Unit 5 (2)

The **clinical features of inflammation** have been recognized since ancient times as swelling, redness, pain, and heat. The underlying mechanisms which produce these symptoms are complex, involving many different cells and cell products. A normal inflammatory response is essential to fight infections and is part of the repair mechanism and removal of debris following tissue damage. Inflammation can also cause disease, due to damage of healthy tissue. This may occur if the response is over-vigorous, or persists longer than is necessary. Additionally, some conditions have a previously unrecognized inflammatory component, e.g. atherosclerosis.

*The **inflammatory response occurs in vascularised tissues** in response to injury*. It is part of the innate **nonspecific immune response**. Inflammatory responses require *activation of leukocytes: neutrophils, eosinophils, basophils, mast cells, monocytes, and lymphocytes*, although not all cell types need be involved in an inflammatory episode. The cells migrate to the area of tissue damage from the systemic circulation and become activated.

Diseases with a chronic inflammatory component

Inflammatory disease	Inflammatory cell infiltrate
Acute respiratory distress syndrome	Neutrophil
Bronchial asthma	Eosinophil,T cell, monocyte, basophil
Atherosclerosis	T cell, monocyte
Glomerulonephritis	Monocyte,T cell, neutrophil
Inflammatory bowel disease	Monocyte, neutrophil,T cell, eosinophil
Osteoarthritis	Monocyte, neutrophil
Psoriasis	T cell, neutrophil
Rheumatoid arthritis	Monocyte, neutrophil
Sarcoidosis	T cell, monocyte

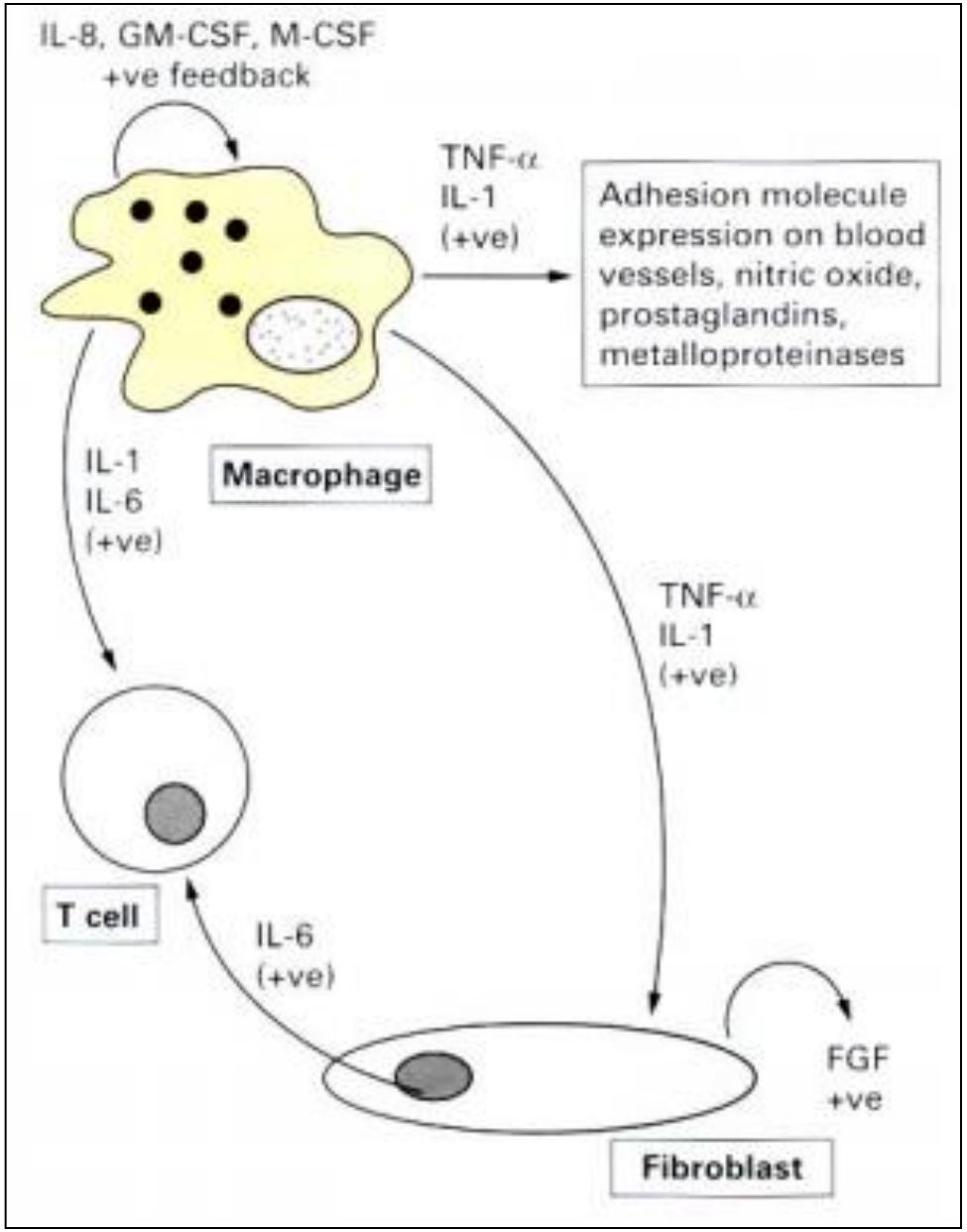
Inflammatory mediators

Activated ***leukocytes*** at a site of inflammation release compounds which enhance the inflammatory response mainly ***cytokines and eicosanoids*** (arachidonic acid metabolites). But the complexity of the response is indicated by the range of **many mediators**: **complement products**, **kinins** (bradykinin) and the **contact system** (coagulation factors XI and XII, pre-kallikrein, high molecular weight kininogen); **nitric oxide and vasoactive amines** (histamine, serotonin and adenosine); **activated forms of oxygen**; **platelet activating factor** (PAF); **metalloproteinases** (collagenases, gelatinases, and proteoglycanase), etc.

Cytokines (***ILs, TNFs, IFNs, CSFs,*** etc.) are peptides regulating cell growth, differentiation, and activation, and some have therapeutic value:

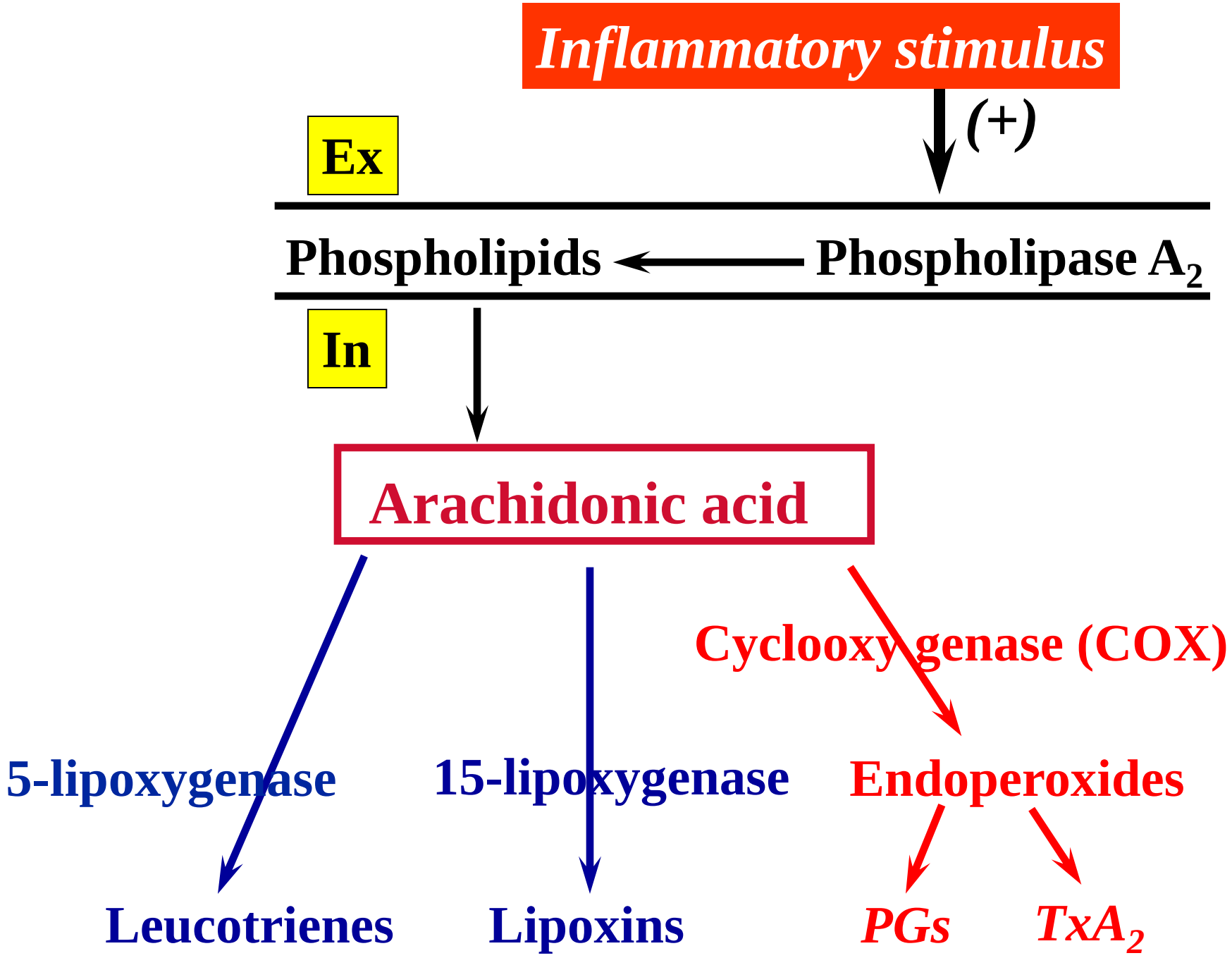
- **IL-1** plays a part in the sepsis syndrome and rheumatoid arthritis, and successful blockade of its receptor offers a therapeutic approach for these conditions.
- **TNFα** is similar to IL-1. Agents that block him, e.g. etanercept, infliximab are finding their place among **Disease modifying antirheumatic drugs.**

The main cell and inflammatory cytokines in chronic inflammatory diseases



Clinical Pharmacology – 9th Ed. (2003)

Eicosanoids *(prostaglandins, thromboxanes, leukotrienes, lipoxins)* is the name given to a group of 20-carbon unsaturated fatty acids, derived principally from arachidonic acid in cell walls. They are *short-lived, extremely potent, and formed in almost every tissue* in the body. Eicosanoids are involved in most types of inflammation and it is on manipulation of their biosynthesis that most current antiinflammatory therapy is based. Their biosynthetic paths appear in the next slides.


Inflammatory stimulus
(+)
Ex
Phospholipids
Phospholipase A2
In
Arachidonic acid
Cyclooxygenase (COX)
5-lipoxygenase
15-lipoxygenase
Endoperoxides
Leucotrienes
Lipoxins
PGs
TxA2

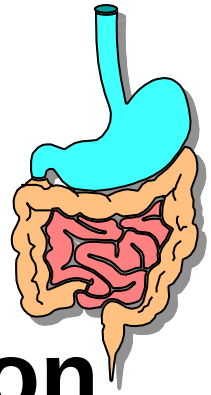
PROSTANOIDS (PGs & Txs)

PGI_2 (prostacyclin) is located predominantly in vascular endothelium. Main effects:

- **vasodilatation**
- **inhibition of platelet aggregation**

TxA_2 is found in the platelets. Main effects:

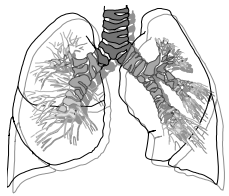
- **platelet aggregation**
- **vasoconstriction**



PGE_2 causes:

- **inhibition of gastric acid secretion**
- **contraction of pregnant uterus**
- **contraction of GI smooth muscles**

