Drugs for rheumatoid arthritis and gout

Drug-Induced Musculoskeletal Disorders

1. Drug-induced lupus:

Procainamide HCl

hydralazine HCl

INH

quinidine sulfate

phenytoin

2. Acute gout

Low-dose aspirin

diuretics

Alcohol

cytotoxic drugs

Pyrazinamide

3. Muscle pain cramps

HMG-CoA reductase inhibitors

Diuretics

Clofibrate

Corticosteroids

Estrogen and oral contraceptives

Succinylcholine

4. Bone growth inhibition Corticosteroids, tetracyclines

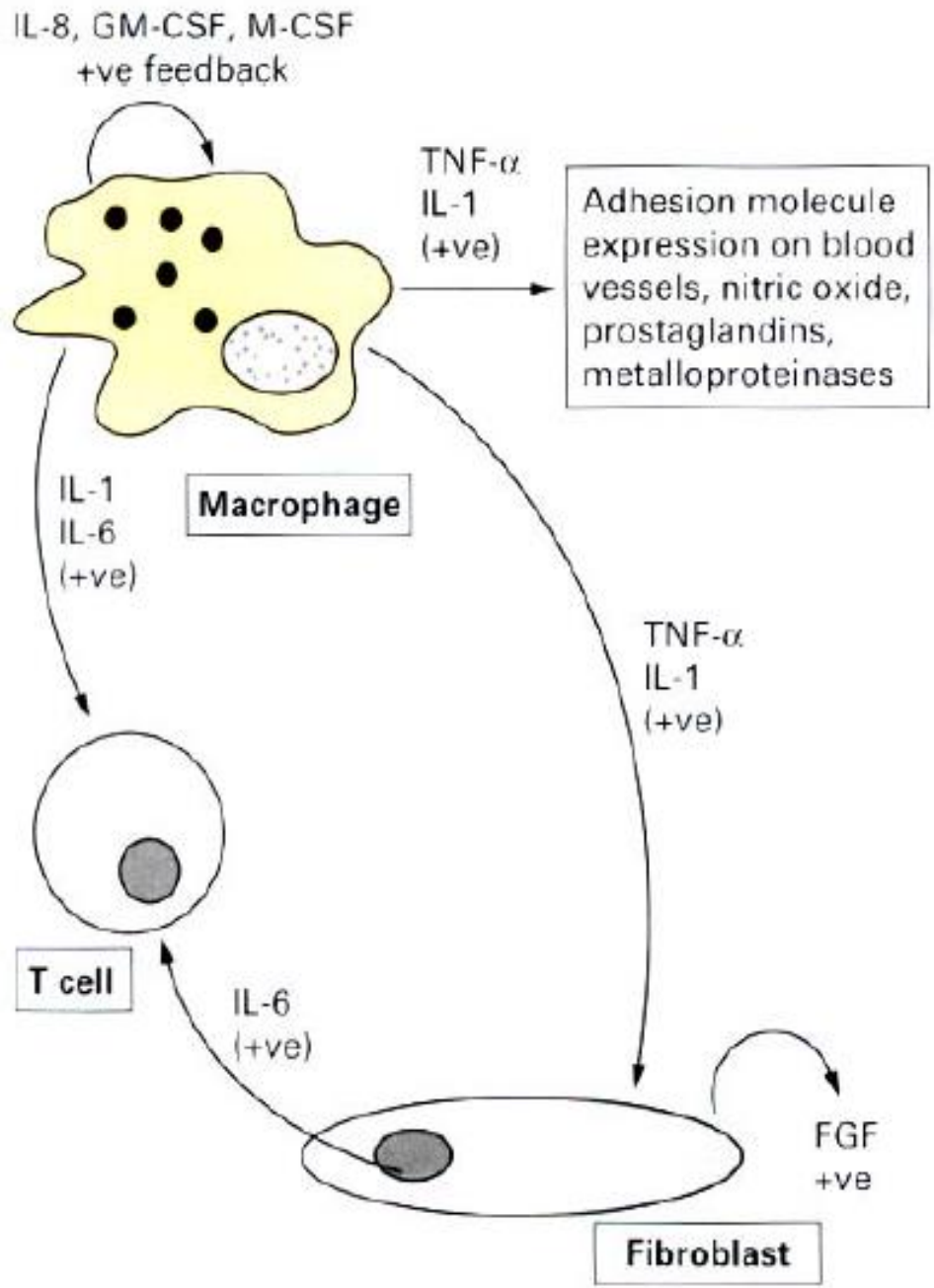
5. Osteoporosis Corticosteroids, heparin, methotrexate sodium,TZD

CHRONIC INFLAMMATORY DISEASE

→ The pathological process is *chronic inflammation* together with the predominant inflammatory cell infiltrates.

→An imbalance of the inflammatory response occurs in many conditions,

because proinflammatory mediators are present in excess.

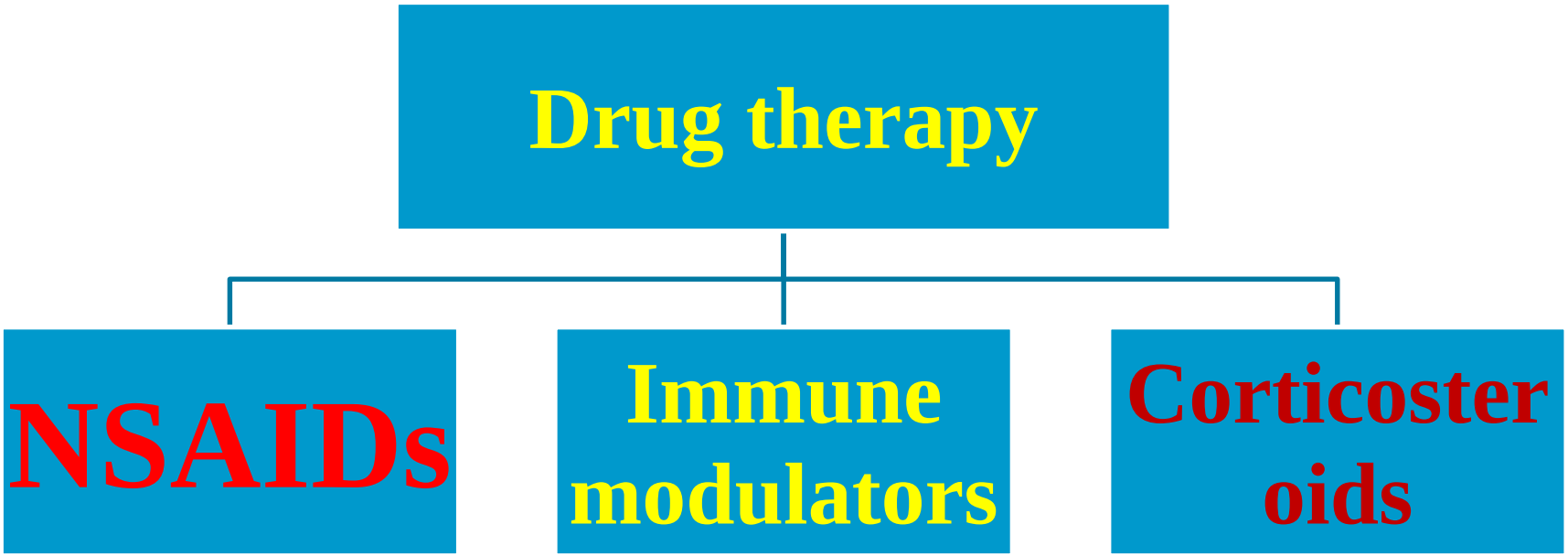

IL-8, GM-CSF, M-CSF
+ve feedback
TNF-α
IL-1
(+ve)
Adhesion molecule expression on blood vessels, nitric oxide, prostaglandins, metalloproteinases
IL-1
IL-6
(+ve)
Macrophage
TNF-α
IL-1
(+ve)
T cell
IL-6
(+ve)
FGF
+ve
Fibroblast

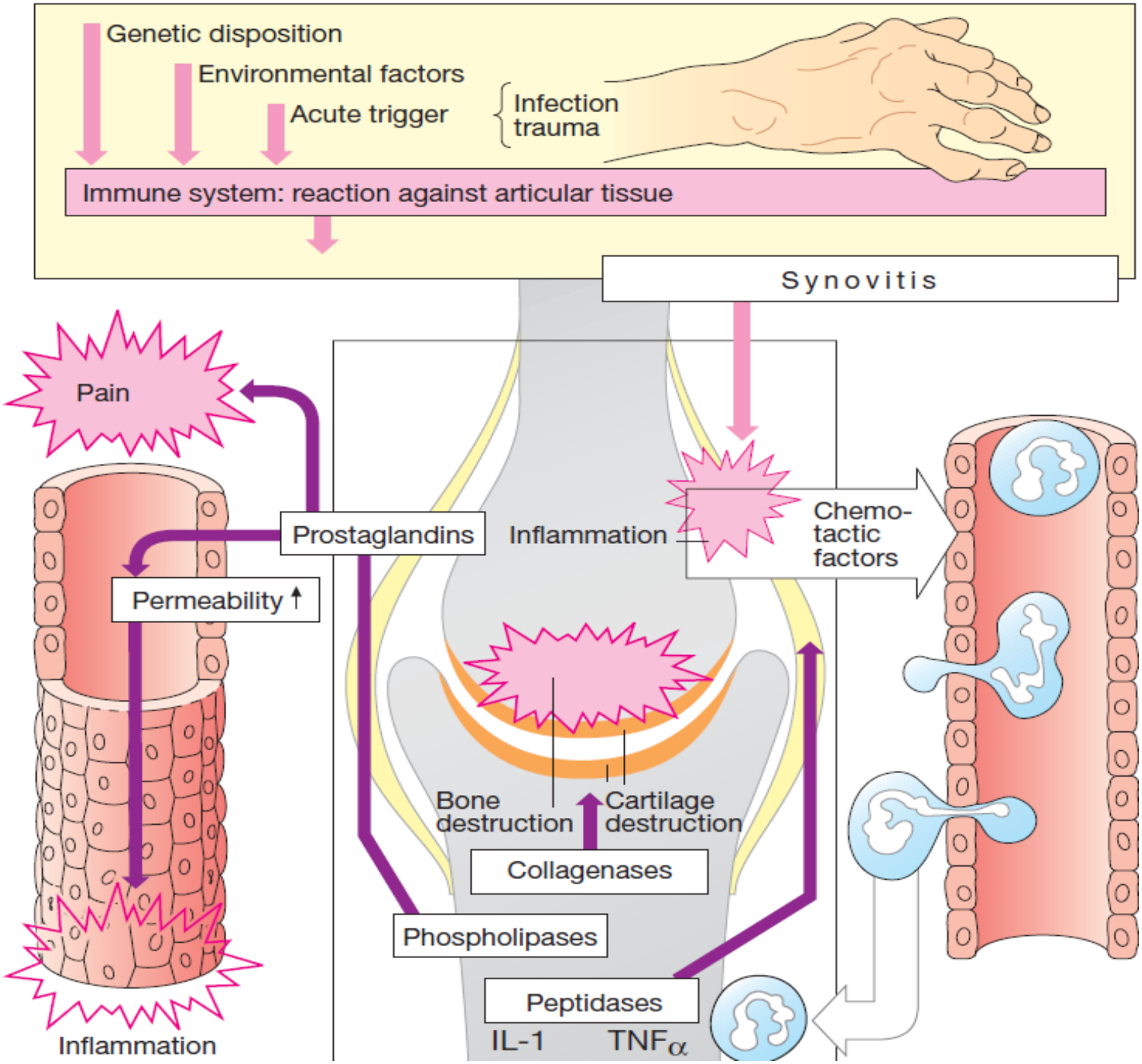
Arthritis

Most common types of arthritis in the UK *Osteoarthritis* (UK prevalence 23%) and rheumatoid arthritis (1%).

