NSAIDs, analgesic-antipyretics, antirheumatic drugs

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Nonsteroidal anti-inflammatory drugs

(NSAIDs)

Inflammation = a normal, protective response to tissue injury caused by physical trauma, chemicals, microbiologic agents – i.e., it is the body's effort to inactivate or destroy invading organisms or irritants, and set the stage for tissue repair.

Sometimes inappropriately triggered by an different agent (pollen, an autoimmune response – e.g. in asthma, rheumatoid arthritis) - then the defense reactions themselves may cause progressive tissue injury.

Anti-inflammatory or immuno-suppressive drugs may be required to modulate the inflammatory process.

Mechanism of action

Inhibition of prostagladin synthesis

PROSTAGLANDINS

A. Role of PGS as local mediators

- **Produced by virtually all tissues; act locally on the tissues where are synthesized; rapidly metabolized. PGS do not circulate in the blood in significant concentrations.**

- **Thromboxanes and leukotrienes are related lipids.**

B. Synthesis of PGS

Arachidonic acid - the precursor

Free AA is released from tissue phospholipids by PLA_2

Two major pathways in the synthesis of the eicosanoids from arachidonic acid.

1. **Cyclooxygenase pathway: PGS, thromboxanes, prostacyclins are synthesized via the COX pathway.**

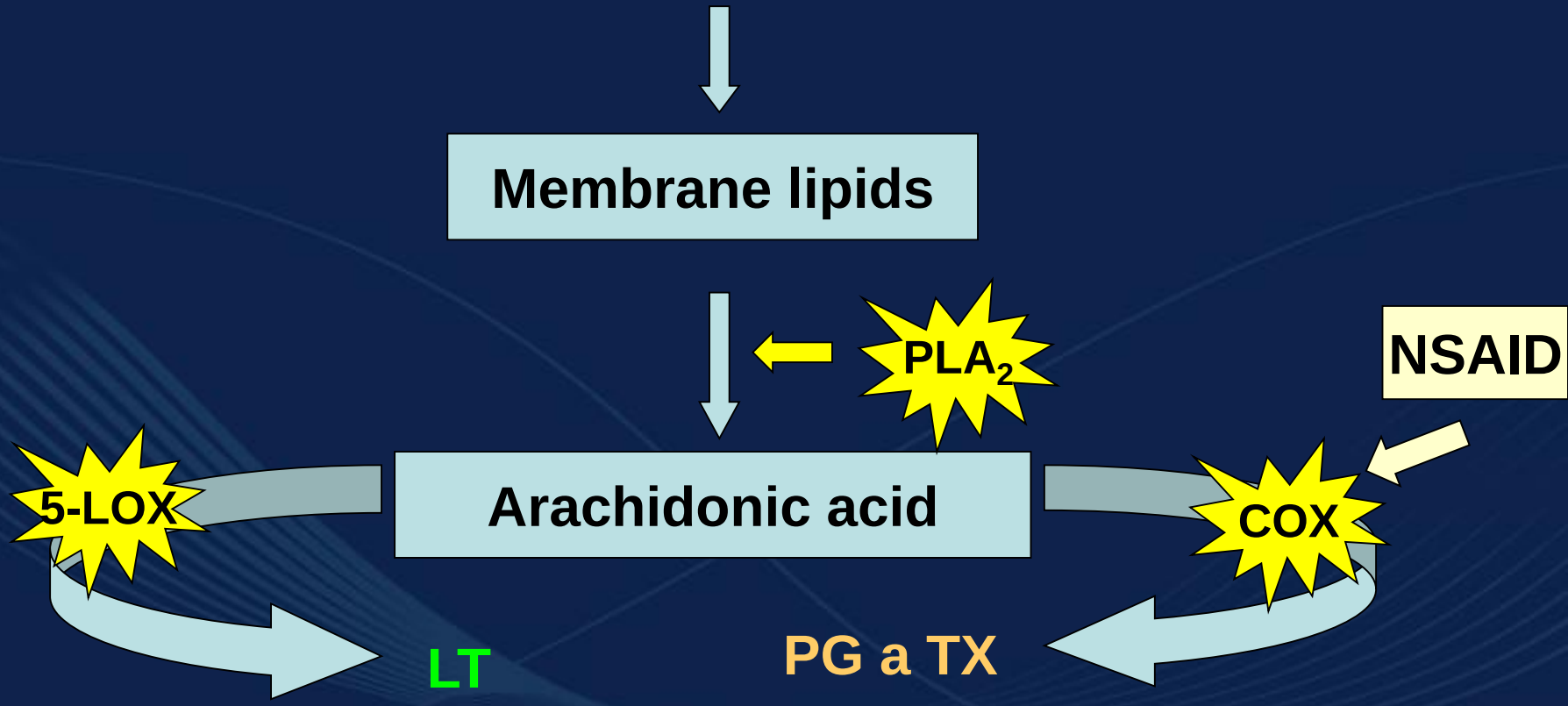
Two related isoforms of the cyclooxygenase:

Cyclooxygenase-1 (constitutive; COX-1)

Cyclooxygenase-2 (inducible; COX-2)

Prostaglandins synthesis (PG)

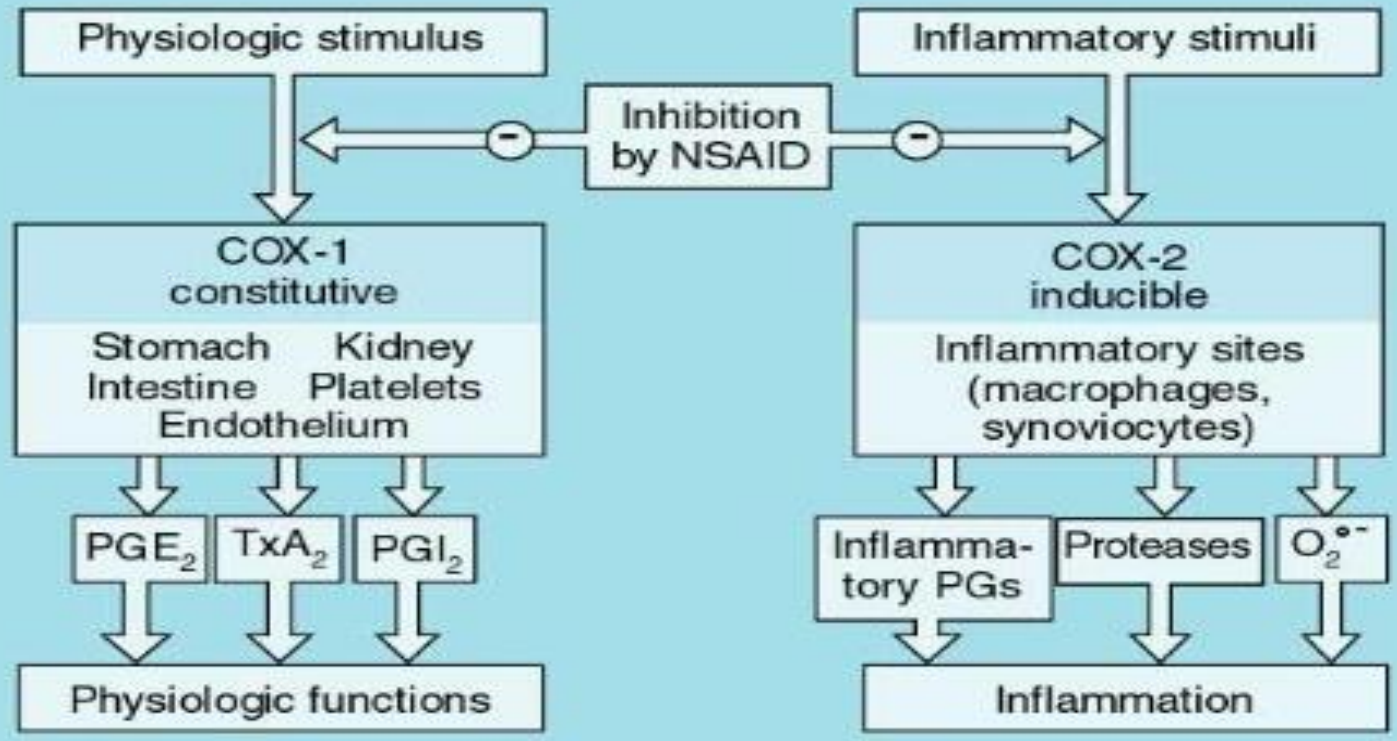
Chemical, physical, biological stimulation



COX-1 - responsible for the physiologic production of prostanoids; regulates normal cellular processes (e.g. gastric cytoprotection, vascular homeostasis, platelet aggregation, kidney function).

COX-2 - causes the elevated production of prostanoids that occurs in sites of disease and inflammation.

The conformation for the substrate binding sites and catalytic regions are slightly different. (e.g., COX-2 has a large space at the site where inhibitors bind).
The structural differences between COX-1 and COX-2 permitted the development of COX-2-selective inhibitors.

