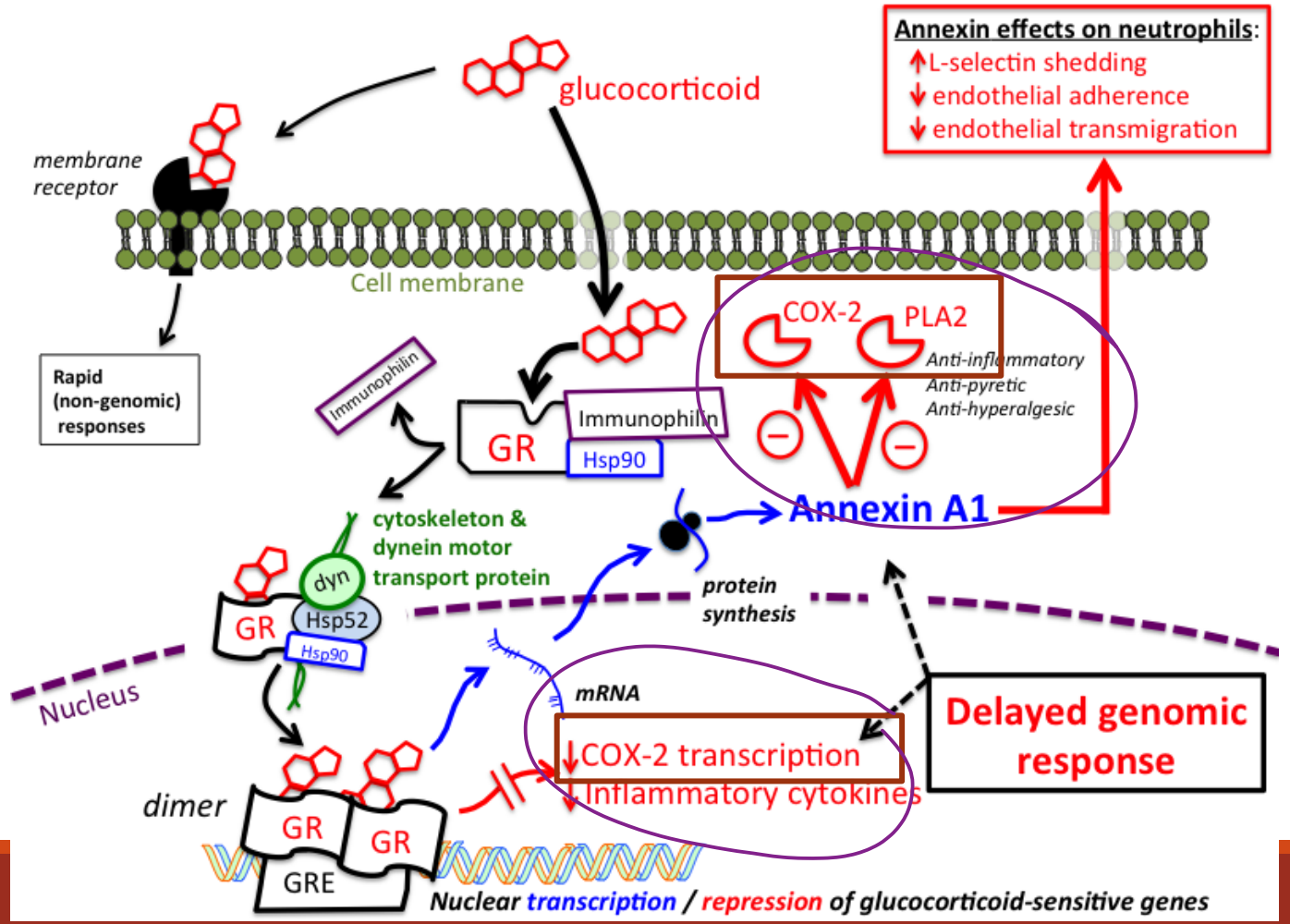
Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

Learning objectives

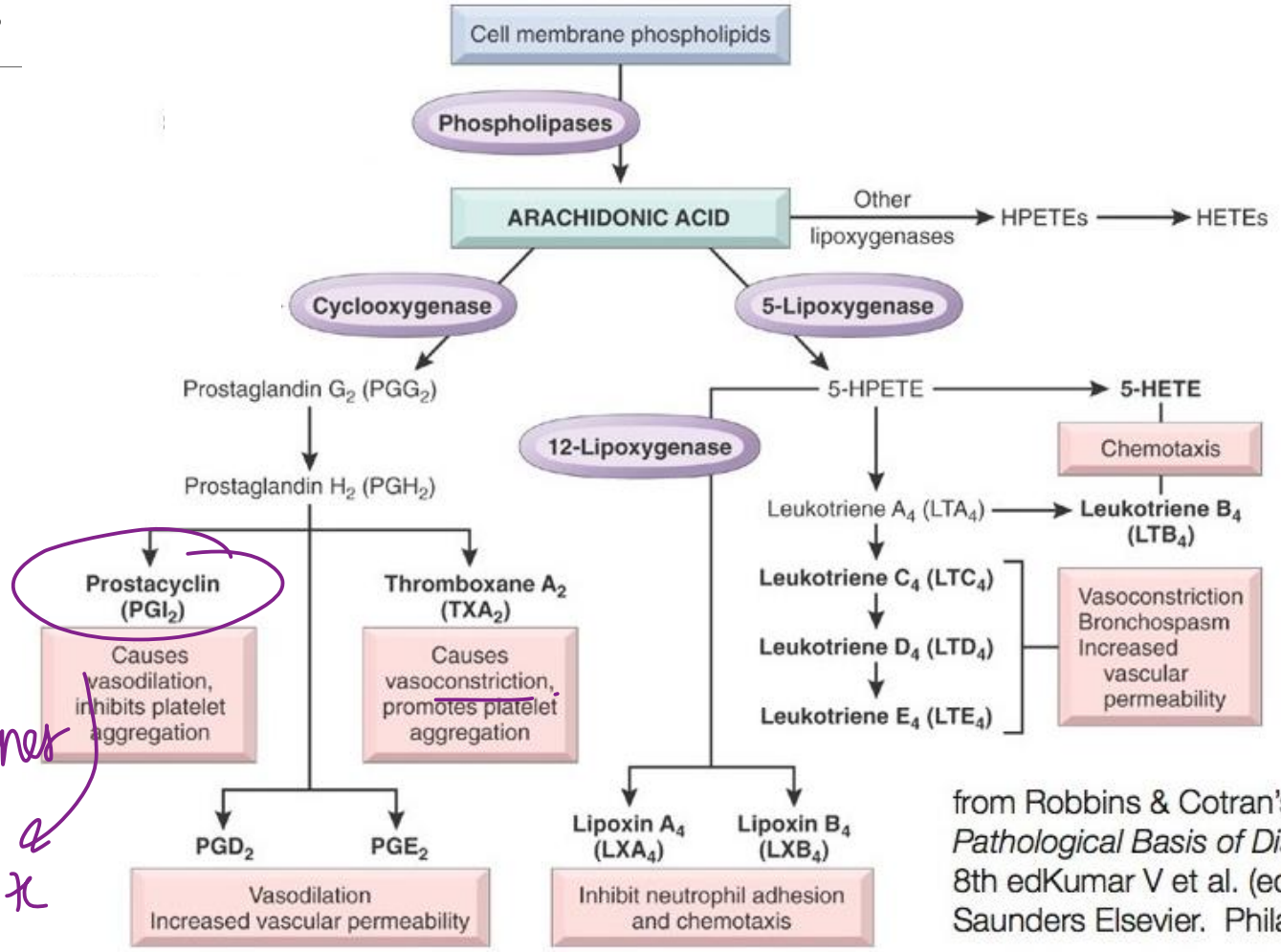
- Understand the mechanism of action of NSAIDs
- Explain the mechanism behind the various side effects of NSAIDs
- Understand and explain the benefit of each new NSAID.
- Explain the mechanism of action of Acetaminophen
- Explain the main side effect of prolonged acetaminophen use