less common types of *inflammatory arthritis*

- ✓ **juvenile idiopathic arthritis;**
- ✓ **ankylosing spondylitis,**
- ✓ **psoriatic arthritis,**
- ✓ **arthritis associated with inflammatory bowel disease)**
- ✓ **Reactive arthritis**

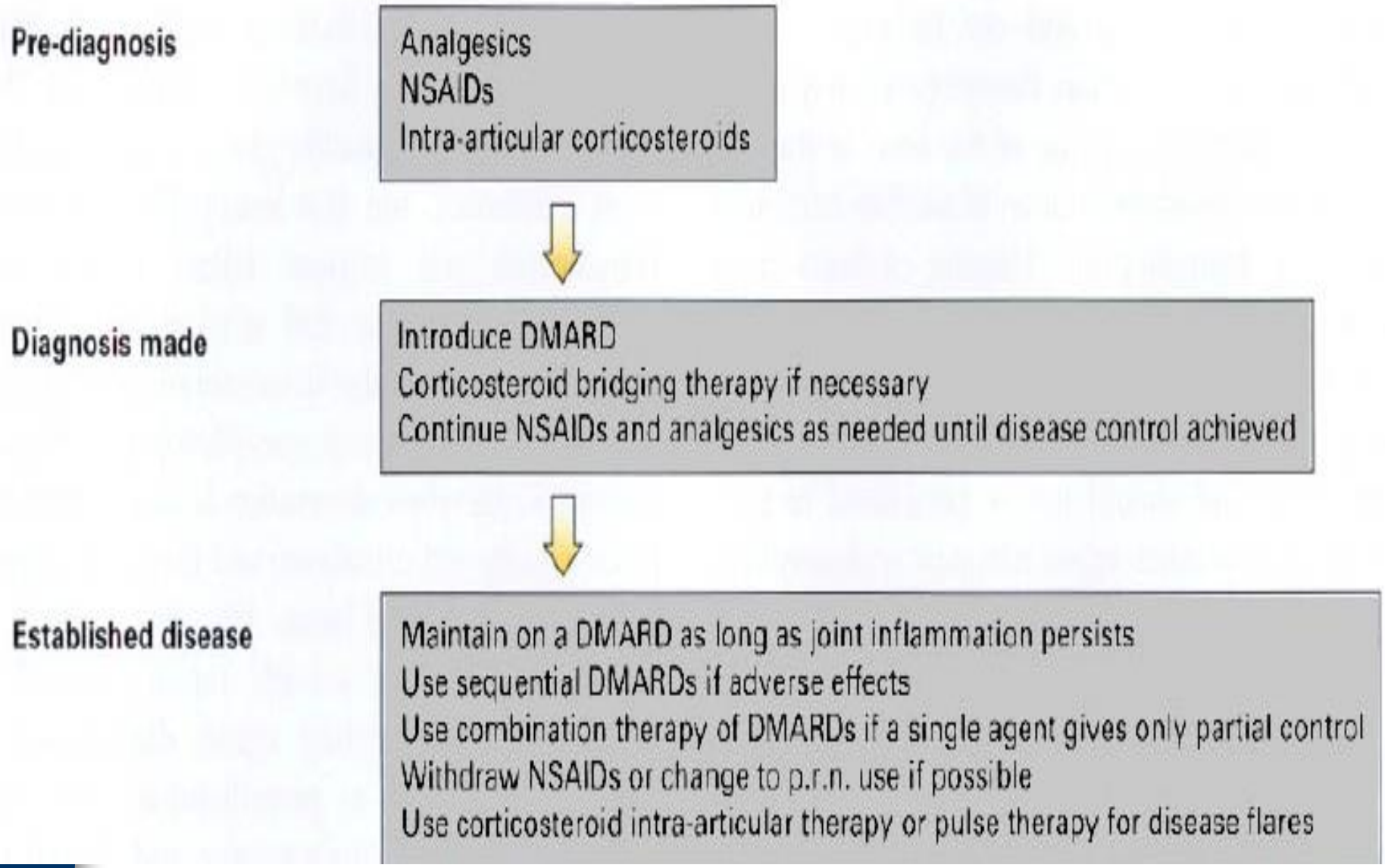

Drug therapy
NSAIDs
Immune modulators
Corticosteroids


Genetic disposition
Environmental factors
Acute trigger
Infection
trauma
Immune system: reaction against articular tissue
Synovitis
Pain
Prostaglandins
Inflammation
Chemo-
tactic
factors
Permeability
Bone
destruction
Cartilage
destruction
Collagenases
Phospholipases
Peptidases
IL-1
TNFα
Inflammation

Principles of treatment

- **patient's priority : relief of joint pain**
  swelling
  stiffness.
- avoid the long-term effects of inadequately treated joint inflammation
- no cure for arthritis

Requires a multidisciplinary approach with physiotherapy & occupational therapy


Pre-diagnosis
Analgesics
NSAIDs
Intra-articular corticosteroids
Diagnosis made
Introduce DMARD
Corticosteroid bridging therapy if necessary
Continue NSAIDs and analgesics as needed until disease control achieved
Established disease
Maintain on a DMARD as long as joint inflammation persists
Use sequential DMARDs if adverse effects
Use combination therapy of DMARDs if a single agent gives only partial control
Withdraw NSAIDs or change to p.r.n. use if possible
Use corticosteroid intra-articular therapy or pulse therapy for disease flares

DMARD'S

Immune Modulators

- ✓ Methotrexate
- ✓ Leflunomide
- ✓ Sulfasalazine
- ✓ Hydroxychloroquine
- ✓ Azathioprine
- ✓ Gold salts

Biological response modifiers

Etanercept

Infliximab

Anakinra

TABLE 38–5 ■ DISEASE-MODIFYING ANTIRHEUMATIC DRUGS

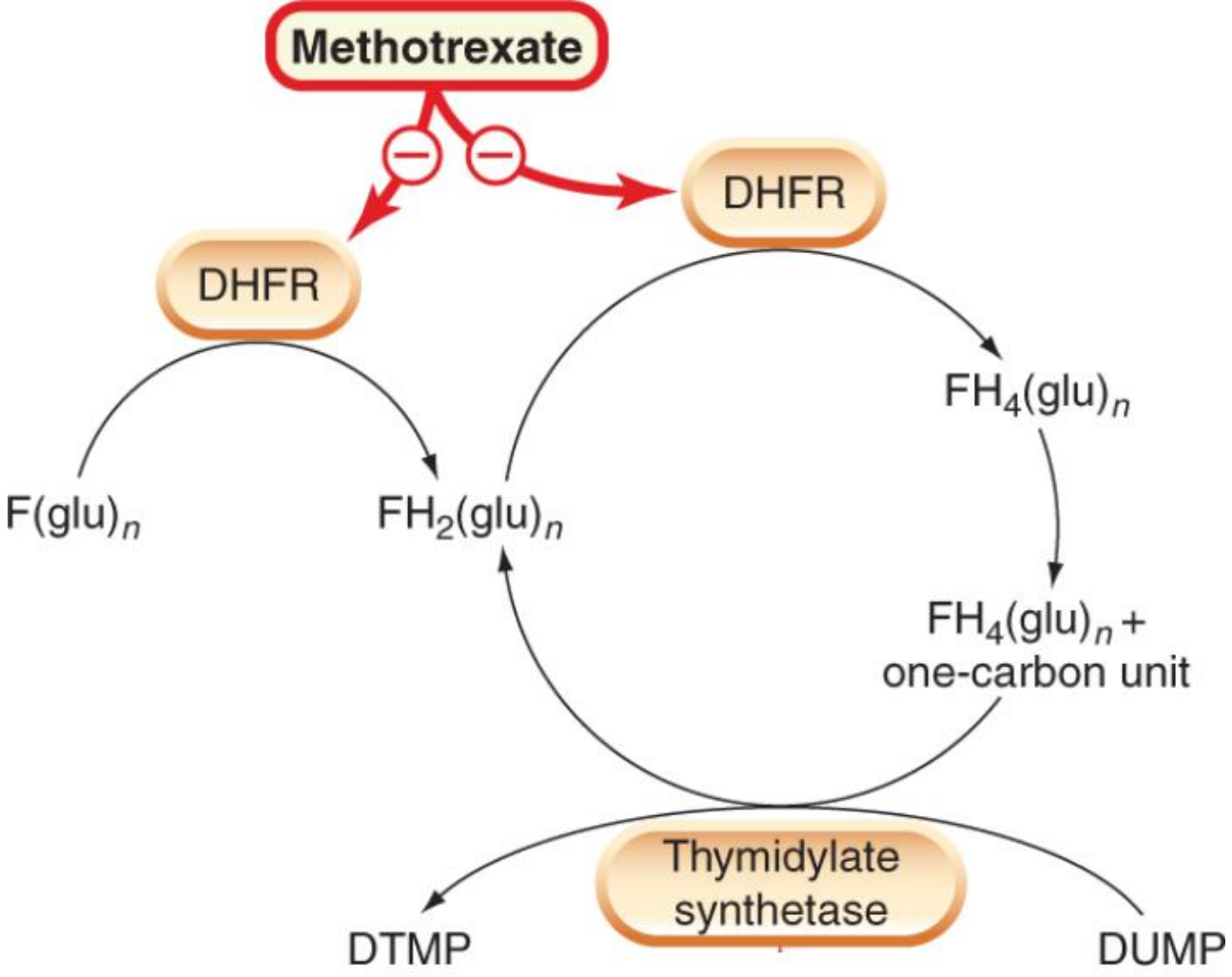
DRUG	CLASS OR ACTION
Small molecules	
Methotrexate	Antifolate
Leflunomide	Pyrimidine synthase inhibitor
Hydroxychloroquine	Antimalarial
Minocycline	5-Lipoxygenase inhibitor, tetracycline antibiotic
Sulfasalazine	Salicylate
Azathioprine	Purine synthase inhibitor
Cyclosporine	Calcineurin inhibitor
Cyclophosphamide	Alkylating agent
Penicillamine	Chelating agent
Auranofin	Gold compound
Biologicals	
Adalimumab	Ab, TNF-α antagonist
Golimumab	Ab, TNF-α antagonist
Etanercept	Ab, TNF-α antagonist
Infliximab	IgG-TNF receptor fusion protein (anti-TNF)
Certolizumab	Fab fragment toward TNF-α
Abatacept	T-cell costimulation inhibitor (binds B7 protein on antigen-presenting cell)
Rituximab	Ab toward CD20 (cytotoxic toward B cells)
Anakinra	IL-1 receptor antagonist
Tocilizumab	IL-6 receptor antagonist
Tofacitinib	Janus kinase inhibitor

