



Antipyretic-analgesic and Anti- inflammatory Drugs



Pain

An unpleasant experience
associated with actual or potential
tissue damage.



Outline

- NSAIDs
- Indications
- Mechanism(s) of Action
- Non-specific Cox or Cox-2
- Side-effects
- Selection



Pain Treatment

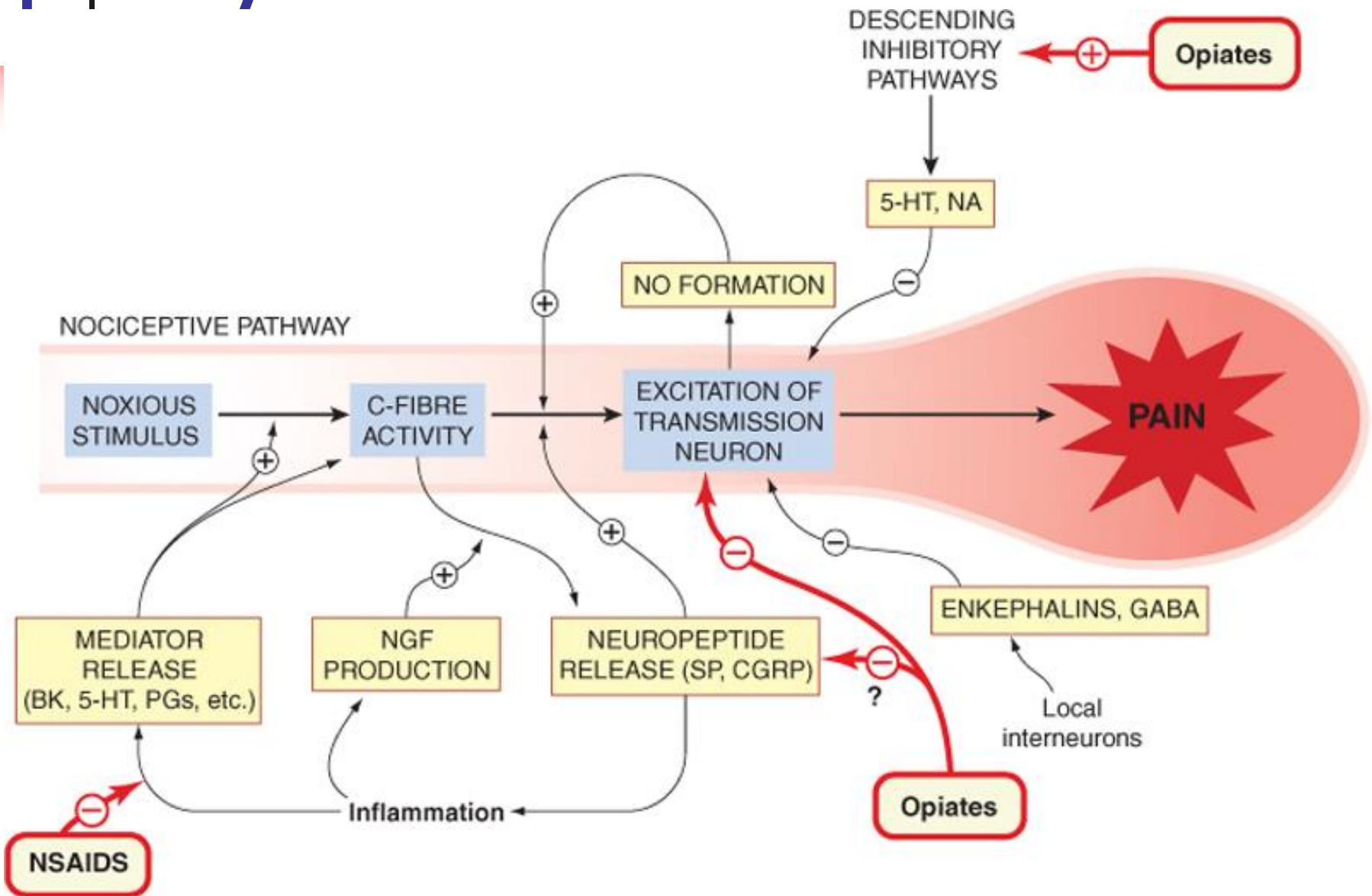
- Analgesics
- Antipyretic-analgesic and anti-inflammatory drugs*

*Pain is a disabling
accompaniment of
many medical
conditions*

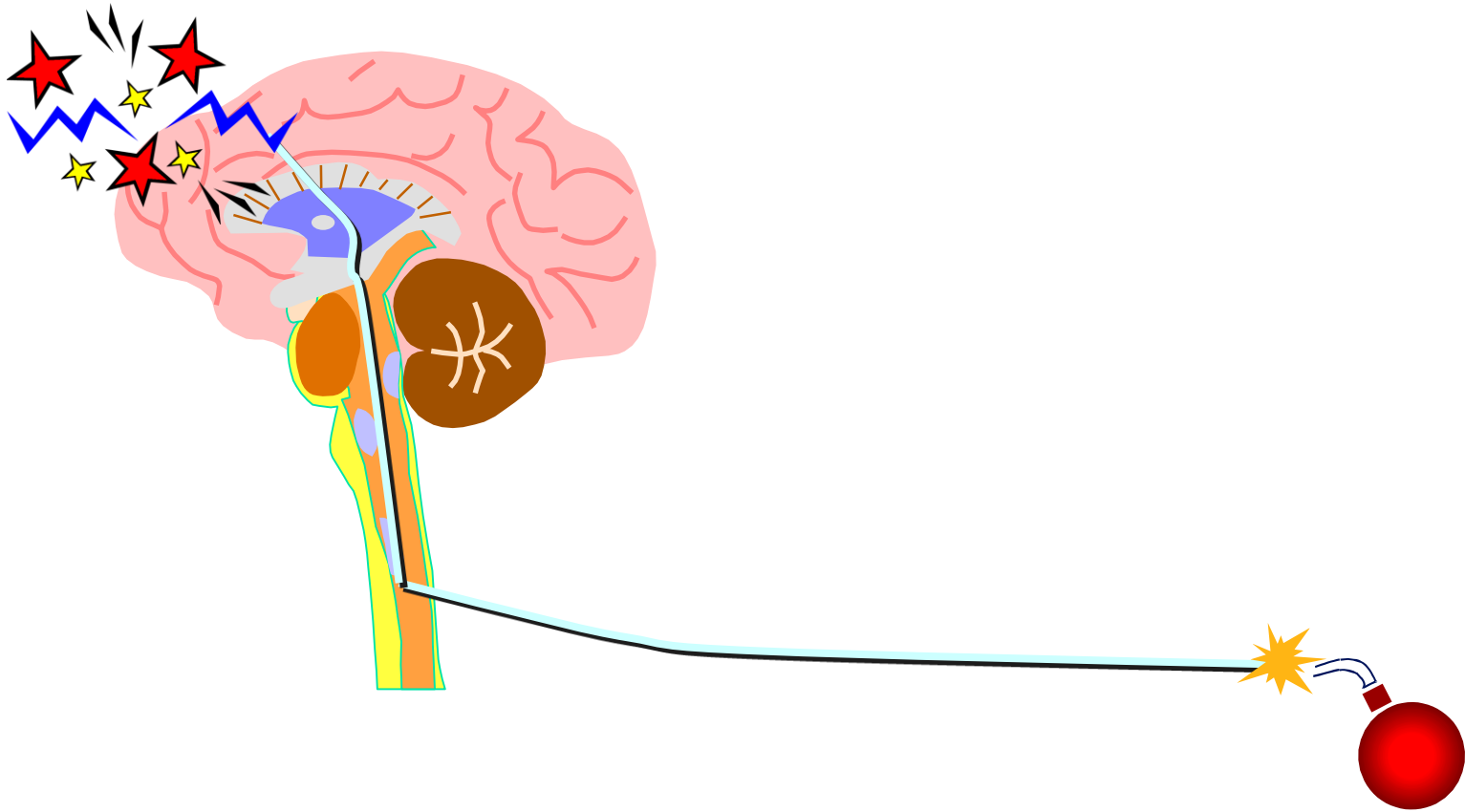
&

**Pain control is one of the most
important therapeutic priorities.**

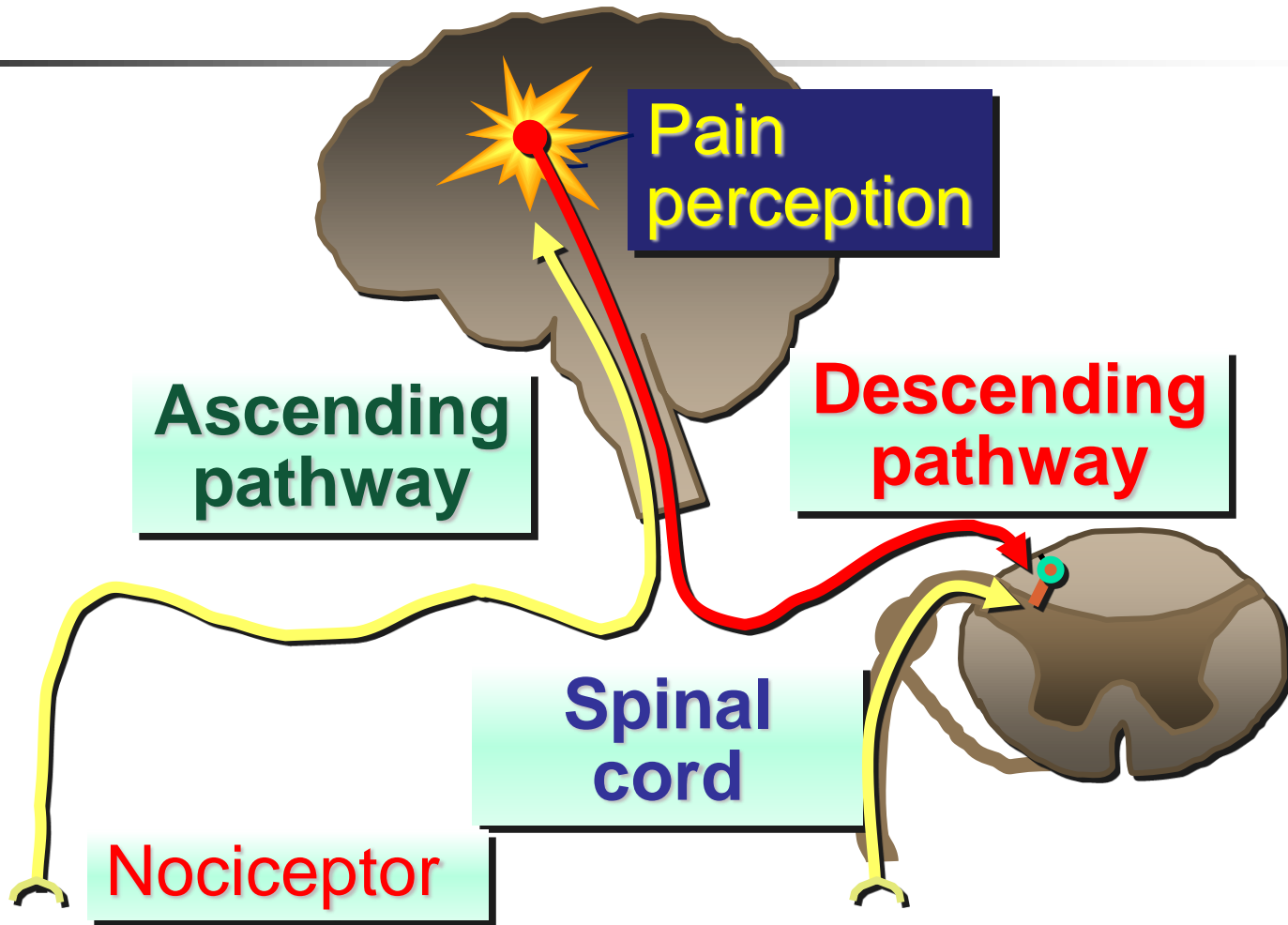
Modulatory mechanisms in the nociceptive pathway



