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Crystalline Arthritis

Seetha Monrad M.D.

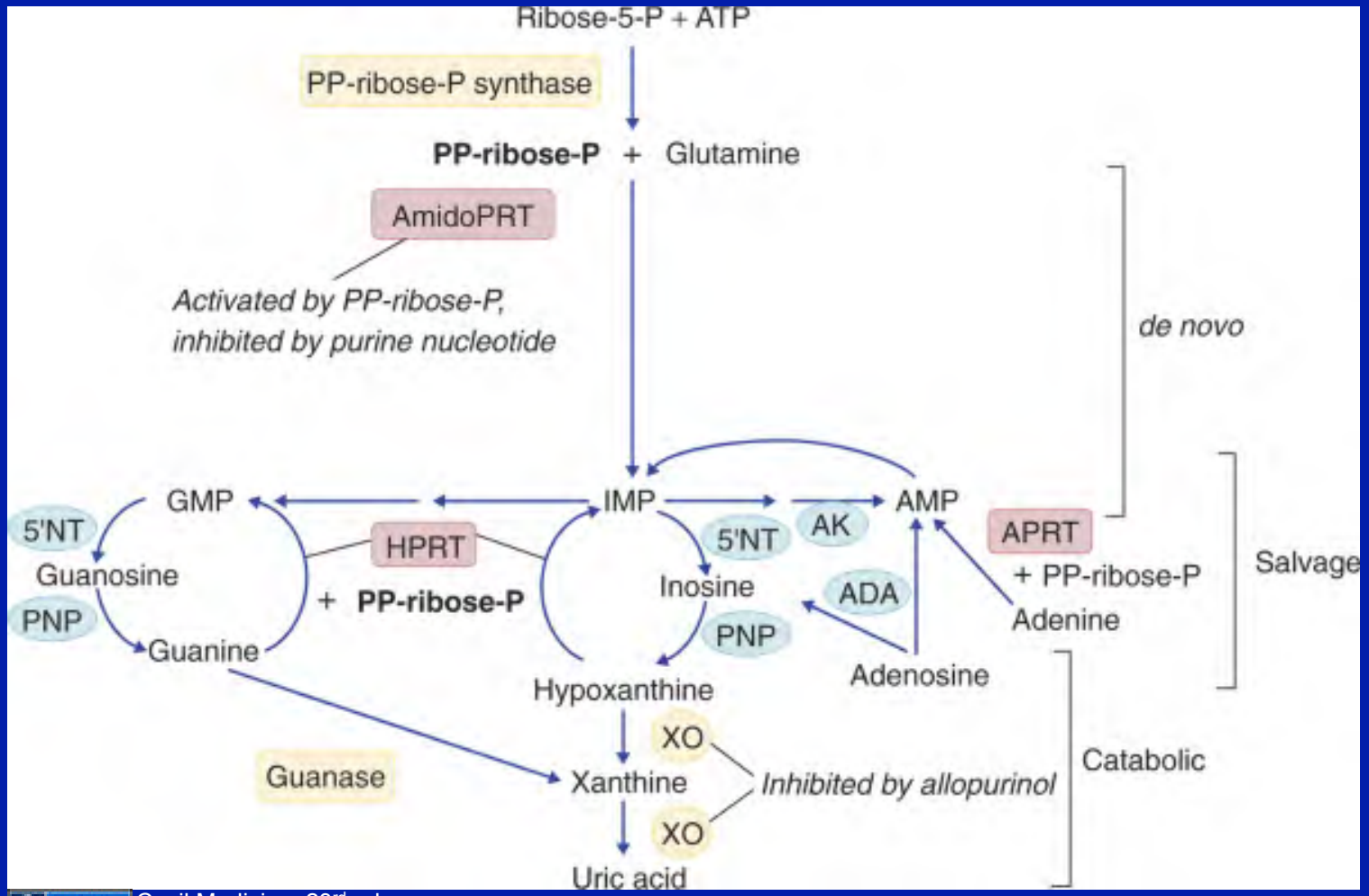
Fall 2009

University of Michigan
Medical School

What is gout?

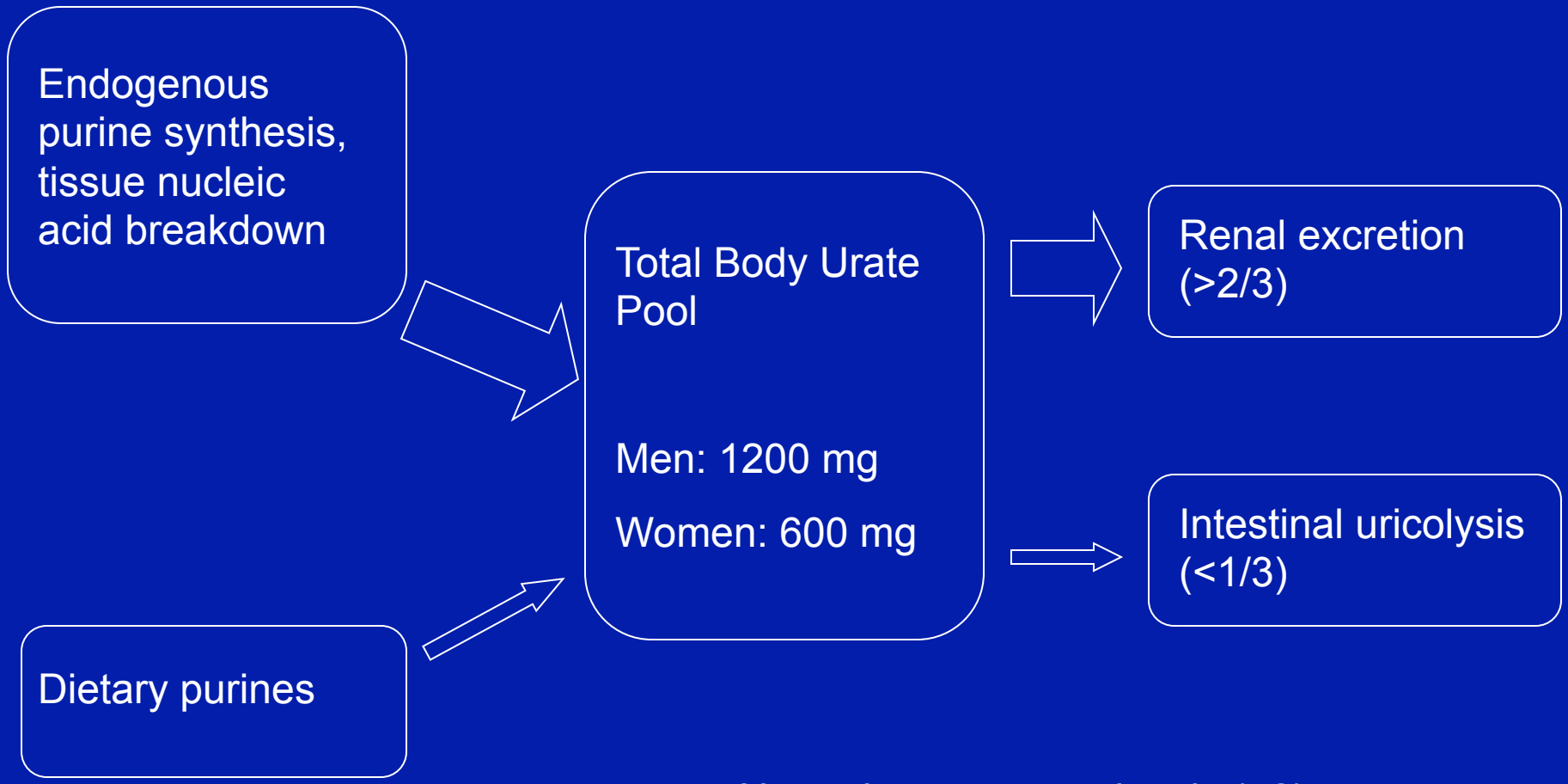
- Disease state arising from the deposition of monosodium urate crystals in assorted tissues, with accompanying inflammatory and/or degenerative consequences
  - In joints -> inflammatory arthritis
  - In soft tissue -> tophi
  - In kidneys -> nephrolithiasis, nephropathy
- Most common inflammatory arthritis in men >40

Purine metabolism



Cecil Medicine, 23rd ed.

