

# Athletes and Rheumatic Diseases

## Hour 3: Athletes with Inflammatory MSK disease

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- Clinical Research Funding:
  - Amgen
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- Speaker:
  - Novartis



- Case – 22 yo overweight equestrian with numerous minor falls, spontaneous L knee swelling - intermittently with stiffness.
- SH: no tob/etoh/drugs
- FH: no rheumatic conditions, inflammatory bowel, psoriasis
- Labs: normal ESR/CRP, CBC, uric acid, RF, anti-ccp

# Recall: Case 1

“Philip” is a 40 year old local male athlete with the following story:

“In the months leading up to .... 2010 ... I developed pain near my ankle that made it difficult to walk, and my left index finger and right wrist felt as if they were sprained. At first, I thought these aches could be caused by years of practicing... and that they would eventually pass. Then, after two days of preparing ..... I awoke and the pain in my joints was so intense I could hardly get out of bed.”



# Psoriatic Arthritis

- Psoriasis in 3% of population
  - ~20% develop PsA
- M = F (RA is F>M)
- Age of onset is 30-50 yrs
- Unknown etiology of polygenic origin
  - HLA-B27
  - Role of trauma
  - FH: spondyloarthritis
    - Ankylosing spondylitis
    - IBD (crohn's, ulcerative colitis)
    - Reactive arthritis

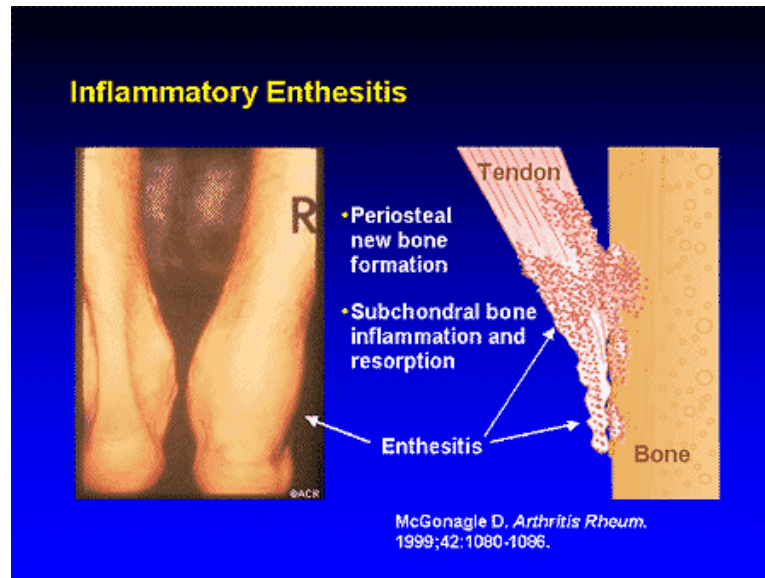
# Psoriasis → PsA

- >70% develop rash prior to arthritis
  - ~15% develop arthritis concomitantly
  - Rare cases of PsA without rash (future?)
- 
- Pearls:
    - “Ray phenomenon”
    - Psoriasis is a risk factor for gout

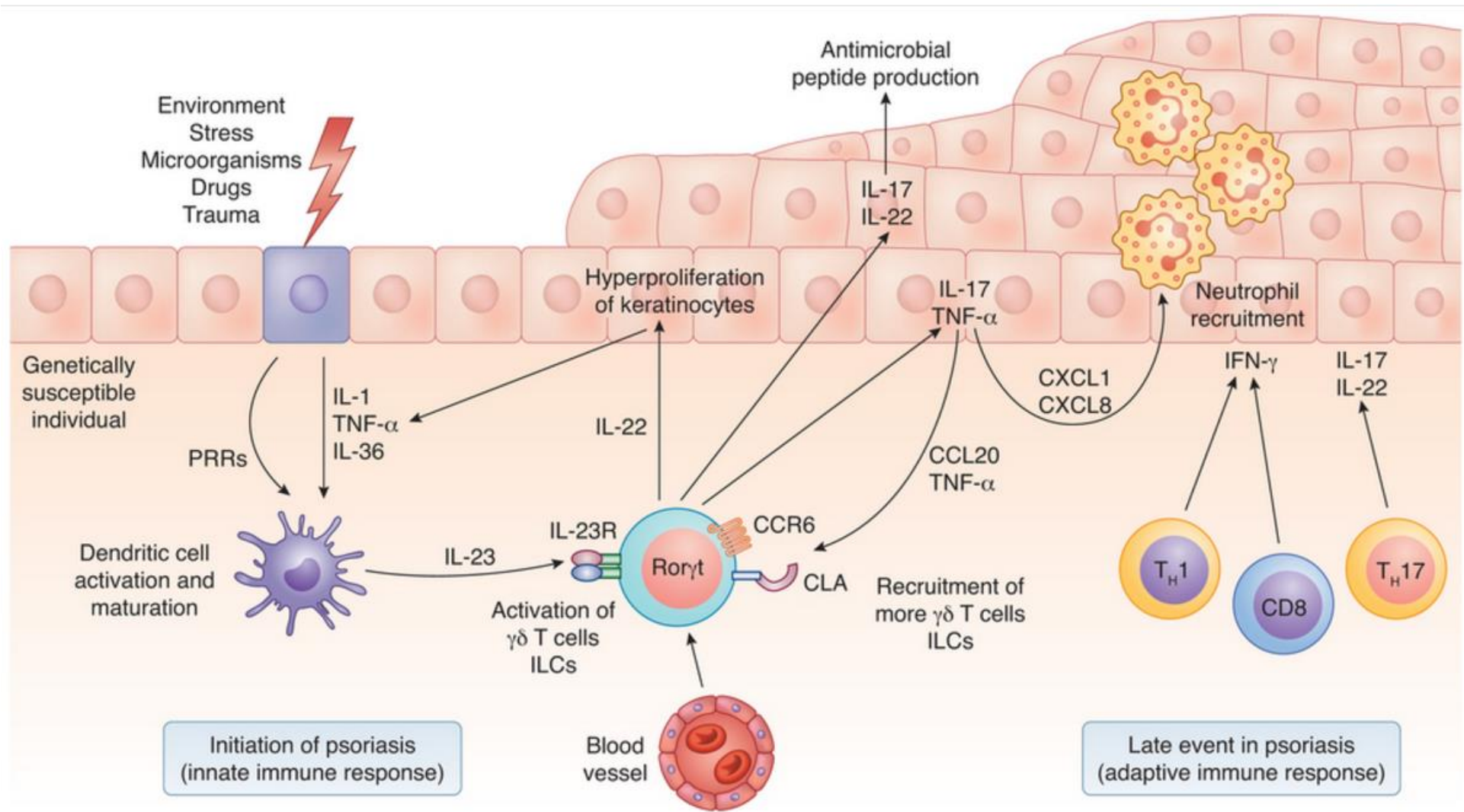


# PsA domains

- Peripheral arthritis
- Dactylitis/Enthesitis
- Axial disease
- Skin domain
  - Nail disease
- Arthritis mutilans