Pain Physiology



Pain Transmission





Opportunities for Pain Treatment

- At the receptor
- Along the nerve
- At receptors in spinal column and brain

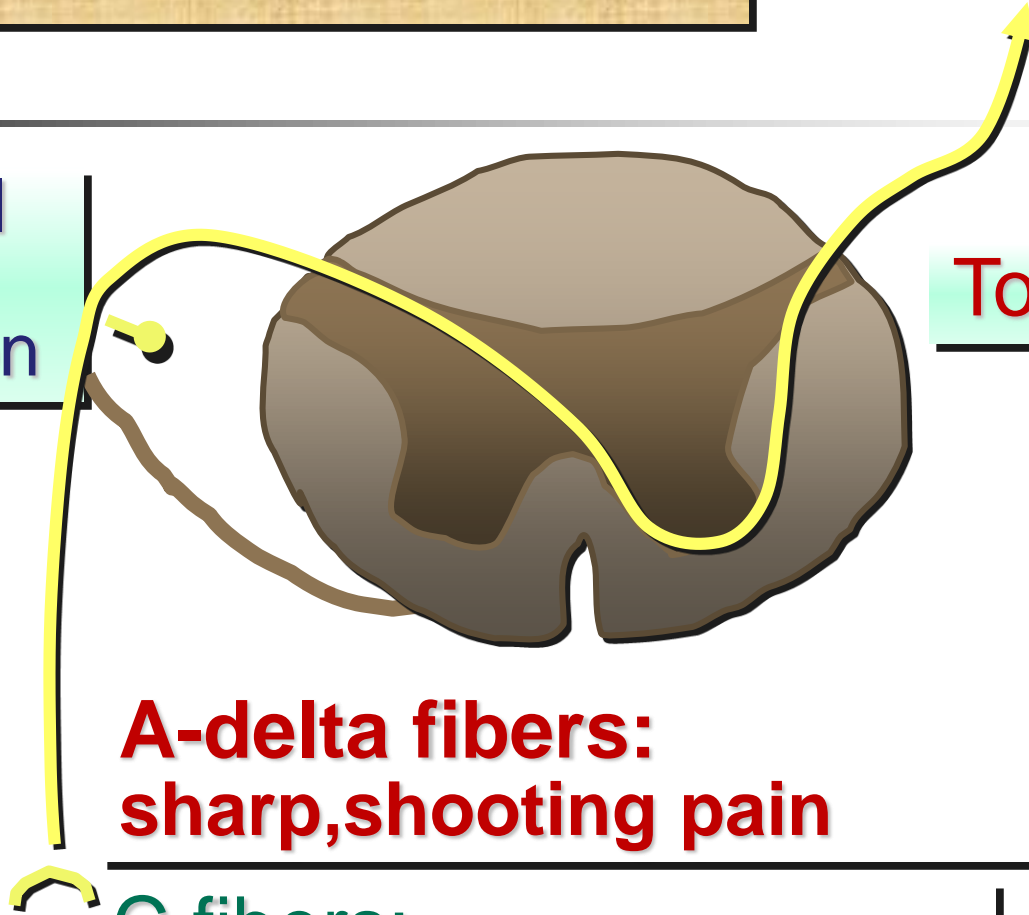
Acute vs. Chronic Pain

Dorsal
root
ganglion

To brain

A-delta fibers:
sharp, shooting pain

C fibers:
dull, aching, burning pain







Pain

- Acute Vs chronic
- Nociceptive vs Neuropathic

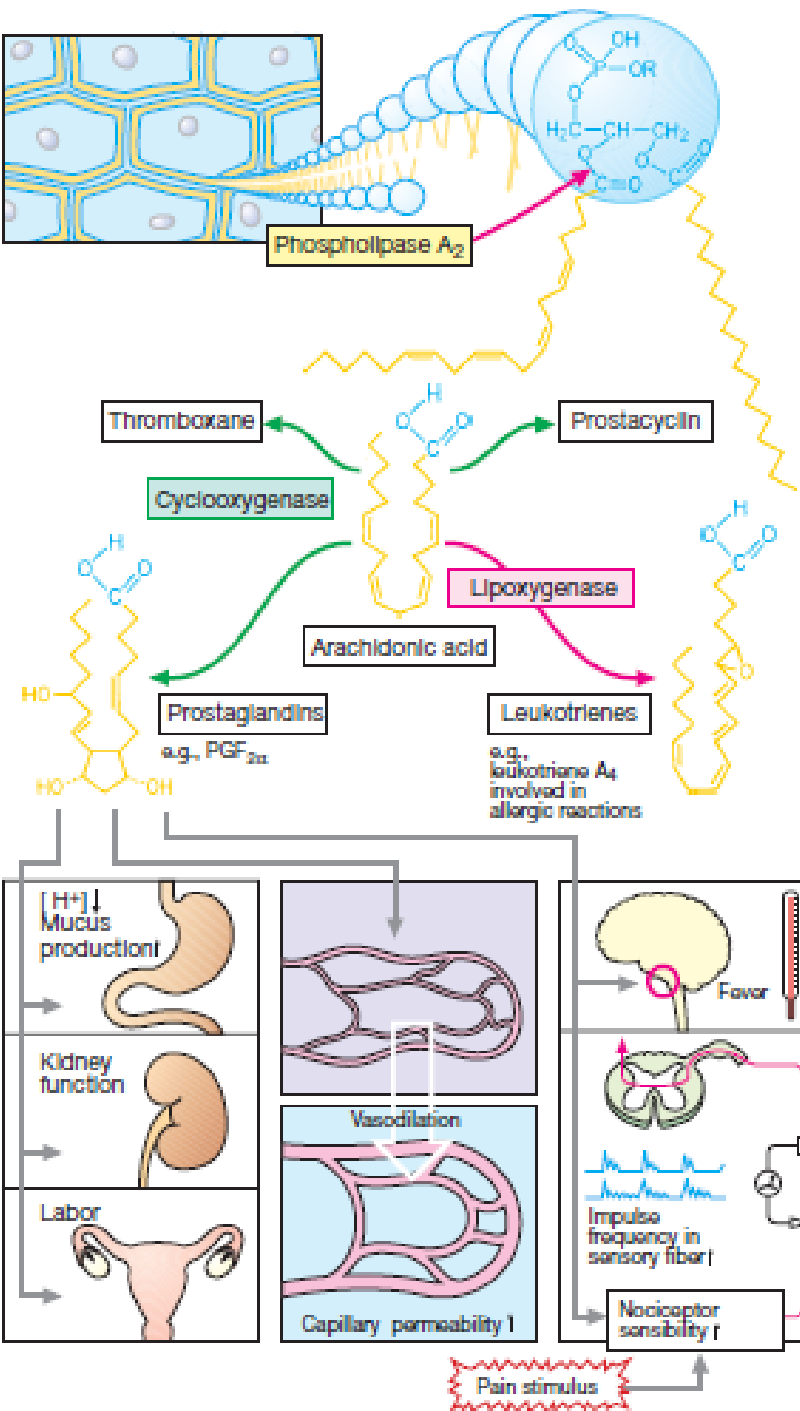
Acute pain -well accounted for in terms of *nociception*

An excessive noxious stimulus giving rise to an intense and unpleasant sensation.

In contrast

chronic pain states associated with **aberrations** of the normal physiological pathway

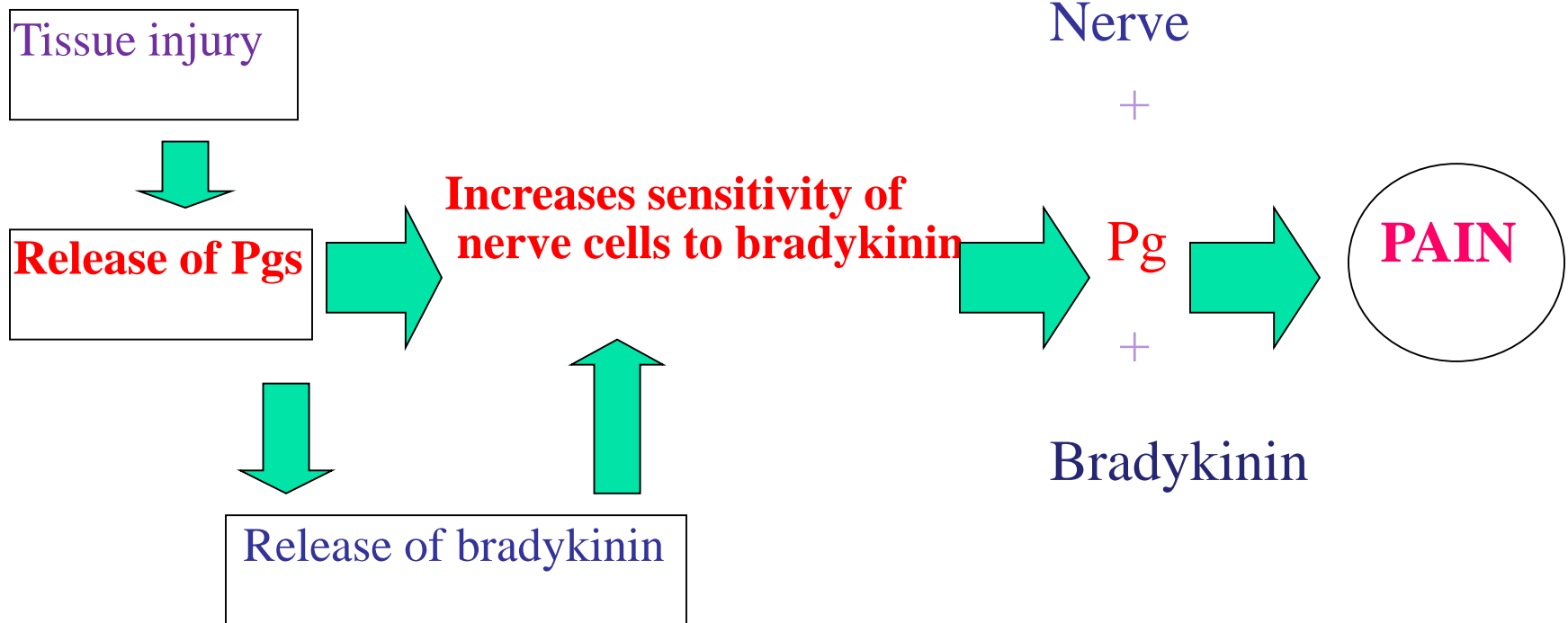
1. *hyperalgesia* (an increased amount of pain associated with a mild noxious stimulus),
2. *allodynia* (pain evoked by a non-noxious stimulus)
3. *spontaneous pain* without any precipitating stimulus.



ORIGIN AND EFFECT OF PROSTAGLANDINS

Physiology of Pain

- Pain receptors (nociceptors) activated by noxious stimuli





Ideal Analgesic

- Relieves severe pain in non-sedating doses
- Effective orally and parenterally (and any other route)
- Rapid onset and long duration of action
- Minimal side effects and toxicity
- Tolerance and dependence free



Principles of Pain Management

- Gold standard: patient determines severity
- Pain kills
- Pain is real
- Balance pain relief with side effects of drugs



Antipyretic-analgesic and Anti-inflammatory Drugs

- Non-steroidal anti-inflammatory drugs, NSAIDs.
- Aspirin-like drugs.