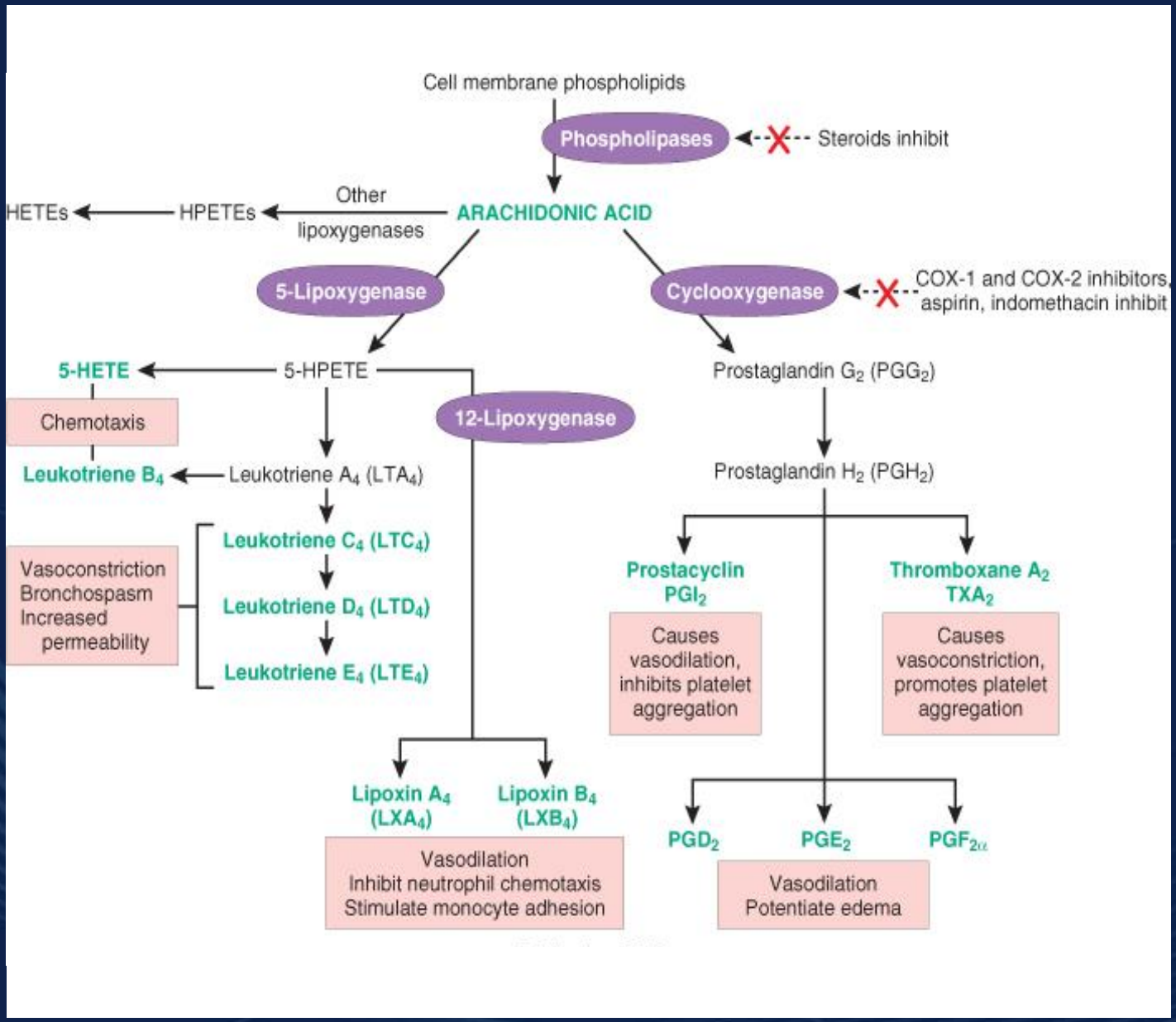

Physiologic stimulus
Inflammatory stimuli
Inhibition by NSAID
COX-1 constitutive
Stomach Kidney
Intestine Platelets
Endothelium
COX-2 inducible
Inflammatory sites (macrophages, synoviocytes)
PGE2
TxA2
PGI2
Inflamma-tory PGs
Proteases
O2°-
Physiologic functions
Inflammation

2. Lipoxygenase pathway:

Lipoxygenases can act on arachidonic acid to form

5-HETE (5-Hydroxyeicosatetraenoic acid) or to **leukotrienes (5-LOX) or lipoxins (12-LOX)**, depending on the tissue.

Antileukotriene drugs, e.g., zileuton, zafirlukast, and montelukast, **are useful for the treatment of moderate to severe allergic asthma.**


Cell membrane phospholipids
Phospholipases
Steroids inhibit
ARACHIDONIC ACID
Other lipoxygenases
HPETEs
HETEs
5-Lipoxygenase
Cyclooxygenase
COX-1 and COX-2 inhibitors, aspirin, indomethacin inhibit
5-HPETE
5-HETE
Chemotaxis
12-Lipoxygenase
Prostaglandin G2 (PGG2)
Prostaglandin H2 (PGH2)
Leukotriene A4 (LTA4)
Leukotriene B4
Leukotriene C4 (LTC4)
Leukotriene D4 (LTD4)
Leukotriene E4 (LTE4)
Vasoconstriction
Bronchospasm
Increased permeability
Prostacyclin PGI2
Causes vasodilation, inhibits platelet aggregation
Thromboxane A2 TXA2
Causes vasoconstriction, promotes platelet aggregation
Lipoxin A4 (LXA4)
Lipoxin B4 (LXB4)
Vasodilation
Inhibit neutrophil chemotaxis
Stimulate monocyte adhesion
PGD2
PGE2
PGF2α
Vasodilation
Potentiate edema

C. Functions in the body

PGS act as local signals.

Their functions vary widely depending on the tissue

PGD_2 **– vasodilatation, inhibition of platelet aggregation, relaxation of GIT muscles, uterus relaxation;**

$PGF_{2\alpha}$ **- uterus contraction, bronchoconstriction, vasoconstriction in myometrium;**

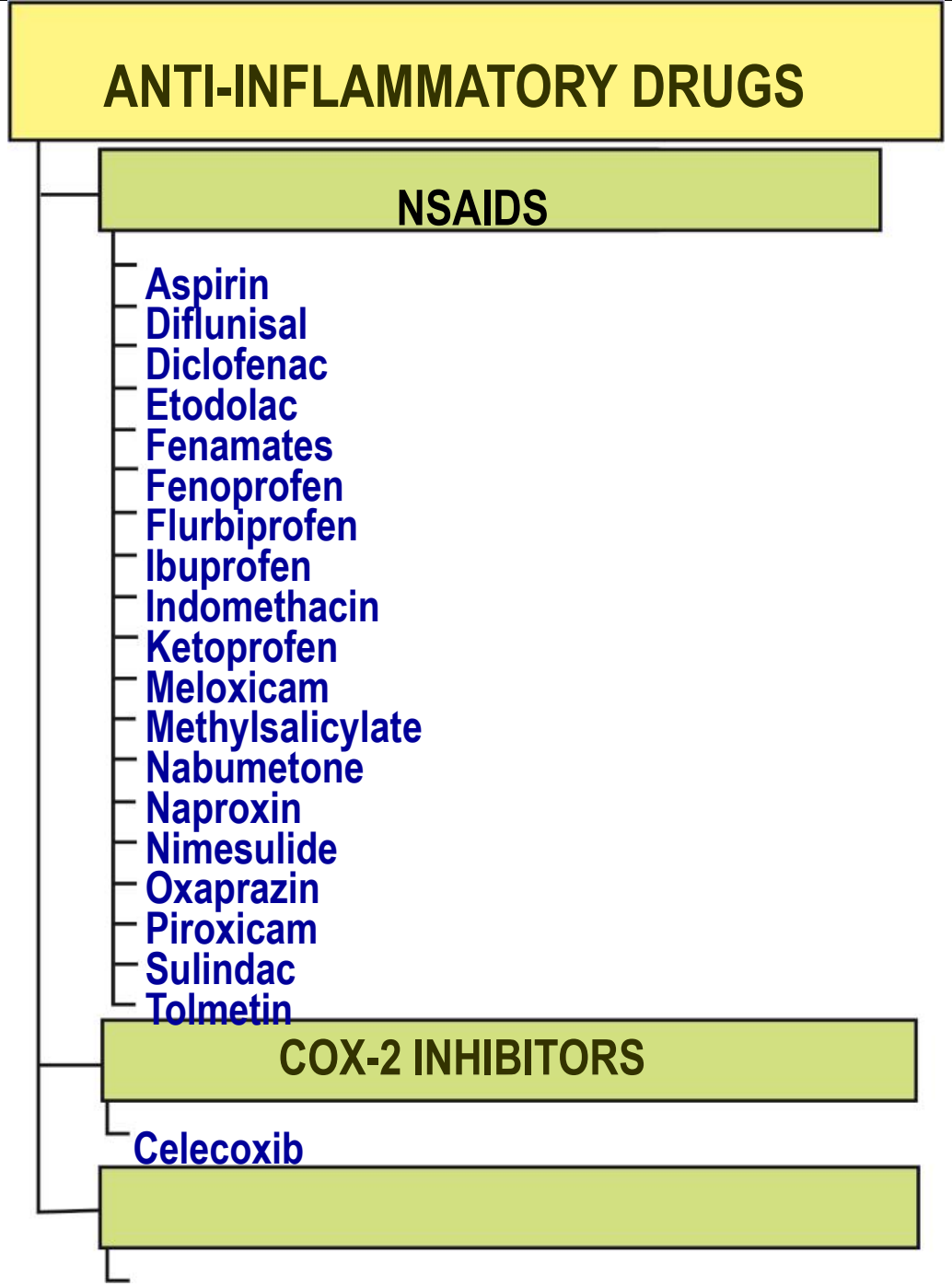
PGI_2 **(prostacyclin) – vasodilatation, inhibition of platelet aggregation, renin release**