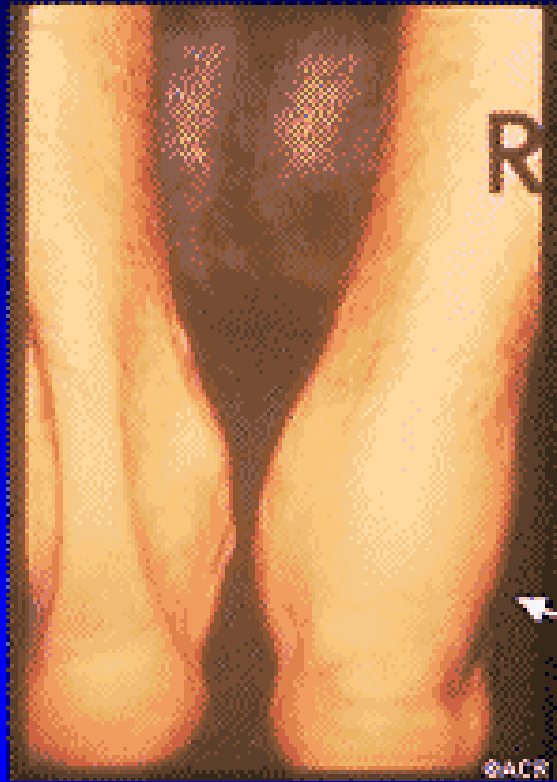


Taylor, W. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. *Arthritis Rheum.* 2006 Aug;54(8):2665-73.