Disease-Modifying antirheumatoid agents(DMARD'S)

- induce remission,prevent further destruction of the joints and tissues.
- American College of Rheumatology : initiation of therapy with DMARDs within 3 months of diagnosis (in addition to NSAIDs, low-dose corticosteroids, physical therapy, and occupational therapy).
- Therapy initiated rapidly to help stop the progression of the disease at the earlier stages.

Methotrexate

- ✓ used alone or in combination, mainstay in patients with rheumatoid or psoriatic arthritis.
- ✓ slows appearance of new erosions.
- ✓ Response seen within 3 -6 wks of treatment.
- ✓ immunosuppressant, accounting for its effectiveness in autoimmune disease.
- ✓ Doses required much lower than needed in cancer chemotherapy: given once a week;



Competitive inhibition of the enzyme dihydrofolate reductase

New mechanisms of methotrexate

Methotrexate: How does it really work, Nature reviews Rheumatology,2010

- Inhibits AICAR transformylase, a folate dependent enzyme
- AICAR (5 – aminoimidazole-4-carboxamide ribonucleotide),accumulates.
- AICAR inhibits adenosine deaminase preventing degradation of adenosine
- Adenosine –antiinflammatory effects

Extracellular adenosine

- binds to transmembrane-spanning adenosine surface receptors,A2a and A3,
- resulting in the subsequent inhibition of phagocytosis, lymphocyte proliferation,
- altered synthesis and/or secretion of several proinflammatory cytokines, such as TNF-α, IL-12 and IFN-γ.

Prescription

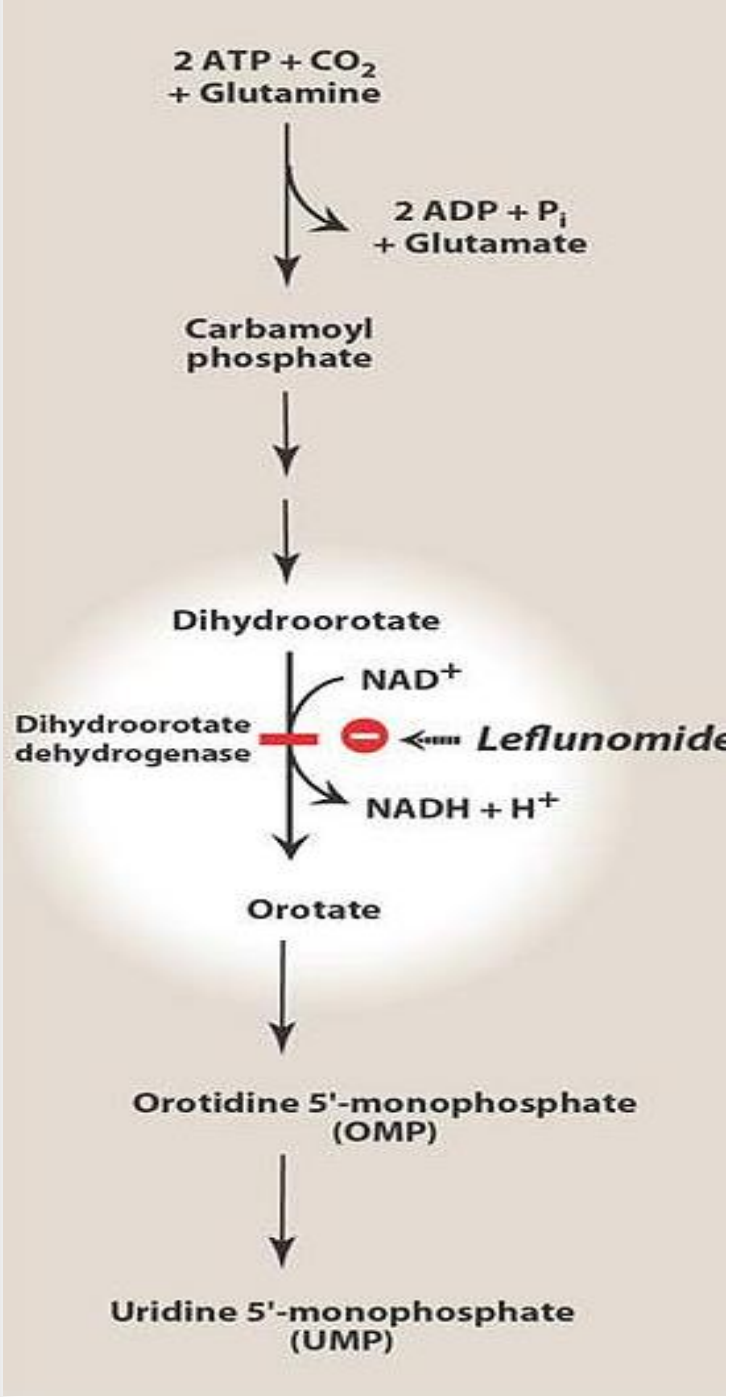
- Given orally starting at a dose of 7.5-10 mg once weekly and increasing as bone marrow and liver function allow up to 25 mg
- Folic acid prescribed thrice weekly in the dose of 5 mg.
- Little effect as compared to folinic acid

Methotrexate- Adverse effects…

1. Mucosal ulceration and nausea.
2. Bone marrow toxicity
3. Cirrhosis of the liver
4. Acute pneumonia-like syndrome chronic administration.
5. leucovorin OD after methotrexate ↓severity of adverse effects
6. Monthly monitoring of LFT/blood counts

Leflunomide

- Immunomodulatory agent -causes cell arrest of autoimmune lymphocytes through its action on dihydroorotate dehydrogenase (DHODH),a mitochondrial enzyme
- After biotransformation, becomes reversible inhibitor of DHODH
- Approved for the RA monotherapy/ combination therapy.

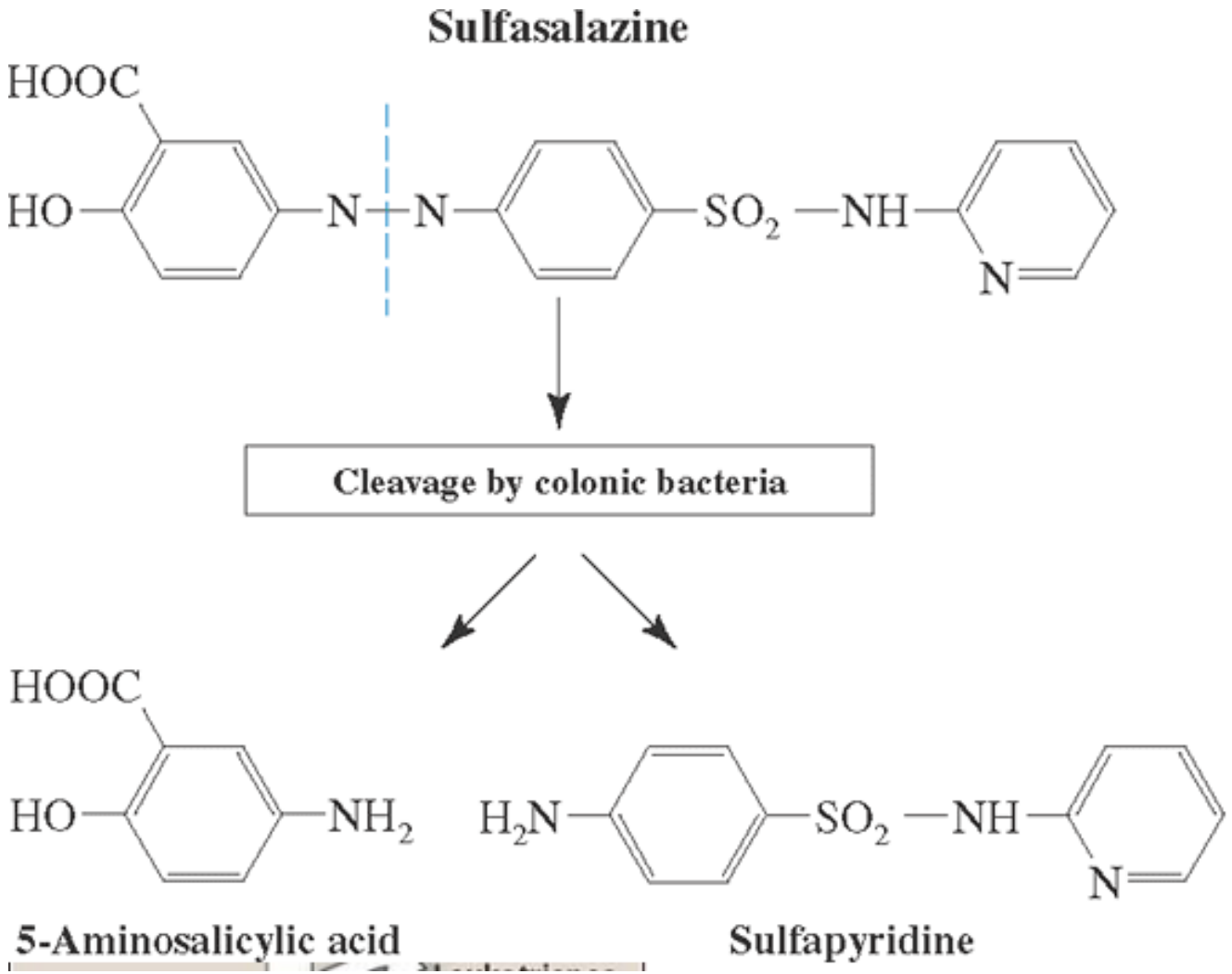


LEFLUNOMIDE

- Inhibits synthesis of pyrimidines
- Depresses antibody production by B –cells
- 100 mg Loading dose -20 mg OD
- Combination with Mtx hepatotoxic
- teratogenic

Sulfasalazine

- sulfapyridine and 5-aminosalicylic acid linked - azo-bond,split by colonic bacteria
- Sulfapyridine, as a sulphonamide, has an antifolate action which is believed to benefit RA
- Rheumatoid arthritis, spondyloarthropathy, psoriatic arthritis.



