# Acetylsalicylic acid and salicylates

# Aspirin

# Willow

Papyrus of Ebers 1500 a.c.

bark and willow leaves

Hippocrates: V a.c. analgesic action of the sap extracted from the bark of the willow tree

Reverend Edward Stone, botanist expert, who tasted by chance a piece of bark of a willow, the bitter taste made him remember that of the cinchona from which quinine was extracted. Report (1763) to the Royal Society of London

# Towards Aspirin

- 1826-29: various researchers isolate a glycoside active ingredient of the willow bark (salicin)
- In 1835, in Switzerland, from a wild bush - spirea ulmaria - a similar substance was obtained: it was called "spirsauro“. A few years later it was realized that it was pure salicylic acid
- A Calabrian chemist, Raffaele Piria discovered that salicylic acid could be derived from salicin

# Raffaele Pirìa (1814-1865) chemist

- Ardent patriot, involved in First Independence War in 1848

- Ordinary Member of Superior Council del Consiglio Public Education in 1859
- Senator in 1862

*Together with his student Stanislao Cannizzaro promoted a real "national program" of research in chemistry, both in institutional terms and concerning research themes*

# Pirìa gave seminal contributions to the history of aspirin

willow

willow bark

In 1838, Pirìa, in Paris, isolated and purified salicylic acid from compounds extracted from willow bark (“salicilin”)

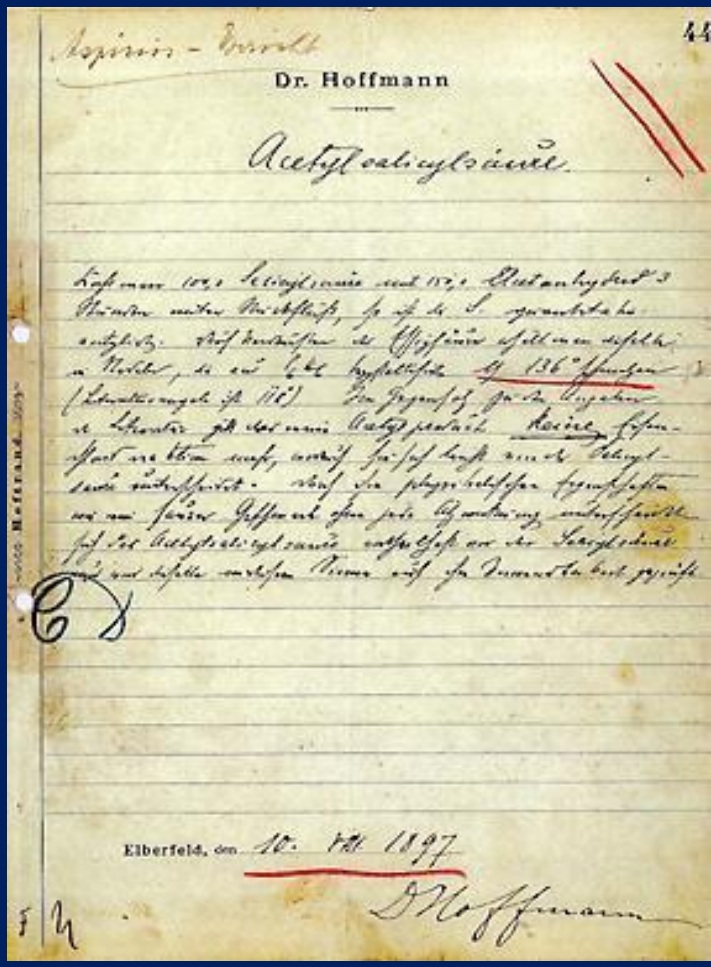
He returned to Italy in 1839

# Towards Aspirin

In 1853: the French chemist Charles Frédéric Gerhardt first obtained **salicylic acid**, but did not market it

Later the German Hermann Kolbe discovered the structure of **salicylic acid** and synthesized it
In 1874 the industrial production of **salicylic acid** could be started. Because of its acidity, it caused severe irritation of the mucous membranes of the mouth, throat and stomach

The laboratory note in which Hoffmann describes acetylsalicylic acid (ASA), which he synthesized in a chemically pure and stable form




The turning point came in 1893, when Felix Hoffmann, a chemist from the German company Bayer, rediscovered Gerhardt's formula, capable of treating his father's rheumatism, developing an advantageous synthesis of acetylsalicylic acid, with the same therapeutic properties as salicylic acid, without however irritate the oral and gastric mucosa





**1899 Aspirin (acetyl-spirea)**

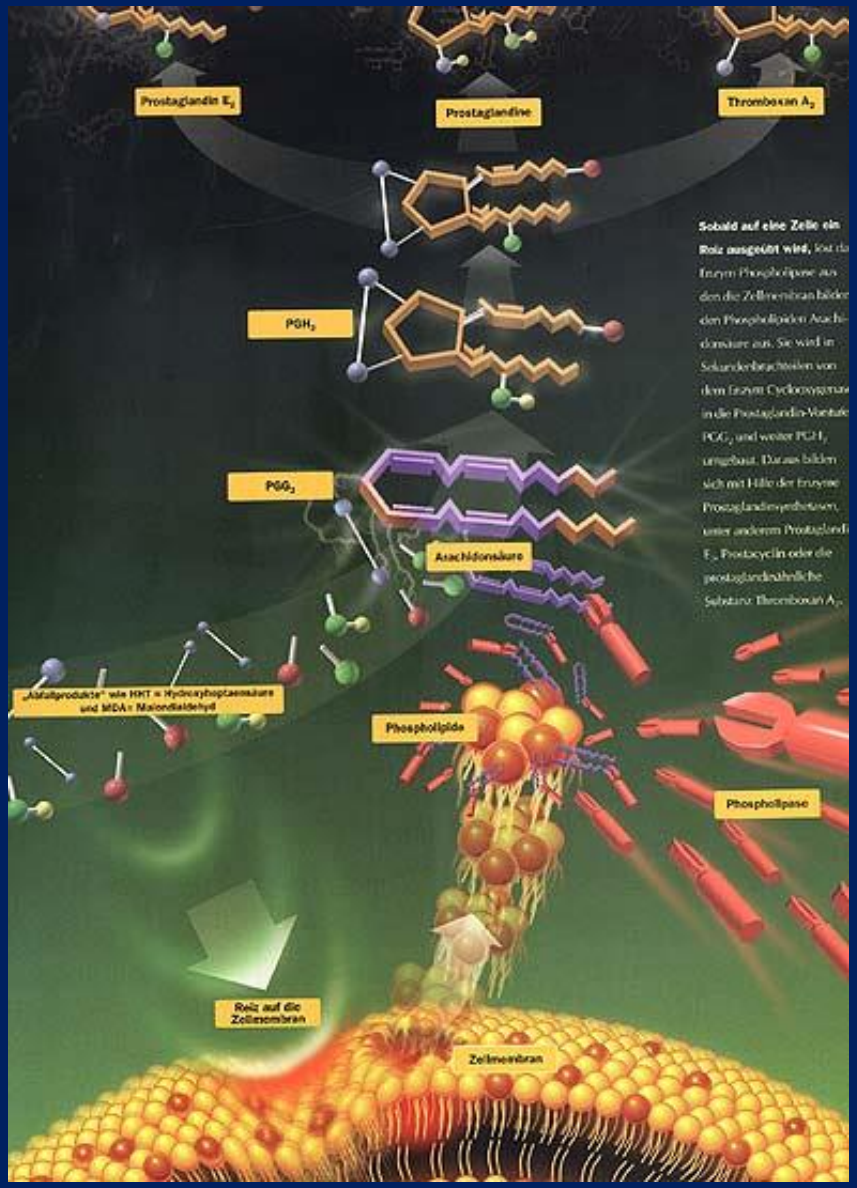


**From the early 1950s Aspirin is the most well-known drug in the world for the most common disorders, from cold to migraine**

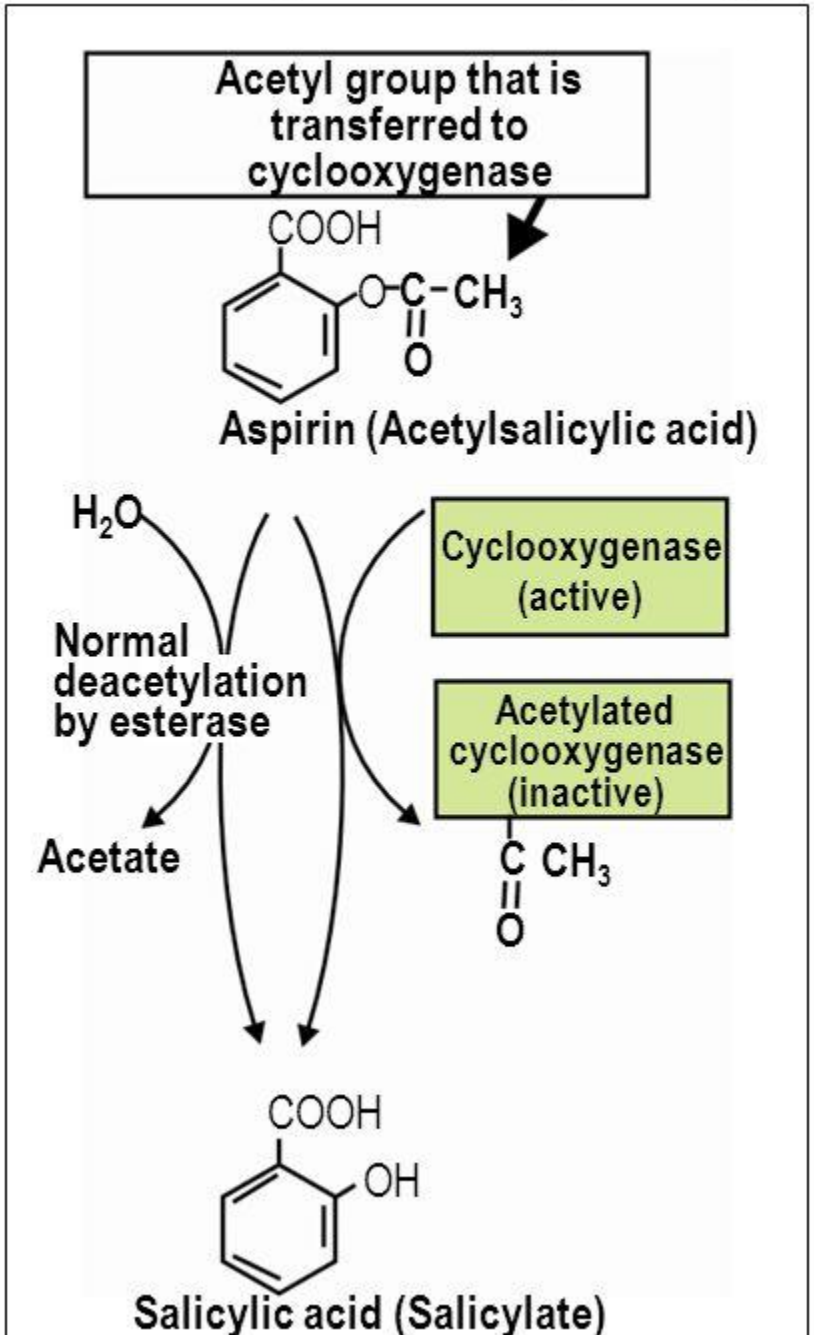
# Discovery of the mechanism of action of NSAID