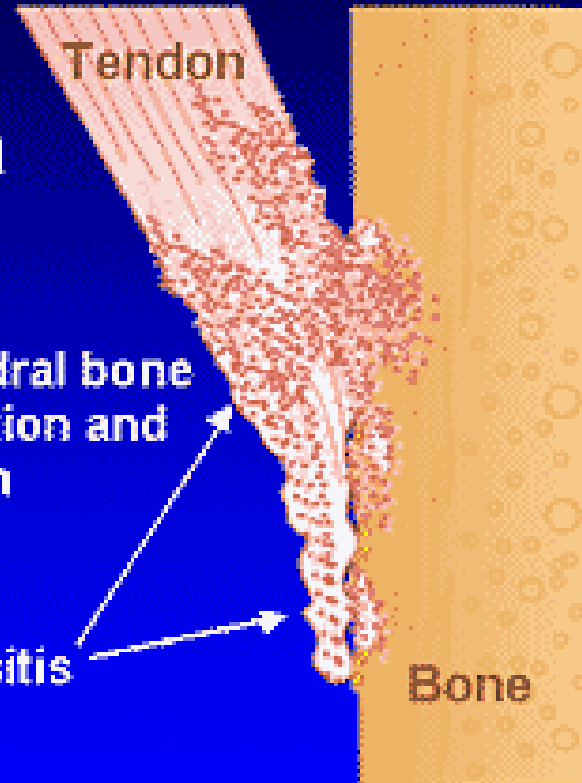
## Inflammatory Enthesitis



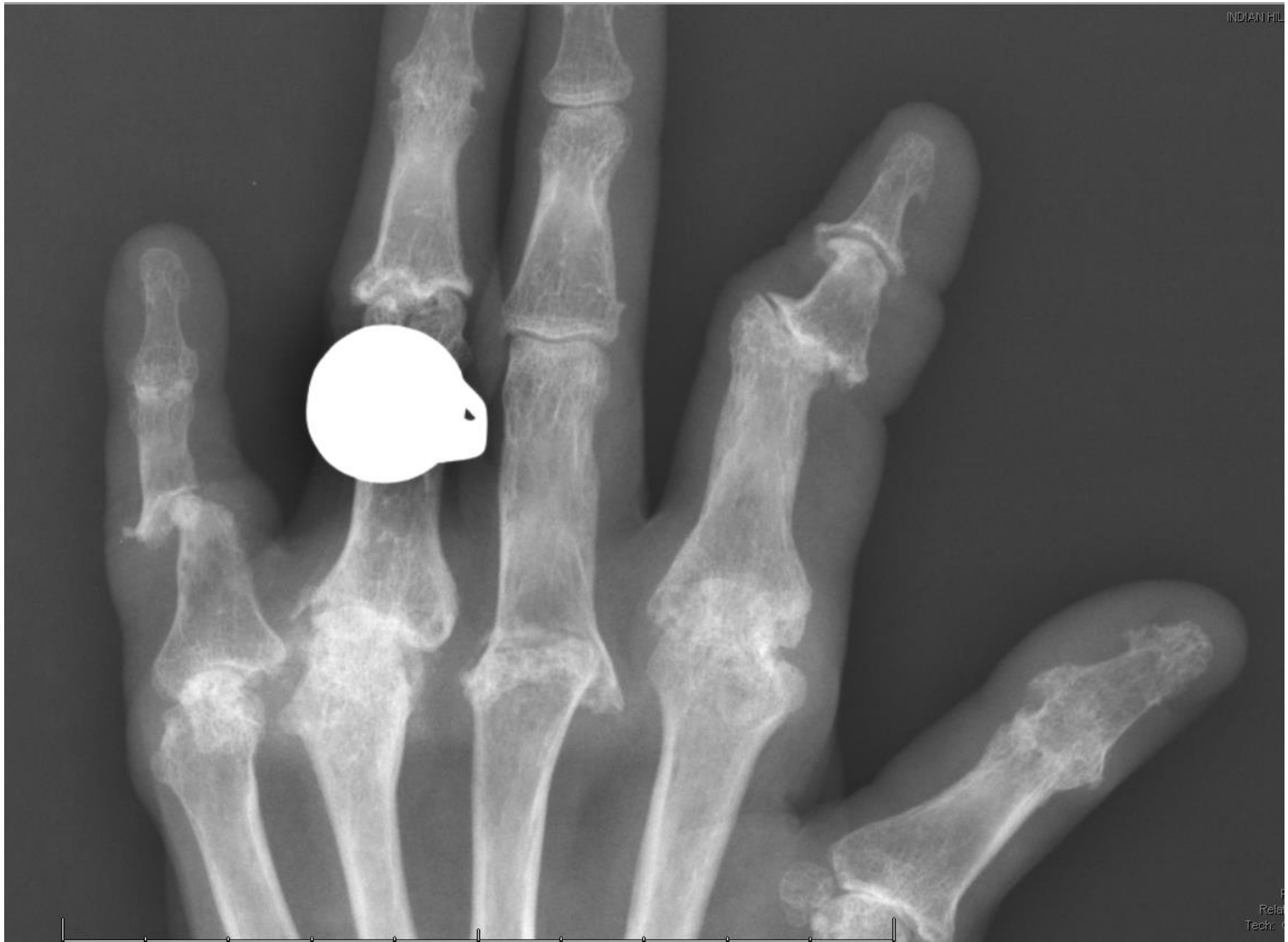
- Periosteal new bone formation

- Subchondral bone inflammation and resorption

Enthesitis



McGonagle D. *Arthritis Rheum.* 1999;42:1060-1066.



# Psoriatic Arthritis Treatment

- NSAIDs
- Steroids (topical, IA)
- DMARDS
  - Leflunomide
  - Sulfasalazine
  - Methotrexate
- Others:
  - Ustekinumab/Stelara (IL12/23)
  - Apremilast/Otezla (PDE4 – not PDE5!)
  - Secukinumab/Cosentyx (IL17)
  - Ixekizumab/Taltz (IL17)
  - Tofacitinib/Xeljanz (JAKi)
  - Upadacitinib/Rinvoq (JAKi)
  - Abatacept/Orencia (T cell costim)
  - Guselkumab/Tremfya (IL 23)
  - Risankizumab/Skyrizi (IL 23)
- Tumor necrosis factor inhibitors
  - Etanercept/Enbrel
  - Infliximab/Remicade
  - Adalimumab/Humira
  - Certolizumab/Cimzia
  - Golimumab/Simponi
  - Biosimilars....

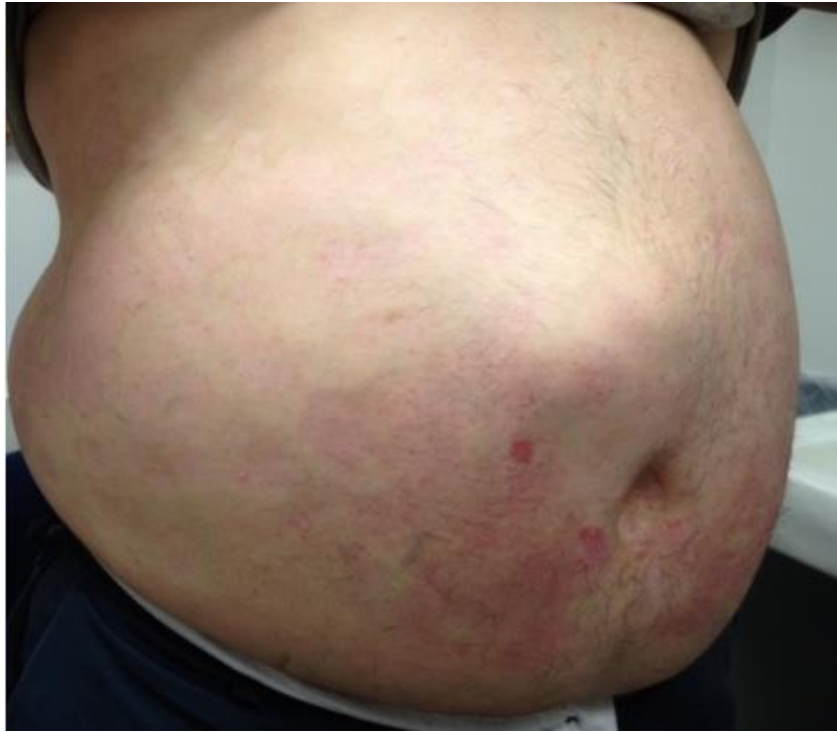






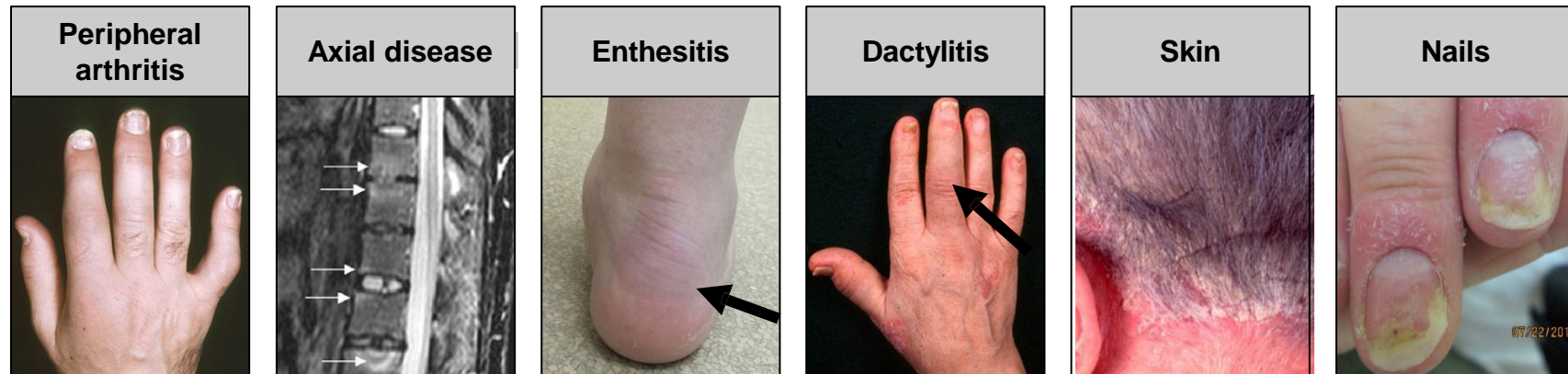






# Psoriatic arthritis key points

- A multi-domain condition that can mimic athletic injuries in young patients
- Recognition and refer
- Newer therapies depending on domains
  - Traditional dmards
  - Biologics



