Hashemite University
H·U·M
Medical School Committee

Scientific Team
الفريق العلمي

PATHOLOGY

Lecture :Gout

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gout

لم يتم حذف ا معلومة بالسلايدات فقط اعادة ترتيب للمعلومات

سلايدات الدكتور باللون الاسود،
ماركز عليه الدكتور باللون الاصفر
والشرح الخارجي باللون الاخضر.

بسم الله الرحمن الرحيم.

Gout Disorder caused by the tissue accumulation o**f excessive amounts of uric acid, an end product of purine metabolism**.

ال purine هو احد انواع النيوكليوتيدات الموجودة فيه

nucleic acids (purines ,pyrimidens)

يلي تكسيره يؤدي الى uric acid بالنهاية يلي يتعبر low soluble in body fluids

الطريقة يلي يتم التخلص فيها منه هي عن طريق kidney (urine)

هايمقدمة لابد منها

بالنهاية هوعبارة عن

inflammatory disease in which result from precipitation of **monosodium urate crystals from supersaturated body fluids.**

طب شوهوال monosodium urate ؟؟؟

Uric acid loose proton (h+) >>>> become uriate ion (-) >>> theen bind to na+

سبب تكون هاي الكريستالز رح نجيله بعدين.....

Most common site first metatarsophalangeal joint why ??

طبعا بالاضافة ل knee joints

ملاحظة هاي العلامة بنسميها podagra

لانه رح نشوف عشان يصير gout لازم يتوفرتلت اشيا:

Hyperuricemia

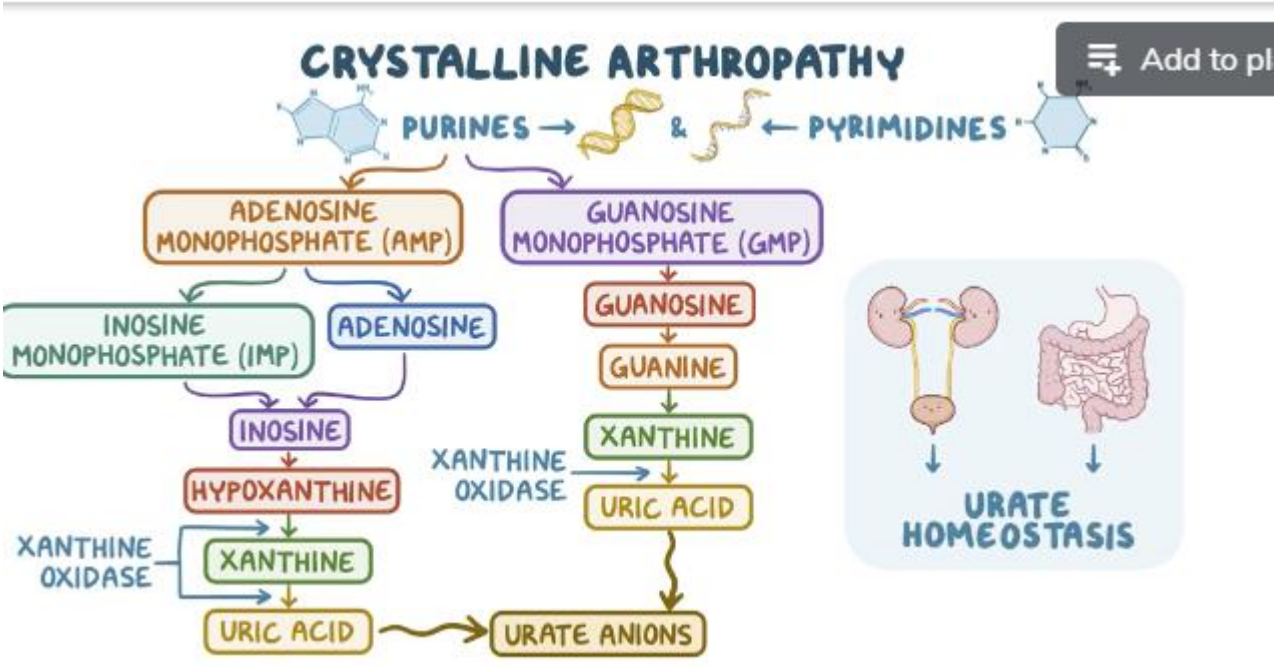
بالتالي هيصير بأطراف الجسم اكتر cold temperature