June 23rd, 1971

John Vane, professor of pharmacology at the Royal College of Surgery London published his studies on the mechanism of action of ASA, under the title **"Inhibition of Prostaglandin Synthesis as a Mechanism of Action of Aspirin-like Drugs"** in the journal Nature. He discovered that ASA had analgesic, antipyretic effects and anti-inflammatory properties because it inhibits the synthesis of some messenger substances (prostaglandins) in the body

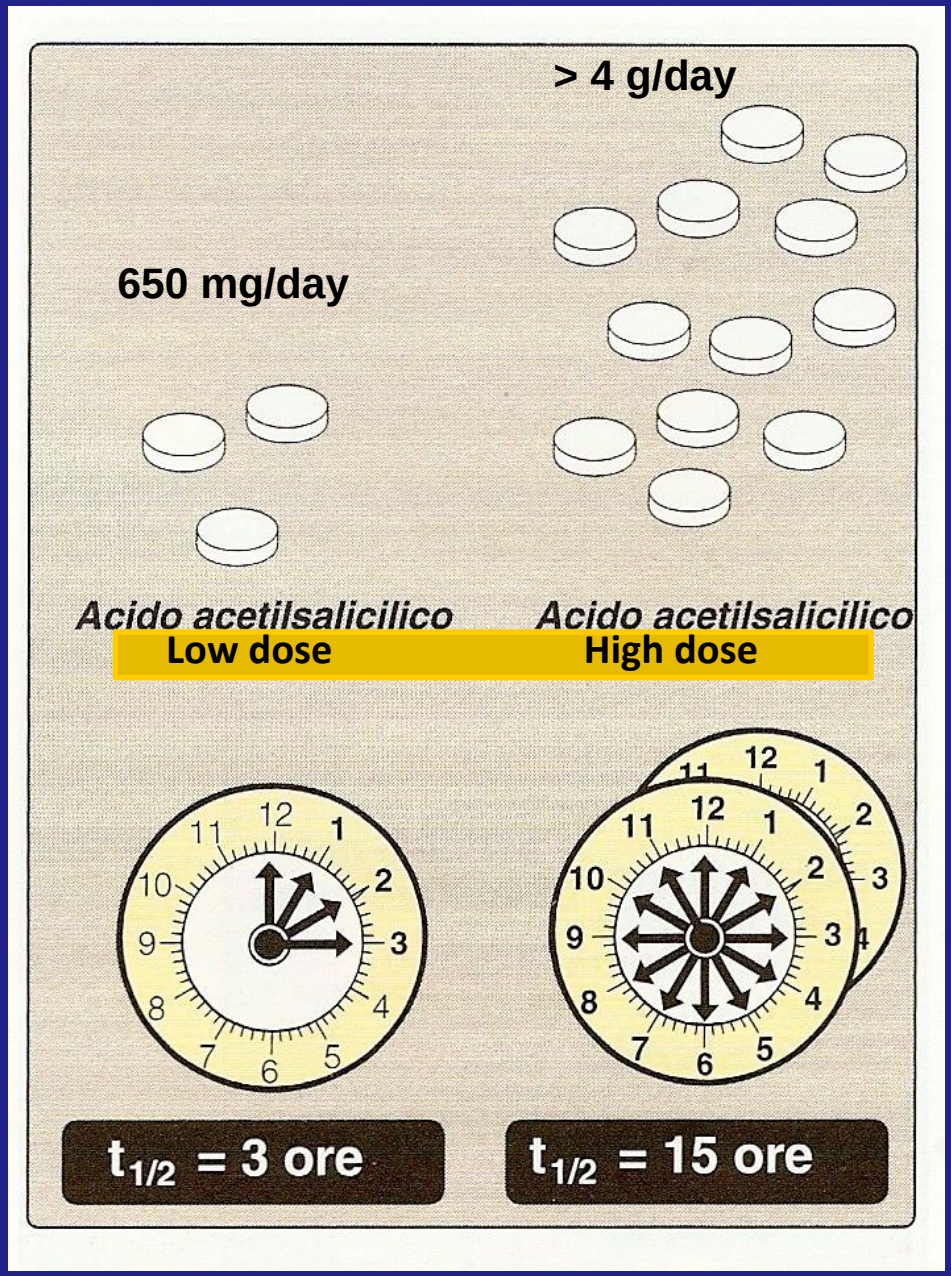


# Metabolism of aspirin and acetylation of cyclooxygenase by aspirin




**Irreversible**
Acetylation

(according to Lippincott´s Pharmacology, 2006

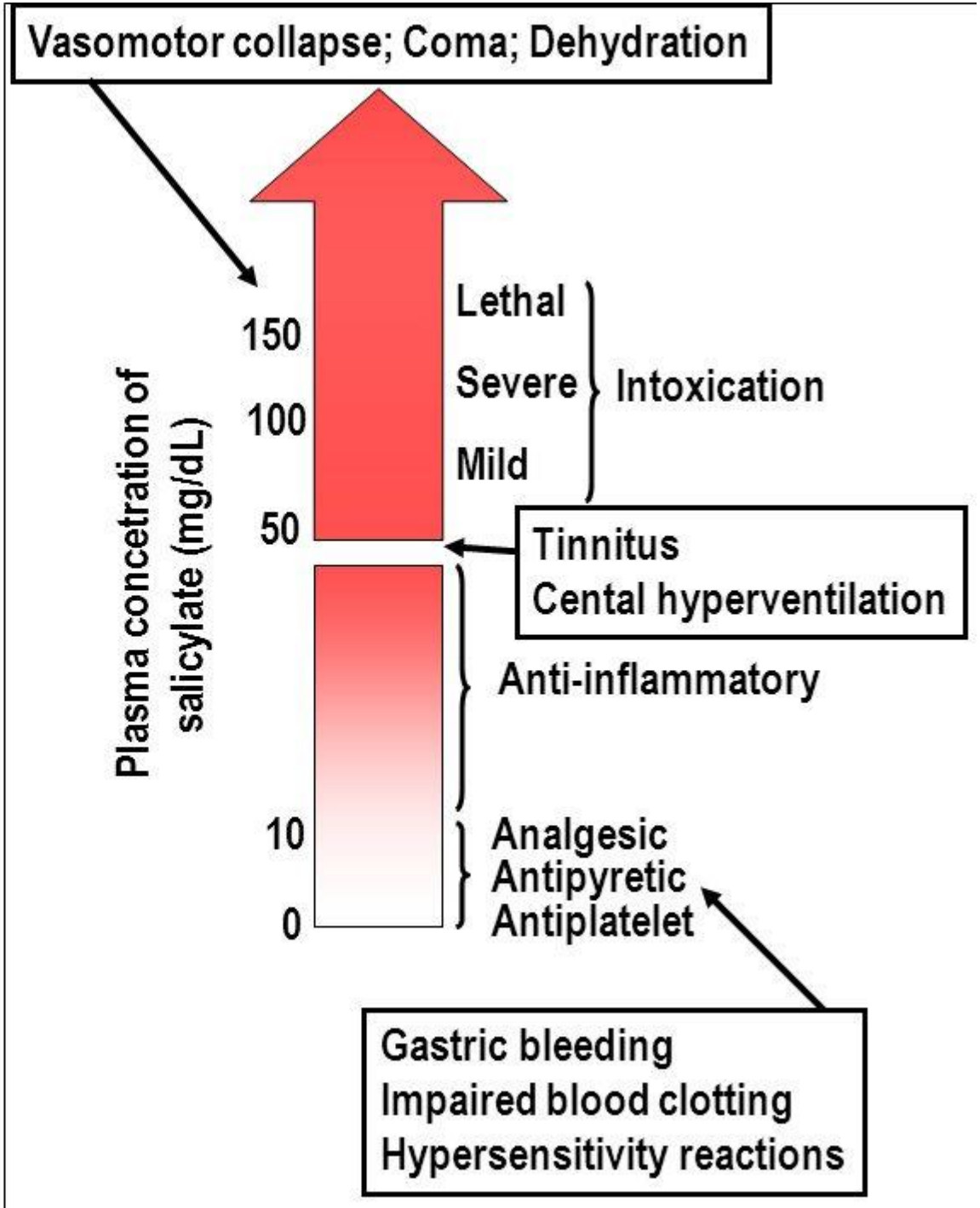



**Kinetics: 1 order 0 order (saturation)**

# EFFECT OF THE DOSE ON THE HALF-LIFE OF ASPIRIN

Dissolution (low in stomach)
Absorption (facilitated in stomach)
Dosage
In the liver water-soluble conjugates are formed, excreted by the kidney

