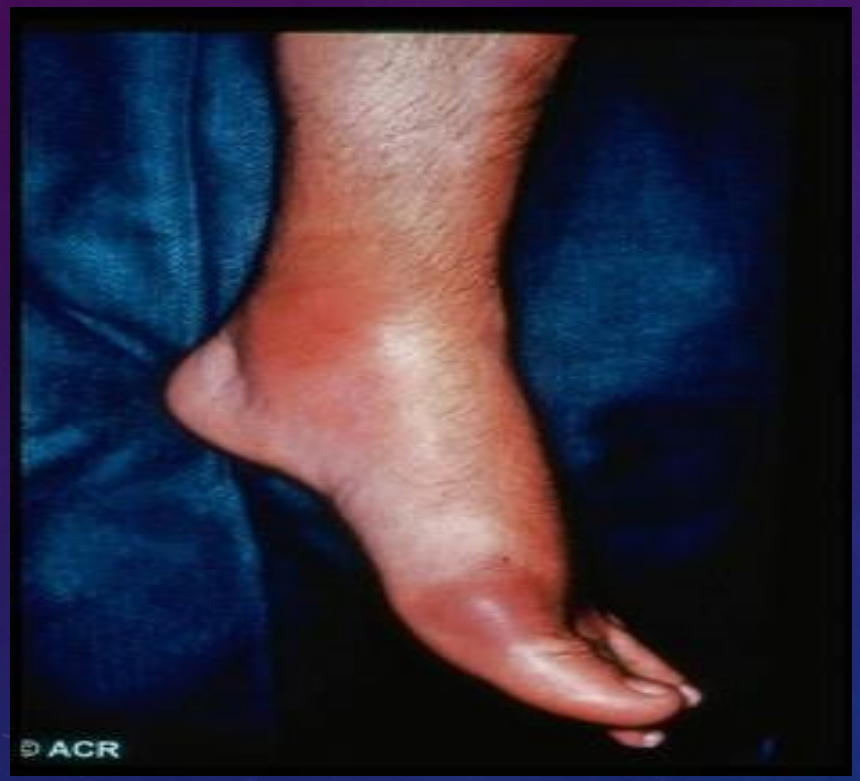
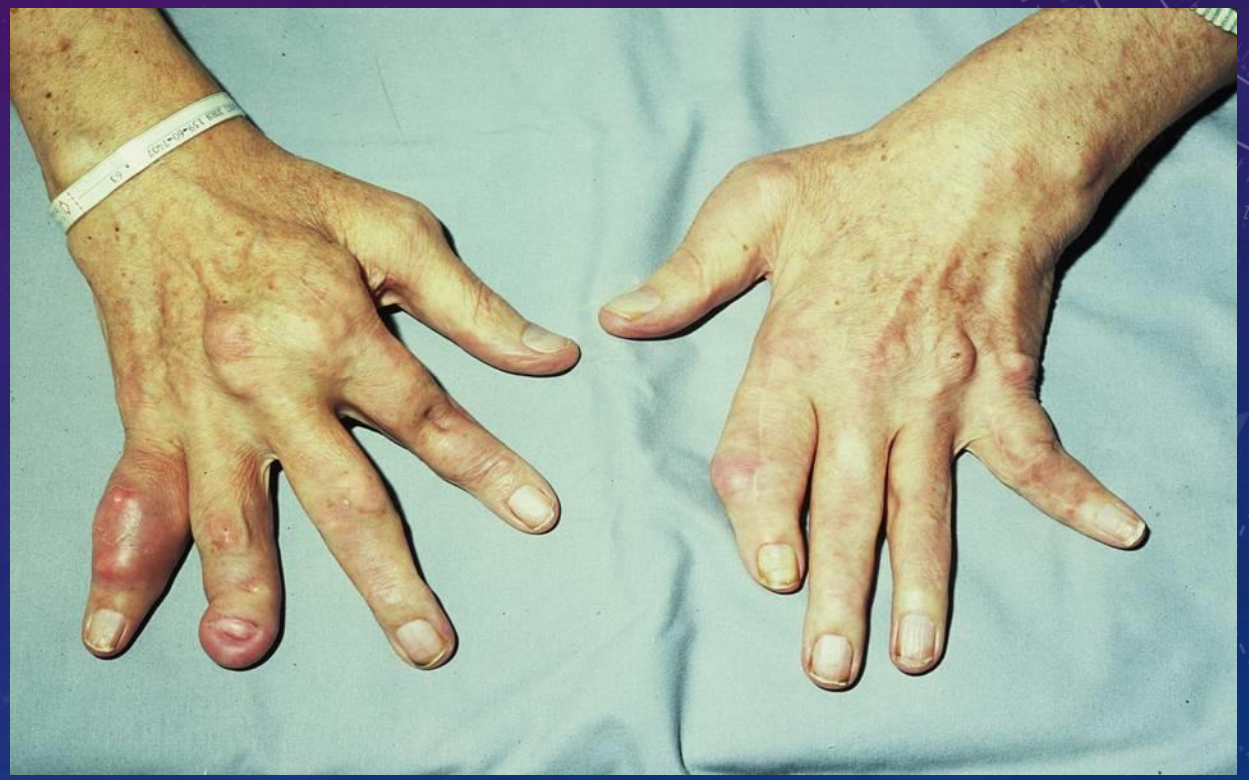
DRUGS IN GOUT



