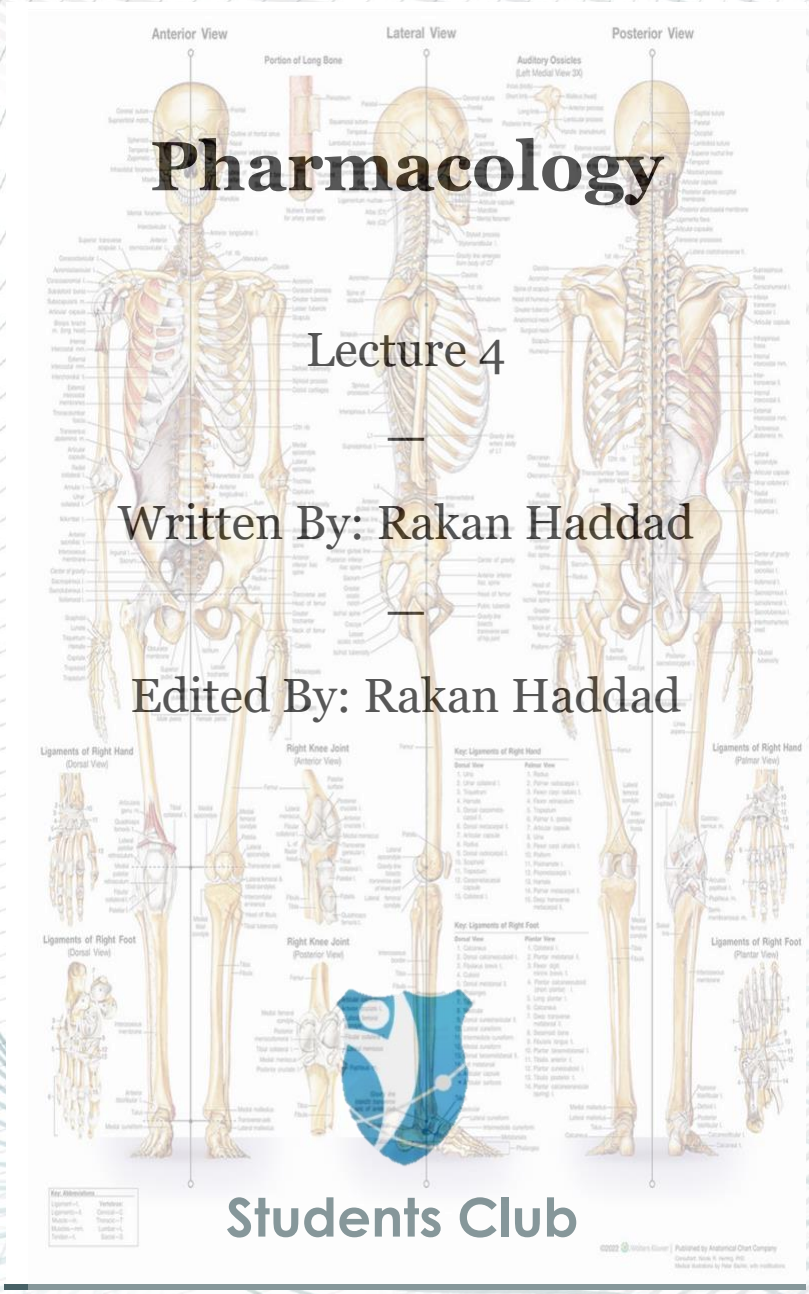
MUSCULOSKELETAL SYSTEM



Lecture 4

—

Written By: Rakan Haddad

—

Edited By: Rakan Haddad

- **Drug therapy of gout:**

-What Is Gout?

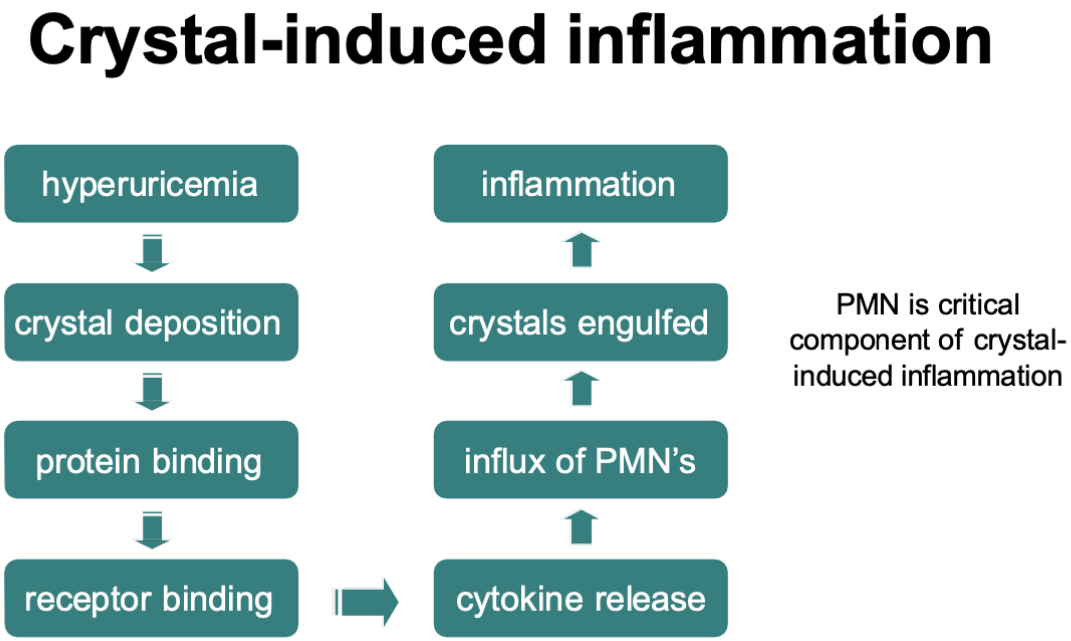
→Gout is a form of complex arthritis, characterized by sudden, severe attacks of pain, swelling in the joints, redness, and tenderness. It can affect one or more joints, with the big toe being one of the most commonly inflamed joints during a gout attack. These attacks can occur suddenly, often in the middle of the night when someone is sleeping, causing them to feel as if their big toe is on fire. The affected joint will become hot, swollen, and painful. These symptoms are typically the result of an inflammatory reaction at that site.

