

Pharmacology - MSS

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NSAID Analgesics

The non-steroidal anti-inflammatory drugs

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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

Pain is defined as an unpleasant sensation that can either be acute or chronic, usually pain is a consequence of **changes** that are happening in our body; such as **neurochemical processes**.

These can happen either **peripherally or centrally** in the nervous system.

Analgesics (Definition)

-Pain killers analgesics are medications that are used to suppress the pain

- Derived from Greek **an-** "without" & **-algia** "pain". Analgesics=without 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, without altering sensory perception, or affecting consciousness. **“this is the main difference between analgesics and anesthetics “.**

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

Comparison of Analgesics important

Feature	Narcotic (Opioids) “drugs working on the central nervous system”	Nonnarcotic (nonopioid) NSAIDs
Efficacy	Strong	Weak
Prototype	Morphine	Aspirin
Pain Relieved	Any Type	Musculoskeletal
Site of Action	Central	Peripheral and Central
Mechanism	Specific Receptors “opioid receptors”	PG Synthesis
Danger	Tolerance & Dependence	G.I irritation
Anti-inflammatory	No	Yes
Antipyretic	No	Yes
Antiplatelets	No	Yes

Analgesics

so we can classify analgesics into :

- The non-steroidal anti-inflammatory drugs (NSAID) these drugs work peripherally so they're not part of the central nervous system pharmacology, but they're a type of analgesics that's used a lot.
- Paracetamol = *Acetaminophen* as a separate group, inhibits the prostaglandin synthesis as the NSAIDs, but it has some distinct characteristics that'll be described later.
- Opioid drugs; mainly target opioid receptor and the central nervous system

NSAIDs

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

So they are compounds that have distinct chemical structure that are different from each other, but they share common properties regarding their activity, **All** these drugs are :

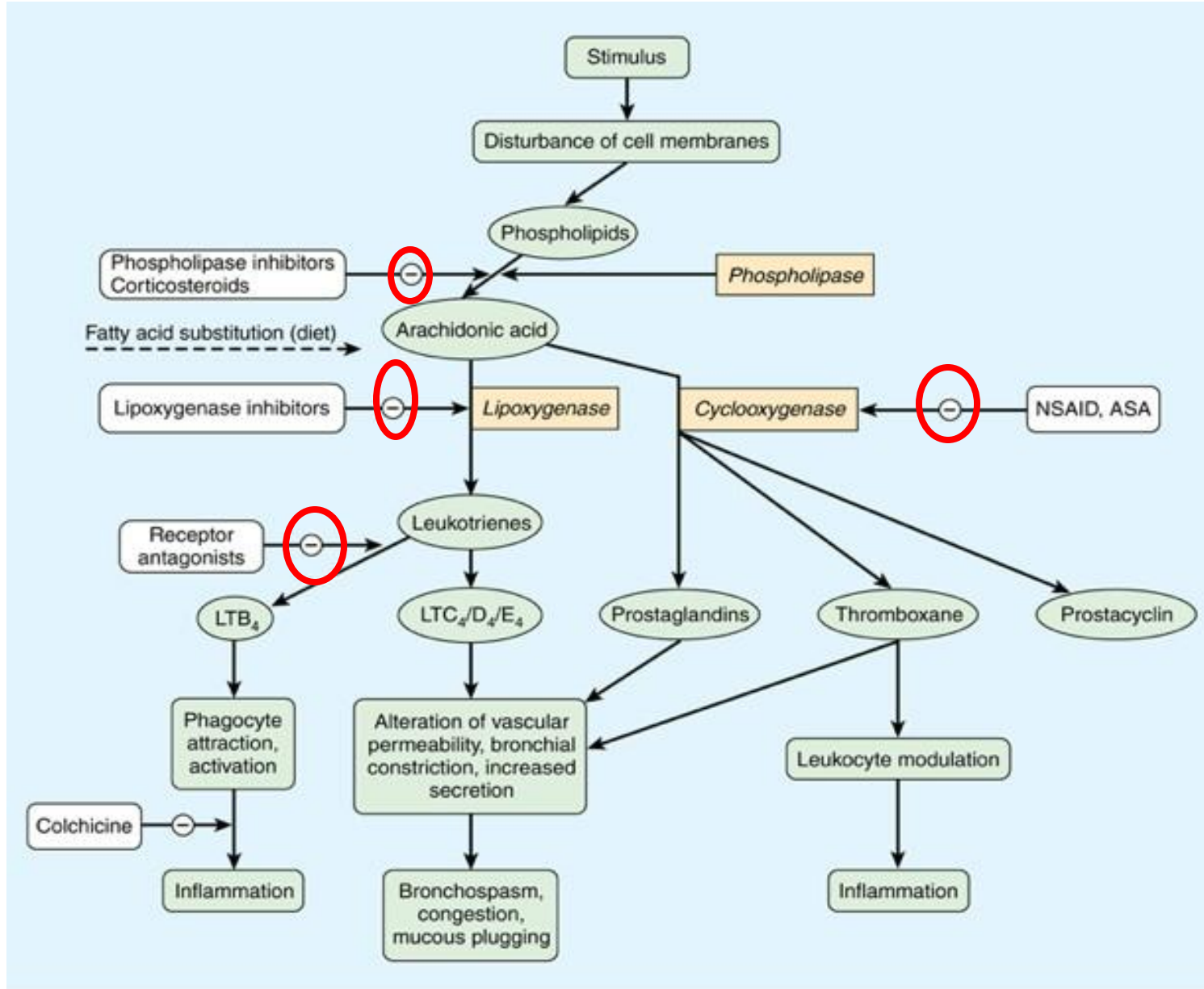
- ❑ antipyretic = they lower the elevated body temperature (fever)
- ❑ analgesics = painkiller
- ❑ anti-inflammatory.