# Dose-dependent effects of salicylate




(according to Lippincott´s Pharmacology, 2006

# Aspirin

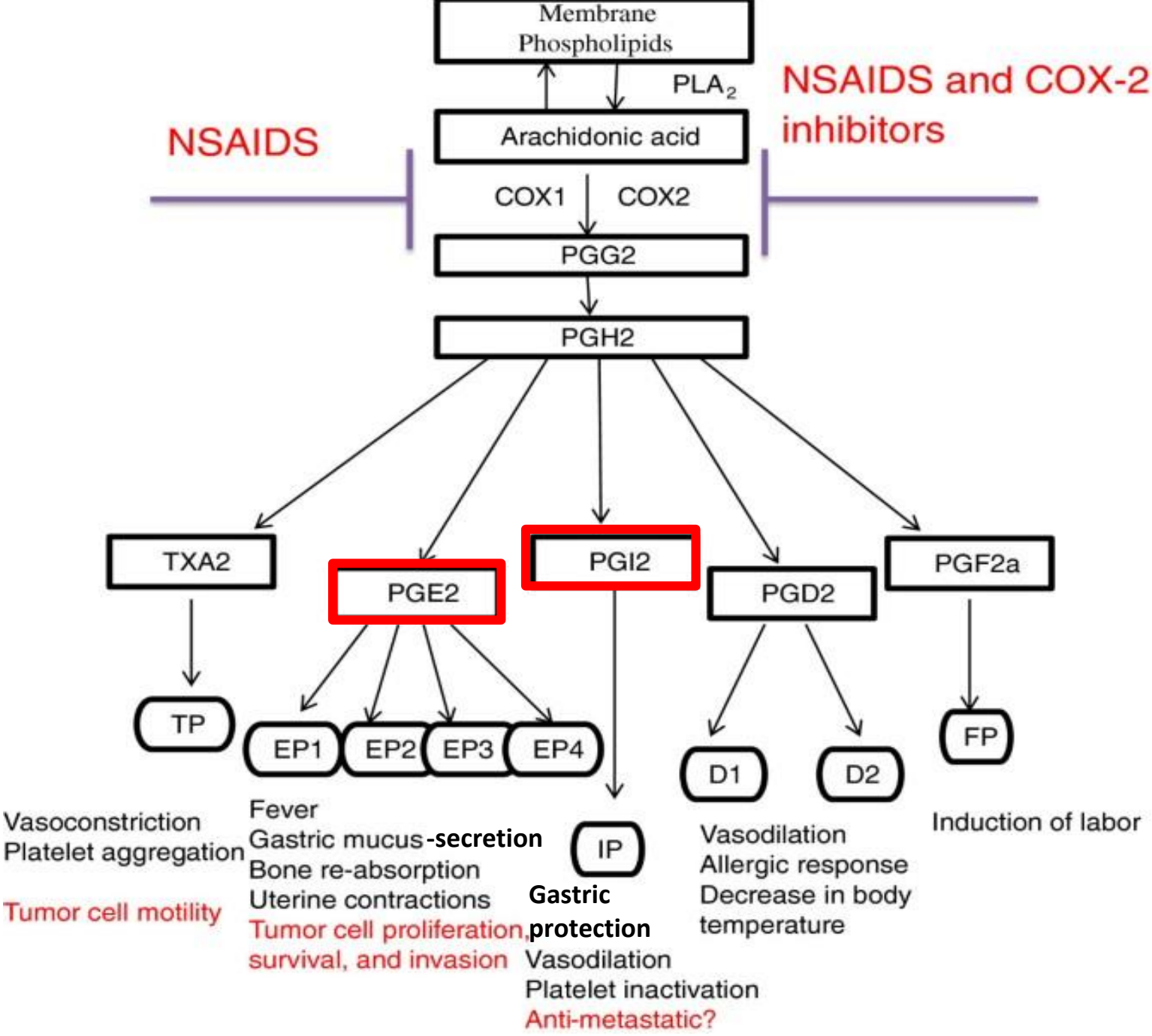
Low Doses ← 1) Uncoupling oxidative phosphorylation + $O_2$ + $CO_2$ + breathing (respiratory center stimulation)

High Doses ← 2) Hyperventilation and alkalosis (+ bicarbonate excretion)

Toxic Doses ← 3) Respiratory paralysis + $CO_2$ + escretion bicarbonate (acidosis resp.)

Reye's Syndrome (pediatric age)

# Gastrointestinal effects


Membrane Phospholipids
PLA2
NSAIDS
NSAIDS and COX-2 inhibitors
Arachidonic acid
COX1
COX2
PGG2
PGH2
TXA2
PGE2
PGI2
PGD2
PGF2a
TP
EP1
EP2
EP3
EP4
IP
D1
D2
FP
Vasoconstriction
Platelet aggregation
Tumor cell motility
Fever
Gastric mucus-secretion
Bone re-absorption
Uterine contractions
Tumor cell proliferation, survival, and invasion
Gastric protection
Vasodilation
Platelet inactivation
Anti-metastatic?
Vasodilation
Allergic response
Decrease in body temperature
Induction of labor

# Risk factors for NSAID gastropathy

**- General**

Age
Gender (female)
Stress, anxiety
Abuse of substances: smoke, alcohol….
Other drugs interaction

**- Specific**

Presence of past gastritis or other gastric pathologies
Intollerance to NSAID

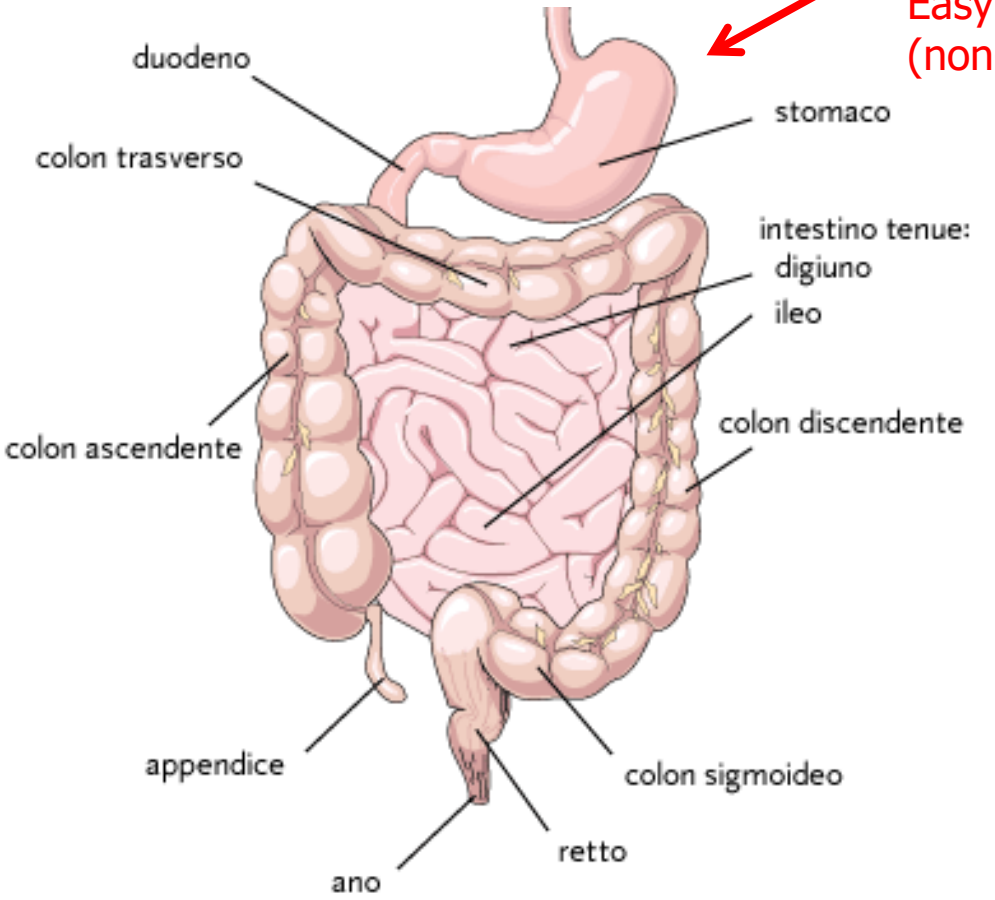
**Tab. 4.3.** Meccanismi di danno dell'epitelio gastrointestinale indotto dai FANS.

- **Azione sistemica dei FANS**
  - Riduzione della secrezione e della viscosità del muco
  - Riduzione della secrezione di bicarbonati
  - Inibizione dei processi di rigenerazione tissutale
  - Alterazioni del flusso ematico locale
  - Aumentata sintesi locale di sostanze ad azione lesiva
  - Aumentata infiltrazione mucosa da parte dei polimorfonucleati
  - Interazioni negative con i sali biliari
  - Ritardo di cicatrizzazione di lesioni preesistenti
- **Azione lesiva topica dei FANS**
  - Assottigliamento e riduzione della viscosità del muco
  - Ridotta produzione di bicarbonati
  - Riduzione del flusso ematico locale
  - Ridotta secrezione di fattori di crescita
  - Penetrazione intracellulare con effetto tossico diretto (ASA)

# Aspirin

Low dissolution
(Gastrointestinal side)

Easy absorption
(non-ionized, basic plasma)



# NSAID gastropathy and peptic disease

| | Gastropatia da FANS | Malattia peptica |
|---|---|---|
| Eziologia | Uso di FANS | Multifattoriale |
| Patogenesi | Inibizione sintesi PG<br>Caduta difese di barriera della mucosa<br>Modificazioni dei fattori di protezione | Ipersecrezione acida non compensata da incremento dei fattori di protezione |
| Localizzazione | Stomaco (70% casi) | Duodeno |
| Età insorgenza | Più frequente negli anziani | Più frequente nei giovani |
| Sintomatologia | Varia, spesso assente | Dolore, pirosi, dispepsia |

# Prevention and therapy of gastropathy

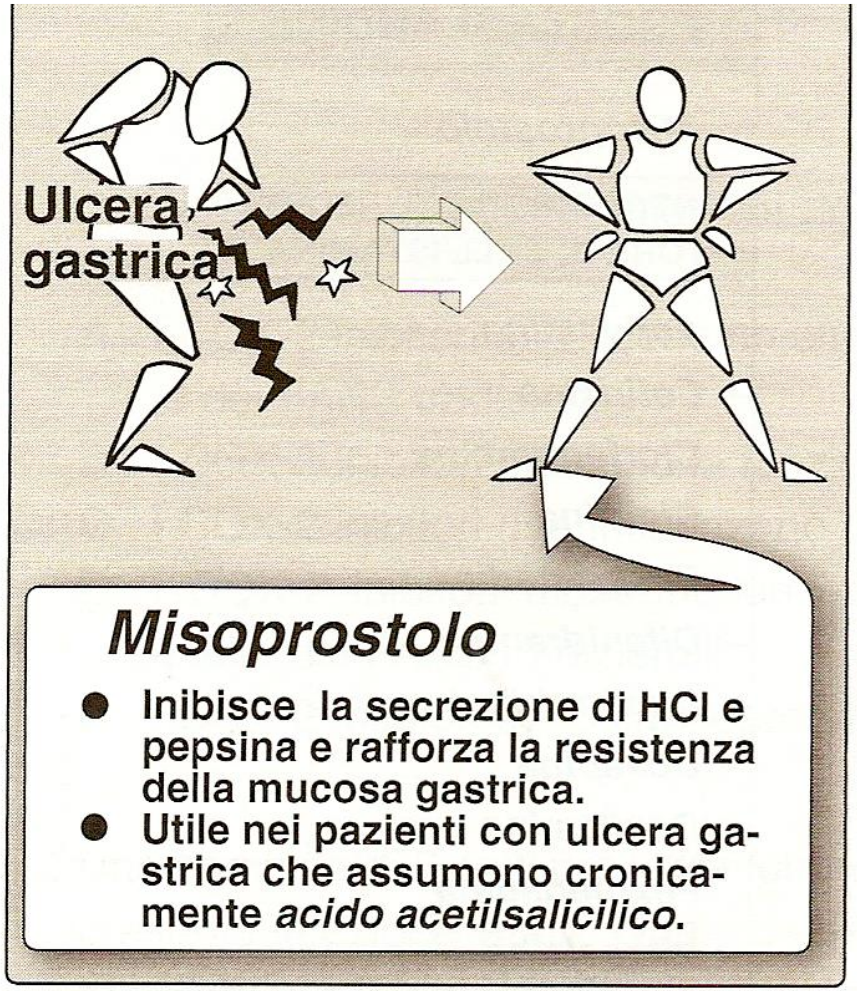
- **General Prevention**

Correction of risk factors
Correct diagnosis and real need to use NSAIDs
Choice of the less  harmful drug
Avoid NSAIDs association
Choose the most suitable route of administration
Utilization of gastro-protective formulation
Posology
Regular clinical check (endoscopy)
Cito-protectors

