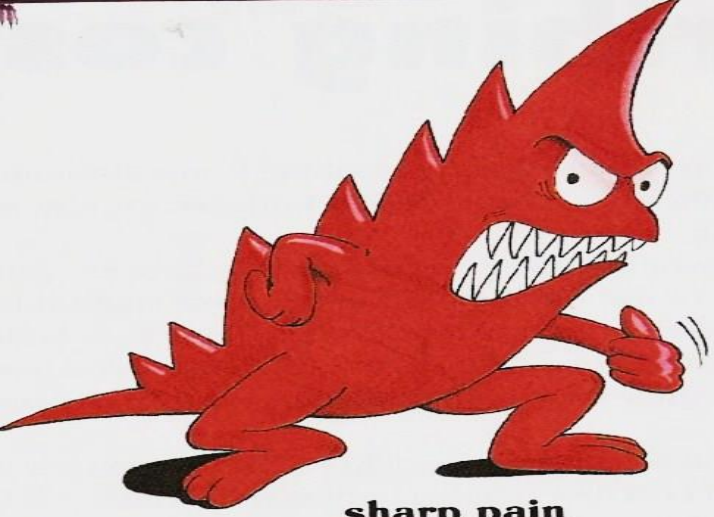
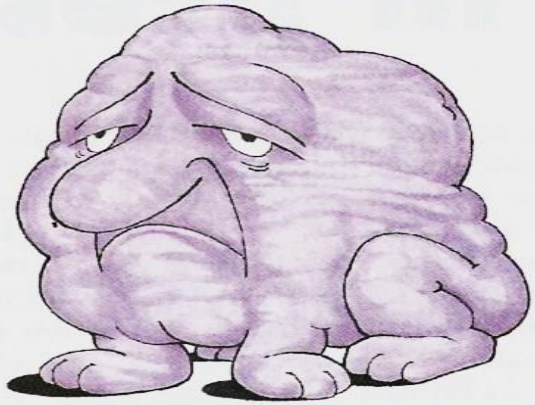
NSAID Analgesics