They also share the mechanism of action, **by inhibiting** the **cyclooxygenase** enzymes that catalyze the first step in prostanoid biosynthesis.

Remember that we have an enzyme called cyclooxygenase that is a part of the arachidonic acid metabolism which produces **prostaglandin**.

By inhibiting this enzyme >> prostaglandin synthesis would decrease >> that would have some beneficial effect that **we use therapeutically**, and other **unwanted side effects**

Inflammatory pathways



Check next slide for further explanation, gonna be a long ride, hope you're ready ;).

Inflammatory pathways pt 2

once we have a stimulus that causes a disruption of the cell membrane >> the enzyme phospholipase converts some phospholipids to arachidonic acid which is worked on by two pathways:

the **cyclooxygenase pathway** or **the lipoxygenase pathway** .

1. The cyclooxygenase pathway produces prostaglandin ,thromboxane and prostacyclin all of these are proteinoids
2. The lipoxygenase pathway produces leukotrienes which are involved in inflammation. For example; leukotriene b4 is associated with attraction or activation of phagocytes, leukotrienes C ,D &E can cause alteration of vascular permeability, a bronchial constriction and increase secretion leading to bronchospasm, congestion and mucus plugging.

now focusing on the **cyclooxygenase pathway**, the prostaglandins also can cause modulation of the leukocyte to activate the inflammatory pathways. In addition to that they cause changes in the bronchial tree causing increased edema, permeability ,increased constriction and increased secretion.

Inflammatory pathways pt 3

- 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.

Inflammatory pathways pt 4 “sorry”

➔ “red circles in slide 9”

we have some drugs that target all these different pathways :

