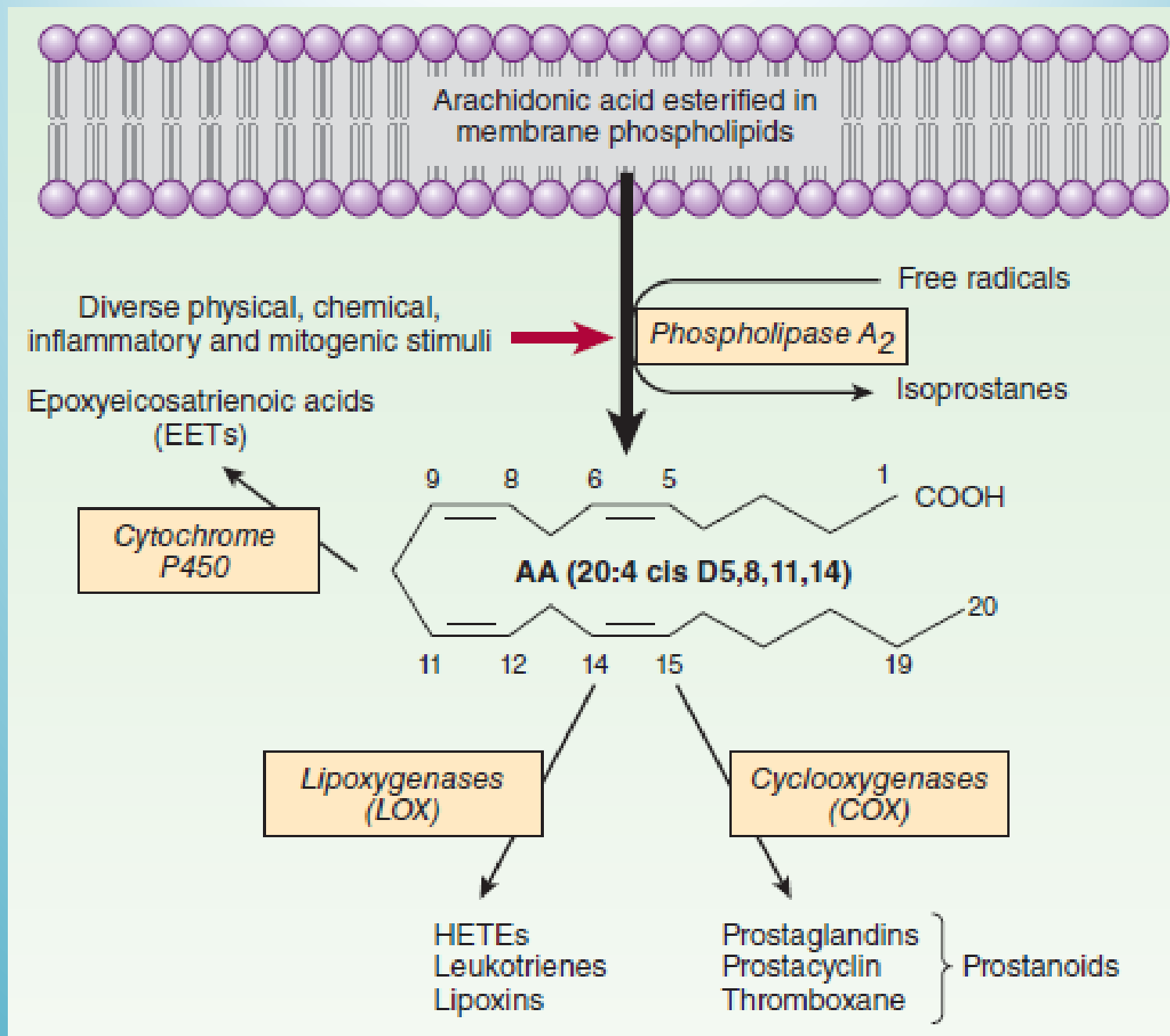