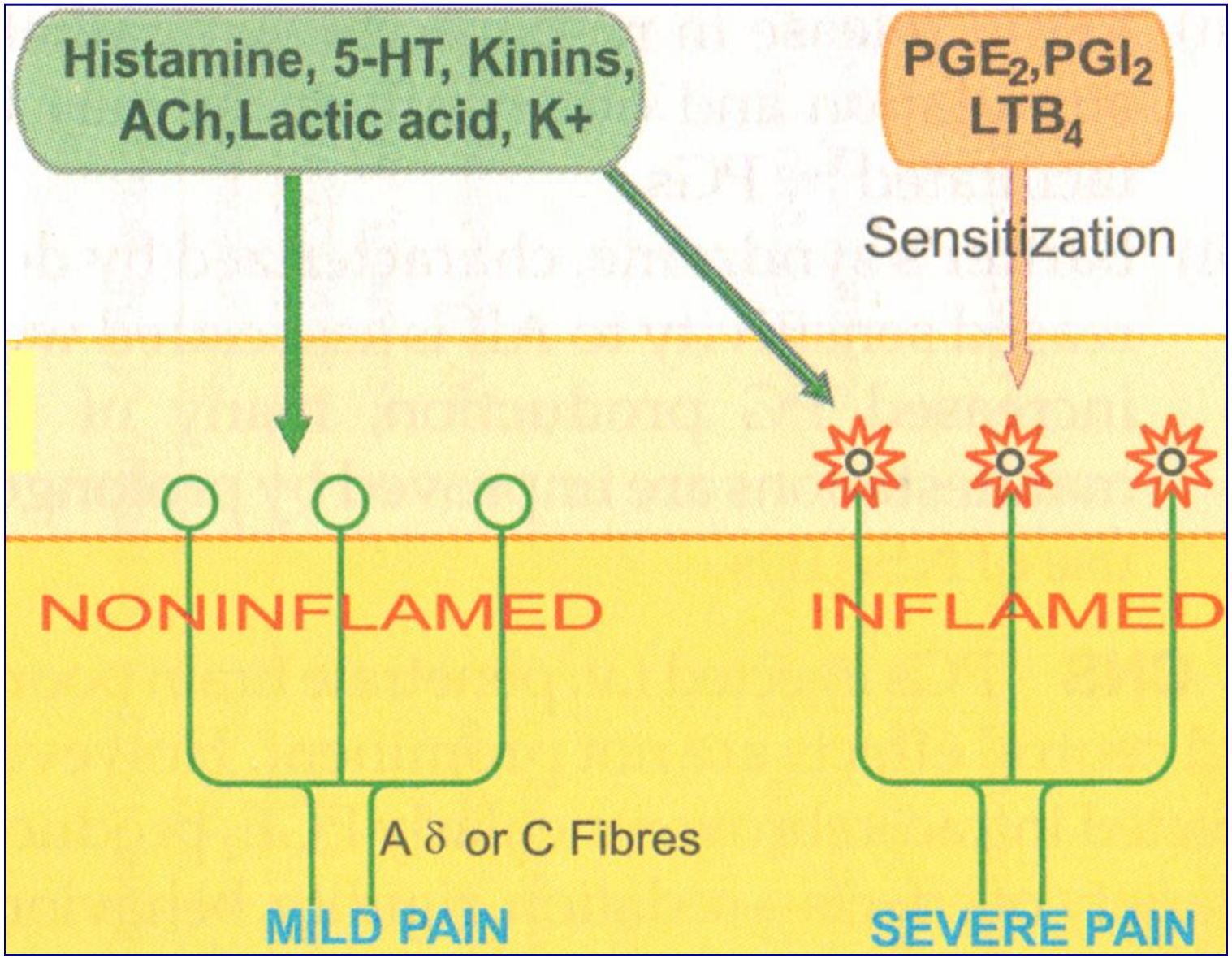
$PGF_{2\alpha}$ – main effects:



- **contraction of bronchi**
- **contraction of miometrium**

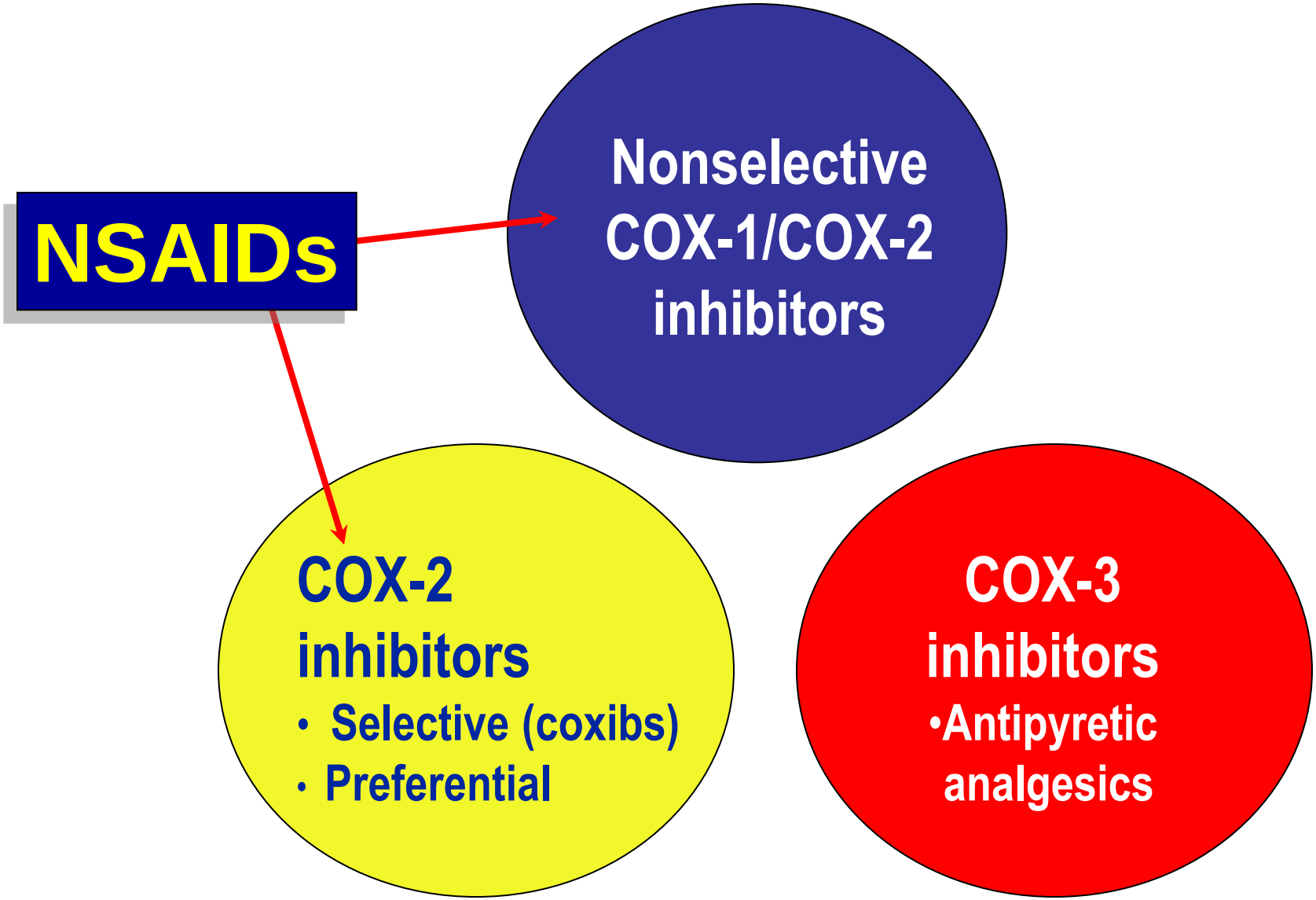
Cyclooxygenase (COX) is found bound to the endoplasmatic reticulum. It exists in 3 isoforms:

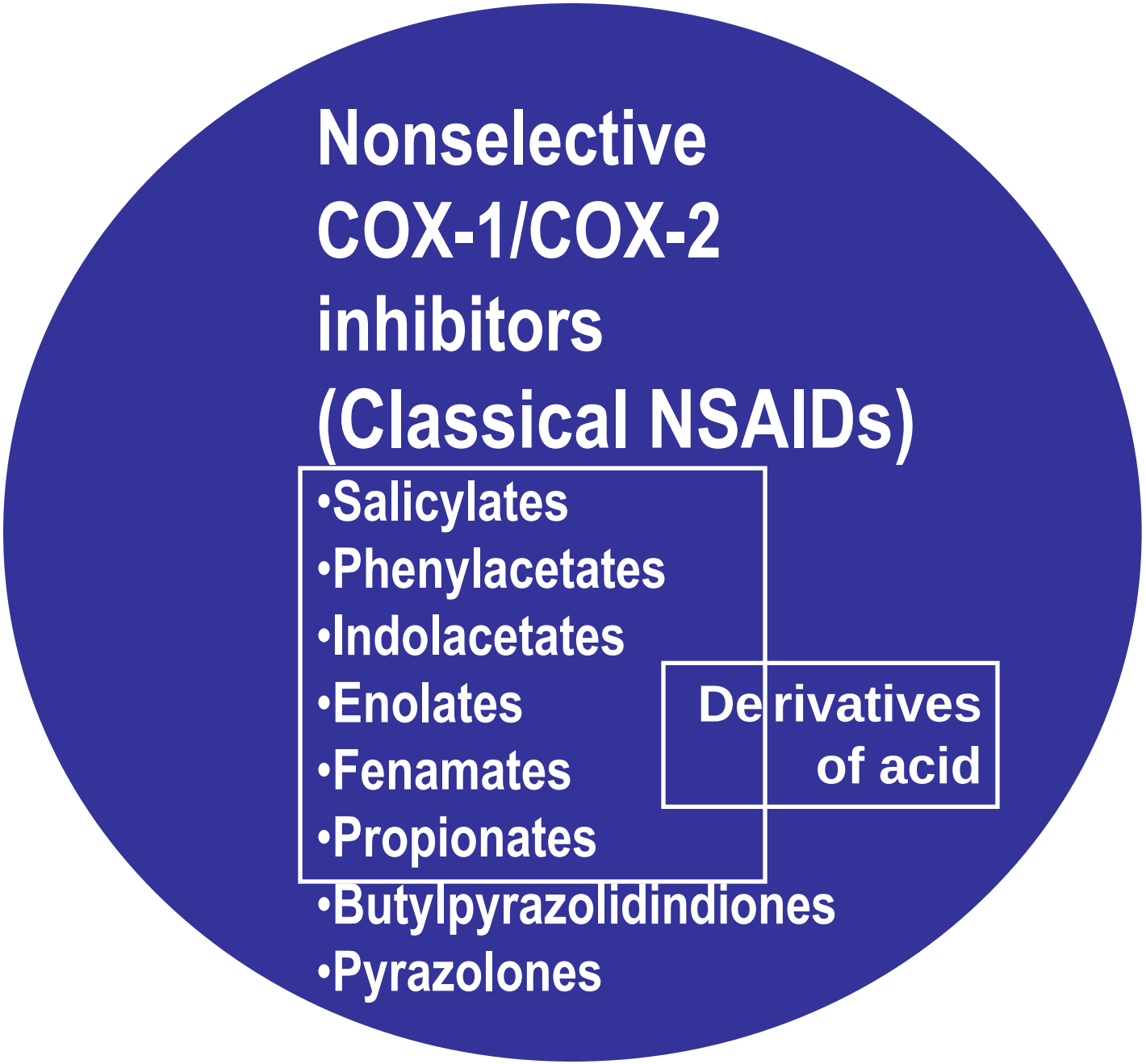
- **COX-1 (constitutive) acts in physiological conditions.**
- **COX-2 (inducible) is induced in inflammatory cells by pathological stimulus.**
- **COX-3 (in brain).**



Essential of Medical Pharmacology – 5st Ed. (2003)

COX inhibitors




Nonselective COX-1/COX-2 inhibitors (Classical NSAIDs)
•Salicylates
•Phenylacetates
•Indolacetates
•Enolates
•Fenamates
•Propionates
Derivatives of acid
•Butylpyrazolidindiones
•Pyrazolones

Nonselective COX-1/COX-2 inhibitors

DERIVATIVES OF ACIDS

Salicylates

Acetylsalicylic acid (*Aspirin®, 1899*), Diflunisal

Methyl salicylate (*revulsive drug*)

Phenylacetates: Acelcofenac, Diclofenac

Indolacetates: Indometacin, Sulindac

Enolates (oxicams)

Piroxicam, Piroxicam beta-cyclodextrin (*prodrug*), Lornoxicam, Tenoxicam

Propionates

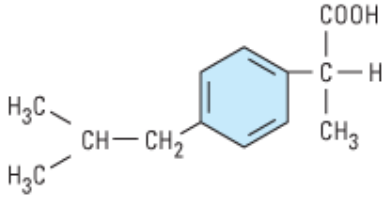
Flurbiprofen, Ibuprofen, Ketoprofen, Naproxen

OTHERS (with less application)

Pyrazolones: Phenazone, Propyphenazone, etc.