1. Starting upstream the phospholipase enzyme is inhibited by corticosteroids.

2. The lipoxygenase enzyme is inhibited by lipoxygenase inhibitors.

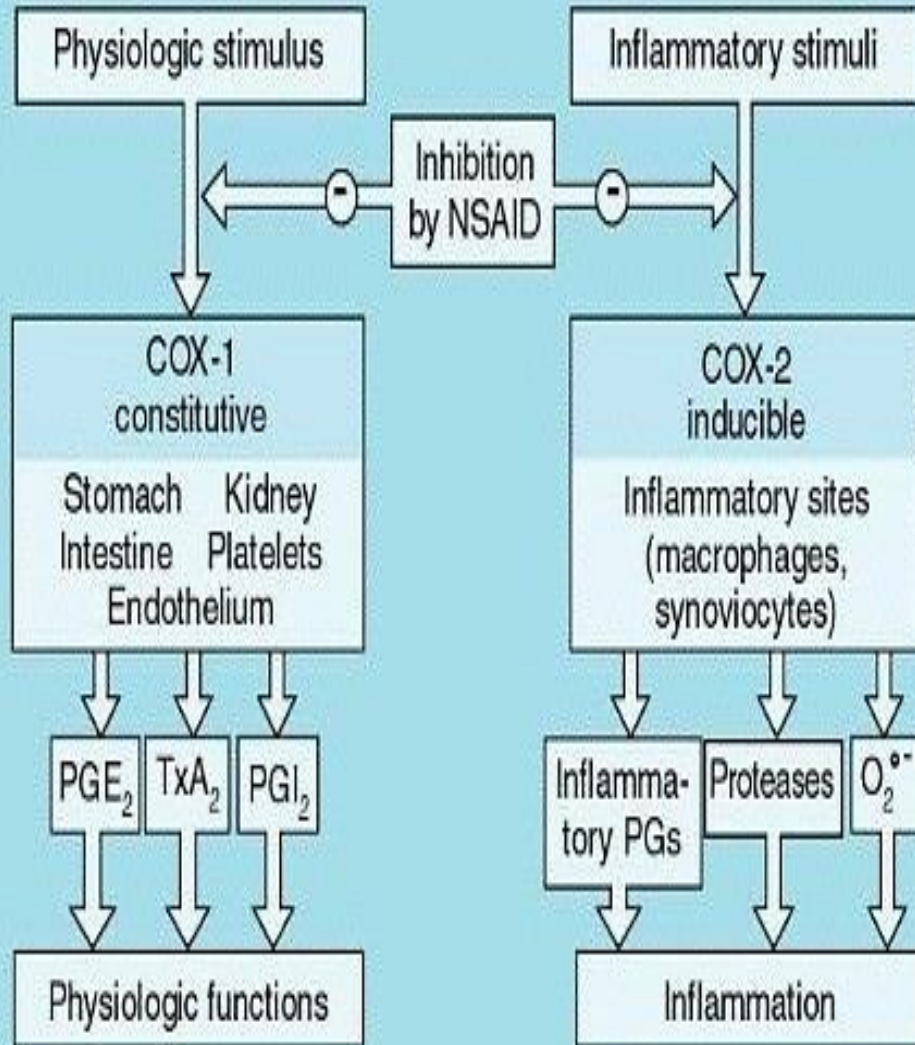
3. The cyclooxygenase enzyme which can be inhibited **by non-steroidal anti-inflammatory drugs or aspirin**. Thus, by blocking this pathway we will have less prostaglandin synthesis and less modulation of the inflammation .

we have **two isoforms of cyclooxygenase enzyme** :

COX-1 which is existing in the tissues as a constitutive form.

COX-2 which is in an inducible form, mainly present at the site of inflammation when we have a stimuli such as cytokines to produce inflammatory prostaglandin, proteases and superoxide.

Inhibiting both isoforms will inhibit the production of their products which are prostaglandins.



Jump to the next slide for more notes!!

Notes for prev slide :

- ❖ For COX-1 we have production of **thromboxane & prostacyclin** which have important physiological functions.
- ❖ when we inhibit prostaglandins not only do we inhibit the inflammatory pathways, **but we will also lose some important functions that they target.**

Example : In the stomach **prostaglandin E** is associated with protecting the stomach from excessive acid secretion, it causes increase in the **mucus protection** of the stomach and lowers acid secretion from the parietal cells.

- when we inhibit COX-1 in the stomach >> over secretion of HCl or stomach acidity >> lower protection of the mucous layer in the stomach; therefore, we **see GI irritation** side effects when using these drug .

➤ **Solution ?**

If we mainly inhibit the COX-2 we can avoid these side effects on the stomach to only have the beneficial ones by inhibiting inflammatory prostaglandins and thus inhibiting inflammation. “inhibition of COX-2”.

