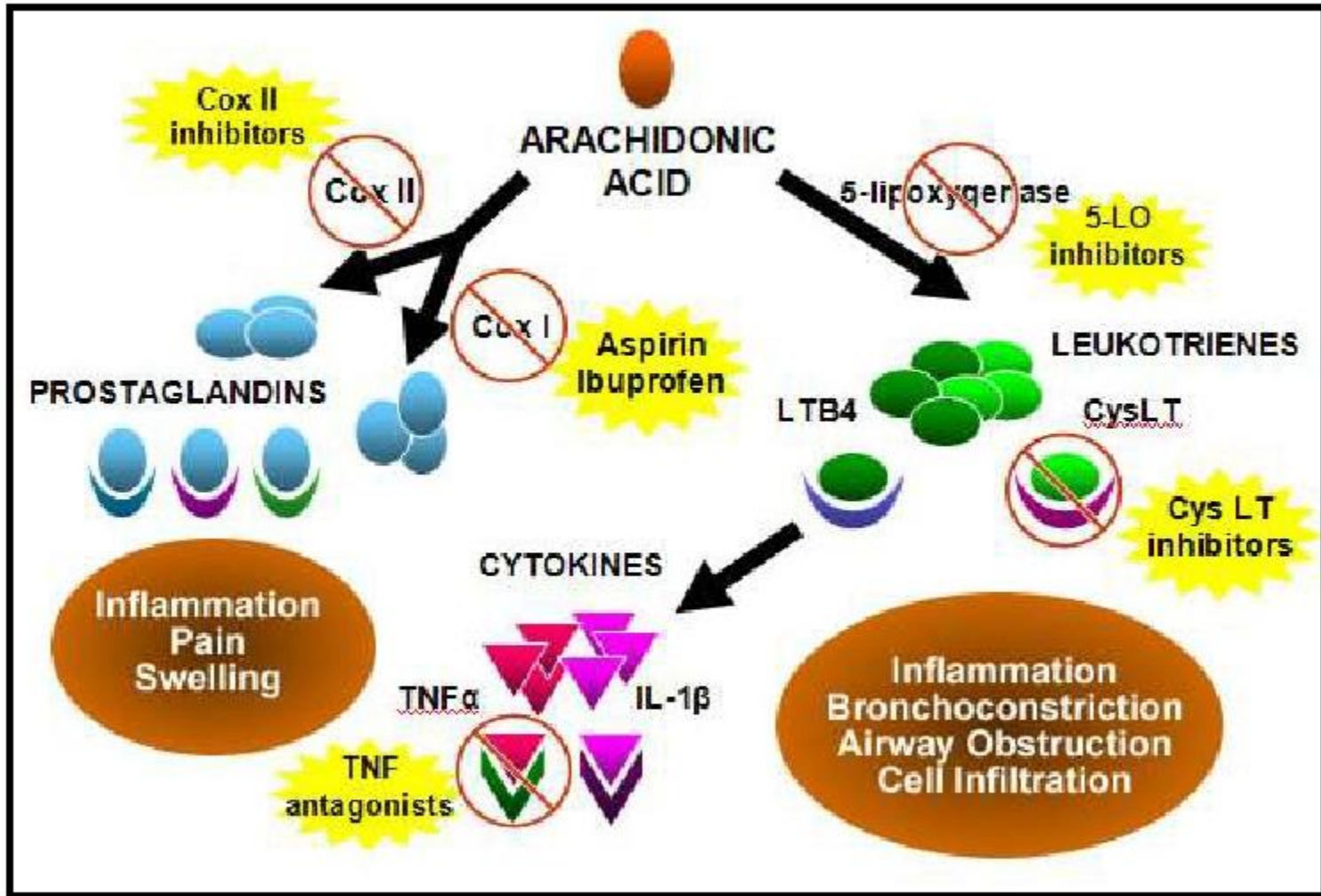