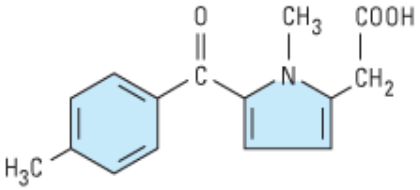
Pyrazolidinediones: Oxyphenbutazone, Phenylbutazone

PROPIONIC ACID DERIVATIVE



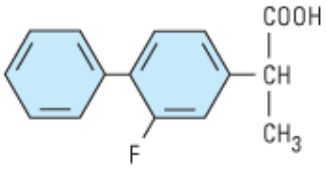
Ibuprofen

PYRROLEALKANOIC ACID DERIVATIVE



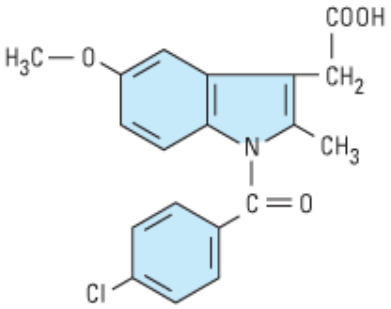
Tolmetin

PHENYLALKANOIC ACID DERIVATIVE



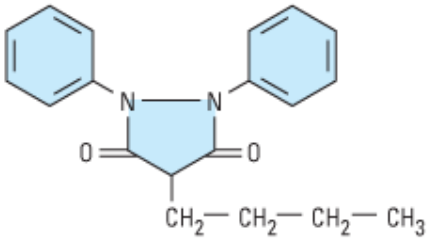
Flurbiprofen

INDOLE DERIVATIVE



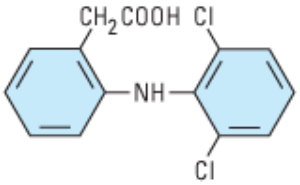
Indomethacin

PYRAZOLONE DERIVATIVE



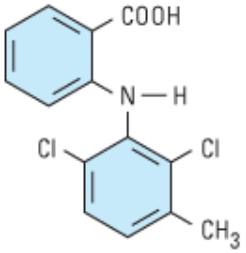
Phenylbutazone

PHENYLACETIC ACID DERIVATIVE



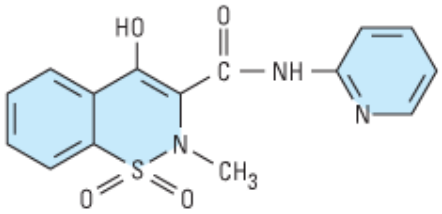
Diclofenac

FENAMATE



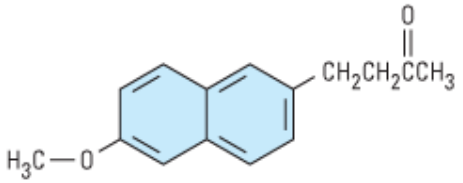
Meclofenamic acid

OXICAM



Piroxicam

NAPHTHYLACETIC ACID PRODRUG



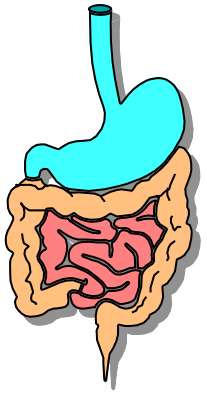
Nabumetone

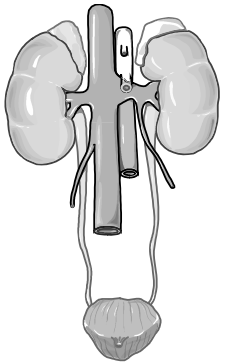
Beneficial actions of NSAIDs due to prostanoid synthesis inhibition

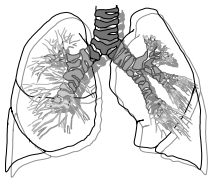
1. **Analgesia**
   prevention of pain nerve ending sensitization
2. **Antipyresis**
   connected with influence of thermoregulatory centre in the hypothalamus
3. **Antiinflammatory action**
   mainly antiexudative effect
4. **Antithrombotic action**
   in very low daily doses
5. **Closure** of ductus arteriosus

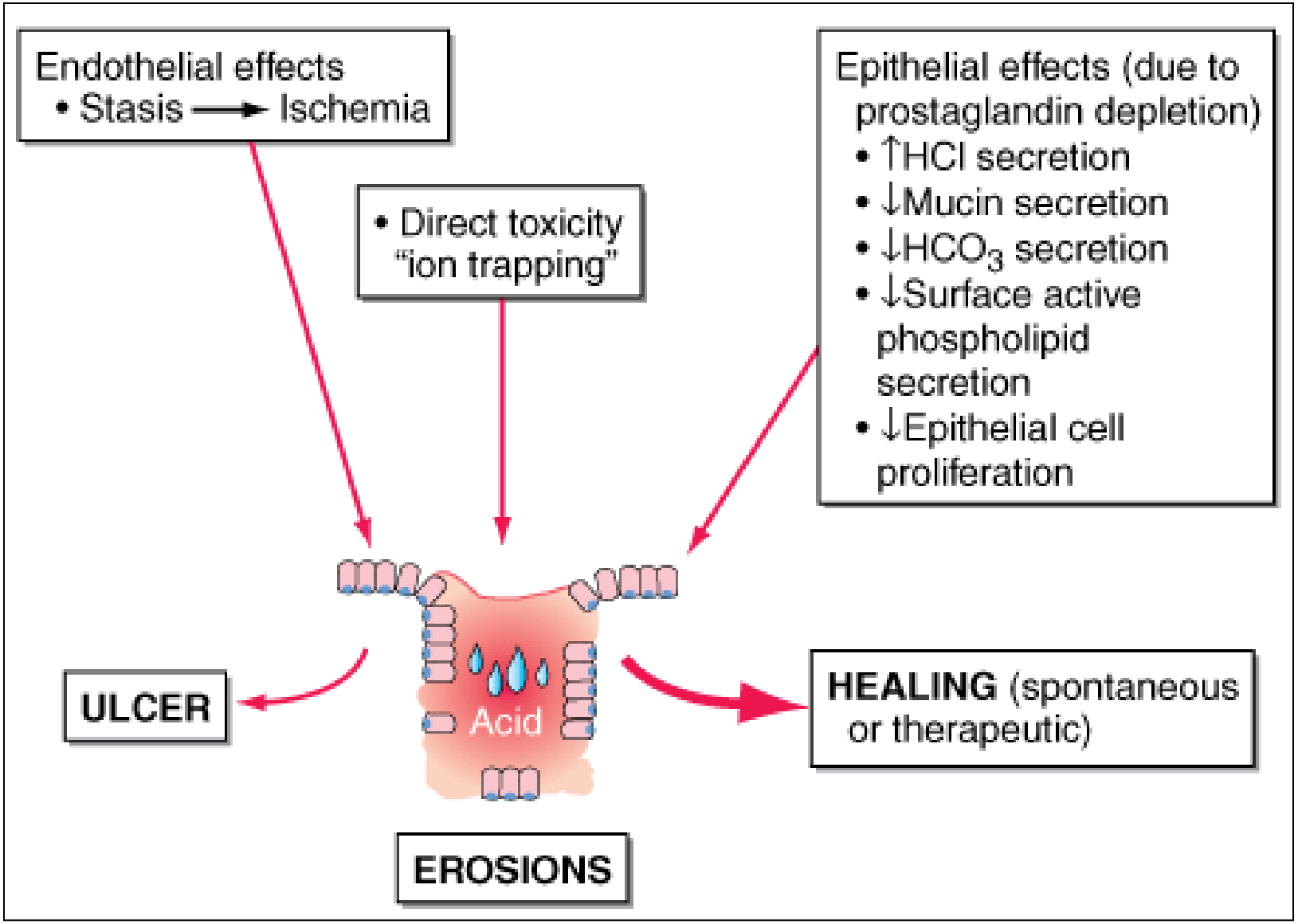
Shared toxicities of NSAIDs due to prostanoid synthesis inhibition

1. **Gastric mucosal damage**
   connected with PGE inhibition
2. **Bleeding:** inhibition of platelet function (TxA_2 synthesis)
3. **Limitation of renal blood flow**
   Na^+ and water retention
4. **Delay / prolongation of labour**
   connected with $PGF_{2\alpha}$ inhibition
5. **Asthma and anaphylactoid reactions**
   connected with $PGF_{2\alpha}$ inhibition



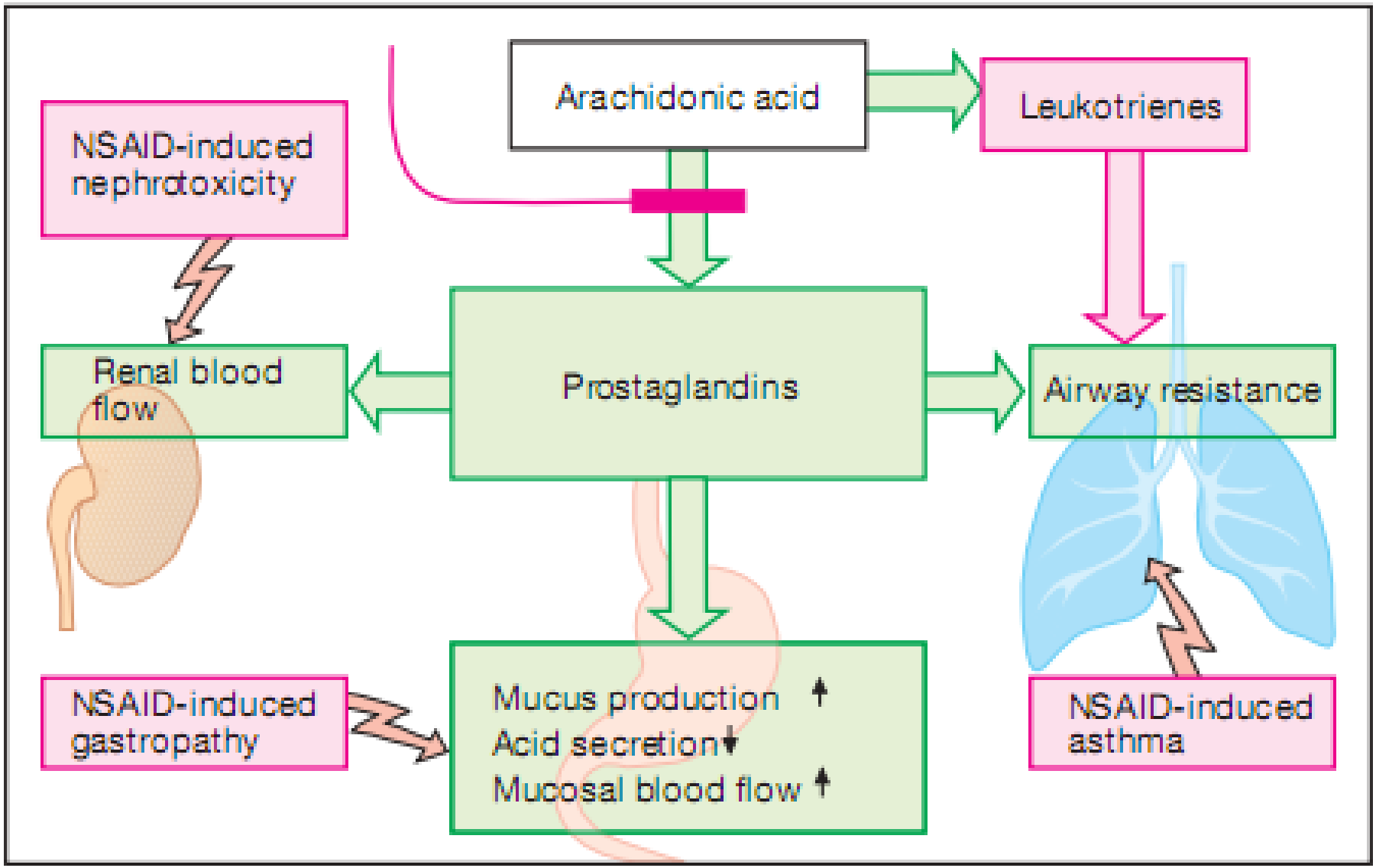






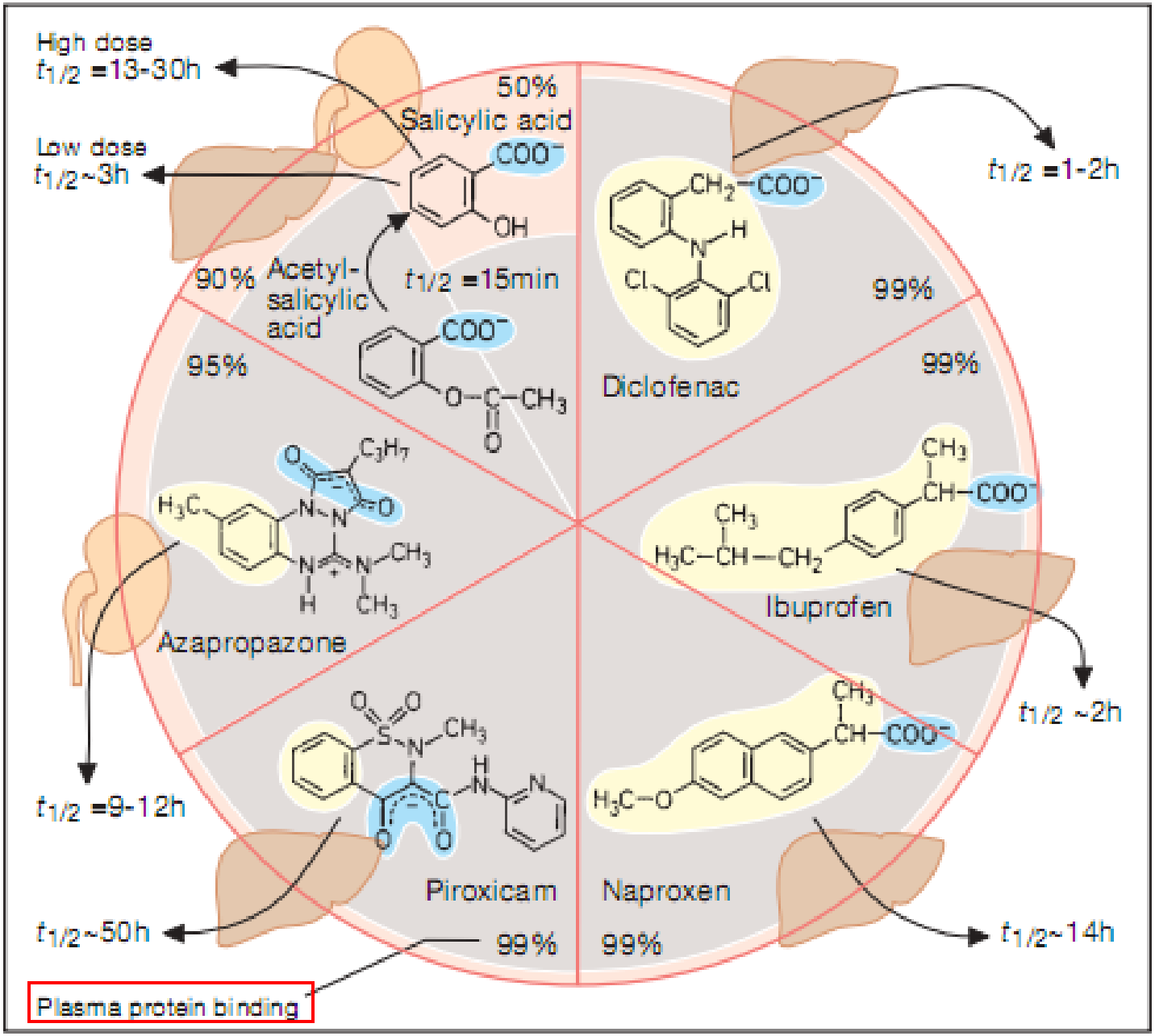
Mechanisms by which NSAIDs may induce mucosal injury