1-3 gm/day in 2-3 divided doses

Azathioprine

- Acts by inhibiting purine biosynthesis
- Preferentially acts on proliferating lymphocytes
- In the presence of glutathione ,undergoes reduction to 6-mercaptopurine and then to 6-thioguanine
- False purine nucleotide formed ,gets incorporated into DNA ,inhibits replication and proliferation
- Metabolized by TPMT
- Pharmacogenetic application

Hydroxychloroquine, chloroquine

- ✓ in addition to antimalarial action exert anti-inflammatory and immuno modulating effects
- ✓ accumulates within lymphocytes, macrophages, polymorphs and fibroblasts, and inhibits phagocyte function
- ✓ t1/2 :18 days
- ✓ arthralgias associated with connective tissue disorders (e.g. SLE)
- ✓ rheumatoid arthritis :best combined with another DMARD. 6.5 mg/kg/d,

Gold salts

- Modify variety of cellular and humoral immune responses;formation of aurocyanide in areas of inflammation.
- Sodium aurothiomalate deep i.m. injection /**auranofin** orally but oral gold less effective
- Disposition of gold complex; binds extensively to plasma albumin and is also distributed to inflamed synovium, kidney and liver.
- *tl/2 -22 days,* steady-state after 3 months.
- Retention in deep tissue compartments persist up to 23 yrs after therapy stopped.

Adverse effects

- occur in one-third of patients and in some gold may have to be discontinued.
- pruritus, dermatitis,glossitis and stomatitis,
- leucopenia, thrombocytopenia & marrow failure
- nephrotic syndrome due to membranous nephritis)
- peripheral neuritis

BIOLOGICAL AGENTS

- agents derived from natural substances, and chemically altered, are finding their place in therapy

- TNF-α inhibitors

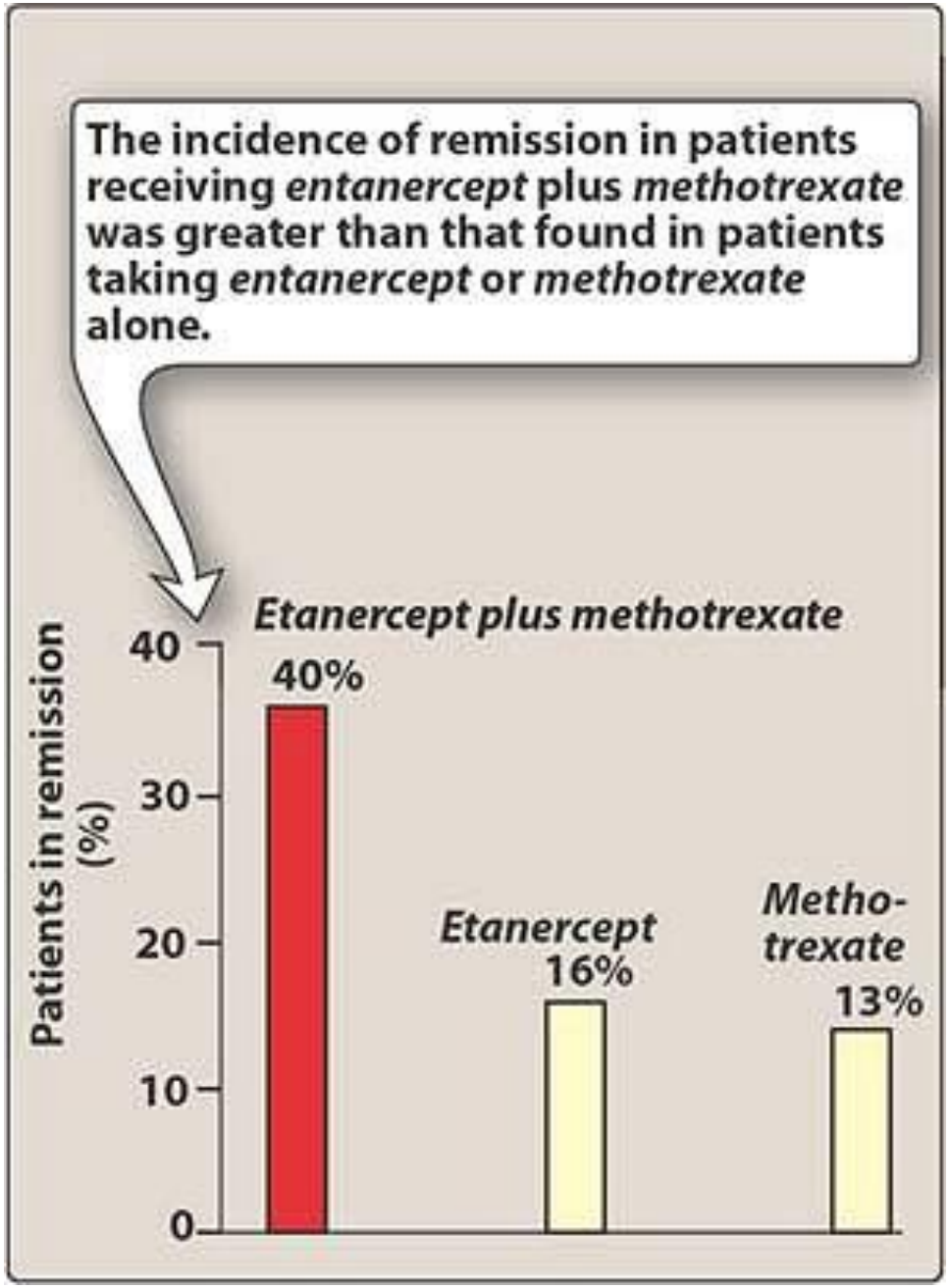
Etanercept

Adalimumab

Infliximab

Etanercept

- genetically engineered fusion protein that binds to TNF-α, thereby blocking its interaction with cell surface TNF receptors.
- approved for use in patients with moderate to severe RA, either alone or in combination with methotrexate.
- given subcutaneously twice a week.
- half-life is 115 hours


The incidence of remission in patients receiving *entanercept* plus *methotrexate* was greater than that found in patients taking *entanercept* or *methotrexate* alone.
Patients in remission (%)
40
30
20
10
0
Etanercept plus methotrexate
40%
Etanercept
16%
Metho-
trexate
13%

Infliximab

- chimeric IgG monoclonal antibody composed of human and murine regions.
- The antibody binds specifically to human TNF-α, thereby neutralizing that cytokine
- Infused IV over at least 2 hours.

half-life of 9.5 days

Adalimumab

- recombinant monoclonal antibody that binds to human TNFα receptor sites, thereby interfering with endogenous TNF-α activity.

- administered subcutaneously weekly

Anakinra

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

Anakinra is an **IL-1 receptor antagonist** because it binds to the IL-1 receptor, thus preventing actions of IL-1.

tofacitinib

- Oral inhibitor of Janus – kinases indicated for treatment of moderate to severe RA in patients who have had an inadequate response or intolerence to methotrexate

role of adrenal corticosteroids

- To provide interim relief of inflammatory symptoms during the weeks that it takes DMARDs to act.
- Spaced single enormous doses (pulse treatment), used to suppress highly active inflammatory disease
- In extreme severity, high-dose prednisolone (20-40 mg/d)
- **Where DMARDs have failed or have produced intolerable adverse effects.**

Intra-articular injection of corticosteroid (triamcinolone, hydrocortisone, prednisolone or dexamethasone)

=Benefit from one injection last many weeks.

=Aseptic precautions extreme, for any introduced infection spreads dramatically.

= Too frequent resort to injection may actually promote joint damage by removing the protective limitation conferred by pain;

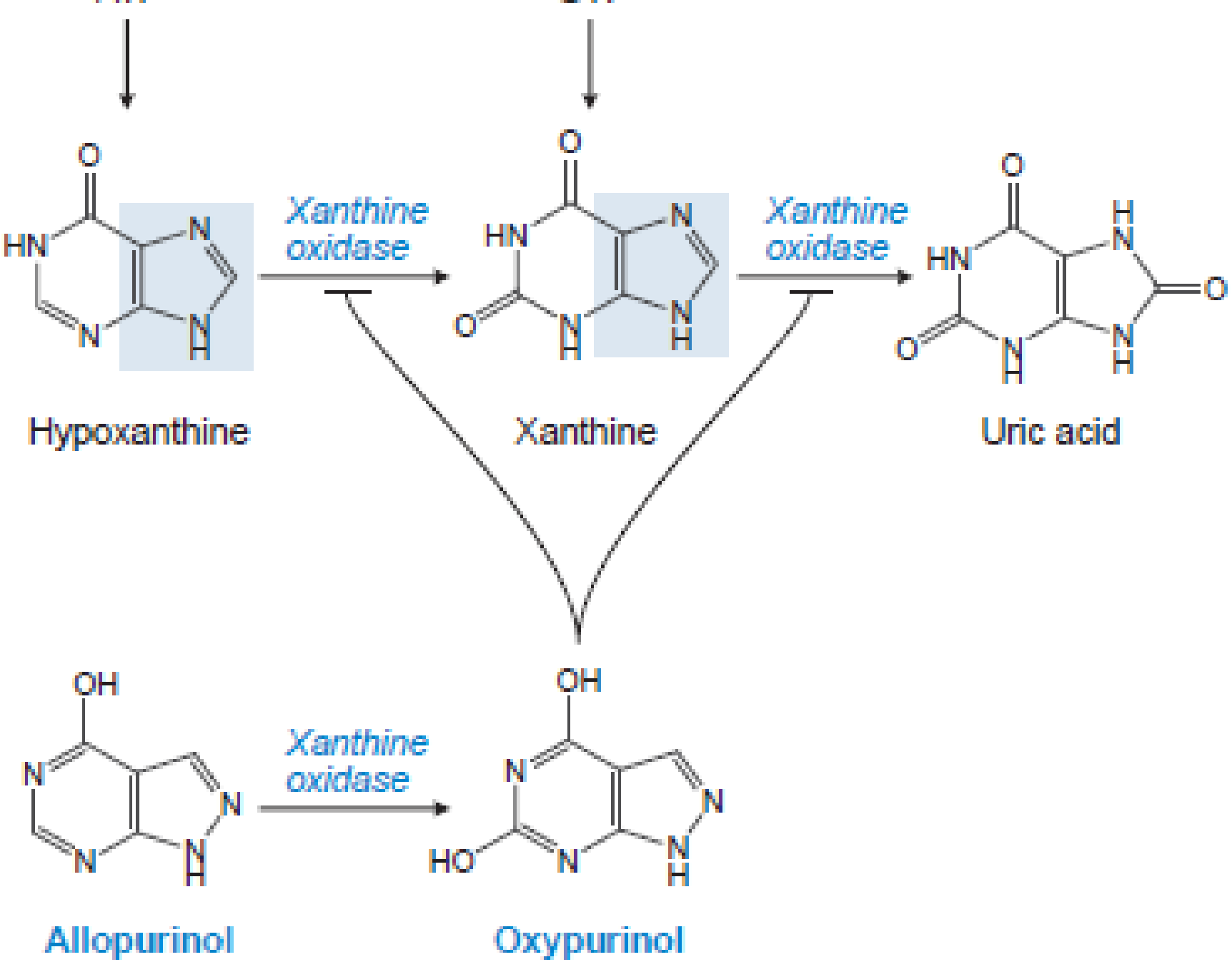
=such injections in a single joint would not normally exceed three per year.