- **Therapy of gastropathy**

H2 inhibitors, protonic pump inhibitors
Anti-acid compounds
Mucosa protection (sucralfate)
Administration of prostaglandine analogs

# Misoprostol (PGE1)




Omeprazole
(proton pump inhibitor)
Cimetidine, ranitidine
(H2 antagonists)

# Antiplatelet drugs

# MAIN AGGREGATING AGENTS

**THROMBIN**

**ARACHIDONIC ACID**

ADP

COLLAGEN

RISTOCETIN

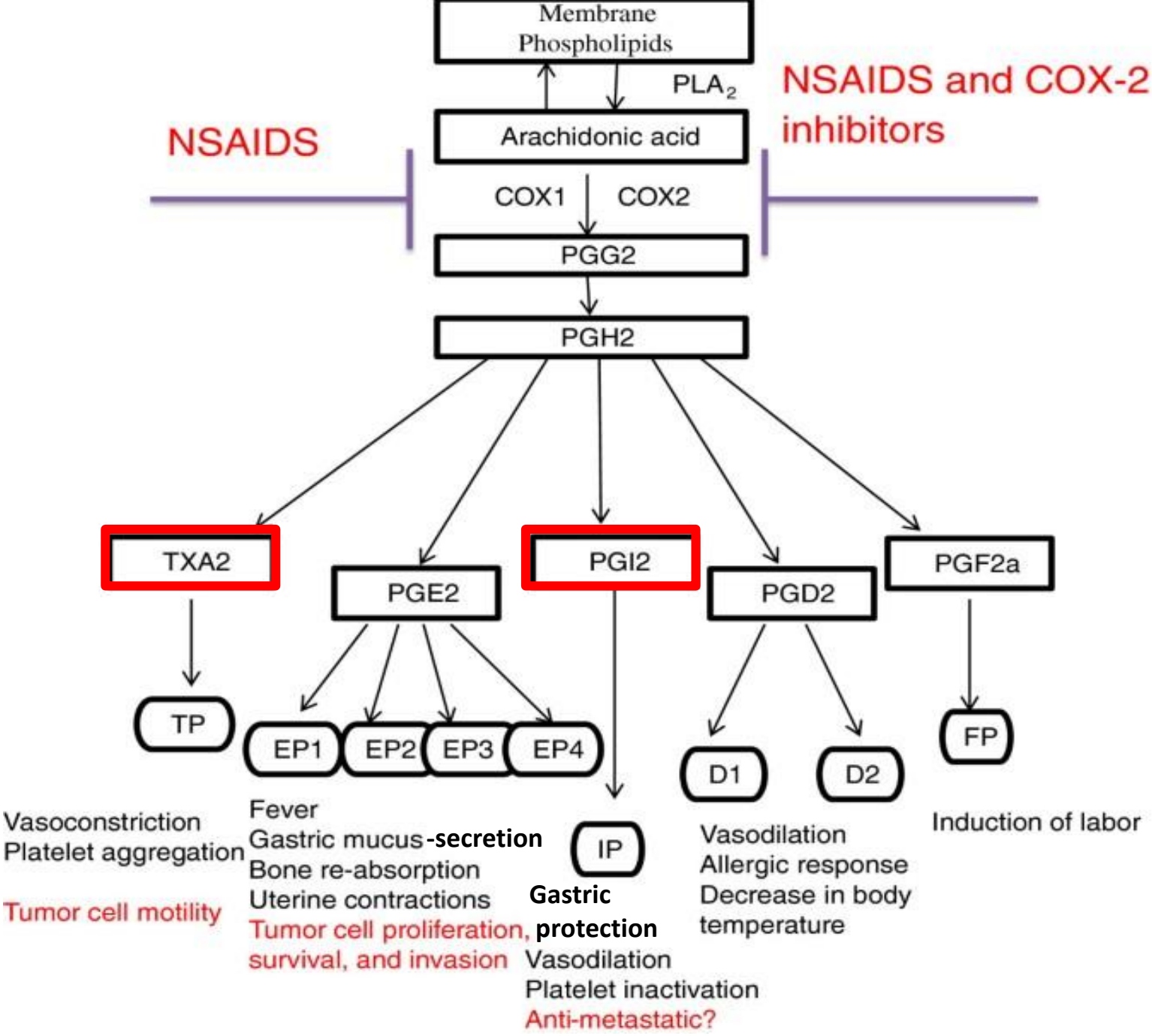
ADRENALINE

PAF

ENDOPEROXIDE ANALOGUES

IONOPHORS OF Ca++

SEROTONIN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NSAIDS and COX-2 inhibitors
NSAIDS
Arachidonic acid
COX1
COX2
PGG2
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TXA2
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PGI2
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PGF2a
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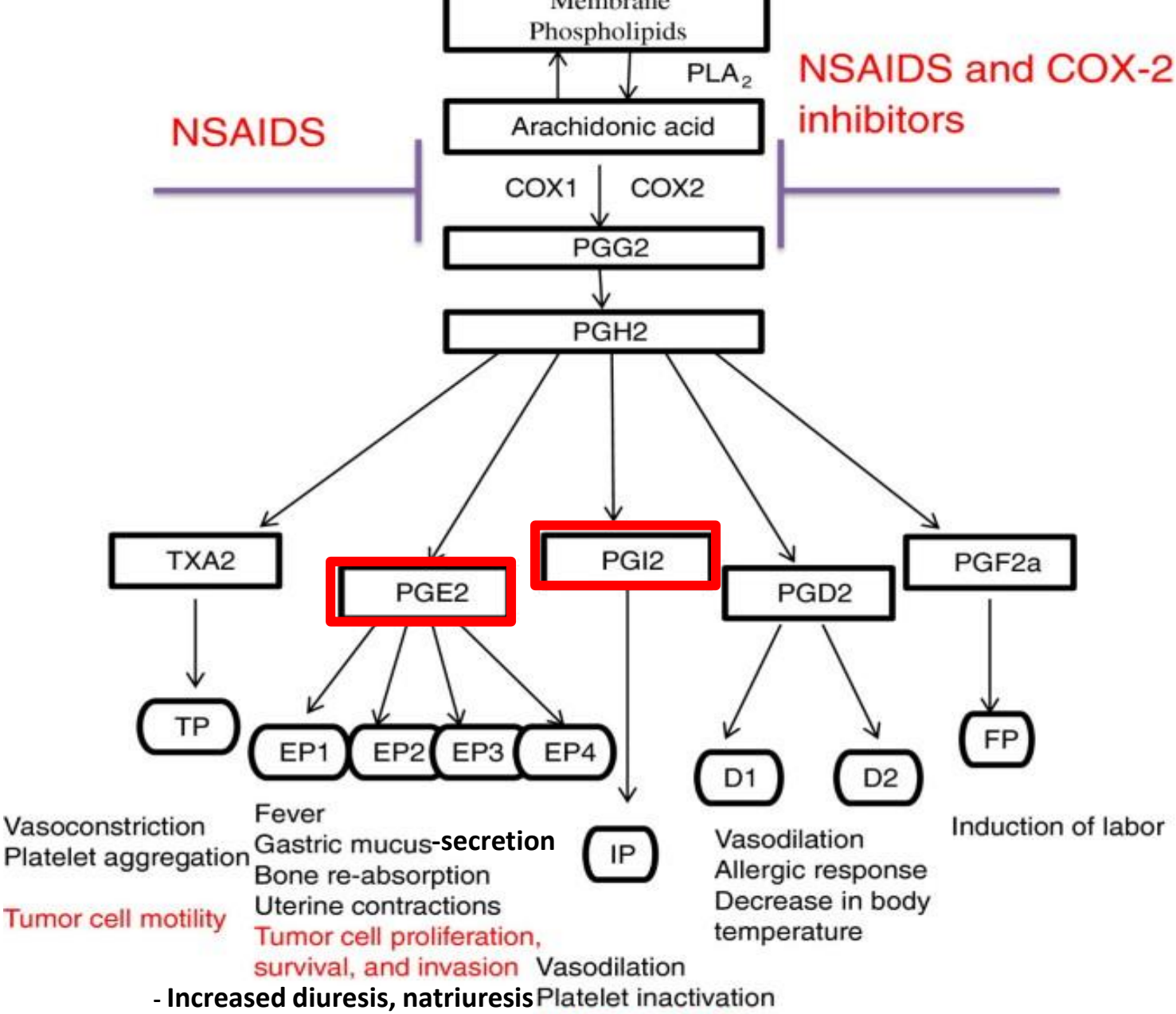
IP
Vasoconstriction
Platelet aggregation
Tumor cell motility
Fever
Gastric mucus-secretion
Bone re-absorption
Uterine contractions
Tumor cell proliferation, survival, and invasion
Gastric protection
Vasodilation
Platelet inactivation
Anti-metastatic?
Vasodilation
Allergic response
Decrease in body temperature
Induction of labor

1 – Farmaci che interferiscono con il metabolismo dell'acido arachidonico
Acido acetilsalicilico
Indobufene
Sulfinpirazone
Inibitori della trombossano-sintetasi
2 – Farmaci che interferiscono con i livelli intrapiastrinici di AMP ciclico
Dipiridamolo
Prostaciclicina ed analoghi
3 – Farmaci che interferiscono con recettori specifici
Antagonisti recettoriali del PAF
Antagonisti recettoriali del trombossano
4 – Farmaci che inibiscono la trombina
Eparina
Eparine a basso peso molecolare
Peptidi sintetici
5 – Alcuni farmaci (non utilizzati come antiaggreganti) che possono alterare la funzione piastrinica
Alpha-antagonisti
Beta-bloccanti
Anestetici locali (procaina)
Antiistaminici
Calcio antagonisti (nifedipina, verapamile)
Antidepressivi triciclici (amitriptilina, imipramina)
Fenotiazine (clorprozamina, trifluoperazina)
Papaverina
Xantinici (caffeina, teofillina)
Corticosteroidi
Antimalarici (clorochina, mepacrina)
Acido nicotinico
Beta-lattamina
Nitrofurantoina
6 – Altri
Destrano
Etanolo
Clofibrato
Aglio