Lüllmann, Color Atlas of Pharmacology – 2nd Ed. (2000)

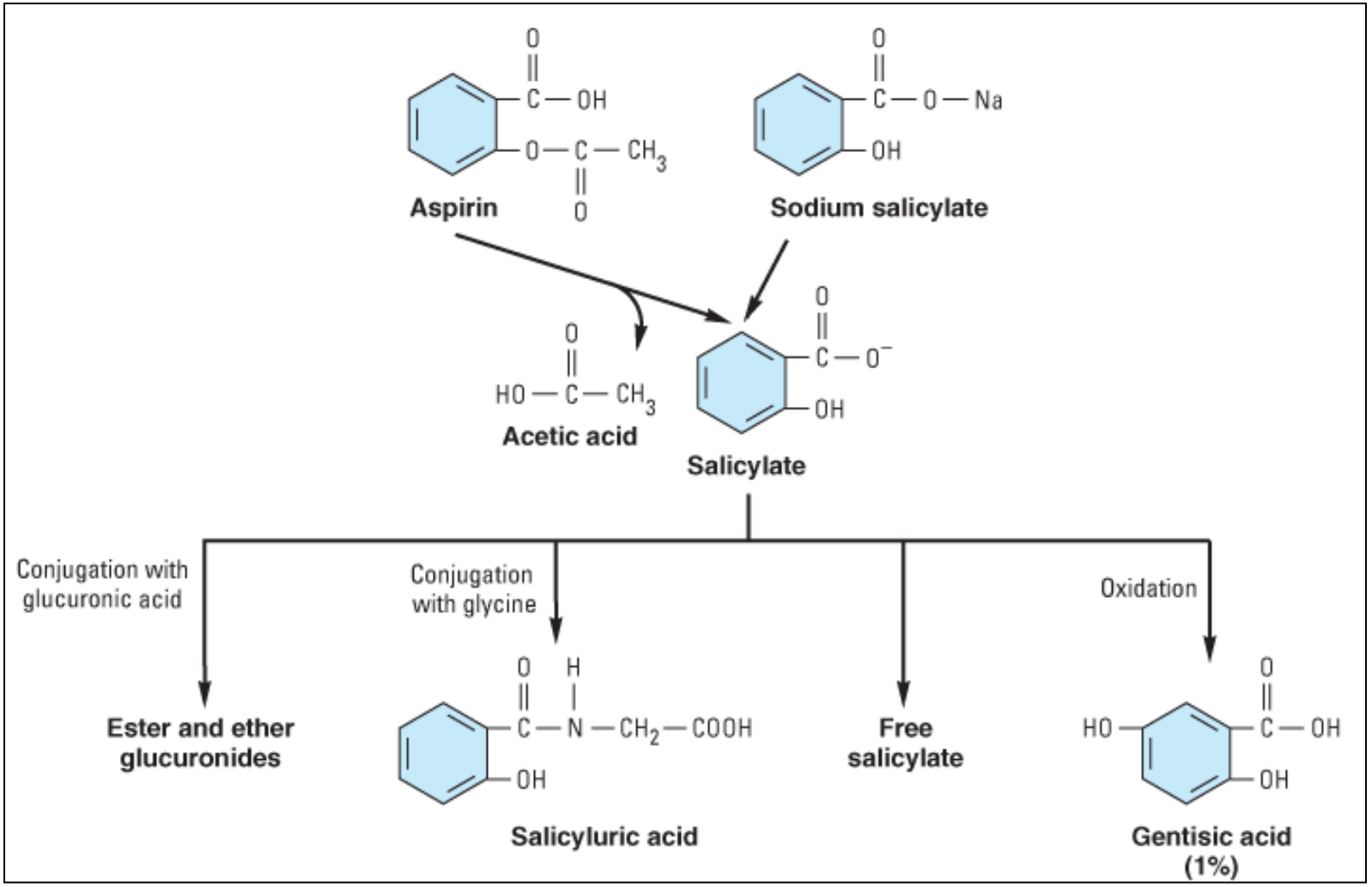


NSAIDs: group-specific adverse effects

Lüllmann, Color Atlas of Pharmacology – 2nd Ed. (2000)

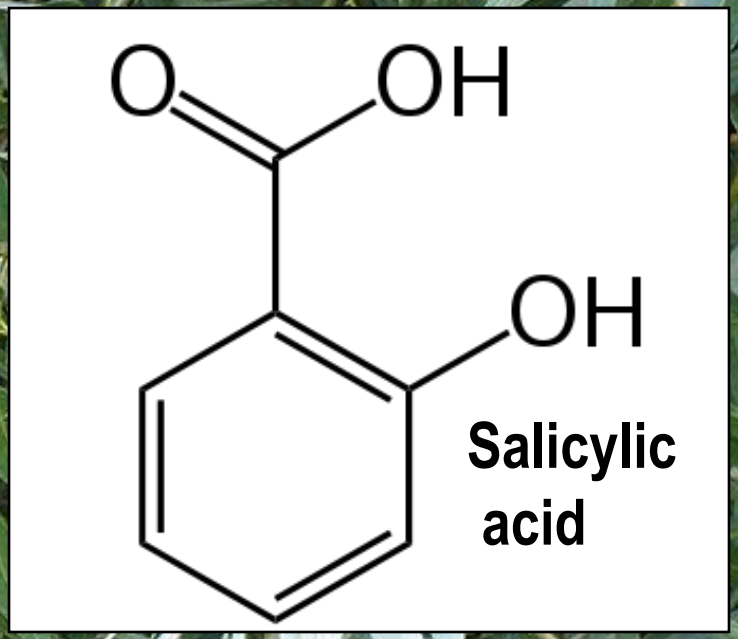


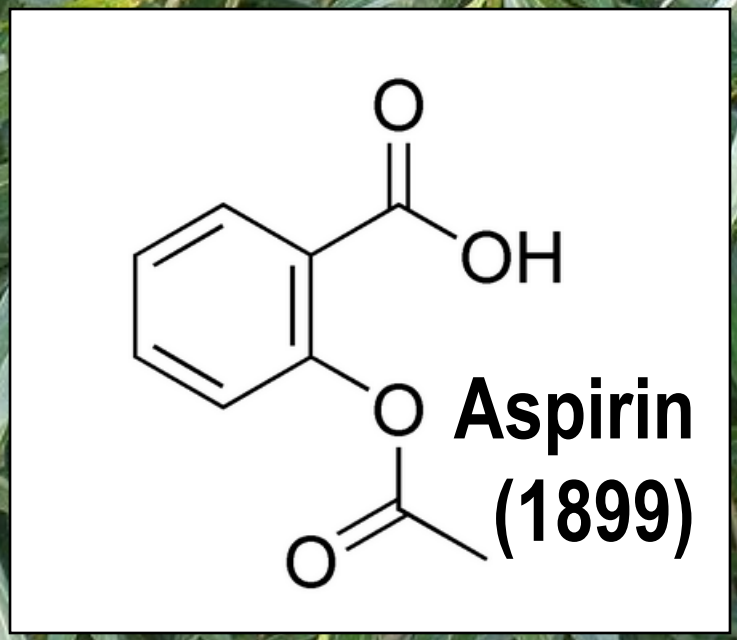
Lüllmann, Color Atlas of Pharmacology – 2nd Ed. (2000)



Metabolism of Aspirin

Basic & Clinical Pharmacology – 10th Ed. (2007)





Cortex
Salicis albae

Effects of NSAIDs

1. Analgesic and antipyretic action

Aspirin is a weaker analgesic than morphine-type drugs

Aspirin 600 mg < Codeine 60 mg < 6 mg Morphine

Aspirin relieves inflammatory, tissue injury related, connective tissue and integumental pain but is relatively ineffective in severe visceral and ischemic pain. The **analgesic action** is mainly due to obtunding peripheral pain receptors and prevention of PG mediated sensitization of nerve endings. A central subcortical action, raising threshold to pain perception also contributes. *No sedation, tolerance, and dependence are produced.*

Aspirin ***resets the hypothalamic thermostat*** and rapidly reduces fever by promoting heat loss (sweating, cutaneous vasodilation), but does not decrease heat production.

2. Antiinflammatory action is exerted at high daily doses of Aspirin (3 to 6 g). Clinical symptoms of inflammation are suppressed, but prolongation of the underlying disease in rheumatoid arthritis, rheumatic fever, and osteoarthritis is not affect.

3. Inhibition of platelet aggregation in low doses (75–100 mg/24 h Aspirin).

4. Metabolic effects of Aspirin and other NSAIDs are significant only at antiinflammatory doses. Cellular metabolism is increased, especially in skeletal muscles, due to uncoupling of oxidative phosphorylation as a

result of increased heat production. There is increased utilization of glucose and blood sugar may decrease (specially in diabetics) and liver glycogen is depleted. However, *hyperglycemia is often seen at toxic doses*: this is due to central sympathetic stimulation and release of adrenaline and GCS. Chronic use of large doses cause negative nitrogen balance by increased conversion of protein to carbohydrate. Plasma free fatty and cholesterol are reduced.

5. Respirations. At antiinflammatory doses respiration is stimulated by peripheral (increased CO_2 production) and central (increased sensitivity of respiratory centre to CO_2) action. Hyperventilation is prominent in salicylate poisoning. Further raise in the salicylate level causes respiratory depression and failure, and death.

6. Acid-base and electrolyte balance. Antiinflammatory doses produce significant changes. Initially respiratory stimulation predominates and tends to wash out CO_2 despite increased production and the result is respiratory **alkalosis**, which is compensated by increased renal excretion of HCO_3^- (with accompanying Na^+, K^+, and water). Most adults treated with 4–6 g/daily of Aspirin stay in a state of compensated respiratory alkalosis. Still higher doses cause respiratory depression with CO_2 retention, while excess CO_2 production continues to develop respiratory **acidosis**. To this are added dissociated salicylic acid as well as metabolic acid (because there is rebound depression). It develops **uncompensated metabolic acidosis**. **Dehydration** occurs in poisoning due to increased water loss in urine.

7. CVS. Larger doses of Aspirin increase cardiac output to meet increased peripheral oxygen demand and cause direct vasodilatation. Toxic doses depress vaso-motor centre: BP falls. Because of increased cardiac work as well as sodium and water retention, CHF my develop if the heart reserves are low.

8. GIT. Aspirin and its metabolite salicylic acid irritate gastric mucosa and cause epigastralgia, nausea, and vomiting. In higher doses it also stimulates CTZ. Aspirin (pKa 3.5) remains unionized and diffusible in the acid gastric juice, but on entering the mucosal cell (pH 7.1) it ionizes and becomes indiffusible. This “ion trapping” in the gastric mucosal cell enhances gastric toxicity.

Further, Aspirin partial contact with gastric mucosa promotes local back diffusion of acid, respectively focal necrosis of mucosal cells and capillaries, acute ulcers, erosive gastritis, congestio, and microscopic haemorrhages. The occult blood loss in stools is increased with any dose of Aspirin, averaging 5 ml/24 h at antinflammatory doses.
Soluble Aspirin tablets containing calcium carbonat + citric acid and other buffered preparations have less gastric toxicity.

Alcohol increasis
GI toxicity of NSAIDs.