Drug therapy for Gout

Characterized biochemically as a disorder of uric acid metabolism

hyperuricemia

- Recurrent attacks of acute arthritis. Gouty arthritis
- Increased plasma levels of uric acid are the strongest risk factor for gout,
- Not everyone with high plasma uric acid levels develops gout.


Xanthine oxidase
Xanthine oxidase
Hypoxanthine
Xanthine
Uric acid
Xanthine oxidase
Allopurinol
Oxypurinol

UNIQUE IN HUMANS….

- Most mammals possess uricase, an enzyme that metabolizes purine breakdown products into a freely water-soluble substance, allantoin.
- Humans, in contrast, excrete most purines as sparingly soluble uric acid.
- High plasma levels of uric acid can lead to deposition of uric acid crystals in joints, most frequently the first metatarsophalangeal joint (great toe).

- Uric acid is eliminated by the kidney (65%) and the GIT tract (35%).
- In humans, urate is filtered ,secreted and reabsorbed by the kidney.
- Reabsorption predominates,so that the amount excreted is usually 10% of that filtered.
- Organic anion transporter family member(URAT1) which can be inhibited.

TABLE 48-1 Natural History of Gout

STAGE	FEATURES	PHARMACOLOGIC INTERVENTION
1. Asymptomatic hyperuricemia	Plasma urate >6.0 mg/dL in women, >7.0 mg/dL in men	None
2. Acute gout	Acute arthritis Typically first metatarsophalangeal joint Excruciating pain	NSAIDs Colchicine Glucocorticoids
3. Intercritical phase	Asymptomatic hyperuricemia 10% may never have another acute attack	None
4. Chronic gout	Hyperuricemia Development of tophi Recurrent attacks of acute gout	Allopurinol Probenecid Sulfinpyrazone

The degree of hyperuricemia correlates with the likelihood of developing gout; however, developing gout without hyperuricemia is possible. No pharmacologic intervention is indicated for asymptomatic hyperuricemia, but the cause should be investigated.

- Uric acid, the end product of purine metabolism, is relatively insoluble compared to its hypoxanthine and xanthine precursors In most patients
- with gout, hyperuricemia arises from underexcretion rather than overproduction of urate.
- Urate tends to crystallize as monosodium urate in colder or more acidic conditions.

- MSU crystals activate monocytes/macrophages via the toll-like receptor pathway mounting
- an innate immune response. This results in the activation of the cryopyrin
- inflammasome, the secretion of cytokines, including IL-1β and TNF-α,
- endothelial activation, and attraction of neutrophils to the site of inflammation.