* we're going to be talking a little bit later about COX -2 selective inhibitors, because even though they were tailored to decrease some of the side effects associated with COX-1 inhibition, they have some distinct side effects of their own *

Again to revise about Cyclo-oxygenase (COX)

- It comes in two isoforms 1 and 2.
- 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)

share common activities in inhibiting:

pain

fever

Inflammation

The Key point

By inhibition of cyclo-oxygenase enzymes COX1 & COX2.

- **COX:**
- **COX-1** is involved in tissue homeostasis, platelet aggregation, gastric cytoprotection.
- **COX-2** is responsible for the production of mediators of inflammation.

NSAIDs

An anti-inflammatory action by:

- (1) decrease Vasodilator PG (PGE_2 , PGI_2) leads to less vasodilatation so, indirectly causes less edema.
- (2) The inhibition of activity of adhesion molecule.
- (3) Accumulation of inflammatory cells is also reduced.

NSAIDs

An analgesic effect happens because of “How do they reduce pain ?”:

- Decreased prostaglandin generation means decrease sensitivity of **nociceptive** nerve endings to inflammatory mediators.
- Relief of **headache** is due to decreased prostaglandin-mediated vasodilatation **in the brain**.

An antipyretic effect “How they reduce FEVER ?”:

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**.

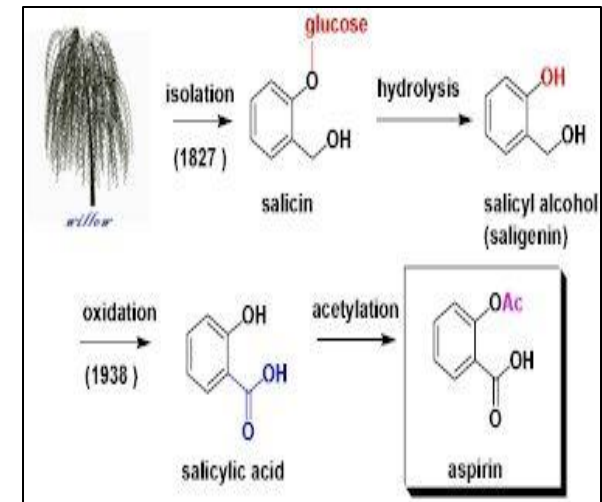
Classification

- **Non-selective COX inhibitor**
- **Selective COX inhibitor**

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 the **most** commonly used and is the drug to which all other anti-inflammatory agents are compared to **aspirin** because it is the prototype of this group
- ❑ It's a modified natural source, comes from **salicylic acid** (**salicin**) which is one of the important constituents of the bark of the willow tree (لحاء شجرة الصفصاف).

These natural products have been used a long time ago by ancient Chinese, they used to use the bark of the willow tree to ease up pain and inflammation, they didn't know what were the constituents of it at that time. later early in the 20th century, a scientist "Hoffman" synthesized **acetyl salicylic acid** from the salicin, which is present in the bark of willow tree, and this was the first use of these agents in inflammatory condition. He developed this drug to use it for treatment for his dad who had rheumatoid arthritis.



Mechanism of action

- ▶ Aspirin is a weak organic acid that is unique among the NSAIDs in that it **irreversibly** inactivates cyclooxygenase “all the other NSAIDs are reversibly acting”
- ▶ **How is it metabolized in the body ?** Aspirin is rapidly **deacetylated** by esterases in the body producing **salicylate**, which has anti-inflammatory, antipyretic and analgesic effects.

Effects of Aspirin

- ▶ 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

ACTIONS

- ▶ The NSAIDs, including aspirin, have three major therapeutic actions, they reduce **inflammation** (anti-inflammation), **pain** (analgesia), and **fever** (antipyretic).