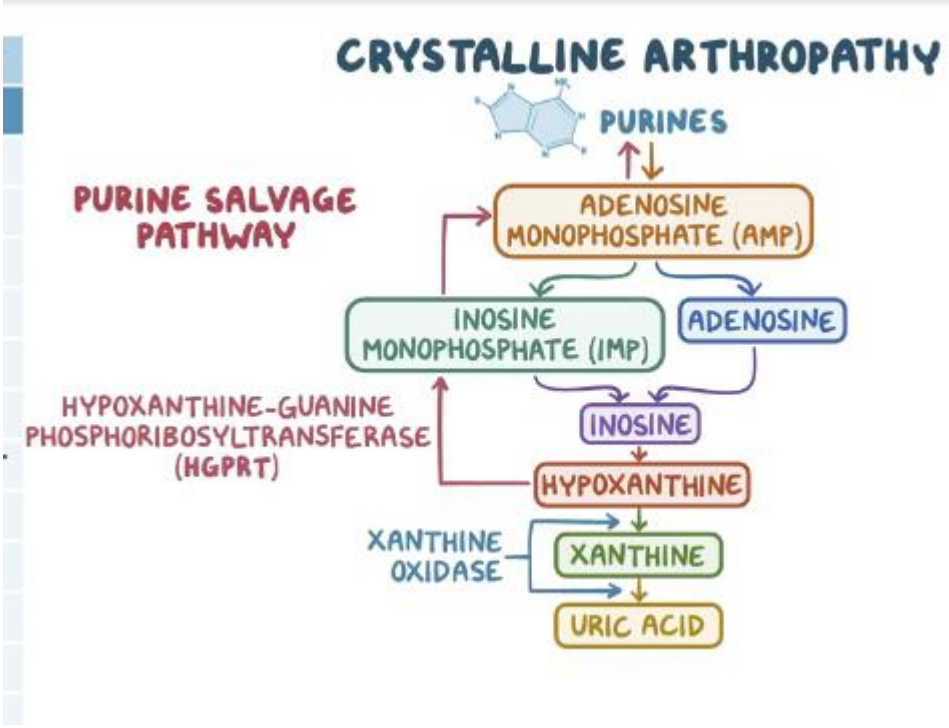
genes

غير هيك blood flow بهاي المناطق بكون slow بالتالي اسهل انه يصير

Deposition of uric acid crystals

هون كيف بتم التخلص من purines زمان اخدناها بالبيوكم





- **It is marked by recurrent episodes** of

(1) acute arthritis, sometimes accompanied by the formation of large crystalline aggregates called (2) tophi

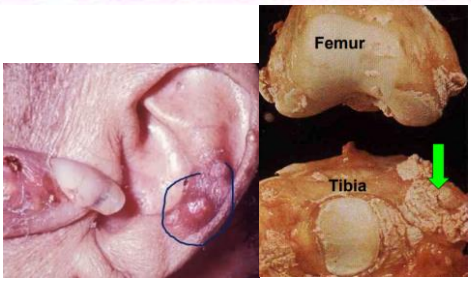
Tophi??

® **pathognomonic hallmarks of gout**, are large aggregates of urate crystals surrounded by an intense inflammatory reaction of lymphocytes, macrophages, & foreignbody giant cells, attempting to engulf the masses of crystals Tophi can appear in the joints articular **cartilage, periarticular ligaments, tendons & soft tissues** including the **ear** lobes, nasal cartilages, & skin of the fingertips

Superficial tophi can lead to large ulcerations of the overlying skin

Seen with long standing hyperuricemia

B, Gouty tophus.
An aggregate of dissolvec urate crystals is surrounded by reactive fibroblasts, mononuclear inflammatory cells & giant cells.