- So basically, gout is an inflammatory disease. But what causes it? Gout can also be considered a metabolic disorder. It occurs due to inflammation, or what we refer to as arthritis, which is caused by the deposition of monosodium urate crystals. These crystals can deposit in the joints, as mentioned, but they can also accumulate in other areas, such as the cartilage. Additionally, uric acid deposits can form in the kidneys, leading to renal calculi. This can also result in intestinal nephritis.

- **Gouty arthritis-characteristics**

- sudden onset→ acute gout can occur at any time.
- middle aged males
- severe pain→ due to cytokines (IL-1 and PG's)
- distal joints→ typically occurs here, can occur to other joints tho.
- Intense inflammation→ propagated by chemotaxis (PMN leukocytes) and later on they start accumulating and storing urate crystals.
- recurrent episodes
- influenced by diet
- bony erosions on Xray
- Hyperuricemia

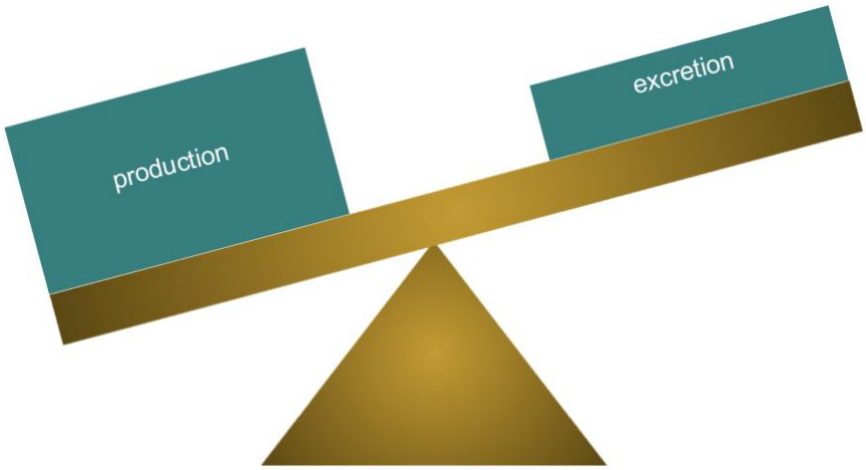
- As mentioned, gout can start in the middle of the night. It usually affects males, particularly middle-aged men. Its characterized by severe pain in distal joints, such as the toes. This condition involves intense inflammation, and episodes that can recur at any time. It is influenced by diet, and changes in the bone can be identified through X-rays.



-Soooo… How does gout start? Or what is the cascade of events that lead to this inflammation? As we mentioned, we usually have high levels of serum uric acid, which we characterize as hyperuricemia.

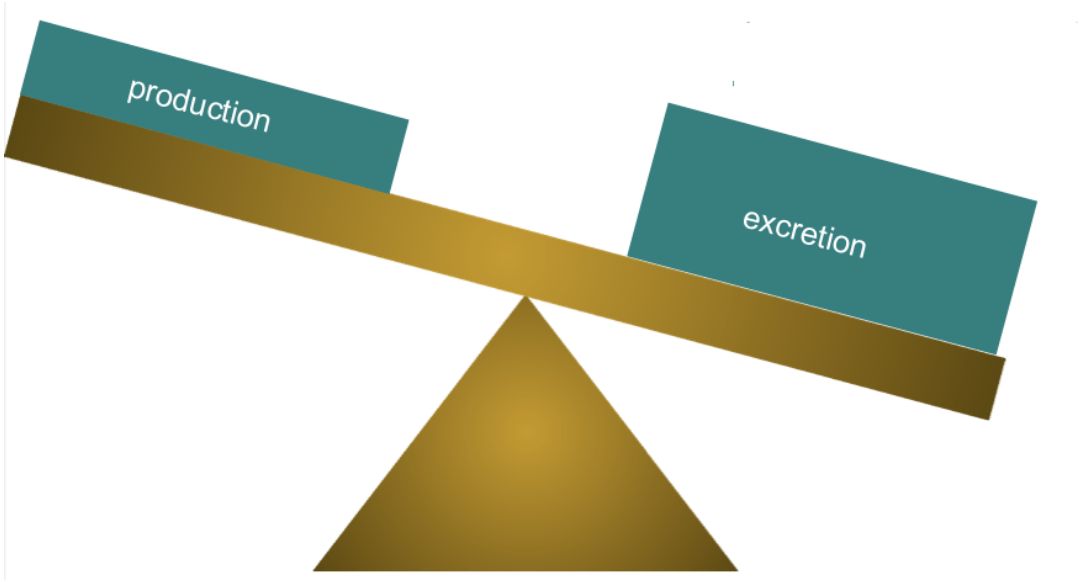
-Uric acid is a poorly soluble substance and the major end product of purine metabolism. Many mammals possess an enzyme called uricase, which typically converts uric acid into the more soluble substance allantoin. Unfortunately, humans do not have this enzyme. Therefore, we must control the levels of uric acid through its excretion by the kidneys. In any situation where there is an imbalance between the uptake and elimination (or excretion) of uric acid, we may have elevated levels of uric acid in the serum, leading to deposition of the substance in joints, kidneys, intestines, and sometimes even in cartilage.