1. 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. **so when we inhibit the production of this prostaglandin, we will desensitize the nerve ending and thus decrease the pain sensation**
- ✓ It's used for the management of pain of low to moderate intensity arising from musculoskeletal disorders rather than that arising from the viscera. **so it's mainly used for muscle pain, headaches and bone pain BUT visceral pain or deep pain usually requires a much higher efficient treatment, and we can do that by **opioids**.**

2. Antipyretic action:

- ✓ Fever occurs when the set-point of the anterior hypothalamic thermoregulatory center is elevated.
- ✓ impeding **“inhibiting”** PGE₂ synthesis and release resets the hypothalamus toward normal.
- ✓ it rapidly lowers the body temperature of febrile patients
by increasing heat dissipation as a result of peripheral vasodilation and sweating.
- ✓ Aspirin has no effect on normal body temperature. if you give these agents to a patient with fever, he will have a reduction in his fever. But if you give it to a normal patient, temperature won't decrease below normal levels.

3. Respiratory actions:

- ✓ At therapeutic doses, aspirin increases alveolar ventilation. This results in uncoupling of 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 leading to **acidosis**

4. 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, omeprazole. “drugs used to prevent this side effect associated with the use of non-steroidal antimatter agents”

5. Effect on platelets:

- ✓ **TXA2** enhances platelet aggregation . At **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**.

Remember we said COX-1 produces thromboxane (TXA2) which enhances platelet aggregation. They found out that daily administration of a low dose of aspirin can irreversibly inhibit thromboxane production in platelet, since this drug is working irreversibly, the drug will stop after the body produces the new enzyme it was inhibiting, note that platelets lack nuclei, so they cannot synthesize a new enzyme, so the effect of aspirin on thromboxane inhibition persists for the lifetime of the platelet which is about 7 days.
It can result in prolonged bleeding time so we must pay attention to that.

6. 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 except aspirin

COX-1 can induce the production of PGE₂ and prostacyclin “PGI₂” these are responsible for maintaining renal blood flow. So when we inhibit COX-1 in the patient, we also inhibit the production of these prostaglandin >> this could lead to **interstitial nephritis** or a **kidney injury** because of reduction of renal blood flow.

Additionally, the effect of prostaglandins inhibition can result in retention of sodium and water which may lead to edema and hyperkalemia.

Therapeutic uses

Anti-inflammatory, antipyretic, and analgesic 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. -any kind of pain associated with the musculoskeletal system

External applications:

- ▶ Salicylic acid is used topically to treat corns and warts. because of its keratolytic ability.

Cardiovascular applications:

Aspirin is used to inhibit platelet aggregation. Low doses are used **prophylactically** to

- 1) Reduce the risk of recurring transient ischemic attacks (**TIAs**) and stroke or death

we see many patients with history of cardiovascular disease, hypertension or elderly with diabetes all are prescribed aspirin due to its prophylactic effect ,so it provides protection from ischemia or other thrombotic events.

- 2) reduce the risk of death in those having an acute **myocardial infarction or angina**

pharmacokinetics

Administration and distribution:

- ▶ After oral administration, the un-ionized salicylates are passively absorbed from the **stomach** and the **small intestine**
- ▶ **Rectal administration using suppository**, **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 or 12 years old) with varicella (chickenpox) or influenza [a viral infection in general] to prevent **Reye's** syndrome.

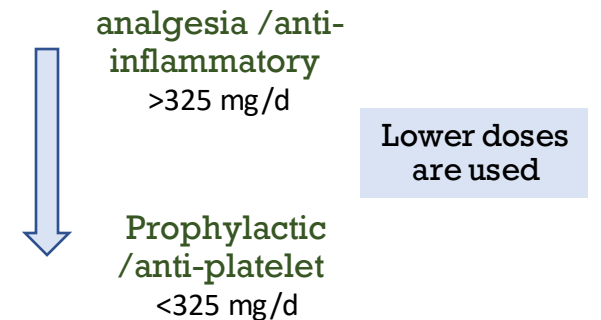
Reye's syndrome: causes fatal disorders, the underlying reason is unknown.

Therefore, salicylic -containing drugs should be avoided in pediatrics younger than 15 who are suspected to have viral infection. Instead, a much safer option is used which is paracetamol.

Dosage:

we usually use a higher dose in Aspirin than that used for the anti-platelet activity.

- ▶ 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



"memorizing the doses of each of the different drugs is not required"

Fate:

- ▶ 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.