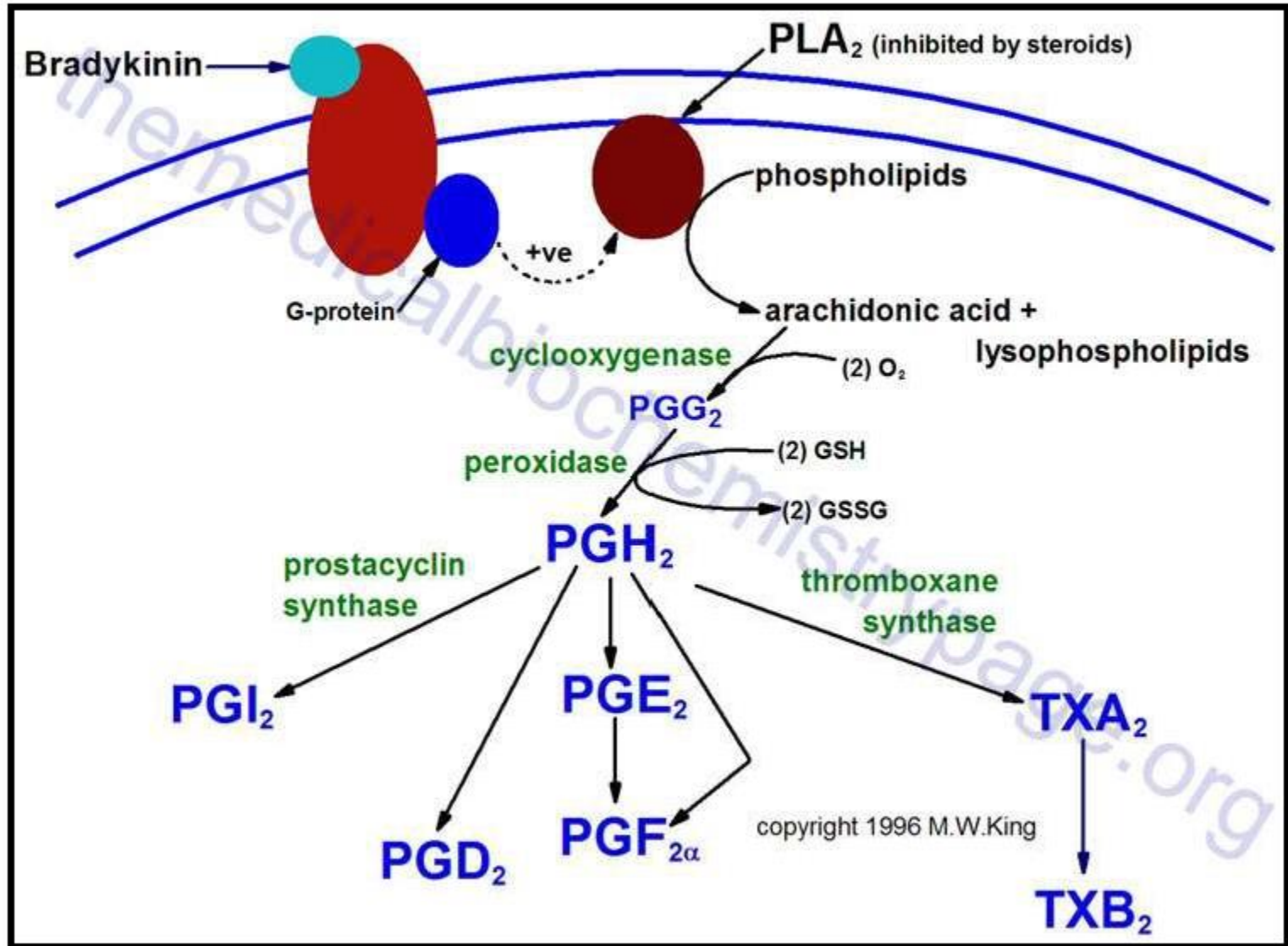