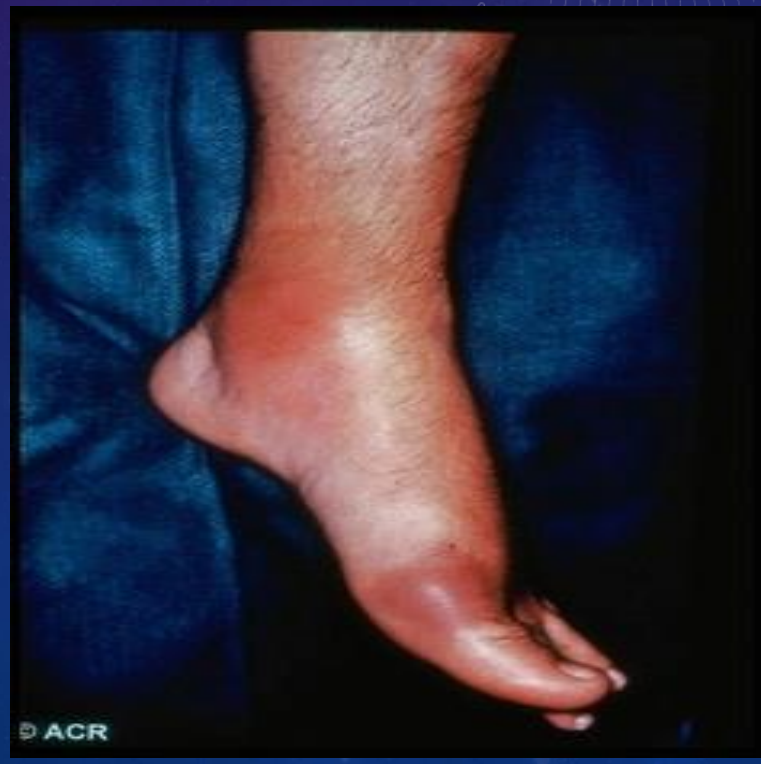


ILOS

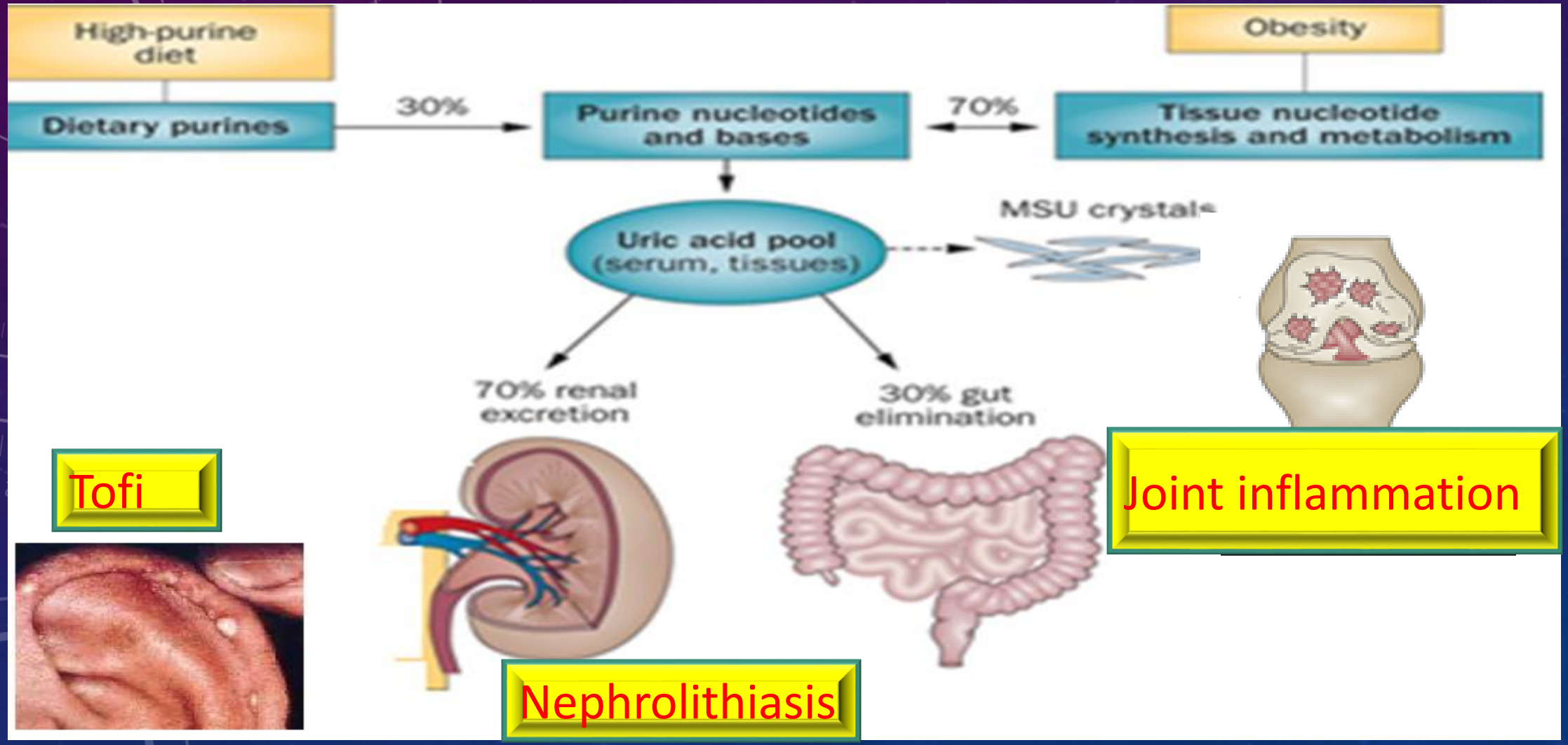
- Know the pathophysiology of gout
- Outline the stages of gout and the therapeutic objectives in each stage
- Describe drug and non-drug treatment of gout
- Classify drugs used for treatment of gout
- Identify the mechanism of action of drugs used for treatment of gout
- Study in detail the pharmacology of drugs used for treatment of gout

WHAT IS GOUT?

- Gout is usually characterized by recurrent attacks of acute inflammatory arthritis with red, tender, hot and swollen joints
- Deposits of sodium urate crystals in articular, peri-articular, and subcutaneous tissues
- May be primary or secondary
  - Primary – hereditary error of purine metabolism
  - Secondary – drugs that inhibit uric acid excretion or increase rate of cell death or another acquired disorder



Untreated gout may Lead to… Tophaceous masses of MSU crystals in cartilage & joints, Renal stones, Urate nephropathy