-These urate crystals will bind to certain proteins and receptors on the surface of the cells lining the joints, which are called synoviocytes. Synoviocytes will engulf these urate crystals, leading to the release of many cytokines, prostaglandins, lysosomal enzymes, and interleukin-1. This cytokine release causes the attraction of various cells, including polymorphonuclear leukocytes. These cells will migrate into the joint space and amplify the ongoing inflammatory process. Polymorphonuclear leukocytes are a critical component of crystal-induced inflammation.

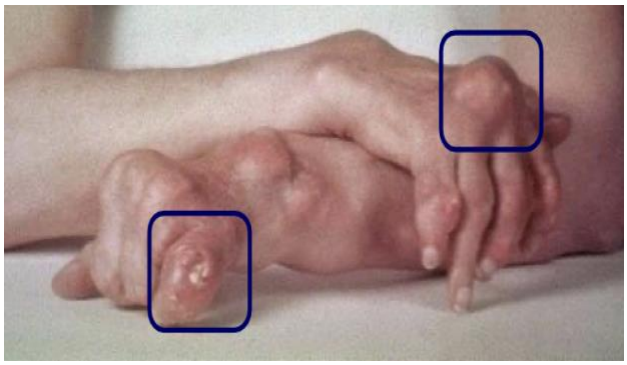


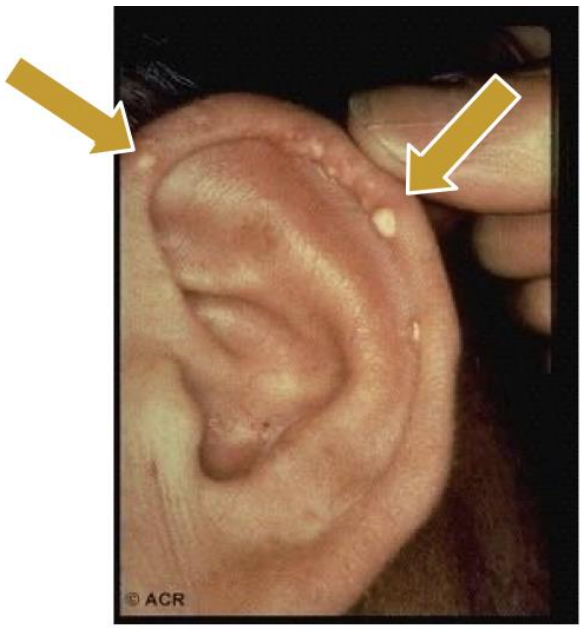
- Hyperuricemia occurs when:

    1. Uric acid production exceeds uric acid secretion
    2. If there is an underlying problem that causes a malfunction in uric acid secretion.
    3. So, we usually have a balance. If we intake too many substances that are converted into uric acid in our body, what kind of substances are we talking about? Typically, red meats are digested in our body and produce purines. These purines are then metabolized into uric acid. Therefore, people with gout who consume too much red meat or protein often end up with hyperuricemia.



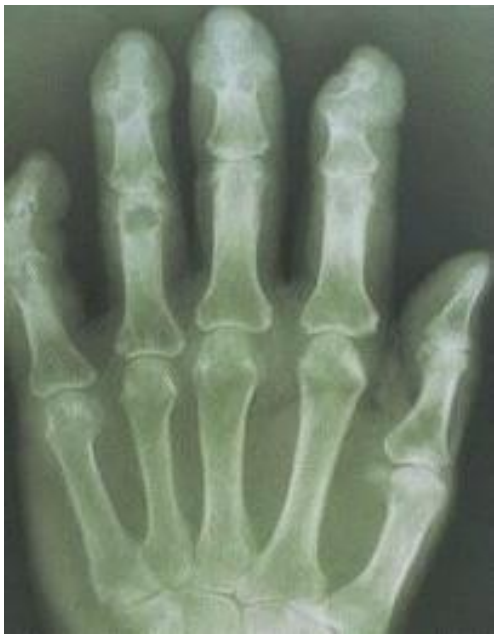
- In this case, uric acid excretion exceeds production which means theres a net loss of uric acid.
- **Chronic tophaceous gout:**
- Let's remember that gout doesn't only present as arthritis.
- It can also present in other forms, such as chronic tophaceous gout. Tophaceous refers to localized deposits of monosodium urate crystals. Tophaceous gout is a chronic form of gout where we see nodular masses, or nodes, of uric acid crystals deposited in various tissues and areas of the body. These tophi are present as hard nodules, most commonly found around the fingers, as shown in this picture.
- This condition is not only a painful inflammatory process but also disfiguring for the patient. As we mentioned, tophi can be present in the toes, fingers, and elbows.
- tophus = localized deposit of monosodium urate crystals





A classic location of the tophi on the helix of the ear

- **<u>Gout - X-ray changes:</u>**



→DIP (*Distal interphalangeal joint)* joint destruction phalangeal bone cysts

→Additionally, we talked about the changes that can be detected on an X-Ray. We can notice, in the distal interphalangeal joint, joint destruction, and we can see the formation of cysts in the bone.