Anti-inflammatory drugs





Cyclooxygenase pathway



COX-1 gene transcription



COX-2 gene transcription

Induced by:

- Oxidative stress
- Injury
- Ischemia
- Seizures
- Neurodegenerative diseases



Glucocorticoids



mRNA

mRNA

Membrane phospholipids

Arachidonic acid

COX-1

COX-2

Nonsteroidal anti-inflammatory drugs (NSAIDs)

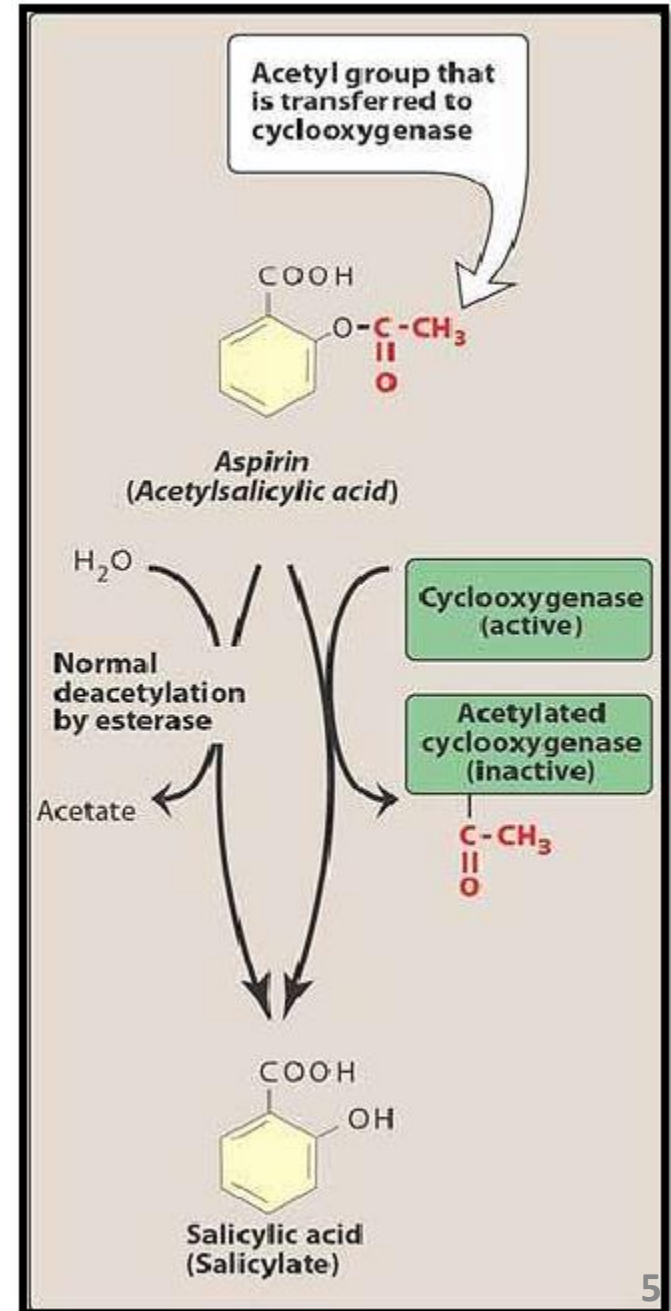
Selective COX-2 inhibitors

Prostaglandins

Prostaglandins

Non-steroidal antiinflammatory (NSAIDs)

1. Aspirin (acetylsalicylic acid)



1. Aspirin

- Anti-inflammatory actions
- Analgesic action
 - ✓ Inhibits synthesis of Prostaglandin E2 (PGE2) “thought to sensitize nerve endings to the action of bradykinin, histamine, and other chemical mediators released locally by the inflammatory process”.
 - ✓ Used for the management of pain of low to moderate intensity arising from musculoskeletal disorders rather than that arising from the viscera
- Antipyretic action
- Fever occurs when the set-point of the anterior hypothalamic thermoregulatory center is elevated. This can be caused by PGE2 synthesis, which is stimulated when an endogenous fever-producing agent (pyrogen), such as a cytokine, is released from white cells that are activated by infection, hypersensitivity, malignancy, or inflammation.
- The salicylates lower body temperature in patients with fever by impeding PGE2 synthesis and release

1. Aspirin

- Respiratory actions

- ✓ At therapeutic doses, aspirin increases alveolar ventilation
- ✓ Higher doses work directly on the respiratory center in the medulla, resulting in hyperventilation and respiratory alkalosis that usually is adequately compensated by the kidney.
- ✓ At toxic levels, central respiratory paralysis occurs, and respiratory acidosis results due to continued production of CO₂.