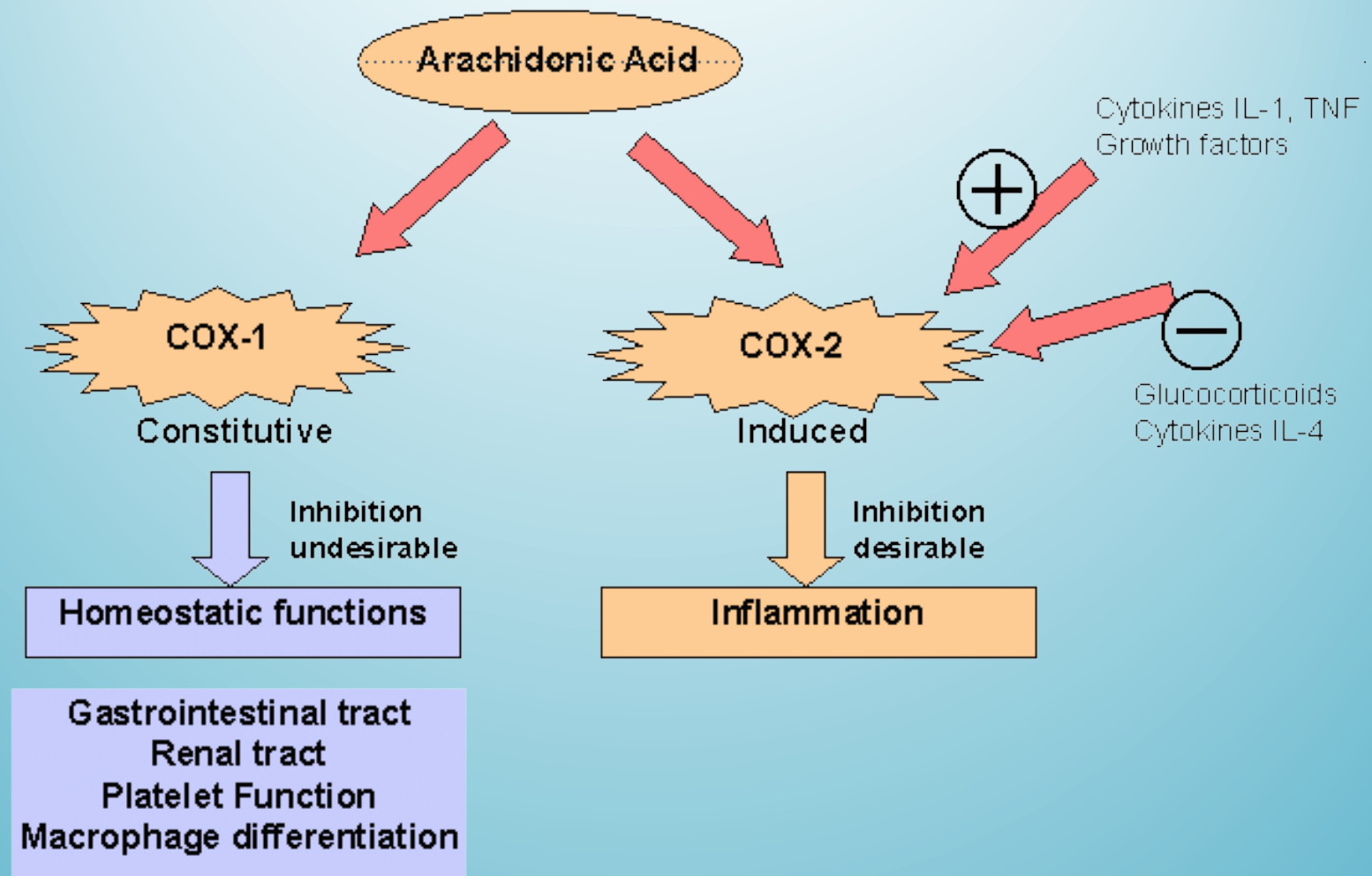