(3) chronic joint deformity.

سيتم شرحها لاحقا

- Although an elevated level of uric acid is an essential component of gout, not all such individuals develop gout, indicating that influences besides hyperuricemia contribute to the pathogenesis

هاي الجملة مهمة ومعناها انه صحيح جميع حالات ال gout بكون فيها high levels of uric acid

ولكن ليش بالضرورة انه وجود ال hyperuricemia يكون في gout يعني هو من الاسباب المهمة لحدوث ال gout بس مو لحاله

صورة الميكروسكوب مهمة

لانه ممكن يحدث RAخربطة مع

لانه برضه بصير عنا subcatenous swelling

بس رح يكون عبارة عن fibrous tissue

اما هون الكريستالز ذابوا واحنا بنحضر بينوا عشكل غمامة بيضة حولها

Gaint cells

لانه هاي الكرستالز تعبتر مادة غريبة

Gout is traditionally divided into

Primary gout	secondary gout
(90% of cases)	In (10% of cases)
Where in the basic cause is unknown or (less commonly) when it is due to **an inborn metabolic defect** that causes hyperuricemia.	the cause of the hyperuricemia is known, but gout is not necessarily the main or even dominant clinical disorder .
Most cases are characterized by overproduction of uric acid. **Less commonly**, uric acid is produced at normal rates, & hyperuricemia occurs because of ↓ renal excretion of urate	↑ urate production: (e.g., rapid cell lysis during chemotherapy for lymphoma or leukemia) ↓ excretion : #chronic renal insufficiency. #caused **by drugs such as thiazide diuretics,** presumably because of effects on uric acid tubular transport. or both شرح تحت

حكينا انه ال uric acid بطلع من metabolism of purines يلي هي من nucleic acids يلي موجودة بالنواة

واخدنا زمان عن سرطانات الدم myloepoliferative disorders زي

Myeliod leukemia – polycethemia vera – thrombocytosis

Which are associated with high level of production

بس برضه كنا نحكي انه life span لهدول الخلايا قليلة وبموتوا بسرعة وبالتالي هيكون عنا برضه

High level of cell turn over

وبس تموت الخلية رح يطلع منها ال purines >>>uric acid

هاي بنسميها tumor lysis syndrome بصير فيها تلت شغلات

Hyperkalemia,phosphatemia,uricemia

غير هيك برضه ال chemotherapy رح تصير الخلايا تموت ب faster rate

حكينا انه ال excretion بصير عن طريقال kidney

بالتالي :

Any reduction in glomerular filtration rate >>> decrease uric acid excretion

طب شووو الحالات يلي بصير فيها هيك ؟؟؟

Renale failure / dehydration (not enough water) (volume depletion)

Diuretics such as thiazide

طبيب لي ؟؟؟

ال diuretics كنا نستخدمها بعلاج الضغط وكمان لانها بتخلصنا من excessive fluid

فكنا نستخدمها لعلاج ال edema والية عملها انها كانت بتقلل (intravascular volume)

وبالتالي رح تقلل ال GFR غير هيك هي بتعمل

Block the uric acid excretion

معلومة كمان انه زي ما بنعرف النقرص مرض الملوك طب لي ؟؟؟ لانه ال uric acid

بزيد ب

Primary gout triggered by consumption of purines such as red meet(muscle tissue of animal) , shellfish …… ++ alcohol

Pathogenesis

الدكتور كتير ركز عترتيب الخطوات

Whatever the cause

→ The ↑ levels of uric acid in the blood & other body fluids (e.g., synovium)

lead to → the precipitation of monosodium urate crystals….which are → directly chemotactic, & can also **activate complement** to generate chemotactic C3a & C5a fragments.

→ leading to a **local accumulation of neutrophils & macrophages in the joints & synovial membranes;** in attempting to phagocytize the crystals, these cells **become activated**, leading to **the release a host of additional mediators including chemokines, toxic FR, & LT B4.**

→**activated neutrophils liberate destructive lysosomal enzymes**.