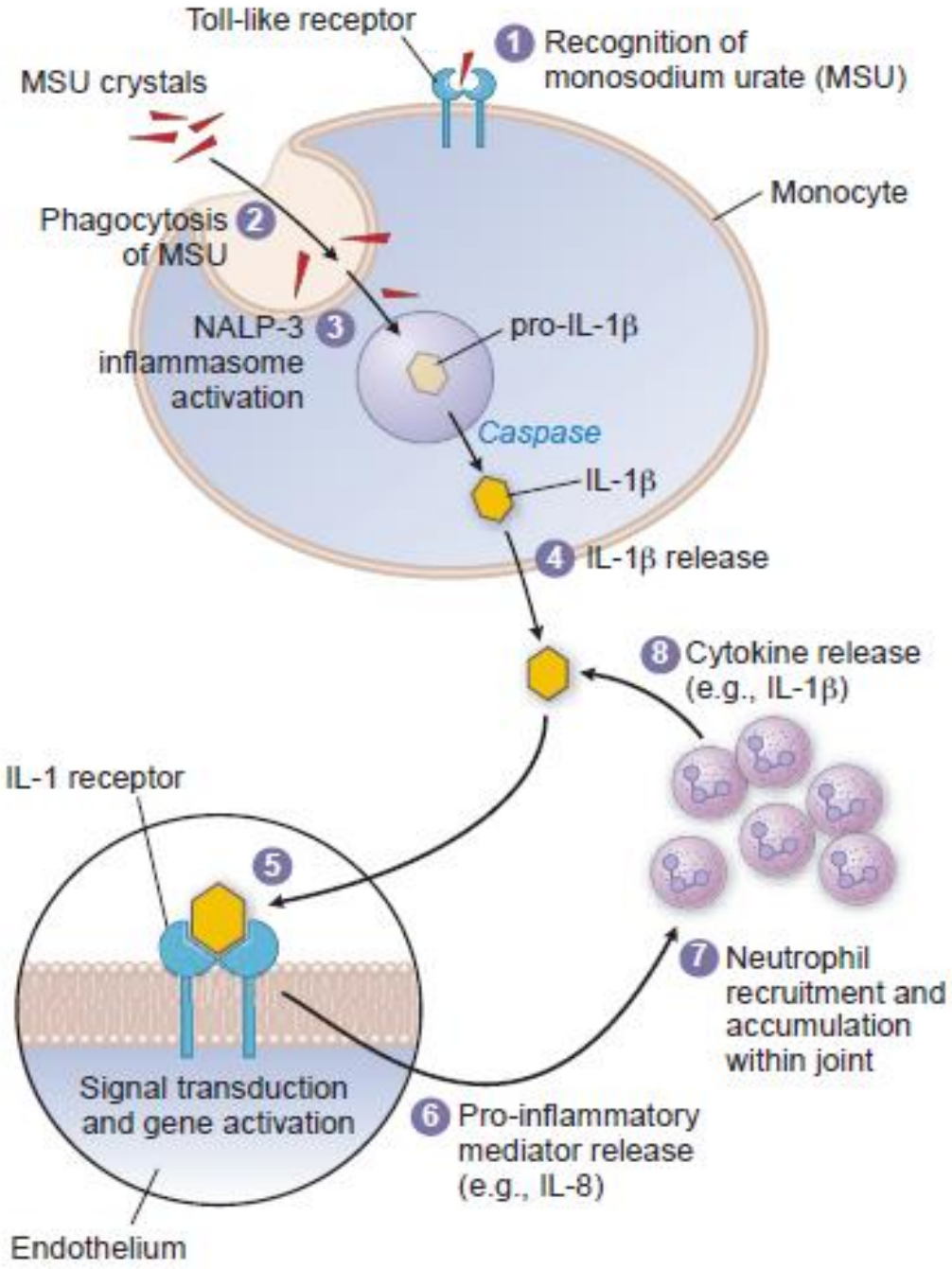
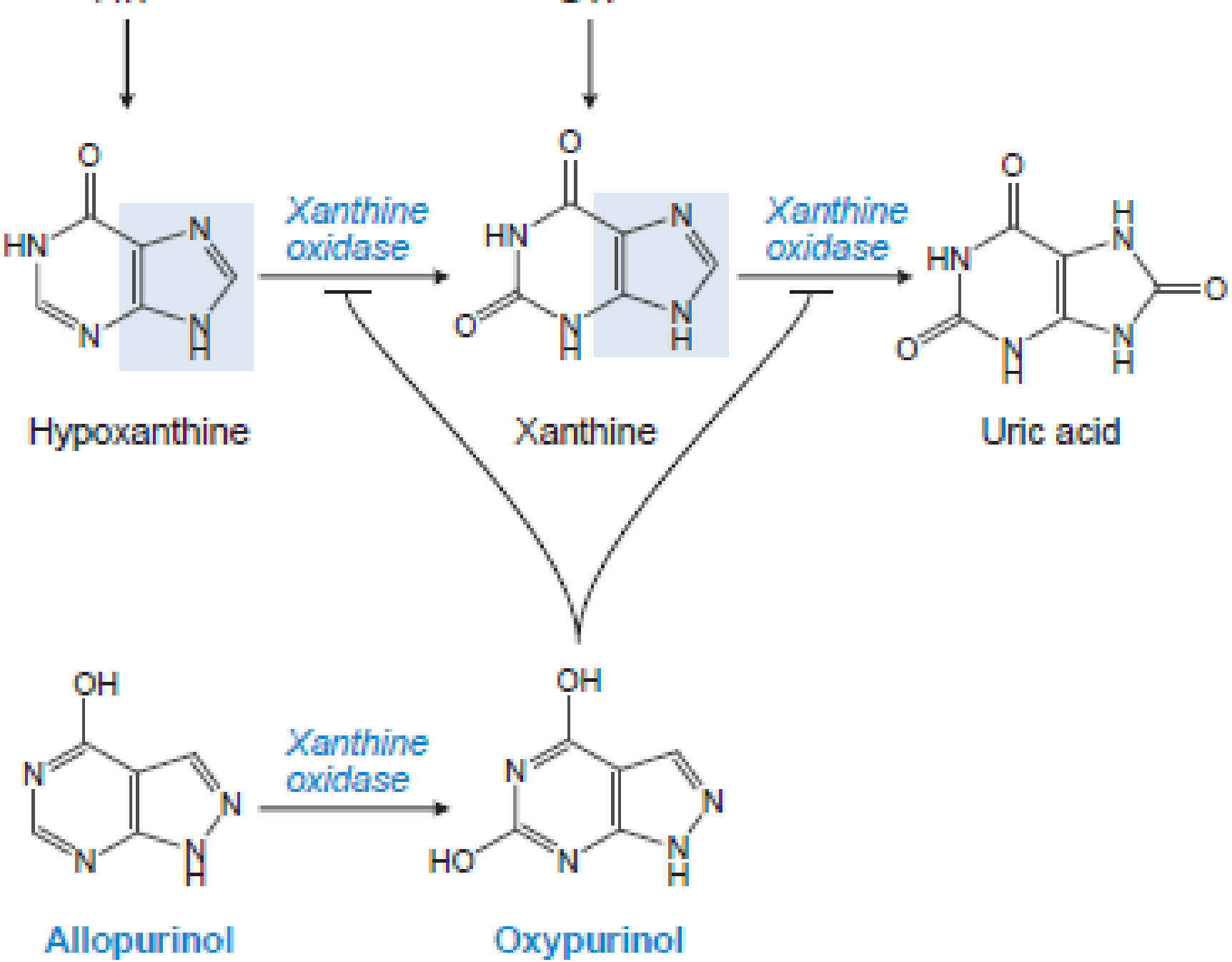
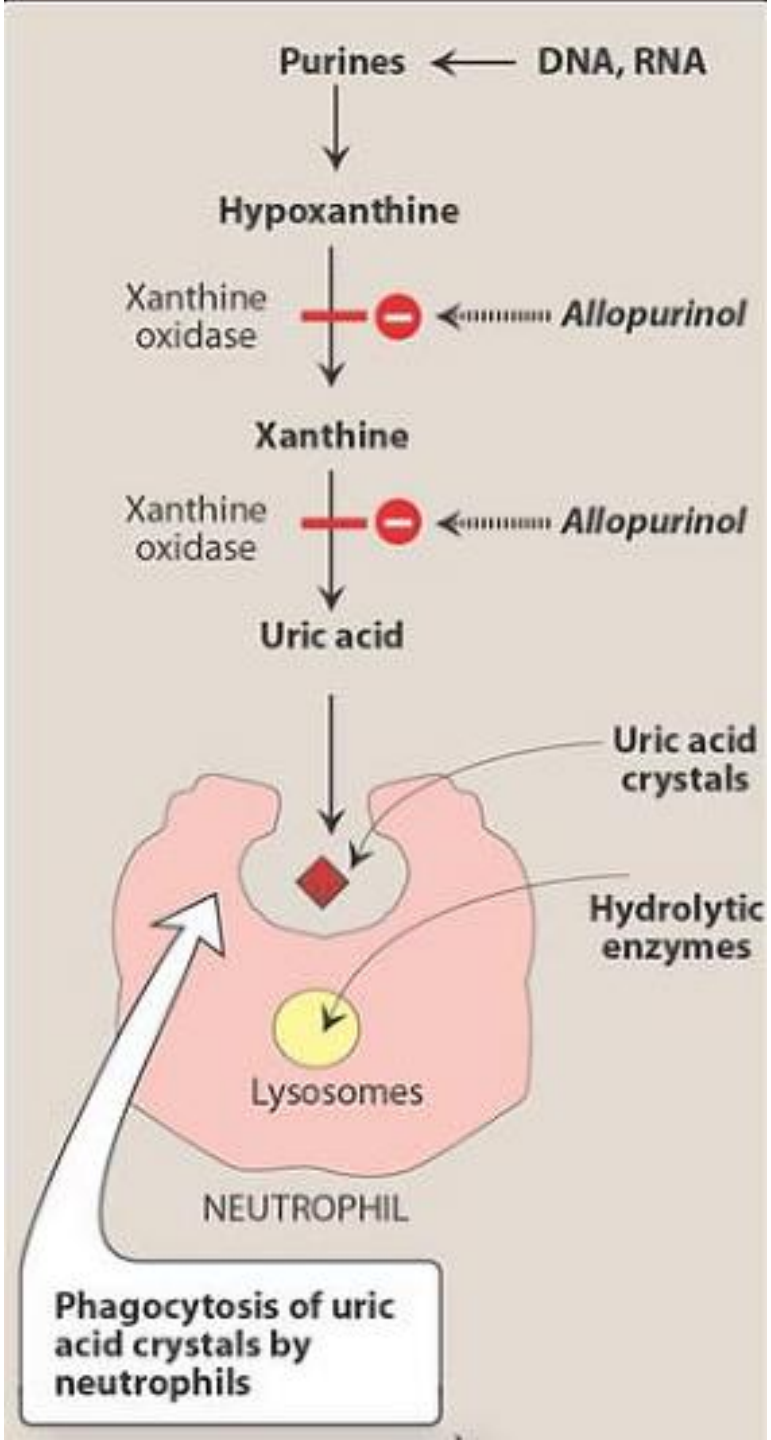
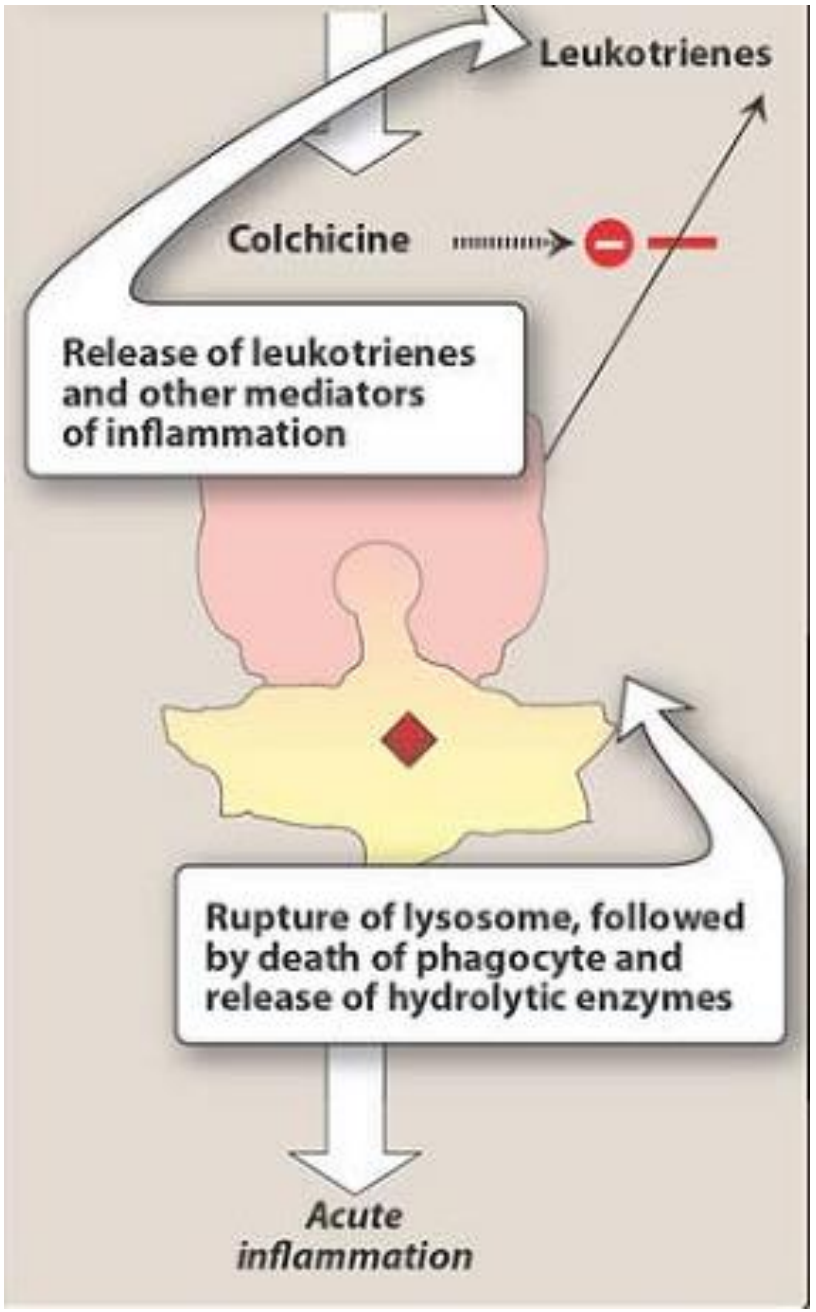
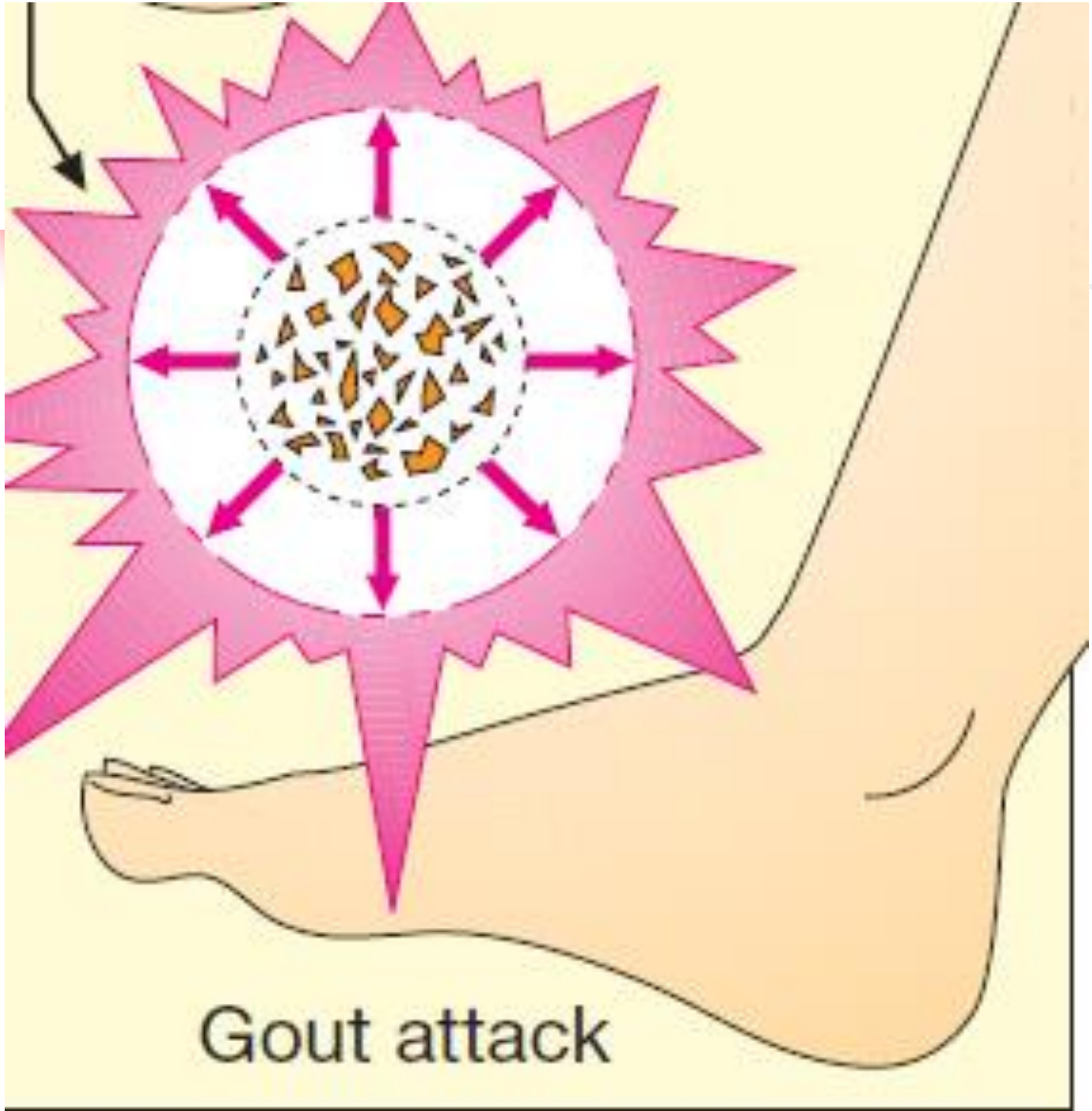