Two key steps in the activity of Steroid Anti-inflammatories



Cox-2 and PLA2

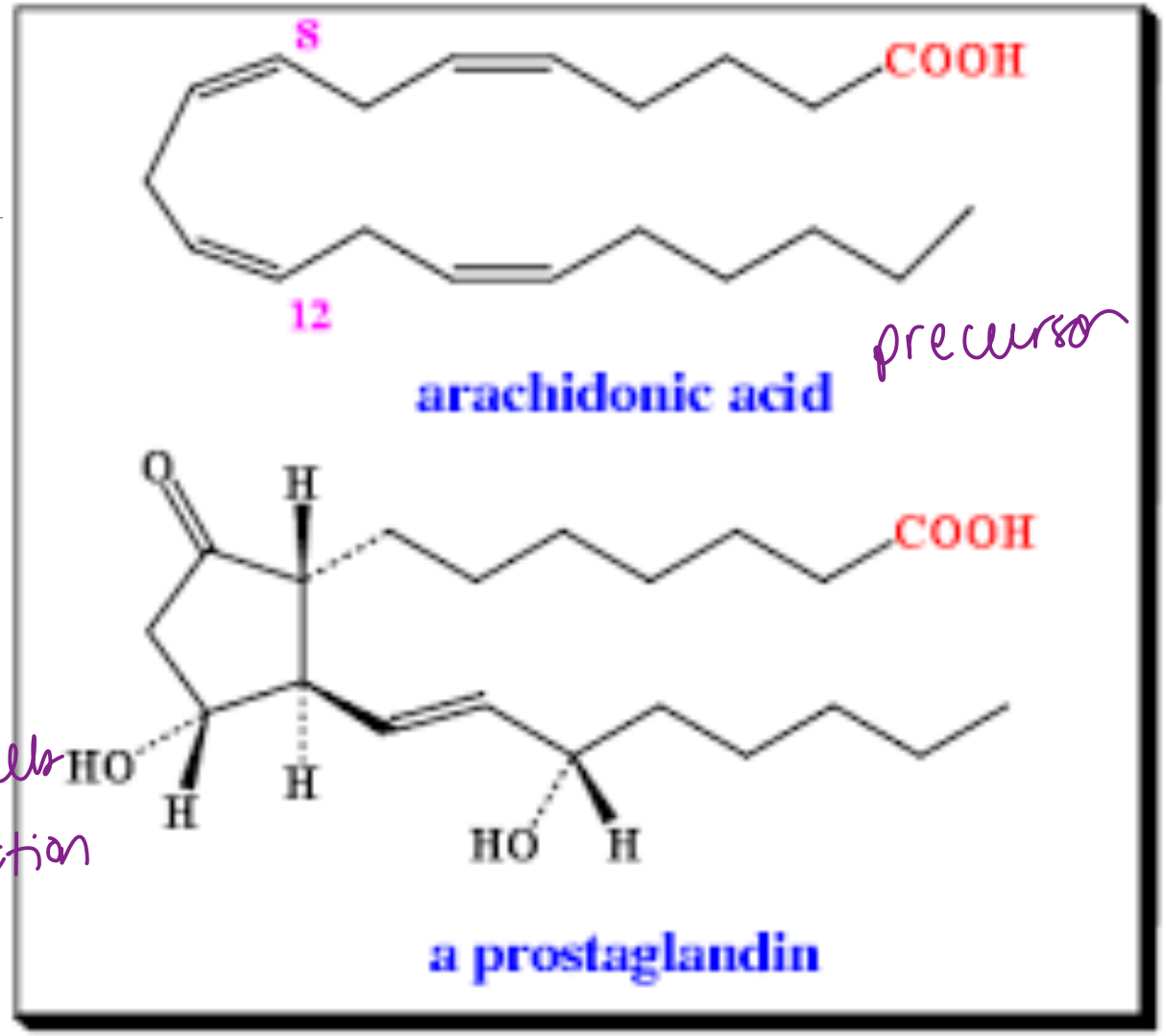
- PLA2 activity is essential for the cleavage of arachidonic acid from the phospholipid of the membrane
- Cox-2 is essential for the synthesis of prostaglandins from Arachidonic acid



from Robbins & Cotran's *Pathological Basis of Disease* 8th edKumar V et al. (eds). Saunders Elsevier. Philadelphia (2010)

Prostaglandins

- Prostaglandins are a group of lipids that the body makes primarily at sites of tissue damage or infection. There are several different types of prostaglandins, and they play several essential roles in regulating bodily processes, including:
  - Blood clot formation at the site of an injury.
  - Blood flow. ⇝ eg: vasodil ; vasoconstrict.
  - Healing. ⇝ form of scar.
  - Inflammation. ⇝ bind to macrophage & inm. cells
  - Labor induction in pregnancy. ⇝ promote contraction
  - Menstruation.
  - Ovulation.

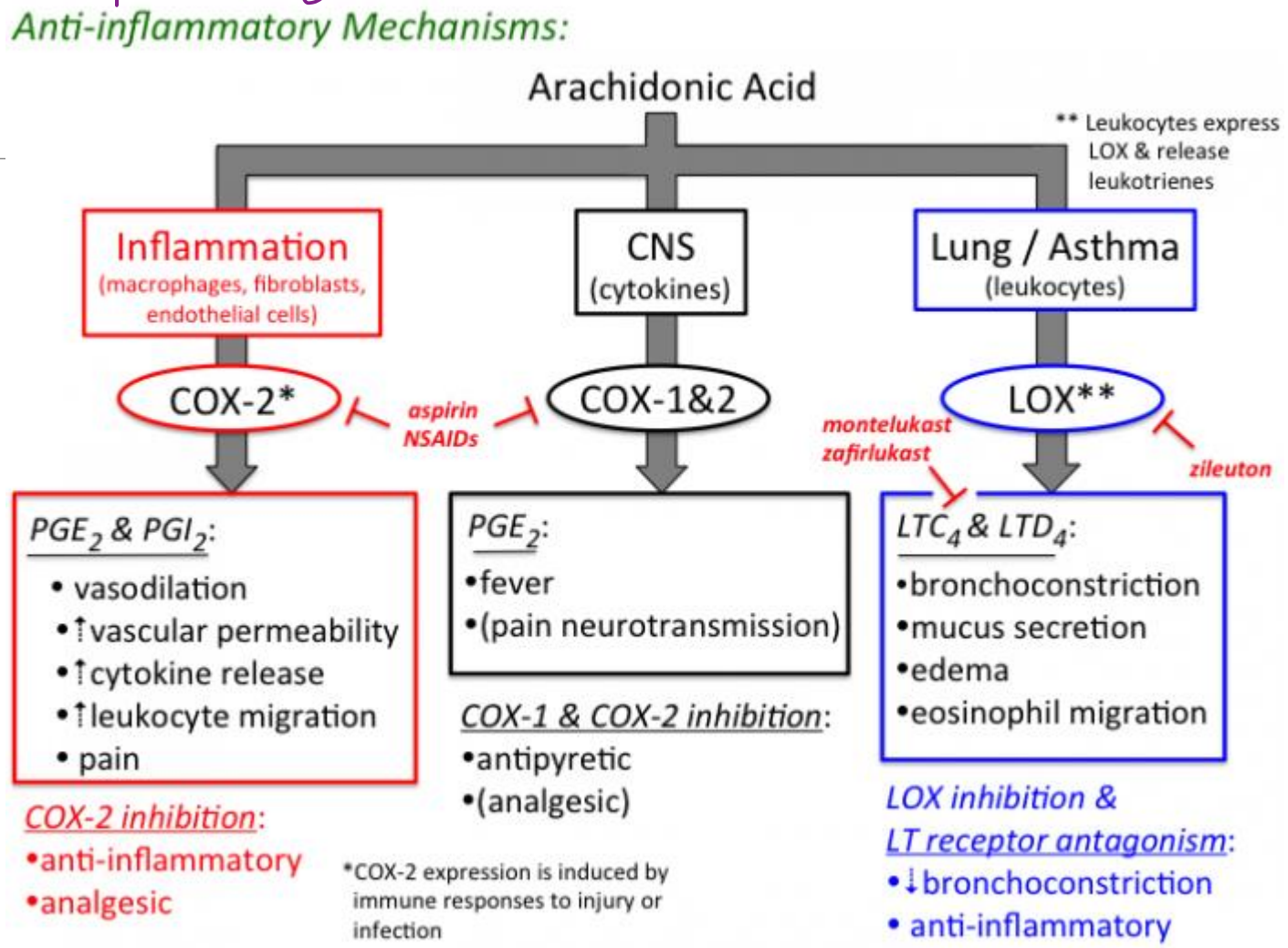


https://my.clevelandclinic.org/health/articles/24411-prostaglandins#:~:text=Prostaglandins%20are%20a%20group%20of,the%20site%20of%20an%20injury.