→ **Macrophages secret IL-1, IL-6, & TNF which intensify the** inflammatory response, & can also directly activate synovial cells & **cartilage cells to release proteases (e.g., collagenase) that cause tissue injury.**

بالنهاية يعني بكون عنا

Inflammatory response >>> inflammatory features (redness ,swelling ,warmth)

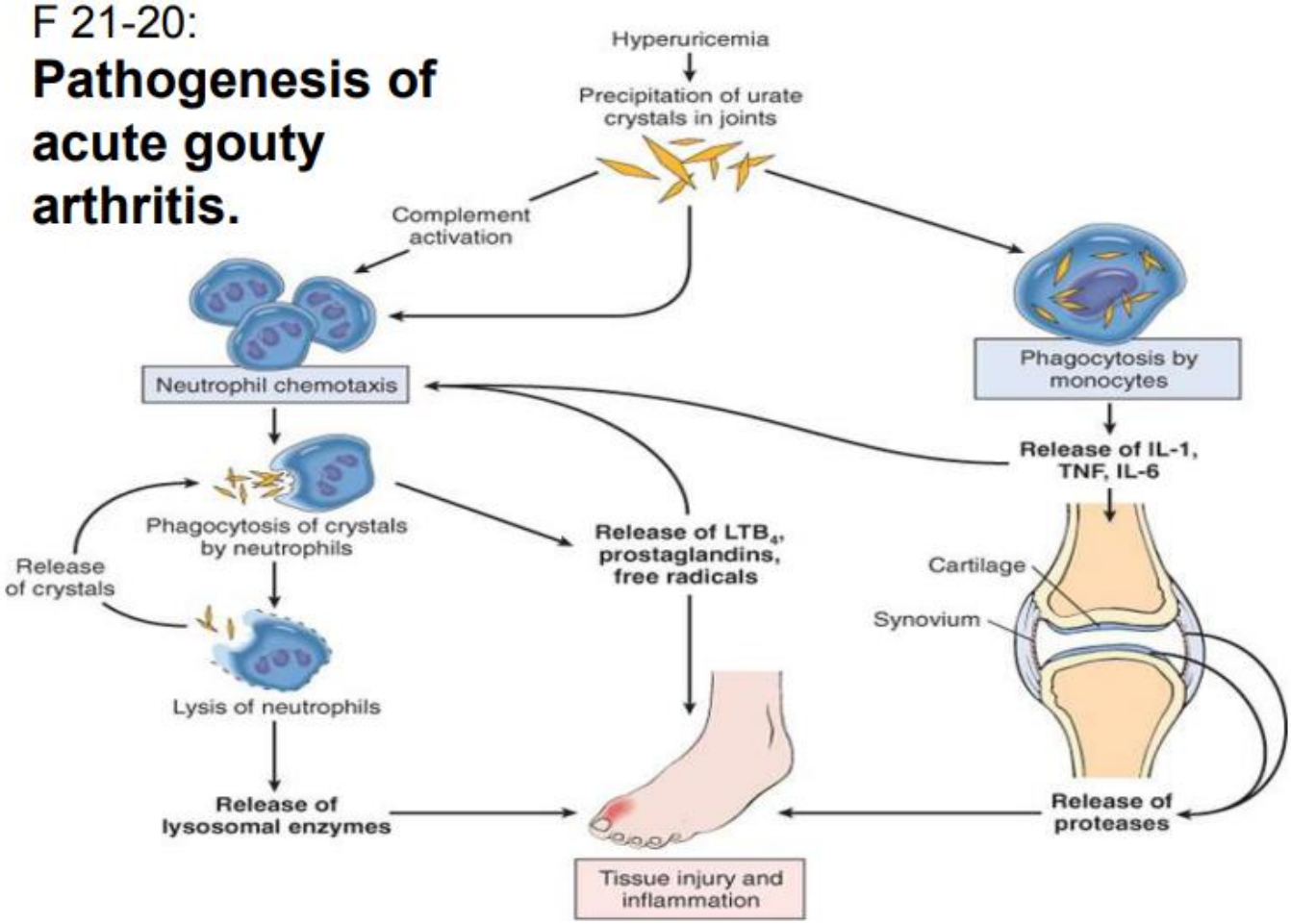
-

The resulting acute arthritis typically remits in days to weeks, even if untreated. Repeated bouts(attacks), however, can lead to the permanent damage seen in chronic tophaceous arthritis.