NSAIDs

- Non-steroidal anti-inflammatory drugs
- Compare with opioid analgesics (usually required for moderate to severe pain; narcotic; usually addictive) e.g. morphine; pethidine
- Compare with paracetamol which has very little or no anti-inflammatory activity
- Most are organic ACIDS





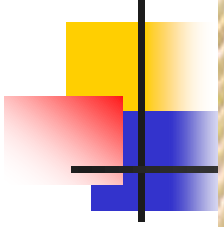


WILLOW BARK

NATURE'S ASPIRIN

history of aspirin

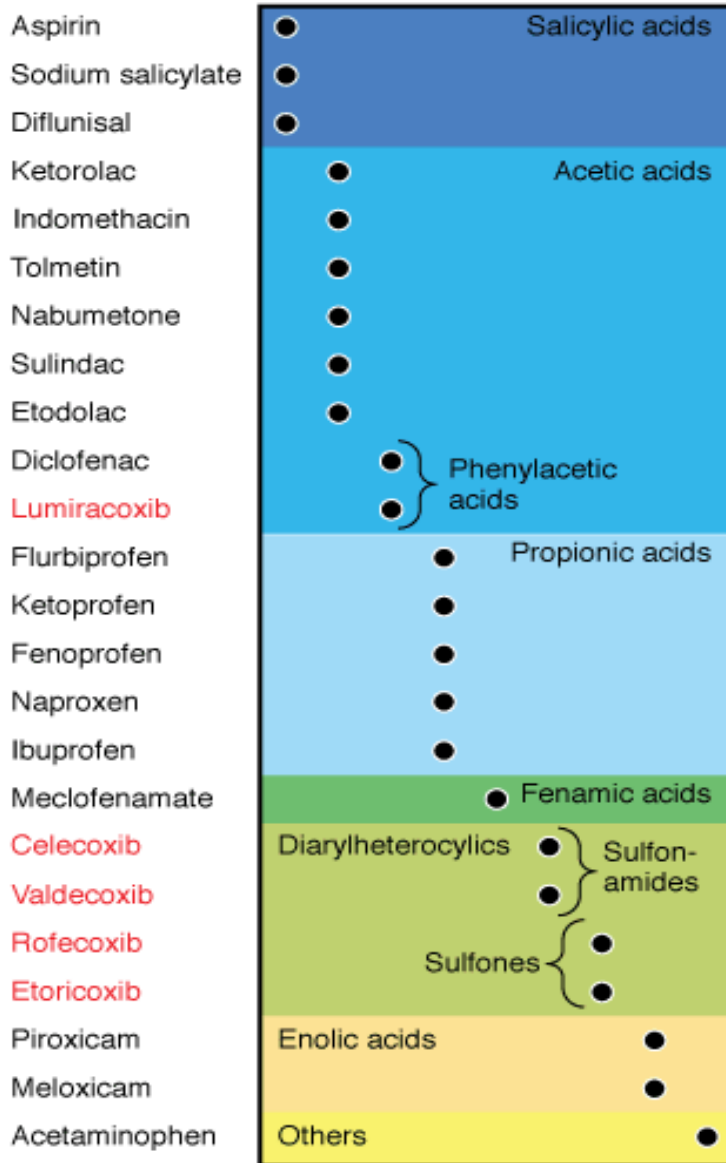
- interesting example of the translation of a compound from the realm of herbal folklore to contemporary therapeutics.
- Use of willow bark and leaves to relieve fever attributed to Hippocrates.
- Soon used for rheumatic fever, gout ,as a general antipyretic.
- Hoffmann, a chemist at Bayer Laboratories, sought to improve the adverse-effect profile of salicylic acid (which his father was taking with difficulty for arthritis).
- Hoffmann came across the earlier work of the French chemist, Gerhardt, who had acetylated salicylic acid in 1853
- Hoffmann began testing acetylsalicylic acid (ASA) in animals by 1899—the first time that a drug was tested on animals in an industrial setting—and proceeded soon thereafter to human studies and the marketing of aspirin.



HISTORY OF Paracetamol

- Acetaminophen first used in medicine by von Mering in 1893, recognized as the major active metabolite of phenacetin..
- employed in analgesic mixtures until implicated in analgesic-abuse nephropathy, hemolytic anemia, and bladder cancer; it was withdrawn in the 1980s

A Chemical similarity (arbitrary scale)

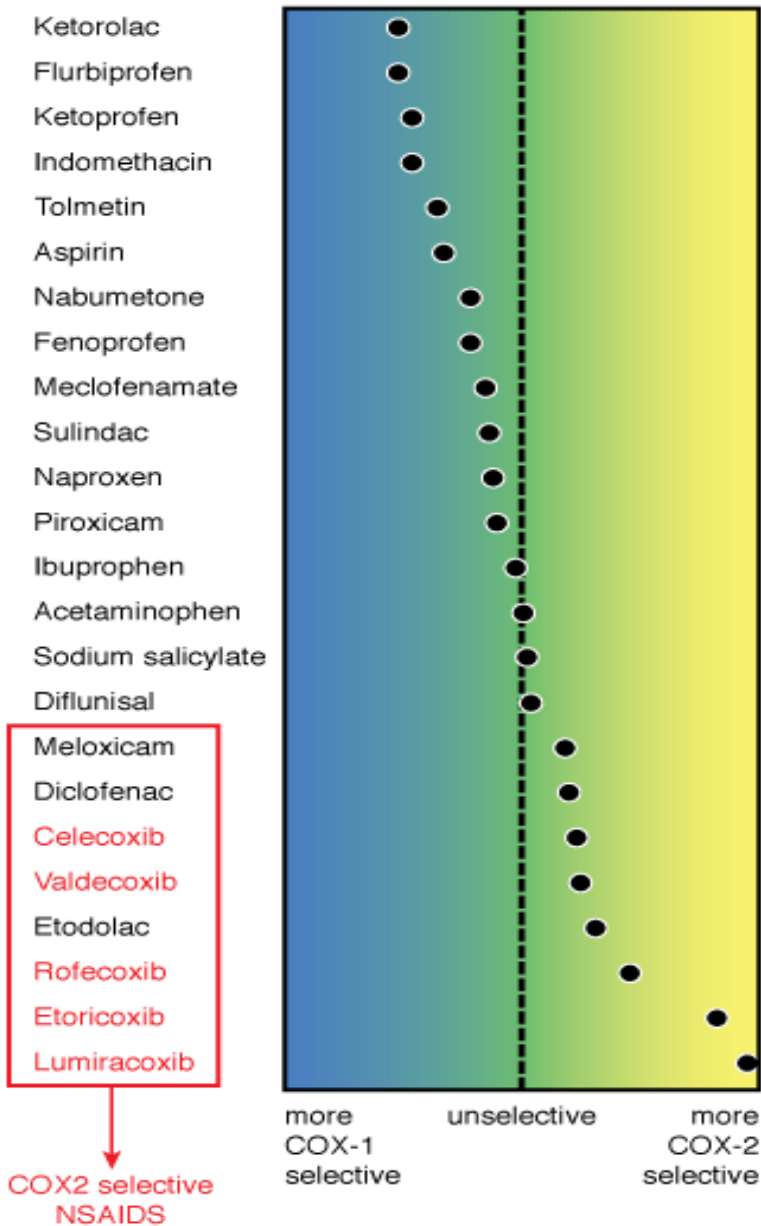


CHEMICAL CLASSIFICATION

Black: tNSAID

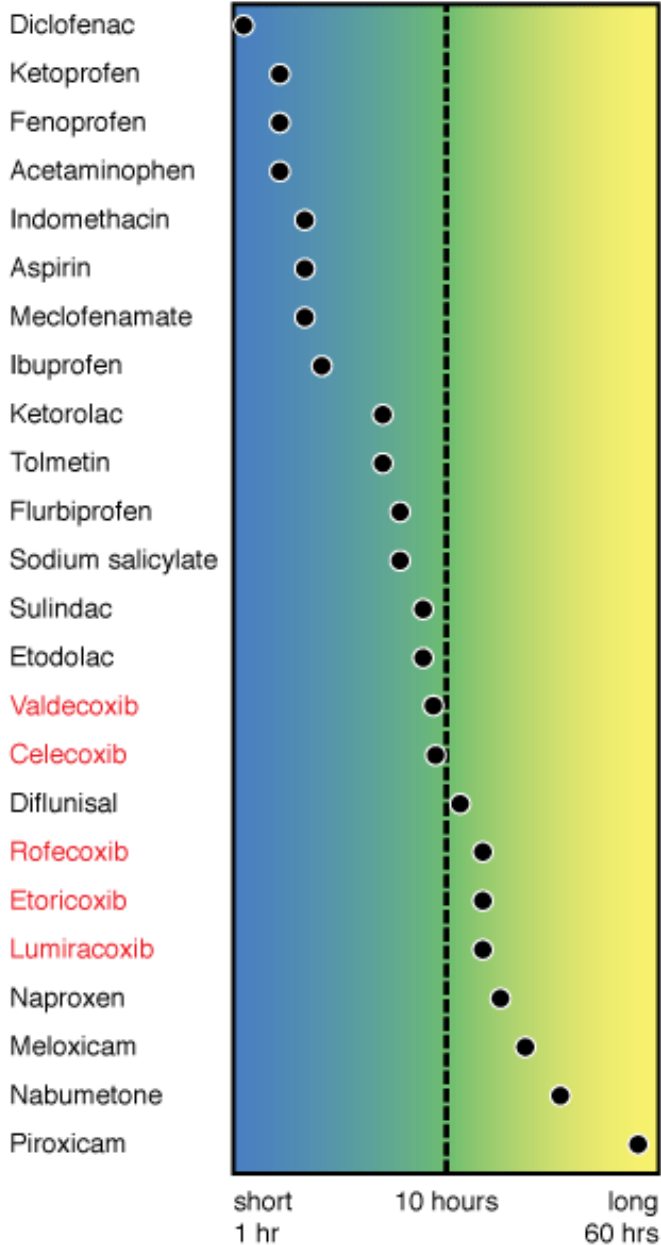
Red: COX-2 inhibitors

B COX isoform selectivity (log scale)



CLASSIFICATION BASED ON COX SELECTIVITY

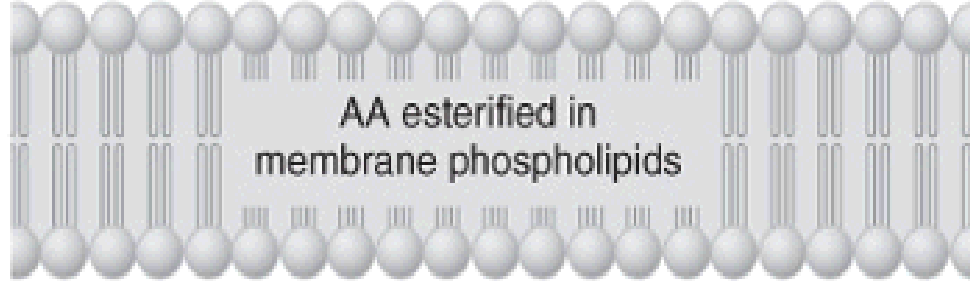
Plasma $t_{1/2}$ (log scale)



CLASSIFICATION BASED ON HALF LIFE

Antipyretic-analgesic and anti-inflammatory drugs

- **Be grouped in different classes according to their chemical structures**
- **Share similar pharmacological effects mechanism of action and adverse effects**
- **They all inhibit the biosynthesis of PGs**



Diverse physical, chemical, inflammatory and mitogenic stimuli



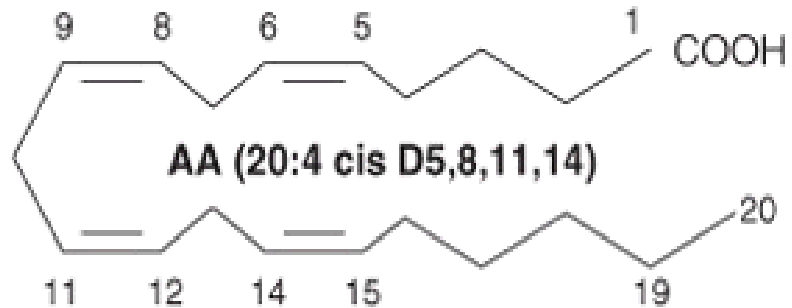
Phospholipase A₂

Free radicals

Isoprostanes

Epoxyeicosatrienoic acids (EETs)

Cytochrome p450



Lipoxygenases (LOX)