Prostaglandins

each has a diff pathway depending on the COX enzyme

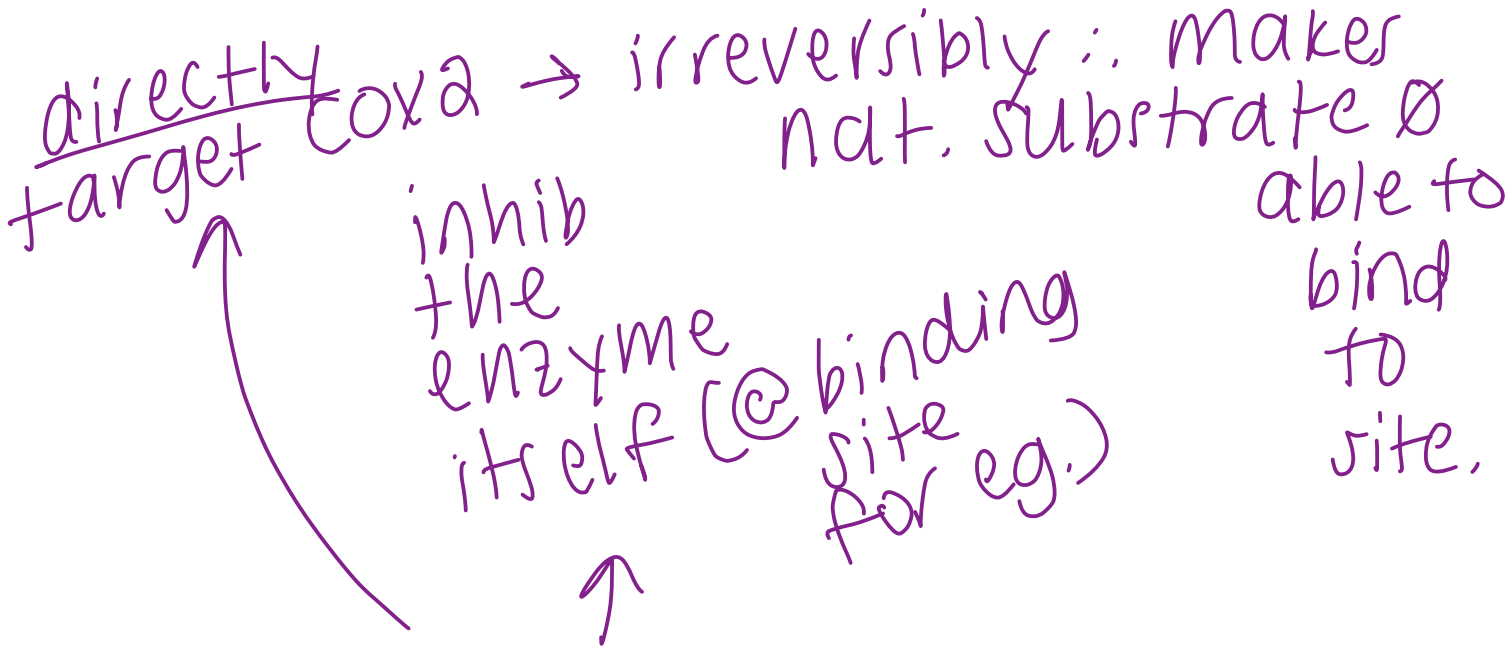
- Interact with G coupled receptors
- During inflammation:
  - Increase vasopermeability and aid in diapedesis of phagocytic cells
  - Dilate precapillary arterioles while constricting postcapillary venules to increase blood supply → to site of infx
  - Promote clotting to prevent bleeding
    - ↳ mediated by platelets. (platelets have COX1 not COX2)



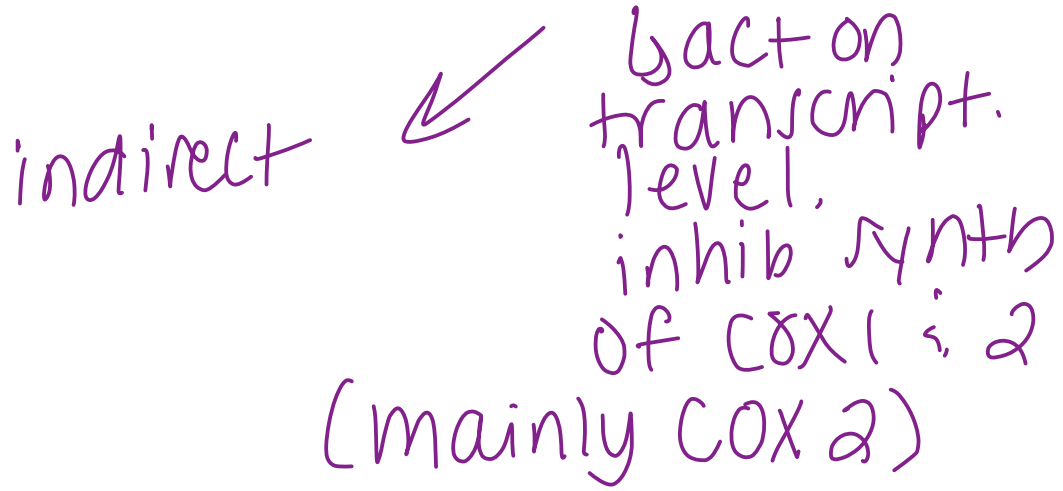
Salicylate

- Plant hormone responsible for pathogen defense
- First recognized medicinal properties of willow bark (salicin) ~1750
- Purified in 1829
- Found in other plants including spirea, wintergreen
- In 1897, it was synthesized into the acetylsalicylic acid which had improved properties and decreased allergy.
- Aspirin has an analgesic, antipyretic & anti-inflammatory effects: inhibits PG activity by inhibiting their synthesis

inhib key steps in synth of PG



What is the difference between NSAIDs and steroids?

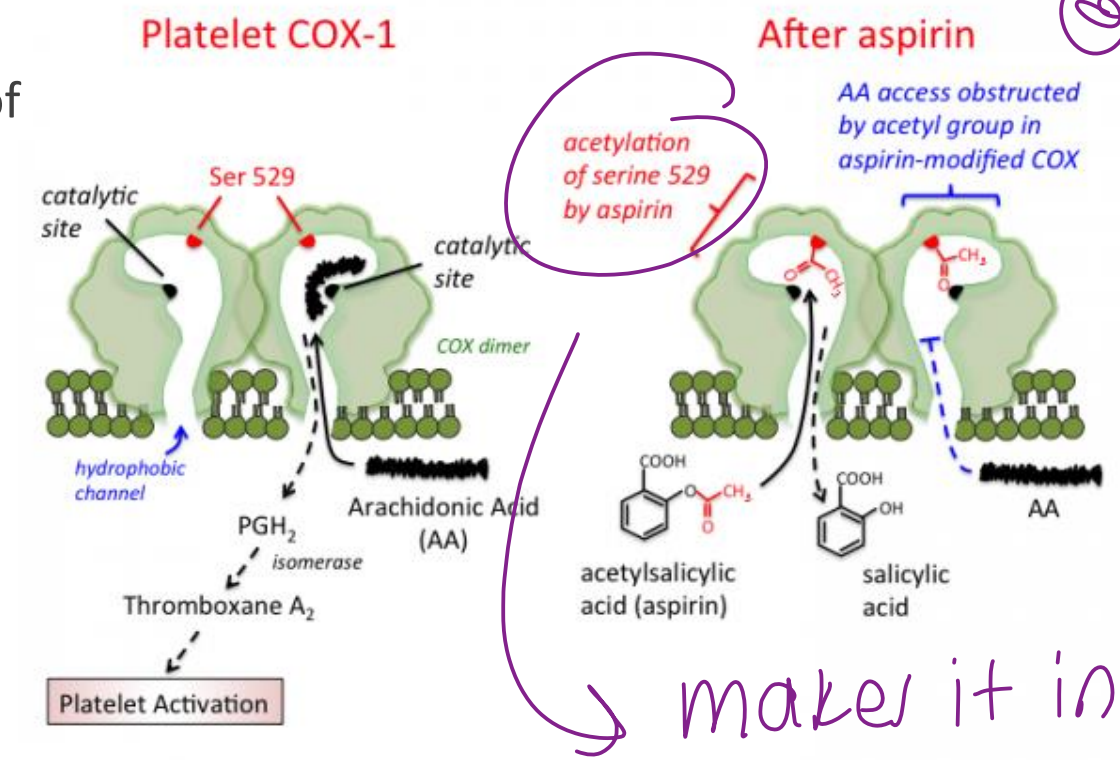


What type of inhibition is this?

Mechanism of action of aspirin

irreversibly acetylate serine residue @ catalytic site.

- Plant hormone responsible for pathogen defense
- First recognized medicinal properties of willow bark (salicin) ~1750
- Purified in 1829
- Found in other plants including spirea, wintergreen
- In 1897, it was synthesized into the acetylsalicylic acid which had improved properties and decreased allergy.