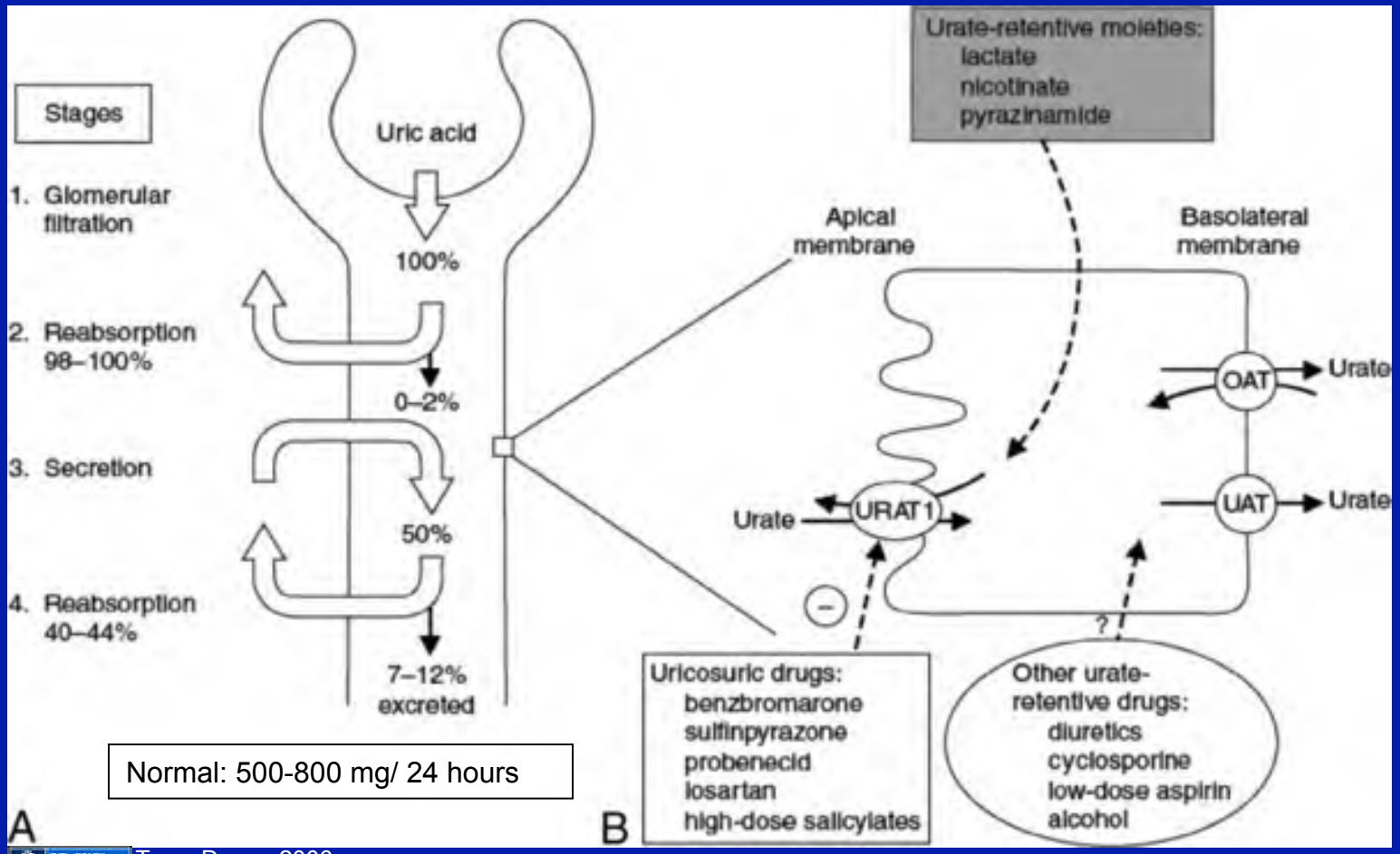
Normal uric acid metabolism



Normal serum urate levels (±2)

Men: 5.0 mg/dL, Women: 4.0 mg/dL

Renal handling of uric acid



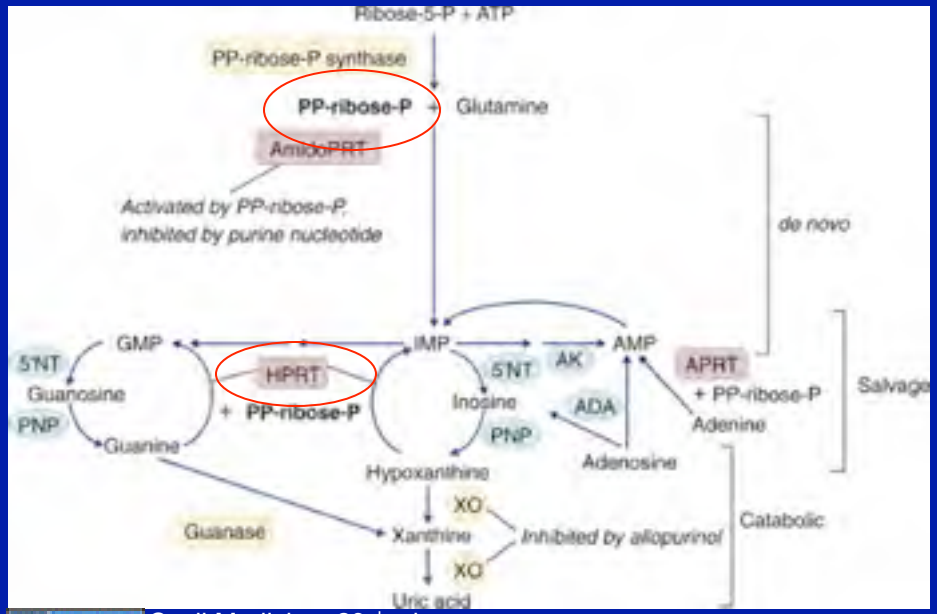
Teng, Drugs, 2006

Hyperuricemia

- Serum uric acid >6.8 mg/dL
- Caused by uric acid overproduction and/or underexcretion
- Total body urate pool >2000 mg -> becomes insoluble
  - Non-tophaceous gout: 2-4 g
  - Tophaceous gout: 10-1000 g

Uric acid overproduction

- 10% of cases
- 24 hour urinalysis >1000 mg/d
- Causes
  - Genetic
    - Glucose-6-phosphatase deficiency (glycogen storage disease type I)
    - Hypoxanthine guanine phosphoribosyltransferase deficiency (HGPRT)
    - PRPP-synthetase superactivity



Cecil Medicine, 23rd ed.