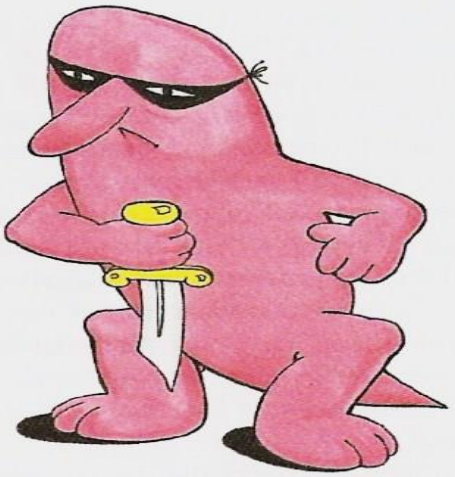
Dr. Alia Shatanawi



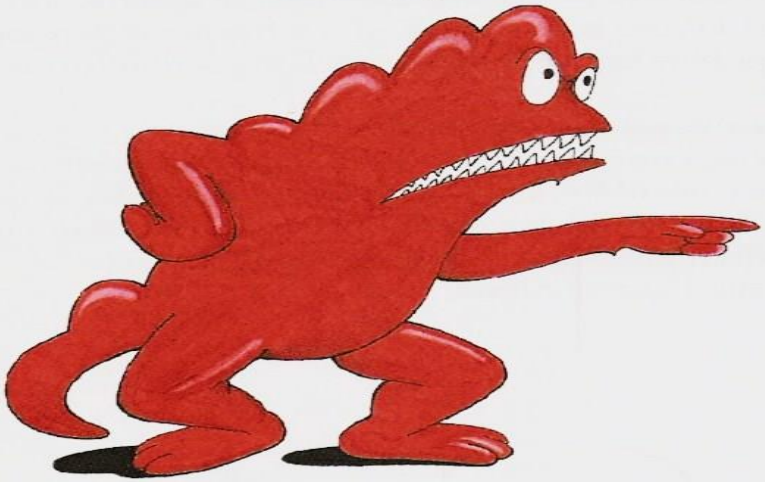
sharp pain



dull aching pain

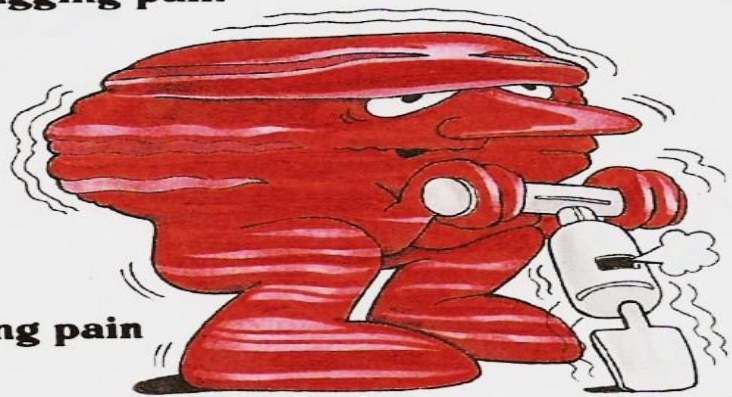


stabbing pain



nagging pain

burning pain



throbbing pain

boring pain

Pain

- Universal, Complex, Subjective experience

- No. 1 Reason people take medications

- Generally is related to some type of tissue damage and serves as a warning signal

Analgesics

-Pain killers

- Derived from Greek **an**- "without" & -**algia** "pain".

An **analgesic**, or **painkiller**, is any member of the group of drugs used to achieve analgesia — relief from pain .

- Drugs that relieve pain **selectively** without blocking the conduction of nerve impulses, markedly altering sensory perception, or affecting consciousness.

- Act in various ways on the peripheral and central nervous systems.

Comparison of Analgesics

Feature	Narcotic (Opioids)	Nonnarcotic (nonopioid)
Efficacy	Strong	Weak
Prototype	Morphine	Aspirin
Pain Relieved	Any Type	Musculoskeletal
Site of Action	Central	Peripheral and Central
Mechanism	Specific Receptors	PG Synthesis
Danger	Tolerance & Dependence	G.I irritation
Anti-inflammatory	No	Yes
Antipyretic	No	Yes
Antiplatelets	No	Yes

Analgesics

- The non-steroidal anti-inflammatory drugs (NSAIDs)
- Paracetamol = acetaminophen
- Opioid drugs