## Case – no athlete this time!

- 75 yo man with 10 yrs of intermittent joint swelling in toes, ankles, knees, wrist of late
- PMH: Heart failure – uses lasix QID
- 249 lbs, loves SPAM

Component <i>Latest Ref Rng</i>	1/17/2009
CREAT <i>0.7 - 1.3 MG/DL</i>	1.5 (H)
GFR <i>mL/min</i>	49-NB
URIC <i>3.4 - 7.2 mg/dL</i>	13.2 (H)



This record setting running back was told he had abnormal blood test results in his early 30's while asymptomatic but later developed swollen toes at approximately age 42 and has battled this condition since then:

Recall: Case 2

Calcium pyrophosphate deposition (CPPD)

Gout

Turf toe

Dactylitis

Hydroxyapatite crystal arthritis

### **Emmitt Smith Gains Ground on Gout**

**The football Hall of Famer and Super Bowl champ talks about living with the painful arthritic condition.**

Everyday Health—May 29, 2013



# Key Learning Objectives

- Diagnosis, epidemiology
- Pathogenesis, crystal analysis
- Acute treatments
- Chronic therapies



# General Principles

- Initially: Acute arthritis
  - Inflammatory response: monosodium urate (MSU) crystals
- Most common form of inflammatory arthritis in men
- Urate: end product of purine metabolism
- Blood level of urate > physiologic limit of solubility (**6.8mg/dl**):  
Tissue crystallization

\* Terkeltaub RA. N Eng J Med 2003; 349:1647-1655

## Signs & Symptoms

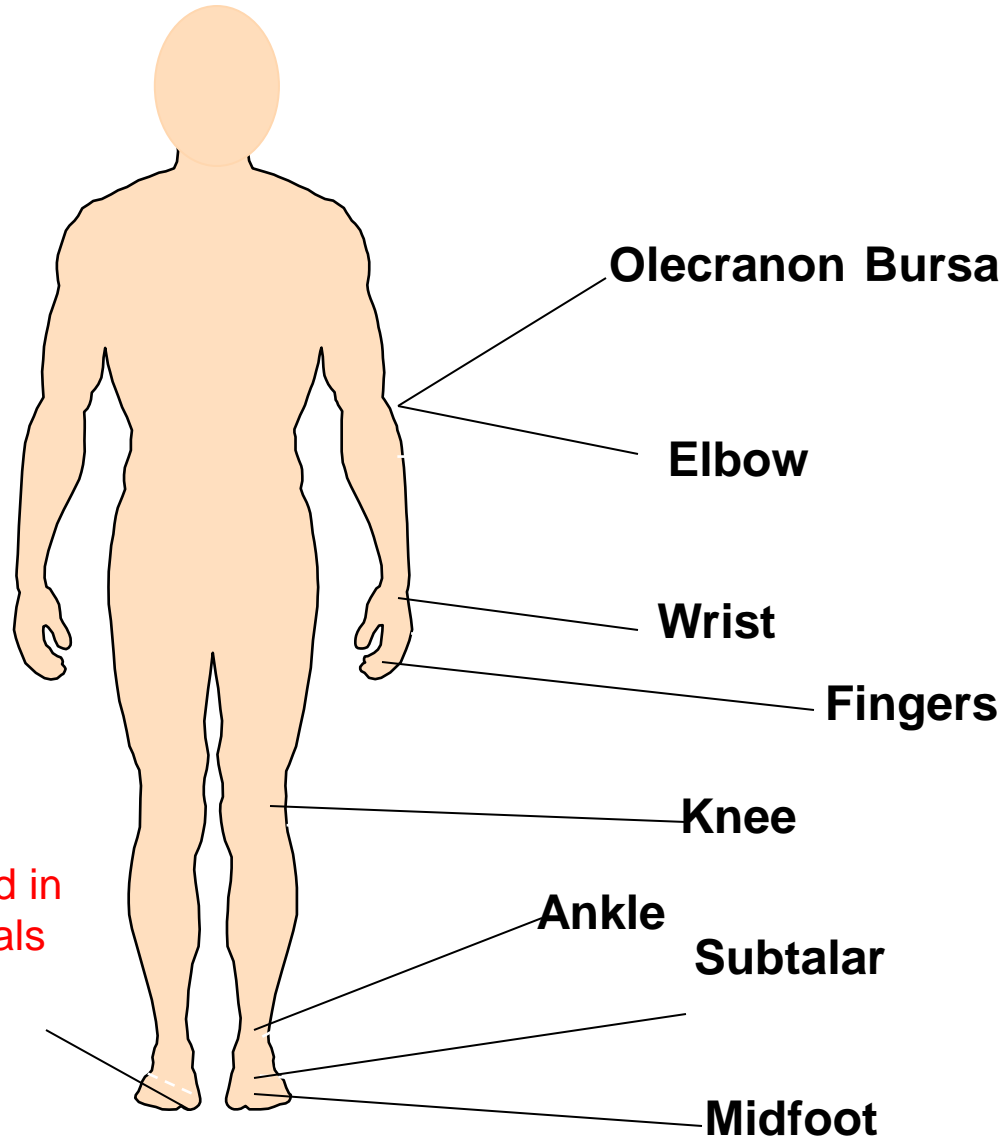
- acute monoarticular; distal lower extremities (50%)
- pain and tenderness, swelling, warmth and erythema; occasionally fevers
- frequently nocturnal
- attack may subside in 3-10 days without treatment

# Common Sites of Acute Attacks



**Gout can occur  
in bursae, tendons,  
and joints**

**1st MTP**  
(eventually affected in  
~ 90% of individuals  
with gout)



# Diagnosis of Gout

- “Gold Standard” – demonstration of MSU crystals in PMNs in synovial fluid
- Classical history of attack(s) in typically involved joint with or without elevated serum uric acid
- Serum uric acid will be elevated at some point in time:
  - May be **normal or low** at time of attack
  - Retest several weeks after attack