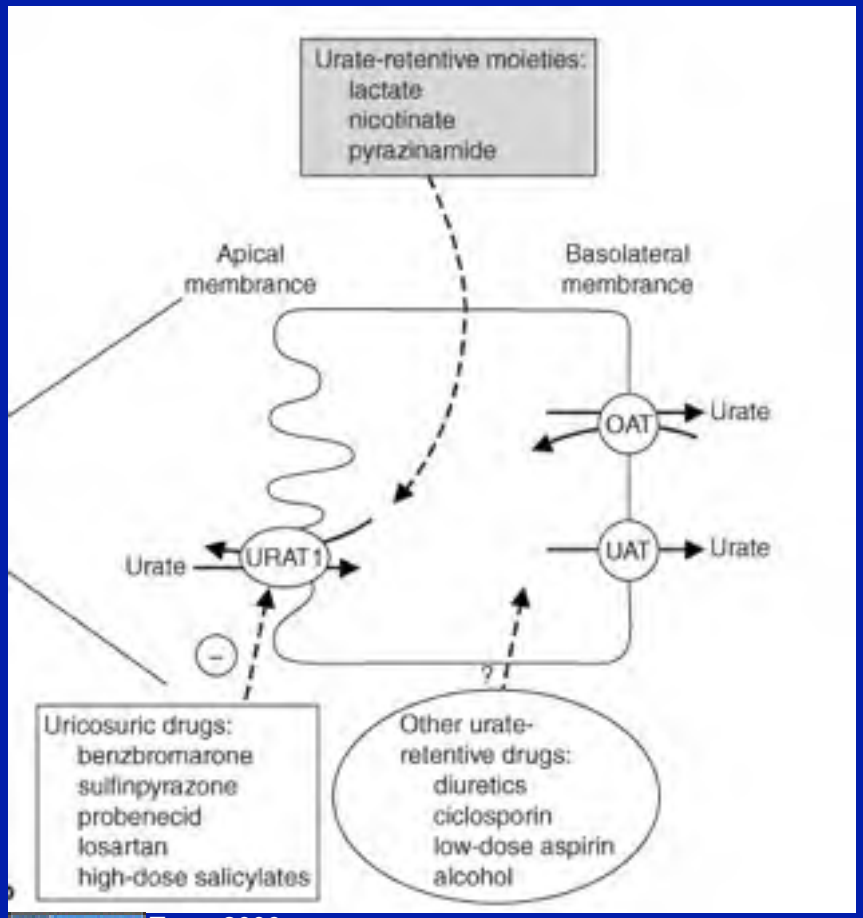
Uric acid overproduction

- Causes (con't)
  - Excessive purine intake
  - Ethanol
  - Drugs: nicotinic acid, warfarin, chemotherapy (tumor lysis)
  - Obesity
  - Malignancies (myeloproliferative, lymphoproliferative)
  - Psoriasis
  - Hemolytic anemia
  - Tissue destruction (hypoxia, ischemia, trauma)

Uric acid underexcretion

- 90% of cases
- <500 mg/d excretion
- Causes
  - Genetic (polycystic kidney disease, etc.)
  - Decreased GFR
  - Organic acidosis
  - Lead nephropathy
  - Drugs

Drugs



Teng, 2006

- Cyclosporin
  - Reduced GFR
  - Reduces urate secretion
- Aspirin
  - Low dose (eg. 81 mg): inhibits urate secretion
  - High dose (>3g): decreases tubular reabsorption
- Diuretics
  - Volume depletion -> increased reabsorption
  - Thiazides interfere with secretion

Ethanol

- Overproduction
  - High purines (especially beer)
  - Produces excess AMP -> metabolized into uric acid
- Underexcretion
  - Dehydration
  - Organic acids -> overwhelm urate transporter

Hyperuricemia is NOT Gout

- Hyperuricemia present in 5-10% of adult men
- 80% of hyperuricemic patients do not develop gout

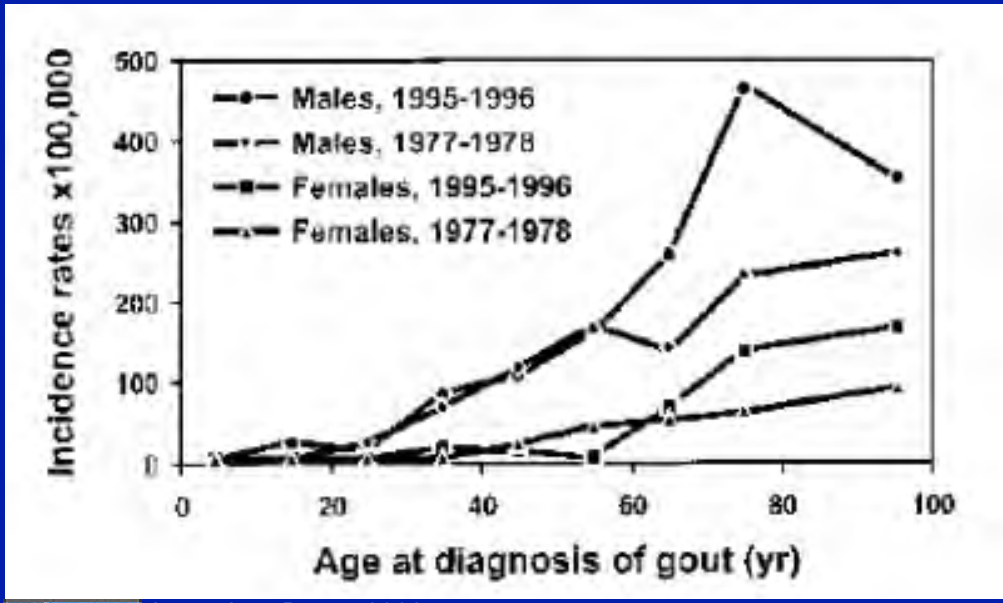
Is hyperuricemia bad?

- Hyperuricemia is associated with hypertension, renal disease, metabolic syndrome, cardiovascular disease
- Studies are beginning to suggest that uric acid is an independent risk factor for these conditions and may be involved in their pathogenesis
  - An elevated uric acid level consistently predicts the development of hypertension.
  - An elevated uric acid level is observed in 25–60% of patients with untreated essential hypertension and in nearly 90% of adolescents with essential hypertension of recent onset.
  - Raising the uric acid level in rodents results in hypertension with the clinical, hemodynamic, and histologic characteristics of hypertension.
  - Reducing the uric acid level with xanthine oxidase inhibitors lowers blood pressure in adolescents with hypertension of recent onset
- However, currently not sufficient evidence to support treatment of asymptomatic hyperuricemia