Acute arthritis	Chronic tophaceous arthritis
(I) monosodium urate crystals, long, slender, needle-shaped crystals are frequently found in the cytoplasm of the neutrophils as well as in small clusters in the synovium, (II) there is characteristic dense neutrophils infiltration of the synovium & synovial fluid. The synovium is congested & edematous & contains scattered mononuclear inflammatory cells. ☹ ☺ When the crystals resolubilized & the episode of crystallization ends; the attack remits.	#developed from repetitive precipitation of urate crystals during acute attacks. #The urates can heavily encrust the articular surfaces & form visible deposits in the synovium. #The synovium becomes hyperplastic, fibrotic, & thickened by inflammatory cells, forming → a **pannus** that destroys the underlying cartilage, & leading to juxta-articular bone erosions. #In severe cases, fibrous or bony ankylosis ensues, resulting in loss of joint function. **#Gout major morphologic manifestations** are: acute & chronic tophaceous arthritis, tophi in various sites, & gouty nephropathy

F 21-20:

Pathogenesis of acute gouty arthritis.



Clinically

gout is more common in men than in women

it usually cause symptoms after the age of 30

in four Stages:

(1) Asymptomatic hyperuricemia appears around puberty in males & after menopause in women. After many years….

(2) acute arthritis appears in the form of sudden onset of excruciating joint pain associated with localized erythema & warmth. The vast majority of first attacks are**; monoarticular**

معناها بمفصل واحد

50% occur in the first metatarsophalangeal joint (great or big toe),

90% in the instep, ankle, heal, or wrist.

Untreated, acute gouty arthritis may last for hours to weeks, but it gradually completely resolves & the patient enters an…

(3) asymptomatic intercritical period. Although some individuals never have another attack, most experience a second episode within months to a few years. In the absence of appropriate therapy, the attacks recur at shorter intervals & become **polyarticular**.

Eventually, after a decade or so, symptoms fail to resolve completely after each attack, & the disease…

(4) progresses to chronic tophaceous gout. At this stage, radiographs show characteristic juxta-articular bone erosion caused by the crystal deposits & loss of the joint space. Progression leads to severe crippling disease.

Renal manifestations of gout can appear as

#with urate deposition, variously forming medullary tophi, intratubular precipitations, or free uric acid crystals & renal calculi