Adverse effects

Gastrointestinal:

- ▶ The most common GI effects of the salicylates are **epigastric distress**, nausea, and vomiting.
- ▶ Microscopic **GI bleeding** is almost universal in patients treated with salicylates.
- ▶ 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. (1 week)

Respiration:

- ▶ In toxic doses, salicylates cause respiratory depression and a combination of uncompensated respiratory and metabolic **acidosis**.

Metabolic processes:

- ▶ Large doses of salicylates **uncouple oxidative phosphorylation**. The energy normally used for the production of adenosine triphosphate is dissipated as heat, which explains the **hyperthermia** caused by salicylates when taken in toxic quantities

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 or paracetamol instead of aspirin

▶ Drug interactions:

- ▶ Salicylate is 90 to 95 percent protein bound -binds to plasma protein like albumin- 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 **therefor having drug-drug interaction with other protein bound drugs.**

So we need to be careful when co-administrating aspirin with one of them
[warfarin=anti-coagulant] or [phenytoin =anti-epileptic drug]

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

- ▶ 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.

sometimes the use of low doses of aspirin during first trimester of pregnancy is encouraged in women who have experienced miscarriage due to formation of antibodies resulted in fetal rejection, administration of aspirin will increase circulation to fetus .

Toxicity:

- ▶ **The mild form is called salicylism**
- ▶ nausea, vomiting, marked hyperventilation, headache, mental confusion, dizziness, and tinnitus (ringing or roaring in the ears).
- ▶ Ingestion of as little as 10 g of *aspirin* can cause death in children.
- ▶ In serious cases, mandatory measures include the intravenous administration of **fluid, dialysis**
- ▶ correction of **acid-base** and electrolyte balances.

Propionic acid derivatives

Other non-steroidal anti-inflammatory drugs

- ▶ **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 irritation** , ranging from dyspepsia to bleeding.
- ▶ Side effects involving the central nervous system (**CNS**), such as headache, tinnitus, and dizziness, have also been reported.