NSAIDs

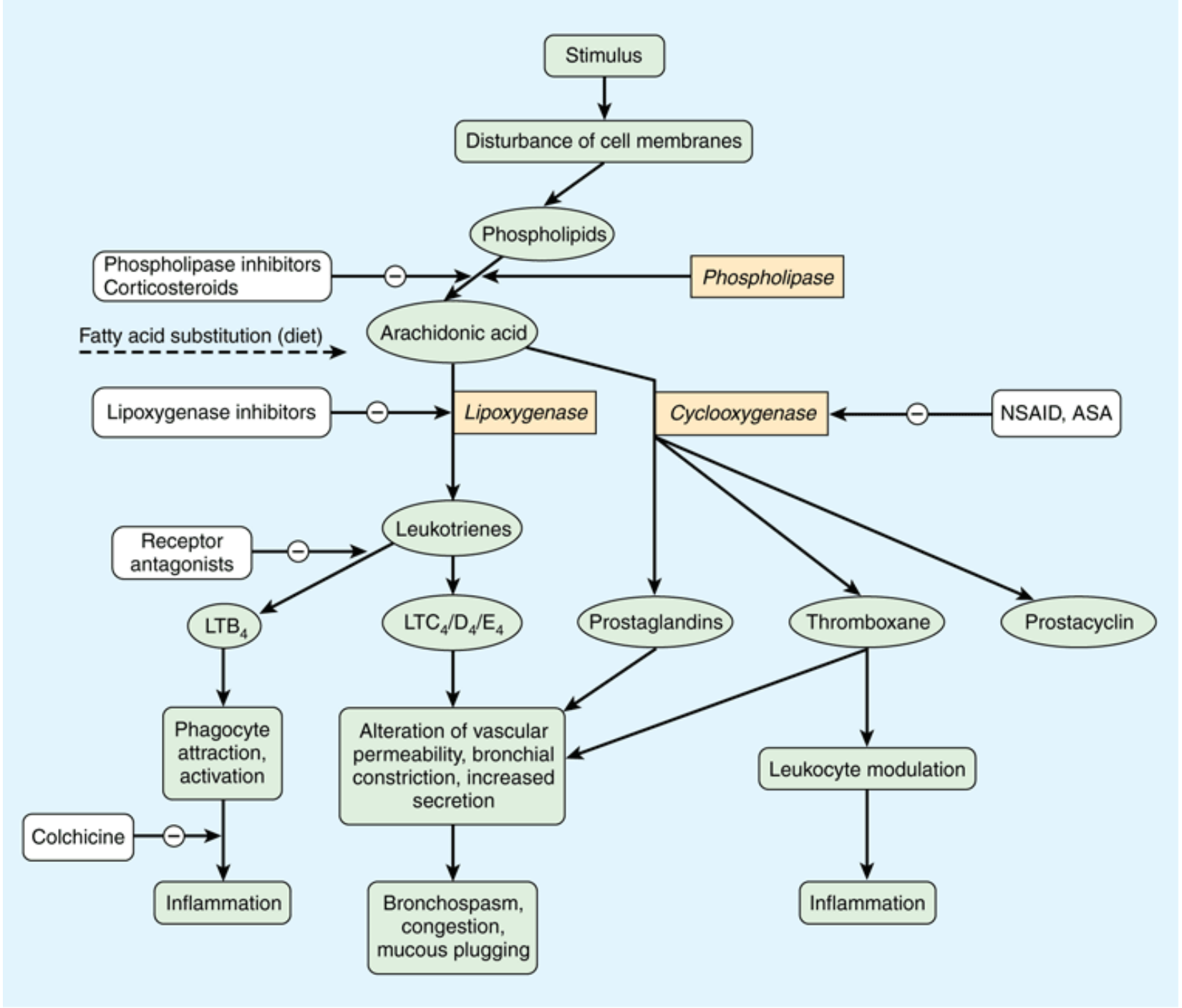
- The NSAIDs are a group of chemically dissimilar agents that differ in their **antipyretic**, **analgesic**, and **anti-inflammatory** activities.

- **inhibiting** the **cyclooxygenase** enzymes that catalyze the first step in prostanoid biosynthesis.