renal colic (ranele stones) associated with the passage of gravel & stones,

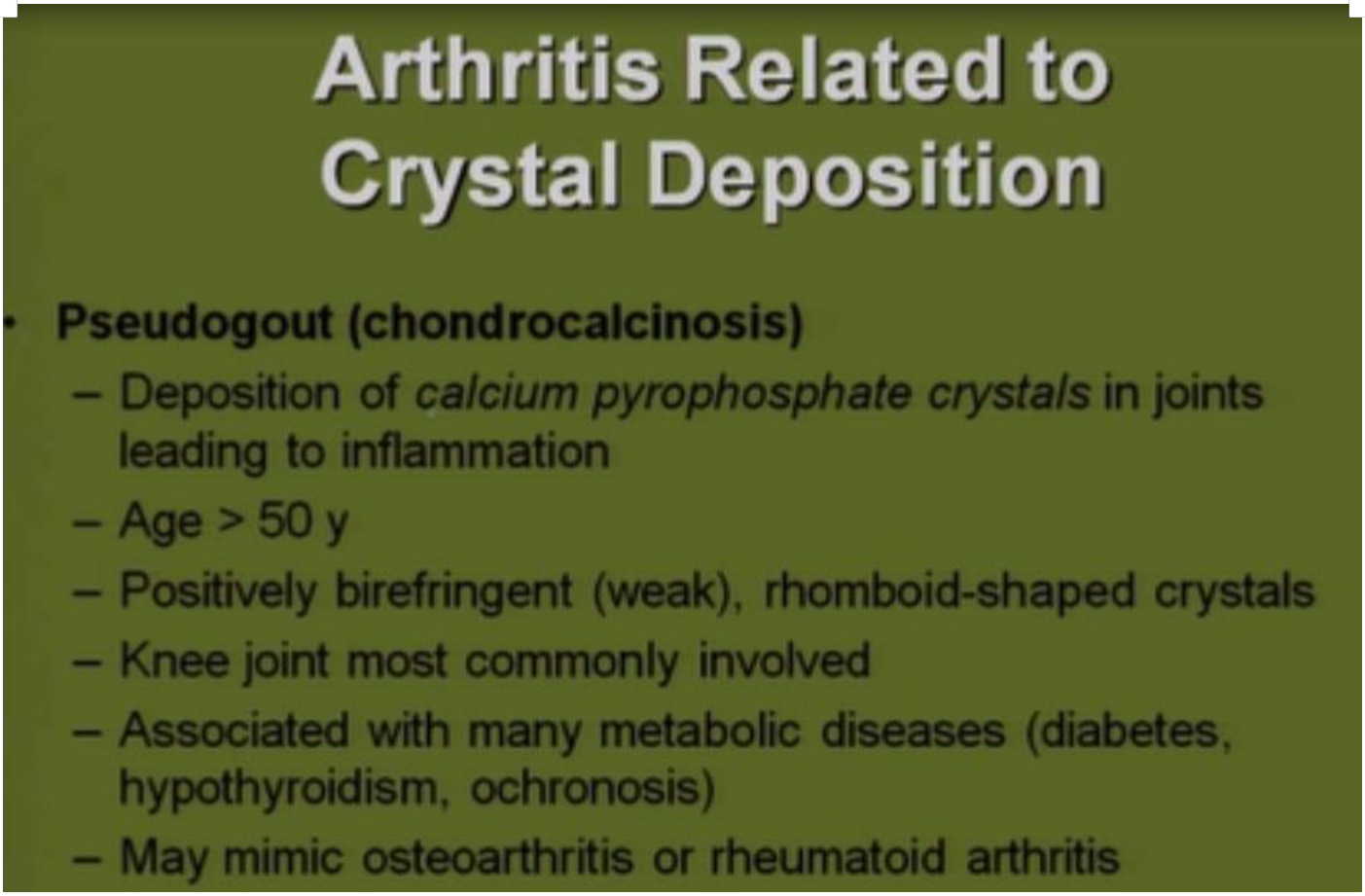
#can evolve into chronic gouty nephropathy, N 20% of individuals with chronic gout die of Renal failure

pyelonephritis can occur, especially when there is urinary obstruction

Pseudogout = chondrocalcinosis

- Is **calcium pyrophosphate** crystal deposition disease.
- Typically first **occurs after the age 50**, becoming more common with ↑ age.
- **No gender or race predilection**. Λ Joint pathology in pseudogout involves the recruitment & activation of inflammatory cells, & is reminiscent of gout
- Joint involvement can last from several days to weeks & may be monoarticular or polyarticular;
- **The most commonly affected joints are the knees,** followed by the wrists, elbows, shoulders, & ankles.

Ultimately, 50% of patients have significant joint damage. No known treatment prevents or retards crystal formation.