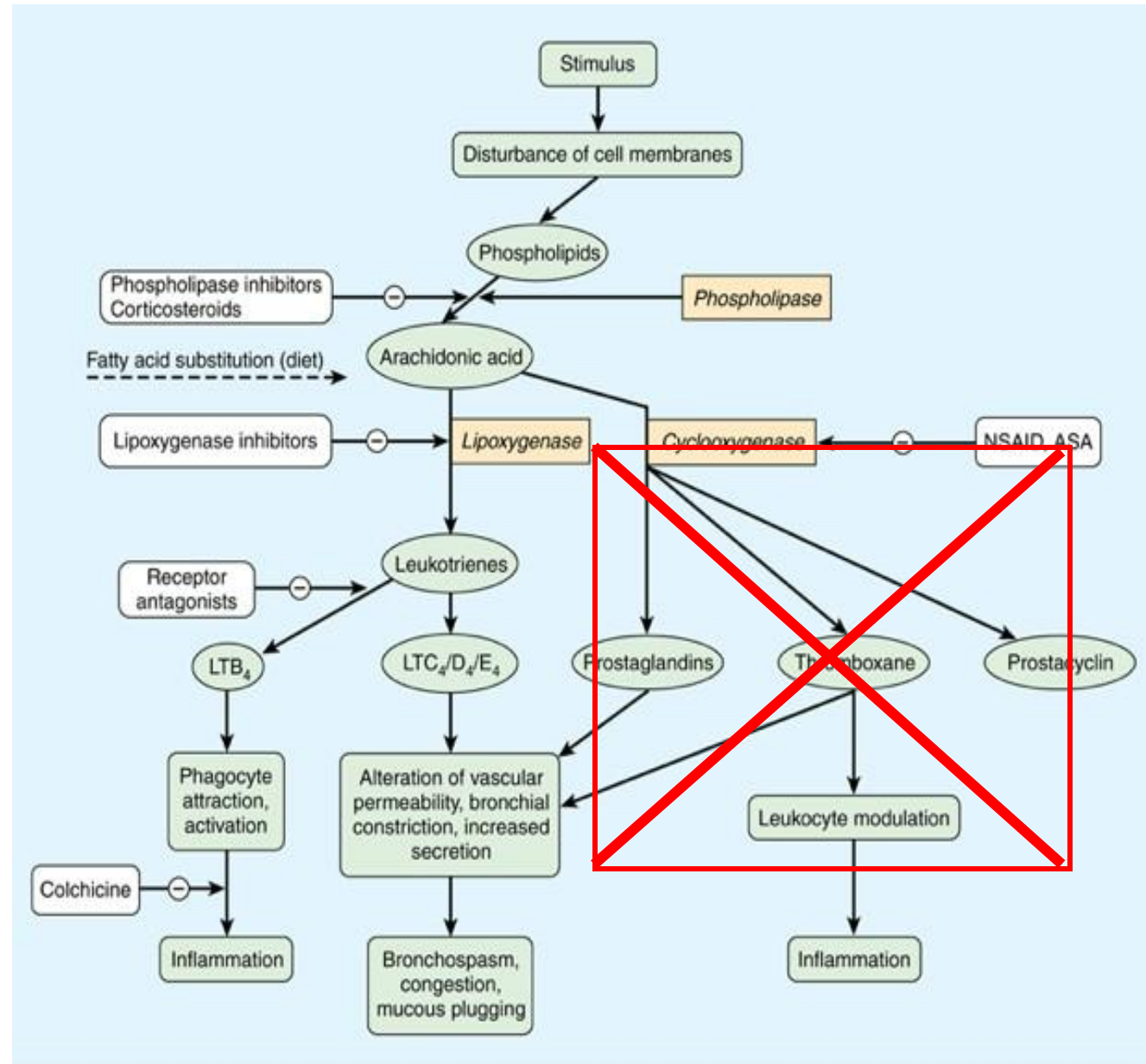
Naproxen and Ibuprofen

- ▶ Pregnancy : category C, category D **from the 3rd trimester.**
- ▶ Increase the risk of cardiovascular thrombotic event, MI [[myocardial infarction](#)] and stroke.
- ▶ Increase risk of GI bleeding.
- ▶ [The dose of Ibuprofen should](#) not exceed 3200mg/day, taken with food or with water to avoid GI effect.
- ▶ In Asthmatic patient [it is contraindicated or it should be given with caution.](#)

Why is it contraindicated for asthmatic patients?

Remember the 2 arms of arachidonic acid pathway [cyclooxygenase - lipoxygenase] if we inhibit one of them the other will show more activity, due to increase in substrate availability.

Here prostaglandin synthesis is inhibited so more leukotrienes will be produced. leukotriene production can exaggerate an asthmatic response because it causes bronchospasm, bronchial edema and increased secretion.



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

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 so it is considered somewhat selective inhibitor to COX2 , and at low to moderate doses shows less GI irritation than *piroxicam*.

Fenamates

- ▶ **Mefenamic**
- ▶ *have **no advantages** over other NSAIDs as anti-inflammatory agents. therefor all have the same mechanism of action and effects.*
- ▶ 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 , ketorolac**

❑ 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 [**therefor it is used in joints inflammation**], and the primary route of excretion for the drug and its metabolites is the **kidney**.

Diclofenac sodium

- ▶ oral administration Used PO 50mg after food, Intramuscular injection I.M. inj 75mg
- ▶ Diclofenac potassium is prompt release and has quicker onset where as the Diclofenac sodium is delayed release.
- ▶ Pregnancy: category C
- ▶ Toxicity similar to others

Diclofenac sodium

Other side effects.

- ▶ **C/I**
- ▶ Hypersensitivity.
- ▶ Asthmatic patient.
- ▶ Patient with history of peptic ulcer.
- ▶ Metabolism: liver.
- ▶ Excretion: urine.

Selective COX-2 inhibitor

Celecoxib, Meloxicam and Rofecoxib

- ▶ 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.