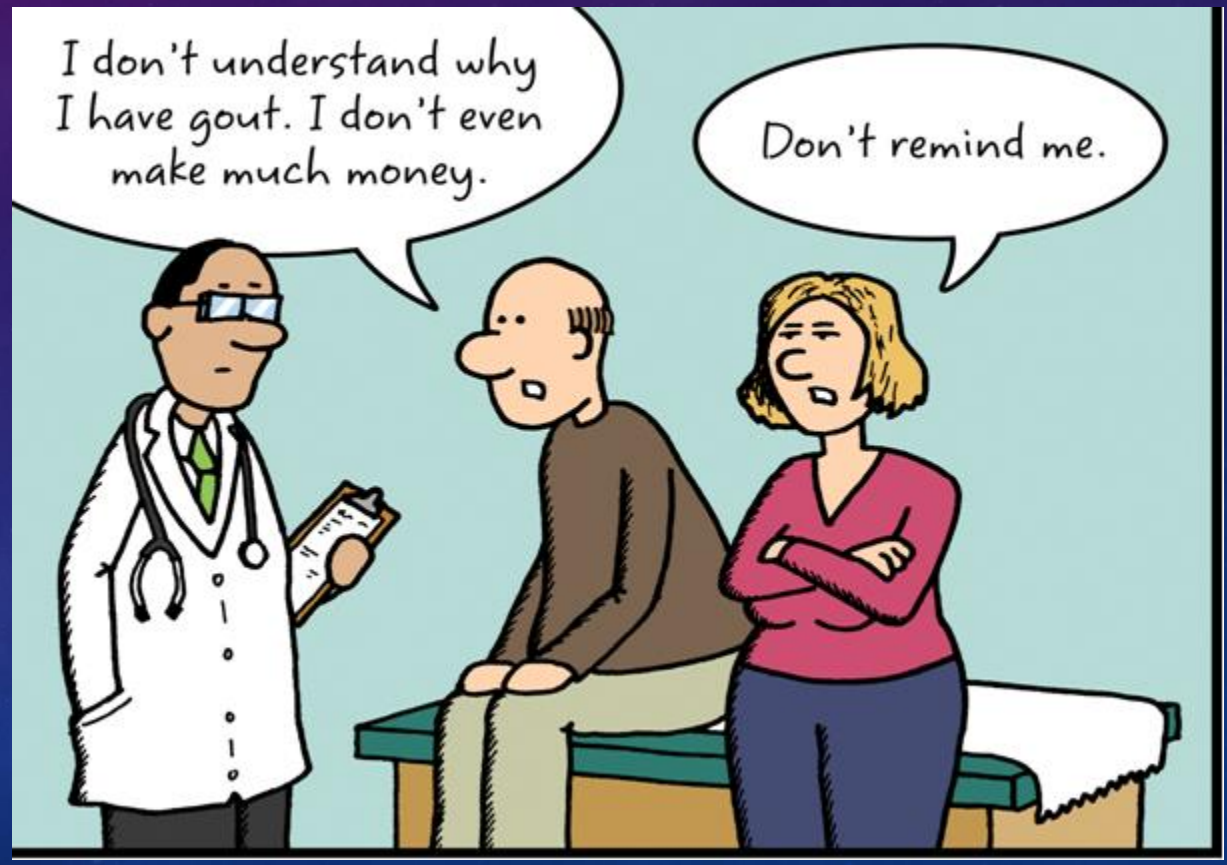
EPIDEMIOLOGY

Gout was historically known as "the disease of kings" or "rich man's disease."

Prevalence of hyperuricemia 5%

Prevalence of gout 0.2%

Male to female ratio 10:1



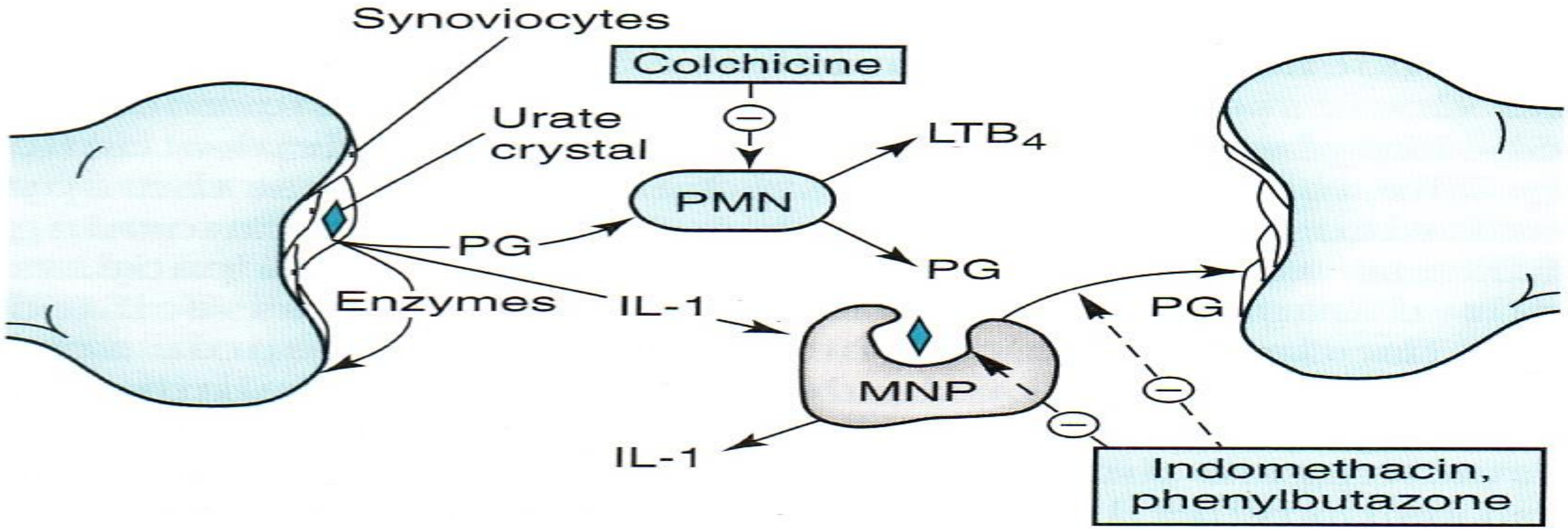
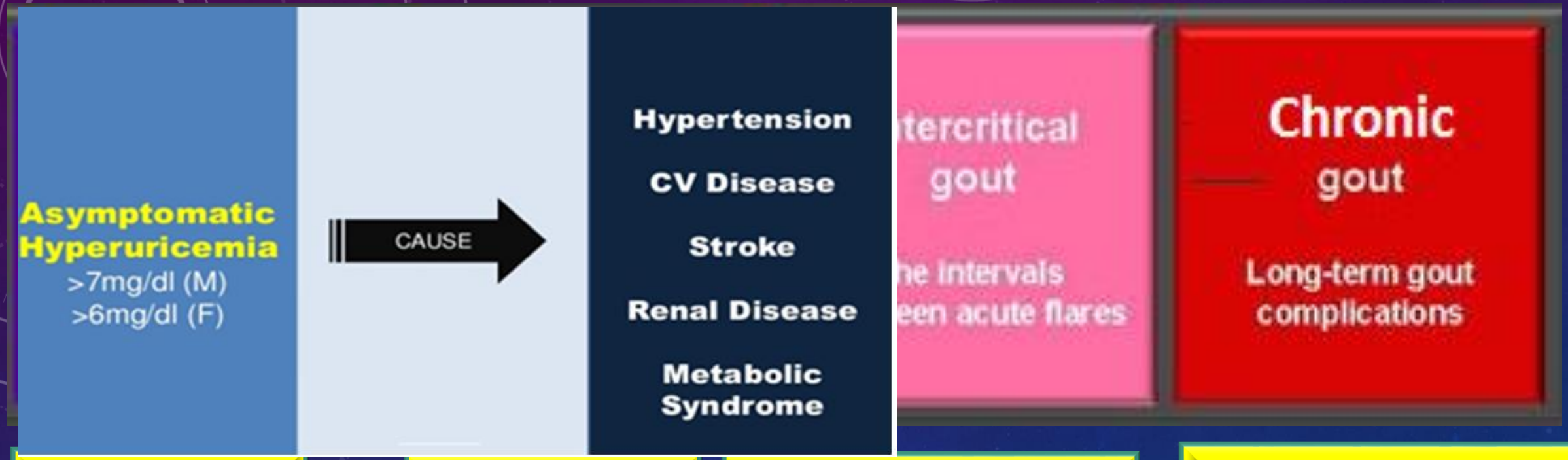


Figure 36–5. Pathophysiologic events in a gouty joint. Synoviocytes phagocytose urate crystals and then secrete inflammatory mediators, which attract and activate polymorphonuclear leukocytes (PMN) and mononuclear phagocytes (MNP) (macrophages). Drugs active in gout inhibit crystal phagocytosis and polymorphonuclear leukocyte and macrophage release of inflammatory mediators. (PG, prostaglandin; IL-1, interleukin-1; LTB4, leukotriene B4.)

STAGES OF GOUT

- Four distinct stages: a)asymptomatic hyper-uricemia; b) acute intermittent gout; c) Intercritical stage ; d) chronic gout



Treat or not to treat?