# Differential Diagnosis of Gout

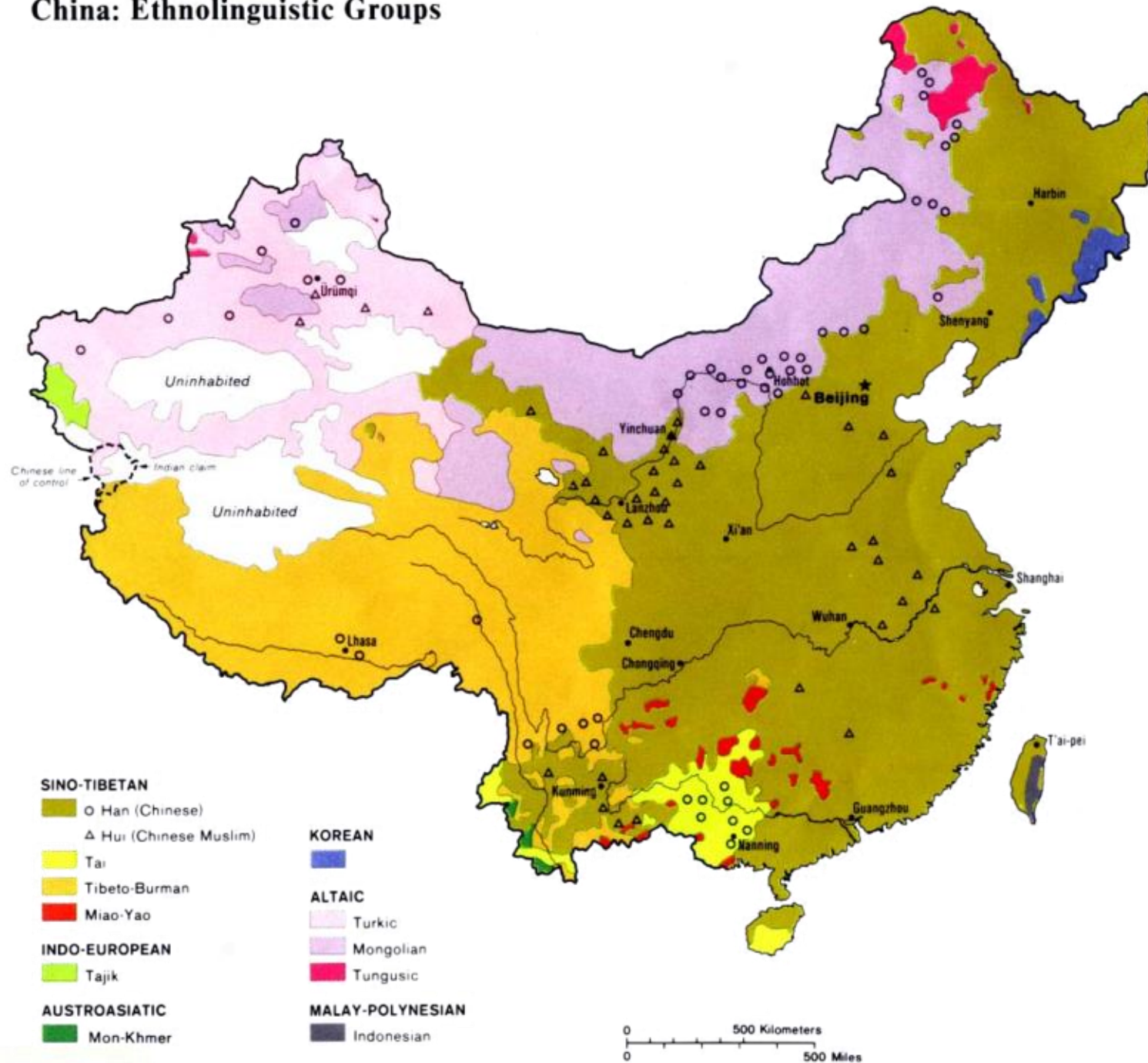
- Exclusion of other possible diagnoses:
  - Septic joint (risk factors)
  - Reactive arthritis (antecedent infection – GU/GI)
  - Spondyloarthritis – young men, psoriasis
  - Trauma, hemarthrosis
  - Pseudogout (CPPD, older athletes)
  - Hyperuricemia unrelated to diagnosis (RA, PsA, OA)