9. Urate excretion. Aspirin in high dose reduces renal tubular excretion of urate (both substances are transported by the same mechanism).

Uses of Aspirin® (Bayer, 1899)

As analgesic (300 to 600 mg during 6 to 8 h) for headache, backache, pulled muscle, toothache, neuralgias.

As antipyretic in fever of any origin in the same doses as for analglesia. However, *paracetamol and metamizole are safer*, and generally preferred.

Acute rheumatic fever. *Aspirin is the first drug of choice. Other drugs substitute Aspirin only when it fails or in severe cases*. Antirheumatic doses are 75 to 100 mg/kg/24 h (resp. 4–6 g daily) in the first weeks.

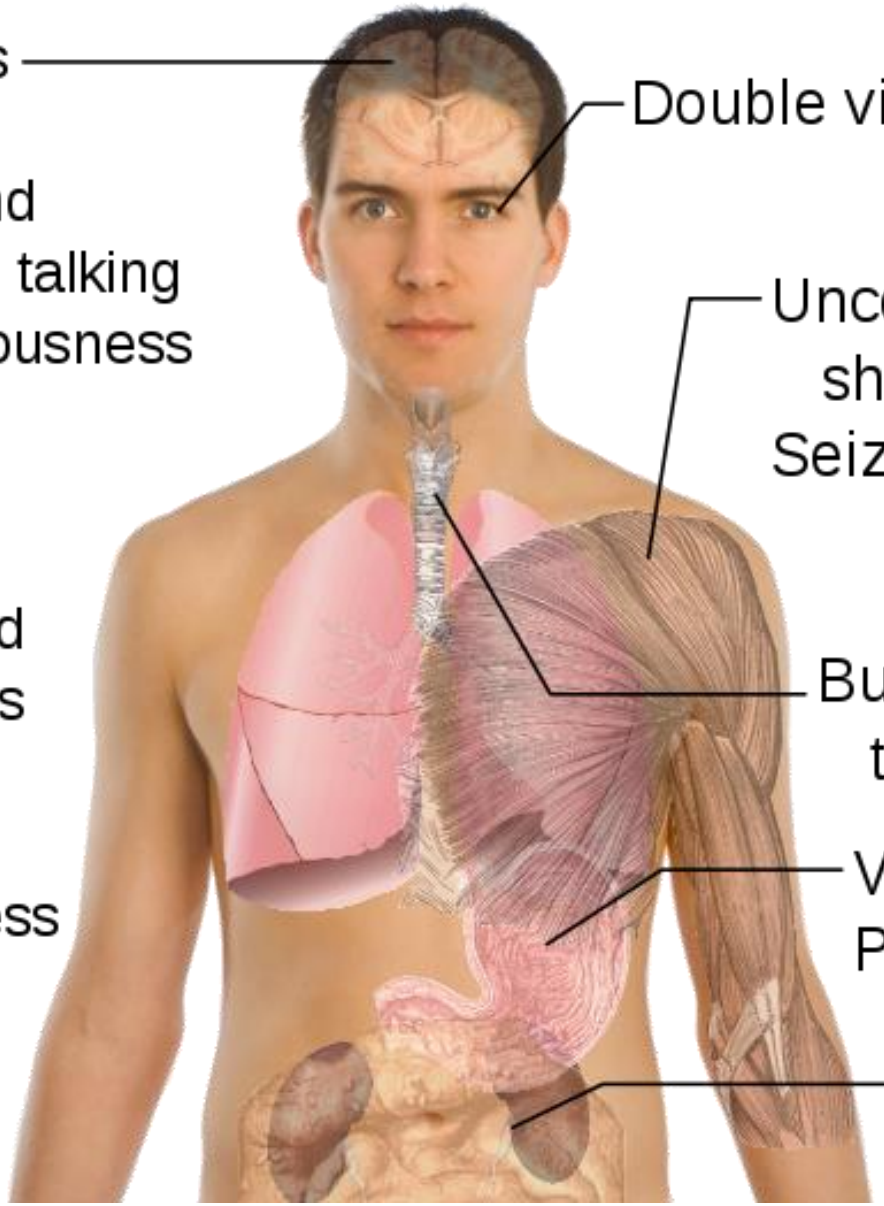
Rheumatoid arthritis. Aspirin a dose of 3 to 5 g/24 h ***after meal*** is effective in most cases. Since large doses of Aspirin are poorly tolerated for a long time, the new NSAIDs (diclofenac, ibuprofen, etc.) in depot form are preferred.

Aspirin therapy in **children** with rheumatoid arthritis has been found to raise serum concentration trans-aminases, indicating liver damage. Most cases are asymptomatic but it is potentially dangerous.
An association between salicylate therapy and "**Reye's syndrome**", *a rare form of hepatic encephalopathy seen in children, having viral infection* (varicella, influenza), has been noted.
Aspirin should not be given to children under 15 years unless specifically indicated, e.g. for juvenile arthritis (paracetamol is preferred).

Postmyocardial infarction and poststroke patients. By inhibiting platelet aggregation in low doses (100 mg daily) Aspirin decreases the incidence of reinfarction.

Symptoms of

Aspirin overdose



Restlessness
Irritability
Excessive and unorganized talking
Fear or nervousness
Dizziness
Confusion
Abnormally excited mood
Hallucinations
Drowsiness
Loss of consciousness

Systemic:
Fever

Double vision

Uncontrollable shaking
Seizures

Burning throat pain

Vomiting
Pain

Decreased urination

Arachidonic acid

Cyclooxygenase (COX)

(–) >1 g/24 h

Aspirin

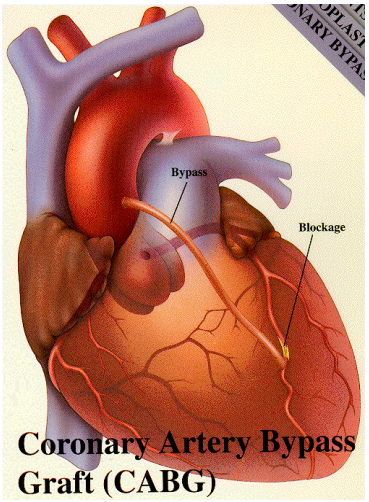
Endoperoxides

(–) 100 mg/24 h

Thromboxane A_2 synthase

PGs

TxA_2

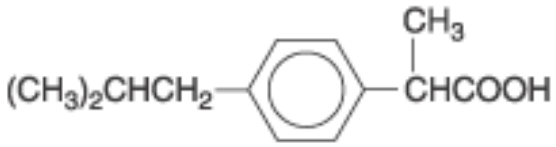


Coronary Artery Bypass Graft (CABG)

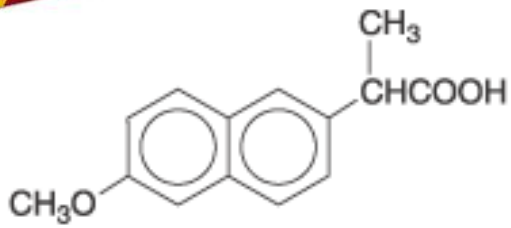
Drug interactions with NSAIDs

Drugs	Result
Diuretics	Decrease diuresis
Beta-blockers	Decrease antihypertensive effect
ACE inhibitors	Decrease antihypertensive effect
Anticoagulants	Increase of GI bleeding
Sulfonylurea	Increase hypoglycemic risk
Cyclosporine	Increase nephrotoxicity
GCS	Increase of GI bleeding
Alcohol	Increase of GI bleeding

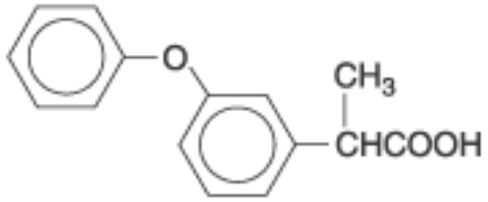
Ibuprofen is a derivative of phenylpropionic acid. In doses of 2.4 g daily it is is equivalent to 4 g of Aspirin in anti-inflammatory effect. Oral ibuprofen is often prescribed *in lower doses* (< 2.4 g/d), at which it *has analgesic but not antiinflammatory efficacy*. It is available in low dose forms under several trade names (e. g. *Nurofen® – film-tabl. 400 mg)*. A topical cream preparation is absorbed into fascia and muscle. A liquid gel preparation of ibuprofen provides prompt relief in postsurgical dental pain. In comparison with indometacin, ibuprofen decreases urine output less and also causes less fluid retention. It is effective in closing ductus arteriosus in preterm infants, with much the same efficacy as indometacin.



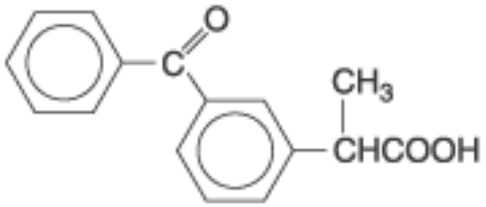
IBUPROFEN



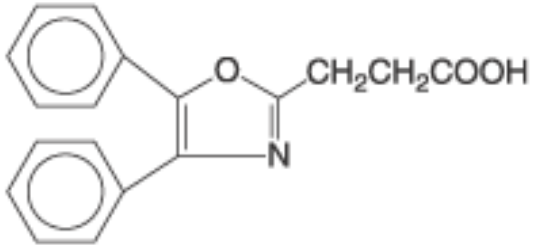
NAPROXEN



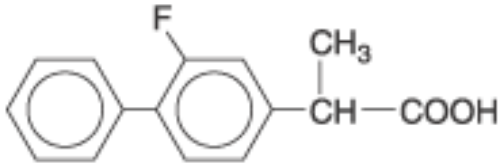
FENOPROFEN



KETOPROFEN



OXAPROZIN



FLURBIPROFEN

Chemical structures of the propionic acid derivatives (propionates)

Flurbiprofen is a propionic acid derivative with a possibly more complex mechanism of action than other NSAIDs. *Its (S)(-) enantiomer inhibits COX nonselectively, but* it has been shown in rat tissue to also *affect TNF-α and NO synthesis*. Hepatic metabolism is extensive. It does demonstrate *enterohepatic circulation*. The efficacy of flurbiprofen at dosages of 200–400 mg/d is comparable to that of Aspirin and other NSAIDs for patients with rheumatoid arthritis, ankylosing spondylitis, gout, and osteoarthritis. Flurbiprofen i.v. is effective for perioperative analgesia in minor ear, neck, and nose surgery and in lozenge form for sore throat. Its adverse effect profile is similar to other NSAIDs.

Ketoprofen is a propionic acid derivative that *inhibits both COX (nonselectively) and lipoxygenase*. Concurrent administration of probenecid elevates ketoprofen levels and prolongs its plasma half-life. The effectiveness of ketoprofen at dosages of 100–300 mg/d is equivalent to that of other NSAIDs in the treatment of rheumatoid arthritis, osteoarthritis, gout, dysmenorrhea, and other painful conditions. In spite of its **dual effect on prostaglandins and leukotrienes**, ketoprofen is not superior to other NSAIDs. Its major adverse effects are on the GIT and the CNS.

Phenylbutazone is a derivative of pyrazolidinedione with a high GI toxicity. It is rarely used now.

Indometacin is a potent ***nonselective COX inhibitor and may also inhibit phospholipase A and C, reduce neutrophil migration, and decrease T cell and B cell proliferation***. Probenecid prolongs indometacin's half-life by inhibiting both renal and biliary clearance. Indometacin is indicated for use in juvenile rheumatoid arthritis, gout and ankylosing spondylitis, postepisiotomy pain, etc. It has been used to **treat patent ductus arteriosus**. An ophthalmic preparation seems to be efficacious for conjunctival inflammation and to reduce pain after traumatic corneal abrasion. **Gingival inflammation** is reduced after administration of indometacin **oral rinse**. A high incidence (up to 50%) of GI and CNS side effects is produced: GI bleeding, diarrhoea, frontal headache, **mental confusion**, etc.

Diclofenac is a phenylacetic acid derivative. A 0.1% ophthalmic preparation is recommended for prevention of postoperative ophthalmic inflammation and can be used after intraocular lens implantation and strabismus surgery. A topical gel containing 3% diclofenac is effective for solar keratoses. Diclofenac in rectal suppository form can be considered a drug of choice for analgesia and postoperative nausea. It is also available for intramuscular and oral administration (***Voltaren® and Feloran® – SR tablet: 100 mg/24 h***). Side effects occur in approximately 20%: GI distress and occult bleeding, gastric ulceration. A preparation combining diclofenac and misoprostol (PGE_1) decreases upper GI ulceration but may result in diarrhoea.

Piroxicam, an oxicam (enolate derivative), is a ***nonselective COX-1/COX-2 inhibitor*** that at high concentrations ***also inhibits polymorphonuclear leukocyte migration, decreases oxygen radical production, and inhibits lymphocyte function***.
Its **long half-life** permits once-daily dosing. Piroxicam can be used for the usual rheumatic indications. Toxicity includes GI symptoms (20% of patients), dizziness, tinnitus, headache, rash. When piroxicam is used *in dosages higher than 20 mg/d, an* ***increased incidence of peptic ulcer and bleeding*** *is encountered*. ***This risk is as much as 10 times higher with piroxicam than with other NSAIDs***.