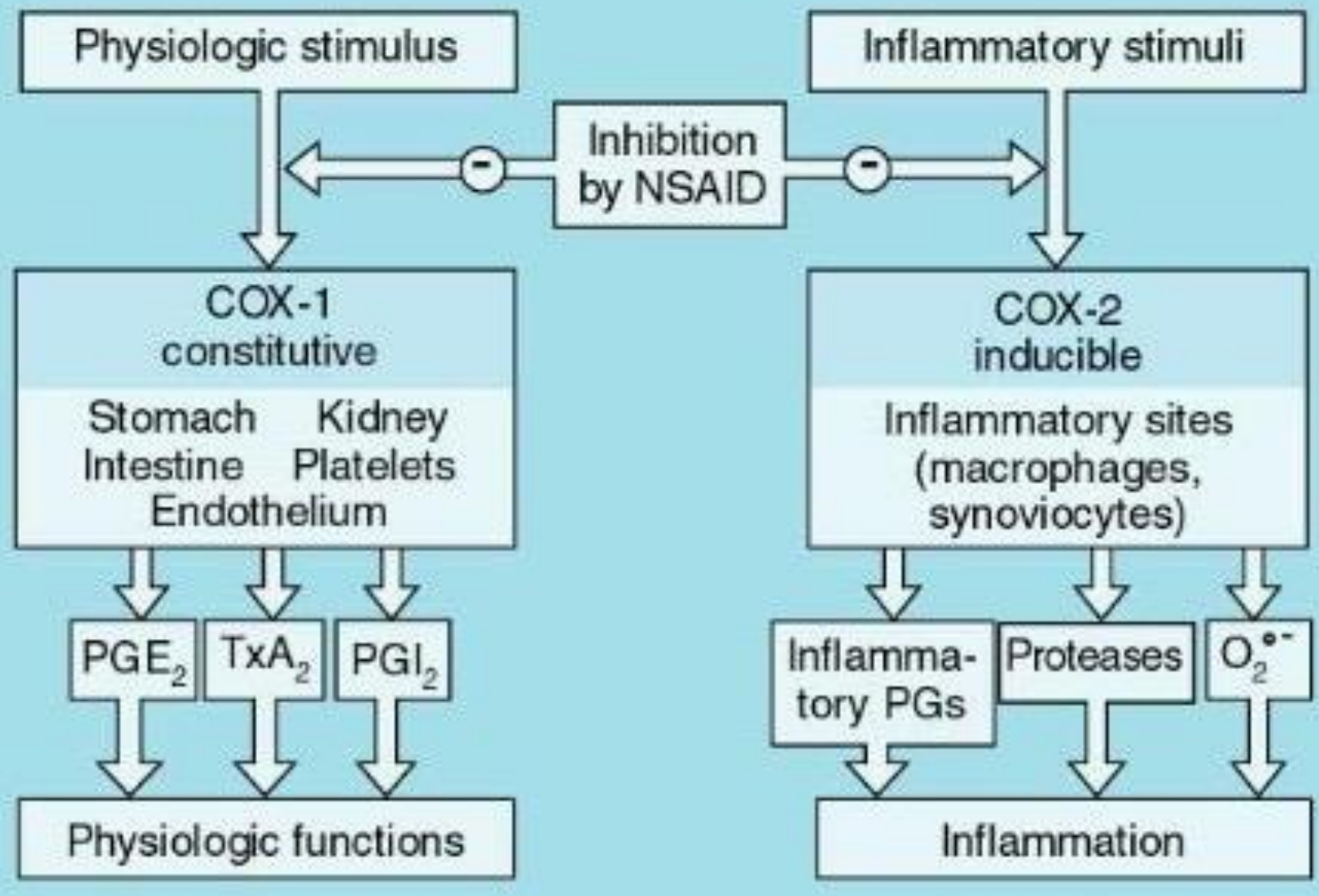
>>>> decreased prostaglandin synthesis with both **beneficial** and **unwanted** effects.

Inflammatory pathways

- Cyclooxygenase (COX) pathway of arachidonate metabolism produces prostaglandins
- Effects on blood vessels, on nerve endings, and on cells involved in inflammation.
- The lipoxygenase pathway of arachidonate metabolism yields leukotrienes
- have a powerful chemotactic effect on eosinophils, neutrophils, and macrophages and promote bronchoconstriction and alterations in vascular permeability.



Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology*, 12th edition:


Physiologic stimulus
Inflammatory stimuli
Inhibition by NSAID
COX-1 constitutive
Stomach Kidney
Intestine Platelets
Endothelium
COX-2 inducible
Inflammatory sites (macrophages, synoviocytes)
PGE2
TxA2
PGI2
Inflamma-tory PGs
Proteases
O2°-
Physiologic functions
Inflammation

Cyclo-oxygenase (COX)

- Exists in the tissue as constitutive isoform (COX-1).
- At site of inflammation, cytokines stimulates the induction of the 2nd isoform (COX-2).
- Inhibition of COX-2 is thought to be due to the anti-inflammatory actions of NSAIDs.
- Inhibition of COX-1 is responsible for their GIT toxicity.
- Most currently used NSAIDs are somewhat selective for COX-1, but selective COX-2 inhibitors are available.

Non-steroidal anti-inflammatory drugs (NSAIDs)

pain

fever

Inflammation

By inhibition of cyclo-oxygenase enzymes COX1 & COX2.

- **COX:**

- **COX-1** is involved in tissue hemeostasis, platelet aggregation, gasric cytoprotection.

- **COX- 2** is responsible for the production of mediators of inflammation.

NSAIDs

An anti-inflammatory action:

(1) decrease Vasodilator PG (PGE_2, PGI_2) leads to less vasodilatation and, indirectly, less edema.

(2) The inhibition of activity of adhesion molecule.

(3) Accumulation of inflammatory cells is also reduced.

NSAIDs

An analgesic effect:

- Decreased prostaglandin generation means decrese sensitivty of **nociceptive** nerve endings to inflammatory mediators.
- Relief of **headache** is due to decreased prostaglandin-mediated vasodilatation.