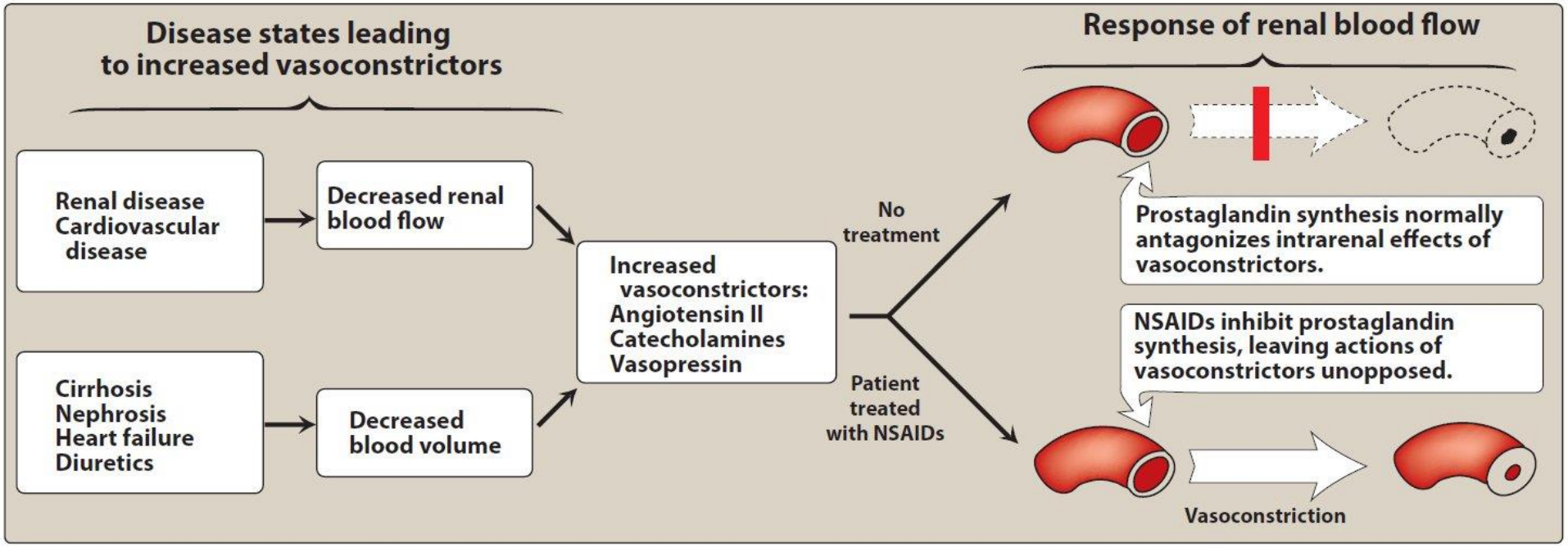
# Actions on Kidney




- **Increased diuresis, natriuresis**

**Increased renal blood flow**
**Glomerular filtration**
**Gastric protection**

# EFFECT ON THE KIDNEY OF THE INHIBITION OF THE SYNTHESIS OF PROSTAGLANDINS BY ACETYLSALICYLIC ACID

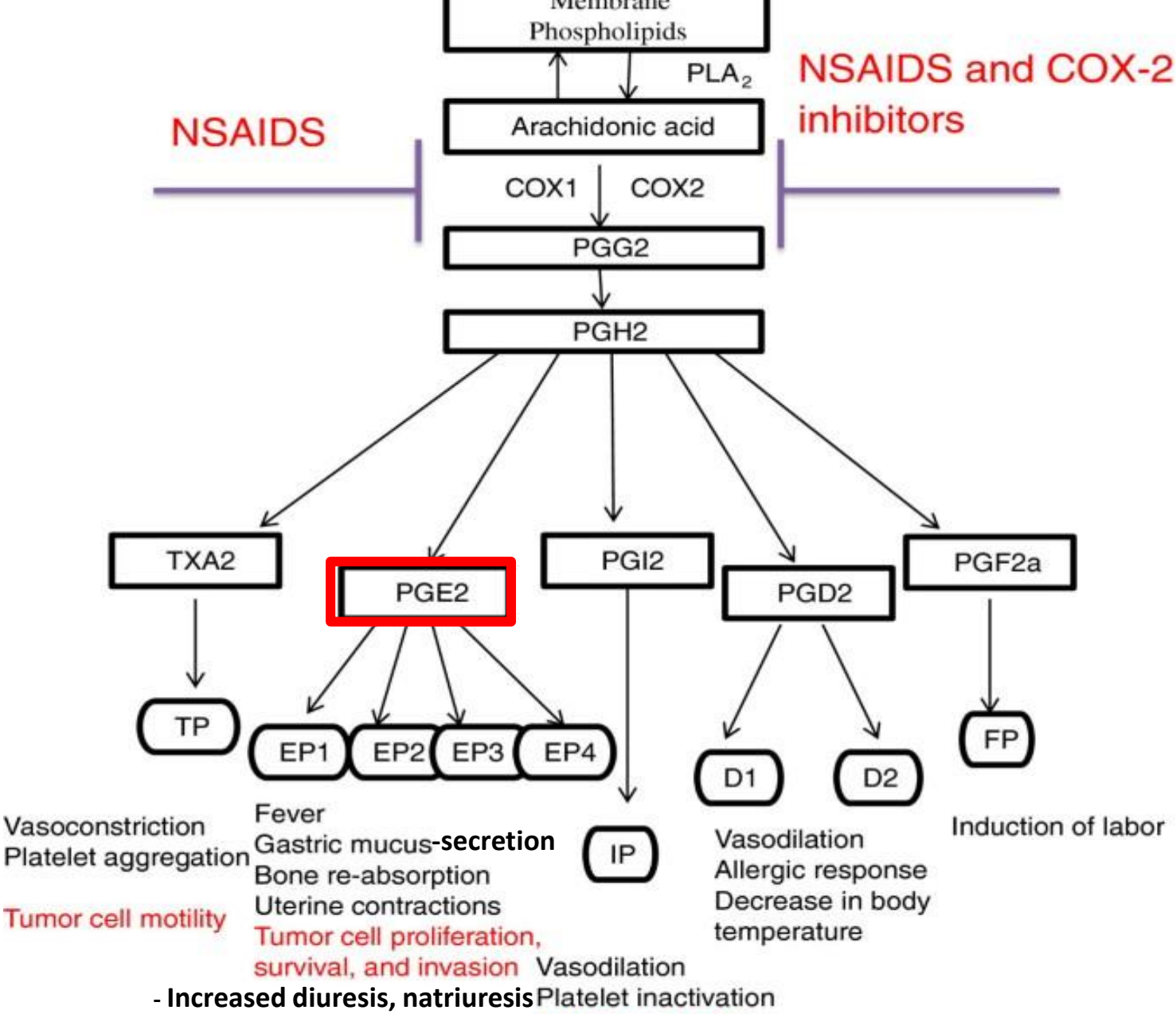



Renal effect of NSAIDs inhibition of prostaglandin synthesis. NSAIDs = nonsteroidal anti-inflammatory drugs.

Source : Lippincott Illustrated Reviews, Pharmacology - Whalen, Karen

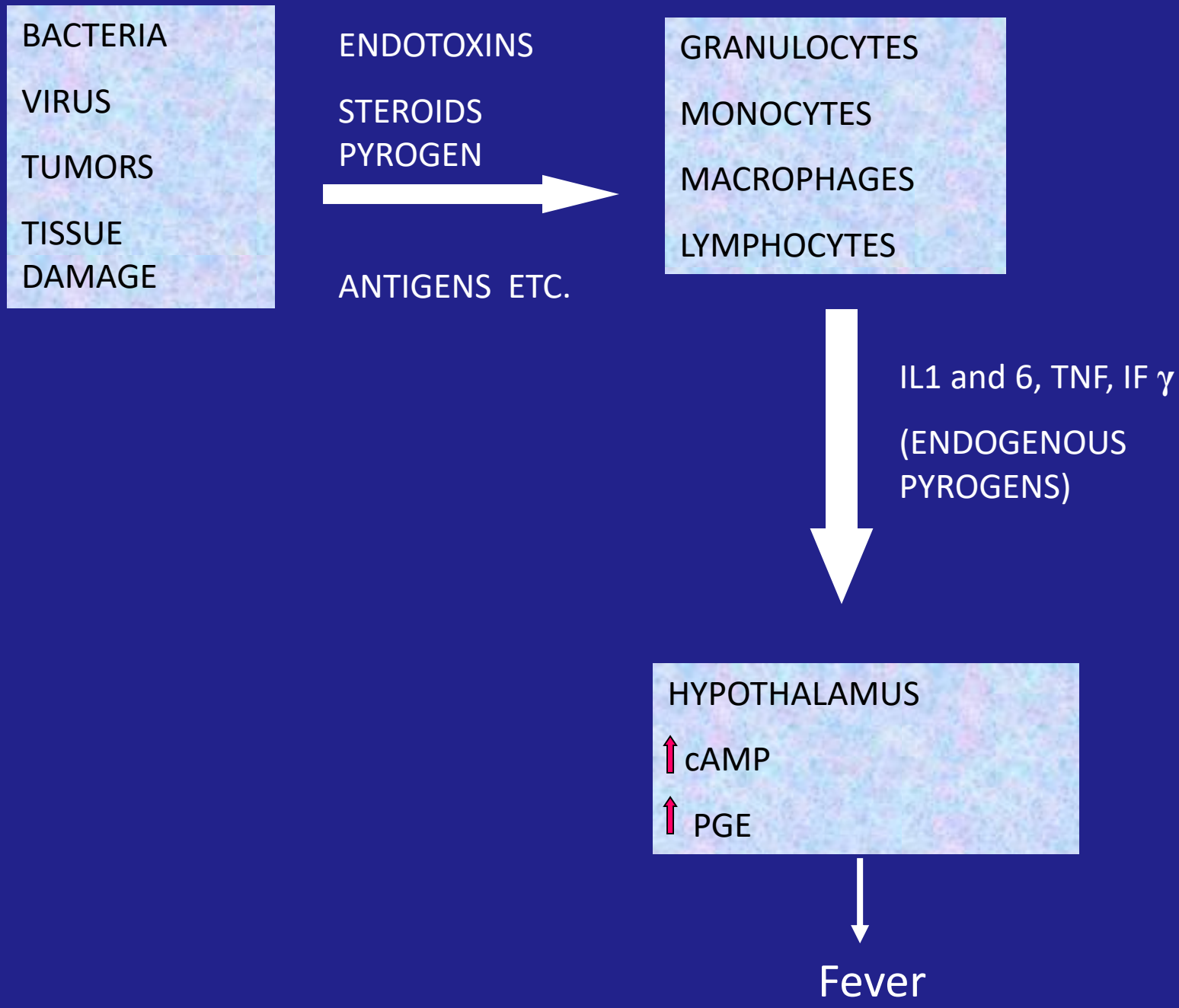
NSAIDs: Na+ and $H_2O$ retention, edema, hyperkalemia

# Antipyretic effect




- **Increased diuresis, natriuresis**

**Increased renal blood flow**
**Glomerular filtration**
**Gastric protection**


BACTERIA
VIRUS
TUMORS
TISSUE DAMAGE
ENDOTOXINS
STEROIDS
PYROGEN
ANTIGENS ETC.
GRANULOCYTES
MONOCYTES
MACROPHAGES
LYMPHOCYTES
IL1 and 6, TNF, IF γ
(ENDOGENOUS PYROGENS)
HYPOTHALAMUS
cAMP
PGE
Fever

## Heat Loss

Heat is lost from the body by the following channels:

(1) Heat loss from the skin,
  (*a*) by conduction and radiation,
  (*b*) by evaporation of sweat.
(2) Heat loss from the respiratory passages,
  (*a*) from warming of the inspired air,
  (*b*) by evaporation of water.

