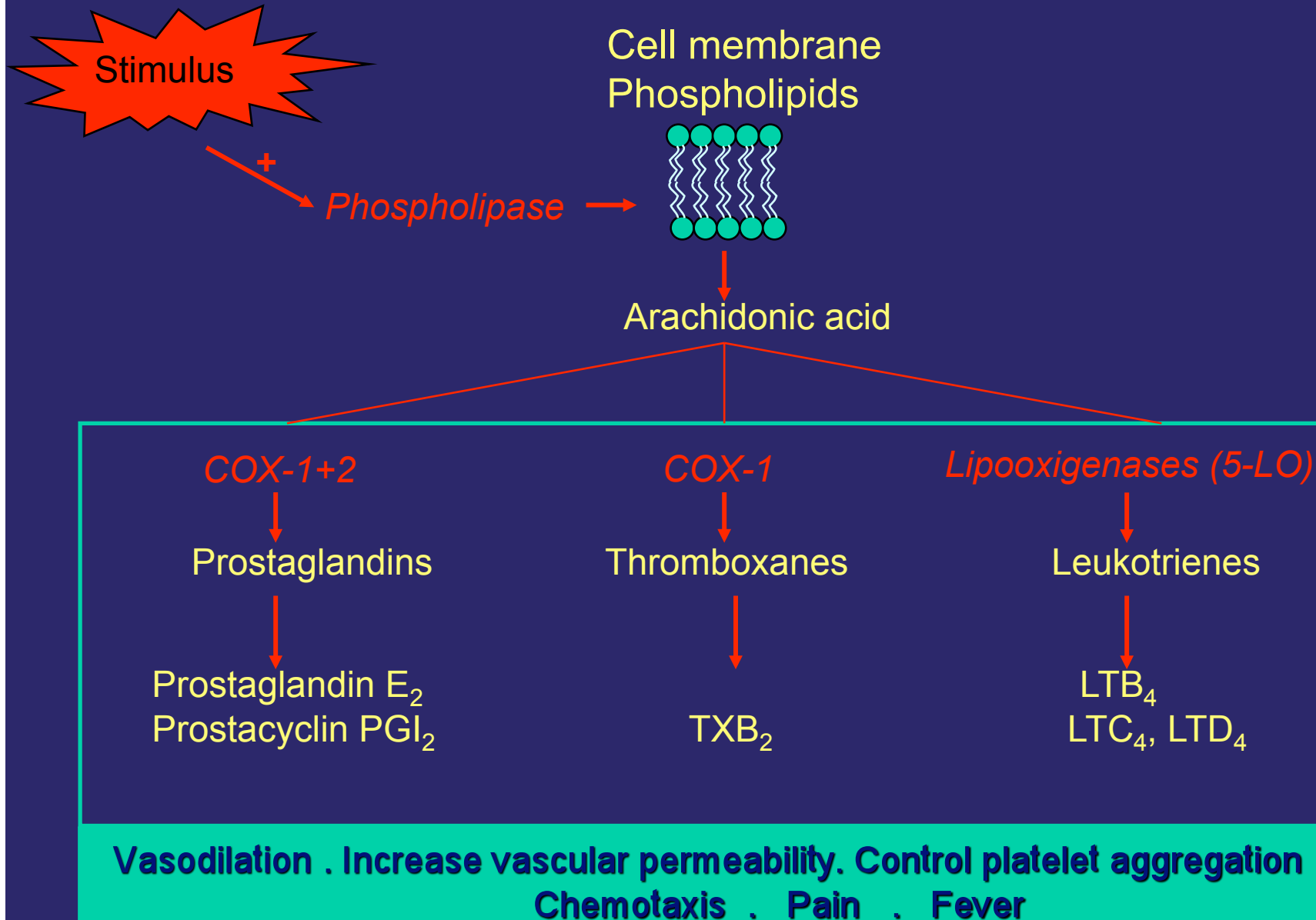
lipid mediators of Inflammation



Acute inflammation: lipid mediators

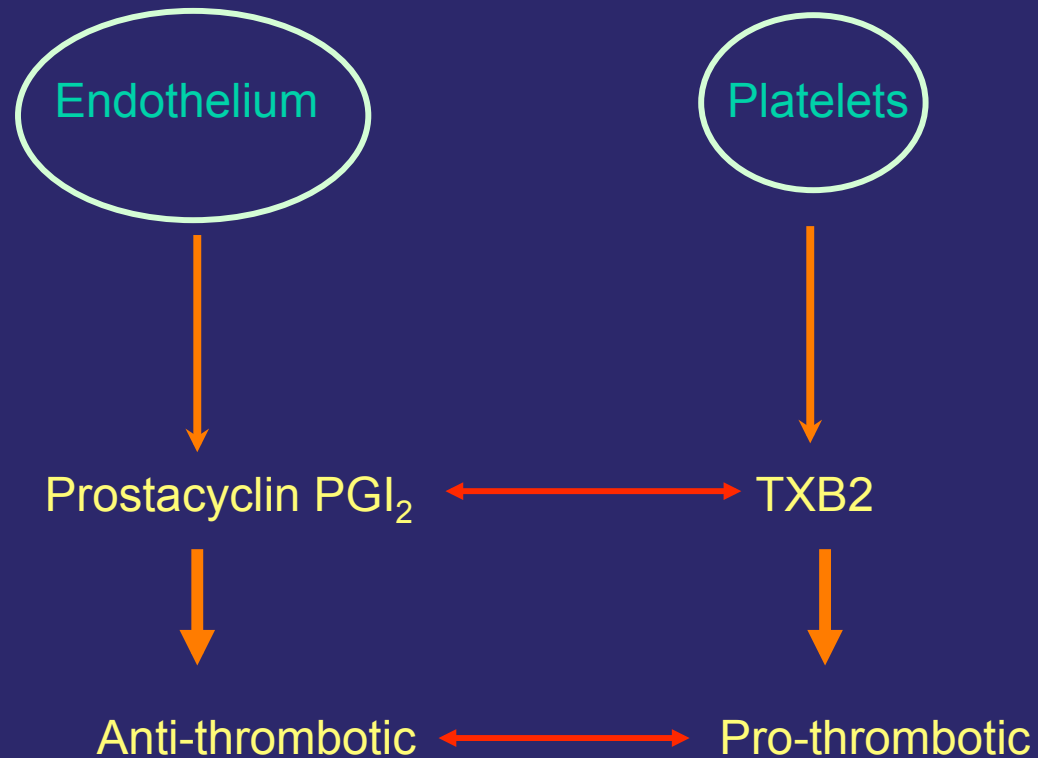