- **Gout - X-ray changes:**

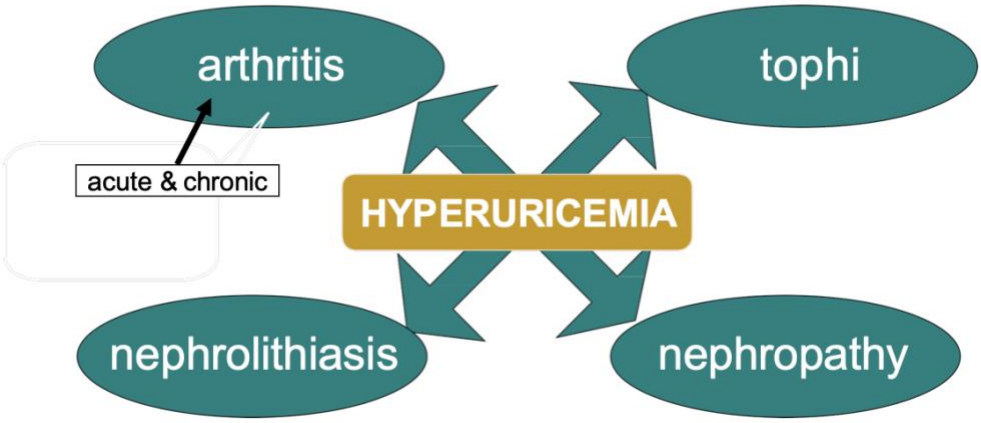
→Bony erosions:

Here, we notice bony erosions in the joints. These are some of the clinical manifestations of gout in the body. Obviously it can also occur in other areas. As mentioned, uric acid renal calculi can form (kidney stines).

→Clinical gouty episodes are usually associated with hyperuricemia. However, most individuals with hyperuricemia may never develop clinical symptoms from urate crystal deposition.

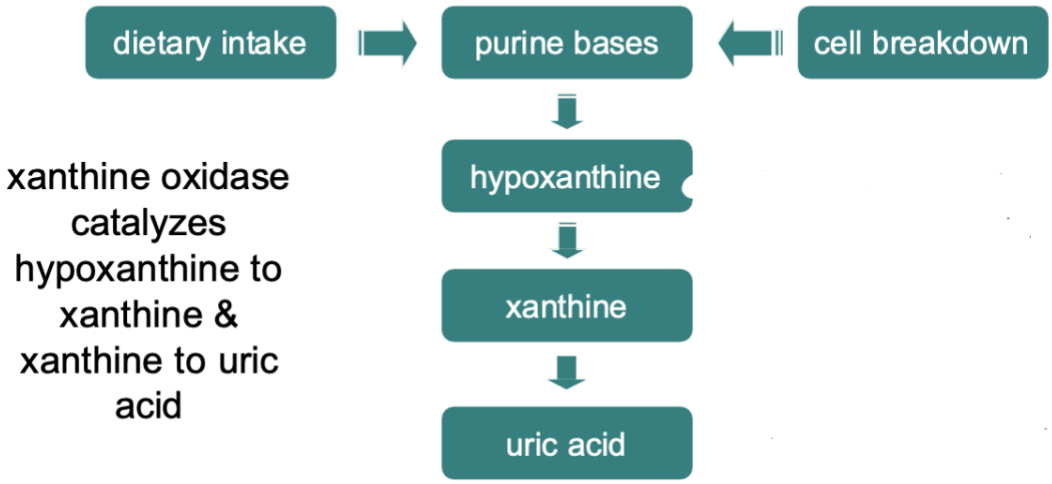
→Before starting chronic urate lowering therapy for gout patients where hyperuricemia is associated with gout and urate stone formation, it is essential to distinguish between individuals who have asymptomatic hyperuricemia and those who experience gouty episodes due to it.However, Long-term drug treatment for asymptomatic hyperuricemia has not been proven to be effective, meaning some individuals with high uric acid levels may go through life without developing any adverse consequences.

Gout - cardinal manifestations



→nephrolithiasis means kidney stones.

Uric acid metabolism

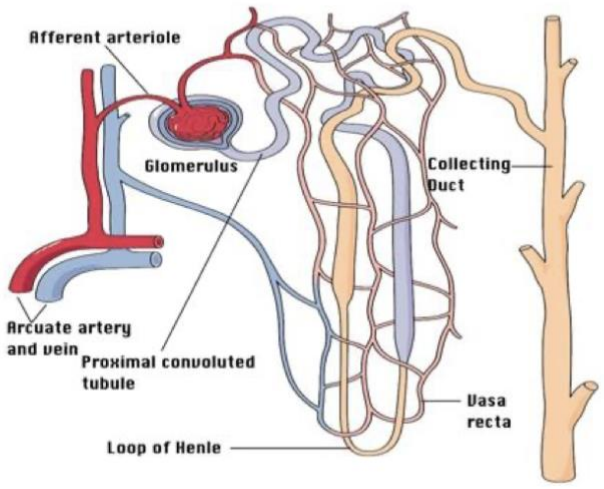


-A persons diet plays a major role in influencing their uric acid levels, which ultimately affects the condition of gout. A high dietary intake of protein is metabolized in the body into purine bases. Additionally, when cells in our body lyse and die, purine bases are also released, leading to the formation of hypoxanthine.