Terminate The attack

Prevent recurrent attacks

-Prevent complications
-Lower serum uric acid

DRUGS IN GOUT

Treatment of gout

Non-pharmacologic

Pharmacologic

NON-PHARMACOLOGIC THERAPY

LIFESTYLE MODIFICATIONS

- Loss of weight
- Exercise
- Diet control
- Smoking cessation

Aim of pharmacotherapy

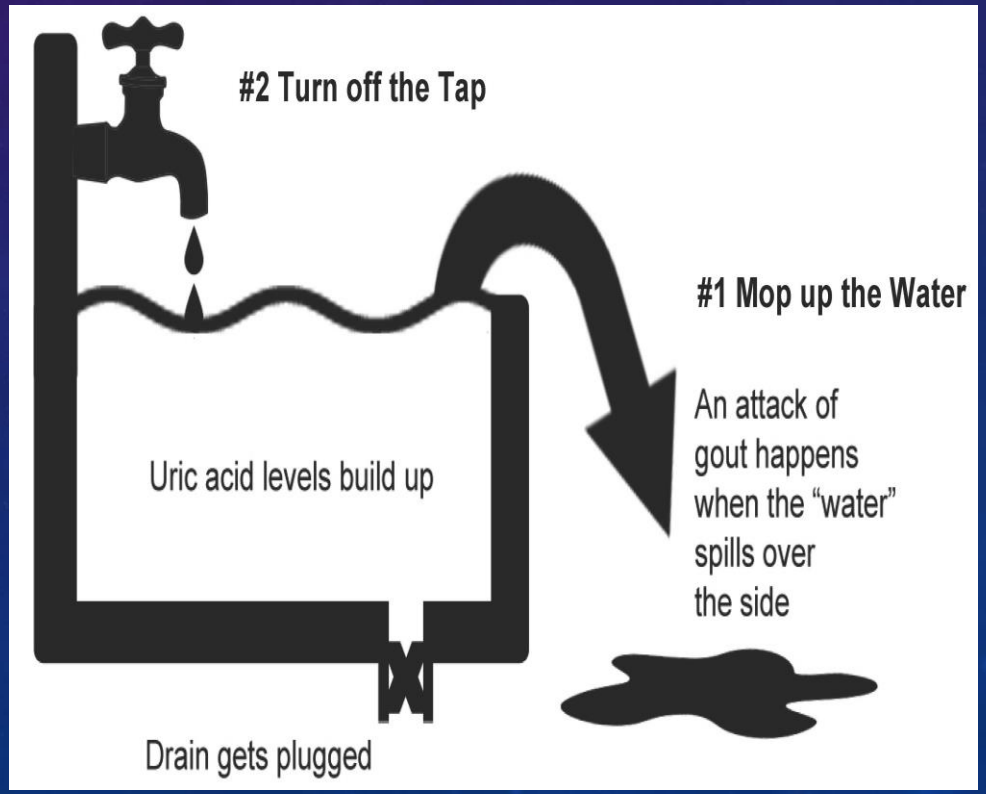
Most therapeutic strategies for gout involve lowering the uric acid level below the saturation point (<6 mg/dL), thus preventing the deposition of urate crystals.

This can be accomplished by:

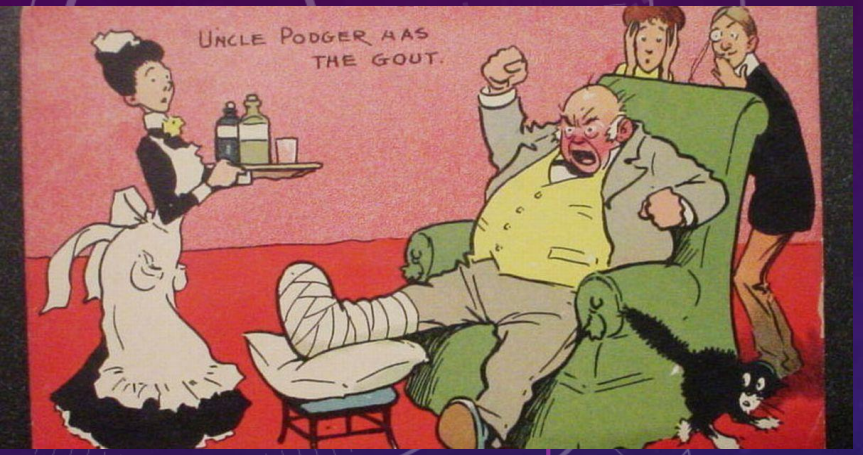
1. interfering with uric acid synthesis with allopurinol, Febuxostat
2. increasing uric acid excretion with probenecid or sulfinpyrazone
3. inhibiting leukocyte entry into the affected joint with colchicine
4. administration of NSAIDs

DRUGS IN GOUT

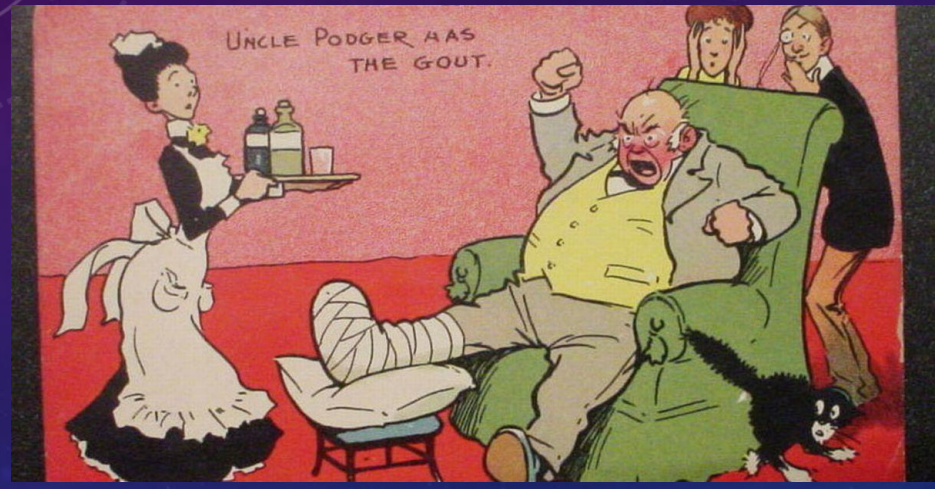
Uricostatic	Allopurinol , Febuxostat
Uricosuric	Probenecid , Sulfinpyrazone
Anti- inflammatory	NSAIDs, Steroids
Tubulin inhibitors	Colchicine



TREATMENT OF ACUTE GOUT



Acute gouty arthritis



- **Colchicine**
- **NSAIDs**
- **Corticosteroids**

NSAIDS

NSAIDs are the most commonly used first-line treatment

Head-to-head studies show few differences between drugs

Full doses of NSAIDs should be initiated immediately and tapered after resolution of symptoms

Avoid NSAIDs:

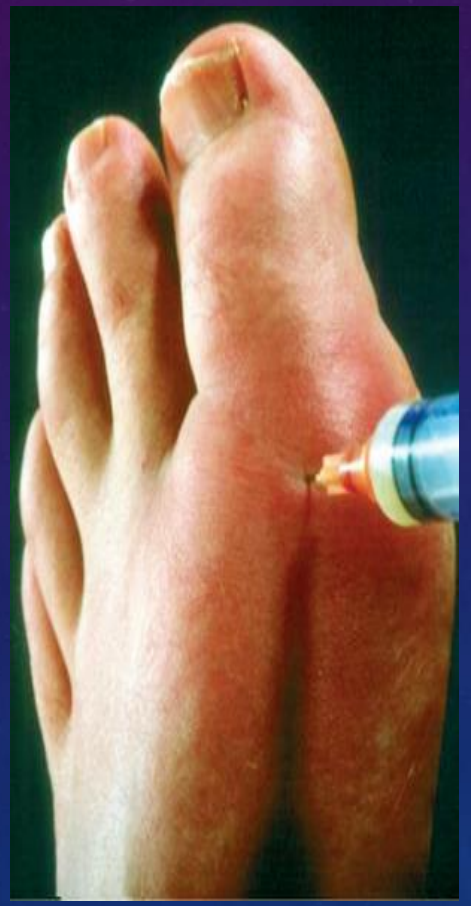
- GI ulcer
- Bleeding or perforation
- Renal insufficiency
- Heart failure
- Use of oral anticoagulants

STEROIDS

Corticosteroids are a good alternative where NSAIDs and colchicine cannot be used or in refractory cases

Studies showed equal efficacy between corticosteroid and NSAIDs, with no reported side-effects with short-term use of corticosteroids

In elderly people, patients with liver or hepatic impairment, Peptic ulcer disease IHD : ischemic heart disease , hypersensitivity to NSAIDs



-Intra articularly (preferred route if one or two joints affected)
-Orally
-Intramuscularly or intravenously.

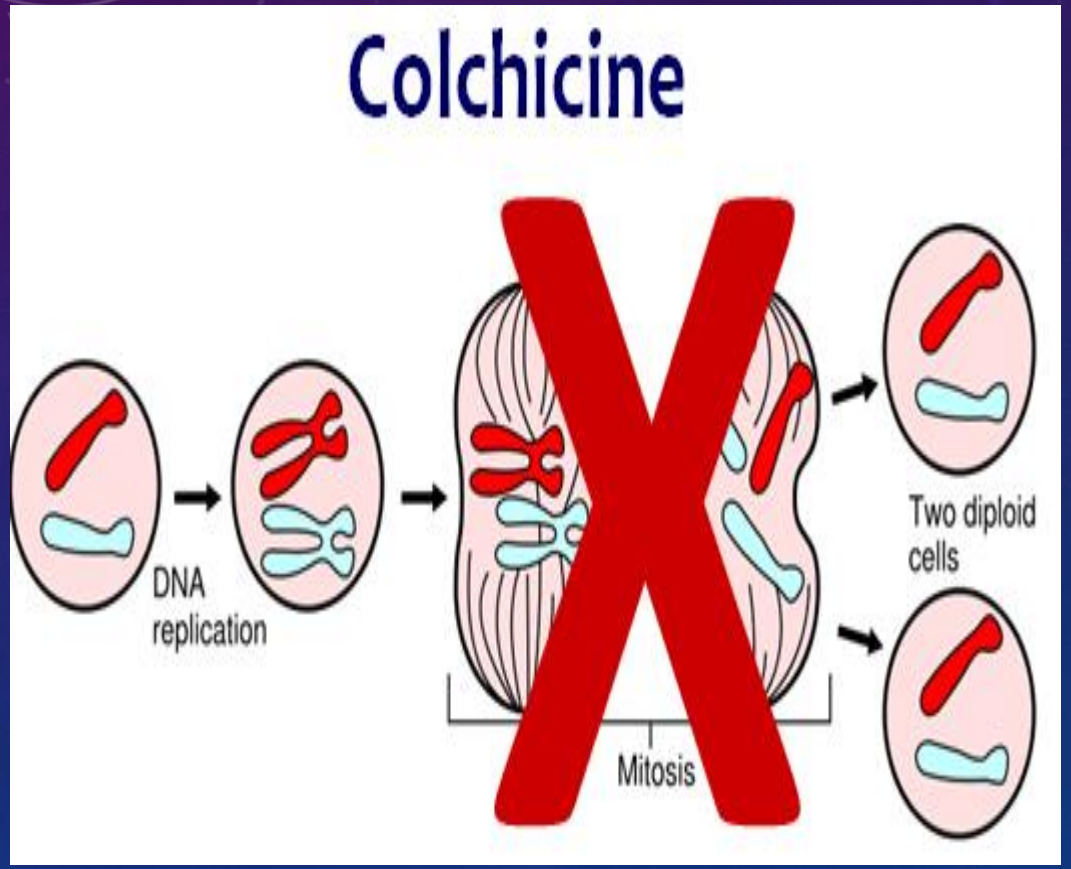
Colchicine

Alkaloid obtained from autumn crocus

Minimal effect on uric acid synthesis , excretion & is not analgesic

MECHANISM

- Binds to microtubules in neutrophils
- Inhibits cell division
- Inhibits chemotactic factors
- Inhibits inflamosomes & IL-1 production



Colchicine

PHARMACOKINETICS

Administered orally, rapidly absorbed from the GI tract

Reaches peak plasma levels within 2 hours

Recycled in the bile and is excreted unchanged in the faeces or urine

Use should be avoided in patients with a creatinine clearance of less than 50 ml/min.

Colchicine

CLINICAL USES

- Treatment of gout flares
- Prophylaxis of gout flares
- Treatment of Mediterranean fever

ADRS

-Diarrhea (sometimes severe)