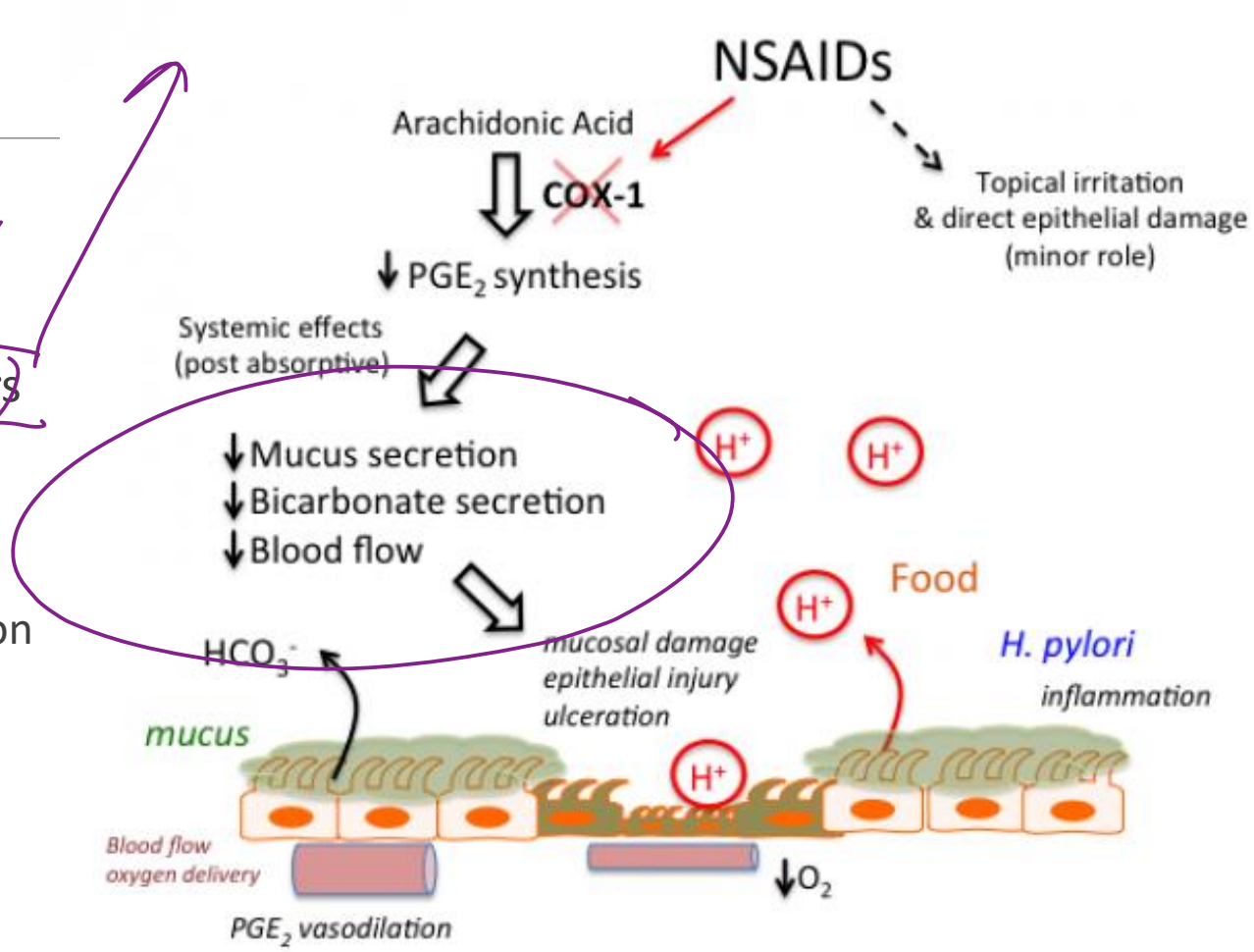
make it inaccessible.

Side effects

one of main SE of NSAIDs.

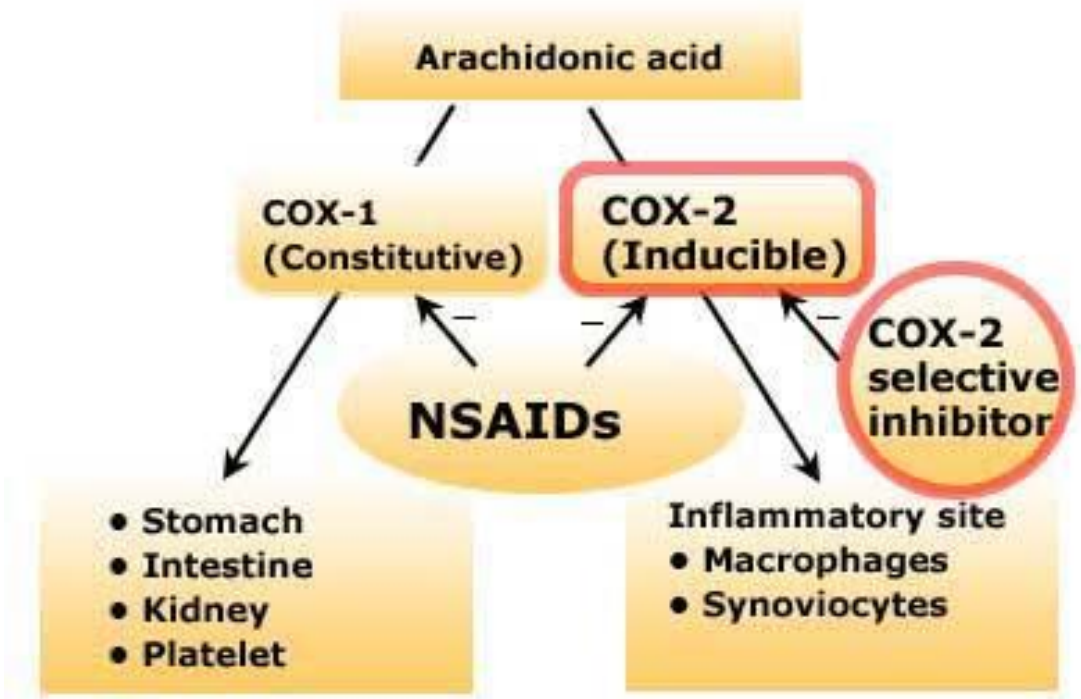
∴ stomach lining vulnerable to acidity of the stomach.

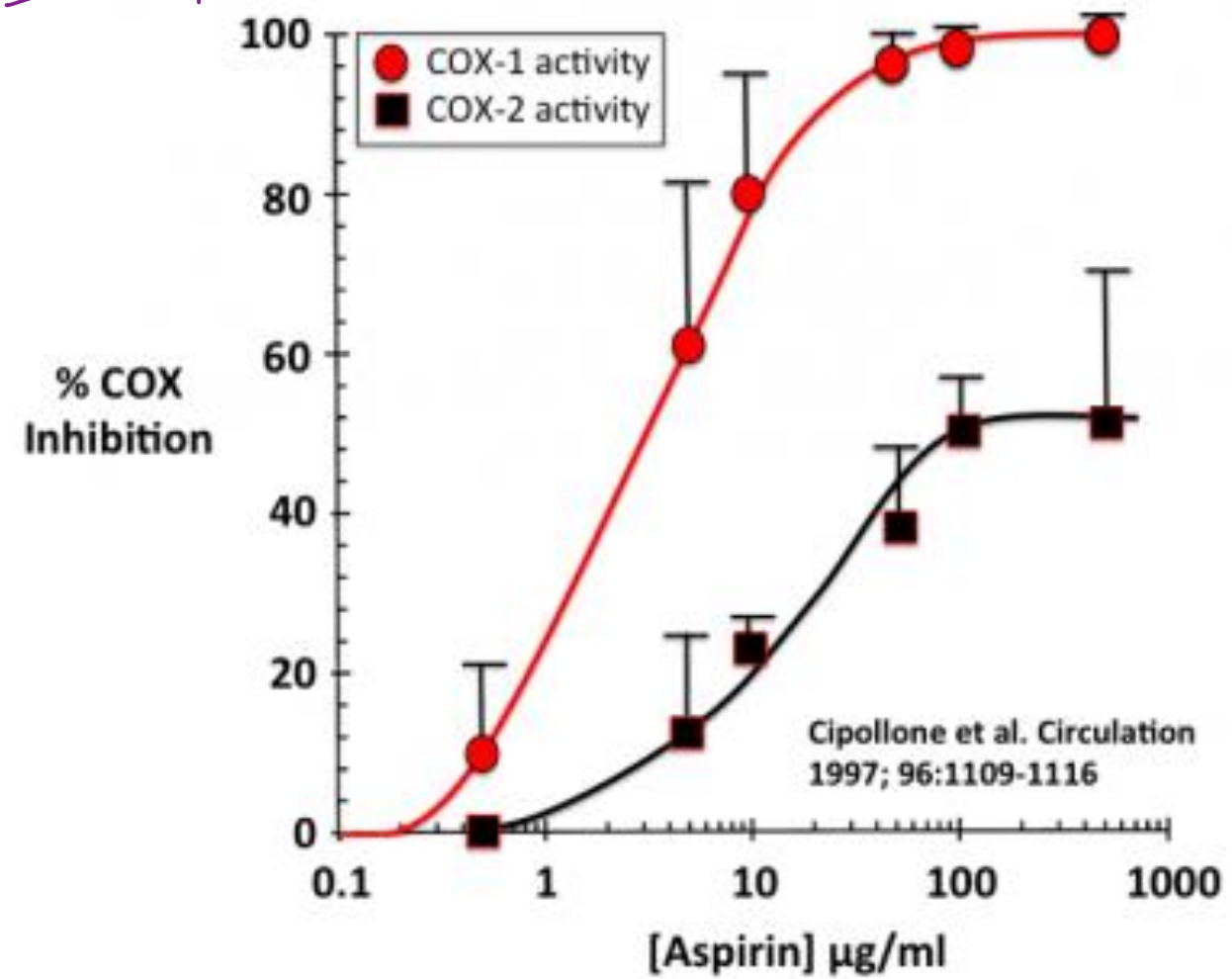
- Gastric upset, gastric and duodenal ulcers are the most common side effects due to Cox1 activity:
  - Decreased blood flow
  - Decreased mucus and bicarbonate secretion
- Excessive bleeding → ∅ b/c thromboxane A2 which aggregates platelet