Hypoxanthine is then converted into xanthine by an enzyme called xanthine oxidase. This same enzyme, xanthine oxidase, further converts xanthine into uric acid.

Renal handling of uric acid

- glomerular filtration ⬇
- tubular reabsorption ⬆
- tubular excretion ⬇
- post-secretory reabsorption ⬆
- net excretion



→ How do our kidneys handle uric acid?

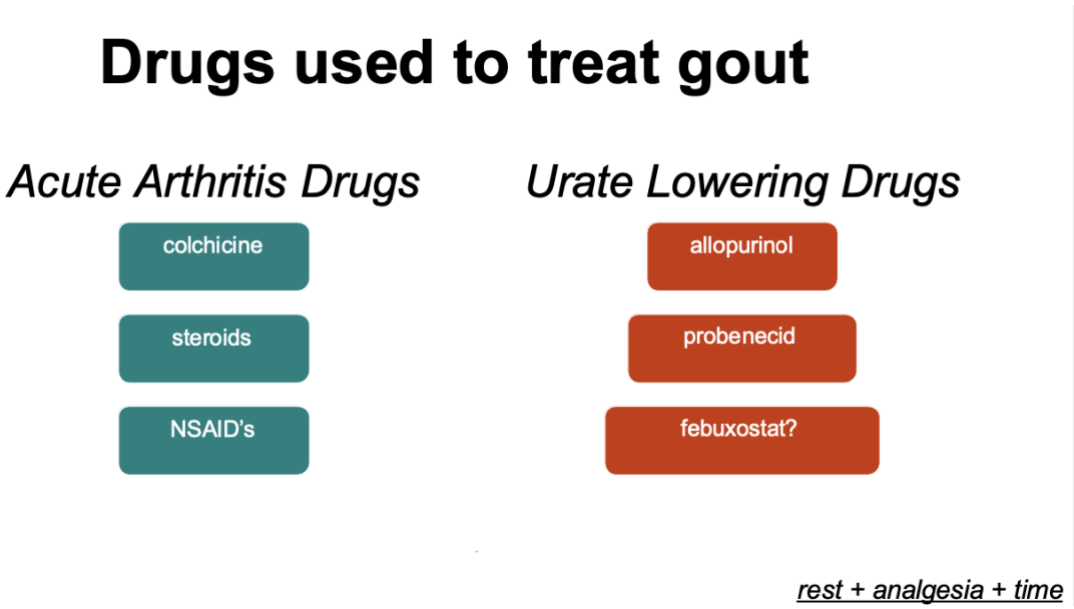
- The net effect of all the processes occurring in the renal glomeruli is the excretion of uric acid. The process begins with glomerular filtration, which decreases the concentration of uric acid in the plasma. Later, in the proximal convoluted tubule, uric acid undergoes reabsorption, followed by a stage of tubular excretion. Finally, there is some post-secretory reabsorption. However, the overall net effect remains the excretion of uric acid.
- To regulate this process, we can use certain pharmacological agents to inhibit tubular reabsorption or post-secretory reabsorption, thereby promoting uric acid excretion.

- **Gout – problems:**

- excessive total body levels of uric acid
- deposition of monosodium urate crystals in joints & other tissues
- crystal-induced inflammation

- **Treating acute gouty arthritis:**

- colchicine→ not first line treatment but it used to be.
- NSAID's
- steroids
- rest, analgesia, ice, time (plays a crucial role in addition to drug treatment).



- **Drugs used to treat gout:**
  → NSAID's:
  - Indomethacin (Indocin) 25 to 50 mg four times daily

  →Indomethacin can inhibit urate crystal phagocytosis. Most of the other NSAIDs mentioned also have this property, except for one drug, aspirin. Aspirin is not used in the treatment of acute gouty arthritis because it can cause renal retention of uric acid when used at low doses (less than 2.6 grams per day). On the other hand, at high doses, it is uricoseuric, but these are doses higher than 3.6 grams per day.

  Sooo whats the procedure taken? Indomethacin is commonly used in the initial treatment of gout as a replacement for colchicine.
  How is it administered? We can use 25 to 50 milligrams, up to four times a day, usually for 5 to 7 days.

  - Naproxen (Naprosyn) 500 mg two times daily
  - Ibuprofen (Motrin) 800 mg four times daily
  - Sulindac (Clinoril) 200 mg two times daily
  - Ketoprofen (Orudis) 75 mg four times daily

→ Colchicine - plant alkaloid

colchicum autumnale (autumn crocus or meadow saffron)

- Colchicine is a plant alkaloid that comes from a plant called Colchicum autumnale. This plant is also known as autumn crocus or meadow saffron.