Small quantities of heat are also lost in the excretion of urine and fæces.

The centres which regulate temperature can cause an increase in the heat loss by the following means:

(1) By causing vasodilatation of the skin, and thus increasing the heat lost by conduction and radiation.

(2) By increasing the volume of air respired and thus increasing the heat lost by evaporation and by warming the inspired air.

(3) By causing sweating and thus increasing the heat lost by evaporation.

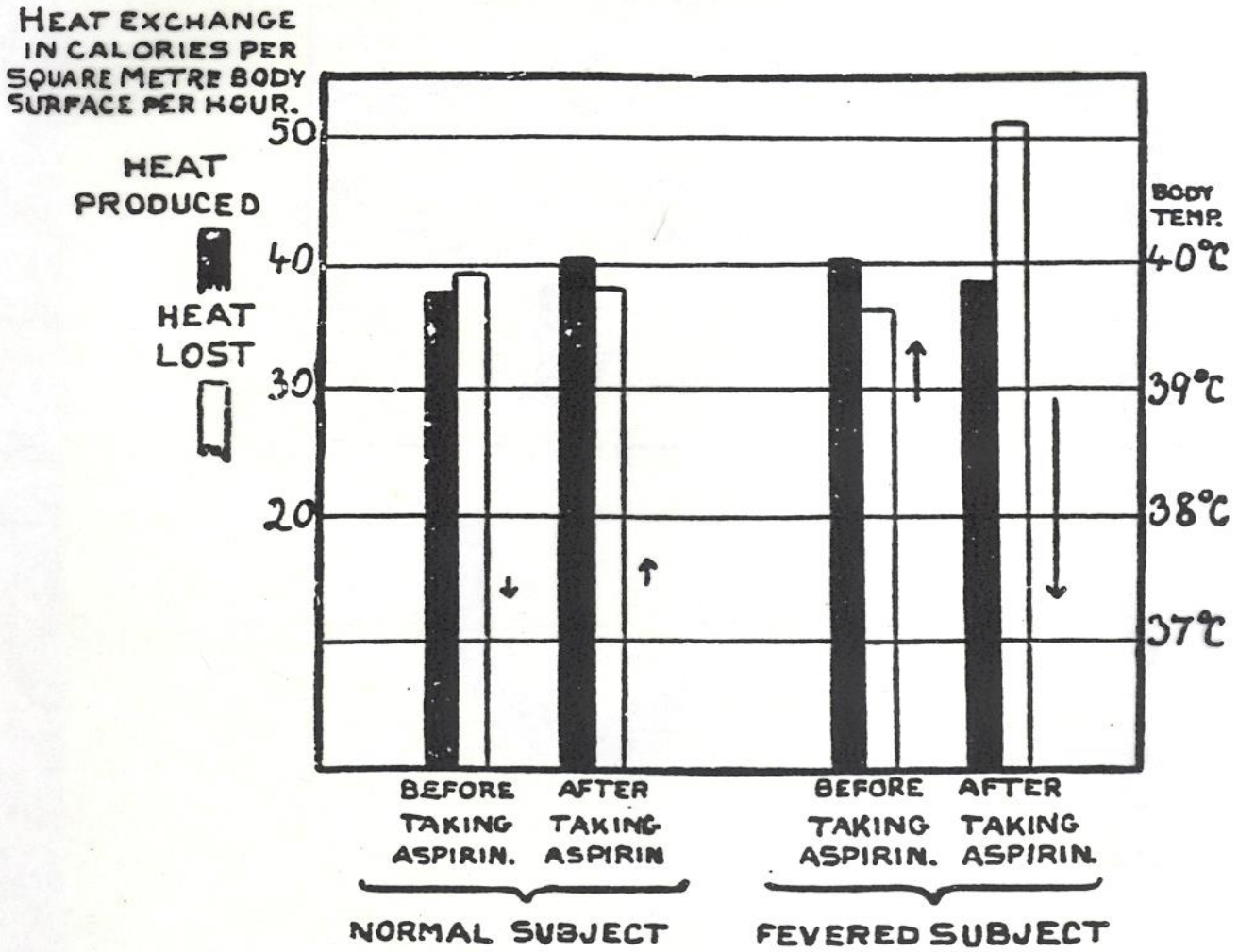
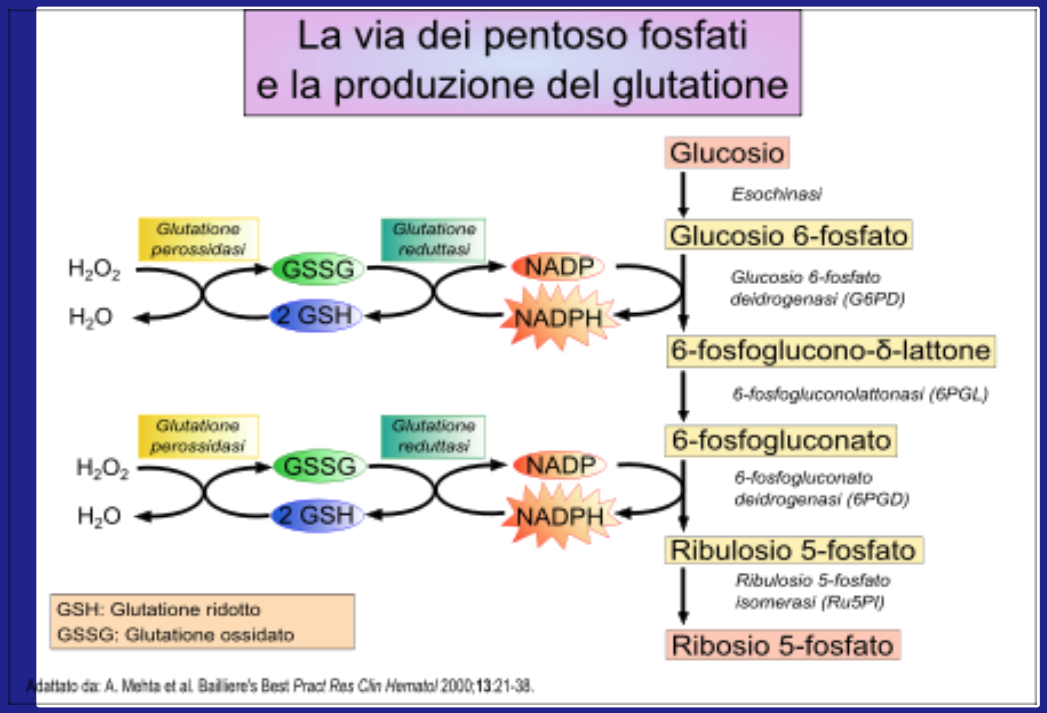
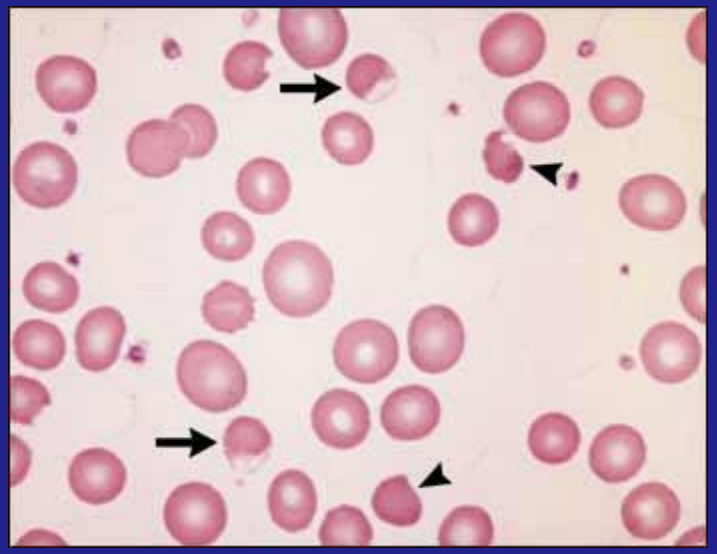



FIG. 19.2. Diagram showing the action of acetylsalicylic acid (1 G.) on the heat exchange in a normal and in a fevered subject. The heat exchange and the change in temperature were measured over two-hour periods before and after administration of the drug. The drug produced little effect on the normal person, but in the fevered subject it caused a great increase in heat loss and a consequent fall in temperature. The arrows show the direction and extent of the change of body temperature. (From figures by Barbour, 1919.)