- Gastrointestinal effects

- ✓ Epigastric distress, ulceration, haemorrhage, and iron-deficiency anaemia
- ✓ Due to inhibition of PGE₂ (stimulate synthesis of protective mucus in both the stomach and small intestine)
- ✓ Misoprostol (PGE₁-derivative) and the proton-pump inhibitors (lansoprazole, omeprazole, pantoprazole) can also be used for the treatment of an NSAID-induced ulcer

1. Aspirin

- Effect on platelets (anticoagulant effect)

- ✓ Low doses of aspirin can irreversibly inhibit thromboxane (enhances platelet aggregation) production in platelets
- ✓ Because platelets lack nuclei, they cannot synthesize new enzyme, and the lack of thromboxane persists for the lifetime of the platelet (3-7 days).
- ✓ As a result of the decrease in TXA₂, platelet aggregation (the first step in thrombus formation) is reduced, producing an anticoagulant effect
- ✓ Aspirin also inhibits cyclooxygenase in endothelial cells, resulting in reduced PGI₂ (decreases platelet aggregation) formation
- ✓ Endothelial cells possess nuclei able to re-synthesize new cyclooxygenase. Therefore, PGI₂ is available for antiplatelet action.

1. **Aspirin**

- Actions on the kidney
 - ✓ Cyclooxygenase inhibitors prevent the synthesis of PGE₂ and PGI₂-prostaglandins that are responsible for maintaining renal blood flow
 - ✓ Decreased synthesis of prostaglandins can result in retention of sodium and water and may cause edema and hyperkalemia in some patients

Therapeutic indications

- Anti-inflammatory, antipyretic, and analgesic uses
 - ✓ The salicylic acid derivatives are used in the treatment of rheumatic fever, osteoarthritis, and rheumatoid arthritis
- External applications
 - ✓ Salicylic acid is used topically to treat corns and warts.
- Cardiovascular applications
 - ✓ Aspirin is used to inhibit platelet aggregation.

1. Aspirin

Adverse effects

- GIT

- ✓ epigastric distress, nausea, and vomiting.
- ✓ Aspirin is an acid and at stomach pH, aspirin is uncharged; consequently, it readily crosses into mucosal cells, where it ionizes (becomes negatively charged) and becomes trapped, thus potentially causing direct damage to the cells.

- Blood

- ✓ inhibition of platelet aggregation and a prolonged bleeding time
- ✓ aspirin should not be taken for at least 1 week prior to surgery.