- **Colchicine:**

• “only effective in gouty arthritis”

• not an analgesic (opposite to NSAID’s)
• does not affect renal excretion of uric acid

• does not alter plasma solubility of uric acid

• neither raises nor lowers serum uric acid

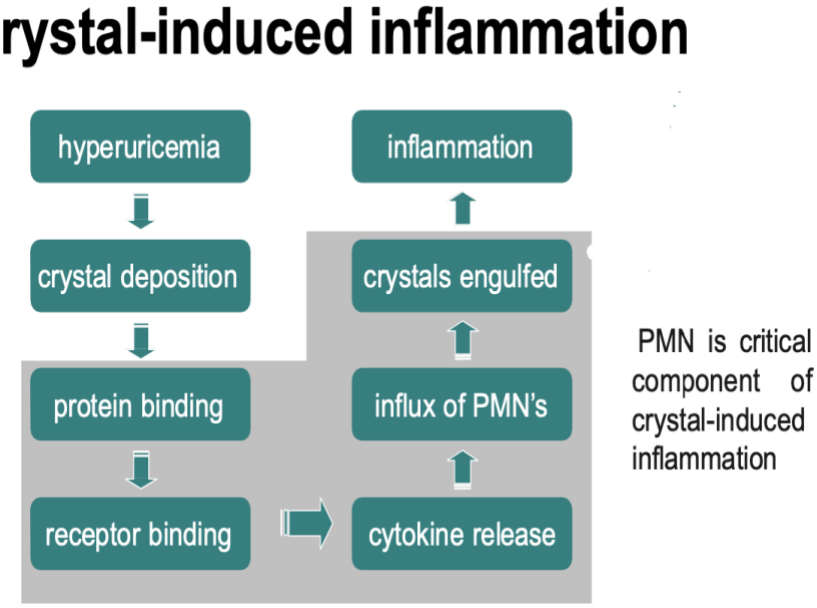
- Colchicine works by preventing the polymerization of tubulin subunits, which is necessary for the formation of microtubules.

• Colchicine inhibits microtubule polymerization by binding to tubulin, one of the main constituents of microtubules
• diminishes PMN phagocytosis of crystals
• reduces inflammatory response to deposited crystals.
• blocks cellular response to deposited crystals

- Phagocytosis plays a major role in the inflammatory process associated with gouty arthritis. For cells to engulf urate crystals, they need continuous microtubule formation and polymerization to move and perform phagocytosis.

→By inhibiting microtubule polymerization, colchicine prevents phagocytosis, reducing the inflammatory response to the deposited urate crystals. Additionally, it diminishes polymorphonuclear leukocyte phagocytosis of crystals, blocking the cellular response to these deposits. This, in turn, reduces inflammation, cytokine release, and the signs and symptoms of inflammatory arthritis associated with gout.

→So what colchhicine would do is prevent synoviocytes from phagocytosing urate crystals preventing cytokine release and influx of PMNs and in general the events that lead to inflammation.



Colchicine Dose	Indication
High	Treatment of acute gouty arthritis
Low	Prevention of recurrent gouty arthritis (maintenance therapy to prevent further flare ups or attacks of gout)

→ Colchicine - toxicity (Side Effects): *adverse effects dose-related & more common when patient has renal or hepatic disease*

- gastrointestinal (nausea, vomiting, cramping, diarrhea, abdominal pain)
- hematologic (agranulocytosis, aplastic anemia, thrombocytopenia)
- muscular weakness

→Colchicine prevents the polymerization of microtubules which are very important in the formation of "mitotic spindles" which means that in highly replicating cells Colchicine can affect the replication process of these cells and that is why it affects the blood forming cells like platelets, RBCs, WBCs.

- **Gout - colchicine therapy:**

  - more useful for daily prophylaxis (low dose)

→ prevents recurrent attacks

→colchicine 0.6 mg qd – bid (Twice a day)

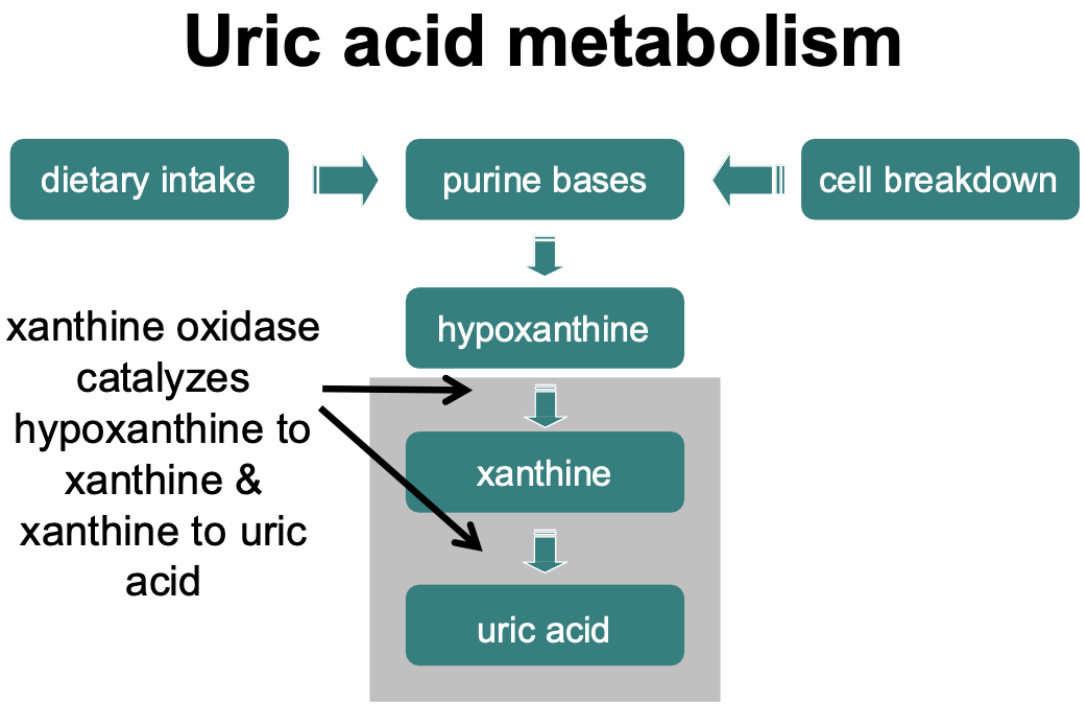
  - Recently , there is declining use of it in acute gout (high dose) =>Replaced by NSAIDs as the first line medication for these acute conditions.