Acute inflammation: lipid mediators



Acute inflammation: lipid mediators

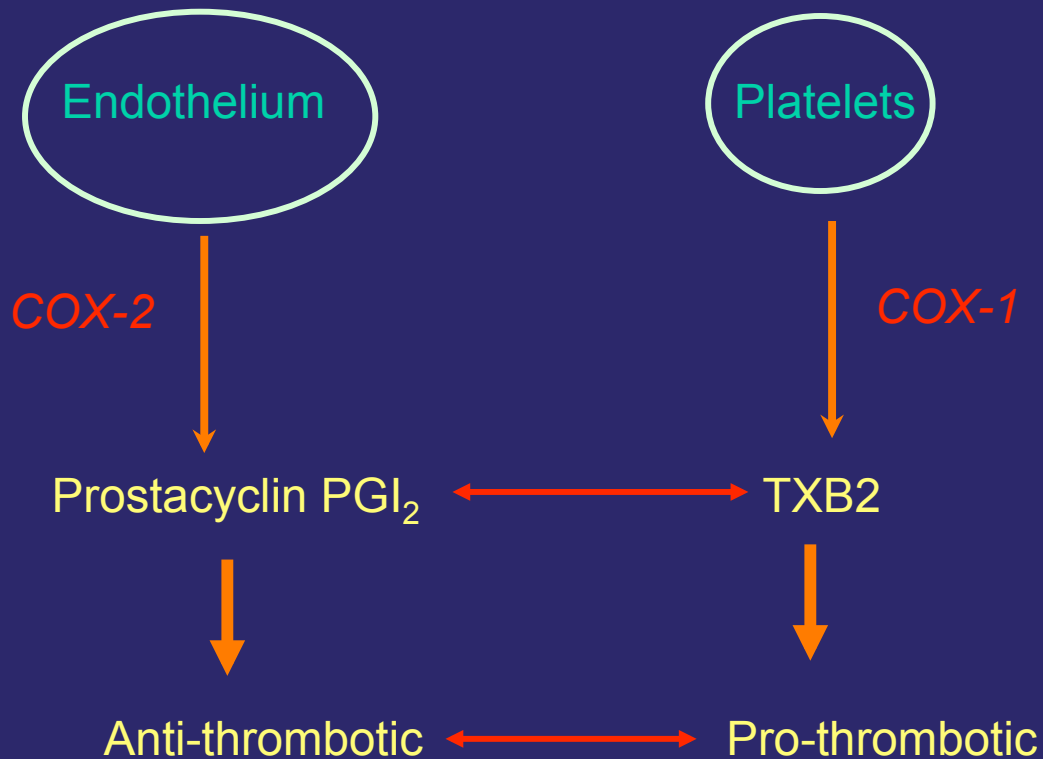
An important role in vascular homeostasis