FIGURE 48-2. **Mechanisms of the inflammatory response to urate crystals.**


Xanthine oxidase
Xanthine oxidase
Hypoxanthine
Xanthine
Uric acid
Xanthine oxidase
Allopurinol
Oxypurinol


Purines
DNA, RNA
Hypoxanthine
Xanthine oxidase
Allopurinol
Xanthine
Xanthine oxidase
Allopurinol
Uric acid
Uric acid crystals
Hydrolytic enzymes
Lysosomes
NEUTROPHIL
Phagocytosis of uric acid crystals by neutrophils


Leukotrienes
Colchicine
Release of leukotrienes and other mediators of inflammation
Rupture of lysosome, followed by death of phagocyte and release of hydrolytic enzymes
Acute inflammation


Gout attack

Aims of therapy

1. Suppress the symptoms of an acute attack
2. Decrease the risk of recurrent attacks
3. Lower serum urate levels

The drugs available for these purposes are:

drugs that relieve inflammation and pain (NSAIDs, colchicine, glucocorticoids)

drugs that prevent inflammatory responses to crystals (colchicine and NSAIDs)

drugs that act by inhibition of urate formation (allopurinol, febuxostat) or to augment urate excretion (probenecid)

Treating acute gout

- ✓ treated with indomethacin/naproxen added benefit to ↓ movement of granulocytes into the affected area;
- ✓ initial NSAID dose doubled within first 24-48 hrs ↓ over next few days.
- ✓ Intra-articular glucocorticoids (when only one/ two joints are affected) is appropriate in an acute setting

prophylactic therapy

1. >2 attacks/year.
2. 1st attack severe with kidney stones
3. serum urate > 10 mg/dL/ urinary urate excretion> 1000 mg per 24 hours

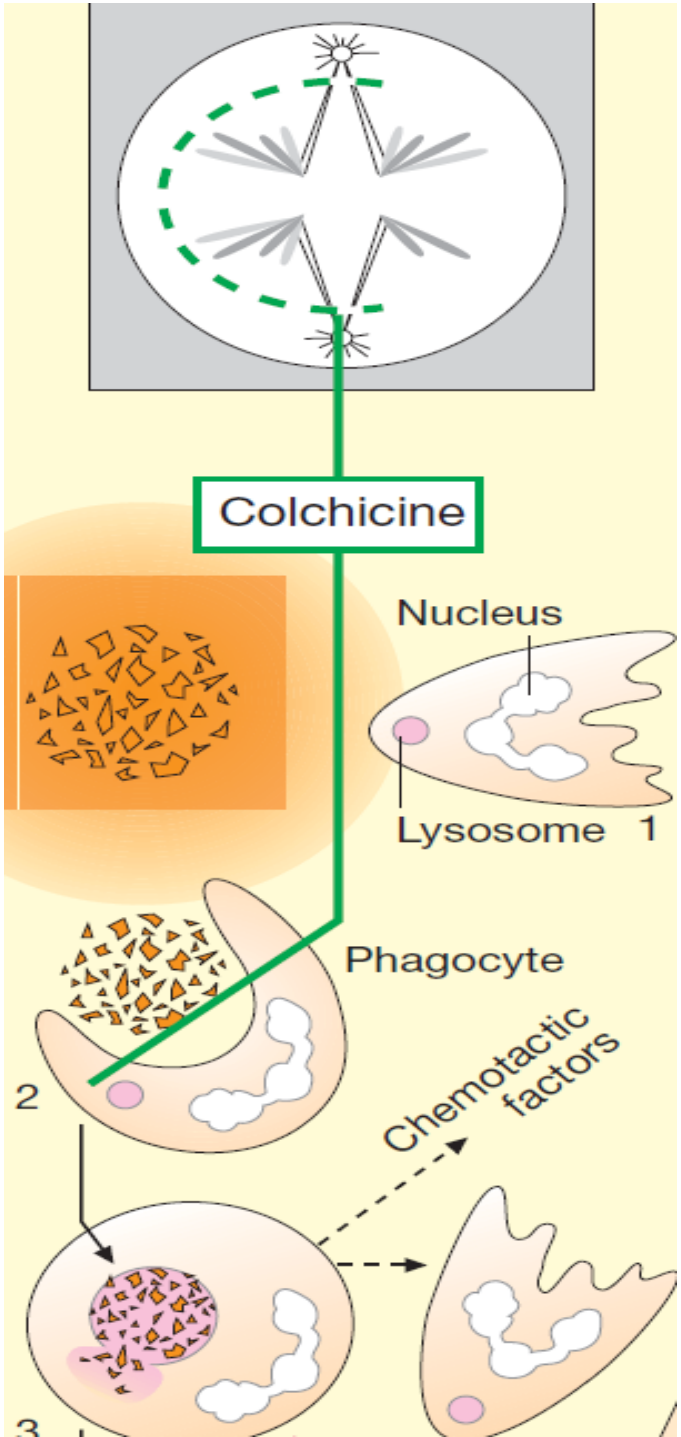
Colchicine

Plant alkaloid, used for the treatment of acute gouty attacks

neither a uricosuric nor an analgesic but relieves pain in acute attacks of gout.

Mechanism of action

1. binds to tubulin, a microtubular protein, inhibiting its polymerization and preventing formation of microtubules
2. Disrupts mobility of granulocytes, ↓ing migration into affected area.
3. Blocks cell division by binding to mitotic spindles.
4. Effect greatest on cells with rapid turnover(GI epithelium, neutrophils)
5. decreases crystal-induced secretion of chemotactic factors and superoxide anions by activated neutrophils.


Colchicine
Nucleus
Lysosome
1
Phagocyte
2
Chemotactic factors
3

Colchicine: Adverse effects

Nausea

GI disturbance

Diarrhea

Agranulocytosis
aplastic anemia

Alopecia

Colchicine

- Toxicity if co-admnistered with cimetidine
- Contraindicated in patients receiving P- glycoprotein inhibitors

Therapeutic status in gout

Acute gout

- ✓ dramatically relieves acute attacks
- ✓ effective in two thirds of patients if given within 24 hours of attack onset.
- ✓ Pain, swelling, and redness abate within 12 hours
- ✓ New regimen of FDA in 2009
- ✓ *total of only two doses taken 1 hour apart: 1.2 mg (two tablets) at the first sign of a gout flare followed by 0.6 mg (one tablet) 1 hour later*

Prevention of acute gout

The main off-label indication for colchicine

prevention of recurrent gout, particularly in the early stages of antihyperuricemic therapy.

The typical dose for prophylaxis is 0.6 mg taken orally 3 or 4 days/wk for patients who have <1 attack per year

0.6 mg daily for patients who have >1 attack per year

0.6 mg two or three times daily for patients who have severe attacks.