# NSAIDs, DMARDs and drugs used in Gout

*By*  
*Ahmed Shubbar*







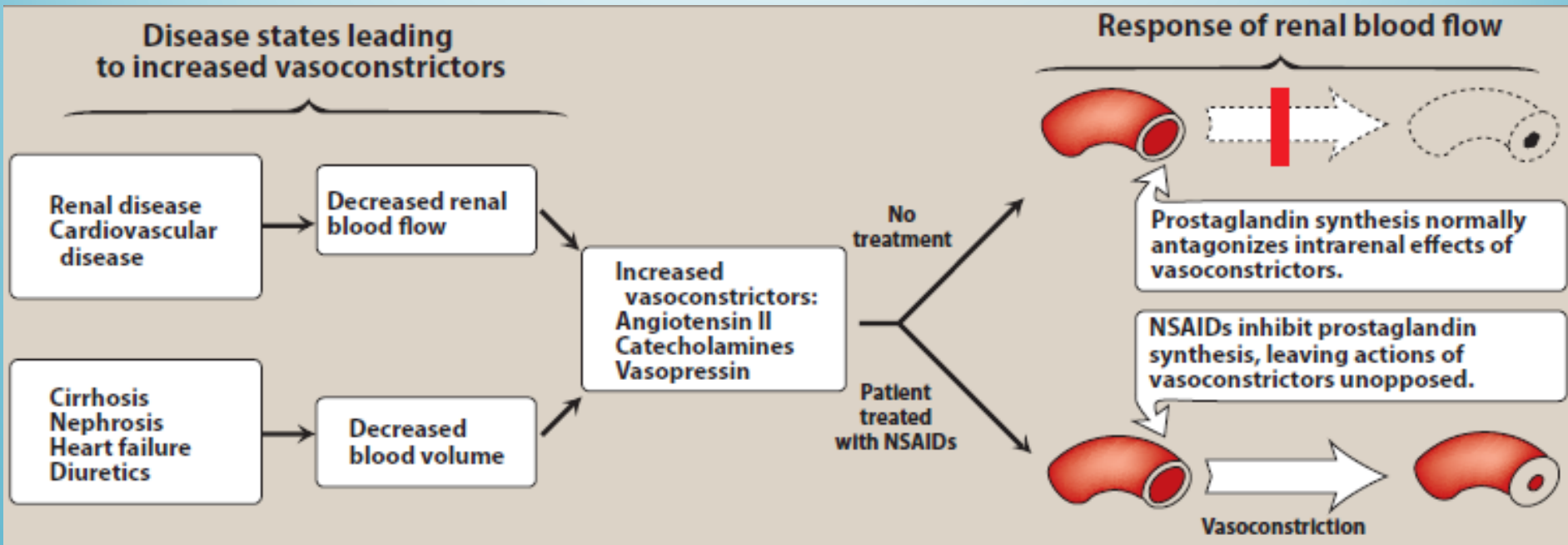
# NSAIDs

- Either ***non-selective COX inhibitors*** or ***COX-2 selective inhibitors***.

## ***Indications***

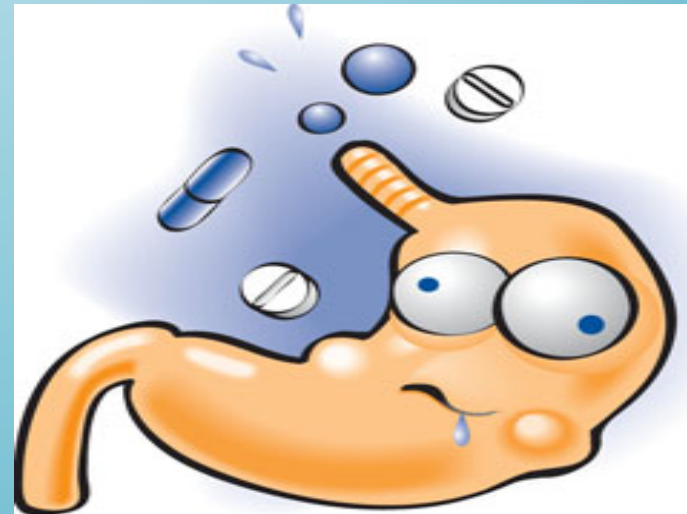
- *RA / OA.*
- *Gout and other musculoskeletal diseases.*
- *Migraine, Headache.*
- *Pyrexia.*
- *Dysmenorrhea.*