## G6PD deficiency



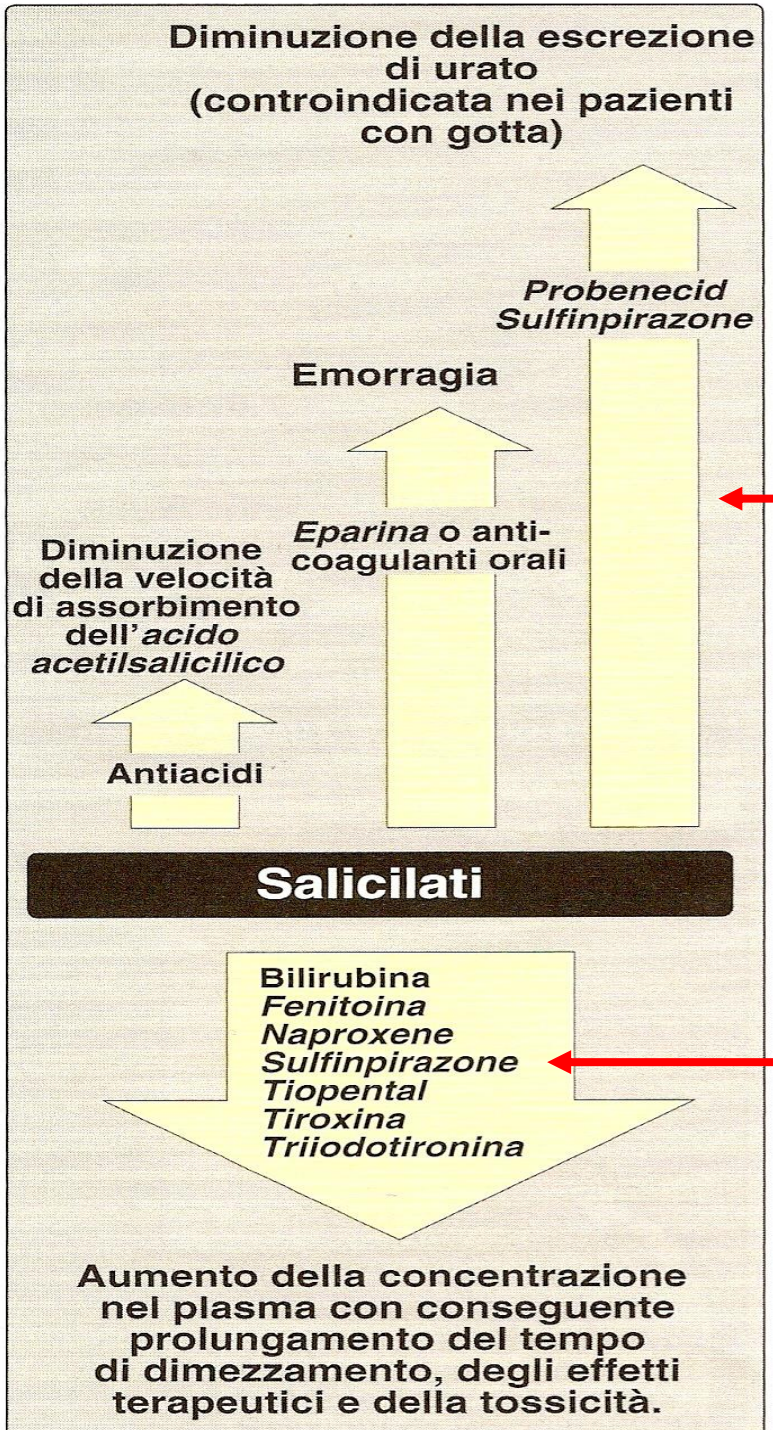

## Red blod cells in hemolysis



-SH

Oxidants are produced continuously inside red blood cells, but are also generated by activated phagocytes (for example during infections). In the absence of G6PD, the ability of reduced glutathione to "detoxify" cells from the oxidants produced, which accumulate, damaging the vital components of the cells themselves, decreases. Hemoglobin oxidation produces inactive methaemoglobin and intracellular precipitates of oxidized hemoglobin known as Heinz bodies. Hemolysis represents the final outcome of oxidative damage. **Aspirin**, when taken at the usual therapeutic dosages by patients suffering from the common variants of G6PD deficiency is not responsible for hemolysis and, if this occurs, it is almost certainly due to an infection or fever. The drug is safe even when used chronically at low doses as an antiplatelet treatment. The same is true for **paracetamol**: in studies conducted in patients with even severe variants of G6PD deficiency, the drug, at therapeutic doses, did not cause hemolysis and the cases that continue to be reported can be attributed to the combination of fever or infections. The instruction card contained in paracetamol and acetylsalicylic acid still report as a prudent measure, maintained by the manufacturers, the warning to "administer with caution" these drugs to patients with G6PD deficiency

# INTERACTION WITH OTHER DRUGS




Aspirin and probenecid compete for organic acid transporter
Excretion of salicylate may affect uric acid
Low doses of salicylate reduced uric acid excretion

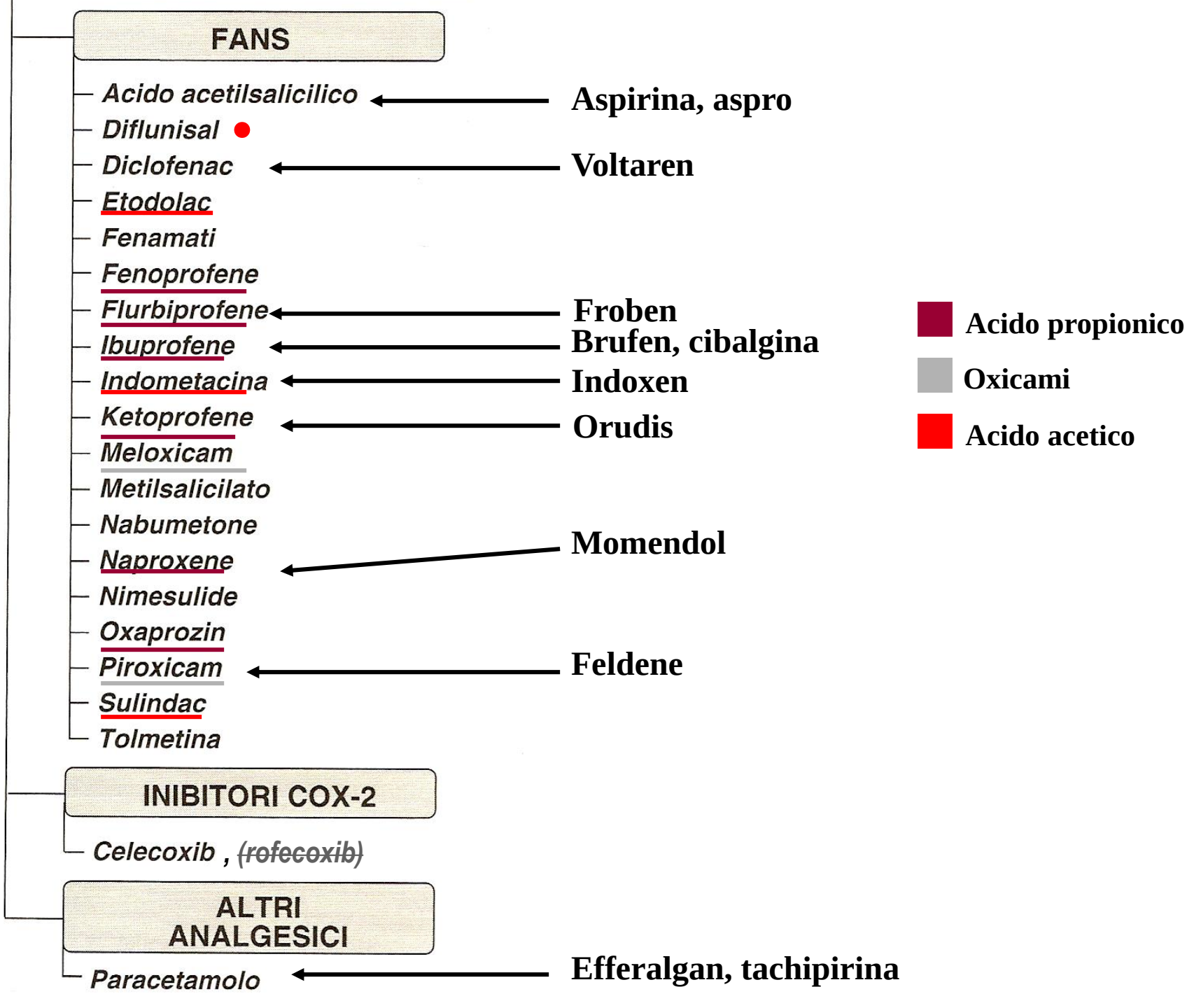
Decrese of aspirin clerance

# Chronic pain treatment

Inflammatory pain
Neuropathic pain

Antidepressants
Antiepileptic
NSAIDs
Opioids

# Therapeutic Utilization of NSAID


FANS
Acido acetilsalicilico
Diflunisal
Diclofenac
Etodolac
Fenamati
Fenoprofene
Flurbiprofene
Ibuprofene
Indometacina
Ketoprofene
Meloxicam
Metilsalicilato
Nabumetone
Naproxene
Nimesulide
Oxaprozin
Piroxicam
Sulindac
Tolmetina
Aspirina, aspro
Voltaren
Froben
Brufen, cibalgina
Indoxen
Orudis
Momendol
Feldene
Acido propionico
Oxicami
Acido acetico
INIBITORI COX-2
Celecoxib , (rofecoxib)
ALTRI ANALGESICI
Paracetamolo
Efferalgan, tachipirina

# OTHER NSAIDs 1

## PROPIONIC ACID DERIVATIVES

Ibuprofen, naproxen, fenoprofen, ketoprofen, flurbiprofen, oxaprozin
AR> AN / AP

## DERIVATIVES OF ACETIC ACID

Indomethacin AR> AN / AP (toxicity), sulindac, etodolac (COX-2)

## OXICAM

Piroxicam, meloxicam (long half-life) AR> AN / AP

## FENAMATES

Mephenaminic acid, meclofenamate (little used)

AP = antipyretic
AR = arthritis-rheumatoid, arthrosis, anti-inflammatory
AN = analgesic

# OTHER NSAIDs 2

## ETHERO-aryl

Diclofenac AP / AR / AN + powerful than other NSAIDs

Ketorolac (+ analgesic, - AR)

Tolmetidine AR (ASA similar but better tolerated potency)

## PARA-AMINOPHENOLIC

Paracetamol AP / AN

Nabumetone AR (prodrug, ASA similar potency, better tolerated)