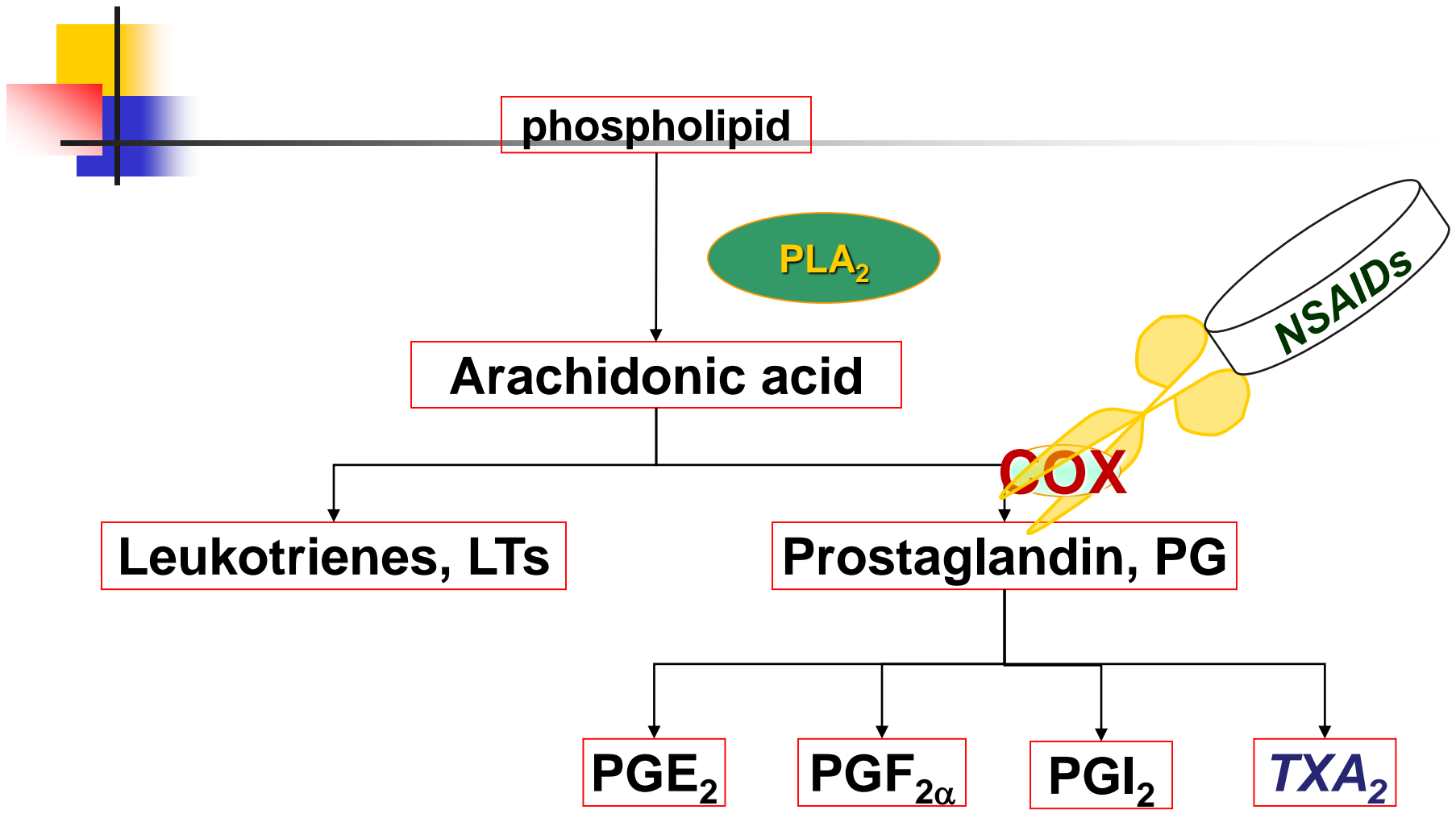
Cyclooxygenases (COX)

HETEs
Leukotrienes
Lipoxins

Prostaglandins
Prostacyclin
Thromboxane

Prostanoids

Mechanism of NSAIDs



At higher concentrations ,NSAIDs

- reduce production of superoxide radicals,
- induce apoptosis
- inhibit the expression of adhesion molecules,
- decrease NO synthase,
- decrease pro-inflammatory cytokines (e.g., TNF-, IL-1),
- modify lymphocyte activity

Acetaminophen: M/A

- weak anti-inflammatory agent (1000mg).
- associated with a reduced incidence of GI adverse effects.
- At this dose, inhibits both COXs by 50%.
- The ability of acetaminophen to inhibit the enzyme is conditioned by the peroxide tone of the immediate environment (Boutaud et al, 2002).
- sites of inflammation contain increased concentrations of leukocyte-generated peroxides.

Irreversible COX Inhibition by Aspirin

- Covalently modifies COX-1 and COX-2,
- Acetylates a serine residue in COX1
- duration of aspirin's effects -turnover rate of COXs in different target tissues.
- Non-aspirin NSAIDs- inhibit the COX enzymes **competitively**, relates to the time course of drug disposition.
- most notable in platelets, which, being anucleate, have a markedly limited capacity for protein synthesis.

- Inhibition of platelet COX-1–dependent TxA₂ cumulative with repeated doses of aspirin (at least as low as 30 mg/day)
- takes 8-12 days—the platelet turnover time—to recover fully once therapy has been stopped.

An important fact.....

- Unique sensitivity of platelets to inhibition by **low doses of aspirin** related to their presystemic inhibition in the portal circulation before aspirin is deacetylated to salicylate on first pass through the liver (Pedersen and FitzGerald, 1984).
- Salicylic acid- no acetylating capacity.
- weak, reversible, competitive inhibitor of COX
- Forms the basis for the use of the drug in prevention and treatment of arterial thrombosis

The Different biological Activities of the Products of AA

- **PGI₂: vasodilators, opposes platelet aggregation**
- **TXA₂: platelet aggregation , vasoconstrictor. mitogenic**
- **PGE₂: induce inflammation fever and pain vasodilation and hyperalgesia**
- **PGF_{2α}: bronchial constriction and vasoconstriction.**

The Different biological Activities of the metabolites of AA

**LTs : Allergy, bronchoconstriction
chemotaxis**

**↑ vascular permeability & induce
inflammation**

The different anti-inflammatory mechanism

- **Glucocorticoids : inhibit PLA_2**
- **NSAIDs: inhibit COX and reduce the production of PGs**

Important features

1. Majority of NSAID compounds are organic acids with relatively low pK_a values.
2. well absorbed orally, highly bound to plasma proteins, and excreted either by glomerular filtration or by tubular secretion.
3. accumulate in sites of inflammation, where the pH is lower, **potentially confounding** the relationship between plasma concentrations and duration of drug effect



Role of Prostaglandins

- Inflammation
- Pain
- Fever
- Dysmenorrhea
- Thrombus Formation

Arachidonic Acid

COX-1

(constitutive)

Prostaglandins

- GI cytoprotection
- Platelet aggregation



GI effects
of inhibition



COX-2

(inducible by proinflammatory stimuli)

Prostaglandins

- Inflammation
- Pain
- Fever



local effects
of inhibition



TABLE 42-1 Comparison of COX-1 and COX-2

PROPERTY	COX-1	COX-2
Expression	Constitutive	Inducible; not normally present in most tissues Constitutive in parts of nervous system
Tissue location	Ubiquitous expression	Inflamed and activated tissues
Cellular localization	Endoplasmic reticulum (ER)	ER and nuclear membrane
Substrate selectivity	Arachidonic acid, eicosapentaenoic acids	Arachidonic acid, γ -linolenate, α -linolenate, linoleate, eicosapentaenoic acids
Role	Protection and maintenance functions	Proinflammatory and mitogenic functions

TABLE 42-1 Comparison of COX-1 and COX-2

PROPERTY	COX-1	COX-2
Induction	Generally no induction hCG can up-regulate COX-1 in amnion	Induced by LPS, TNF- α , IL-1, IL-2, EGF, IFN- γ mRNA rises 20- to 80-fold upon induction Regulated within 1–3 hours
Inhibition	Pharmacologic: NSAIDs (low-dose aspirin)	<i>In vivo</i> : Anti-inflammatory glucocorticoids, IL-1 β , IL-4, IL-10, IL-13 Pharmacologic: NSAIDs, COX-2 selective inhibitors

NSAIDs-classification



Salicylates (Salicylic acid derivatives)	Aspirin Diflusal Sodium Salicylate
Acetic Acid derivatives	Indometacin Sulindac Etodolac Diclofenac

NSAIDs -classification

Propionic Acid Derivatives	Ibuprofen Naproxen Ketoprofen Flurbiprofen
Enolic Acids	Piroxicam Phenylbutazone
Non-acidic compounds	Nabumetone

Mechanism of NSAIDs



The basis of action of NSAIDs is primarily to the inhibition of prostaglandin(PGs) synthesis.



NSAIDs

Drugs with the following properties:

- Analgesic
- Anti-inflammatory
- Antipyretic
- Antirheumatic

Pharmacological effects of NSAIDs

1. Analgesic action

mild or moderate pain following injury, disease or minor surgery, as well as chronic pain states including arthritis and cancer.

lacks unwanted adverse effects of opiates ,respiratory depression and the potential for development of physical dependence.



As analgesics....

- effective when inflammation has caused peripheral and/or central sensitization of pain perception.
- postoperative pain / pain arising from inflammation, controlled well.
- pain arising from the hollow viscera usually is not relieved.
- **An exception to this is menstrual pain.**



2. Anti-inflammatory action

Provide symptomatic relief for chronic inflammatory disorders pain, and other signs of rheumatic or rheumatoid arthritis

but

does not arrest the progression of pathological injury to tissue.

3. Antipyretic action

Resets the set-point to the normal level and lowers the elevated body temperature in patients with fever by inhibiting cytokine induced prostaglandins synthesis in the hypothalamus.

4. Antiplatelet actions

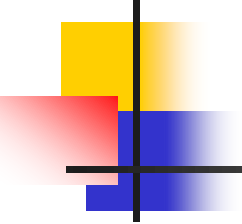
Other Nonselective NSAIDs variable antiplatelet effects.

Ibuprofen interferes with cardioprotective effects of aspirin when taken regularly

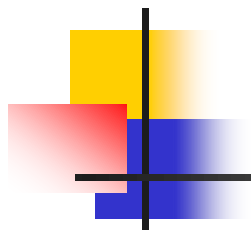
Selective Inhibition of COX 2 reduces endothelial prostacyclin allowing continued production of COX-1 derived thromboxane A_2

PROTHROMBOTIC ENVIRONMENT –increase risk of cardiovascular events

Class effect of the COXIBS

- 
-
- Importantly, even a partially recovered platelet pool—just a few days after
 - the last aspirin dose—may afford recovery of sufficient hemostatic integrity
 - for some types of elective surgery to be performed. However, such a
 - partial platelet function also may predispose noncompliant patients on

Classification of NSAIDs



**Nonselective COX
inhibitors**



**aspirin (sodium
salicylate)**

Acetaminophen

Indomethacin

Ibuprofen

Phenylbutazone

**Selective COX-2
inhibitors**



Rofecoxib

Celecoxib

Etodolac

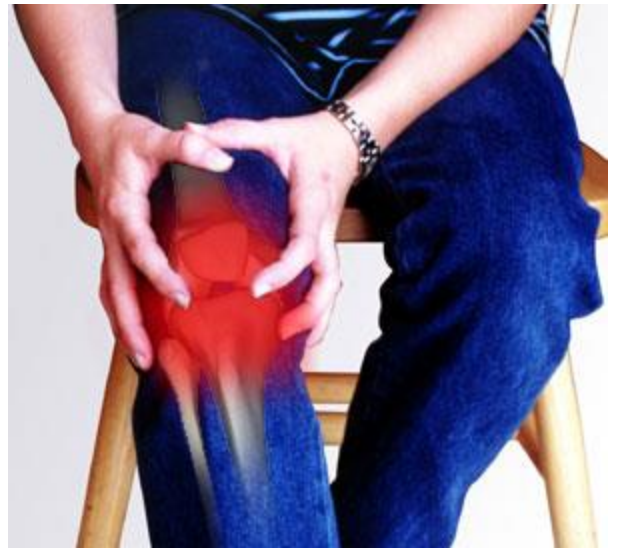
Nimesulide

Pharmacokinetics

- Weak organic acids (nabumetone)
- Well absorbed
- Food doesn't change their bioavailability.
- Metabolized in phase I and II.
- Renal, most important route of excretion.
- 98% Bound to Albumin.
- Found synovial fluid after repeating doses.