COX-2 inhibitors

(1) *Selective COX-2 inhibitors (Coxibs)*

- Celecoxib
- Etoricoxib
- Parecoxib

(2) *Preferential COX-2 inhibitors*

- Meloxicam
- Nimesulide
- Nabumetone

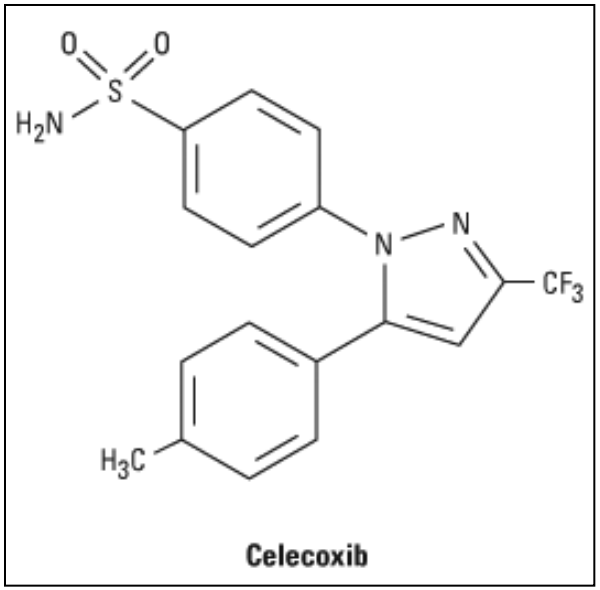
Inhibiting activity rate (COX-2/COX-1)

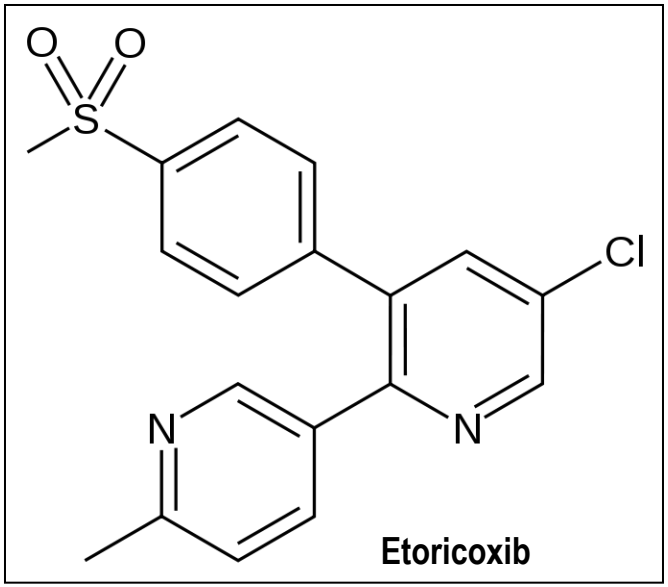
- **Aspirin 155**
- **Indometacin 60**

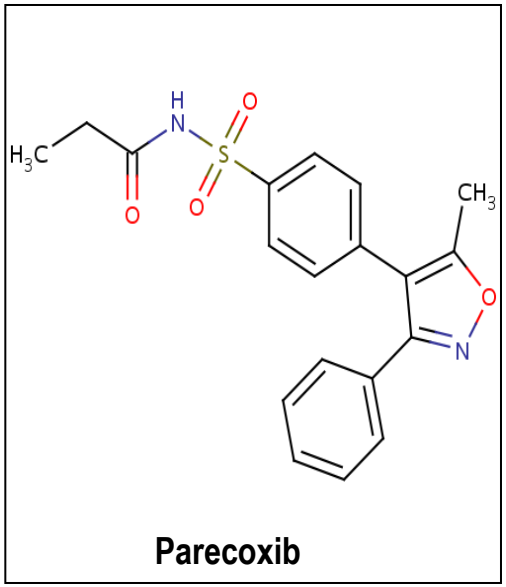
Classical NSAIDs

- **Meloxicam 0,8**

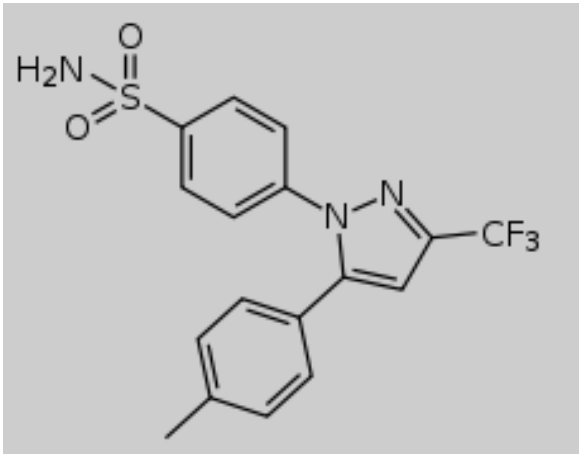
(***Preferential COX-2 inhibitor***)







Coxibs are selective COX-2 inhibitors. They exert antiinflammatory, analgesic, and antipyretic action with low ulcerogenic potential. **Coxibs can cause infertility. They have prothrombotic cardiovascular risk.** **The ulcerogenic potential of preferential COX-2 inhibitors** Meloxicam, Nabumetone, and Nimesulide (Aulin®) is significant.



Celecoxib is as effective as other NSAIDs in the treatment of rheumatoid arthritis and osteoarthritis, and in trials it has caused fewer endoscopic ulcers than most other NSAIDs. Probably because it is ***a sulfonamide***, celecoxib may cause ***rashes***.
It does not affect platelet aggregation at usual doses. It interacts occasionally with warfarin – would be expected of a drug metabolized via CYP 2C9.

Etoricoxib is a *second-generation* COX-2-selective inhibitor with the highest selectivity ratio of any coxibs. It is extensively metabolized by hepatic CYP450 enzymes followed by renal excretion and has an elimination $t_{1/2}$ *of 22 h*. Etoricoxib is approved in the UK for the treatment of the symptoms of osteoarthritis (60 mg once daily) and rheumatoid arthritis (90 mg once daily), acute gouty arthritis (120 mg once daily), and for the relief of acute musculoskeletal pain (60 mg once daily). Ninety mg daily of etoricoxib has superior efficacy compared with 500 mg of naproxen twice daily in the treatment of rheumatoid arthritis over 12 weeks. Etoricoxib has similar efficacy to traditional NSAIDs for osteoarthritis, acute gouty arthritis, and primary dysmenorrhea and has a GI safety profile similar to other coxibs.

Meloxicam is an enolcarboxamide related to piroxicam that has been shown to preferentially inhibit COX-2 over COX-1, particularly at its lowest therapeutic dose of 7.5 mg/d. It is not as selective as the other coxibs and may be considered “ ***preferentially" selective*** ***rather than “highly” selective.***

The drug has been approved for the treatment of osteoarthritis and rheumatoid arthritis.

It is associated with fewer clinical GI symptoms and complications than piroxicam, diclofenac, and naproxen. Other toxicities are similar to those of other NSAIDs.

Comparative action between COX inhibitors	COX-1/COX-2 inhibitors	COX-2 inhibitors
1. Analgesic action	(+)	(+) (+)
2. Antipyretic action	(+)	(+)
3. Antiinflammatory action	(+)	(+) (+)
4. Antiplatelet aggregatory	(+)	(-)
5. Gastric mucosal damage	(+) (+) (+)	(+)
6. Renal salt / water retention	(+)	(+)
7. Delay/prolongation of labor	(+) (+)	(+)
8. Infertility	(-)	(+) (+)
9. Ductus arteriosus closure	(+)	?
10. Aspirin-like asthma	(+)	?
11. Cardiotoxicity	(-)	(+) (+)

Bextra® (Valde[illegible]): Pfizer (penalty!)

Many severe side effects

- Infertility (> $PGF_{2\alpha}$)
- Thrombosis (< PGI_2; > TxA_2)

NONOPIOID ANALGESICS

(1) Anilides

Paracetamol – tabl. 500 mg

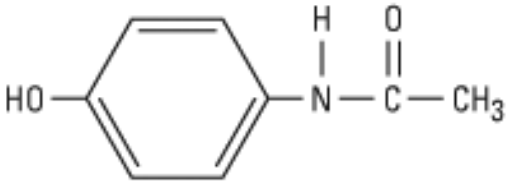
(Acetaminophen – USAN)

Propacetamol (prodrug)

(2) Pyrazolones

Metamizole

(Analgin® – tabl. 500 mg)



COX-3 inhibitors (antipyretic analgesics)

(3) COX-1/COX-2 inhibitors

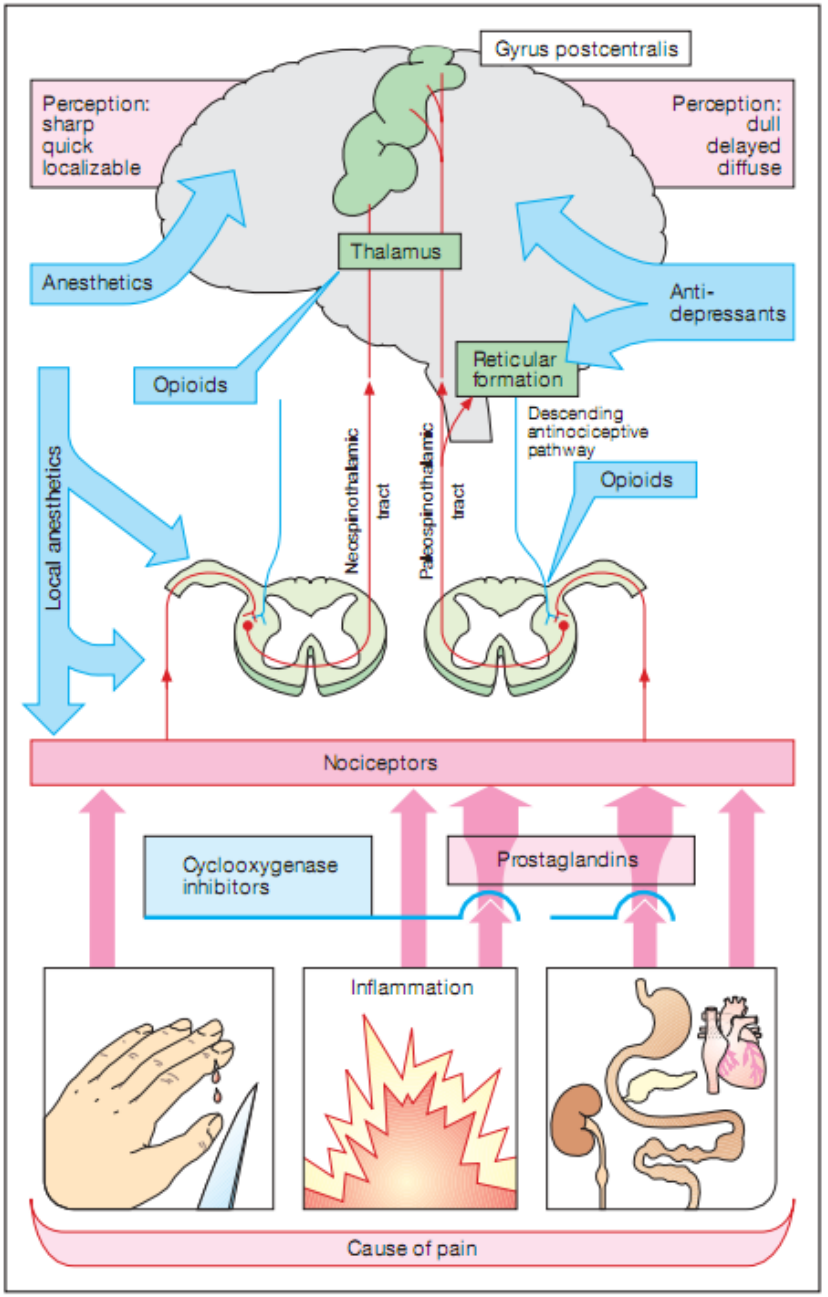
Aspirin®, Diclofenac,

Ibuprofen, Naproxen etc.