Historically

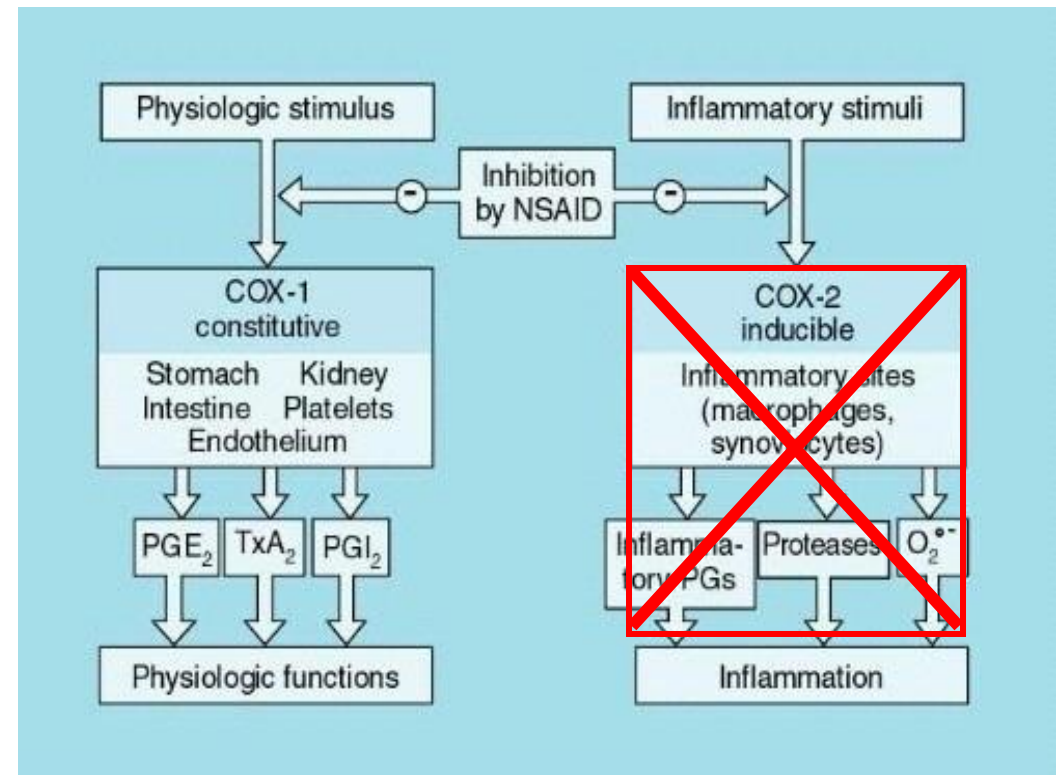
- they are developed late in 20th century
- approved in 2000
- produced drugs such as Celecoxib & Rofecoxib
- the reason behind their development is to avoid the GI side effects associated with non-selective inhibition of both COXs
- Rofecoxib was withdrawn from markets due to its association with deaths related to thromboembolic events.
- Celecoxib is still available as Celebrex.
- indicated for the use in chronic inflammatory conditions such as Rheumatoid arthritis

Side effect of Selective COX-2 inhibitor

Thromboembolic events, remember the 2 COX enzymes if one of them is inhibited, substrate availability increases for the other, therefore showing more activity

Here COX2 is selectively inhibited, COX1 will be more activated producing more of thromboxane leading to thromboembolic events.

for that reason, Celecoxib has a **black box warning** that says you have to be careful in using the drug if you are prone to thromboembolic events.



a **black box** warning is where serious side effects are written on the box of the drug to warn the patient.

Acetaminophen

distinct group of analgesics

- ▶ 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 **which is toxic for liver cells** .

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

Acetaminophen is a very safe drug, but if taken in high doses toxic metabolites will accumulate, so it is important to monitor the dose of drug that patient takes.

the recommended dose for adults is 1-2 pills every 6h [each pill with 500mg of acetaminophen] , the safe dose is up to 8 pills [4g of acetaminophen], so it is easy to exceed this limit and start to see the toxicity of drug on the liver due to accumulation of toxic metabolites.

- 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. (treatment in this situation is a drug called **Acetylcysteine** which scavenges the free radicals produced by acetaminophen, to be effective drug should be given during the first 8-12h after overdose ,otherwise hepatic necrosis will take place)
- ❑ Renal tubular necrosis may also occur.
- ❑ Periodic monitoring of liver enzymes tests is recommended for those on high-dose acetaminophen.