TXA_2 **– vasoconstriction, platelet aggregation**

PGE2-

- **bronchial and GIT contraction (EP_1 receptors),**
- **bronchodilatation, vasodilatation, GIT relaxation, stimulates GIT secretion (EP_2 receptors),**
- **inhibition of gastric acid secretion, intestinal contraction, increase gastric mucus secretion, lipolysis inhibition, stimulation of pregnat uterus contraction (EP_3 receptors)**

Summary of anti-inflammatory drugs



(according to Lippincott´s Pharmacology, 2006

ANTI-INFLAMMATORY DRUGS (continued)

DRUGS FOR ARTHRITIS

- Adalimumab
- Anakinra
- Chloroquine
- Etanercept
- Gold salts
- Infliximab
- Leflunomide
- Methotrexate
- D-Penicillamine

DRUGS FOR GOUT

- Allopurinol
- Colchicine
- Probenecid
- Sulfinpyrazone

(according to Lippincott´s Pharmacology, 2006

NSAIDs

Most drugs have three major effects:

- *antipyretic* (lowering a raised, not normal temperature) - due to a decrease in PGE_2, which is generated in response to inflammatory proteins and is responsible for elevating the hypothalamic set-point for temperature control

- *analgesic* (reduction of certain sorts of pain) - decrease PGs generation, relief of headache due to decreased PGs-mediated vasodilatation

- *anti-inflammatory* (modification of the inflammatory reaction) - decrease in PGE_2 and PGI_2 »»» less vasodilatation, less oedema

Not all NSAIDs are equally potent in each of these actions.

Short history of aspirin

- 1897 – August 10th – first sample prepared by Hoffman
- **A-** ***A***cetyl, **SPIR** – ***Spir***aea ulmaria (meadowsweet), **IN** – that's what they were ending drug names with in those days.
- 1899 – Bayer releases acetyl-salicylic acid in a powder form for medicinal purposes, credits Hoffman with the discovery, patent approved!

A. ASPIRIN and other salicylates

- the prototype of traditional NSAIDs.

- aspirin (acetylsalicylic acid)
- sodium salicylate
- methylsalicylate (topically used)
- diflunisal

1. Mechanism of action:

Aspirin - unique among the NSAIDs – it irreversibly acetylates (and thus inactivates) COX.

Other NSAIDs, incl. salicylate, are all reversible inhibitors of COX.

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

The antipyretic and anti-inflammatory effects - blockade of PGS synthesis at the thermoregulatory centers in the hypothalamus and at peripheral target sites.

Furthermore - by decreasing PGS synthesis - they also prevent the sensitization of pain receptors to stimuli. Aspirin may also depress pain stimuli at subcortical sites (i.e., the thalamus and hypothalamus).

2. Actions:

Salicylates reduce inflammation, pain, and fever.

a. Anti-inflammatory actions: inhibition of COX activity – decrease in the formation of PGS – it modulates those aspects of inflammation in which PGS act as mediators.

b. Analgesic action:

PGE_2 – it sensitizes nerve endings to bradykinin, histamine, and other mediators released by the inflammatory process. Thus, by decreasing PGE_2 synthesis, aspirin and other NSAIDs suppress the sensation of pain.

Salicylates - used mainly for the management of pain of low to moderate intensity.

NSAIDs are superior to opioids for the management of pain in which inflammation is involved.

Combinations of opioids and NSAIDs - effective in pain caused by a malignancy.

c. Antipyretic action:

Fever occurs when the set-point of the anterior hypothalamic thermoregulatory center is elevated.

This can be caused by PGE_2 synthesis, stimulated when an endogenous fever-producing agent (pyrogen), such as a cytokine, is released from white cells that are activated by infection, hypersensitivity, malignancy, or inflammation.

The salicylates lower body temperature in patients with fever by impeding PGE_2 synthesis and release.

Aspirin resets the "thermostat" toward normal, and it rapidly lowers the body temperature of febrile patients by increasing heat dissipation as a result of peripheral vasodilation and sweating.

Aspirin has no effect on normal body temperature.

d. Effect on platelets (**TXA_2 enhances aggregation, PGI_2 decreases it).**

Low doses (60-80 mg daily) of aspirin can irreversibly inhibit thromboxane production in platelets.

Note: The acetylation of COX is irreversible. Because platelets lack nuclei, they cannot synthesize new enzyme, and the lack of thromboxane persists for the lifetime of the platelet (3 to 7 days). This contrasts with the endothelial cells (with nuclei) – therefore they can produce new COX.

Because of the decrease in TXA_2, platelet aggregation (the first step in thrombus formation) is reduced → anticoagulant effect with a prolonged bleeding time.

e. Respiratory actions:

At **therapeutic doses –** increase in alveolar ventilation. [**Note**: Salicylates uncouple oxidative phosphorylation → elevated CO_2 and increased respiration.] **Higher doses** – direct action on the respiratory center in the medulla → hyperventilation and respiratory alkalosis (usually compensated by the kidney). At **toxic levels**, central respiratory paralysis occurs, and respiratory acidosis ensues due to continued production of CO_2.

- **f. GIT effects: PGI2 inhibits gastric acid secretion, PGE2 and PGF2a stimulate synthesis of protective mucus in both the stomach and small intestine.**

  In the presence of aspirin, they are not formed → increased gastric acid secretion and diminished mucus protection → epigastric distress, ulceration, hemorrhage. At ordinary aspirin doses - as much as 3 to 8 ml of blood may be lost in the feces per day.

- **g. Actions on the kidney: COX inhibitors prevent the synthesis of PGE2 and PGI2 (they are responsible for maintaining renal blood flow). Decreased synthesis of PGS - retention of sodium and water and edema and hyperkalemia may occur. Interstitial nephritis can also occur.**

3. Therapeutic uses:

a. Antipyretics and analgesics:
Aspirin, sodium salicylate, choline salicylate, choline magnesium salicylate - used as antipyretics and analgesics:
- headache, arthralgia, myalgia,
- in the treatment of gout, rheumatic fever, and rheumatoid arthritis.

b. Diflunisal, a diflurofenyl derivate of salicylic acid, is not metabolized to salicylate - it cannot cause salicylism. Diflunisal is 3-4 times more potent than aspirin as an analgesic and an anti-inflammatory agent, but it does not have antipyretic properties. *Note:* Diflunisal does not enter the central nervous system (CNS) and therefore cannot relieve fever.

c. Cardiovascular applications: inhibition of platelet aggregation.

Low doses of aspirin are used prophylactically to decrease the incidence of transient ischemic attack and unstable angina in men as well as that of coronary artery thrombosis.

Aspirin also facilitates closure of the patent ductus arteriosus (PGE_2 is responsible for keeping the ductus arteriosus open).

d. Colon cancer: Chronic use of aspirin may reduce the incidence of colorectal cancer.

4. Pharmacokinetics:

a. Administration and distribution:

After oral administration, the nonionized salicylates are passively **absorbed from the stomach and the small intestine**.

Rectal absorption of the salicylates is slow and unreliable

Salicylates (**except for diflunisal) cross BBB and the placenta.**

Salicylates, especially methyl salicylate, are **absorbed through intact skin**.

b. Dosage:

Analgesic activity at low doses; only at higher doses anti-inflammatory activity.

E.g., about 600 mg of aspirin 4 times a day produces analgesia

about 4 – 6 g per day produce both analgesic and anti-inflammatory activity.

Low dosages of aspirin (160 mg every other day) reduces the incidence of recurrent IM, reduces the mortality in post-myocardial infarction patients.

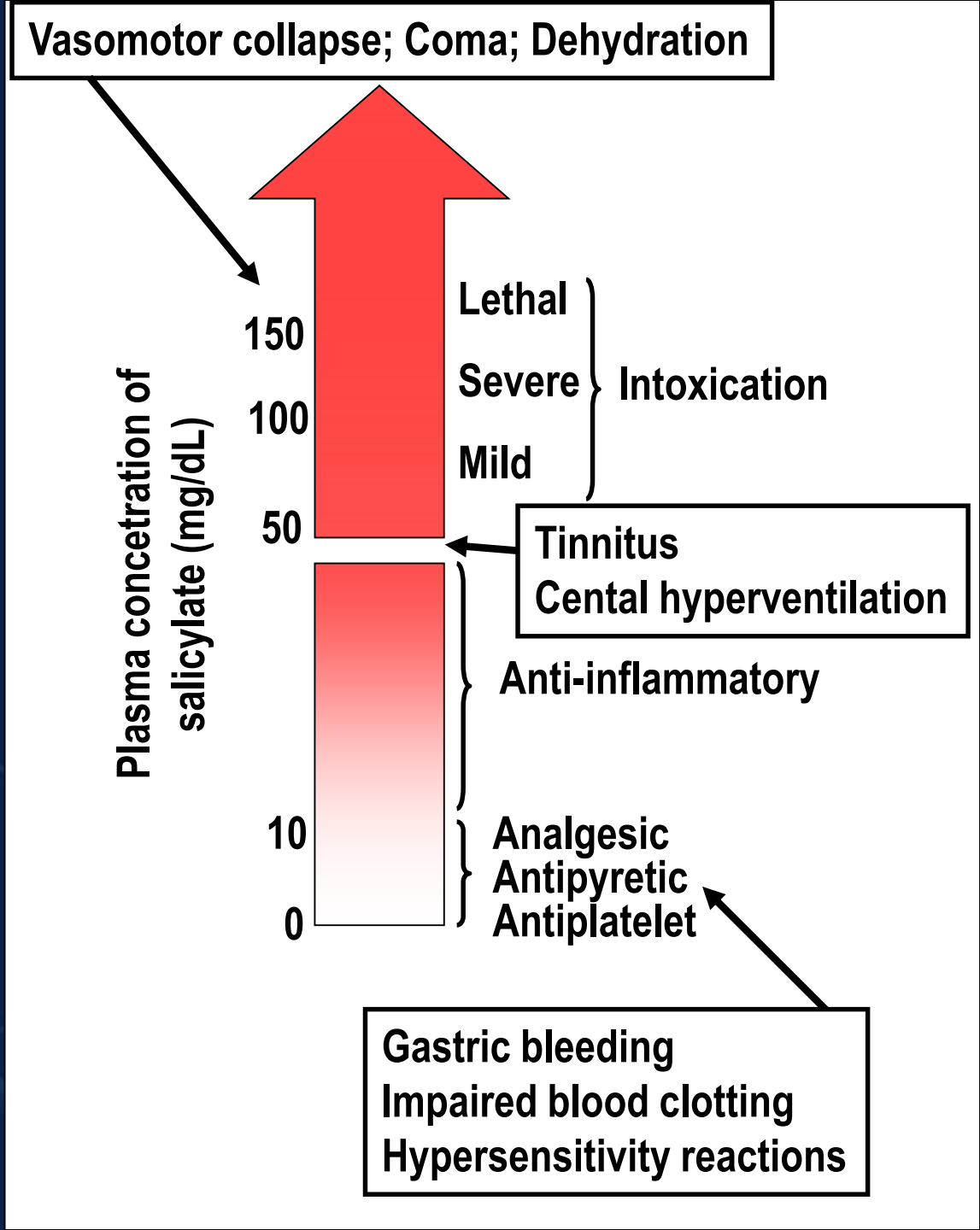
Aspirin in a dose of 160 to 325 mg/day - beneficial in the prevention of the first IM (at least in men over the age of 50 years).