Acute inflammation: lipid mediators



Therapeutic targets

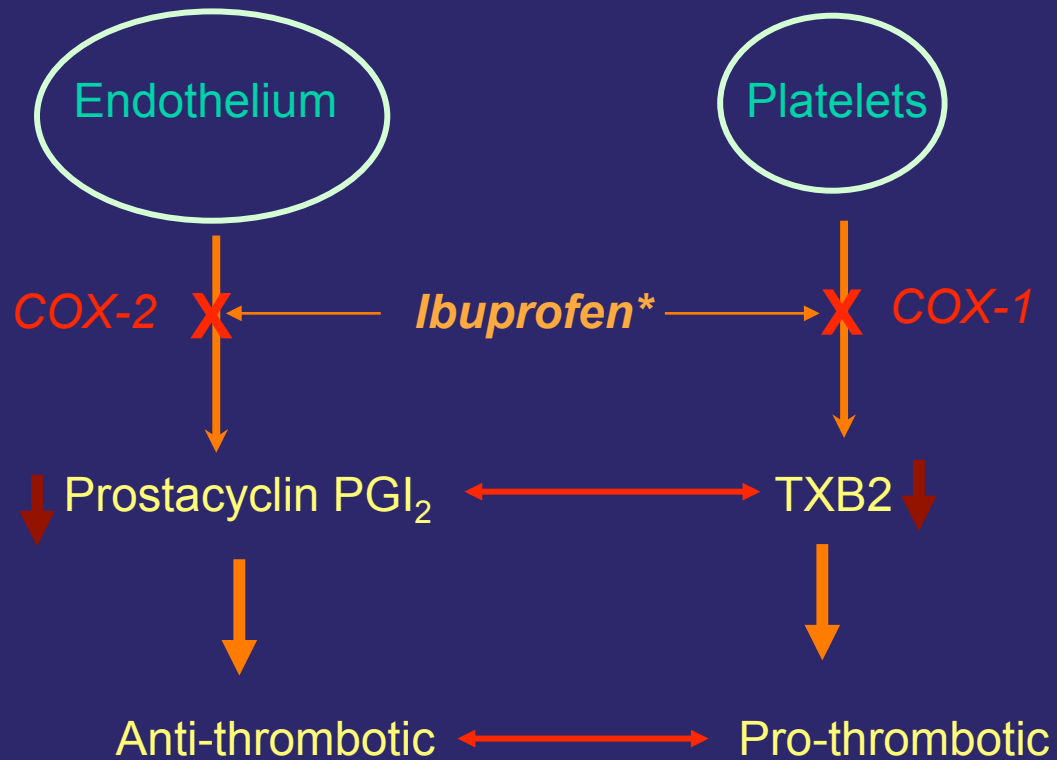


NSAIDs inhibit both COX-1 and COX-2; COXIBs inhibit COX-2

Acute inflammation: lipid mediators



Therapeutic targets

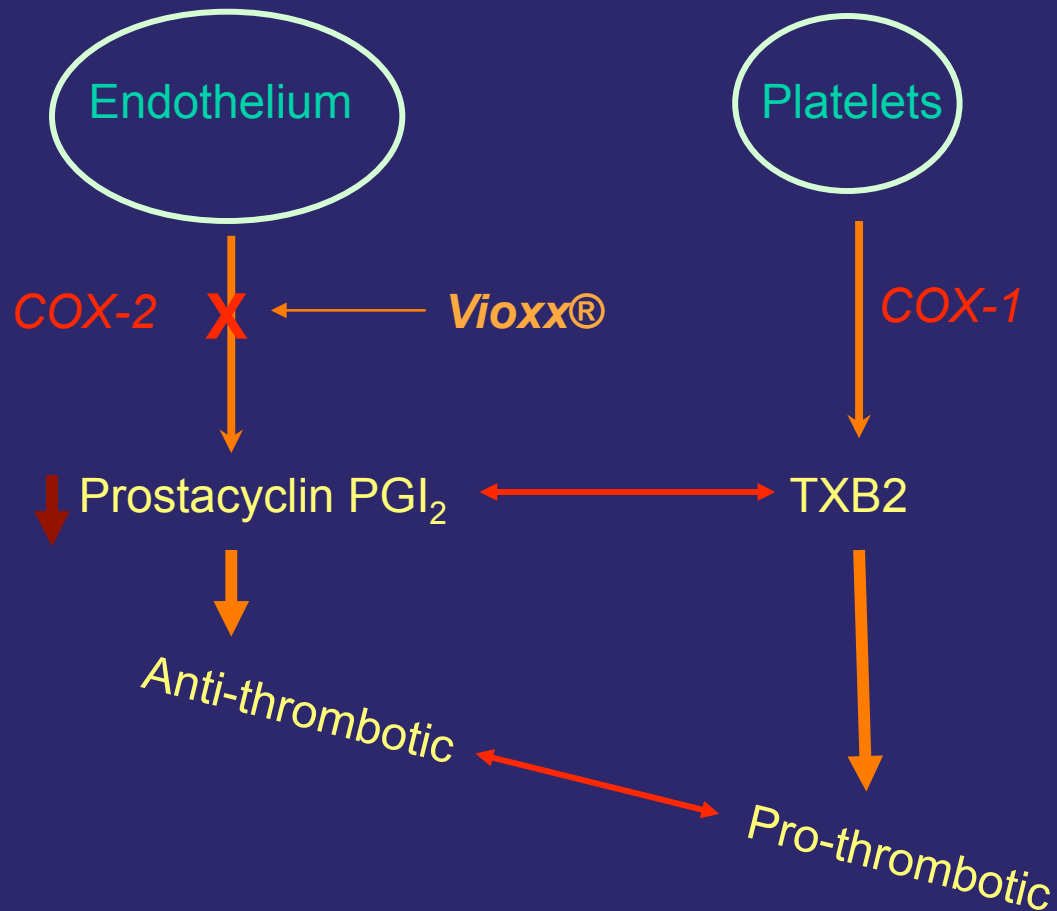


* Classical NSAID, it inhibits both COX enzymes

Acute inflammation: lipid mediators



Therapeutic targets



Acute inflammation: lipid mediators



Therapeutic targets

Endothelium

Platelets

Aspirin

inhibits COX-2 irreversibly



All cells but the platelet
can resynthesize the
enzymes



Aspirin

inhibits COX-1 irreversibly



Prostacyclin PGI₂



TXB2



Pro-thrombotic

Anti-thrombotic



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- CYTOKINES

Interleukins

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Tumor Necrosis Factor

Growth Factors