NSAIDs

An antipyretic effect:

this is partly due to a decrease in the mediator prostaglandin that is responsible for elevating the hypothalamic set-point for temperature control in fever.

Classification

- **Non-selective COX inhibitor**

These include most NSAIDs. (though some have slight preference or selectivity for either COX-1 or COX-2)

- **Selective COX inhibitor**

Celecoxib

Rofecoxib (no longer used)

Meloxicam

Aspirin

- It can cause **irreversible** inactivation of COX-1 and COX-2.
- Aspirin is the prototype of **traditional** NSAIDs and was officially approved by the FDA in 1939.
- It is one of the **most** commonly NSAIDs used and is the drug to which all other anti-inflammatory agents are compared

Mechanism of action

- Aspirin is a weak organic acid that is unique among the NSAIDs in that it **irreversibly** inactivates cyclooxygenase

- The other NSAIDs are all reversible

- Aspirin is rapidly deacetylated by esterases in the body producing salicylate, which has anti-inflammatory, antipyretic, and analgesic effects.

Asprin

- The antipyretic and anti-inflammatory effects of salicylate are due primarily to the blockade of **prostaglandin** synthesis at the thermoregulatory centers in the hypothalamus and at peripheral target sites.

- Furthermore, by decreasing **prostaglandin** synthesis, salicylate also prevents the sensitization of pain receptors to both mechanical and chemical stimuli.

- Aspirin may also depress pain stimuli at **subcortical** sites

Analgesic action:

- Prostaglandin E2 (PGE2) is thought to **sensitize** nerve endings to the action of bradykinin, histamine, and other chemical mediators released locally by the inflammatory process.

- 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

- Impeding PGE2 synthesis and release resets the hypothalamus toward normal

- At higher doses it rapidly lowers the body temperature of febrile patients by increasing heat dissipation as a result of peripheral vasodilation and sweating. (VSMC)
- Aspirin has no effect on normal body temperature.

Respiratory actions:

At therapeutic doses, aspirin increases alveolar ventilation. uncouple oxidative phosphorylation, which leads to **elevated CO2** and increased respiration.

- Higher doses work directly on the **respiratory center** in the medulla, resulting in hyperventilation and respiratory alkalosis

- At **toxic** levels, central respiratory paralysis >> **acidosis**

Toxicity of salicylates

- (1) stimulation of the respiratory center of the brain, leading to hyperpnea and respiratory alkalosis
- (2) uncoupling of oxidative phosphorylation, leading to increased oxygen utilization and glucose demand, increased oxygen utilization and glucose demand, increased glyconeogenesis, and increased heat production
- (3) inhibition of Krebs cycle enzymes, leading to decreased glucose availability and increased organic acids
- (4) alterations in lipid metabolism and amino acid metabolism, enhancing metabolic acidosis
- (5) increased fluid and electrolyte losses, leading to dehydration, sodium depletion, potassium depletion, and loss of buffer capacity.

Gastrointestinal effects:

- **PGE2** stimulate synthesis of protective **mucus** in both the stomach and small intestine.
- In the presence of aspirin, these prostanoids are not formed, resulting in increased gastric acid secretion and diminished mucus protection.
- Agents used for the prevention of gastric and/or duodenal ulcers include proton-pump inhibitors (**PPIs**); esomeprazole, lansoprazole, omeprazol
- 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.**

Effect on platelets:

- **TXA2** enhances platelet aggregation >> **Low doses 81 mg** daily of aspirin can irreversibly **inhibit** thromboxane production in platelets via acetylation of cyclooxygenase.

- Because platelets lack nuclei, they cannot synthesize new enzyme, and the lack of thromboxane persists for the lifetime of the platelet (7 days)>> As a result prolonged **bleeding time.**

Actions on the kidney:

- Cyclooxygenase inhibitors prevent the synthesis of PGE2 and PGI2 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.
- **Interstitial nephritis** can also occur with all NSAIDs but less with aspirin (specially at low dose)

Therapeutic uses

- The salicylic acid derivatives are used in the treatment of gout, rheumatic fever, osteoarthritis, and RA.

- Commonly treated conditions requiring **analgesia** include headache, arthralgia, and myalgia.