Prophylactic aspirin therapy is advocated in patients with clinical manifestations of coronary disease if no contraindications are present.

Aspirin

Dose	Effect
80 – 160 mg	Antiplatelet
325 – 1000 mg	Analgesic, antipyretic
325 mg – 6 grams	Antiinflammatory, tinnitus
6 – 10 grams	Respiratory alkalosis
10 – 20 grams	Fever, dehydration, acidosis
> 20 grams	Shock, coma

Dose-dependent effects of salicylate



(according to Lippincott´s Pharmacology, 2006

c. Fate:

Normal low dosages (analgesic and antipyretic) - aspirin is hydrolyzed to salicylate and acetic acid by esterases in tissues and blood. Salicylate is converted by the liver to water-soluble conjugates that are rapidly excreted by the kidney

Salicylate (organic acid) is secreted into the urine and can affect uric acid excretion.

5. Adverse effects:

a. GIT:

The most common: epigastric distress, nausea, and vomiting.

Microscopic GI bleeding - almost universal in patients treated with salicylates.

Note: Aspirin is an acid. At stomach pH, aspirin is uncharged- i.e., it crosses into mucosal cells, where it ionizes and becomes trapped, thus potentially causing direct damage to the cells. **Aspirin should be taken with food and large volumes of fluids to diminish GI disturbances.**

b. Blood: The irreversible acetylation of platelet COX → reduction of platelet TXA2 → **inhibition of platelet aggregation, prolonged bleeding time.**
Thus, **aspirin should not be taken for at least one week prior to surgery.** When salicylates are administered, anticoagulants may have to be given in reduced dosage.

c. Respiration: In **toxic doses** - respiratory depression, metabolic acidosis.

d. Metabolic processes: Large doses of salicylates uncouple oxidative phosphorylation. The energy normally used for the production of ATP is dissipated as heat → the **hyperthermia caused by salicylates when taken in toxic quantities.**

- **e. Hypersensitivity: About 15 % of patients - (urticaria, bronchoconstriction, angioneurotic edema). Fatal anaphylactic shock is rare.**

- **f. Reye syndrome: Aspirin given during viral infections has been associated with an increased incidence of Reye syndrome** (fever, vomiting, liver dysfunction,delirium, convulsions, cerebral edema, coma, possible death).

- **contraindicated in children (paracetamol).**

6. Toxicity:

Salicylate intoxication may be mild or severe.

The mild form - called salicylism: nausea, vomiting, hyperventilation, headache, mental confusion, dizziness, and tinnitus.

Large doses of salicylate - severe intoxication may result. The symptoms as above plus restlessness, delirium, hallucinations, convulsions, coma, metabolic acidosis, and death from respiratory failure.

Children are particularly prone to salicylate intoxication.
Ingestion of cca 10 g of aspirin → it can cause death in children.

Treatment of salicylism: Mild cases - symptomatic treatment.
Increasing the urinary pH enhances the elimination of salicylate.
Serious cases - i.v. fluid, hemodialysis or peritoneal dialysis, correction of acid-base and electrolyte balances.
Note: **Diflunisal does not cause salicylism.**

B. Propionic acid derivatives

IBUPROFEN and related drugs (**naproxen, fenoprofen, ketoprofen, flurbiprofen, oxaprozin**) are **reversible inhibitors of COX**.

All possess **anti-inflammatory, analgesic, and antipyretic activity**.
Especially for the chronic treatment of rheumatoid arthritis and osteoarthritis (lower frequency of GIT adverse affects).

Well absorbed orally, they are **almost totally bound to serum albumin (99%)**.

Hepatic metabolism, excreted by the kidney.

The most common **AE** are **GI** (dyspepsia, bleeding). CNS side effects (headache, tinnitus, dizziness) also were reported.

C. Acetic acid derivatives

INDOMETHACIN, SULINDAC, ETODOLAC
All have anti-inflammatory, analgesic, and antipyretic activity.

Reversible inhibition of COX.

Very potent; toxicity of indomethacin limits its use (for the treatment of acute gouty arthritis, ankylosing spondylitis, osteoarthritis of the hip). Also beneficial in the pain in uveitis and postoperative ophthalmic pain.

Sulindac (a prodrug, related to indomethacin). Useful in rheumatoid arthritis, ankylosing spondylitis, acute gout and, osteoarthritis.

The adverse reactions are less severe than in indo.
Etodolac - effects similar to other NSAIDs. GIT problems may be less common.

***Adverse effects*:**

In up to 50% patients treated with indomethacin (in 20% - discontinuation in the use).

***a.* GIT: nausea, vomiting, anorexia, diarrhea, abdominal pain. Ulceration of the upper GIT.**

***b.* CNS: The most severe - frontal headache (25-50% patients who chronically use indomethacin). Other: dizziness, vertigo, light-headedness, mental confusion.**

***c.* Acute pancreatitis is known to occur. Hepatic effects are rare (though some fatal cases of hepatitis and jaundice were reported).**

***d.* Hematopoietic reactions: neutropenia, thrombocytopenia, aplastic anemia (rarely).**

***e.* Hypersensitivity reactions: rashes, urticaria, itching, acute attack of asthma, and 100% cross-reactivity with aspirin.**

D. Oxicam derivatives

PIROXICAM and **MELOXICAM -** used to treat rheumatoid arthritis, ankylosing spondylitis, and osteoarthritis.

They have **long half-lives (which permit administration once a day)**.

GIT disturbances in approx. 20 % treated with piroxicam.

Meloxicam is relatively COX-2 selective and at low to moderate doses shows less GI irritation than piroxicam.

However, **at high doses, meloxicam is a nonselective NSAID** (inhibition COX-1 and COX-2).

Excreted in the urine, interference with the excretion of lithium.

E. Fenamates

MEFENAMIC ACID, MECLOFENAMATE - no advantages over other NSAIDs.

Side effects: e.g., diarrhea (even severe with inflammation of the bowel), hemolytic anemia.

F. Other agents

1. DICLOFENAC - long-term use in the treatment of rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis.

It is more potent than indomethacin or naproxen. An ophthalmic preparation is also available. Diclofenac accumulates in synovial fluid. The urine is the primary route of excretion for the drug and its metabolites. Its toxicities are similar to those of the other NSAIDs. GIT problems are common, elevation of hepatic enzymes.

2. KETOROLAC - can be administered i.m. in the treatment of postoperative pain and topically for allergic conjunctivitis.

It undergoes hepatic metabolism; the drug and metabolites are eliminated via the urine. The same side effects as the other NSAIDs.

3. TOLMETIN, NABUMETONE, NIMESULID

as potent as aspirin (in treating rheumatoid arthritis or osteoarthritis), they act preferentially selectivity to COX 2), lower adverse effects.

4. PHENYLBUTAZONE

(and others: oxyphenbutazone, azapropazone, kebuzone, klofezone, propyphenazone, aminophenazon, noramidopyrine, metamizole

Powerful anti-inflammatory effects, weak analgesic and antipyretic activities.

Only in short-term therapy of acute gout and in acute rheumatoid arthritis when other NSAIDs agents have failed.

The usefulness of phenylbutazone is limited by its toxicity.

They are rapidly and completely absorbed after oral or rectal administration.

Adverse effects:

Phenylbutazone - adverse effect occur in nearly 50 % of those treated.

The drug should be given for short periods of time-up to 1 week only.

Patients should be observed, and frequent blood tests should be taken.

- The most common - nausea, vomiting, skin rashes, and epigastric discomfort.

- Other - fluid and electrolyte retention (with edema and decreased urine volume).

- Diarrhea, vertigo, insomnia, blurred vision, nervousness, hematuria.