- Let's remember the main mechanisms in which hyperuricemia occurs… It either occurs when there is EXCESSIVE PRODUCTION or when there is INADEQUATE EXCRETION… Sooooo what do you think would be the way to stop that? Exactly! We could use urate lowering drugs which can either BLOCK PRODUCTION or they can ENHANCE EXCRETION which will cause a net reduction in total body pool of uric acid.
- **Gout - urate-lowering therapy:**

1. prevents arthritis, tophi & stones by lowering total body pool of uric acid
2. not indicated after first attack nor immediately but can worsen the attack if to be used after the first attack.
3. initiation of therapy can worsen or bring on acute gouty arthritis
4. no role to play in managing acute gout

→So it's a must to wait some time before administering these drugs and this is mainly due to their effect in urate crystal being shed from the cartilages of the joints into the joint space which results in a flare up of the acute inflammation. (not good bro ☺)

→ Now we will discuss drugs that block the production of uric acid but first lets look at the pathway in which uric acid is produced!



1) Allopurinol (Zyloprim)

- inhibitor of xanthine oxidase
- effectively blocks formation of uric acid
- how supplied - 100 mg & 300 mg tablets orally
- pregnancy category C

→We can use this drug only ifthe benefits outweigh the risk, it would interfere with the synthesis of uric acid in the infants affecting the purine metabolism which means that it may cause some risks to the fetus.

C	Risk cannot be ruled out: Human studies are lacking, and animal studies are either positive for fetal risk or lacking as well. However, potential benefits may justify potential risk.

→Allopurinol – usage Indications

- management of hyperuricemia of gout
- management of hyperuricemia associated with chemotherapy
- prevention of recurrent calcium oxalate kidney stones

→Allopurinol - common reactions & adverse effects:

• diarrhea, nausea, abnormal liver tests

• acute attacks of gout

• rash

→ After the initiation of allopurinol we will have mobilization of urate crystals from their attached sides in the joint to the joint spaces which results in acute changes in the levels of uric acid serum which can predispose a gout attack.

- Some other effects mentioned by the Dr. :
- necrotizing vasculitis
- bone marrow suppression
- rarely, aplastic anemia
- hepatic toxicity & interstitial nephritis have been reported
- allergic skin reactions → pruritus or rash → into maculopapular lesions which happens in 3% of the patients
- some patients also develop exfoliation of the skin called exfoliative dermatitis
- in rare cases allopurinol can become bound to the lens resulting in cataract

- **Allopurinol – serious reactions:**

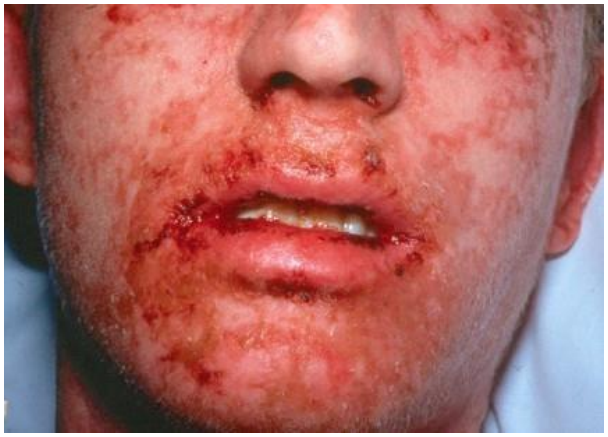
→Steven Johnson Syndrome

- fever, rash, toxic epidermal necrolysis
- hepatotoxicity, marrow suppression
- vasculitis
- drug interactions (ampicillin, thiazides, mercaptopurine, azathioprine)
- death

-target skin lesions

-mucous membrane erosions

-epidermal necrosis with skin detachment which is very rare and happens in less than 2% of the patients



- **Allopurinol hypersensitivity which occurs for some patients:**

• extremely serious problem MUST be recognized early

• prompt recognition required

• first sign usually skin rash

• more common with impaired renal function
• progression to toxic epidermal necrolysis & death

2) Febuxostat

• recently approved by FDA in the 2009 for gout treatment.

• oral xanthine oxidase inhibitor structurally

• chemically (structure) distinct from allopurinol but has the same MOA

• 94% of patients reached urate < 6.0 mg/dl so it can cause reduction of urate to the levels we aim for.

• minimal adverse events in comparisn to allopurinol, it can cause diarrhea, headaches and nausea. It also seems that its more well tolerated in patients who have sensitivity or intolerance to allopurinol which makes it a great alternative.