- Respiration

- ✓ In toxic doses, salicylates cause respiratory depression

1. Aspirin

Adverse effects

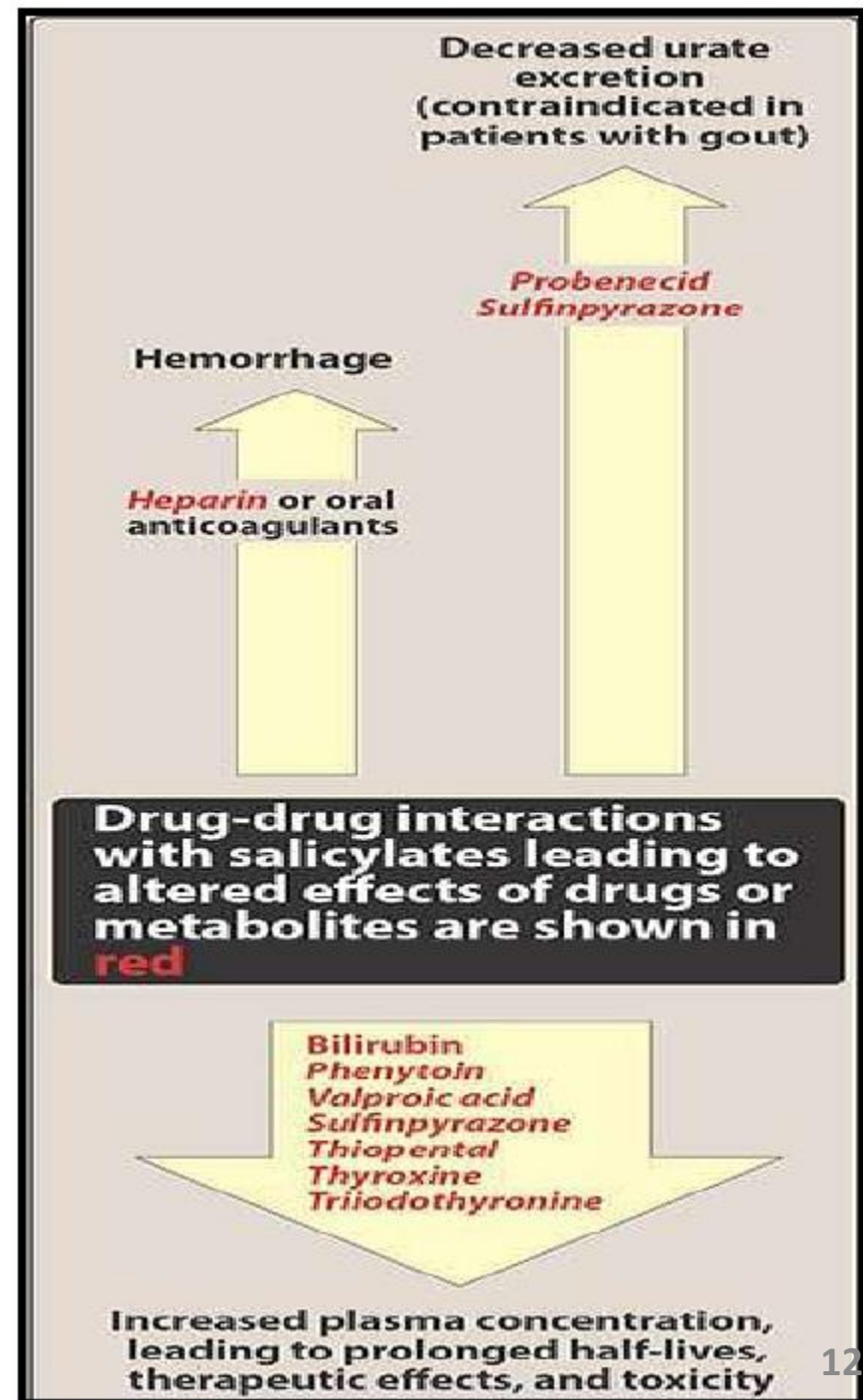
- *Reye's syndrome*

- ✓ Aspirin and other salicylates given during viral infections has been associated with an increased incidence of Reye's syndrome (which is an often fatal, fulminating hepatitis with cerebral edema)
- ✓ This is especially encountered in children, who therefore should be given acetaminophen or Ibuprofen .

1. Aspirin

Adverse effects

- Drug interactions:



2. Propionic acid derivatives

- Ibuprofen, naproxen, fenoprofen, ketoprofen, and oxaprozin
- All these drugs possess anti-inflammatory, analgesic, and antipyretic activity; additionally, they can alter platelet function and prolong bleeding time.
- They have gained wide acceptance in the chronic treatment of RA and osteoarthritis, because their GI effects are generally less intense than those of aspirin.
- These drugs are **reversible** inhibitors of the cyclooxygenases

3. Acetic acid derivatives

- Indomethacin, sulindac, and etodolac
- All have anti-inflammatory, analgesic, and antipyretic activity.
- They act by reversibly inhibiting cyclooxygenase.

4. Oxicam derivatives

- Piroxicam and meloxicam are used to treat RA and osteoarthritis.
- They have long half-lives, which permit once-daily administration

5. Fenamates

- Mefenamic acid and meclofenamate have no advantages over other NSAIDs as anti-inflammatory agents.