Clinical Uses

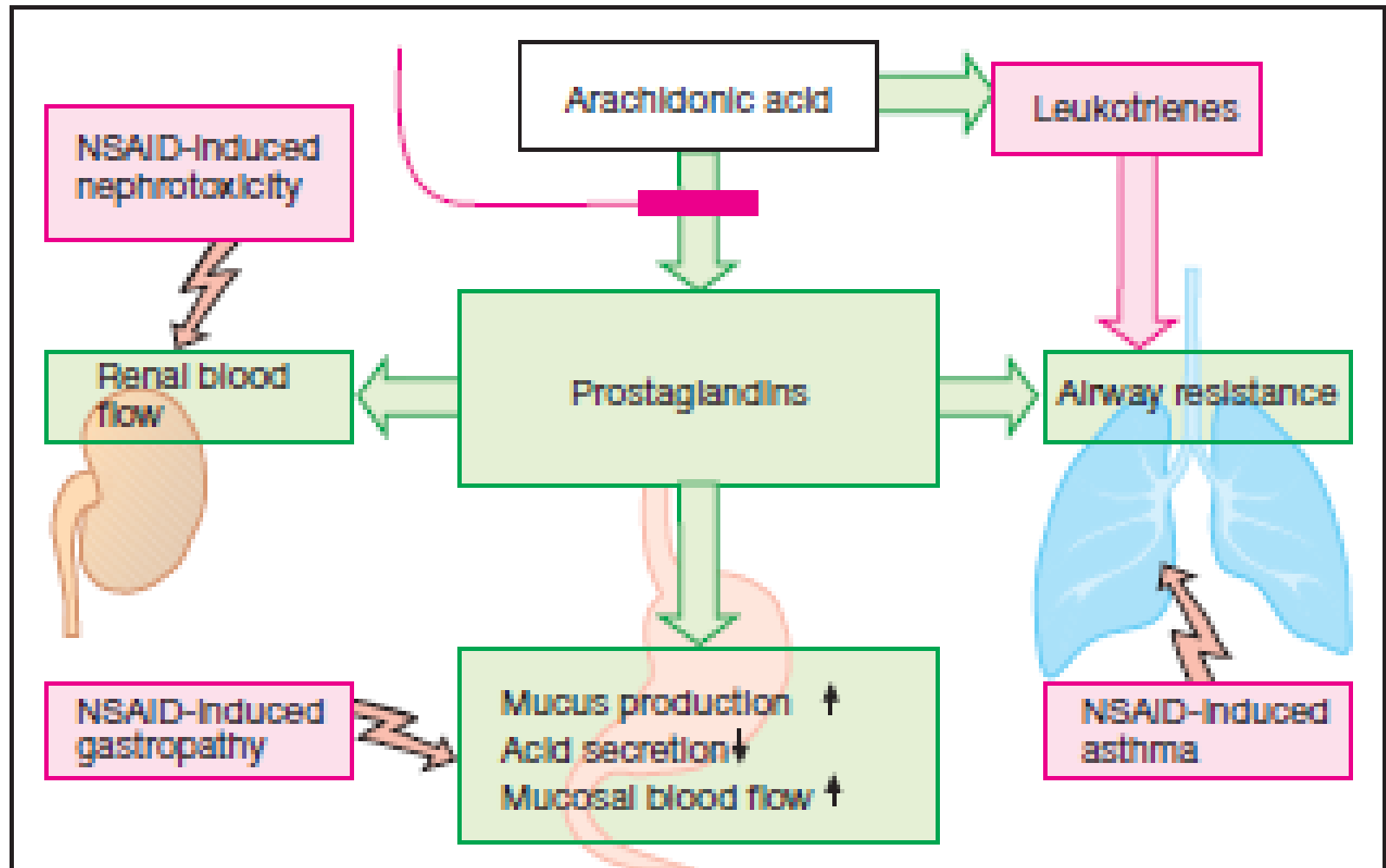
- As analgesic for mild to moderate pain, Dental pain, post operative pain, dysmenorrhoea
- Combine with opioid analgesics-cancer pain.
- As anti-inflammatory in rheumatoid arthritis rheumatic, fever and inflammatory joint conditions.
- Alzheimer's dementia



Clinical Uses

- Antipyretic, when reducing the fever is desirable.
- Prophylaxis of IHD, to ↓ incidence of coronary artery disease.
- Used in neonates to close inappropriately patent ductus
- Systemic mastocytosis
- Cancer chemoprevention-Colorectal
- Niacin tolerability.

A. Nonsteroidal antiInflammatory drugs (NSAIDs)



B. NSAIDs: group-specific adverse effects

Adverse effects of NSAID therapy

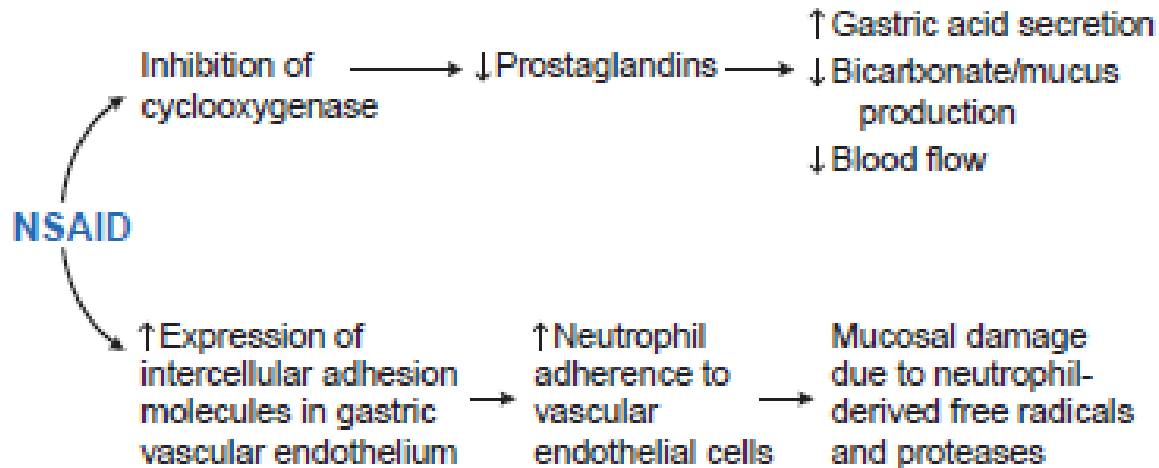
GASTRIC DAMAGE

- 15-40% complain of dyspepsia
- 5-8% duodenal ulcers
- 15-20% gastric ulcers
- 1-2% will have GI bleed

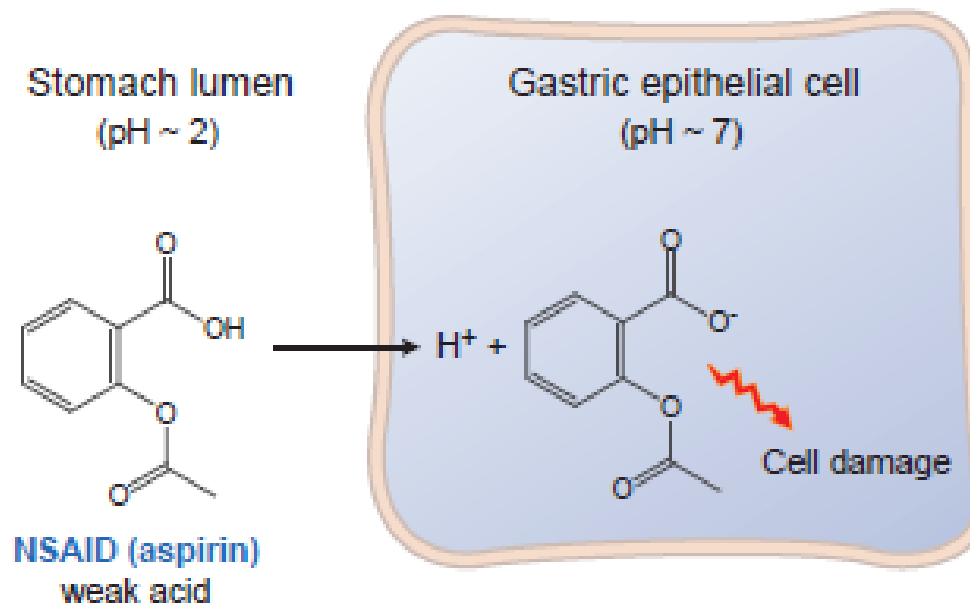
- 30-40% all **GI bleeds** attributable to NSAID

Role of NSAIDs in peptic ulcer disease

A Systemic effects



B Topical injury



Risk Factors for GI complications

- History of peptic ulcer bleed
- Use of anti-coagulants
- Use of 2 NSAIDs (includes low does ASA)
- History peptic ulcer
- High NSAID dose
- Age > 60 years?
- *H. pylori* infection
- Use of corticosteroids

So let's prevent this!



- Misoprostol- prostoglandin E1 analogue
 - Protects gastric mucosa from chemical irritation
- Proton Pump Inhibitors
 - Reduce chances of damaging gastric mucosa
- Cox-2 Inhibitor
 - Allow COX 1 to function

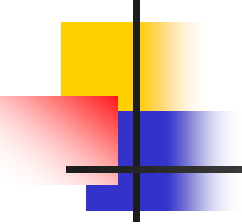


Renal effects

- prevent synthesis of PGE_2 and PGI_2
responsible for maintaining renal blood flow, especially in states where renal perfusion is dependent upon PG induced vasodilatation
- \downarrow synthesis: retention of sodium and water ,B.P \uparrow

Blood Pressure and Renal Adverse Events

- All NSAIDs have been associated with renal and renovascular adverse events. Up to 5% of regular NSAID users can be expected to develop hypertension. Clinical studies suggest that hypertensive complications occur more commonly in patients treated with COX-2–selective than with nonselective NSAIDs. Heart failure risk is roughly doubled.
- The NSAIDs have little effect on renal function or blood pressure in healthy human subjects because of the redundancy of systems that regulate renal function. In situations that challenge the regulatory systems, such as dehydration, hypovolemia, congestive heart failure, hepatic cirrhosis, chronic kidney disease, and other states of activation of the sympathoadrenal or renin-angiotensin systems, regulation of renal function by PG formation becomes crucial (see Chapter 37). NSAIDs impair the PG-induced inhibition of both the reabsorption of Cl⁻ and the action of antidiuretic hormone, which may result in the retention of salt and water. Inhibition of COX-2–derived PGs that contribute to the regulation of renal medullary blood flow may lead to a rise in blood pressure, increasing the risk of cardiovascular thrombotic events and heart failure. NSAIDs promote reabsorption of K⁺ as a result of decreased availability of Na⁺ at distal tubular sites and suppression of the PG-induced secretion of renin. The last effect may account in part for the usefulness of NSAIDs in the treatment of Bartter syndrome (see Bartter Syndrome section).

- 
-
- Pregnancy
 - Myometrial COX-2 expression and levels of PGE2 and PGF2 α increase markedly in the myometrium during labor. Prolongation of gestation by NSAIDs has been demonstrated in humans. Some NSAIDs, particularly indomethacin, have been used off label to stop preterm labor. However, this use is associated with closure of the ductus arteriosus and impaired fetal circulation in utero, particularly in fetuses older than 32 weeks of gestation. COX-2–selective inhibitors have been used off label as tocolytic agents; this use has been associated with stenosis of the ductus arteriosus and oligohydramnios. Low-dose aspirin (81 mg/d) reduces the risk of preeclampsia by 24% when used as (off-label) preventive medication after 12 weeks of gestation in women who are at high risk (LeFevre and Force, 2014).

Disease states leading to increased vasoconstrictors

Renal disease
Cardiovascular disease

Decreased renal blood flow

Cirrhosis
Nephrosis
Heart failure
Diuretics

Decreased blood volume

Increased vasoconstrictors:
Angiotensin II
Catecholamines
Vasopressin

No treatment

Patient treated with aspirin

Response of renal blood flow



Prostaglandin synthesis normally antagonizes intrarenal effects of vasoconstrictors.

NSAIDs inhibit prostaglandin synthesis, leaving actions of vasoconstrictors unopposed.



Vasoconstriction

Analgesic nephropathy

- Mixtures of NSAIDs (rather than single agents) taken repeatedly.
- irreversible renal damage, notably
- chronic interstitial nephritis, renal papillary necrosis and acute renal failure.
- Condition most common in people who take high doses over years.



Cardiovascular

- Selective inhibitors of COX-2 depress PGI₂ formation by **endothelial cells** without concomitant inhibition of platelet thromboxane
- ↑ the risk of thrombosis, myocardial infarction and stroke.

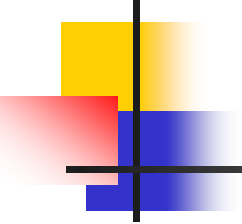
Pregnancy and Lactation.