- Phenylbutazone reduces the uptake of iodine by the thyroid glands, sometimes resulting in goiter and myxedema.

- The most serious adverse effects are agranulocytosis and aplastic anemia.

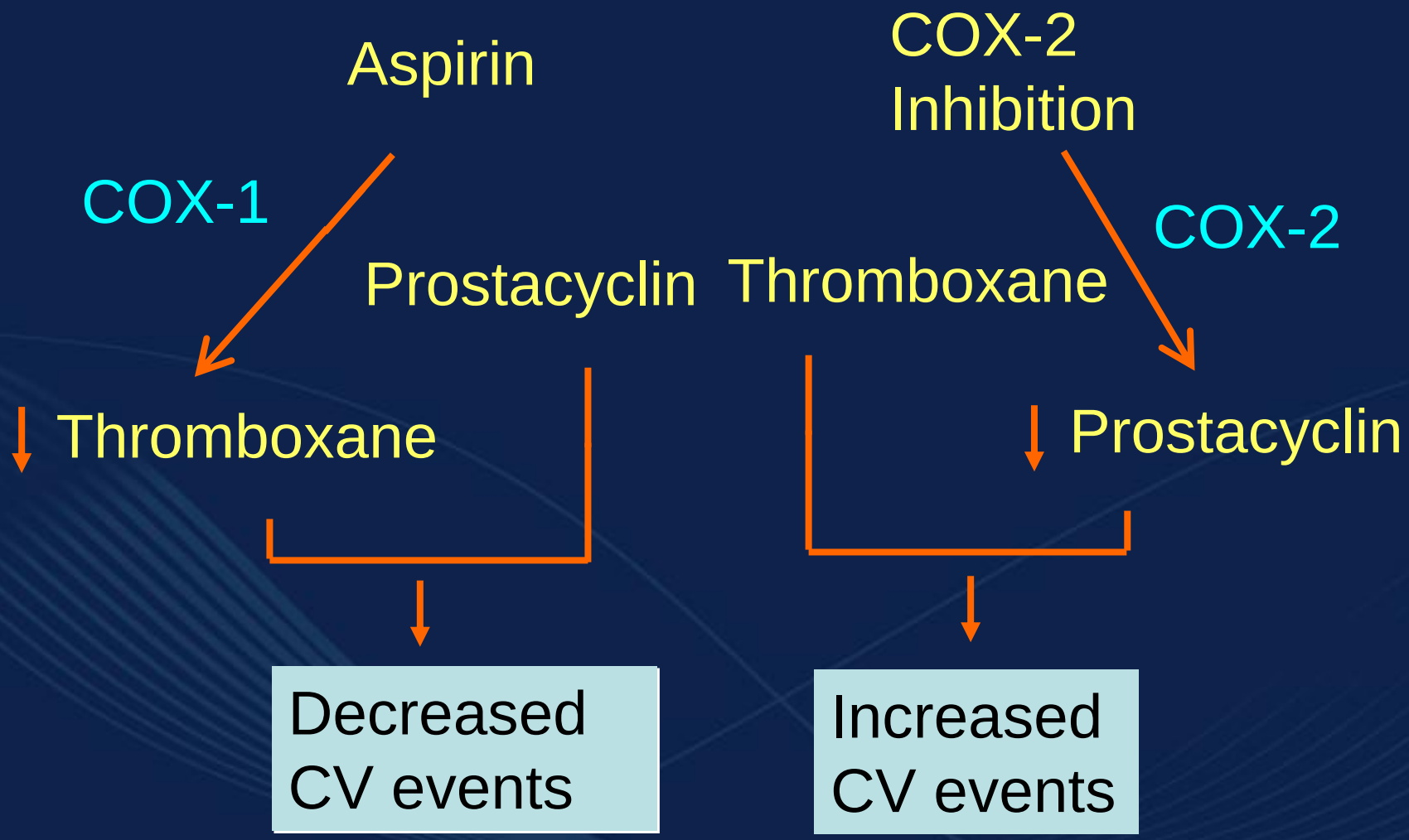
IV. COX-2-SELECTIVE NSAIDs

The structural difference between COX-1 and COX-2 allowed the development of COX-2-selective agents, such as celecoxib and valdecoxib. They differ from traditional NSAIDs, which inhibit both COX-1 and COX-2.

COX-2 inhibitors - an advantage - a lower risk for the development of GI bleeding. They also have no significant effects on platelets. However, the COX-2 drugs (like the traditional NSAIDs) may cause renal insufficiency and increase the risk of hypertension.

- **For patients who require chronic use of NSAIDs and are at high risk for NSAID-related GIT toxicity, primary therapy with a COX-2-selective inhibitor is a reasonable option.**

!!!! But: long-term treatment with COX-2 inhibitors - was shown to increase the risk of myocardial infarction and stroke; several of the drugs was withdrawn (e.g., rofecoxib) !!!!!


Aspirin
COX-1
Prostacyclin
Thromboxane
Decreased
CV events
COX-2
Inhibition
COX-2
Thromboxane
Prostacyclin
Increased
CV events

A. CELECOXIB

More selective inhibition of COX-2 than of COX-1. At concentrations achieved *in vivo*, celecoxib does not block COX-1.

The inhibition of COX-2 is reversible.

Approved for treatment of osteoarthritis and rheumatoid arthritis.

Unlike aspirin, **coxib does not inhibit platelet aggregation and does not increase bleeding.**

1. Pharmacokinetics: readily absorbed (a peak concentration in 3 hrs), **extensively metabolized in the liver** by CYP2C9 and excreted in the feces and urine. Half-life cca 11 hours - usually taken once a day.

2. Adverse effects:

- **GIT:** abdominal pain, diarrhea, dyspepsia; however the incidence of ulcers is lower comparing with nonselective NSAIDs.

- **Contraindicated in patients who are allergic to sulfonamides**. If there is a history of sulfonamide allergy, the use of a nonselective NSAID is recommended.

- **Kidney toxicity** - avoid in patients with chronic renal insufficiency, severe heart disease,

-Patients with anaphylactoid reactions to aspirin or NSAIDs may be at risk for similar effects.

- **Inhibitors of CYP2C9 (e.g. fluconazole, fluvastatin, zafirlukast) may increase serum levels of celecoxib.**

- **Celecoxib inhibits CYP2D6** – it can lead to ⇧ levels of some beta-blockers, antidepressants, and antipsychotic drugs.

The Medicines Healthcare products Regulatory Agency (MHRA), the European Medicines Agency (EMEA), and the Committee on Safety of Medicines (CSM) have all formulated guidelines on the prescribing of coxibs. The CSM have sent their guidelines to all UK doctors (similar guidelines are issued by the EMEA):

- A contraindication is introduced for all COX-2 inhibitors in patients with ischaemic heart disease or stroke

- A warning is introduced for prescribers to exercise caution when prescribing COX-2 inhibitors for patients with risk factors for heart disease, such as hypertension, hyperlipidaemia, DM and smoking, as well as for patients with peripheral arterial disease

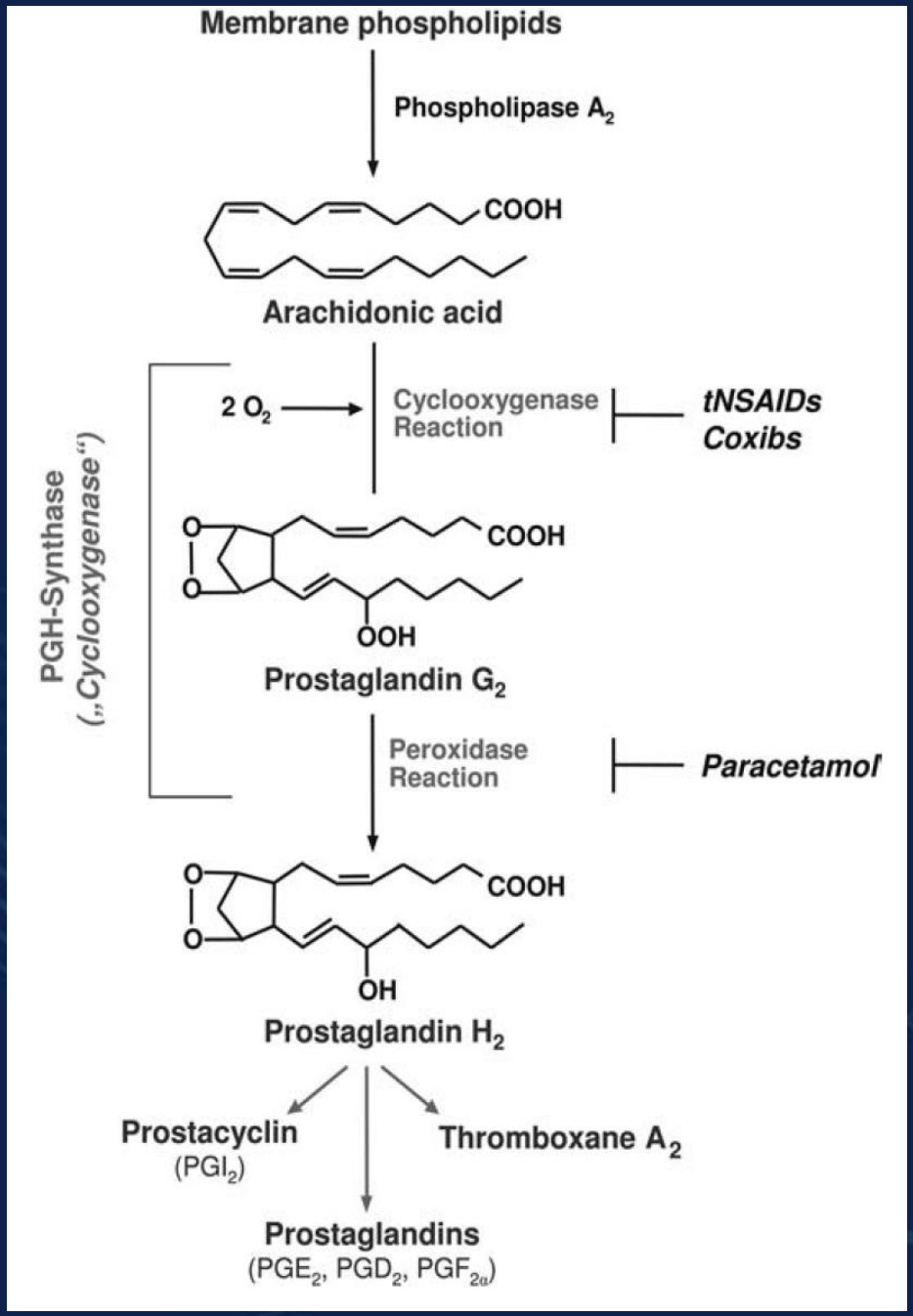
V. OTHER ANALGESICS

Paracetamol has less effect on COX in peripheral tissues → weak anti-inflammatory activity. Paracetamol does not affect platelet function or increase blood clotting time.