Feig et al, *NEJM*, 2008

Epidemiology of gout

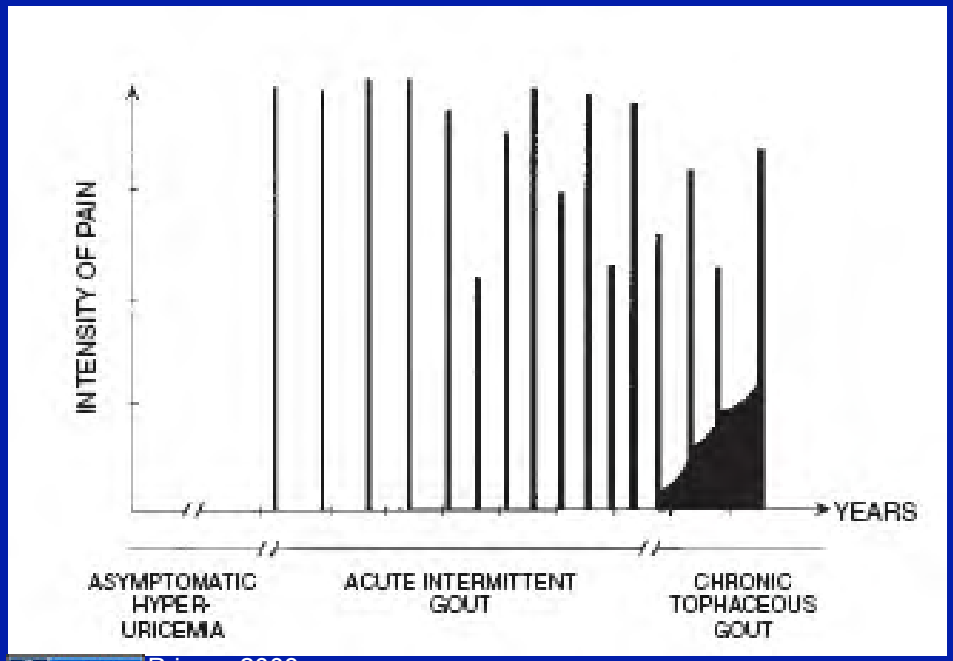
- Most common inflammatory arthritis in men>40
- Total prevalence ~3%; 6-9% if >80
- U.S. incidence may be rising (>2 fold)



PD-INEL Arromdee, *Drugs*, 2002

3 phases of gout

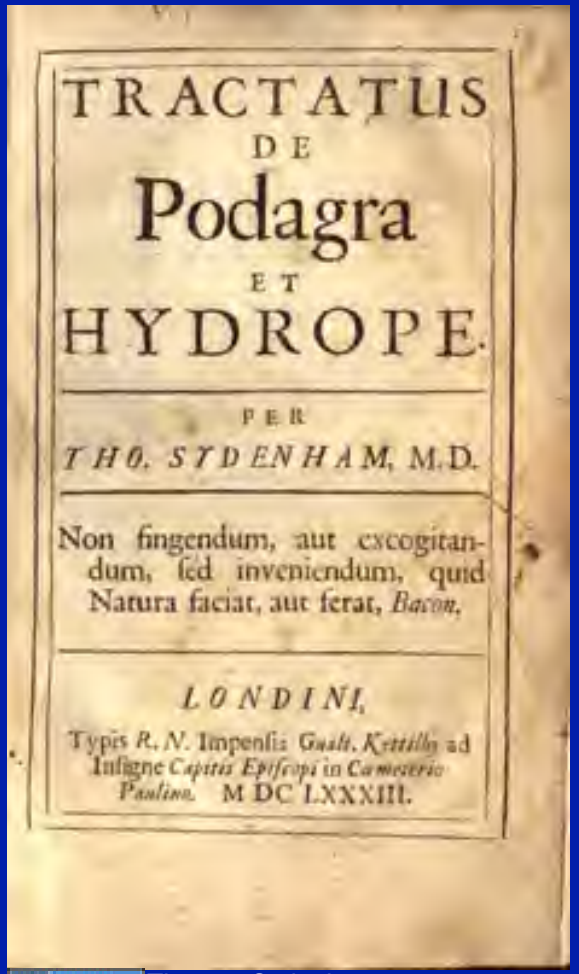
- Asymptomatic hyperuricemia
- Acute gout flares
- Chronic (tophaceous) gout



Primer, 2008

Acute gout

"The victim goes to bed and sleeps in good health. About 2 o'clock in the morning, he is awakened by a severe pain in the great toe; more rarely in the heel, ankle or instep. This pain is like that of a dislocation, and yet the parts feel as if cold water were poured over them. Then follows chills and shiver and a little fever. The pain which at first moderate becomes more intense. With its intensity the chills and shivers increase. After a time this comes to a full height, accommodating itself to the bones and ligaments of the tarsus and metatarsus. Now it is a violent stretching and tearing of the ligaments-- now it is a gnawing pain and now a pressure and tightening. So exquisite and lively meanwhile is the feeling of the part affected, that it cannot bear the weight of bedclothes nor the jar of a person walking in the room."


TRACTATUS
DE
Podagra
ET
HYDROPE.

PER
THO. SYDENHAM, M.D.

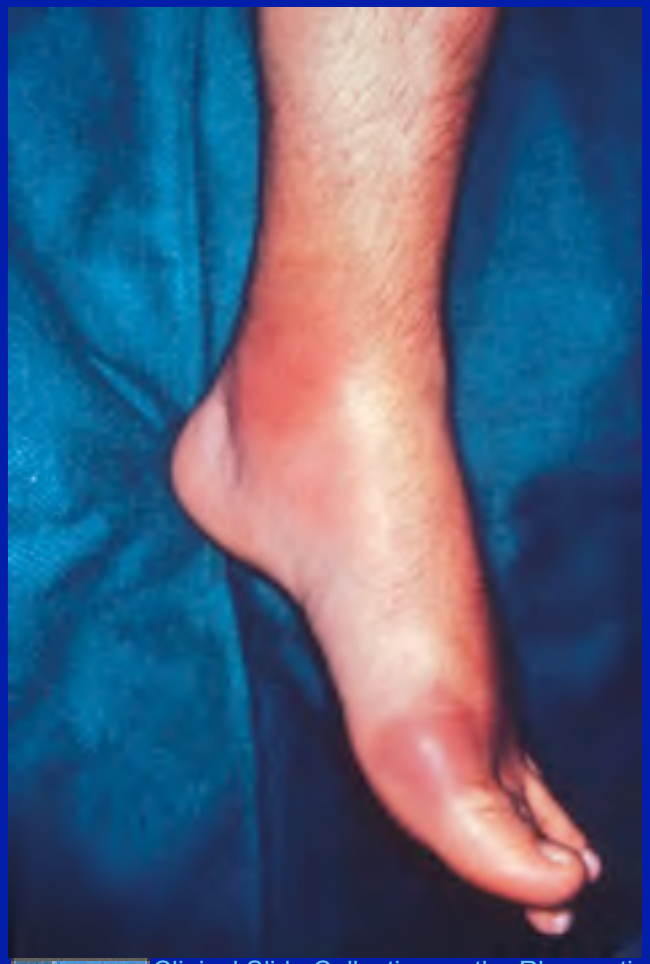
Non fingendum, aut excogitandum, sed inveniendum, quid Natura faciat, aut ferat, *Bacon.*

LONDINI,
Typis R. N. Impensis Guilt. Kettilby ad Insigne Capitis Episcopi in Cœmeterio Paulino. M DC LXXXIII.