6. Heteroaryl acetic acids

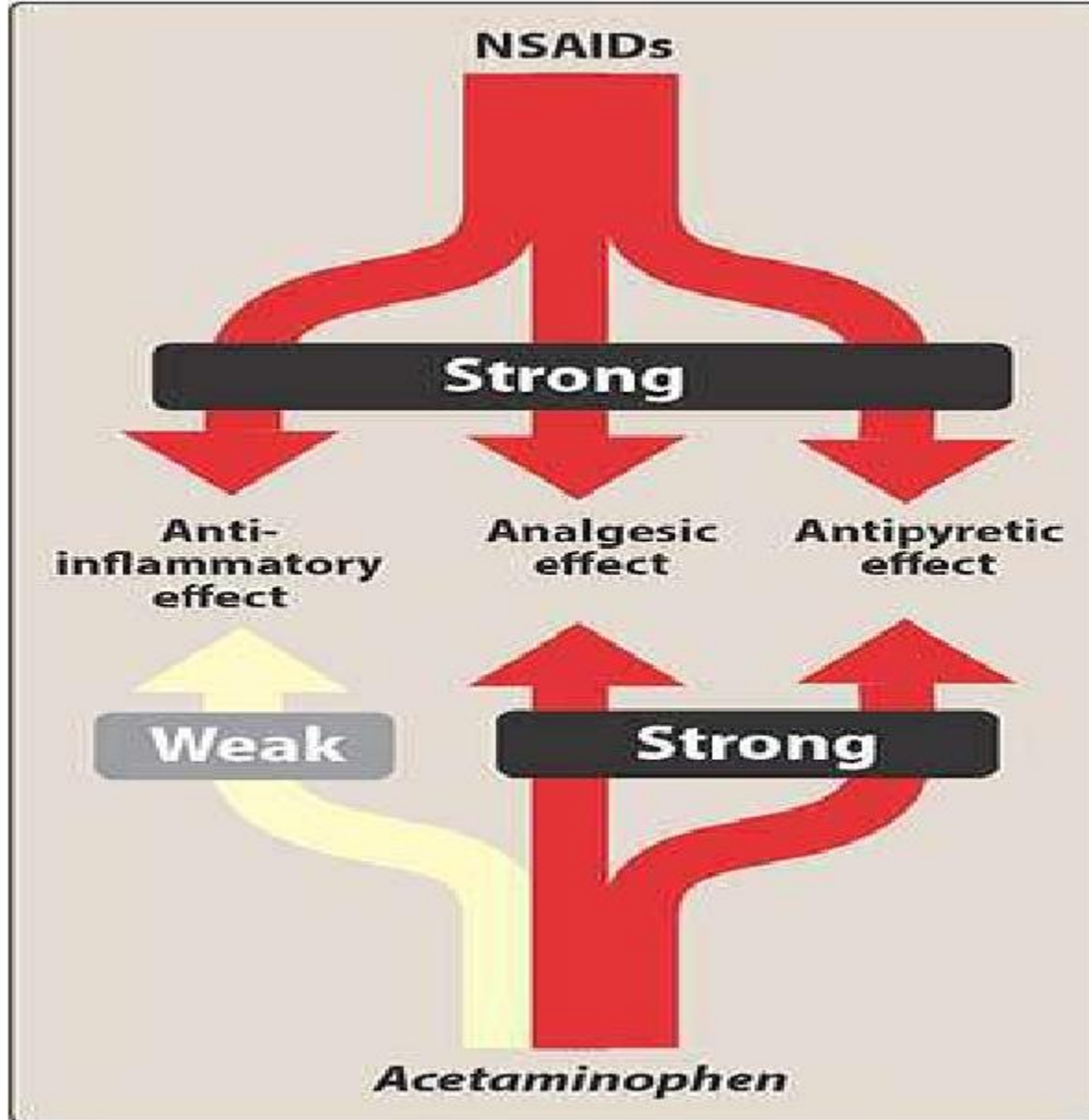
- Diclofenac and tolmetin are approved for long-term use in the treatment of RA, osteoarthritis
- Diclofenac is more potent than indomethacin or naproxen.
- Ketorolac is a potent analgesic but has moderate anti-inflammatory effects.
- for intramuscular use in the treatment of postoperative pain, and for topical use for allergic conjunctivitis.