-Nausea
-Vomiting

-Abdominal cramps
-Dehydration

Bone marrow depression

-Cardiac toxicity, arrhythmia
-Vascular collapse
- Hepatotoxicity , alopecia

Prevention of recurrent attack

Inhibition of uric acid synthesis

-Allopurinol

-Febuxostat

Uricosuric drugs

-Probenacid

-Sulfinpyrazone

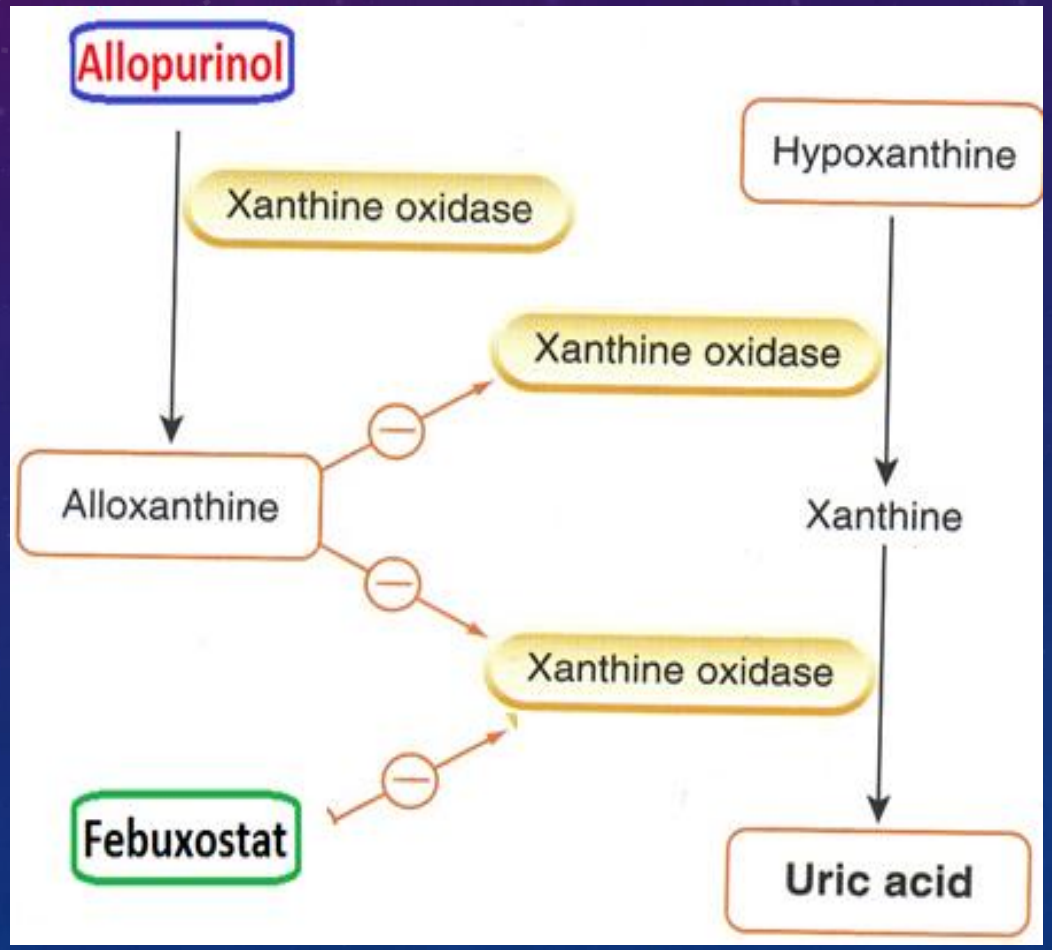
Mammalian Uricase

INHIBITORS OF URIC ACID SYNTHESIS

Inhibit xanthine oxidase

Include allopurinol & febuxostat

Allopurinol is metabolized by xanthine oxidase into alloxanthine which is pharmacologically active



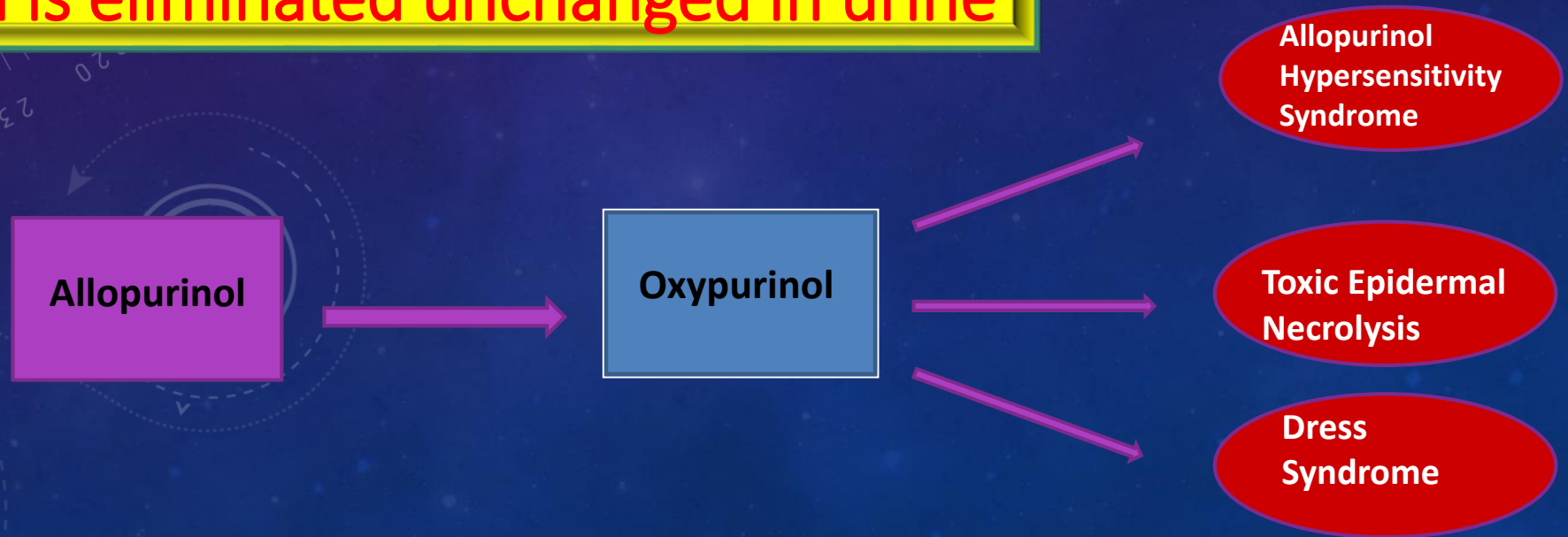
PHARMACOKINETICS

Absorption 70%

Protein binding negligible 5%

Hepatic metabolism, 70% converted to active metabolite (oxypurinol)

Oxypurinol is eliminated unchanged in urine

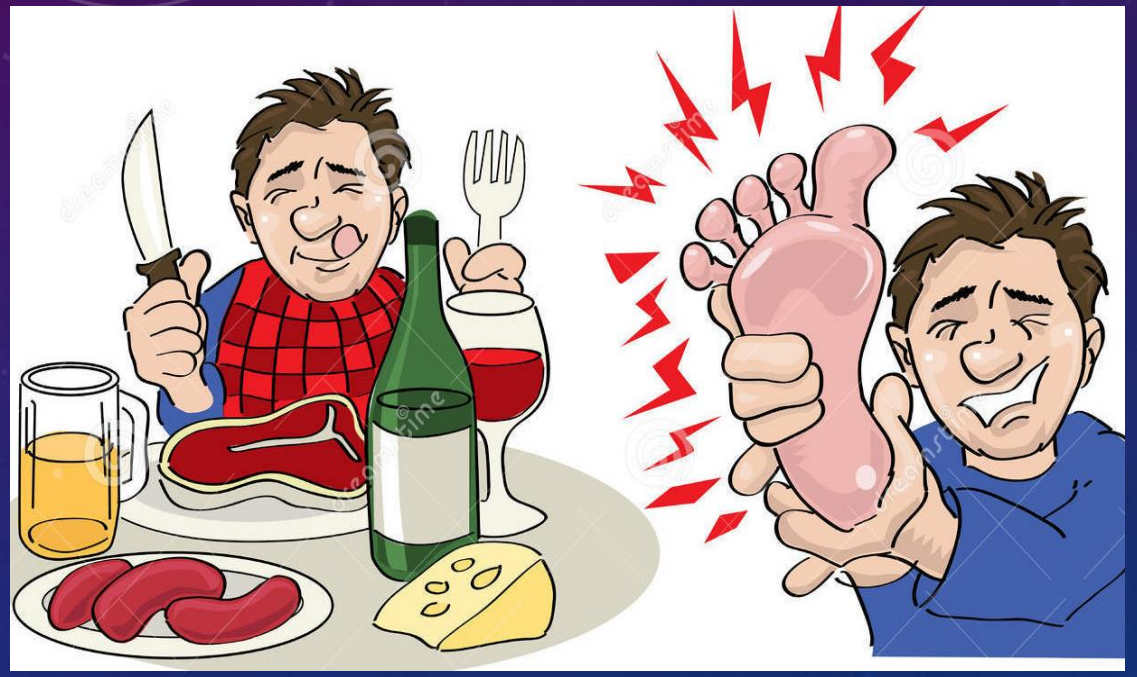


ADRS

Diarrhea, nausea, abnormal liver tests

Acute attacks of gout

Fever, rash, **toxic epidermal necrolysis** hepatotoxicity, marrow suppression vasculitis