PD-EXP Thomas Sydenham

 The Gout by James Gillray, Crankyprofessor.com

Acute gout



Clinical Slide Collection on the Rheumatic Diseases, American college of Rheumatology, 1972-2004

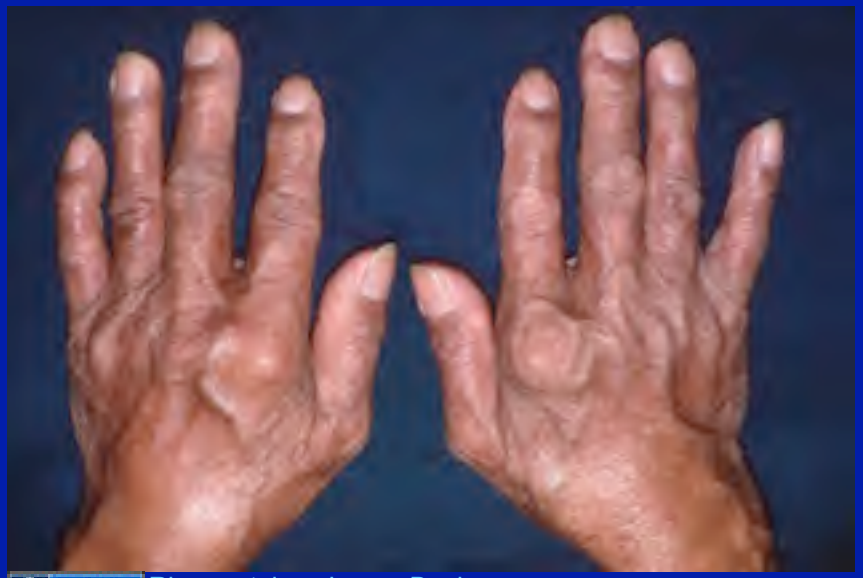
- 4th-6th decade (men); later in women
- Sudden onset, rapid escalation
- 1st MTP (podagra)
  - 50% have as first attack
  - 90% will have eventually
- Other lower extremity joints
- Systemic symptoms
- Extraarticular (bursitis, tenosynovitis)
- Triggered by: trauma, surgery, sepsis, overindulgence (alcohol, purine-rich foods), drugs

Intercritical gout

- Asymptomatic periods between acute flares
- Body urate load still increasing
- Joints still with MSU crystals

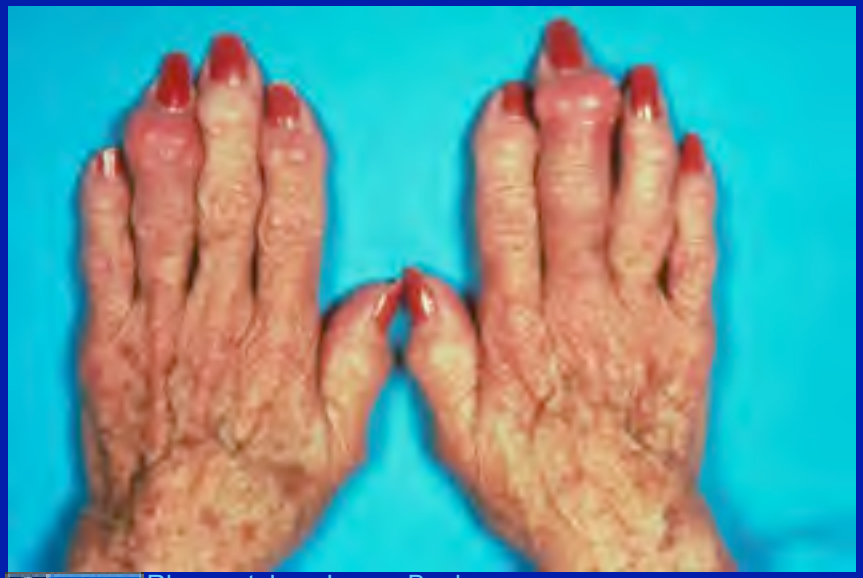
Chronic gout

- Chronic destructive arthritis
- Flares become polyarticular, additive, ascending
- Can be mistaken for rheumatoid arthritis



PD-INEL Rheumatology Image Bank

Tophaceous gout



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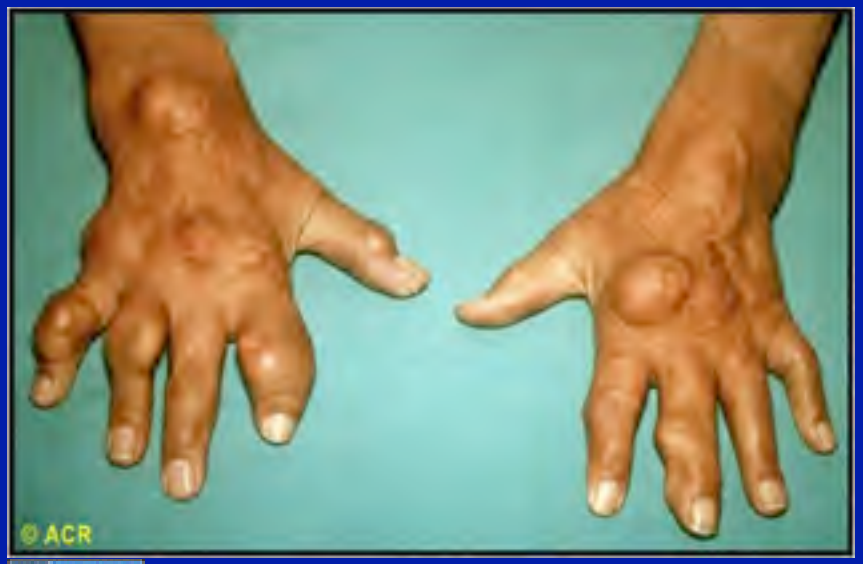
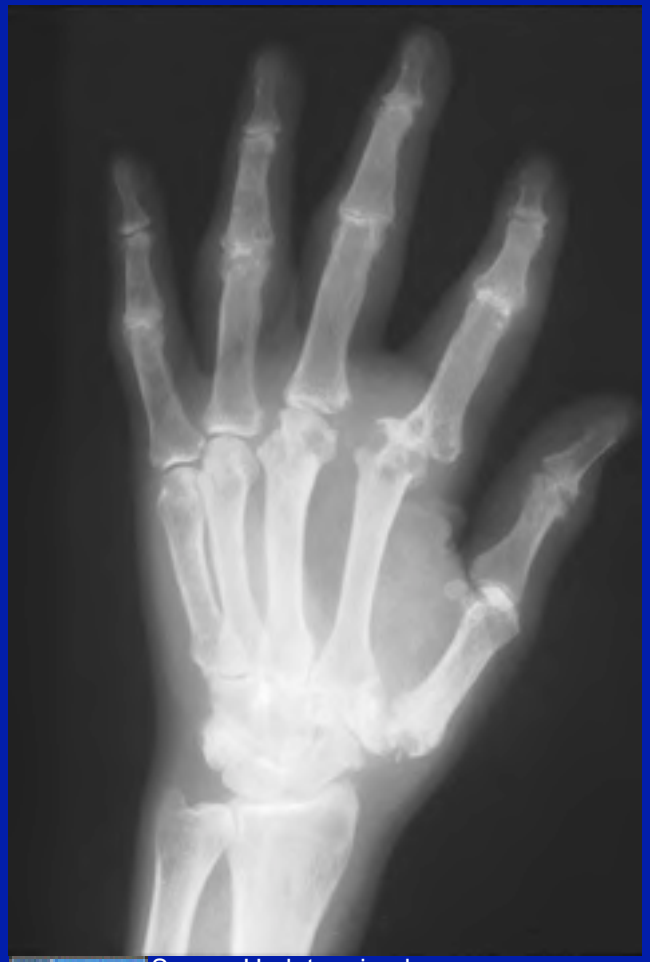