Celecoxib, etoricoxib, lumiracoxib (~~rofecoxib~~, ~~valdecoxib~~) AR

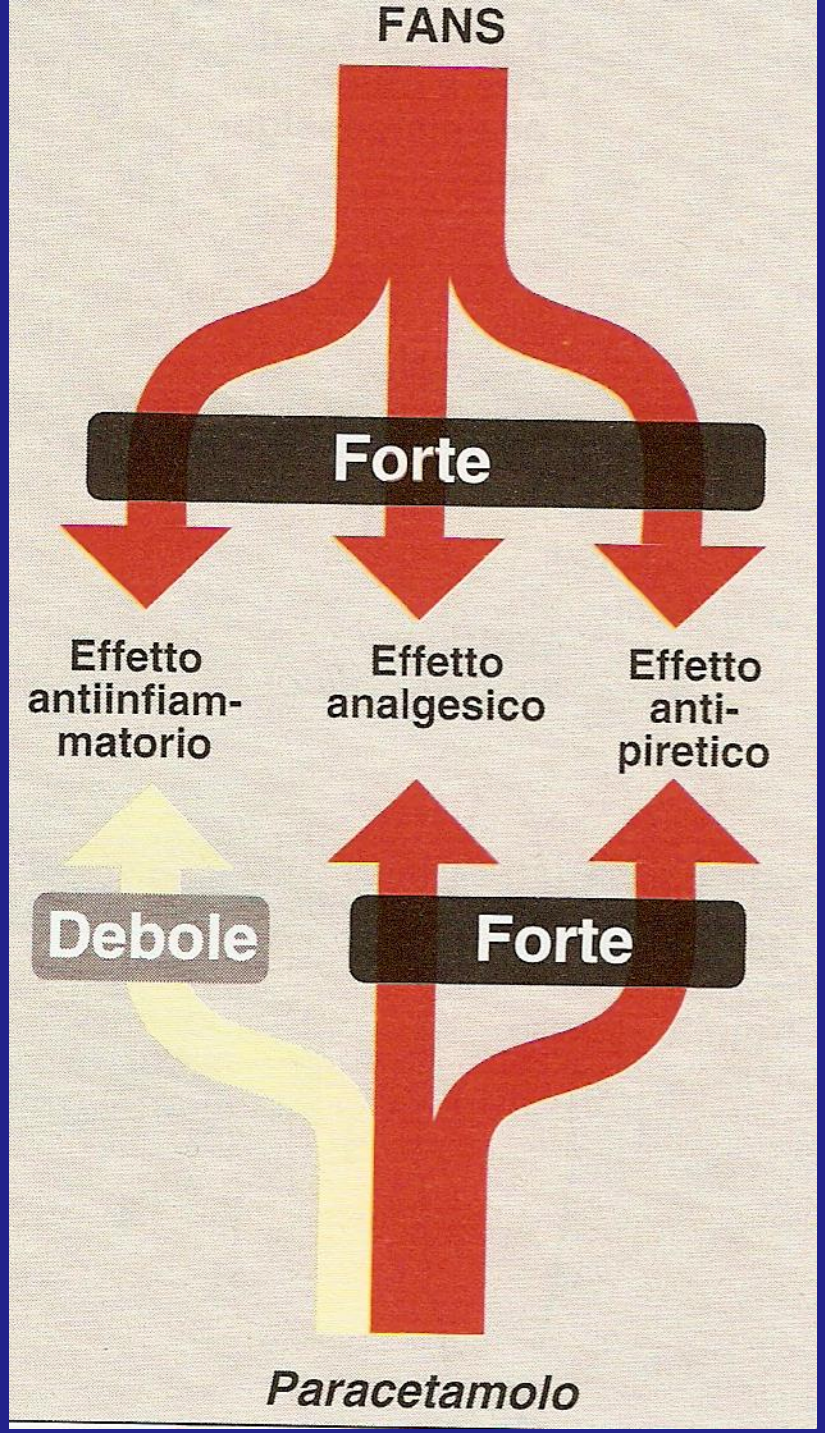
AP = antipyretic
AR = arthritis-rheumatoid, arthrosis, anti-inflammatory
AN = analgesic

| Principio attivo | Effetto | Meccanismo | Comportamento clinico |
|---|---|---|---|
| Antiacidi | Preparati contenenti alluminio e carbone attivo: ridotto assorbimento dei FANS, ridotta efficacia. Preparati contenenti bicarbonato: incremento assorbimento dei FANS, aumento rischio di tossicità | Alterazione dell'assorbimento | Se ne sconsiglia la cosomministrazione |
| Anticoagulanti orali | Possibile aumento dell'effetto anticoagulante delle curarine, del fenindione e delle eparine a basso peso molecolare: rischio di episodi emorragici. | Spiazzamento legami proteici, inibizione del metabolismo e dell'aggregazione piastrinica | Se ne sconsiglia la cosomministrazione |
| Antidepressivi | Aumento del rischio di emorragia con inibitori della ricaptazione della serotonina o venlafaxina. | Non noto | Se ne sconsiglia la cosomminsitrazione |
| Antidiabetici | Aumento dell'effetto delle sulfaniluree, ipoglicemia | Non noto | Monitorare la glicemia |
| Antiipertensivi<br>β-bloccanti<br>ACE-inibitori<br>Diuretici tiazidici | Aumento del rischio di insufficienza renale e antagonismo dell'effetto ipotensivo; aumento del rischio di ipercaliemia con ketorolac | Inibizione della sintesi renale di prostaglandine, riduzione dell'effetto natriuretico | Monitorare la risposta terapeutica |
| Antimicotici | Aumento della concentrazione plasmatica di parecoxib e celecoxib con fluconazolo | Inibizione del metabolismo mediato dal citocromo P450 2C9 | Iniziare la cosomministrazione con la dose più bassa indicata per il coxib |
| Antivirali | Aumento della concentrazione plasmatica di piroxicam con ritonavir (rischio di tossicità); possibile aumento della concentrazione plasmatica di altri FANS con ritonavir; aumento del rischio di tossicità ematologica con zidovudina | Inibizione competitiva della glucuronazione | Monitorare i segni tossici |
| Ciclosporina | Aumento del rischio di nefrotossicità, colestasi, parestesie | Non noto | Monitorare i segni di tossicità da ciclosporina |

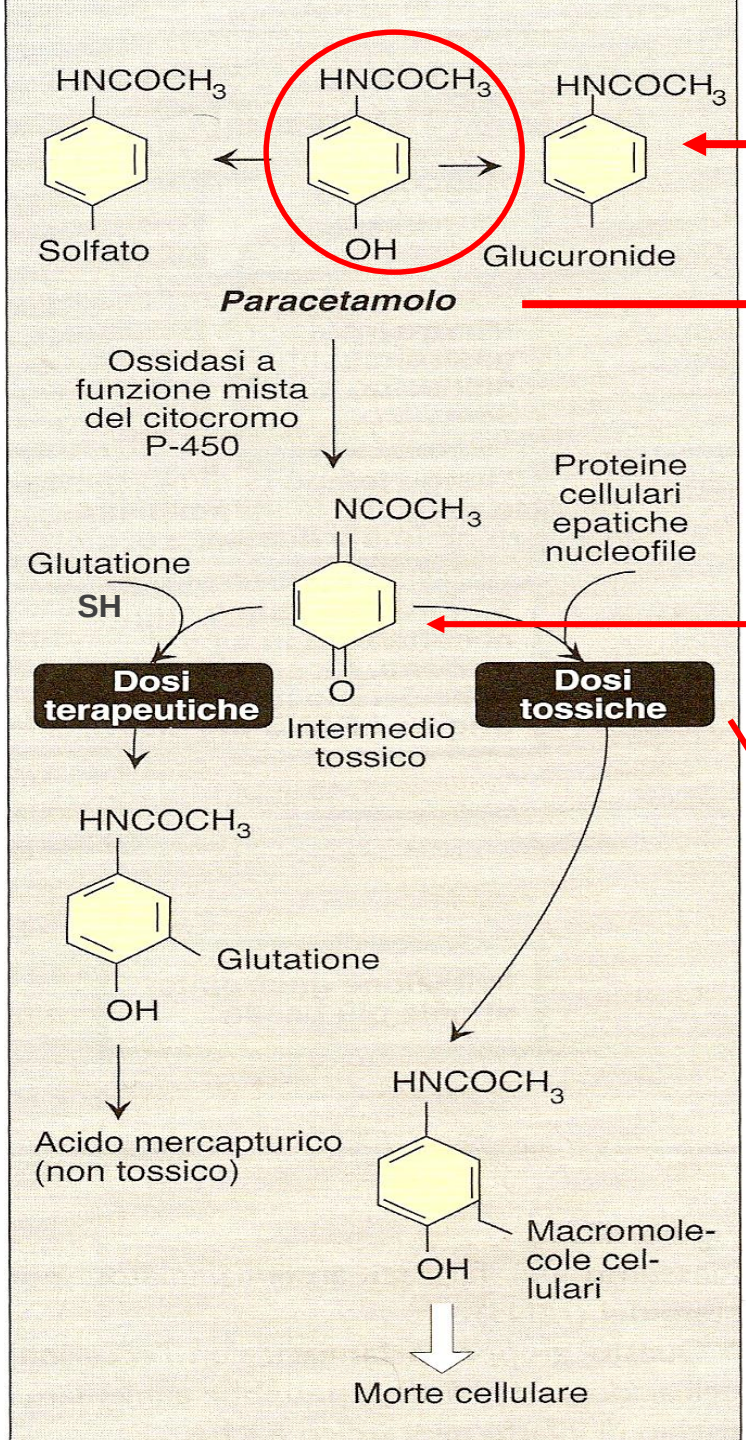
| | | | |
|---|---|---|---|
| Contraccettivi orali | Aumento del catabolismo | Non noto | Cautela nell'uso concomitante |
| Digossina | Aumento del rischio di tossicità da digossina (nausea, vomito, aritmie) | Non noto | Monitorare i segni di tossicità |
| Fluorochinoloni | Possibile aumento del rischio di crisi convulsive | Inibizione del GABA | Evitare cosomministrazione |
| Litio | Aumento del rischio di tossicità da litio (astenia, tremori, sete, confusione) | Riduzione della clearance del litio | Monitorare i segni di tossicità da litio |
| Metotrexato | Riduzione dell'eliminazione di metotrexato con aspirina, aumento di tossicità con altri FANS | Riduzione della clearance | Se ne sconsiglia la cosomministrazione |
| Probenecid | Aumento delle concentrazioni plasmatiche di indometacina, ketoprofene, naproxene e ketorolac | Riduzione della clearance del FANS | Monitorare l'insorgenza di tossicità |
| Tacrolimus | Scompenso renale acuto (principalmente ibuprofene) | Non noto | Evitare cosomministrazione |
| Vaccino antivaricella | Cosomministrato con aspirina comporta un aumento del rischio di sindrome di Reye | Non noto | Non somministrare salicilati prima di 6 settimane dopo la vaccinazione |

## Paracetamol

- Paracetamol has potent analgesic and antipyretic actions but rather weaker anti-inflammatory effects.
- It is given orally and metabolised in liver (half-life 2–4 hours).
- Toxic doses cause nausea and vomiting, then, after 24–48 hours, potentially fatal liver damage by saturating normal conjugating enzymes, causing the drug to be converted by mixed function oxidases to *N*-acetyl-*p*-benzoquinone imine. This, if not inactivated by conjugation with glutathione, reacts with cell proteins and kills the cell.
- Agents that increase glutathione (acetylcysteine intravenous or methionine orally) can prevent liver damage if given early.


FANS
Forte
Effetto antiinfiam-matorio
Effetto analgesico
Effetto anti-piretico
Debole
Forte
Paracetamolo

# Metabolism of paracetamol




Liver

Urine

N-acetyl-p-benzoquinone

Depletion of hepatic glutathione