- Prolongation of gestation
- NSAIDs, indomethacin, used off-label to terminate preterm labor,
- associated with **closure of the** ductus arteriosus and impaired fetal circulation *in utero*, particularly in fetuses older than 32 weeks' gestation.
- NSAIDs and aspirin late in pregnancy may ↑ the risk of postpartum hemorrhage.



Hypersensitivity.

- 1% incidence in normal individual
- Despite the resemblance to anaphylaxis, this reaction is not immunological in nature.
- Aspirin hypersensitivity is associated with an increase in biosynthesis of LTs, perhaps reflecting diversion of AA to lipoxygenase metabolism

- 
-
- Hypersensitivity
 - Hypersensitivity symptoms to aspirin and NSAIDs range from vasomotor
 - rhinitis, generalized urticaria, and bronchial asthma to laryngeal
 - edema, bronchoconstriction, flushing, hypotension, and shock. Aspirin
 - intolerance (including aspirin-associated asthma) is a contraindication
 - to therapy with any other NSAID because of cross sensitivity. Although
 - less common in children, this cross sensitivity may occur in 10%–25%
 - of patients with asthma, nasal polyps, or chronic urticaria and in 1% of
 - apparently healthy individuals. It is provoked by even low doses (<80
 - mg)
 - of aspirin and apparently involves COX inhibition. Treatment of aspirin
 - hypersensitivity is similar to that of other severe hypersensitivity
 - reactions,
 - with support of vital organ function and administration of epinephrine

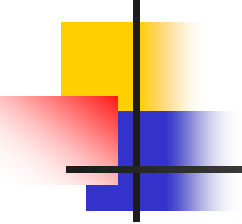
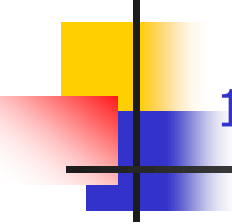
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- Hepatotoxicity
 - Liver injury occurs in 17% of adults with unintentional acetaminophen overdose (Blieden et al., 2014). Liver toxicity from therapeutic doses of acetaminophen is extremely rare (see Acetaminophen section). By contrast, therapeutic dosing of diclofenac may be complicated by hepatotoxicity.
 - INFLAMMATION, IMMUNOMODULATION, AND HEMATOPOIESIS
 - 691
 - SECTION IV
 - While the entire class of NSAIDs has a rate of less than 1 liver injury per 100,000 patients on average, chronic consumption of diclofenac is associated with a risk of 6–11 liver injuries per 100,000 users (Bjornsson et al., 2013; de Abajo et al., 2004) (see Diclofenac section). NSAIDs are not recommended in advanced hepatic or renal disease.
 - Reye Syndrome
 - Due to the possible association with Reye syndrome, aspirin and other salicylates are contraindicated in children and young adults less than 20 years of age with viral illness–associated fever (Schrör, 2007). Reye syndrome, a severe and often fatal disease, is characterized by the acute onset of encephalopathy, liver dysfunction, and fatty infiltration of the liver and other viscera. Although a mechanistic understanding is lacking, the epidemiologic association between aspirin use and Reye syndrome is sufficiently strong that aspirin and bismuth subsalicylate labels must indicate the risk. As the use of aspirin in children has declined dramatically, so has the incidence of Reye syndrome. Acetaminophen and ibuprofen have not been implicated in Reye syndrome and are the agents of choice

TABLE 42-2 Major Adverse Effects of Nonselective COX Inhibitors and COX-2 Selective Inhibitors

ADVERSE EFFECT	NONSELECTIVE COX INHIBITORS (NSAIDs)	COX-2 SELECTIVE INHIBITORS
Gastric ulceration	Yes	Yes*
Inhibit platelet function	Yes	No
Inhibit labor induction	Yes	Yes
Impair renal function	Yes	Yes
Hypersensitivity reaction	Yes	?

INTERACTIONS

- 
1. **ACE inhibitors** & angiotensin II antagonists: risk of renal impairment and hyperkalaemia.
 2. **Quinolone antimicrobials**: convulsions may occur if NSAIDs are co-administered.
 3. **Anticoagulant** (warfarin) and antiplatelet agents (ticlopidine, clopidogrel) ↑ risk of alimentary bleeding.

4. **Antihypertensives**: their effect is ↓ due to inhibition of renal prostaglandin formation.

5. NSAIDs may ↑ haematological toxicity from **zidovudine**.

7. Renal tubular excretion of **methotrexate**
↓ by competition with NSAID ; methotrexate toxicity

8. **Aspirin and corticosteroid**

8. NSAIDs cause sodium retention and
↓ diuretic and antihypertensive efficacy.

9. **Lithium**: NSAIDs delay the excretion of lithium by the kidney and may cause lithium toxicity

Synergistic/beneficial interaction

Decreased urate excretion
(contraindicated in patients with gout)

Probenecid
Sulfinpyrazone

Hemorrhage

Heparin or oral
anticoagulants

Drug-drug interactions with salicylates leading to altered effects of drugs or metabolites are shown in red

Bilirubin
Phenytoin
Valproic acid
Sulfinpyrazone
Thiopental
Thyroxine
Triiodothyronine

Increased plasma concentration,
leading to prolonged half-lives,
therapeutic effects, and toxicity

Salicylates



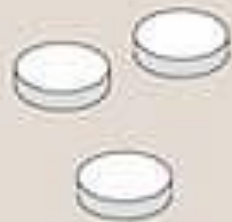
Aspirin or acetylsalicylic acid

- Patented by Bayer in 1893
- One of the oldest drugs
- One of the most consumed drugs
(Production in the US is 10 million Kg/year)

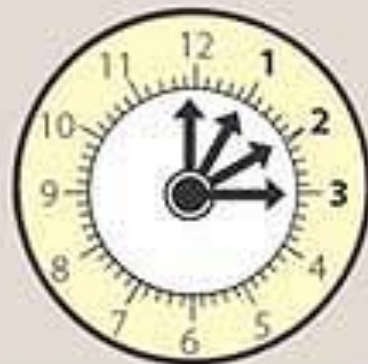


Aspirin - Mechanism of Action

- Irreversible Inhibition of cyclooxygenase
 - Both COX-1 and COX
- *"Irreversible - effect lasts until new enzyme is formed"*



Aspirin
(low dose)



$t_{1/2} = 3$ hours



Aspirin
(high dose)



$t_{1/2} = 15$ hours



Aspirin

- **aspirin p.o. <1.0g: first-order kinetics**

$$t_{1/2} = 2 \sim 3 \text{ hrs}$$

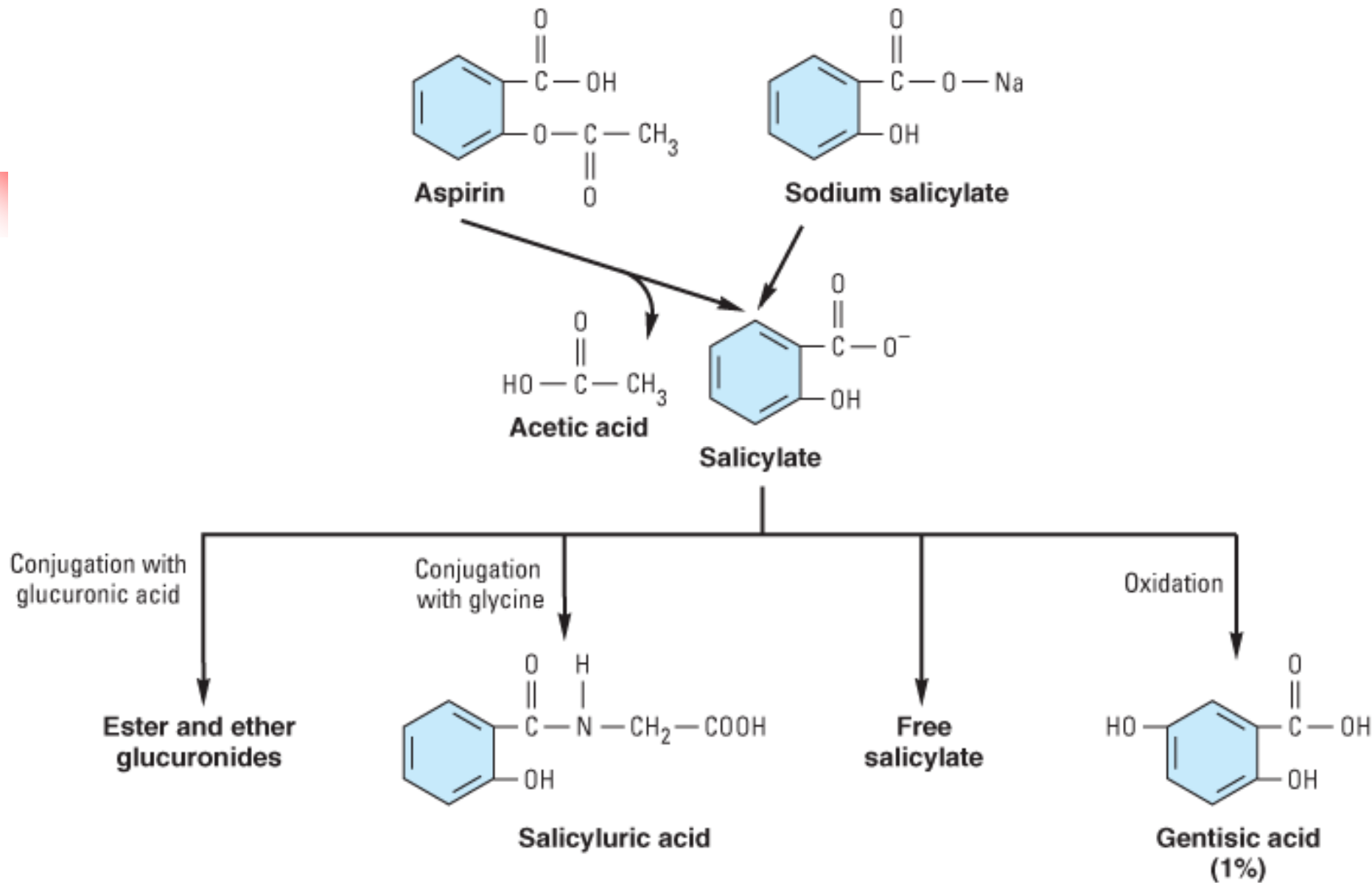
- **aspirin p.o. $\geq 1.0\text{g}$: zero-order kinetics**

$$t_{1/2} = 15 \sim 30 \text{ hrs}$$



Pharmacokinetics-salicylates

- Crosses the placenta
- Compete at the PPB sites with **thyroxine**, **penicillin**, **phenytoin**, **bilirubin**, **naproxen**
- Aspirin acetylates hormones, DNA, **haemoglobin** and other proteins.



Rate of metabolism*



Reye's Syndrome

- Linked to aspirin use by children
 - with chickenpox or flu
- 10-15% mortality rate
- vomiting ,rash
- Confusion > seizures > coma

- ✓ salicylates are contraindicated in children and young adults less than 20 years of age with viral illness–associated fever.
- ✓ association between aspirin use and Reye syndrome is sufficiently strong that aspirin and bismuth subsalicylate labels must indicate the risk.



Process in the Body

- ✧ **Urine pH have a strong influence on the excretion amount of free salicylate from kidney.**

So we can reduce the blood concentration of free salicylate through alkalizing the urine



Pharmacological Effects

1. Antipyretic and analgesic effect

The two effects of aspirin are strong and rapid.

2. Ant-inflammatory and antirheumatic effect

(1)relatively stronger

(2)often used to the dose of tolerance

Pharmacological Effects

3. **Inhibit platelet aggregation and prevent thrombosis**
 - **platelet COX-1 TXA₂ synthetase**
endothelium COX-1 PGI₂ synthetase
 - **Short life only 8-11days and no protein biosynthesis capacity compared with vascular endothelium**
 - **Aspirin administered in low dose can reduce TXA₂ remarkably but have no apparent influence on PGI₂**



Aspirin & Bleeding

- ..promotes bleeding by inhibiting platelet aggregation
- 2 tablets doubles bleeding time for 1 week!!
- [Bleeding time - screening test - small stab in ear lobe or forearm - record time to stop bleeding]
- Contraindicated in pts with bleeding disorders
- Discontinue use
 - 1 week prior to elective surgery or parturition

DIFFERENT REQUIREMENTS, DIFFERENT DOSES

- long-term MI prophylaxis: 81-162mg/d
- RA or osteoarthritis: 3 grams/day
- Stroke prophylaxis: 50- 325 mg/
- Acute myocardial infarction, 162 to 325 mg of non enteric coated aspirin chewed and swallowed immediately.