The newest urate lowering therapy: 3) **PEGLOTICASE**

- recently approved by FDA 2010
- PEG-conjugate of recombinant porcine uricase=> covalently bounded to methoxy polyethylene glycol as we humans do not possess the enzyme that is necessary for the breakdown of uric acid (uricase) while other mammals have it, so this drug is the recombinant form of the enzyme that is present in pigs (porcine)
- treatment-resistant gout
- uricase speeds resolution of tophi

→The addition of PEG conjugation is to increase the half life of the drug and diminish or lower the immune response for this enzyme that is not coming from a human source so it will decrease the antigenicity of the enzyme/protein

→ It's an IV administered drug that works fast (within 24-72 hour) to reach its peak concentration in the body for 6-13 days. Usually clearance is by antibody response… The main importance of adding PEG is to minimize antibody response in the body

→Used for refractory chronic gout (refractory as in the case doesn't respond to other medications).

Our concern→ usage of this drug in patients with Glucose-6-Phosphate dehydrogenase deficiency due to the formation of hydrogen peroxide by the enzyme (uricase). Therefore this drug MUST be avoided is these patients.

- **<u>Adverse effects associated with it</u>**:
  Infusion reaction + flare-ups of gout→especially during the first 3 months of treatment
- **<u>Other side effects</u>** :

1. Nephrolithiasis (kidney stones)
2. Arthralgia
3. Muscle pain and spasms
4. Headache
5. Anemia
6. Nausea
   → and less frequently:
7. Respiratory tract infection - Peripheral edema
8. UTI
9. diarrhea

- *Drugs That Enhance Excretion of Uric Acid*

→Uricosuric therapy

• probenecid
• blocks tubular reabsorption of uric acid • enhances urine uric acid excretion
• increases urine uric acid level
• decreases serum uric acid level

• moderately effective→mainly used in patients who have tophaceous gout or patients who have frequent gouty attacks

• increases risk of nephrolithiasis

• not used in patients with renal disease

• frequent, but mild, side effects (like GI irritation)

• contra-indications

✓ history of nephrolithiasis

✓ elevated urine uric acid level

✓ existing renal disease

• less effective in elderly patients

- **Case presentation:**

• 55 y/o male

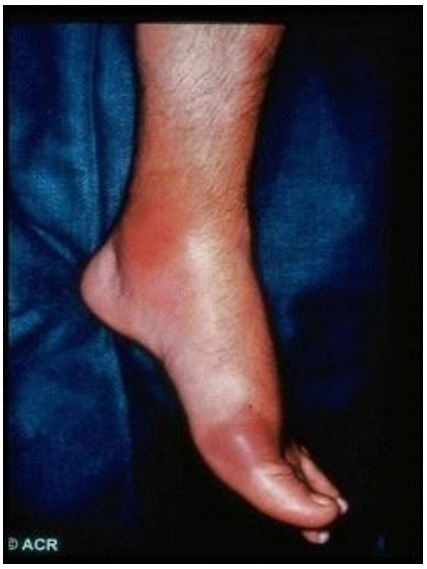
• 12 hours “pain in my big toe & ankle”

• went to bed last night feeling fine

• felt as if had broken toe this morning Past medical history

• PMH of similar problems in right ankle & left wrist

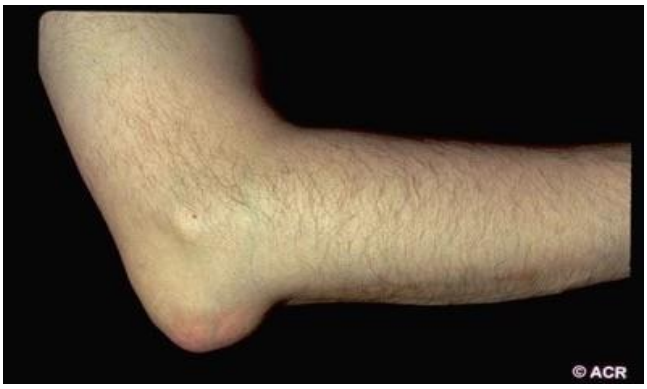
Acute Arthritis



→acute synovitis, ankle & first metatarsophalangyeal joints

→The metatarsophalangeal articulations are the joints between the metatarsal bones of the foot and the proximal bones

Gout - acute bursitis



→acute olecranon bursitis

→Bursitis is inflammation of the fluid-filled sac (bursa) that lies between a tendon and skin, or between a tendon and bone

Treatment for case presentation:

1) Start patient on NSAIDs / Steroids (1-10 days)
2) Before ending NSAIDs we start low dose of colchicine for maintenance therapy to prevent further or future attacks but it isnt recommended due to side effects. (11-365 days)
3) Allopurinol Also for maintenance but given after the acute attack so we let the NSAIDs and colchicine do their work… and when we stop NSAIDs we can give it. (12-365+ days)
4) If any flare up occurs on the long run we can definitely give NSAIDs again.

- **<u>When in the patient is not responding to NSAIDs nor colchicine→ Interleukin 1 receptor antagonist:</u>**

Example:

- Anakinra
- Canakinumab
- Rilonacept

→These are drugs used for treatment of rheumatoid arthritis and currently being investigated for gout→ they tend to target IL-1 pathway so they would suppress the inflammation

<u>Glucocorticotiods</u>

→We can use them for acute gouty arthritis

- Prednisone:
  - Oral
  - Intra-articular
  - Subcutanous

→Depending on the degree of the acute attack and the degree of pain and inflammation in the patient