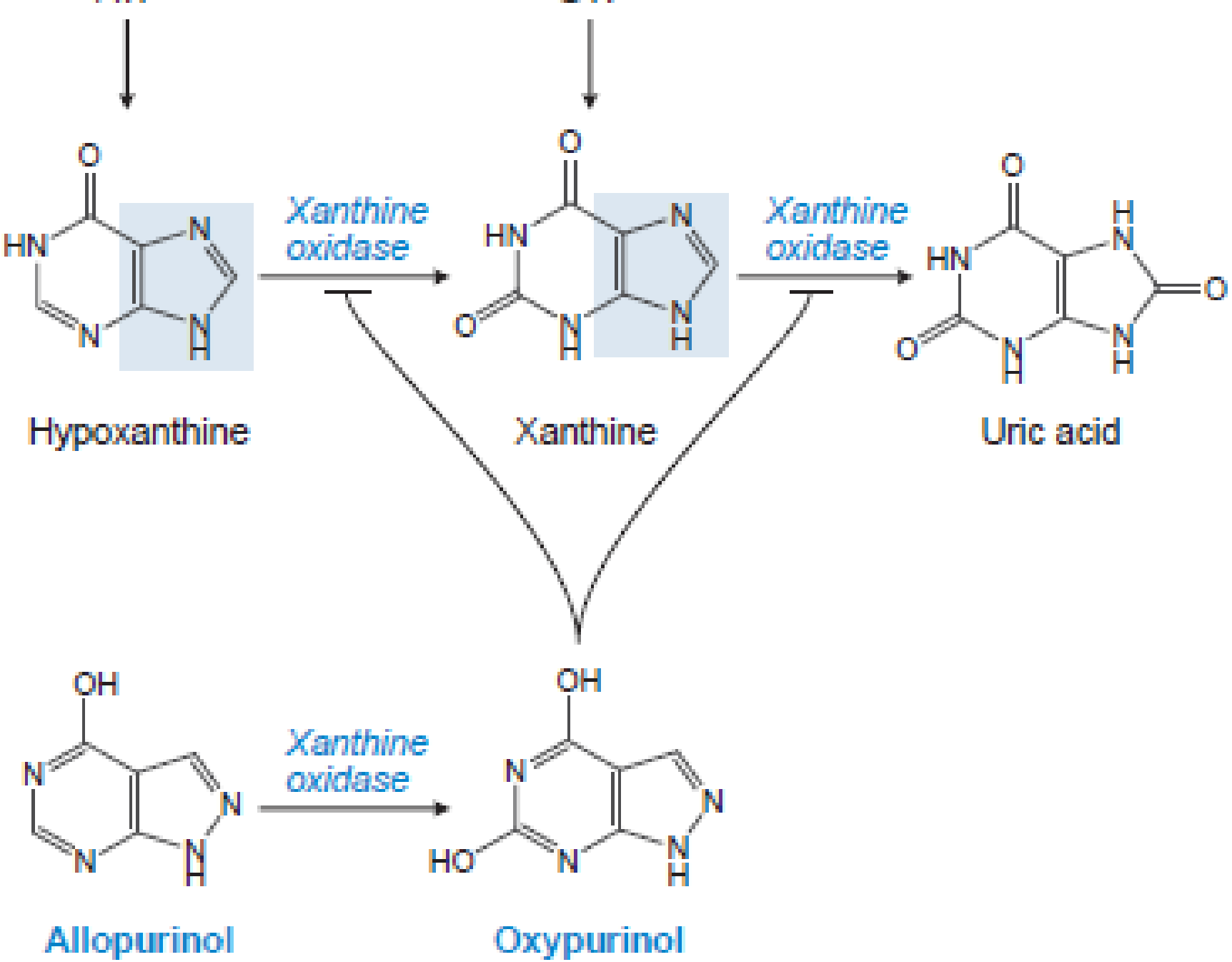
Treating chronic gout

√ **Uricosuric** drugs that ↑ the excretion of uric acid, thereby ↓ its concentration in plasma,

√**Allopurinol**, selective inhibitor of the terminal steps in the biosynthesis of uric acid.

Uricosuric agents are 1st line in gout associated with reduced urinary excretion of uric acid.

Allopurinol preferred in patients with excessive uric acid synthesis


Xanthine oxidase
Xanthine oxidase
Hypoxanthine
Xanthine
Uric acid
Xanthine oxidase
Allopurinol
Oxypurinol

ALLOPURINOL

- A drug designed to inhibit a well undersood biochemical pathway
- Is a structural analogue of Xanthine
- Inhibits the enzyme :suicide inhibitor
- increases plasma levels of xanthine and hypoxanthine, moderately soluble in blood and call be filtered by the kidney without crystal deposition
- *Also used to prevent gout in pts of hematological malignancies about to undergo chemotherapy (acute tumor lysis syndrome*).

Allopurinol

- Not to be administered to treat an acute attack of gout
- Allopurinol facilitates the dissolution of tophi and mobilization of tissue stores of uric acid.
- *Co-administration of colchicine helps suppress such acute attacks.*
- *After reduction of excess tissue stores of uric acid, the incidence of acute attacks decreases and colchicine*

DOSE :100-300 mg/day

Drug interaction with mercaptopurine – lead to toxicity

Along with ampicillin-Increased incidence of rash

ITESELF CAN CAUSE hypersenstivity reactions

Allopurinol also is useful in lowering the high plasma concentrations of uric acid in patients with Lesch-Nyhan syndrome (orphan designation)

orphan uses for allopurinol ex vivo preservation of cadaveric kidneys prior

to transplantation.

Febuxostat

- Febuxostat is a novel xanthine oxidase inhibitor that was recently approved for treatment of hyperuricemia in patients with gout (Pascual et al., 2009).
- Does not require dose adjustment in renal insufficiency
- 40-80 mg/day

Rasburicase

- Rasburicase is a recombinant urate oxidase that catalyzes the enzymatic oxidation of uric acid into the soluble and inactive metabolite allantoin.
- shown to lower urate levels more effectively than allopurinol (Bosly et al., 2003).
- indicated for the initial management of elevated plasma uric acid levels in pediatric patients with leukemia, lymphoma, and solid tumor malignancies who are receiving anticancer therapy
- Produced by a genetically modified *Saccharomyces cerevisiae* strain, the therapeutic efficacy may be hampered by the production of antibodies against the drug.
- Hemolysis in glucose-6-phosphate dehydrogenase (G6PD)-deficient patients, methemoglobinemia,

Pegloticase is a pegylated uricase (urate oxidase)

Lesinurad is FDA approved for combination therapy with an XO inhibitor

in treating hyperuricemia.

Mechanism of Action- Lesinurad inhibits the URAT-1 and OAT- transporters, thereby reducing renal uric acid reabsorption

Uricosuric drugs:

Probenecid **benzbromarone**

Sulfinpyrazone **losartan**

- At therapeutic doses, blocks tubular resorption of uric acid.
- Inhibitor of the basolateral anion exchanger
- Useful in chronic hyperuricemia
- However increasing urate secretion predisposes to urate stones in kidney
- 250- 500 mg daily

Drug induced hyperuricemia

a) Thiazide
b) Loop diuretics
c) Pyrazinamide
d) Ethambutol
e) Ethanol
f) Aspirin
g) Antineoplastic drugs

Knowledge that alcohol induces acute gout is of long standing, and has been celebrated in verse:

A taste for drink, combined with gout,

Had doubled him up for ever.

Of that there is no manner of doubt

No probable, possible shadow of doubt

No possible doubt whatever*

But the author did not know the mechanisms.

***Don Alhambra's song in Act 1 of the Savoy opera, The Gondolires or the King of Barataria. W S Gilbert (1836-1911).**

Methotrexate has the following significant adverse effects, except

a) liver toxicity
b) bone marrow suppression
c) acute pneumonitis
d) deposition in the retina resulting in visual loss

Stepped Approach to the Management of Osteoarthritis

Non pharmacological

- ✓Education,
- ✓joint protection,
- ✓weight loss,
- ✓orthotics, stick if necessary,
- ✓exercise program,
- ✓activities of dailyliving support

Drug therapy of OSTEOARTHRITIS

Acetaminophen up to 4 g daily taken regularly when pain is persistent

↓

Topical anti-inflammatory creams/capsaicin if needed

↓

If pain relief insufficient, add ibuprofen (low dose) up to 400 mg qid if there are no contraindications

↓

If pain relief is inadequate, consider full antiinflammatory dose of NSAID.

Consider prophylaxis for upper GIT damage if patient is at risk

↓

If pain relief is inadequate or joints have reached end stage, consider referral for arthroscopy and possible débridement, osteotomy, or joint replacement

A BIG THANKS TO ALL ….THE FIRST BATCH OF 250

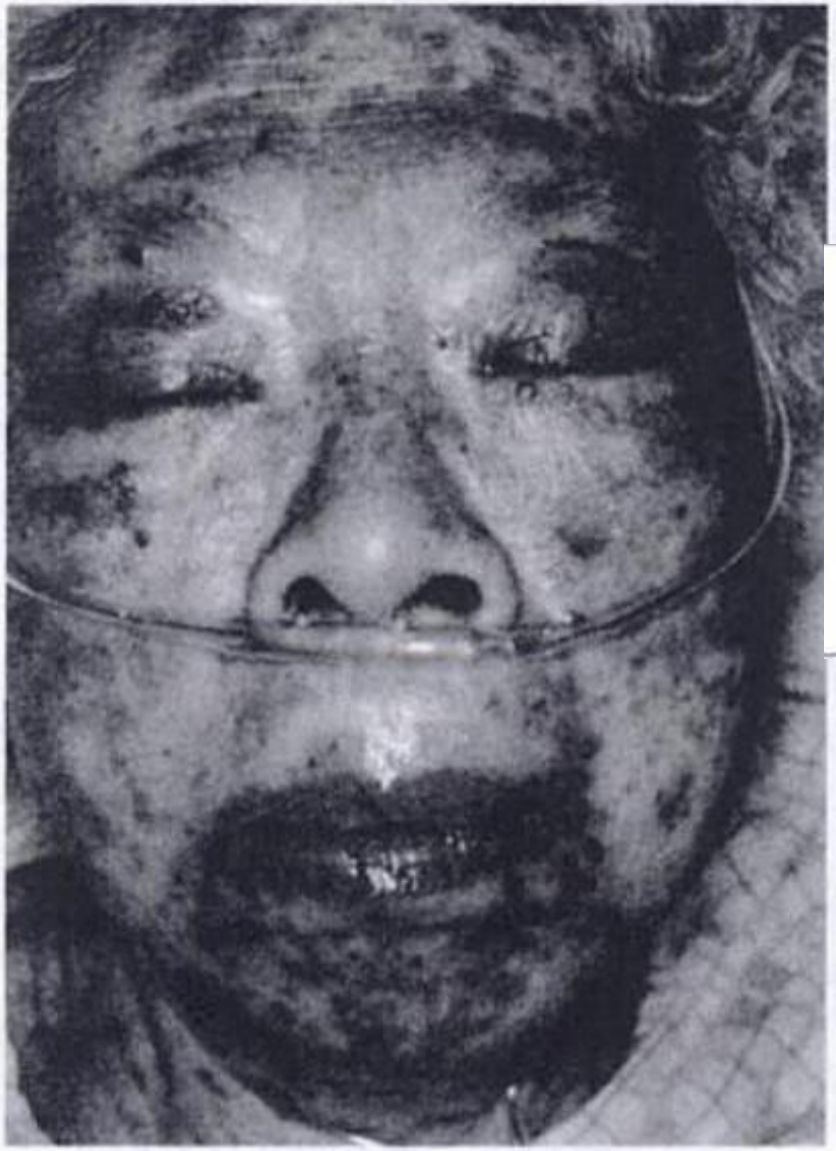
Thank you students for being a wonderful batch .

Thoroughly enjoyed teaching you.

A 19-year-old woman is admitted to the internal medicine ward because of **generalized desquamation** of the skin, high **fever,** and painful **ulcers and bullae in her eyes and vagina.**

She adds that **swallowing** is extremely **painful.** For the past week, she has been on oral **antibiotics** for a urinary tract infection.

VS: **fever** (39.2°C). PE: painful **mucosal ulcerations** in conjunctiva, nose, mouth, oropharynx, and vagina; eyelids swollen and erythematous; **generalized, symmetric rash** on skin with **macules, papules, vesicles,** and **bullae** as well as areas of denudation (epidermis completely separated from dermis) on palms, soles, and extremities.



Drugs that commonly are associated with the development of Stevens–Johnson syndrome:

- Phenytoin
- Sulfonamides
- Ethosuximide
- Lamotrigine