inhib both COX1 & 2

Activity of Aspirin





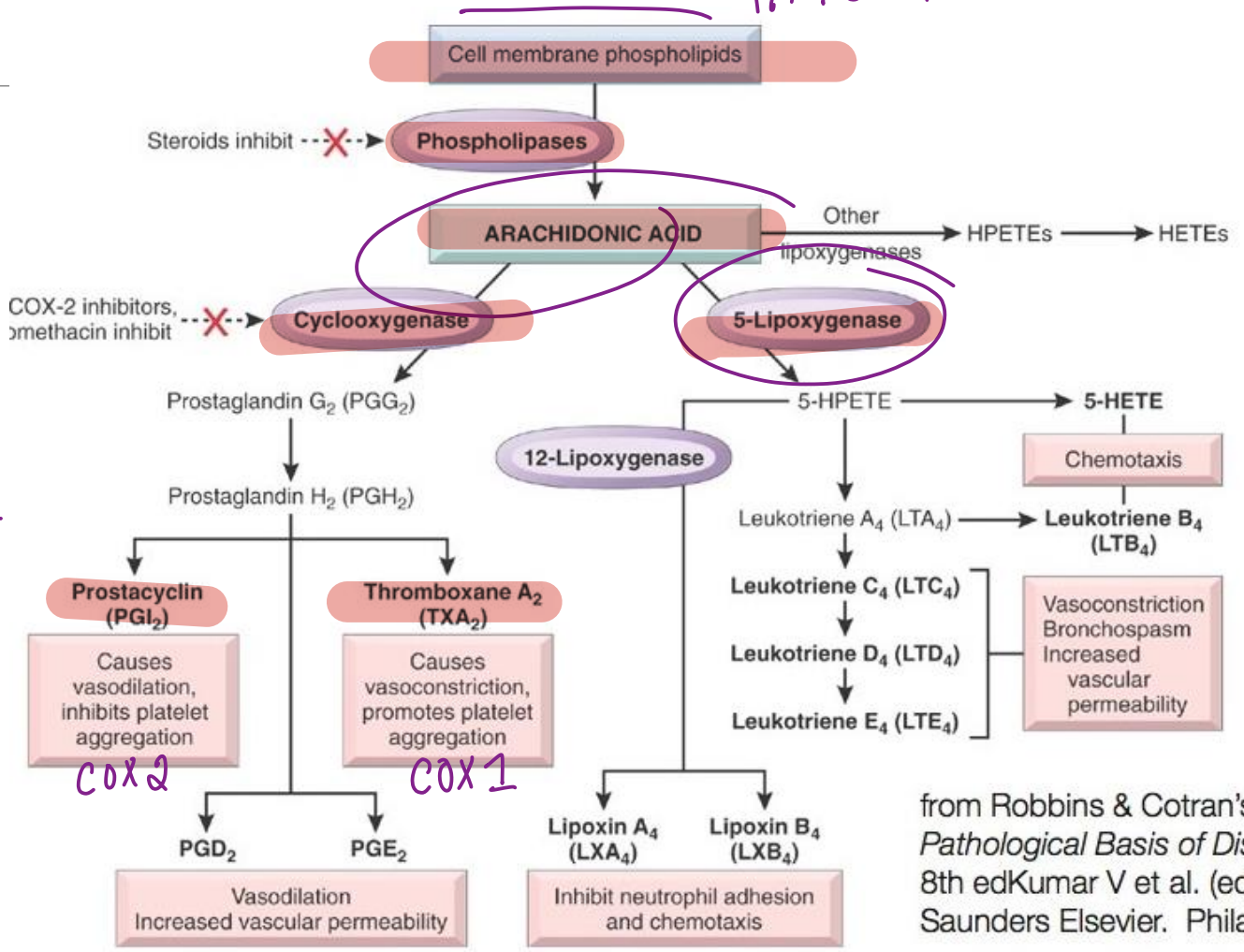
https://tmedweb.tulane.edu/pharmwiki/doku.php/aspirin

Aspirin and Asthma

↑ may ↑ severity of asthma by ↑ conversion of into leukotrienes.

- The inhibition of Cox enzymes favours the conversion of arachidonic acid into Leukotrienes by lipoxygenase.
- Leukotrienes exacerbate the effects of Asthma.

linked to: vasoconst & bronchospasms

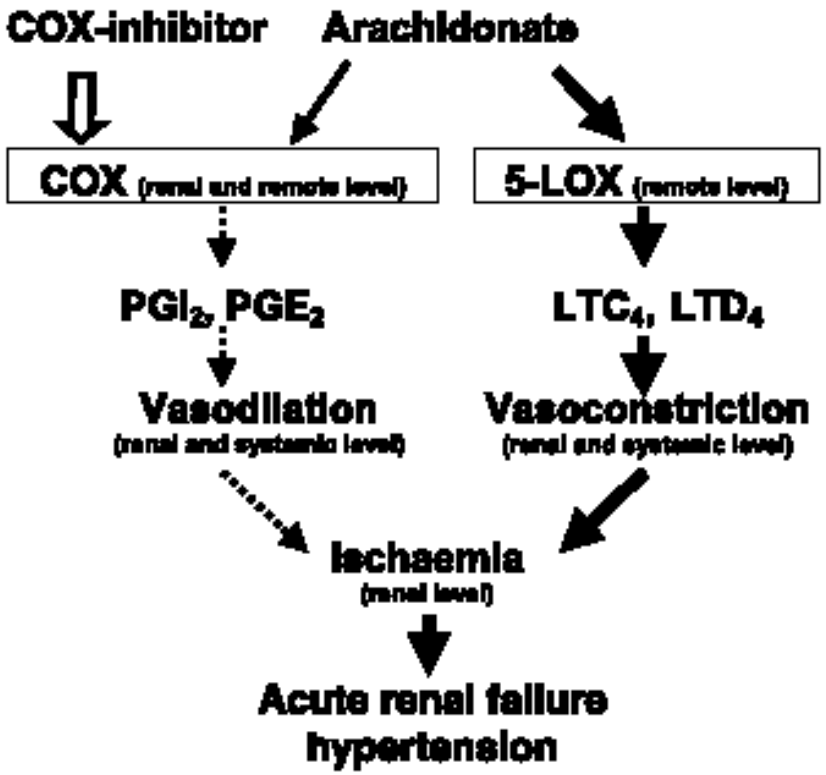


from Robbins & Cotran's *Pathological Basis of Disease* 8th edKumar V et al. (eds). Saunders Elsevier. Philadelphia (2010)

Cardiovascular health

- Plays a hypertensive role (although debatable) by promoting synthesis of Leukotrienes: vasoconstriction in the kidneys (water retention) and to interfere with prostaglandins that increase sodium excretion.