DRESS syndrome:20% mortality rate

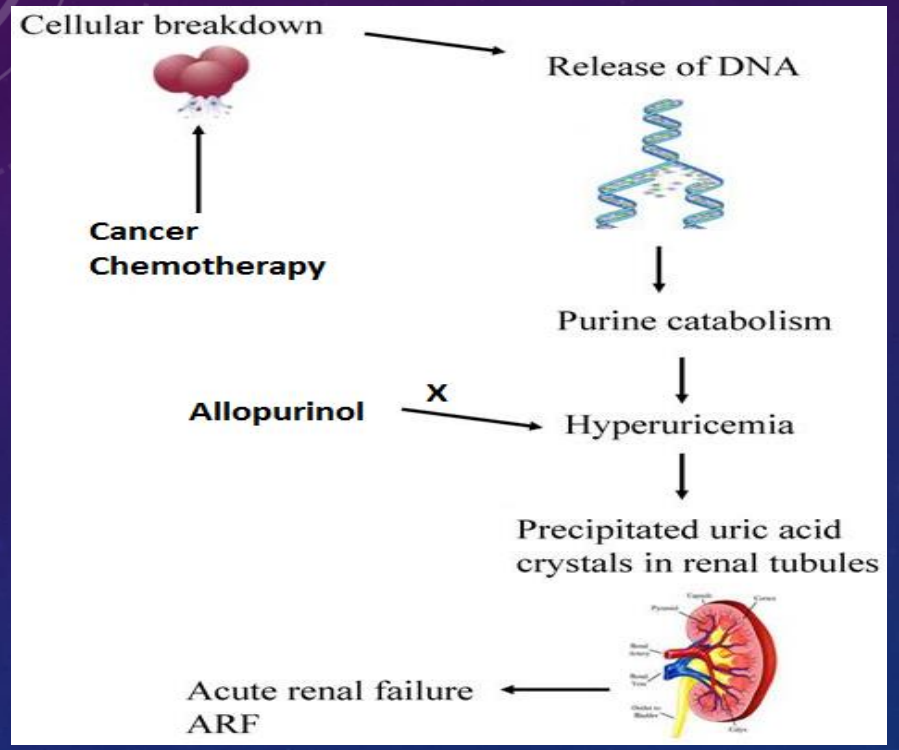
Drug Reaction, Eosinophilia,

Systemic Symptoms: skin rash, fever, lymphadenopathy, and inflammation of the liver, lung, and heart.

Allopurinol

CLINICAL USES

- Management of hyperuricemia of gout
- Uric acid stones or nephropathy
- It is a drug of choice in patients with both gout & ischemic heart disease
- Severe tophaceous deposits (uric acid deposits in tissues)
- Management of hyperuricemia associated with chemotherapy
- Prevention of recurrent calcium oxalate kidney stones

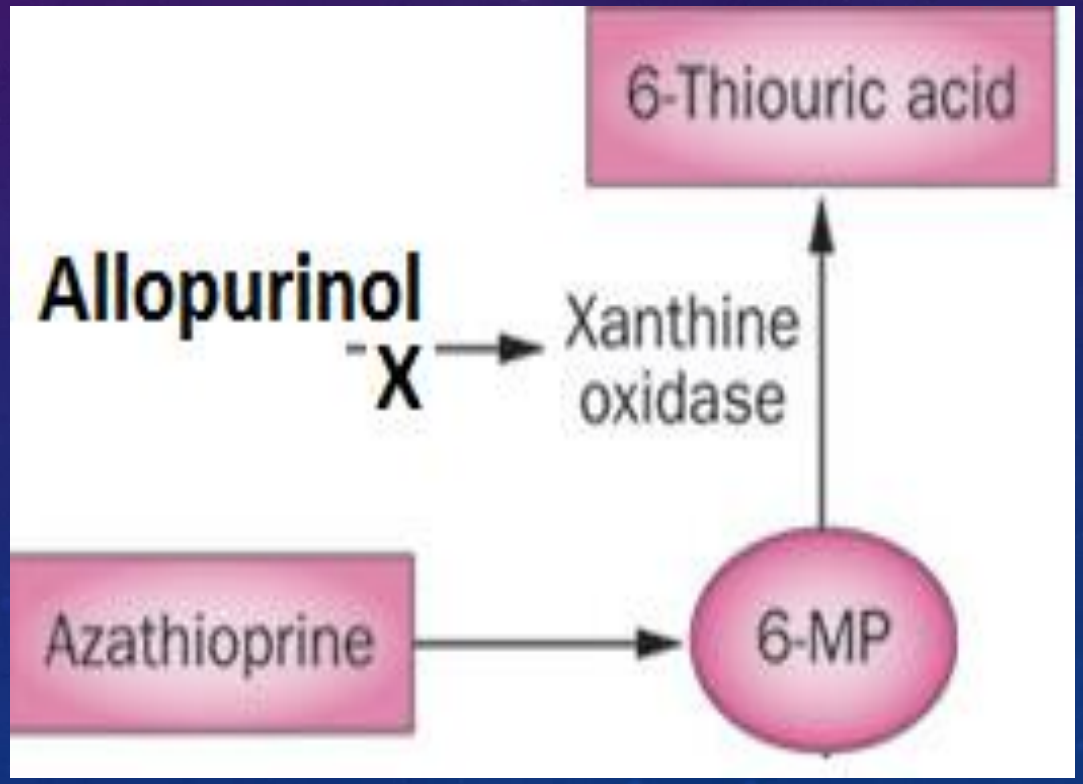


Drug Interactions

Warfarin & dicumarol
- inhibits their metabolism

Reduce the metabolism of **6-mercaptopurine** and **azathioprine**

With ampicillin : Increases frequency of **skin rash**



Febuxostat

- Oral specific xanthine oxidase inhibitor
- Indicated for the management of hyperuricemia in patients with gout (as it reduces serum uric acid levels)
- Chemically distinct from allopurinol (non purine)
- Can be used in patients with renal disease