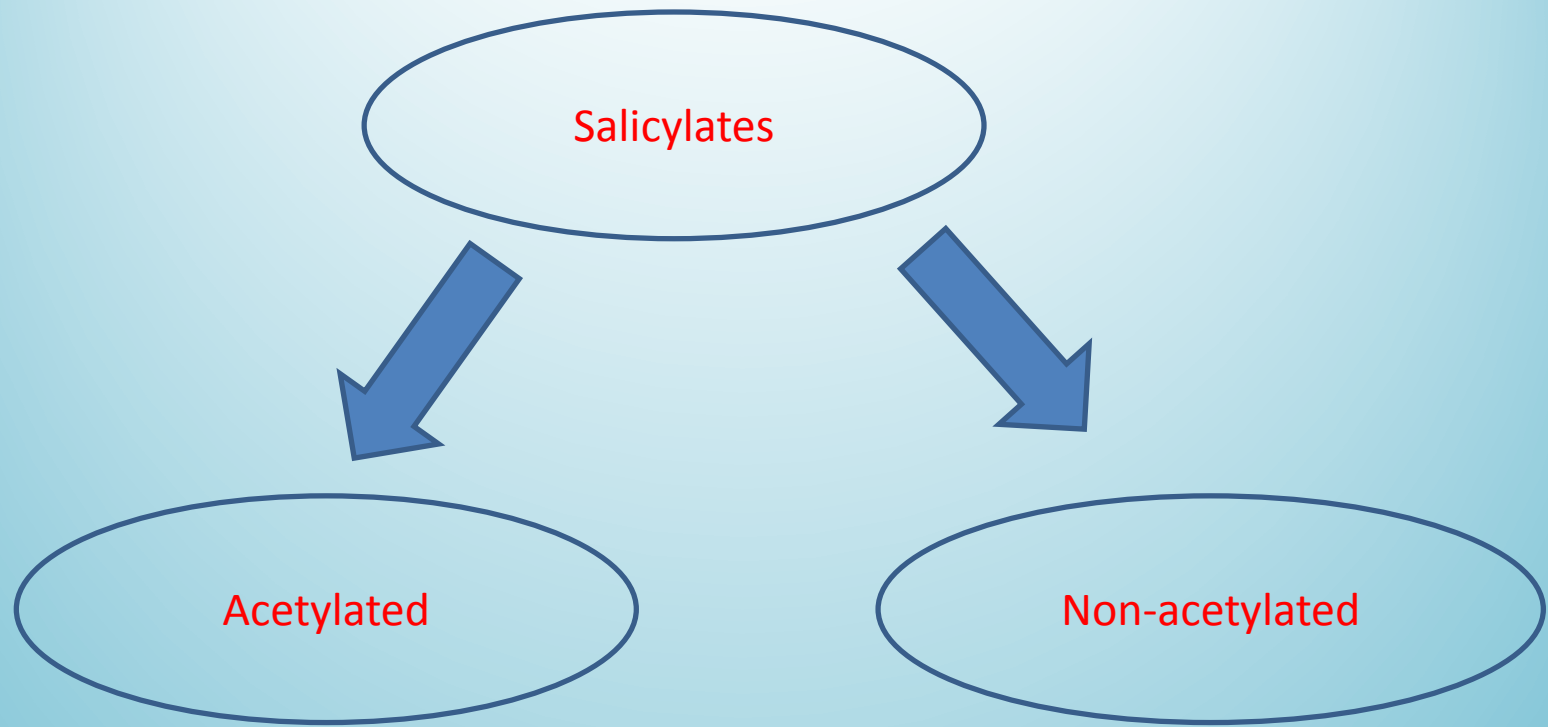
# Adverse effects of NSAIDs

1. **GIT**: ulcer and abdominal pain.
2. **CVS**: fluid retention , HTN and oedema.
3. **Pulmonary**: bronchoconstriction.
4. **Renal**: renal insufficiency ,RF & hyperkalemia.





# Non-selective COX inhibitors



Rarely used as anti-inflammatory and it's mostly used as anti-platelet, why ?

Example: Acetyl-salicylic acid (Aspirin , ASA).

Effective as anti-inflammatory , less effective as analgesics than ASA.

Examples: Salicyl salicylate, Sodium choline salicylate & Magnesium salicylate



Drug	Half-Life (hours)	Urinary Excretion of Unchanged Drug	Recommended Anti-inflammatory Dosage
Aspirin	0.25	<2%	1200–1500 mg tid
Salicylate <sup>1</sup>	2–19	2–30%	See footnote 2
Celecoxib	11	27% <sup>3</sup>	100–200 mg bid
Diclofenac	1.1	<1%	50–75 mg qid
Diflunisal	13	3–9%	500 mg bid
Etodolac	6.5	<1%	200–300 mg qid
Fenoprofen	2.5	30%	600 mg qid
Flurbiprofen	3.8	<1%	300 mg tid
Ibuprofen	2	<1%	600 mg qid
Indomethacin	4–5	16%	50–70 mg tid
Ketoprofen	1.8	<1%	70 mg tid
Ketorolac	4–10	58%	10 mg qid <sup>4</sup>
Meloxicam	20	Data not found	7.5–15 mg qd
Nabumetone <sup>5</sup>	26	1%	1000–2000 mg qd <sup>6</sup>
Naproxen	14	<1%	375 mg bid

# Aspirin

- Irreversibly inhibits COX-1 in platelets (effect lasts 8-10 days, why? ).
- ASA ↓ incidence of TIA, CAD and thrombosis and may be used to treat preeclampsia-eclampsia.
- **AE**: gastric/duodenal ulcer and it's c.i. in patients with hemophilia.



# ***Diclofenac***

- May be combined with misoprostol / omeprazole, why ?
- Diclofenac and Sulindac (also a NSAID) may cause elevation of serum aminotransferases.