External applications:

- Salicylic acid is used topically to treat corns and warts.

Cardiovascular applications:

- Aspirin is used to inhibit platelet aggregation. Low doses are used **prophylactically** to
- reduce the risk of recurring transient ischemic attacks (**TIAs**) and stroke or death
- Studies have shown a reduced risk of death in those having an acute **myocardial infarction**

PHARMACOKINETICS

Administration and distribution:

- After oral administration, the un-ionized salicylates are passively absorbed from the **stomach** and the **small intestine**
- **Rectal** absorption of the salicylates is **slow** and unreliable, but it is a useful route for administration to vomiting children.
- Salicylates must be avoided in children and teenagers (<15 years old) with varicella (chickenpox) or influenza to prevent **Reye's** syndrome.
- Salicylates are highly protein bound

Dosage:

The salicylates exhibit analgesic activity at low doses; only at higher doses do these drugs show anti-inflammatory activity .

- For example, two 325-mg aspirin tablets administered four times daily produce **analgesia**, whereas 12 to 20 tablets per day produce both analgesic and **anti-inflammatory** activity.

- For long-term **myocardial infarction prophylaxis**, the dose is 81 to 162 mg/day
- for those with **RA or osteoarthritis**, the initial dose is 3 grams/day

- for **stroke prophylaxis**, the dose is 50 to 325 mg/day

Metabolism and excretion

- At dosages of 650 mg/day, aspirin is hydrolyzed to salicylate and acetic acid by esterases in tissues and blood .
- Salicylate is converted by the **liver** to water-soluble conjugates that are rapidly cleared by the **kidney**
- Both **hepatic** and **renal** function should be monitored periodically in those receiving long-term, high-dose aspirin therapy.
- aspirin should be avoided in patients with a creatinine clearance of less than 10 mL/min.

Other side effects

Hypersensitivity: Approximately 15 percent of patients taking *aspirin experience hypersensitivity reactions*.

- Symptoms of true allergy include urticaria, bronchoconstriction, or angioedema. Fatal anaphylactic shock is rare.

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 instead of aspirin

Drug interactions:

- Salicylate is 90 to 95 percent protein bound and can be displaced from its protein-binding sites, resulting in increased concentration of free salicylate

- alternatively, aspirin could displace other highly protein-bound drugs, such as **warfarin**, **phenytoin**, or **valproic** acid, resulting in higher free concentrations of the other agent .

- Concomitant use of **ketorolac** and aspirin is contraindicated because of increased risk of GI bleeding and platelet aggregation inhibition.

Aspirin and pregnancy

- In pregnancy: Aspirin is classified as FDA pregnancy category C risk during Trimesters 1 and 2
- category D during Trimester 3.
- Because salicylates are excreted in breast milk, aspirin should be avoided during pregnancy and while breast-feeding.

Reye's syndrome

- Reye's syndrome is a potentially fatal disease that has numerous detrimental effects to many organs, especially the brain and liver, as well as causing a lower than usual level of blood sugar (hypoglycemia) The classic features are a rash, vomiting, and liver damage. The exact cause is unknown and, while it has been associated with aspirin consumption by children with viral illness, it also occurs in the absence of aspirin use.

Propionic acid derivatives

- **Ibuprofen , naproxen, fenoprofe, ketoprofen , flurbiprofen**

- All these drugs possess anti-inflammatory, analgesic, and antipyretic activity
- their **GI** effects are generally less intense than those of aspirin.
- These drugs are **reversible** inhibitors of the cyclooxygenases

- All are well **absorbed** on oral administration and are almost totally bound to serum **albumin**.
- They undergo **hepatic** metabolism and are excreted by the **kidney**.
- The most common adverse effects are **GI**, ranging from dyspepsia to bleeding.
- Side effects involving the central nervous system (**CNS**), such as headache, tinnitus, and dizziness, have also been reported

. The use of sulindac has also been linked to cases of acute pancreatitis.The use of dimethylsulfoxide (DMSO) topically in combination with sulindac has been reported to induce severe neuropathies

Naproxen and Ibuprofen

- Pregnancy : category C, category D from
- Increase the risk of cardiovascular thrombotic event, MI and stroke.
- Increase risk of GI bleeding.
- Ibuprofen not exceed 3200mg/day., and take with food or with water to avoid GI effect.
- Asthmatic patient.