7. Celecoxib

- Celecoxib is significantly more selective for inhibition of COX-2 than of COX-1
- Unlike aspirin, celecoxib does not inhibit platelet aggregation and does not increase bleeding time.
- Detection of serious cardiovascular events associated with COX-2 inhibitors have led to withdrawal of **rofecoxib** and **valdecoxib** from the market

8. Acetaminophen

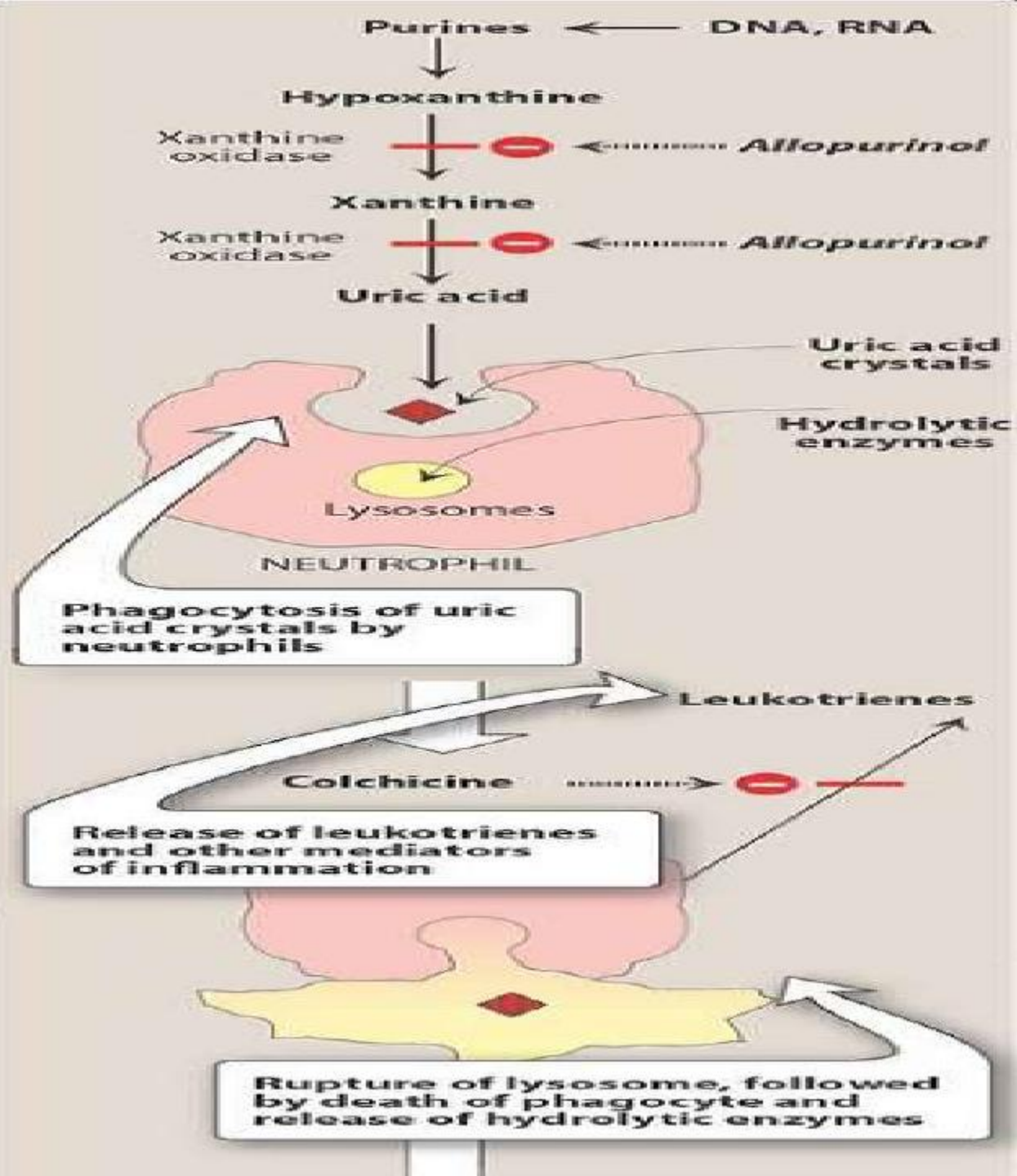
- Acetaminophen inhibits prostaglandin synthesis in the CNS. This explains its antipyretic and analgesic properties.
- Acetaminophen has less effect on cyclooxygenase in peripheral tissues, which accounts for its weak anti-inflammatory activity.
- Acetaminophen does not affect platelet function or increase blood clotting time.
- **Therapeutic indications :**
- Acetaminophen is a suitable substitute for the analgesic and antipyretic effects of aspirin for those patients with:
 - ✓ gastric complaints,
 - ✓ Those in whom prolongation of bleeding time would be a disadvantage,
 - ✓ Those who do not require the anti-inflammatory action of aspirin.
- Acetaminophen is the analgesic/antipyretic of choice for children with viral infections or chickenpox (recall that aspirin increases the risk of Reye's syndrome).
- Acetaminophen does not antagonize the uricosuric agents probenecid or sulfinpyrazone and, therefore, may be used in patients with gout who are taking these drugs.