PD-INEL American College of Rheumatology



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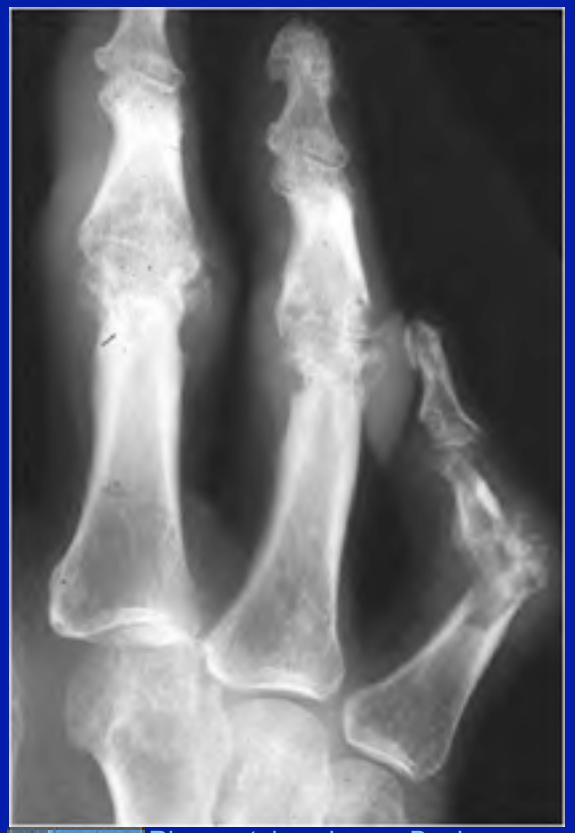

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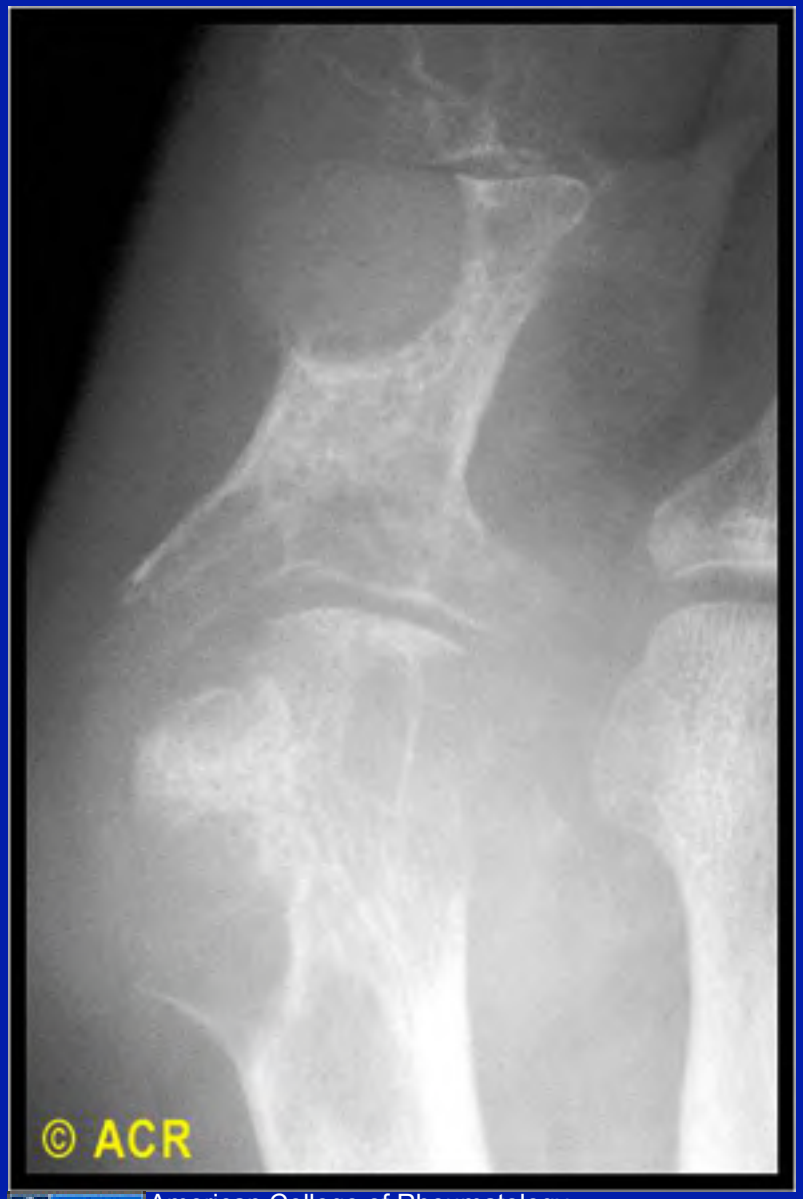
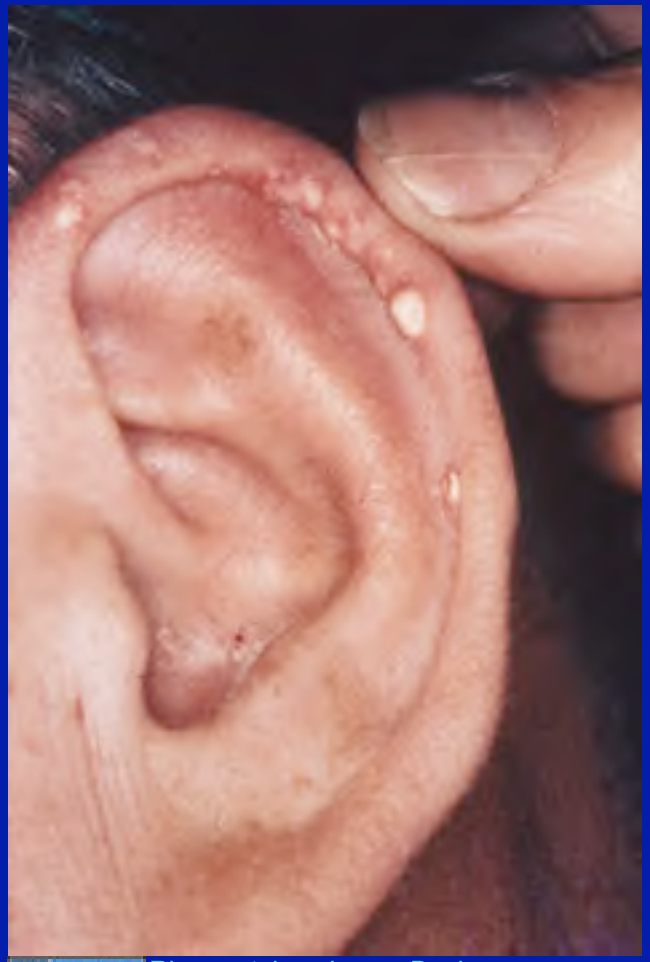
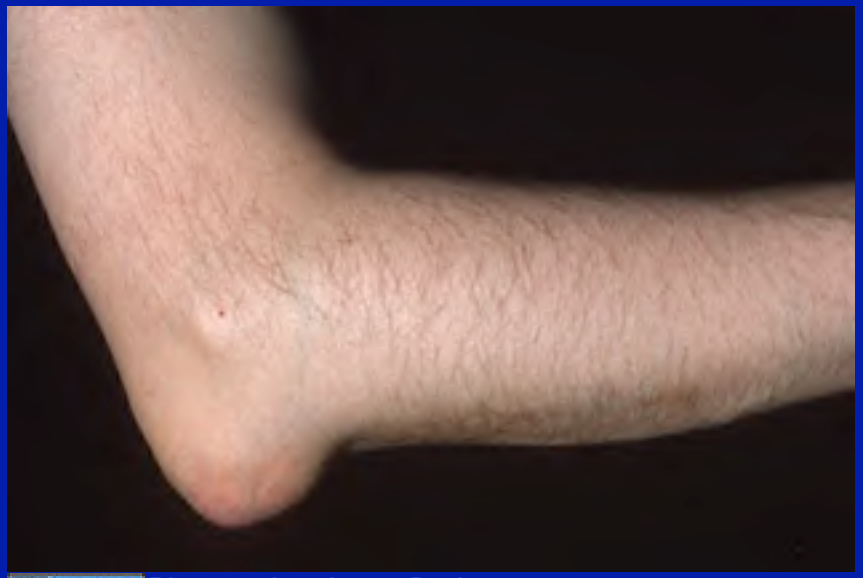