LOCAL USES

Mesalamine (5-ASA)

pH sensitive ,polymer coated ,delayed release tab

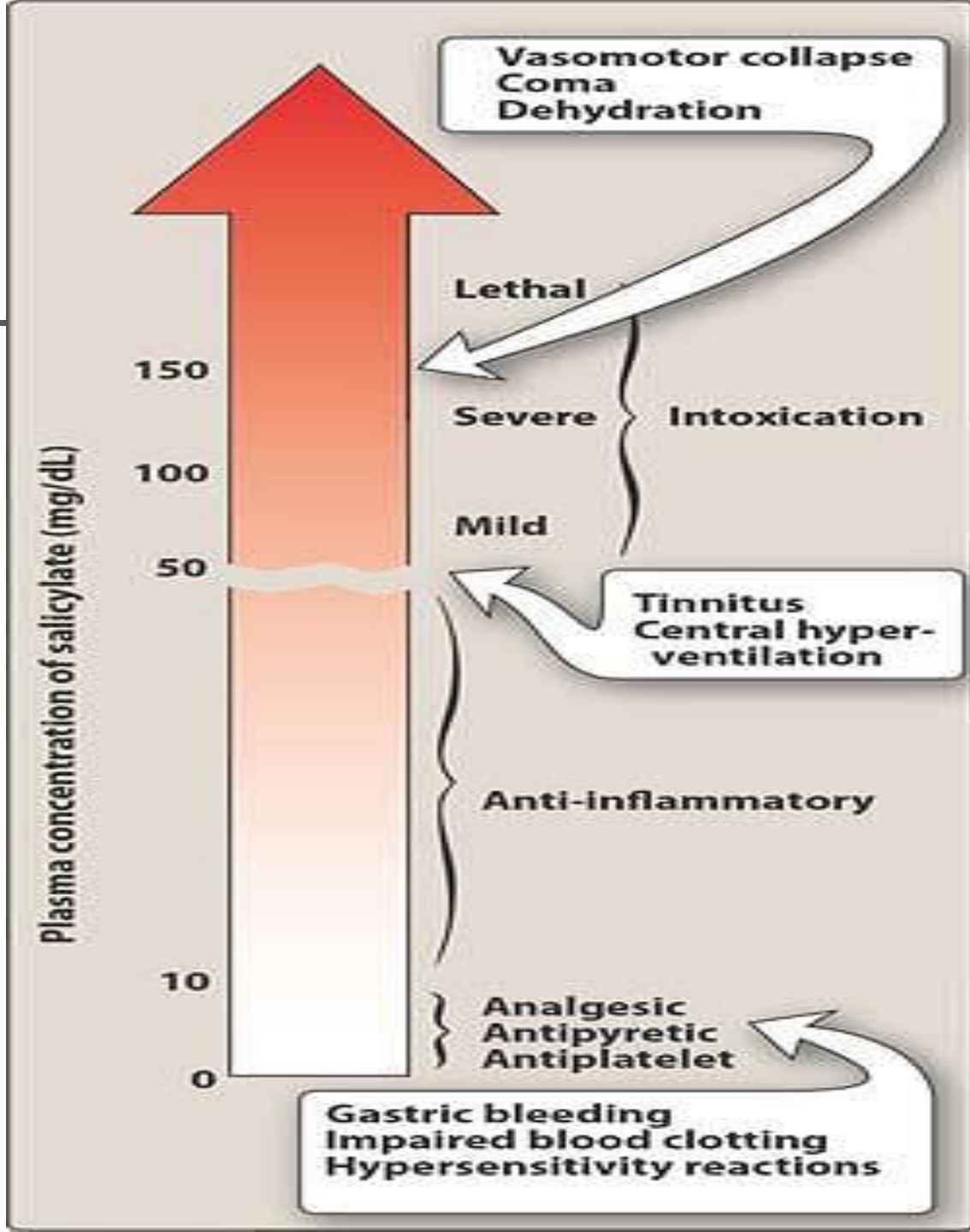
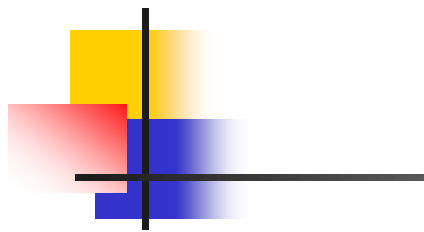
Olsalazine

sulphasalazine

Local keratolytic action of free salicylic acid -
Warts, corns, eczematous dermatitis

Oil of wintergreen

- The keratolytic action of free salicylic acid is employed for the local treatment of warts, corns, fungal infections, and certain types of eczematous dermatitis.
- After treatment with salicylic acid, tissue cells swell, soften, and desquamate.
- Methyl salicylate (oil of wintergreen) is a common ingredient of ointments and deep-heating liniments used in the management of musculoskeletal pain



**Decreased urate excretion
(contraindicated in patients with gout)**

*Probenecid
Sulfinpyrazone*

Hemorrhage

Heparin or oral
anticoagulants

**Drug-drug interactions
with salicylates leading to
altered effects of drugs or
metabolites are shown in
red**

*Bilirubin
Phenytoin
Valproic acid
Sulfinpyrazone
Thiopental
Thyroxine
Triiodothyronine*

**Increased plasma concentration,
leading to prolonged half-lives,
therapeutic effects, and toxicity**



PARACETAMOL

first used clinically by
Von Mering in 1893.

Marketed in US - 1950.

Well tolerated . Rarely produce
side effects of any kind when
administered in recommended doses.



Why paracetamol

- ❄ **Safety.**
- ❄ **Wide therapeutic window.**
- ❄ **Short duration of action.**
- ❄ **Side effect: Over dosing either intentional or accidental.**

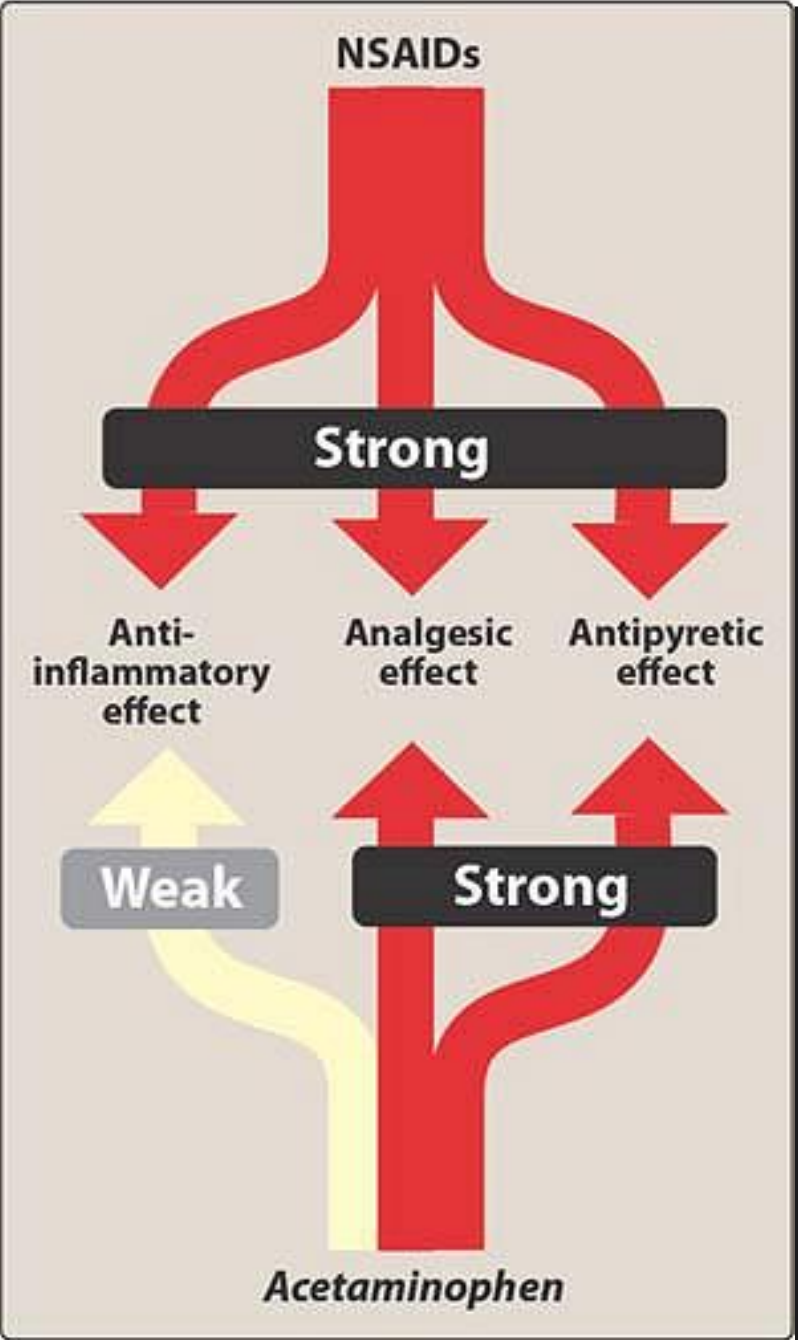
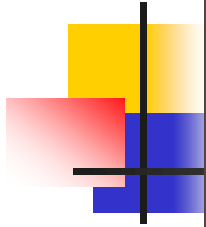
Choice of antipyretic

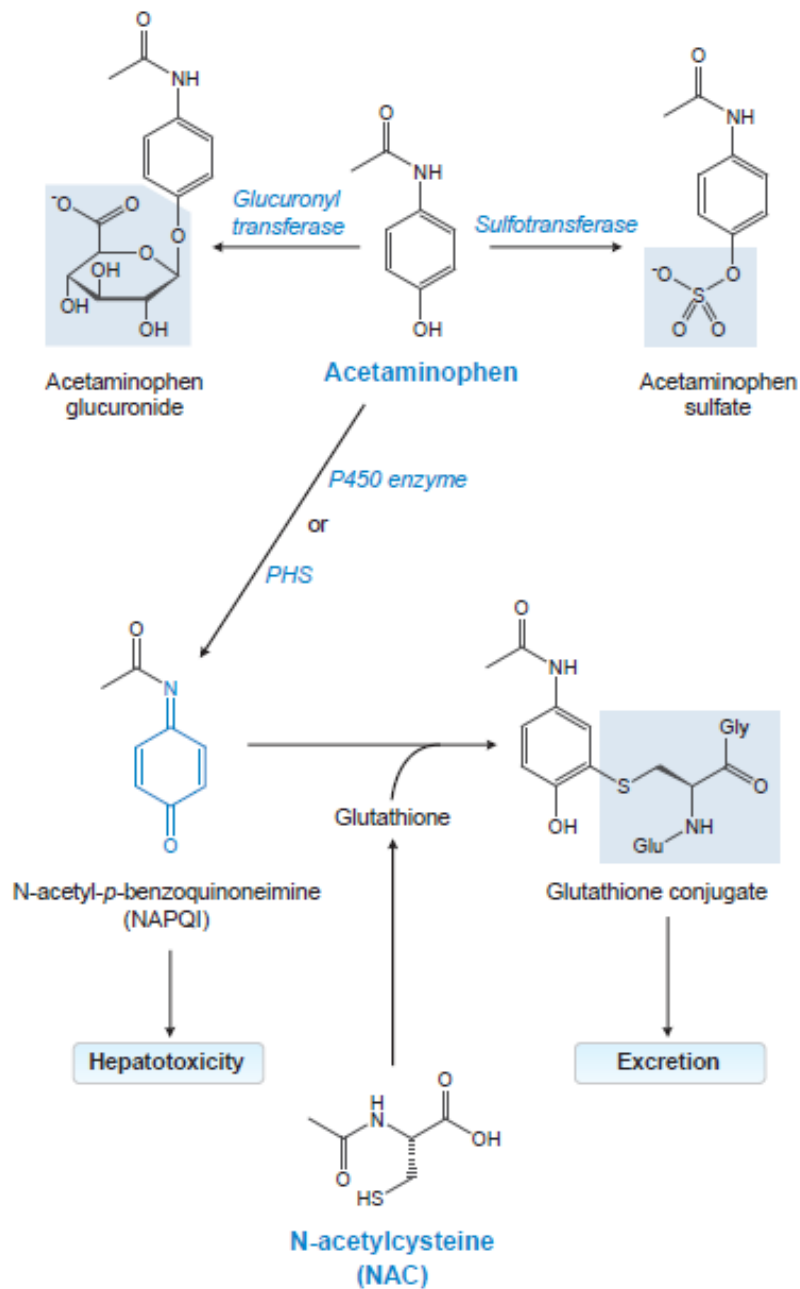
- According to WHO paracetamol is the drug of first choice
- Ibuprofen is a useful 2nd line drug.
- No other NSAID including Nimesulide to be prescribed for children with high grade fever