# ***Indomethacin***

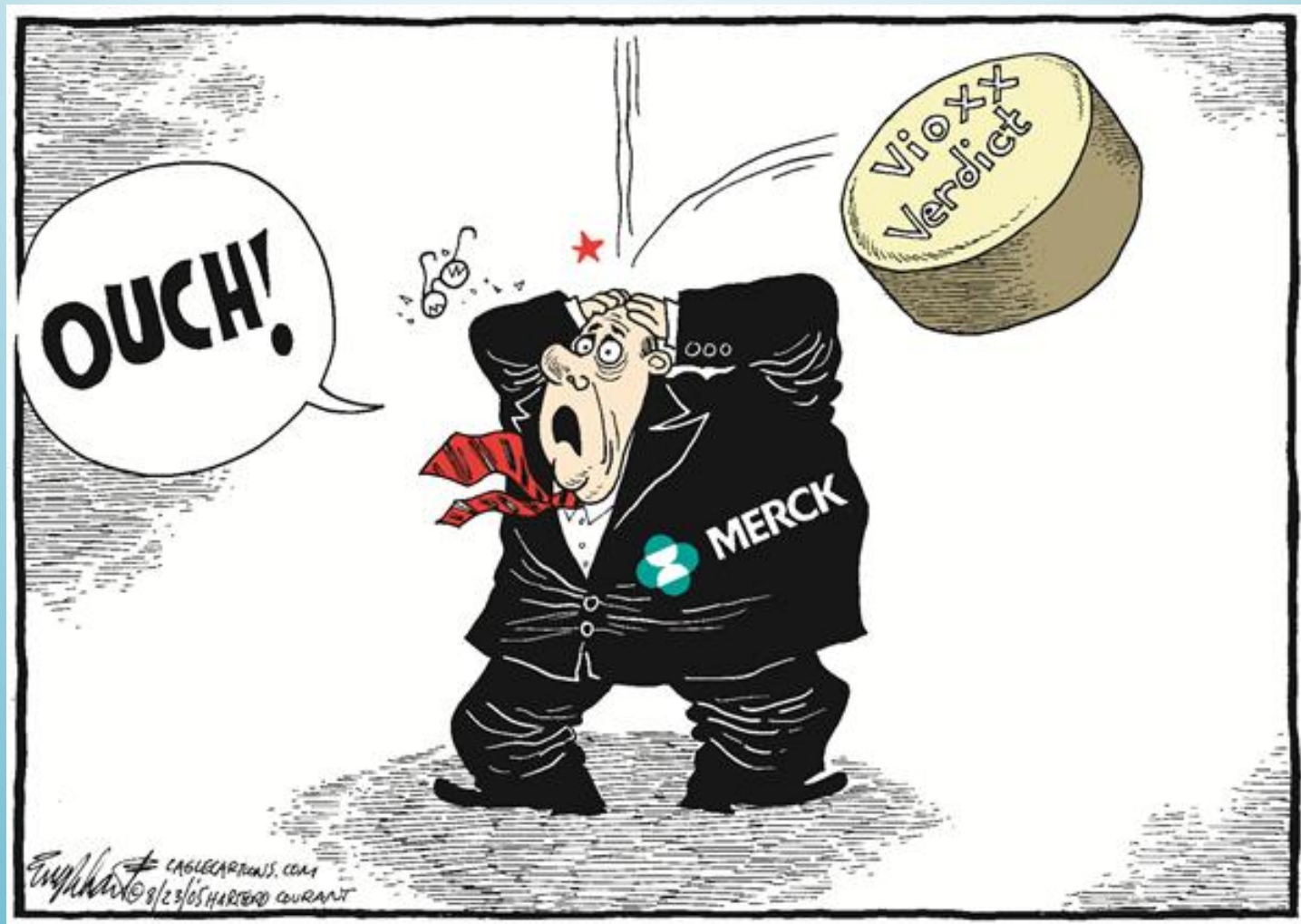
- Used to accelerate closure of ductus arteriosus.
- Probenecid  $\uparrow$  its  $t_{1/2}$ .

# Other non-selective COX inhibitors

- *Ibuprofen.*
- *Ketoprofen.*
- *Flubiprofen.*
- *Piroxicam.*
- *Tenoxicam.*
- *Tolmetin.*
- *Mefenamic acid.*
- *Nimesulide.*
- *Nabumetone.*
- *Naproxen.*
- *Oxaprozin.*
- *Etodolac.*
- *Diflunisal.*



# COX-2 selective inhibitors





# COX-2 selective inhibitors

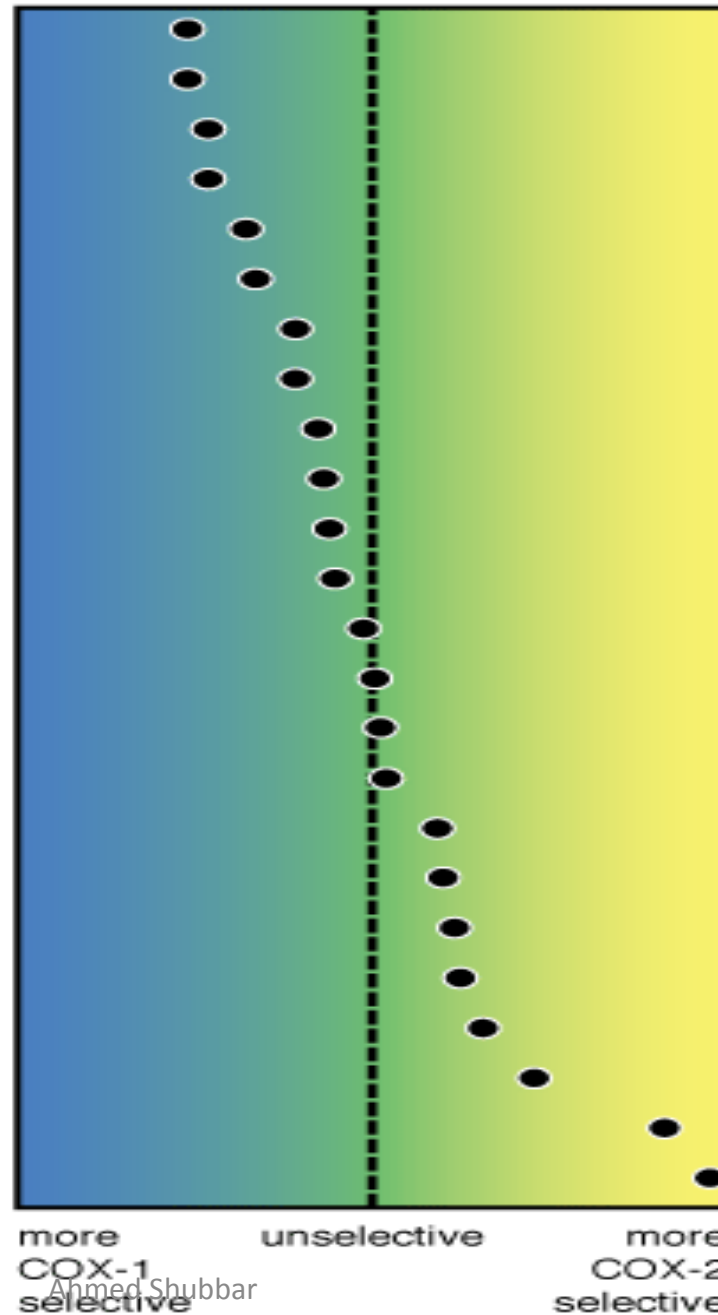
- Selective COX-2 inhibitors do not affect platelets function at usual doses and GI safety may be improved.
- Risk of CV diseases may be increased , why ?
- Like non-selective COX inhibitors, they are also nephrotoxic.