(4) COX-2 inhibitors

NSAIDs in low doses

Pathogenesis of pain



Lüllmann, Color Atlas of Pharmacology – 2nd Ed. (2000)

Acetaminophen (USAN)
(Paracetamol – INN)

- Efferalgan®
- Panadol®
- ParacetaMAX®

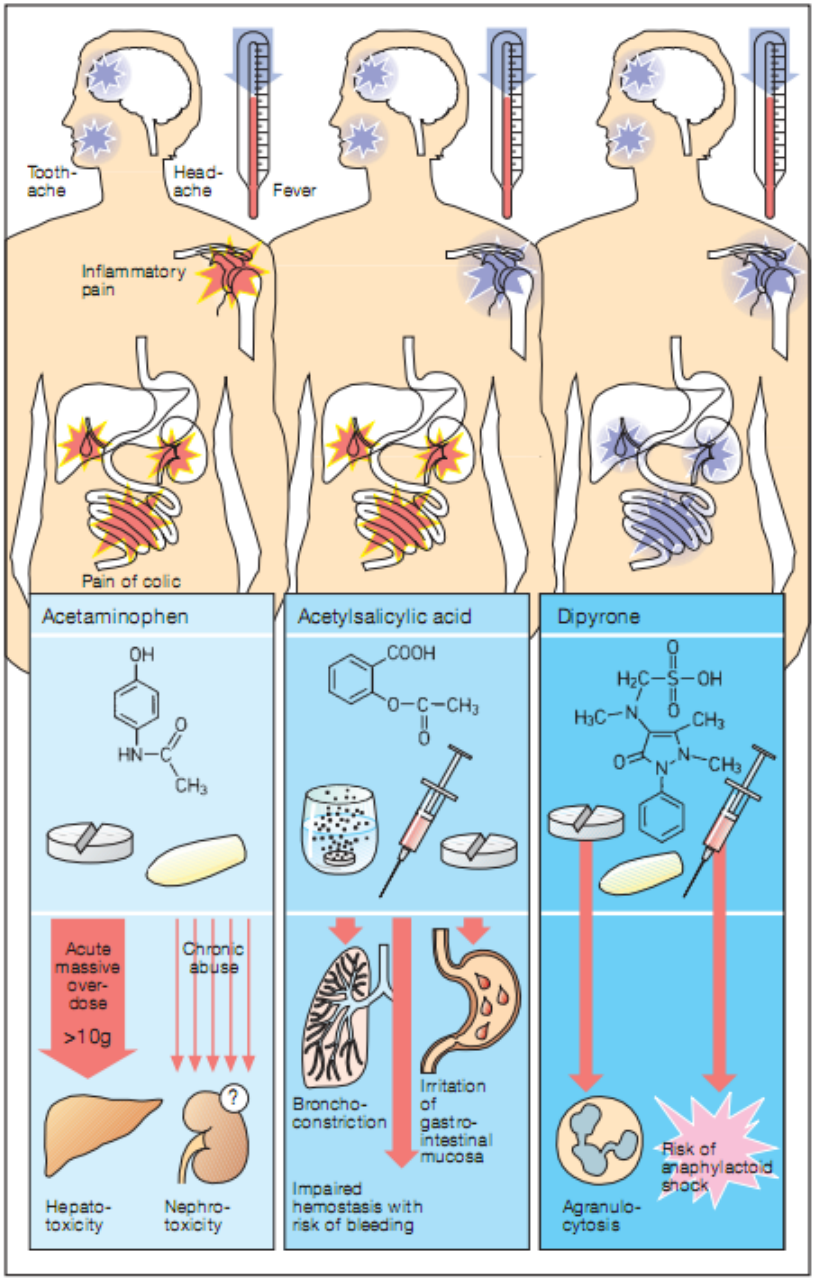
Propacetamol is a prodrug.
It converts into paracetamol.

Acetylsalicylic acid

- Aspirin®
- Aspegic® lisinate

Dipyrione (BAN)
(Metamizole – INN)

- Analgin®
- Proalgin®



Lüllmann, Color Atlas of Pharmacology – 2nd Ed. (2000)

Paracetamol Although equivalent to Aspirin as an effective analgesic and antipyretic agent, paracetamol differs in that it lacks antiinflammatory properties. It does not affect uric acid levels and lacks platelet-inhibiting properties. The drug is useful in mild to moderate pain: headache, myalgia, postpartum pain. Paracetamol alone is inadequate therapy for inflammatory conditions such as rheumatoid arthritis, although it may be used as an analgesic adjunct to antiinflammatory therapy. For mild analgesia, paracetamol is the preferred drug in patients allergic to Aspirin or when salicylates are poorly tolerated. It is preferable to Aspirin in patients with hemophilia or a history of peptic ulcer and bronchospasm. It is preferred to Aspirin in children with viral infections.

Acute paracetamol poisoning occurs especially in small children who have low hepatic glucuronide conjugating ability. If a large dose (> 150 mg/kg or > 10 g in adult) is taken, serious toxicity can occur. The letal dose is 250 mg/kg. **N-acetyl-p-benzoquinoneimine (NABQI)** is a highly reactive arylating metabolite of paracetamol which detoxicated by *conjugation with glutathione*. When a very large doses of paracetamol are taken, the glucuroconjugation capacity is saturated, more NABQI is formed, hepatic glutathione is depleted and NABQI binds covalently to proteins in liver cells (and renal tubules) causing necrosis. In chronic alcoholics even 5-6 g/d taken for a few days can result in hepatotoxicity because ethanol induces CYP 2E2, that metabolizes paracetamol, to NABQI. Treatment needs activated charcoal, given orally or through the tube to prevent GI absorption, **and acetylcysteine** (150 mg/g by i.v. infusion).

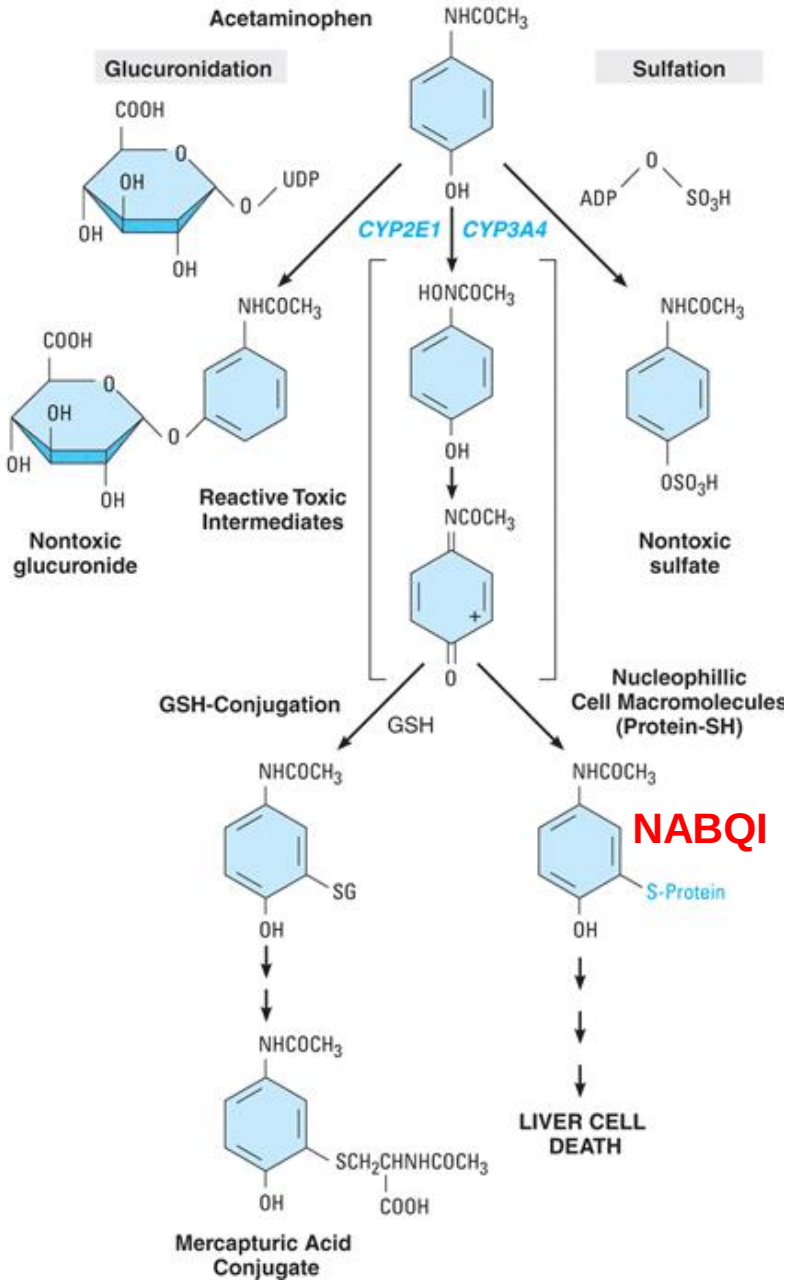
Metabolism of paracetamol to hepatotoxic metabolites (NABQI etc.)

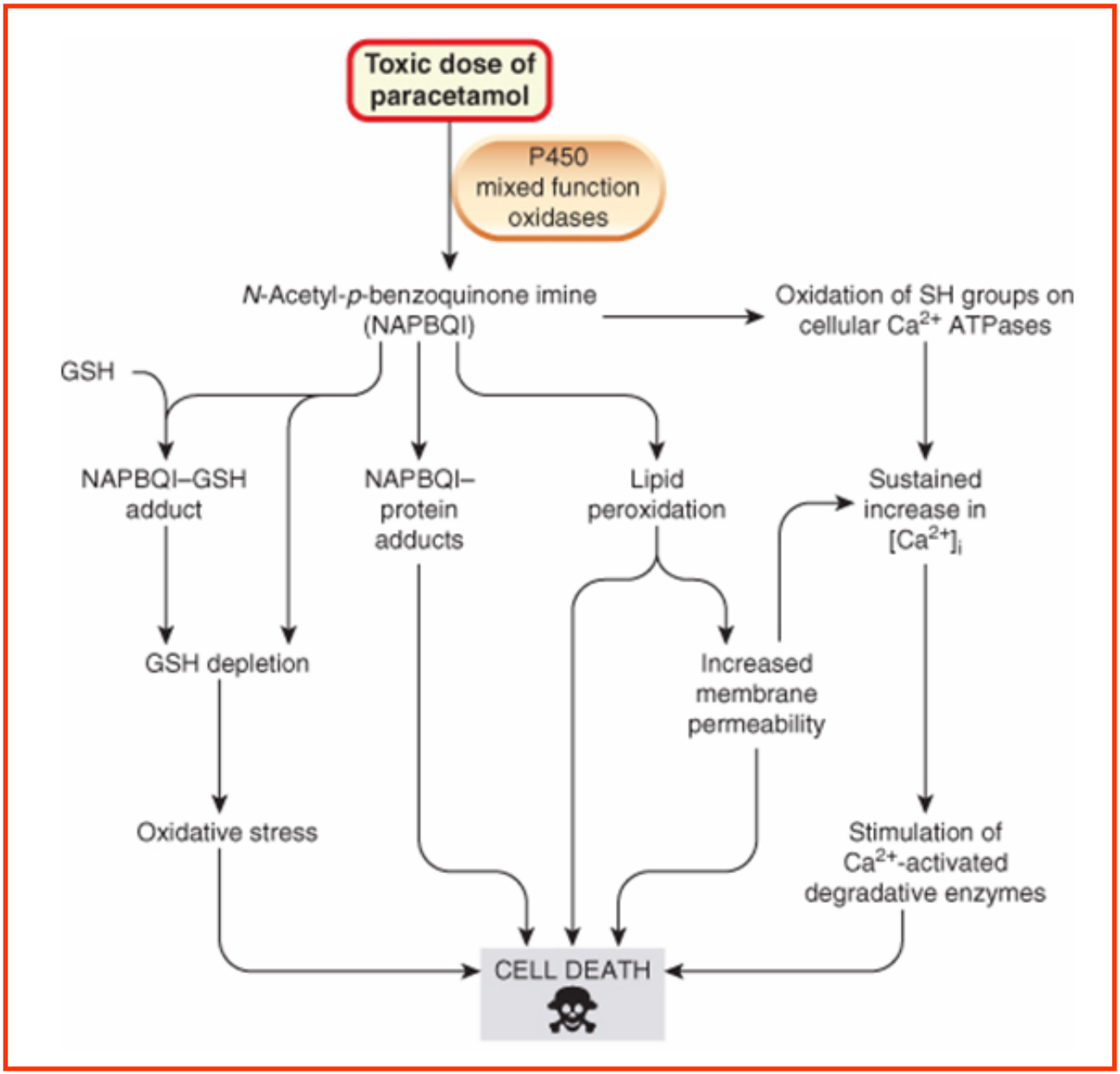
(GSH – glutathione; SG – glutathione moiety)

Daily dose > 7.5 g:
hepatotoxicity and nephrotoxicity

NB: Acetylcysteine and GSH contain **–SH** groups.