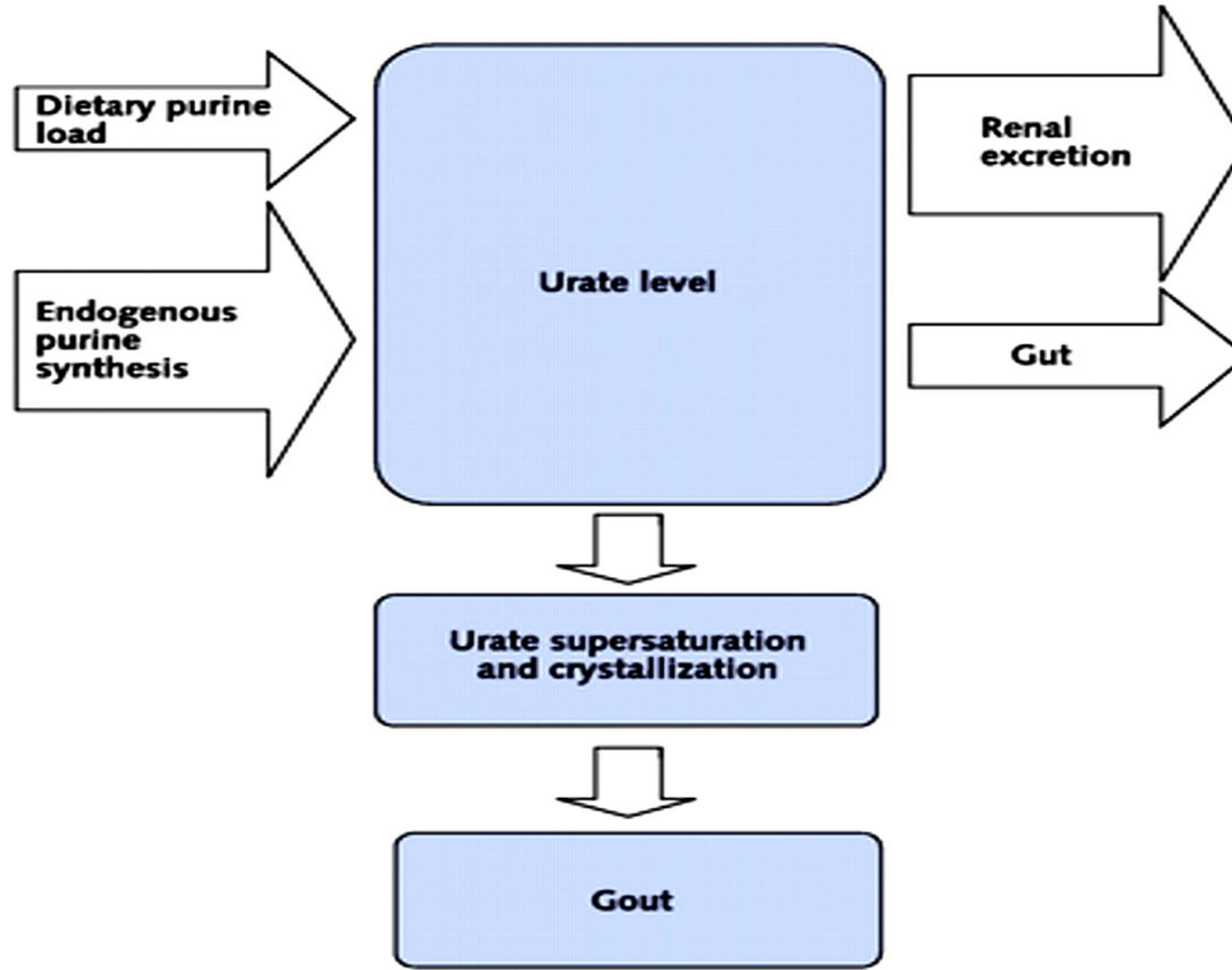
# Evaluation

- Clinical
  - Family history
  - Personal history
  - Medications, diuretic use
  - Diet, alcohol
  - Metabolic Syndrome
- Examination
  - Evaluate all joints
    - tophi
    - bursae, tendons
    - ears
- Radiographic
  - Xrays
  - US; others.....
- Laboratory
  - CBC
  - ESR and/or CRP
  - Chemistry (LFT, Renal, uric acid)
  - TSH
  - HLA-B58 (Han Chinese, Korean)

# China: Ethnolinguistic Groups



# Overview of the Pathogenesis of Gout



# Precipitating Factors

- Trauma/Surgery
- Low dose aspirin
- Diuretics-other medications
- Systemic illness

# Risk Factors for the Development of Gout: Age and Gender

- Men
  - Higher serum urate levels (men > 7.0mg/dl, women >6.0mg/dl)
  - In younger patients, gout overwhelmingly in men
- Women
  - Increased risk after menopause
    - ↓ estrogen → ↓ renal excretion of uric acid

Abbott et al. *J Clin Epidemiol.* 1988;41:237.

Arromdee et al. *J Rheumatol.* 2002;29:2403.

Rott et al. *JAMA.* 2003;289:2857.

# Causes of Hyperuricemia

- **>90% *Under-excretors*:**
  - Reduced proximal tubular excretion of uric acid; genetics
  - Medication induced renal urate clearance impairment
  - Renal insufficiency
- **<10% Over-producers: de novo increased purine biosynthetic rate**
  - Myeloproliferative syndromes
  - Psoriasis
  - Tumor Lysis Syndrome
  - Genetic Disorders
    - Deficient hypoxanthine-guanine phosphoribosyl transferase

# Medications Affecting Urate Excretion

- Thiazides and loop diuretics
- Low dose aspirin
- Cyclosporin A
- Anti-tuberculous medications:
  - pyrazinamide
  - ethambutol
- Niacin

\* Gonzalez EB, Miller ST, Agudelo CA Drugs Aging 1994;4:128-134



# Risk Factors for Development of Gout: Diet

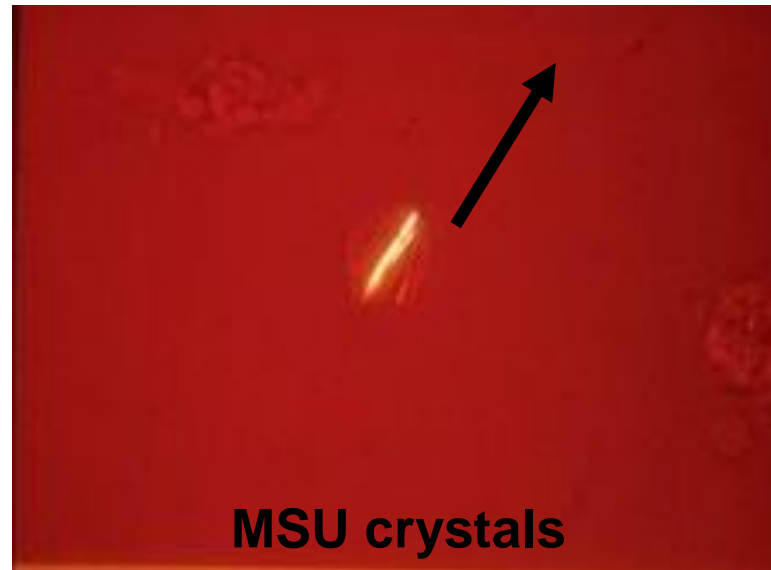
- “Low purine diet” results in modest -1 mg - reduction in serum uric acid
- Risk from alcohol intake: Beer>liquor>wine



- High meat consumption
- High seafood consumption
- High dairy consumption
- High purine-rich vegetables

↑ risk of gout  
↑ risk of gout  
↓ risk of gout  
no association

# Crystals



- CPPD crystals are weakly positively birefringent, rhomboid, rods, squares, or irregular under compensated polarized light

1. <http://www.emedicine.com/med/topic1938.htm>.

2. ACR Clinical Slide Collection on the Rheumatic Diseases, 1998

# Treatment Options for Acute Attack

- Nonsteroidal anti-inflammatory drugs
- Colchicine
- Corticosteroids
  - Intra-articular
  - Intramuscular, PO
- Interleukin – 1 antagonists?
  - Anakinra
  - Canakinumab
  - Riloncept

# Protection Against Further Attacks - Prophylaxis

## Dosing

### Colchicine

0.6-1.8 mg daily

Dose adjusted for renal insufficiency

### NSAIDS

Any NSAID at the lowest effective dose

## Complications of chronic use

Neuromyopathy, rhabdomyolysis

Gastrointestinal

Drug interactions with cyclosporine, statins, macrolides

NSAID gastropathy

Renal dysfunction

Cardiovascular; thrombotic

# Treatment of Chronic Gout and Hyperuricemia

As we discussed there are many strategies for treating gout:

- 1. Flush your kidneys routinely - drink enough water to stay hydrated
- 2. reduce salt in your diet (to help protect your kidneys) and may help you need less water pills
- 3. Reduce your portions and calories to achieve a healthier weight
- 4. Eat any vegetable you want
- 5. Reduce red meat and seafood and animal protein; beer and liquor
- 6. Fruits are ok, but sugary foods make gout worse
- 7. Take a vitamin C supplement - it helps gout
- 8. increase low or nonfat dairy
  
- 9. Use colchicine once - or twice daily if tolerated - avoid grapefruits and grapefruit juice while on colchicine
- 10. We will slowly add low doses of allopurinol - you may experience a flare of gout but don't stop this
- 11. Periodically we will measure your uric acid and adjust your medicines.