- Platelets express Cox-1 which is responsible for synthesis of Thromboxane A2: decreases platelet aggregation **at low doses (81mg):** decreases risk of thrombosis



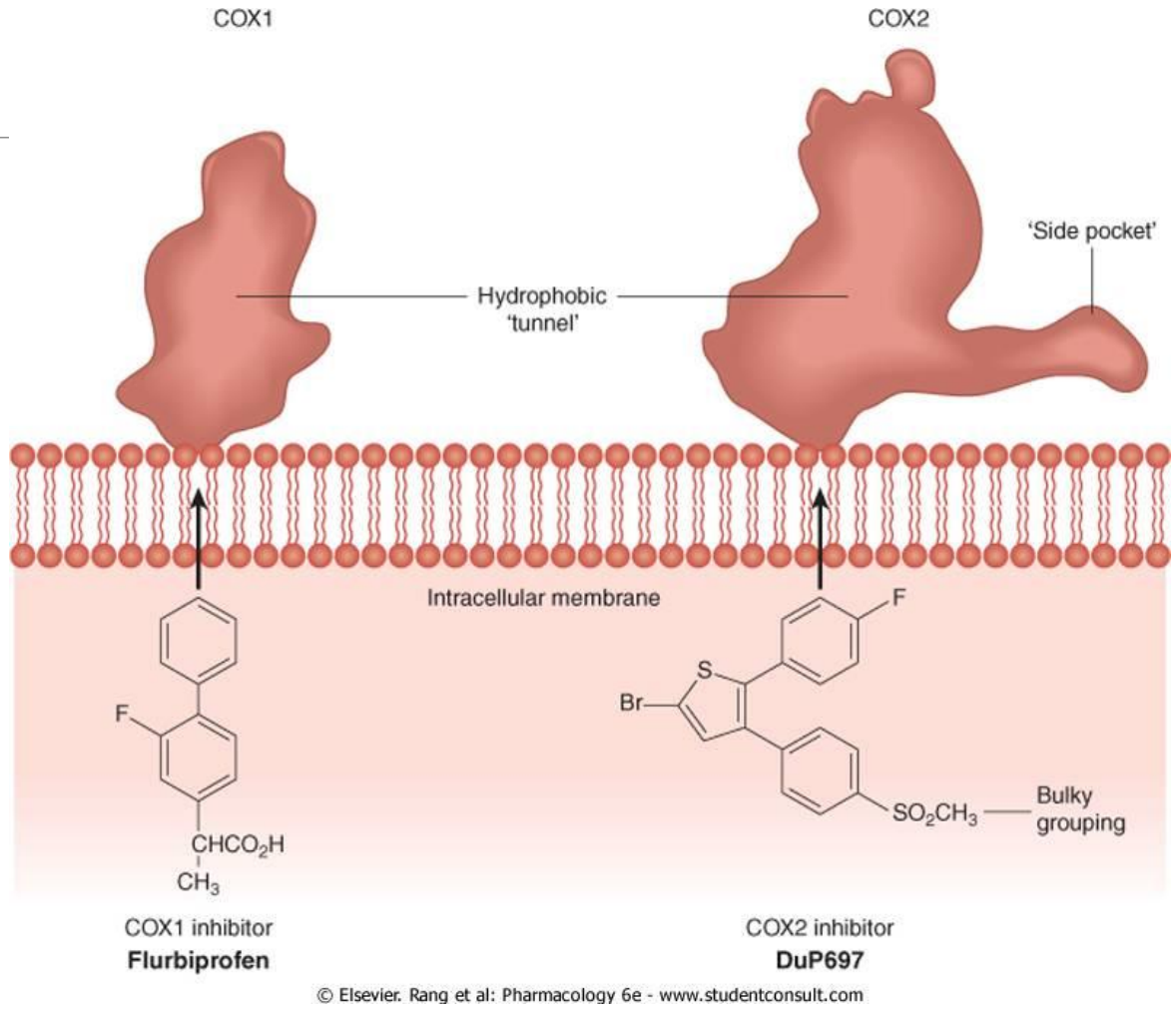
platelet lifespan is ~ 8-10 days. Aspirin inhib until new platelets are made

Why is the effect of Aspirin on platelets long lasting?

The next generation

↳ for purely anti-inflamm effect.

- A drug selective for Cox-2 with less activity against Cox-1



Classes of NSAIDs

1. Carboxylic acids
   - Acetylsalicylic acid (Aspirin)
   - Acetic acid (indomethacin)
   - Propionic acid (naproxen and ibuprofen)
2. Enolic acids
   - Oxicams (piroxicam, meloxicam)
3. Para-aminophenol (acetaminophen)

The next generations aimed to be more selective for Cox-2 and less active on Cox-1

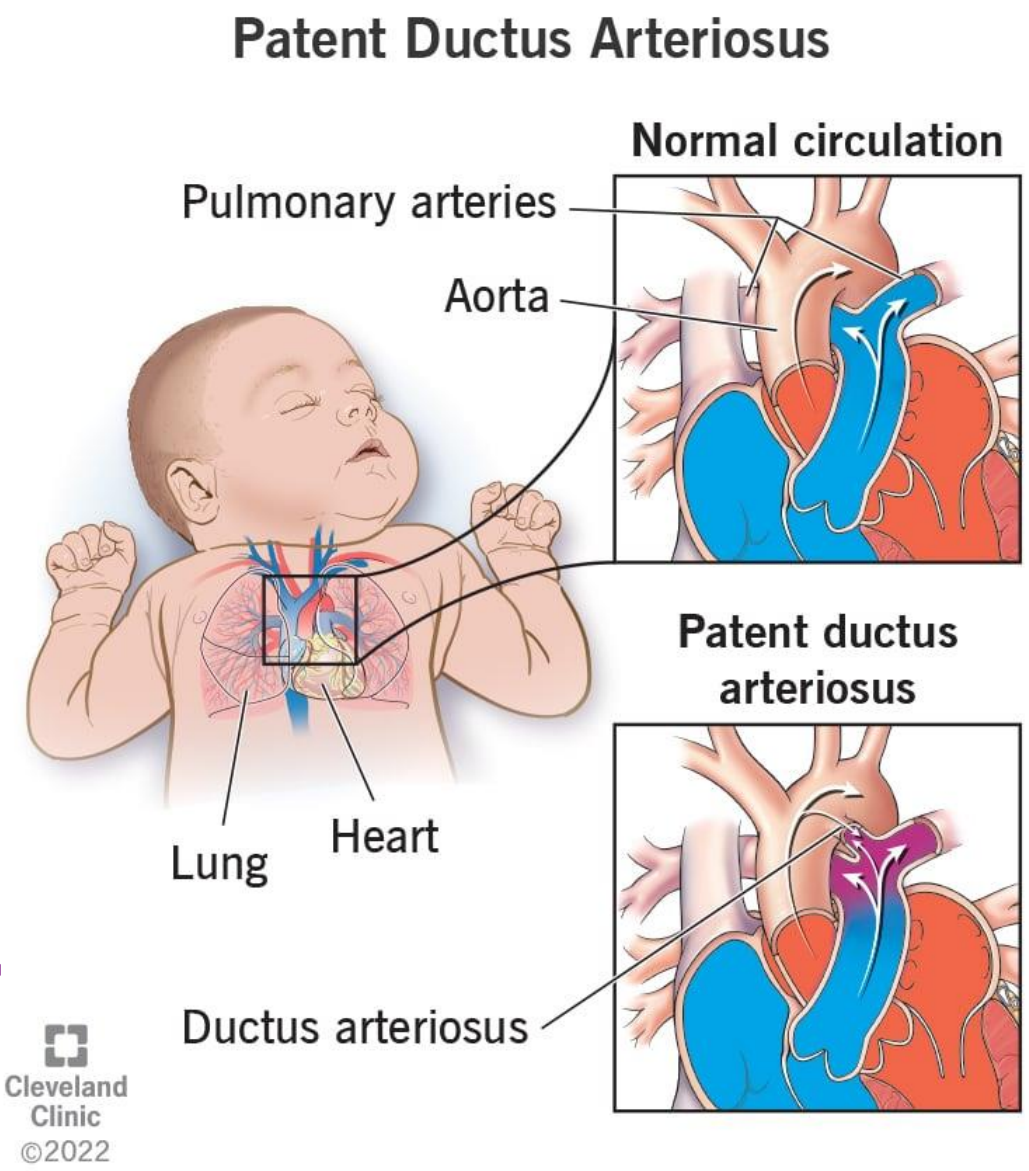
↳ tech not NSAID

Indomethacin

binds better to COX1 & 2 ∴ more SE than Aspirin.