It inhibits PGs synthesis in the CNS - it explains its antipyretic and analgesic properties

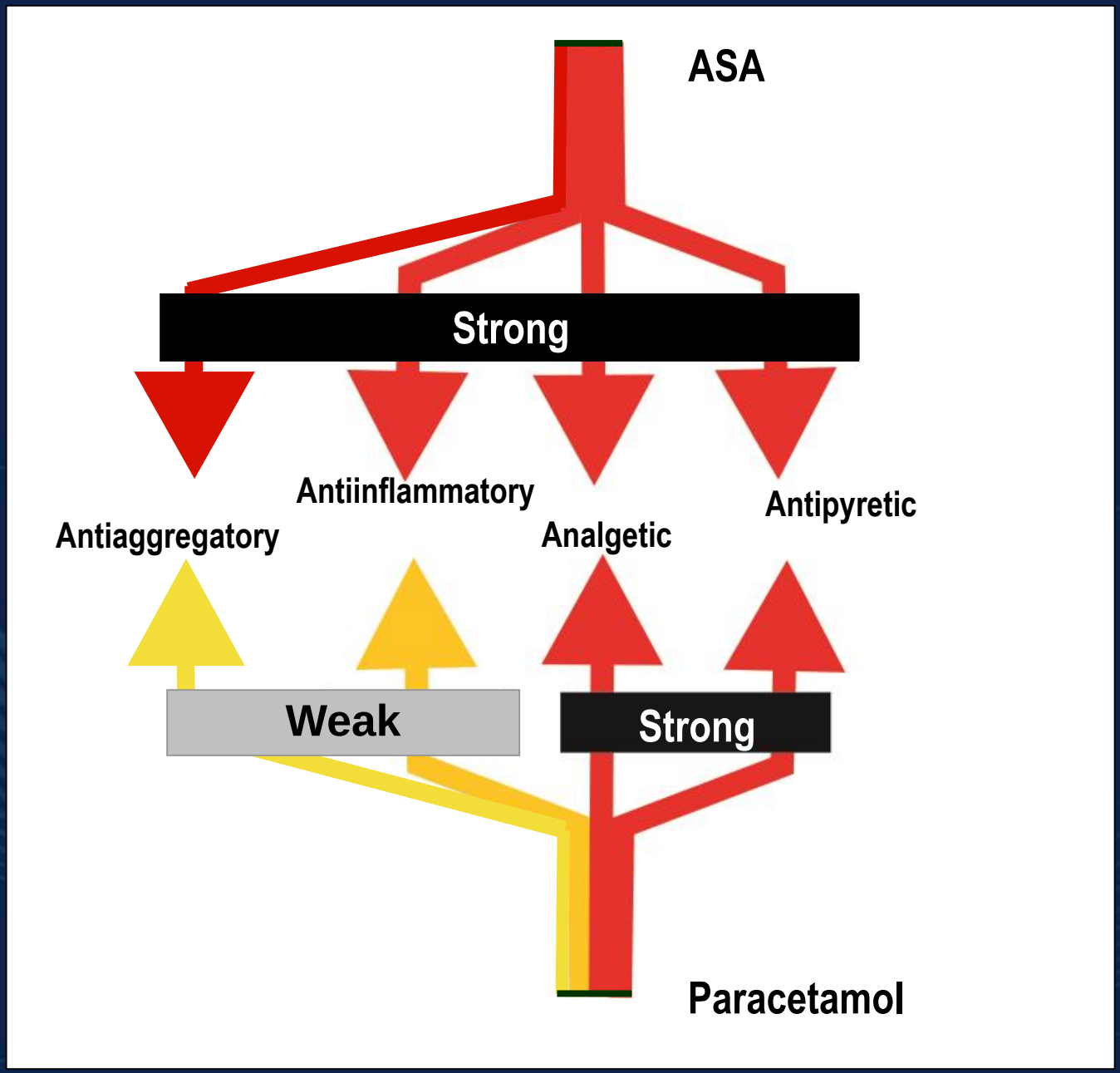
1. Therapeutic uses:

Suitable for the analgesic and antipyretic effects for patients with gastric complaints, where prolongation of bleeding time would be a disadvantage, or those who do not require the anti-inflammatory action of aspirin.



Whereas traditional NSAID and selective COX-2 inhibitors inhibit cyclooxygenase by competing with arachidonic acid for entering the cyclooxygenase reaction,[7 8] paracetamol has been suggested to act as a reducing agent within the peroxidase site. In brief, paracetamol quenches a protoporphyrin radical cation. The latter generates the tyrosine radical in the cyclooxygenase site that is responsible for catalysing the oxygenation of arachidonic acid.[9 10]

Aspirin vs. paracetamol



Analgesic/antipyretic of choice for children with viral infections or chickenpox.
It does not antagonize the uricosuric agent probenecid and may be used in patients with gout who are taking that drug.

2. Pharmacokinetics:
Rapidly absorbed from the GIT.
Under normal circumstances is conjugated in the liver to form inactive glucuronidated or sulfated metabolites.

A portion of paracetamol hydroxylated to form N-acetylbenzoimino- quinone - (NABIQ) a highly reactive and dangerous metabolite that reacts with sulfhydryl groups.
At normal doses, the NABIQ reacts with the sulfhydryl group of glutathione, forming a nontoxic substance.

Excreted in the urine.

3. Adverse effects:

Normal therapeutic doses - minor adverse effects.

Skin rash and minor allergic reactions - rare. Minor alterations in the leukocyte count (generally transient).

Renal tubular necrosis and hypoglycemic coma are rare complications of prolonged, large-dose therapy.

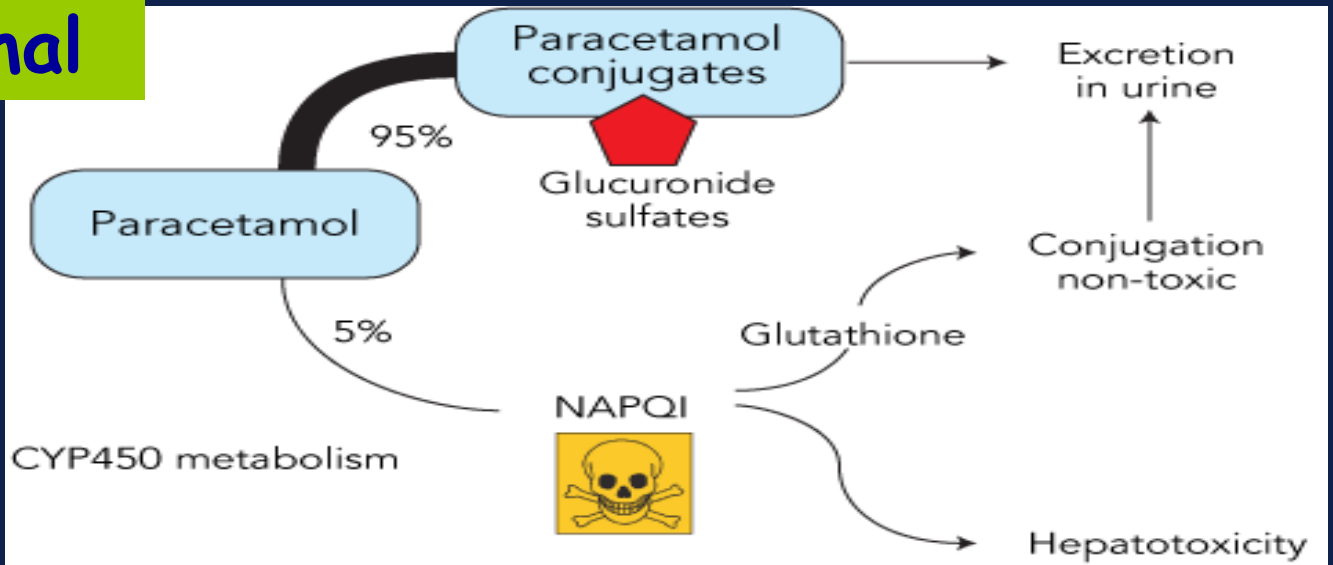
Large doses of paracetamol (about 5 g or more in adult) - the available glutathione in the liver becomes depleted → NABIQ reacts with the sulfhydryl groups of hepatic proteins, forming covalent bonds.