Acetic acid derivatives

- **Indomethacin , sulindac , Etodolac**

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

- Despite its potency as an anti-inflammatory agent, the **toxicity** of **indomethacin** limits its use to the treatment of acute gouty arthritis, ankylosing spondylitis .

- The adverse reactions caused by **sulindac** are similar to, but less severe than, those of the other NSAIDs, including indomethacin.

- **Etodolac** has effects similar to those of the other NSAIDs

Indomethecin

- acute and chronic rheumatoid arthritis and osteoarthritis.
- Also useful in ankylosing spondylitis, acute gouty arthritis, bursitis, and tendinitis.
- Side effects:
  - It produces more CNS side effects than most of the other NSAIDs. Severe headache occurs in 25 to 50% of patients; vertigo, confusion, and psychological disturbances
  - GI symptoms also are more frequent.
  - Hematopoietic side effects (e.g., leukopenia, hemolytic anemia, aplastic anemia, purpura, thrombocytopenia, and agranulocytosis
  - Ocular effects (blurred vision, corneal deposits) Hepatitis, jaundice, pancreatitis, and hypersensitivity reactions

Oxicam derivatives

- ***Piroxicam** and **meloxicam***
- *are used to treat RA, ankylosing spondylitis, and* osteoarthritis.
- They have **long half-lives**, which permit once-daily administration, and the parent drug as well as its metabolites are renally excreted in the urine.
- ***Meloxicam** inhibits both COX-1 and COX-2, with preferential binding for COX-2,* and at low to moderate doses shows less GI irritation than *piroxicam*.

Fenamates

- ***Mefenamic***
- *have* ***no advantages*** *over other* NSAIDs as anti-inflammatory agents.
- Their side effects, such as **diarrhea**, can be severe, and they are associated with inflammation of the bowel.
- Cases of hemolytic anemia have been reported

Heteroaryl acetic acids

- ***Diclofenac and tolmetin , ketorlac***
- *are approved for long-term use in the treatment of RA,* osteoarthritis.
- ***Diclofenac*** *is more potent than indomethacin or naproxen.*
- *An* ***ophthalmic*** preparation is also available.
- *Diclofenac accumulates in synovial fluid, and the primary route of excretion for the* drug and its metabolites is the **kidney**.

Diclofenac sodium

- Used PO 50mg after food, I.M. inj 75mg
- Diclofenac potassium is prompt release and has quicker onset where as the Diclofenac sodium is delayed release.
- Pregnancy: category C

Diclofenac sodium

- **C/I**

- Hypersensitivity.
- Asthmatic patient.
- Patient with history of peptic ulcer.
- Metabolism: liver.
- Excretion: urine.

Selective COX-2 inhibitor

Celecoxib

- more selective for COX-2 than for COX-1.
- Adverse effects are slighter than other NSADs.
- Long-term studies of the incidence of clinically significant gastrointestinal ulcers and bleeding are not yet completed.
- May increase the incidence of edema and hypertension.

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 uses

- 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, or 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).

Pharmacokinetics

- Acetaminophen is rapidly **absorbed** from the GI tract. A significant first-pass metabolism occurs in the **luminal** cells of the intestine and in the **hepatocytes**.

- Under normal circumstances, acetaminophen is conjugated in the **liver** to form inactive metabolites.

- A portion of acetaminophen is hydroxylated to form **N-acetylbenzoiminoquinone** a highly reactive and potentially dangerous metabolite .

- At normal doses of acetaminophen, the N-acetylbenzoiminoquinone reacts with the sulfhydryl group of **glutathione**, forming a nontoxic substance .

- Acetaminophen and its metabolites are excreted in the urine.

Adverse effects

- With normal therapeutic doses, acetaminophen is virtually free of any significant adverse effects.
- Renal tubular necrosis and hypoglycemic coma are rare complications of prolonged, large-dose therapy.
- large doses Hepatic necrosis, a very serious and potentially life-threatening condition can result.
- Renal tubular necrosis may also occur.
- Periodic monitoring of liver enzymes tests is recommended for those on high-dose acetaminophen.

Thank You