- Our patient:
  - Lasix 20 QD
  - Low salt
  - Allopurinol 100 mg qd

Component <i>Latest Ref Rng</i>	1/17/2009	3/13/2009	5/22/2009
CREAT <i>0.7 - 1.3 MG/DL</i>	1.5 (H)	1.3	1.0
GFR <i>mL/min</i>	49-NB	58-NB	78-NB
URIC <i>3.4 - 7.2 mg/dL</i>	13.2 (H)	8.5 (H)	6.0

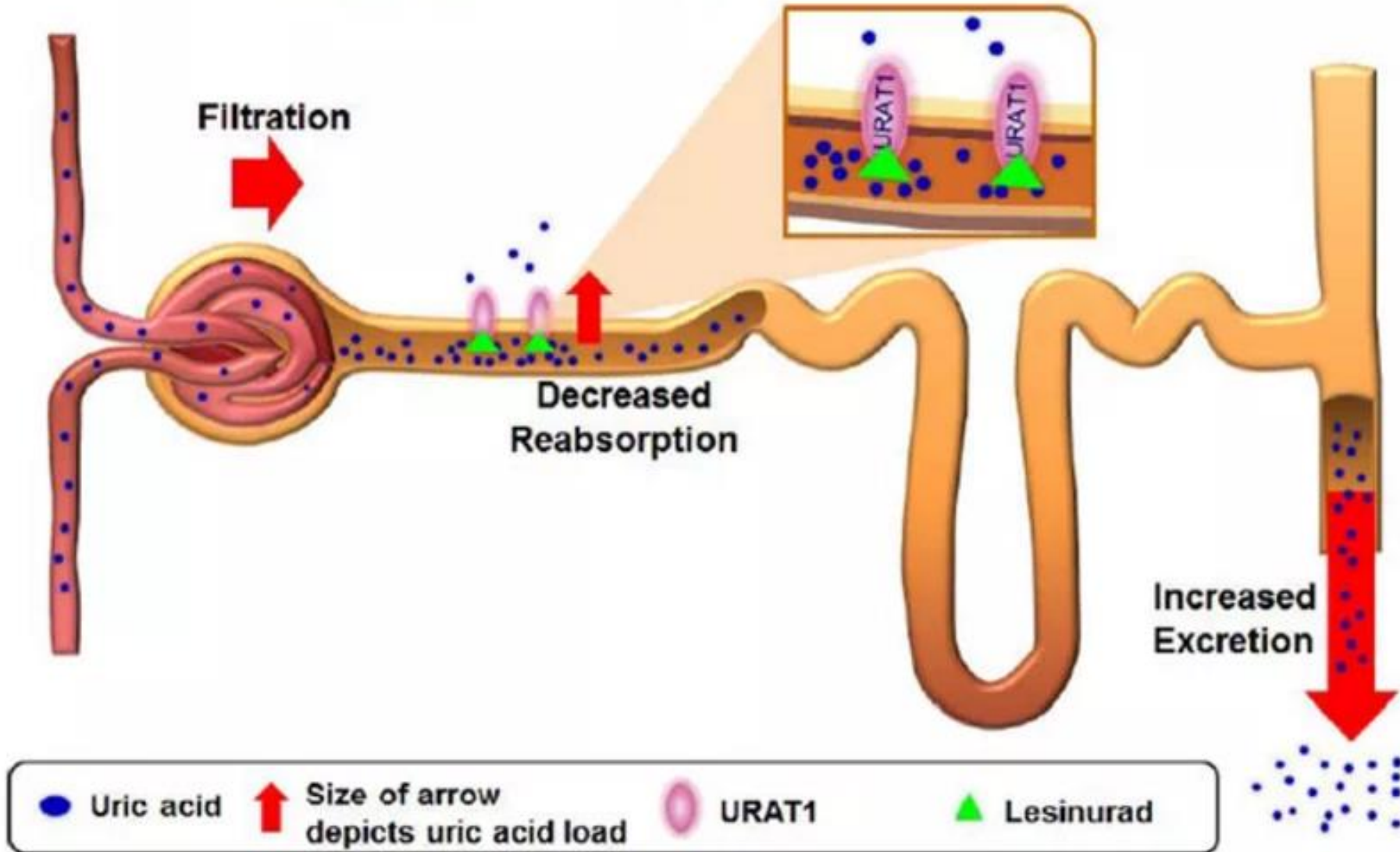


# Urate Lowering Treatments

- Urostatic agents
  - Xanthine oxidase inhibitors
    - **Allopurinol**
    - **Febuxostat/Uloric (2009)**
- Enzymatic-pegloticase
  - Krystexxa (2011)
- Uricosuric Agents
  - Probenecid
  - Losartan
  - Fenofibrate
- Lesinurad (URAT1 inhibitor)
  - Removed from market 2019

# Renal excretion of uric acid

Schematic of Lesinurad's Mechanism of Action



# Treatment of Chronic Gout

Allopurinol: Uricosstatic drug of choice

- Blocks the conversion of hypoxanthine to xanthine to uric acid
- Commonly under-dosed, started too high (my usual is 50-100 mg QD)
- Measure serum uric acid every 3 to 6 months; titrate slowly
- Goal: Serum urate below 6mg/dL; 5mg/dL if tophi
- Monitor for toxicity