## B COX isoform selectivity (log scale)

Ketorolac  
Flurbiprofen  
Ketoprofen  
Indomethacin  
Tolmetin  
Aspirin  
Nabumetone  
Fenoprofen  
Meclofenamate  
Sulindac  
Naproxen  
Piroxicam  
Ibuprophen  
Acetaminophen  
Sodium salicylate  
Diflunisal

Meloxicam  
Diclofenac  
Celecoxib  
Valdecoxib  
Etodolac  
Rofecoxib  
Etoricoxib  
Lumiracoxib



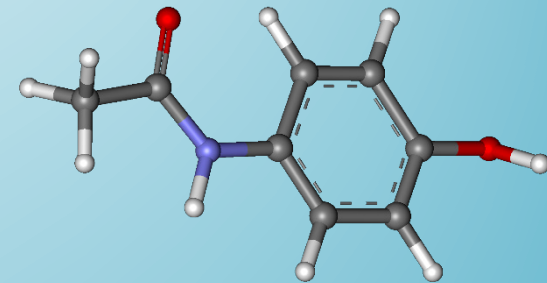
NSAIDs, DMARDS and drugs  
used in Gout

COX2 selective  
NSAIDs

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# Acetaminophen

- Analgesic with very weak anti-inflammatory action (weak COX-1/ COX-2 inhibitor in peripheral tissues, why?).



- The weak anti-inflammatory effect may be due to its inability to inhibit COX in the presence of the elevated cellular peroxides found in inflamed cells.



# ***DMARDS***

- ***Rheumatoid arthritis*** is an autoimmune disease and its pharmacological management includes symptomatic relief through the use of NSAIDs and short-term glucocorticoids often are used to bring the level of inflammation quickly under control.
- ***DMARDs (disease-modifying anti-rheumatic drugs)***, on the other hand, reduce the disease activity of RA and retard the progression of arthritic tissue destruction.





# DMARDS

- Methotrexate.
- Azathioprine.
- Mycophenolate mofetil.
- Cyclophosphamide.
- Cyclosporine.
- Chloroquine / hydroxychloroquine.
- Sulfasalazine.
- Minocycline.
- TNF- $\alpha$  inhibitors.



Anti-metabolites

# TNF- $\alpha$ inhibitors

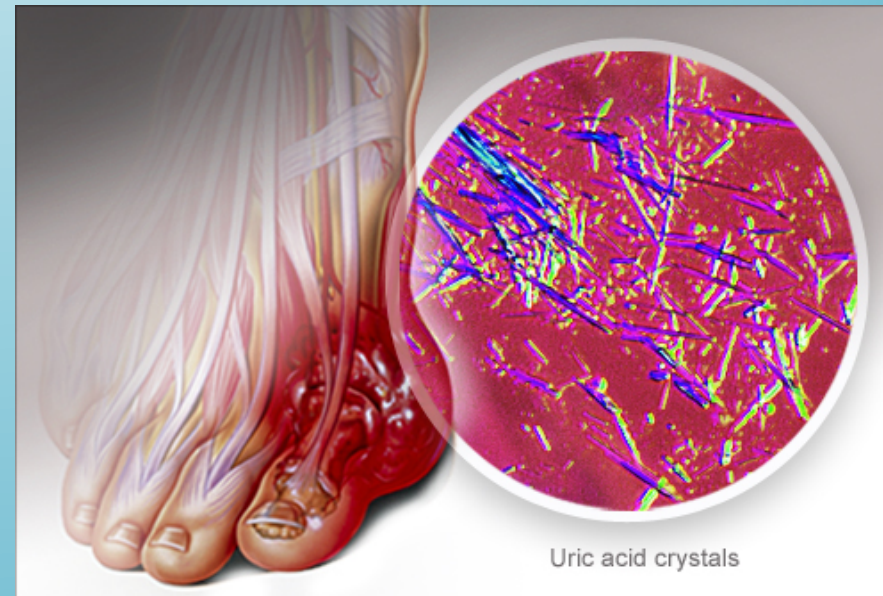
- **Adalimumab.**
- **Infliximab.**
- **Etanercept.**
- **Cetrolizumab.**
- **Golimumab.**