- 20-30x more potent. However more side effects.
- Moderate to severe pain, especially when Aspirin is ineffective (RA). Rheum. arthritis
- Used for the treatment of Patent Ductus Arteriosus (PDA) in premature babies
- Prostaglandins maintain the ductus open: vasoconstriction due to NSAIDs administration closes the ductus

↳ duct will close completely, & will cleave the duct.

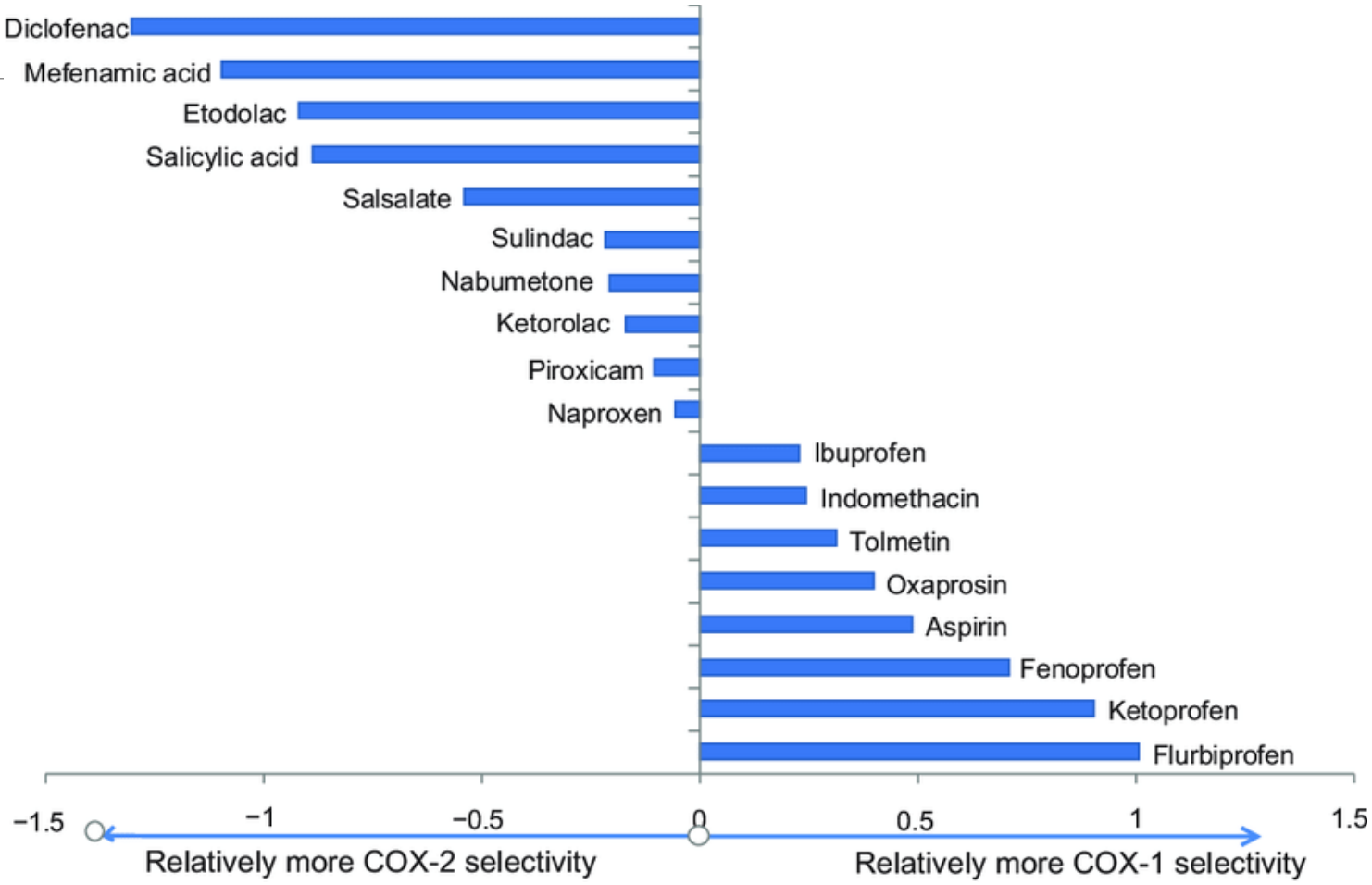


next gen of competitive COX inhib.

Propionic acids

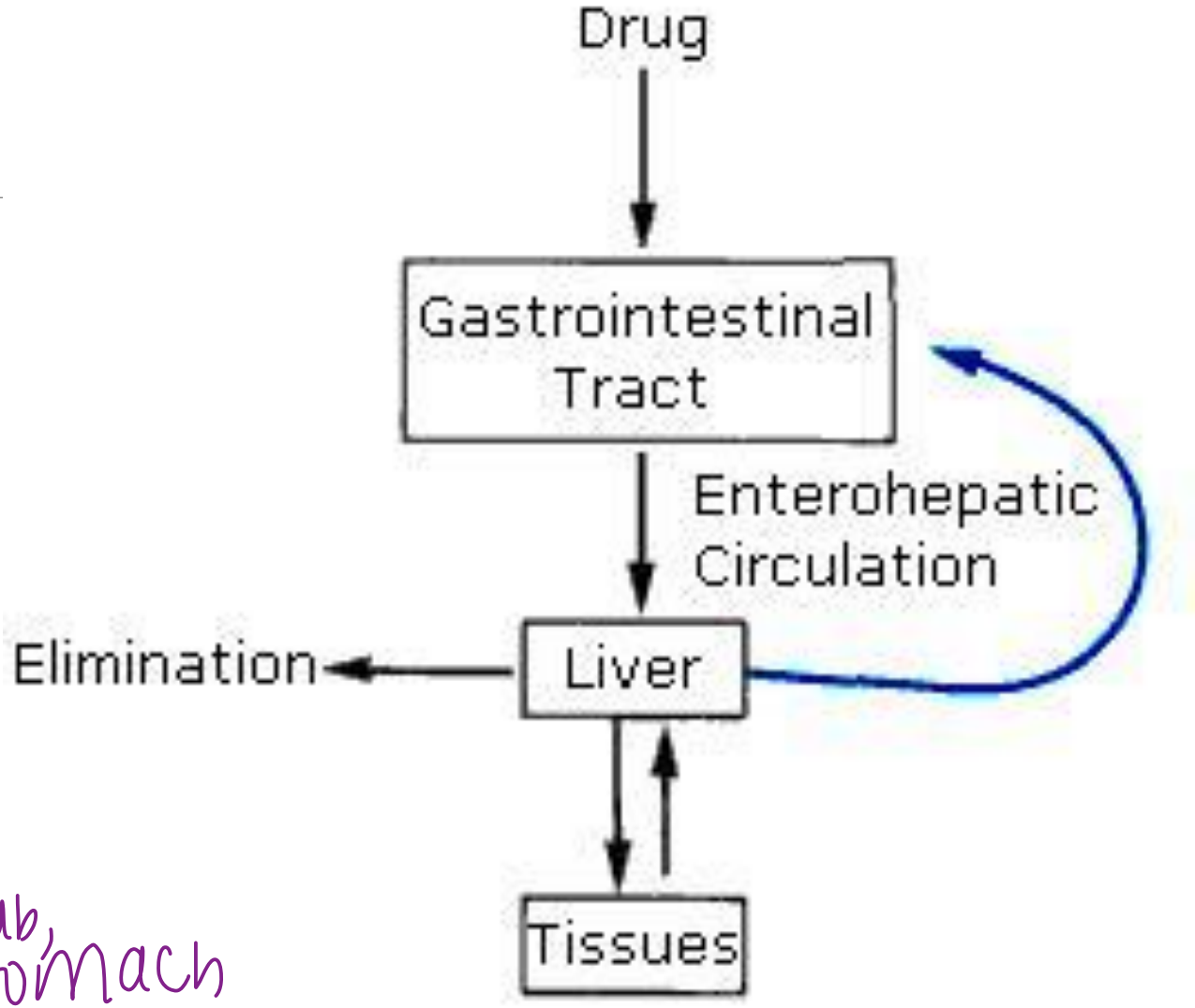
- Competitive Cox inhibitors (reversible binding).
- Less side effects
- Naproxen more Cox-2 selective (10-20 times more potent than Aspirin).