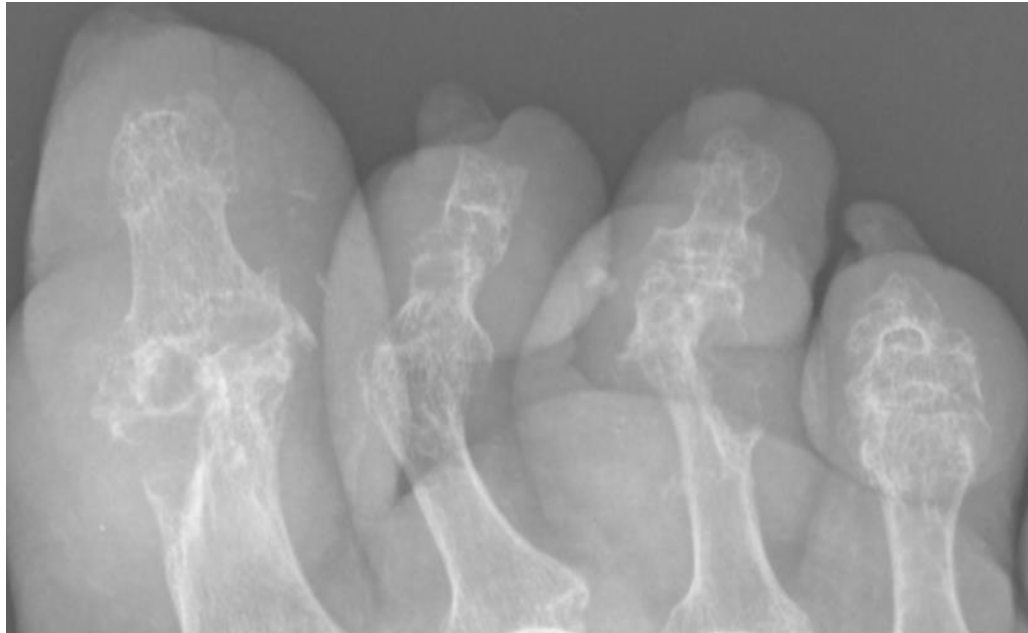


Advanced Chronic Gout:  
Clinically Apparent Tophi



# Advanced Gout: Late Radiographic Changes

- destructive and hypertrophic; “overhanging edges”
- joint space is often preserved until late in disease process

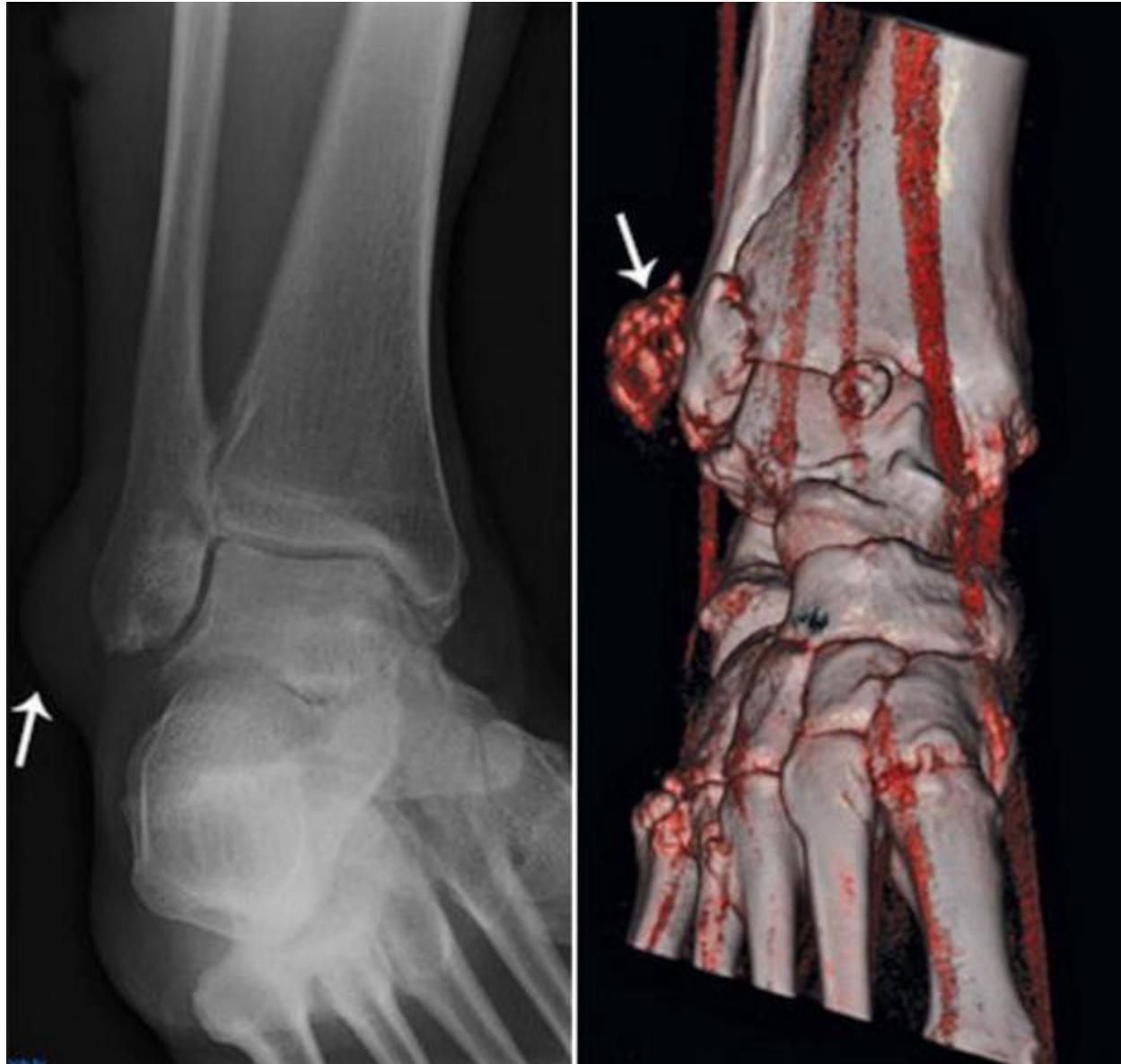


Earlier diagnosis?





# Dual Energy CT (DECT)



# Elderly Onset Gout (EOG)

- subacute/chronic polyarticular hand involvement
- localization of tophi on heberden nodes
- increased female:male ratio
- association with drugs
  - decrease renal urate excretion (diuretics and low-dose aspirin)



Component	URIC
Latest Ref Rng & Units	2.7 - 6.6 mg/dL
11/19/2010	8.1 (H)
5/24/2019	8.6 (H)
10/28/2021	8.3 (H)



# Gout: In Summary:

- Traditional and newer RFs for gout; 5% prevalence
  - Chronic disease (CKD), aging population, obesity, medications
- Pathogenesis of gout – SUA metabolism; systemic disease
- LOW DOSE ALLOPURINOL
- GRADUAL TITRATION
- Treat to target
- Newer therapies