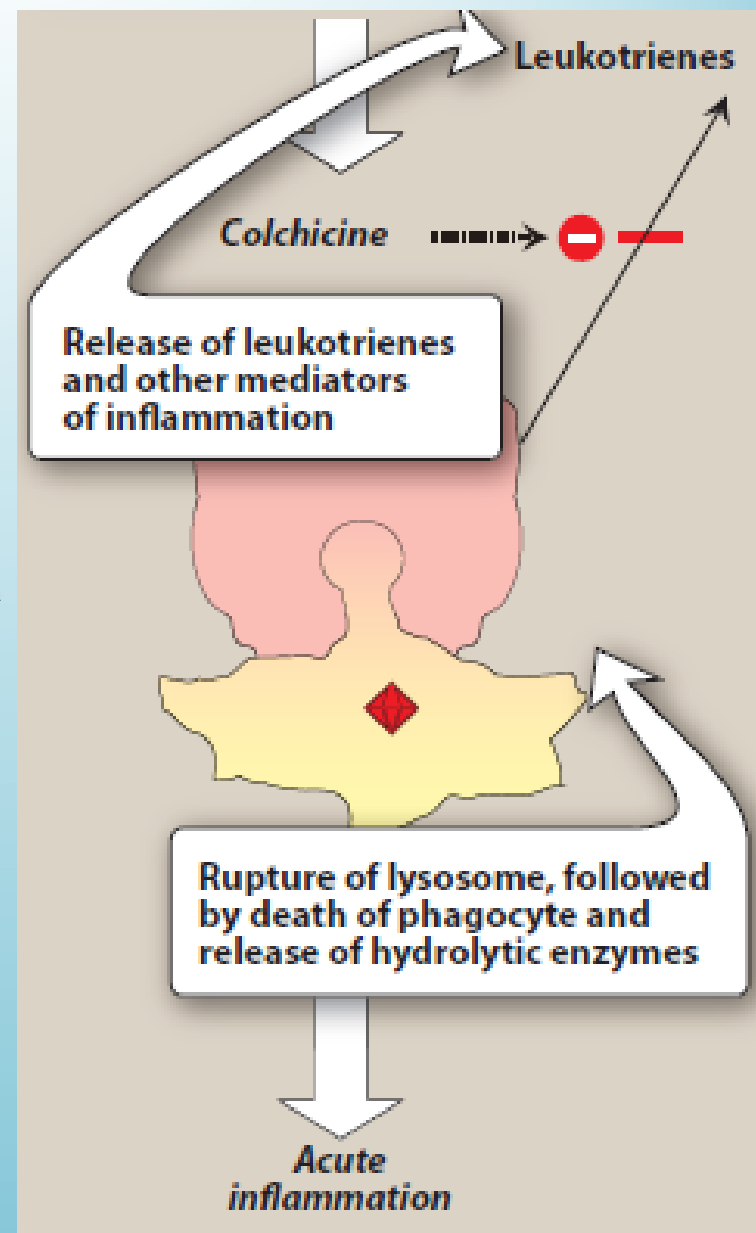
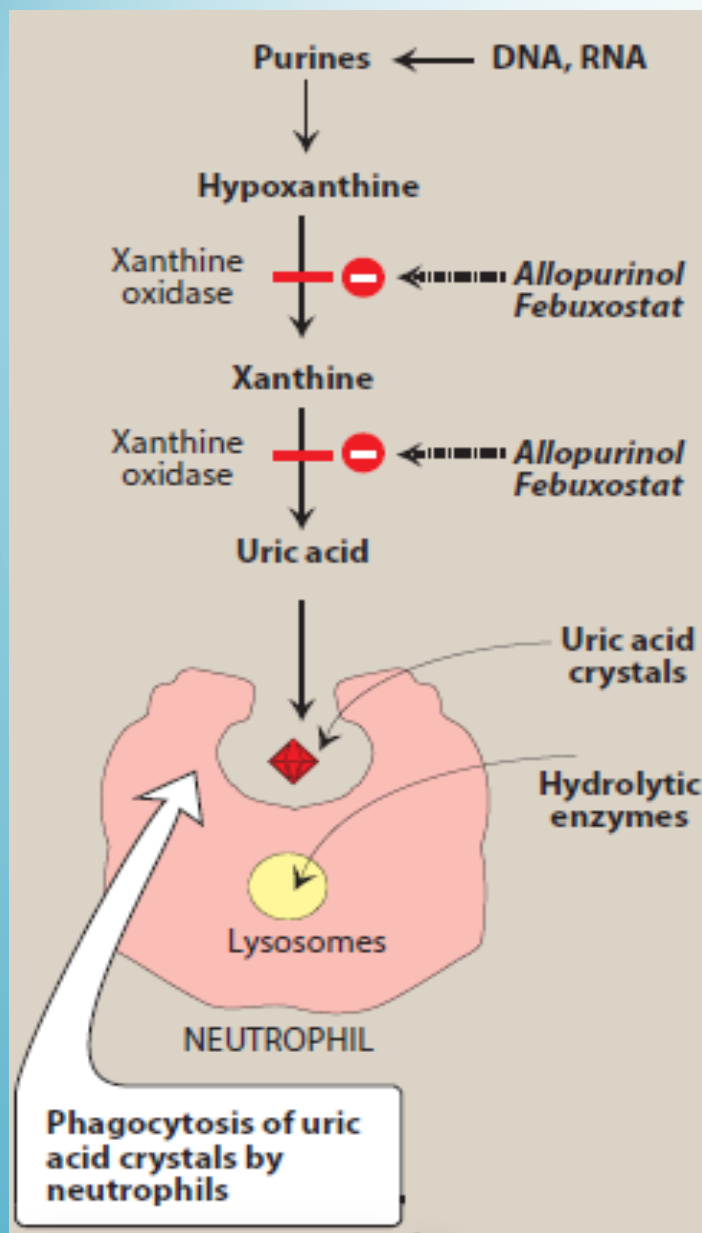
# ***DMARDS***