Hepatic necrosis can result. Renal tubular necrosis may also occur.

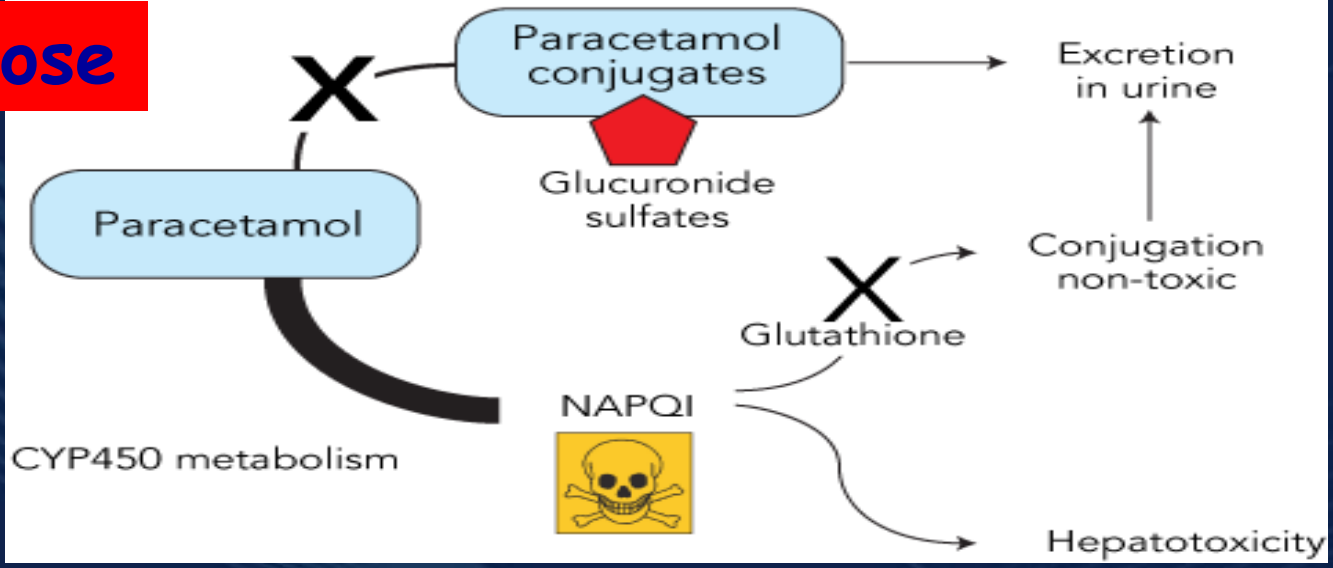
Possibly dangerous in alcoholics.

N-acetylcysteine - can be lifesaving if administered within ten hours of the overdose.

Normal



Overdose



Antirheumatic agenst

Rheumatoid arthritis

It is an autoimmune disease in which the normal immune response is directed against an individual's own tissue, including the joints, tendons, and bones, resulting in inflammation and destruction of these tissues

The cause of rheumatoid arthritis is not known

Rheumatoid arthritis

- **The prevalence of rheumatoid arthritis in most Caucasian populations approaches 1% among adults 18 and over and increases with age, approaching 2% and 5% in men and women, respectively, by age 65**

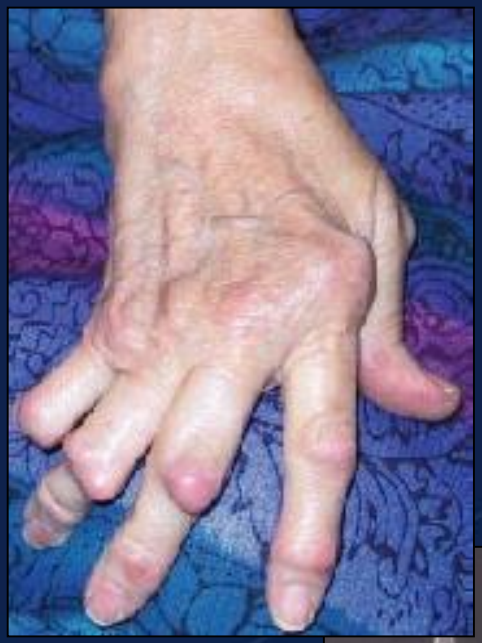
- **The incidence also increases with age, peaking between the 4th and 6th decades**

- **The annual incidence for all adults has been estimated at 67 per 100,000**

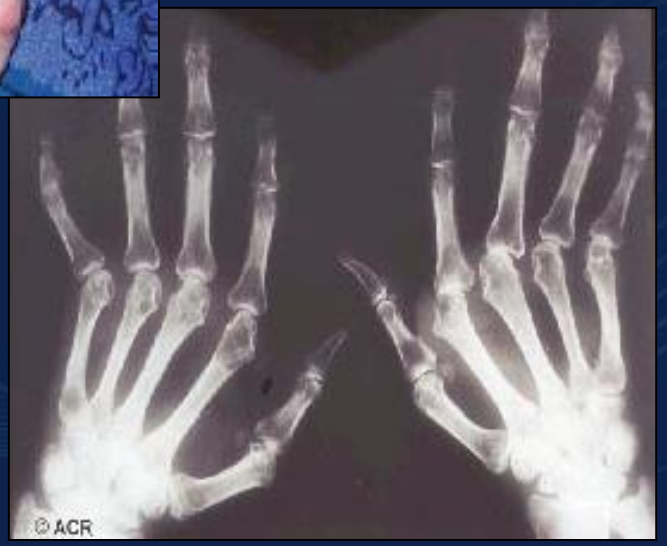
Rheumatoid arthritis

- Both prevalence and incidence are 2-3 times greater in women than in men
- African Americans and native Japanese and Chinese have a lower prevalence than Caucasians
- Several North American Native tribes have a high prevalence
- Genetic factors have an important role in the susceptibility to rheumatoid arthritis

Clinical presentation of RA



Severe RA



Early RA

Intermediate RA

Latinis KM, et al. *The Washington Manual™ Rheumatology Subspecialty Consult.* Philadelphia, Pa: Lippincott Williams & Wilkins; 2004.

DISEASE-MODIFYING ANTIRHEUMATIC AGENTS

A miscellaneous group of drugs - disease-modifying antirheumatic drugs (DMARDs), or slow-acting anti-rheumatic drugs (SAARDs).

The DMARDs slow the course of the disease and can induce remission, preventing further destruction of the joints and involved tissues.

Used especially if the inflammatory disease does not respond to COX inhibitors. They have a long onset of action (sometimes 3 - 4 months).

A.Choice of drug

No one DMARD is efficacious and safe in every patient. Frequently therapy begins with one of the traditional small molecules (methotrexate, hydroxychloroquine) - they are efficacious and generally well tolerated.

Inadequate response to the traditional agent - the use of newer DMARDs (leflunomide, adalimumab, anakinra, etanercept, infliximab)

Combination therapies are both safe and efficacious

In most cases, methotrexate is combined with one of the other DMARDs.

B. METHOTREXATE

in patients with severe RA or psoriatic arthritis who have not responded adequately to NSAIDs

It slows the appearance of new erosions within involved joints. **Response occurs sooner than in other slow-acting agents - often within 3-6 weeks.**

It is an immunosuppressant - this may account for its effectiveness in arthritis, an autoimmune disease.
Doses are much lower than in cancer chemotherapy, given once a week → the adverse effects are minimized.
ADR: mucosal ulceration and nausea (most frequent), cytopenias (WBC), liver cirrhosis, acute pneumonia-like syndrome

[Note: Leucovorin – taken a day after methotrexate - reduces the severity of the adverse effects.]

C. Leflunomide

An immunomodulatory agent that preferentially causes cell arrest of the autoimmune lymphocytes through its action on dihydroorotate dehydrogenase (DHODH).

Inhibition of DHODH deprives the cell of the precursor for uridine monophosphate - a necessary component for RNA synthesis and a precursor of the thymidine-containing nucleotide required for DNA synthesis.

After biotransformation, leflunomide is a reversible inhibitor of DHODH.

Treatment of rheumatoid arthritis. It not only reduces pain and inflammation but also slows the progression of structural damage.

It can be used in monotherapy (an alternative to methotrexate) or as an addition to methotrexate in combination therapy.

Adverse effects: headache, diarrhea, and nausea.

Other: weight loss, allergic reactions including a flu-like syndrome, skin rash, alopecia, and hypokalemia.

Leflunomide is **teratogenic in experimental animals** - **contraindicated in pregnancy** and in women of child-bearing potential.

D. Chloroquine and hydroxychloroquine

Also used in the treatment of malaria.

Reserved for rheumatoid arthritis that does not response to NSAIDs; used in conjunction with NSAID (it allows a lower dose used). They slow progression of erosive bone lesions and may induce remission.

Adverse effects - Nausea, vomiting, stomach upset, cramps, loss of appetite, diarrhea, tiredness, weakness, headache, allergies, blurred vision, trouble seeing at night or problems focusing clearly, ringing in the ears, difficulty hearing

- **E. D-Penicillamine**

- **Analog of the amino acid cysteine; it slows the progress of bone destruction and rheumatoid arthritis.**

- **Prolonged treatment - serious side effects (dermatologic, nephritis and aplastic anemia) - it is used primarily in the treatment of rheumatoid arthritis after use of gold salts has failed but before use of corticosteroids.**

- **Also used in the treatment of poisoning by heavy metals.**

F. Gold salts

They also cannot repair existing damage but can only prevent further injury.