رابط اسموسز :

https://www.youtube.com/watch?v=bznoU5bke4U&vl=tr

نوتات باثوما

فلاش كارد :

- Can be easily treated with antibiotics

Gout

8. What causes gout?
   - Caused due to deposition of MSU (mono sodium urate) crystals in joint.
   - Crystals arise due to hyperuricemia (uric acid is nucleotide breakdown product)
     - Occurs either by too much uric acid in blood
     - Or not enough filtration by kidney (more common cause)

9. What are some etiologies of hyperuricemia?

Overproduction	Underexcretion (more common)
Psoriasis (increased skin turnover)	Renal insufficiency
Strenous exercise	Competition for excretion by - Drugs (thiazides, salicylate) - EtOH - Lactic acid - Ketosis - Glycogen storage disease

10. What is presentation of acute gout?
    - Most commonly seen as highly inflammatory monoarticular arthritis in great toe (podegra)
    - Acute inflammation (crystals activate macrophage)

9. What are secondary causes of gout?
   - Lukemia and Myeloproliferative Disorder - lots of cell turnover
   - Lesch-Nyhan syndrome -
     - breakdown product of purine (xanthine and hypoxanthine) can be recycled. Patients who lack hypoxanthine guanine phosphoribosyl transferase (HGPRT) (enzyme that recycles these breakdown products) have high uric acid in blood. Uric acid is end product of purine breakdown.
   - Renal insufficiency

11. Why do alcohol and meat exacerbate acute gout?
    - EtOH compete with uric acid excretion in kidney.
    - Meat has lots of DNA/RNA and the purine metabolism increases uric acid.

12. What is presentation of chronic gout?
    - Tophi - UA crystals in soft tissue and joints
    - Renal failure -
      - UA deposition in tubules
      - See white chalky deposits in kidney tubules with pink fibrosis
    - Lab-
      - Hyperuricemia
      - Needle shaped crystals without birefringence with plane light in synovial fluid

13. What is pseudogout?
    - It resembles gout but it's deposition of calcium pyrophosphate (not MSU)
    - Knee is to pseudogout (some involvement of wrist) as big toe is to gout.
    - Synovial fluid has weak positive birefringence under polarized light

14. What constitutes a positive birefringence?
    - Crystals that are horizontal are yellow (**l**ow crystals are ye**llow**)

15. What lubricating substance is secreted by synovium?
    - Synovial fluid (rich in hyaluronic acid)

A 45-year-old obese man presents to the emergency department with a swollen, tender big toe on his right foot. He denies any trauma to the toe. Further questioning reveals that he had consumed a large amount of alcohol the night before. An aspirate of synovial fluid from the metatarsophalangeal joint of the right big toe demonstrates neutrophils along with needle-shaped, negatively birefringent crystals. You prescribe colchicine to treat his condition.

Gout

Etiology and Epidemiology	Caused by **joint deposition of urate crystals** owing to hyperuricemia *Primary:* Caused by idiopathic hyperuricemia; risk factors include obesity, alcohol use, and genetic susceptibility; most common in middle-aged men *Secondary:* Owing to hyperuricemia caused by myeloproliferative disorders, decreased urate excretion (renal disease), drugs (ie, diuretics), or Lesch-Nyhan syndrome (HGPRT deficiency)
Pathology	*Joint:* Neutrophils and **urate crystals (needle-shaped, negatively birefringent crystals)** in synovial fluid; edematous synovium with inflammatory infiltrate; later, urate deposits can lead to cartilage erosion *Tophi:* Cluster of urate crystals surrounded by fibroblasts, lymphocytes, and giant cells located in cartilage or soft tissues
Clinical Manifestations	**Swollen, tender joint** with sudden onset, often in **MTP joint** of big toe (podagra), ankles, or knees; chronic arthritis may develop; **tophi** on ears, hands, or feet (appear several months after acute arthritis); **urate nephropathy** with interstitial deposit of urate crystals and obstruction by uric acid stones *Lab findings:* **Hyperuricemia,** increased ESR, leukocytosis
Treatment	Colchicine, **NSAIDs** and/or steroids for acute flare; **allopurinol** or probenecid for chronic treatment
Notes	**Pseudogout** is caused by joint deposition of calcium pyrophosphate crystals (weakly positive, birefringent, rhomboid crystals). It is more common in elderly and usually affects large joints (eg, knee).