Actions of non-steroidal anti inflammatory drugs (NSAIDs) and *acetaminophen*

- **Adverse effects**
- With normal therapeutic doses, acetaminophen is virtually free of any significant adverse effects.
- With large doses of acetaminophen, the available glutathione in the liver becomes depleted, and
- N-acetylbenzoiminoquinone reacts with the sulfhydryl groups of hepatic proteins, forming covalent bonds, hepatic necrosis, a very serious and potentially life-threatening condition, can result.

Gout



Treating acute gout

- Acute gouty attacks can result from excessive alcohol consumption, a diet rich in purines, or kidney disease. Acute attacks are treated with indomethacin to decrease movement of granulocytes into the affected area
- NSAIDs other than indomethacin are also effective at decreasing pain and inflammation.
- *Aspirin* is contraindicated, because it competes with uric acid for the organic acid secretion mechanism in the proximal tubule of the kidney

Treating chronic gout

- Chronic gout can be caused by a genetic defect, renal deficiency; or excessive production of uric acid associated with cancer chemotherapy.

1. Colchicine

- Colchicine a plant alkaloid, has been used for the treatment of acute gouty attacks as well as chronic gout.
- Mechanism of action
- Colchicine binds to tubulin, a microtubular protein, causing its depolymerization. This disrupts cellular functions, such as the mobility of granulocytes, thus decreasing their migration into the affected area.
- Colchicine blocks cell division by binding to mitotic spindles.
- Colchicine also inhibits the synthesis and release of the leukotrienes
- Therapeutic uses
- The anti-inflammatory activity of colchicine is specific for gout, usually alleviating the pain of acute gout within 12 hours.
- Colchicine is currently used for prophylaxis of recurrent attacks

2. **Allopurinol**

- Allopurinol reduces the production of uric acid by competitively inhibiting the last two steps in uric acid biosynthesis that are catalyzed by xanthine oxidase
- Uric acid is less water soluble than its precursors. When xanthine oxidase is inhibited, the circulating purine derivatives (xanthine and hypoxanthine) are more soluble and, therefore, are less likely to precipitate

Therapeutic uses

- Allopurinol is effective in the treatment of primary hyperuricemia of gout and hyperuricemia secondary to other conditions, such as that associated with certain malignancies
- Acute attacks of gout may occur more frequently during the first several weeks of therapy; therefore, colchicine or NSAIDs should be administered concurrently.

3. Uricosuric agents

- Probenecid and sulfinpyrazone
- The uricosuric drugs are weak organic acids that promote renal clearance of uric acid by inhibiting the urate-anion exchanger in the proximal tubule that mediates urate reabsorption.

Good Luck