Febuxostat

PHARMACOKINETICS

- Given orally once daily, well absorbed (85%)
- Metabolized in liver , mainly conjugated to glucouronic acid
- Given to patients who do not tolerate allopurinol
- 99% protein bound
- t½ 8 hours

Febuxostat

ADRS

- Increases number of gout attacks during the first few months of treatment
- Increases level of liver enzymes
- Nausea, Diarrhea
- Headache
- Numbness of arm or leg

URICOSURIC DRUGS

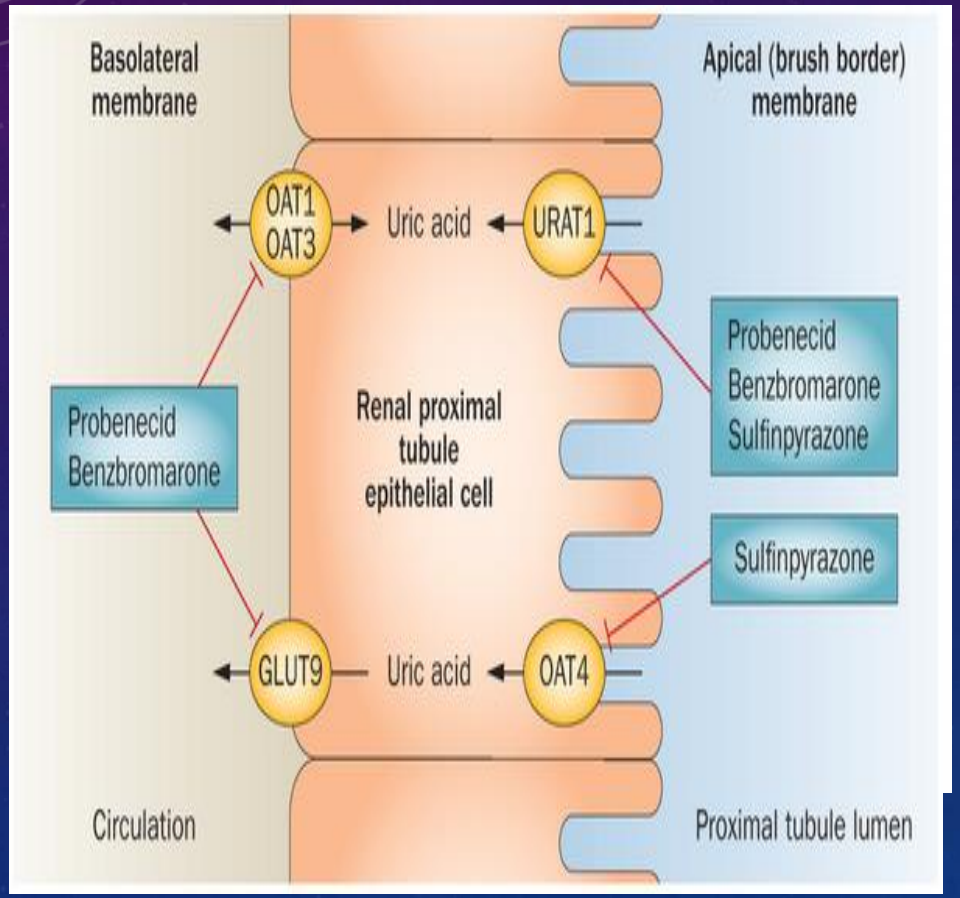
Mechanism

Blocks tubular reabsorption of uric acid & enhances urine uric acid excretion

Probenecid inhibits Urate Transporters (URAT) in the apical membrane of the proximal tubule

It also inhibits organic acid transporter(OAT)→↑plasma concentration of penicilin

Sulfinpyrazol inhibits URAT1 & OAT4



URICOSURIC DRUGS

- Control hyper-uricemia and prevent ophus tformation
- Probenecid is moderately effective
- Increases risk of nephrolithiasis
- Not used in patients with renal disease
- Some drugs reduce efficacy (e.g., aspirin)

ADRS

Probenecid

- Exacerbation of acute attack
- Risk of uric acid stone
- GIT upset
- Allergic rash

CONTRA-INDICATIONS

- History of nephrolithiasis
- Recent acute gout
- Existing renal disease
- Less effective in elderly patients

DRUGS IN GOUT

Sulfinpyrazone

Sulfinpyrazone can aggravate peptic ulcer disease

Aspirin reduces efficacy of sulfinpyrazone

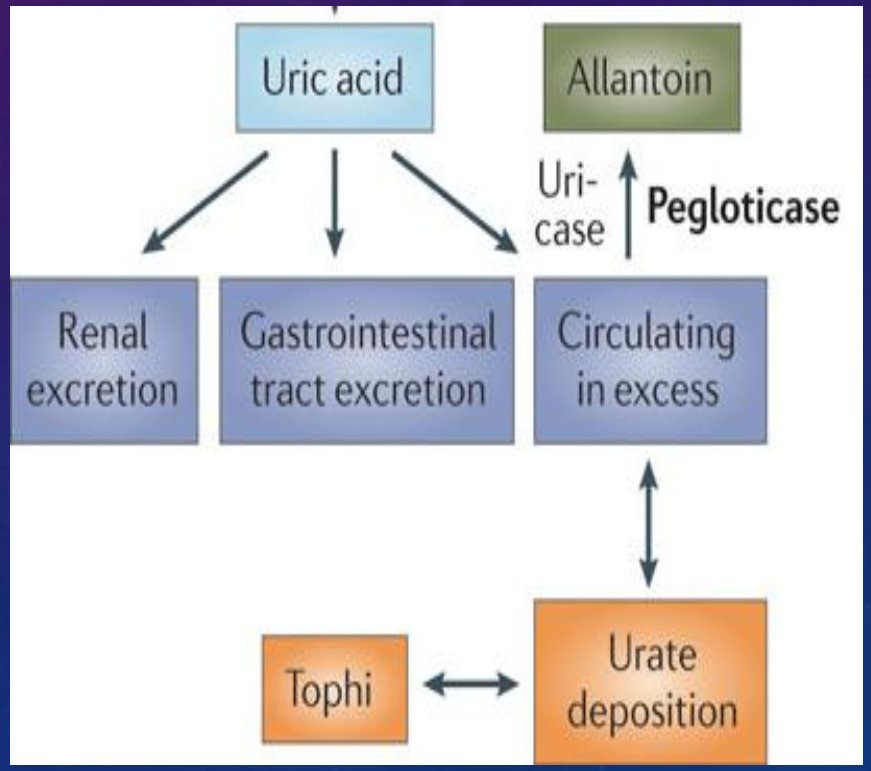
Sulfinpyrazone enhance the action of certain anti-diabetic drugs

Recombinant mammalian uricase

Pegloticase

A uric acid specific enzyme which is a recombinant modified mammalian uricase enzyme

enzymatically convert urate to allantoin, which is more soluble and readily excreted in the urine



Given I.V.➔ peak decline in uric acid level within 24-72 hours

Pegloticase

Used for the treatment of chronic gout in adult patients refractory to conventional therapy

ADRS

- Infusion reactions
- Anaphylaxis
- Gout flare
- Arthralgia, muscle spasm
- Nephrolithiasis