- **Leflunomide** inhibits ribonucleotide synthesis >>> cellular arrest at G<sub>1</sub> phase >>> ↓ T-cell proliferation.
- **Abatacept** prevents T-cell activation through binding to CD80 & CD86.
- **Tofacitinib** oral inhibitor of Janus kinases modulate immune cell activity in response to the binding of inflammatory mediators
- **Rituximab** cytotoxic to CD20 B-lymphocytes.
- **Tocilizumab** anti IL-6 receptor.
- **Anakinra** IL-1 receptor antagonist.

# ***Drugs used in gout***

- **Gout** is a disease characterized by recurrent episodes of acute arthritis due to deposits of urate crystals in joints.
- Urate crystals are initially phagocytosed by synoviocytes >>> release of PG, IL-1 >>> inflammation.

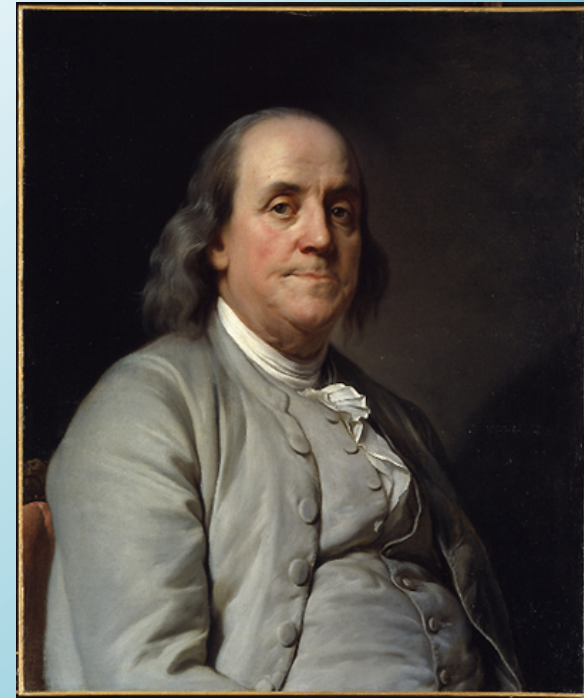






# ***Colchicine***

- Inhibits leukocyte migration, phagocytosis through binding to tubulin & preventing its polymerization into microtubules.
- **AE**: severe GI upset ( NV&D).

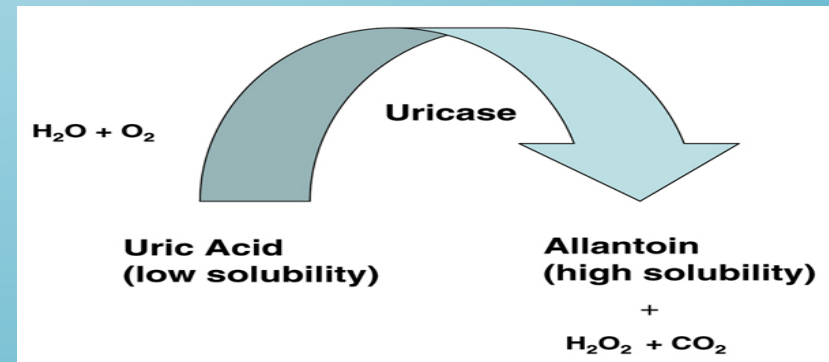


# ***Uricosuric agents***

- Such as ***probenecid*** and ***sulfinpyrazone***.  
They ↓ urate reabsorption in proximal tubules.

# ***Urate lowering agents***

- I. Allopurinol***: purine inhibitor of xanthine oxidase.
- II. Febuxostat***: non-purine inhibitor of xanthine oxidase (more potent than allopurinol).
- III. Pegloticase***: a recombinant mammalian uricase (urate oxidase) that converts uric acid to the more soluble renally eliminated allantoin.



# References

- Lippincott's Illustrated Reviews: Pharmacology ,  
6<sup>th</sup> edition .
- Basic & Clinical Pharmacology , Bertram G. Katzung  
12<sup>th</sup> edition .
- Goodman & Gilman's The Pharmacological Basis of  
Therapeutics, 12<sup>th</sup> ed. .