Acetaminophen & Phenacetin



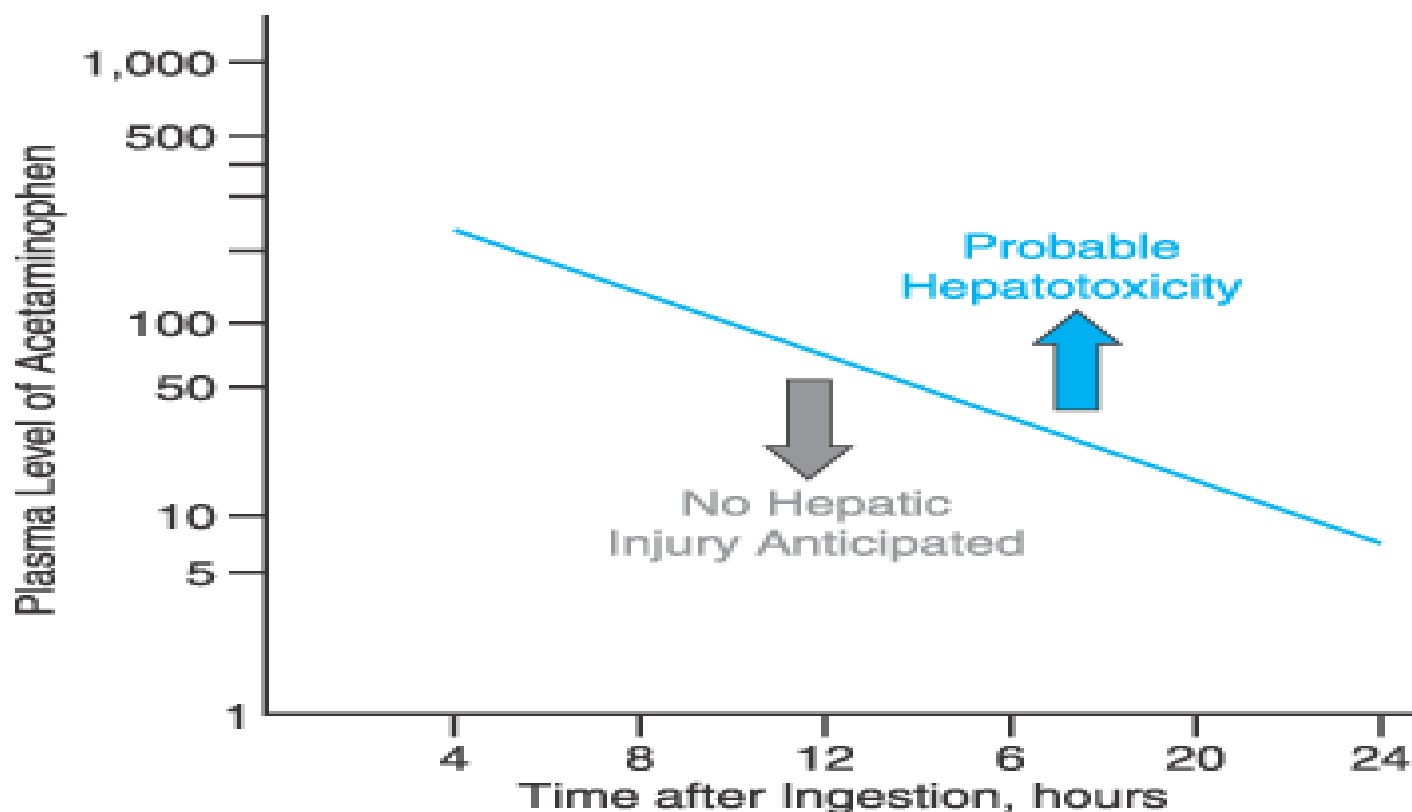
- ▽ Acetaminophen :active metabolite of phenacetin
- ▽ weak prostaglandin inhibitor in peripheral tissues and possesses **no significant anti-inflammatory effects.**
- ▽ one of the most important drugs used for treatment of mild to moderate pain when an anti-inflammatory effect is not necessary.





total daily doses should not exceed 4000 mg

Relationship of plasma levels of acetaminophen and time after acute ingestion to hepatic injury.



Drug conc < 120ug/ml at 4 hrs after ingestion

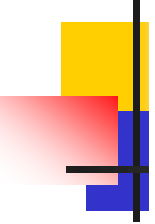
Drug conc < 30 ug/ml at 12 hrs after ingestion

- **N- acetylcysteine** (NAC) MUCOMYST indicated at risk of hepatic injury.
- functions by detoxifying NAPQI.
- repletes GSH stores and conjugate directly with NAPQI by serving as a GSH substitute.
- NAC may protect against extrahepatic injury by its antioxidant antiinflammatory properties

Oral loading dose of 140 mg/kg followed by the administration of 70 mg/kg 4 hrly for 17 doses.

- IV loading dose 150 mg/kg by infusion in 100 ml of 5% dextrose.
- followed by 50 mg/kg by IV - 4 hours,

Diflunisal

- 
- Derived from salicylic acid,
 - More potent than aspirin -antiinflammatory.
 - Appears to be **competitive inhibitor of COX**
 - **Devoid of antipyretic** effects, because of poor penetration into the CNS.
 - Does not produce auditory side effects.
 - Causes less intense gastrointestinal and antiplatelet effects than aspirin.

initial dose is 500- 1000 mg, followed by 250 to 500 mg every 8 to 12 hours.

Maintenance dosage should < 1.5 g per day.

Propionic acid derivatives

■ **Ibuprofen:**

1. contraindicated in individuals with nasal polyps, angioedema, and bronchospastic reactivity to aspirin.
2. tinnitus, dizziness, headache, **aseptic meningitis** fluid retention reported,
3. toxic amblyopia
4. Gained wide acceptance in chronic treatment of RA and osteoarthritis, GI effects - less intense than aspirin.

Naproxen

ketoprofen

fenoprofen

flurbiprofen

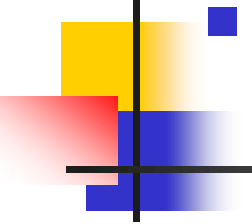
oxaprozin

Heteroaryl acetic acids

Diclofenac sodium

- **approved for long-term treatment of RA, osteoarthritis, and ankylosing spondylitis.**
- **more potent than indomethacin and naproxen**
- **ophthalmic preparation is available.**
- **accumulates in synovial fluid,**

KETOROLAC

- 
- effective analgesic successfully to replace morphine in mild to moderate **postsurgical pain**.
 - given IM or IV, oral dose available.
 - used with an opioid, it may ↓ opioid requirement by 25-50%.
 - An ophthalmic preparation is available for ocular inflammatory conditions

ACETIC ACID DERIVATIVES: INDOMETHACIN, SULINDAC, AND ETODOLAC

- 20 times more potent inhibitor of COX than aspirin.
- inhibits motility of PML and ↓ biosynthesis of mucopolysaccharides.
- may have a direct, cyclooxygenase-independent vasoconstrictor effect
- excellent bioavailability
- not used commonly as analgesic or antipyretic unless the fever has been refractory to other agents (*e.g.*, Hodgkin's disease).

INDOMETHACIN

- FDA approved for **closure of persistent patent ductus arteriosus**, 0.1 to 0.2 mg/kg every 12 hours IV for three doses.
- Therapy indicated- premature infants 500 - 1750 g wt, have a hemodynamically significant patent ductus arteriosus.
- Unexpectedly ↓the incidence & severity of intraventricular hemorrhage in low-birth-weight neonates.
- Principal limitation of treating neonates is Renal toxicity.
- thrombocytopenia

Oxicam derivatives

- Piroxicam - RA, ankylosing spondylitis, and osteoarthritis.
- can inhibit activation of neutrophils, inhibition of proteoglycanase and collagenase in cartilage.
- long $T_{1/2}$, permit once-daily administration
- GI disturbances – 20 % of patients treated with piroxicam.

Meloxicam preferential binding for COX-2, less GI irritation than piroxicam.

high doses, - nonselective NSAID,
7.5 to 15 mg once a day

Nabumetone

- dose typically is 1000 mg given once daily.

- Prodrug; thus it is a weak inhibitor of COX *in vitro* but a potent COX inhibitor *in vivo*.

- Active metabolite, **6-methoxy-2-naphthylacetic acid**, a potent nonselective inhibitor of COX

Upper GI disturbances
are common

No antipyretic
effect

Very potent; should be
used only after less
toxic agents have
proven ineffective

CNS disturbances are
common

Potential for increasing
myocardial infarctions
and strokes

Salicylates:

Aspirin
Salicylate salt
Diflunisal

Acetic acids:

Indomethacin
Sulindac
Tolmetin

Propionic acid:

Ibuprofen
Fenoprofen
Flurbiprofen
Ketoprofen
Naproxen
Oxaprozin

Oxicams:

Piroxicam
Meloxicam

Fenamates:

Mefenamic ac
Meclofenamic

COX-2 inhibito

Celecoxib

Therapeutic advantages of selected NSAIDs

Salicylates:

- ▶ *Aspirin*
- ▶ *Salicylate salts*
- ▶ *Diflunisal*

Low cost; long history of safety

Acetic acids:

- ▶ *Indomethacin*
- ▶ *Sulindac*
- ▶ *Tolmetin*

Less GI irritation than aspirin

Propionic acids:

- ▶ *Ibuprofen*
- ▶ *Fenoprofen*
- ▶ *Flurbiprofen*
- ▶ *Ketoprofen*
- ▶ *Naproxen*
- ▶ *Oxaprozin*

Long half-life permits daily or twice daily dosing

Lower toxicity and better acceptance in some patients. *Naproxen* is considered by some experts as one of the safest NSAIDs

Oxicams:

- ▶ *Piroxicam*
- ▶ *Meloxicam*

Fenamates:

- ▶ *Mefenamic acid*
- ▶ *Meclofenamic acid*

COX-2 inhibitors

- ▶ *Celecoxib*

Less GI irritation than *aspirin*

Pain Management: WHO Analgesic Ladder

Step 1: Mild pain (pain scores 1-4 out of 10)

Non-Opioid Analgesics

Acetaminophen, non-steroidal anti-inflammatory drugs



Step 2: Moderate pain (pain scores 5-7)

Weak Opioids

Codeine, hydrocodone, tramadol



Step 3: Severe pain (pain scores 8-10)

Strong Opioids

Morphine, oxycodone, hydromorphone, fentanyl, methadone



World Health Organization Analgesic Ladder

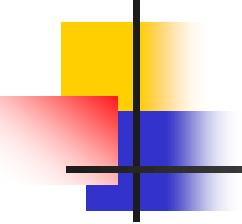


Step 1 Mild to Moderate Pain

Non-opioid \pm adjuvant agent

Acetaminophen or an NSAID should be used, unless contraindicated.

Adjuvant agents are those that enhance analgesic efficacy, treat concurrent symptoms that exacerbate pain, and/or provide independent analgesic activity for specific types of pain.

- 
-
- **Step 2 Mild to Moderate Pain or Pain Uncontrolled after Step 1**
 - Short-acting opioid as required \pm non-opioid around the clock (ATC) \pm adjuvant agent
 - Morphine, oxycodone, or hydromorphone should be added to acetaminophen or an NSAID for maximum flexibility of opioid dose.



- **Step 3 Moderate to Severe Pain or Pain Uncontrolled after Step 2**

- Sustained release/long-acting opioid ATC or continuous infusion + short-acting opioid as required \pm non-opioid \pm adjuvant agent
- Sustained release oxycodone, morphine, oxymorphone or transdermal