Basic & Clinical Pharmacology – 10th Ed. (2007)



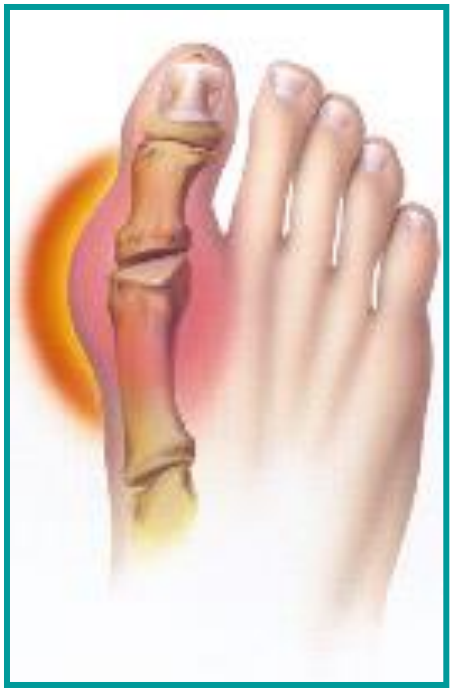


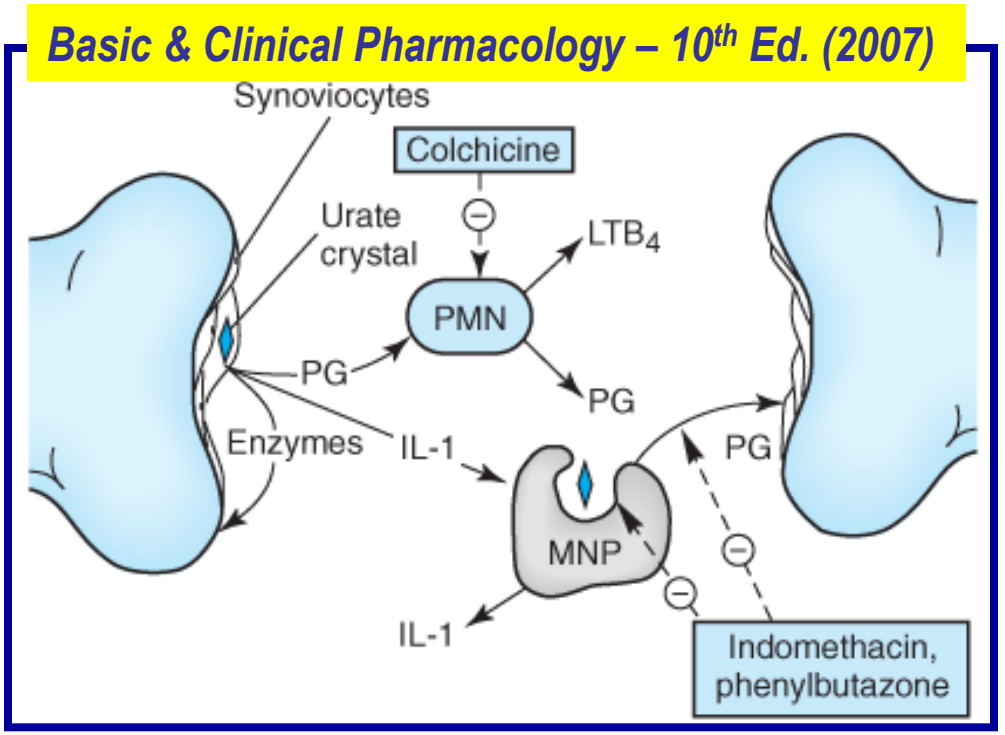
Rang et al. *Pharmacology* – 6th Ed. (2007)

Metamizole (*Analgin*® – tabl. 500 mg, Dipyron) is a derivative of pyrazolone. It is a **potent and promptly acting analgesic, antipyretic, and spasmolytic** but has poor antiinflammatory and not uricosuric activity. Analgin can be given orally, i.m. as well as i.v. (very slowly).

Pain at the i.m. injection site and rarely abscess can occur. *Occasionally an i.v. injection produces fall in BP*. *Few cases of agranulocytosis* were reported and metamizole was banned in the USA and some European country. However, it has been extensively used in Bulgaria and many other European country, as well as in India and Russia. *Adverse reaction data collected* ***over four decades*** *shows that the risk of serious toxicity with metamizole is very low than with Aspirin or many other NSAIDs.*

GOUT



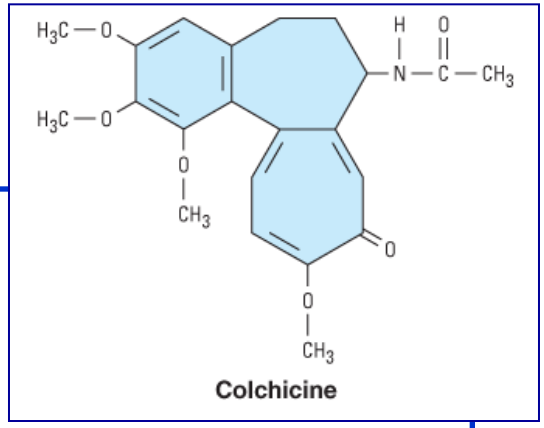


Pathophysiologic events in a gouty joint

Synoviocytes phagocytose urate crystals and then secrete inflammatory mediators, which attract and activate polymorphonuclear leukocytes (PMN) and mononuclear phagocytes (MNP) (macrophages). *Drugs active in gout inhibit crystal phagocytosis and polymorphonuclear leukocyte and macrophage release of inflammatory mediators*.

(**PG** – prostaglandin; **IL-1** – interleukin-1; **LTB_4** – leukotriene B_4)

DRUGS IN GOUT



(1) Acute goat

Colchicine

Diclofenac, Indometacin,

Naproxen, Phenylbutazone, Piroxiam

(2) Chronic gout

Uricostatics (xantine oxidase inhibitors)

Allopurinol, Febuxostat

Uricosurics

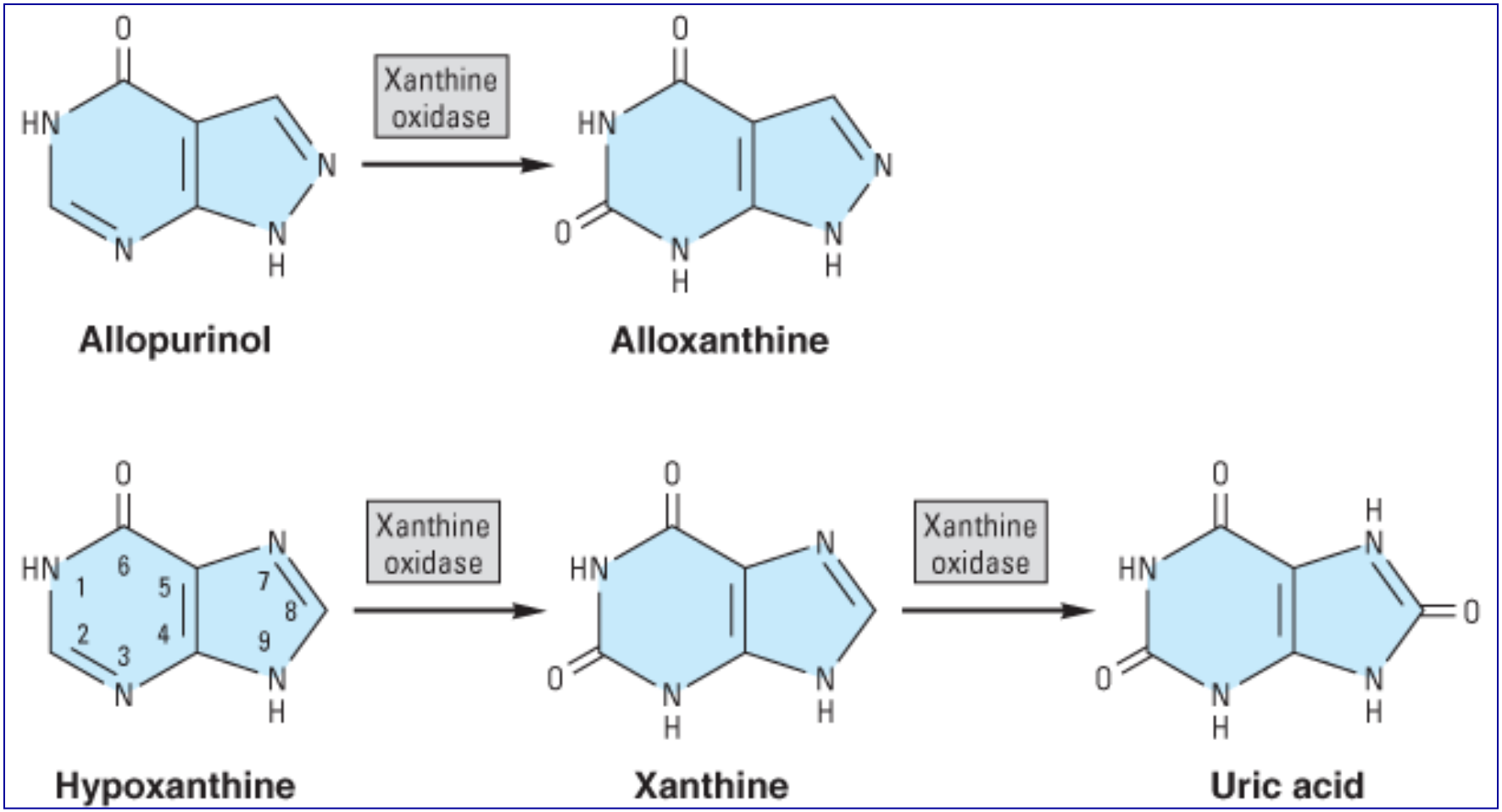
Benzbromarone, Probenecide

Sulfinpyrazone

Uricolytics: Uricase, Rasburicase

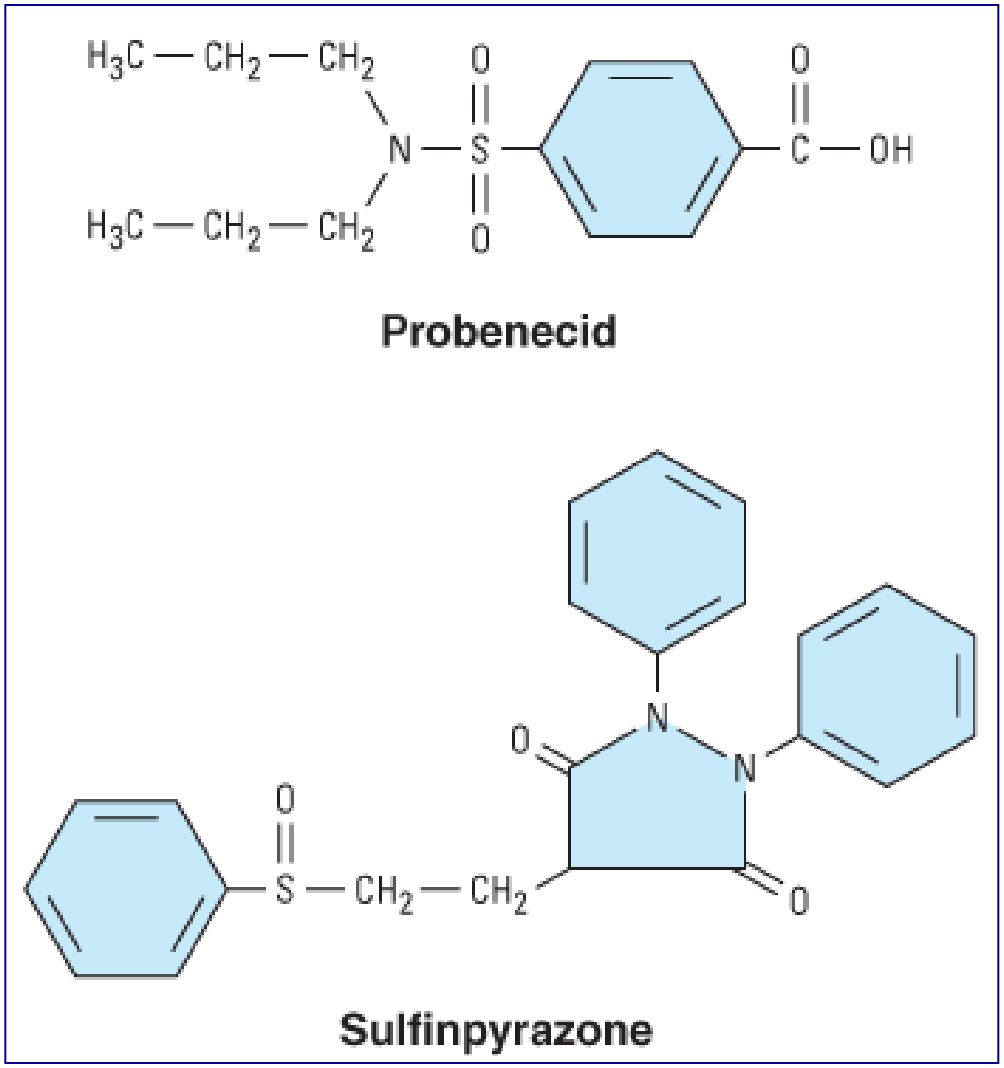
Drug combinations

Harpagin® (allopurinol & benzbromarone)



Inhibition of uric acid synthesis by allopurinol

Basic & Clinical Pharmacology – 10th Ed. (2007)



Uricosuric drugs

ANTIRHEUMATOID DRUGS

❶ **Antiinflammatory drugs**
NSAIDS: diclofenac, celecoxib, ibuprofen, piroxicam, etc.
Glucocorticosteroids: prednisone, methylprednisolone, betamethasone, etc.

❷ **Disease modifying antirheumatic drugs (DMARDs):**
adalimumab, cyclosporine, etanercept, infliximab, leflunomide, methotrexate, sulfasalazine, gold (Auranofin®), etc.