Gold sodium thiomalate and aurothioglucose.
Taken up by macrophages and suppress phagocytosis and lysosomal enzyme activity - it retards the progression of bone and articular destruction.

Used less and less – because of **serious toxicity** (in about **1/3 of patient**); **the most common** - dermatitis of the skin or of the mucous membranes (especially in the mouth) - occurs in up to 20% of patients; other include proteinuria and nephrosis (5-8% of patients) and rare, **severe blood disorders, such as agranulocytosis and aplastic anemia.**

ANTICYTOKINE THERAPIES IN RHEUMATOID ARTHRITIS

Interleukin-1β (IL-1 β) and TNF-α are proinflammatory cytokines involved in the pathogenesis of rheumatoid arthritis.

When secreted by synovial macrophages, they stimulate synovial cells to proliferate and synthesize collagenase → degradation of cartilage, stimulation of bone resorption, and inhibition of proteogjycan synthesis.

Drug antagonists of these cytokines - effective in treating rheumatoid arthritis.

A. Etanercept

TNF plays a key role in the host's immune system. Etanercept binds 2 molecules of TNF; it does not discriminate between TNF-α and TNF-β; given s.c., well tolerated; it should not be administered to patients with life-threatening infection !!.

Treatment of rheumatoid and psoriatic arthritis.

Note: Upon discontinuation of etanercept, the symptoms of arthritis generally return within a month.

The combination of etanercept and methotrexate was more effective than methotrexate or etanercept alone in retarding the disease process.

According to some suggestion - anti- TNF drug + methorexate may be considered as standard therapy for patients with rheumatoid and psoriatic arthritis.

B. Infliximab

IgGkappa monoclonal antibody – it **binds specifically to human TNF-α** and thus it neutralizes this cytokine. Approved for **Crohn's disease**; i.v. infusion; half live 9.5 days;

Long-term treatment - associated with development of anti-infliximab antibodies, unless the drug is used in combination with methotrexate.

Infusion reactions: fever, chill, pruritus, urticaria.

Infections (even life-threatening) - (leading to pneumonia, cellulitis etc.) also reported. Leukopenia, neutropenia, thrombocytopenia, and pancytopenia occurred.

C. Adalimumab

Treatment of active rheumatoid arthritis (moderate to severe) in patients with inadequate response to one or more DMARDs.

It is a **recombinant monoclonal antibody that binds to human TNF-α receptor sites, thereby interfering with endogenous TNF- α activity.**

It decreases signs and symptoms of rheumatoid arthritis and inhibits progression of structural damage.

Only by s.c. injection.

Adverse effects: headache, nausea, rash, reaction at the injection site.

Note: An increased predisposition to infections

D. Anakinra

Interleukin-1 is induced by inflammatory stimuli and mediates a variety of immunologic responses, incl. degradation of cartilage and stimulation of bone resorption.

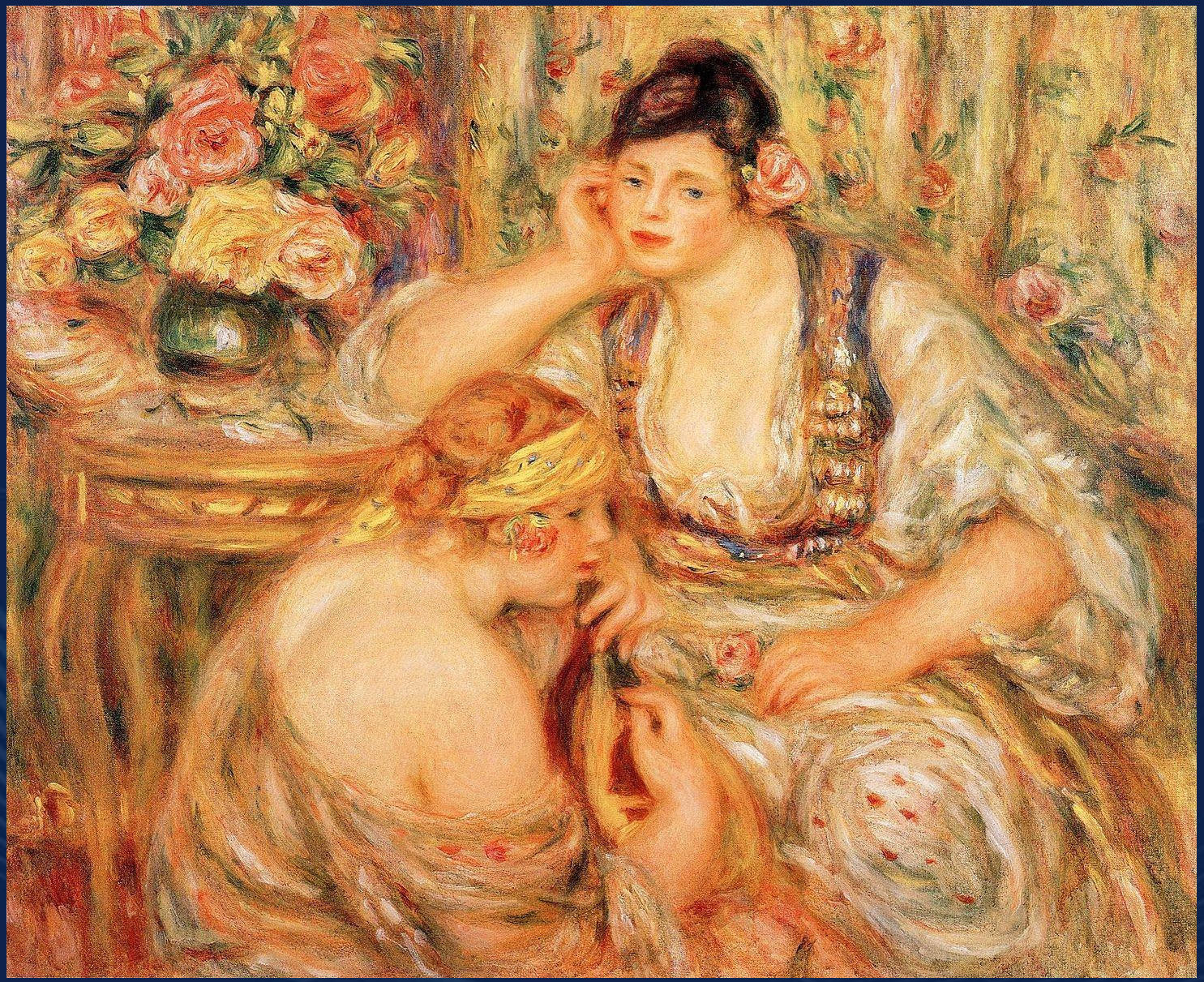
It is an IL-1 receptor antagonist (binds to IL-1 receptor, thus preventing IL-1 actions).

Anakinra treatment leads to the reduction of signs and symptoms of moderately to severely active rheumatoid arthritis in adult patients who have failed one or more DMARDs.

The drug may be used alone or in combination with DMARDs (other than TNF-blocking agents).

“One must from time to time attempt things that are beyond one’s capacity.”

—Pierre-Auguste Renoir (1841-1919)



Pierre-Auguste Renoir „The Concert“ (1918)

URATE LOWERING DRUGS

Uricosurics

1.Probenecid and Sulfinpyrazone

- require: good renal function
  no ASA
  good urine output day and night
- therefore limited use

URATE LOWERING DRUGS

Allopurinol - an inhibitor of xanthine oxidase

- start low eg. 50-100 mg qd
- increase by 50-100 mg every 2-3 weeks according to symptoms and measured serum uric acid
- “average” dose 300 mg daily
  - lower dose if renal/hepatic insufficiency
  - higher dose in non-responders
- prophylactic colchicine until allopurinol dose stable

URATE LOWERING DRUGS

Allopurinol side effects

- pruritic papular rash 3-10%
  consider desensitization protocol

- GI upset, macular or vasculitic skin rash, myelo-suppression, hepatitis, alopecia

- Allopurinol Hypersensitivity (AHS): skin rash, fever, hepatitis, eosinophilia, renal impairment

GOUT -PROPHYLAXIS

Colchicine (at low dose)

- indications:
  -until dose of urate lowering drug optimized
  -if patient cannot take a urate lowering drug

ACUTE GOUT - TREATMENT

A. Colchicine

- must be started in first 24 hours
- narrow therapeutic - toxic ratio
  i.e.,: GI upset in 80%
- limited therapeutic use in acute gout
- other side effects: bone marrow suppression, renal failure, CHF, death

ACUTE GOUT - TREATMENT

B. NSAIDS COX-1 and COX-2

- use in patients without contraindication
- use maximum dose/potent NSAID

  e.g., Indomethacin 50 mg po t.i.d.

  Diclofenic 50 mg po t.i.d.

  Ketorolac 10 mg q4-6hrs
- continue until pain/inflammation absent for 48 hours

ACUTE GOUT - TREATMENT

C. Corticosteroid

- use when • NSAIDS risky or contraindicated

  e.g.,: elderly

  hypertensive

  peptic ulcer disease

  renal impairment

  liver impairment

- use when • NSAIDS ineffective

ACUTE GOUT - TREATMENT

C. Corticosteroid

- mode of administration

1. intra-articular with drainage R/O sepsis
   e.g.,) depomedrol 40-80 mg with lidocaine

2. oral prednisone 30-40 mg qd for 3-4 days. Then taper by 5 mg every 2-3 days and stop over 1-2 weeks