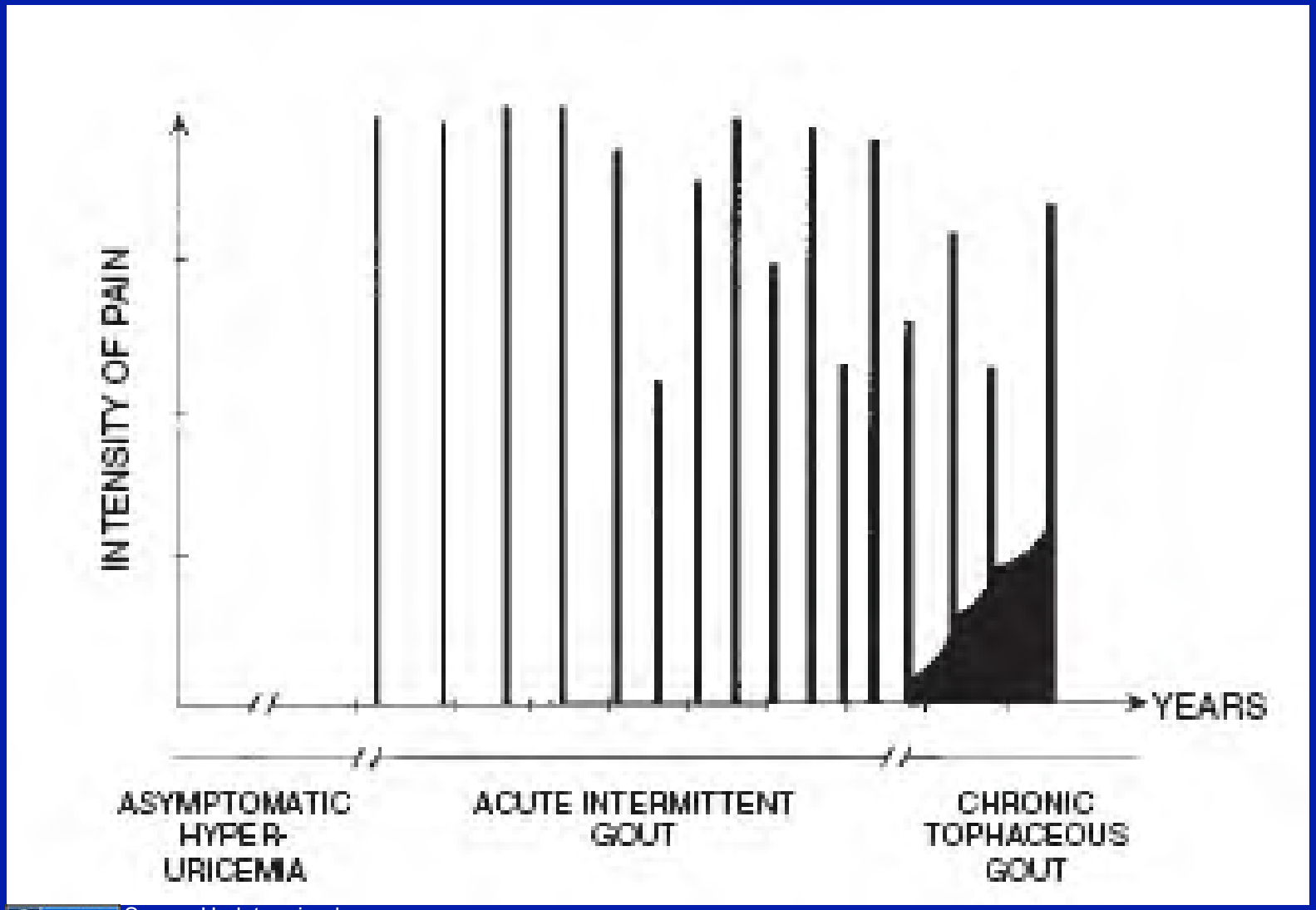
 American College of Rheumatology



Rheumatology Image Bank



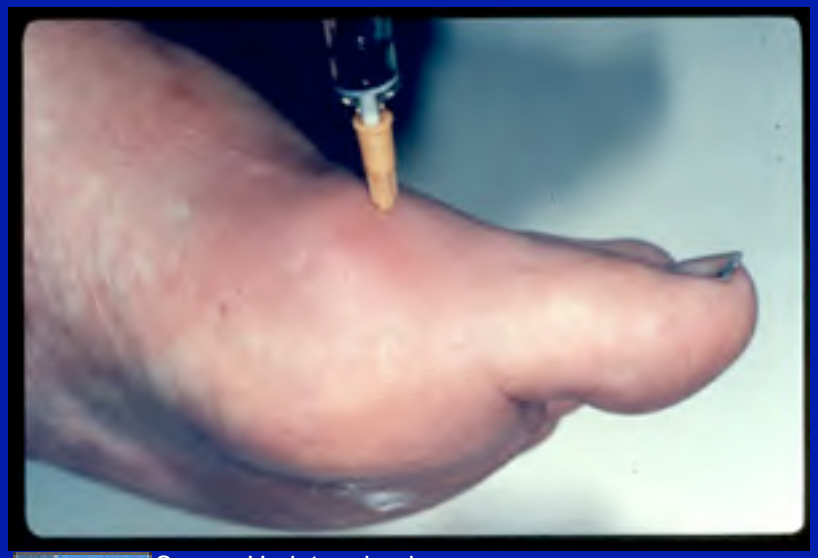
Rheumatology Image Bank



Renal Disease

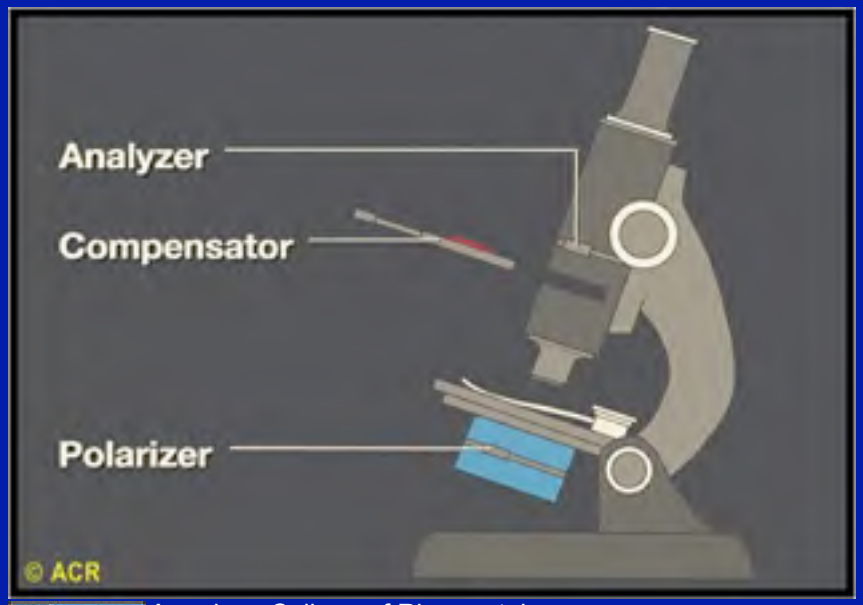
- Acute uric acid nephropathy (tumor lysis syndrome)
- Chronic urate nephropathy (tubulointerstitial disease)
  - MSU deposition in renal medulla
  - Not seen in the absence of gouty arthritis
- Uric acid nephrolithiasis
  - 10-25% of gout patients
  - Increased non-urate nephrolithiasis as well