first disc most select to COX2



Enolic acids

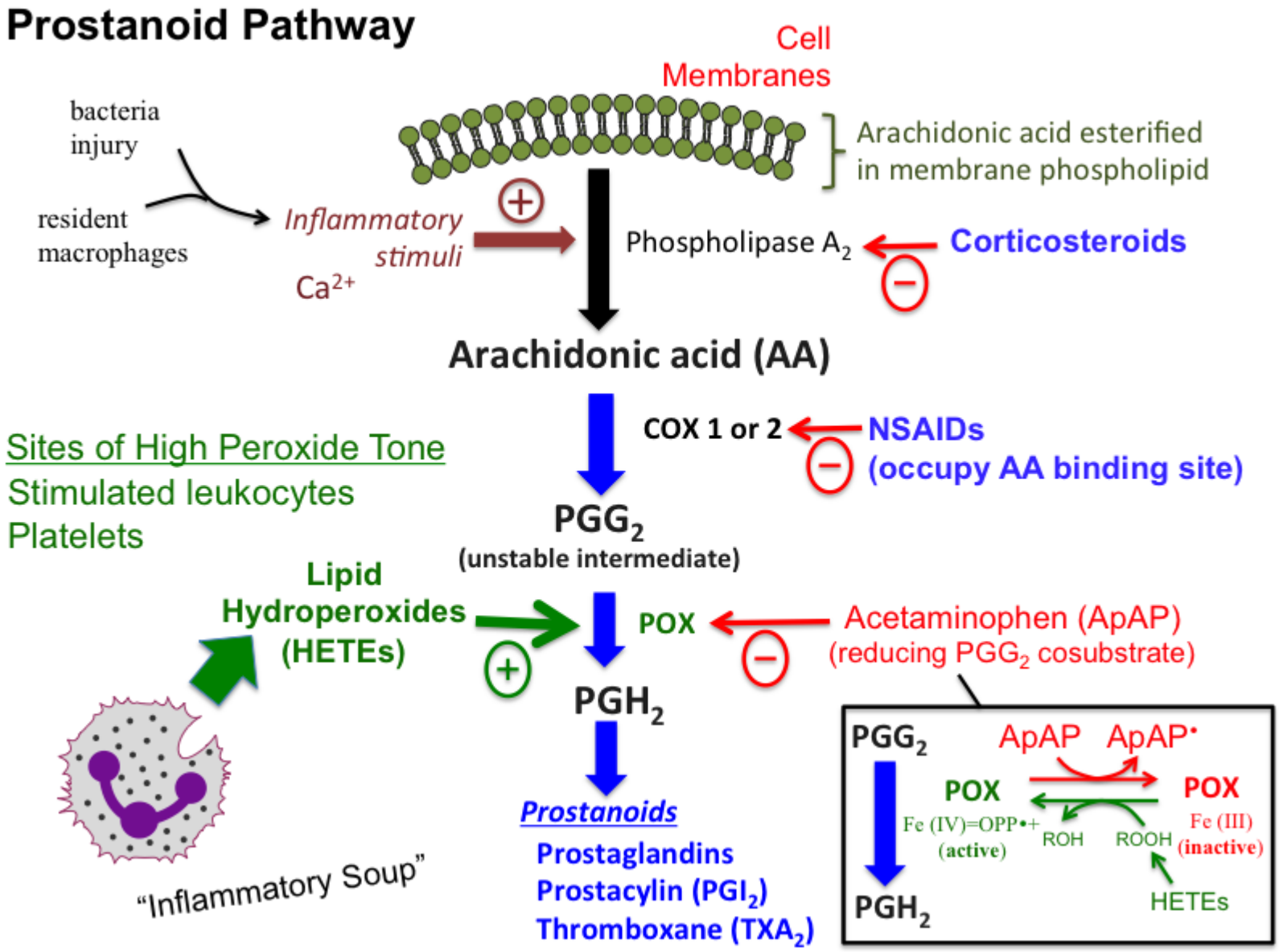
- More selective to Cox-2
- **Piroxicam:**
- Prolonged half-life (30-85hrs) due to active entero-hepatic circulation
- As effective as indomethacin in treatment of rheumatoid diseases but very good patient compliance



can enter GI tract, go thru first pass metab, enters tissue, then stomach then liver → excreted by bile → reabs again

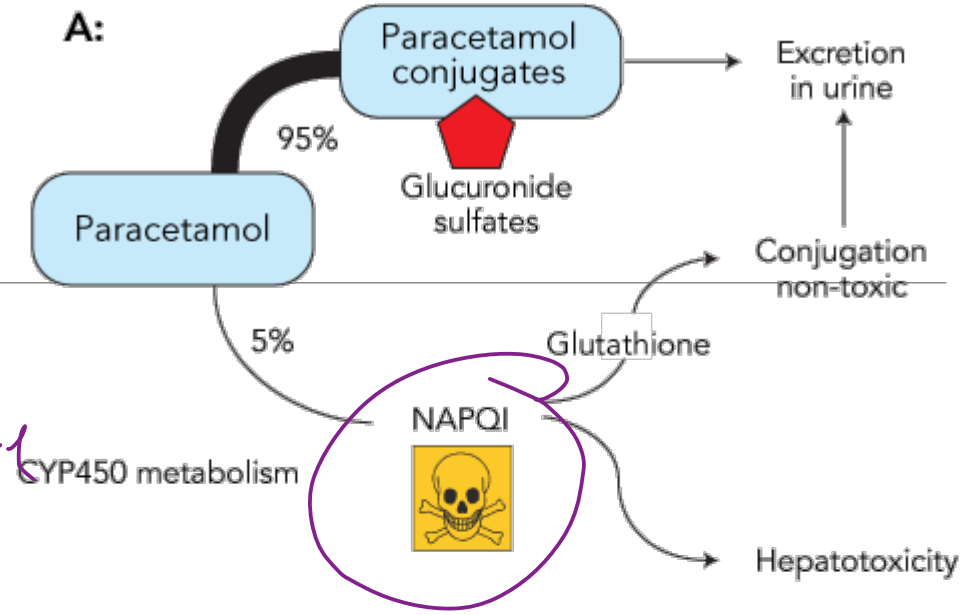
Acetaminophen

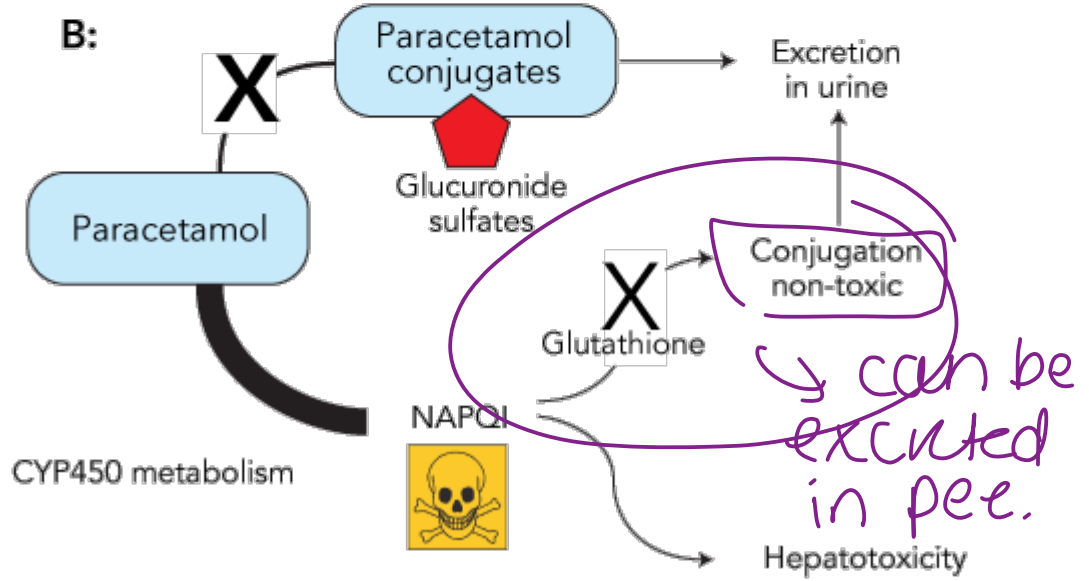
- Derived from coal tar
- **NOT an anti-inflammatory drug**
- **NO effect on platelets**
- No proven activity on Cox-1 and Cox-2
- Mechanism of action- not known –
- Long term high dose liver toxicity
- Other mechanisms involve CBD receptor and serotonin levels?



Side effect

- Normally NAPQI is neutralized by Glutathione conjugation.
- In case of deficiency of glutathione, NAPQI can accumulate in the liver and induce necrosis of hepatocytes.
- Effects can be reversed with N-acetylcysteine.





https://www.ncbi.nlm.nih.gov/books/NBK482369/#:~:text=Mechanism%20of%20Action&text=Regardless%2C%20the%20reduction%20of%20the,its%20analgesic%20and%20antipyretic%20effects.

Questions?