Diagnosis: Arthrocentesis



PD-INEL Source Undetermined

- Can be performed even if not in acute attack
- Inflammatory joint fluid, sometimes septic appearing



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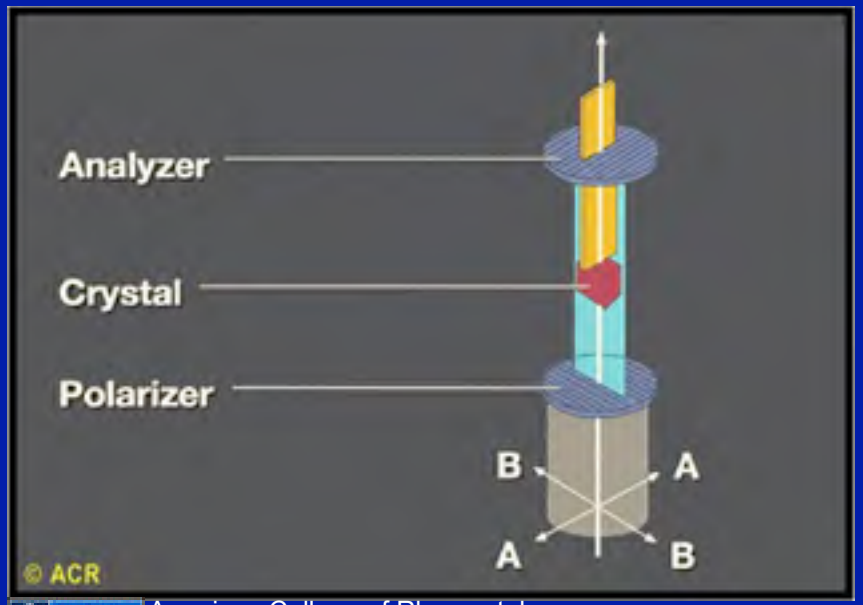

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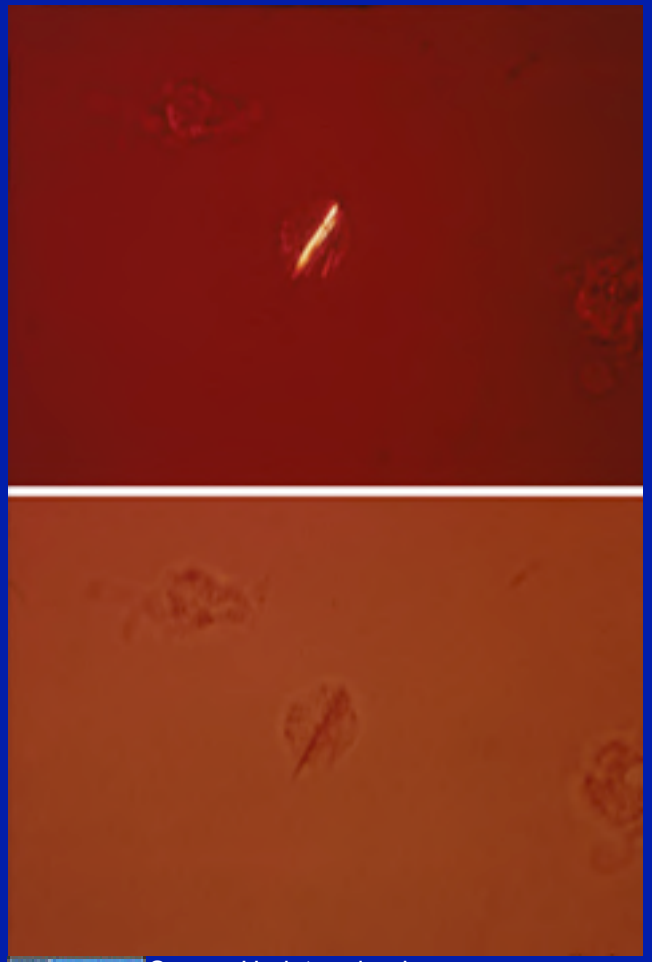

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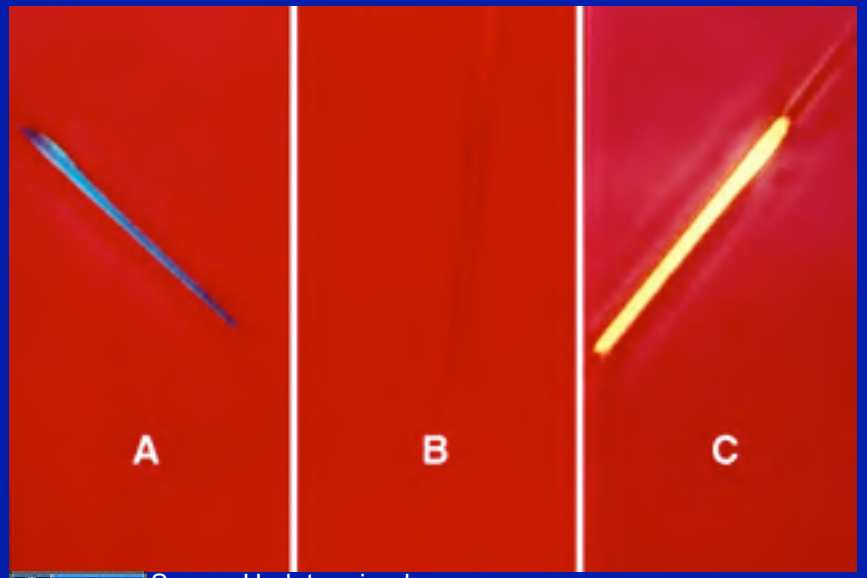

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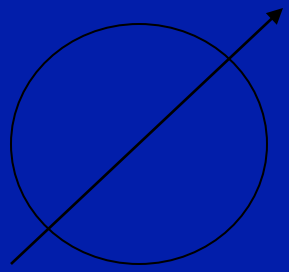
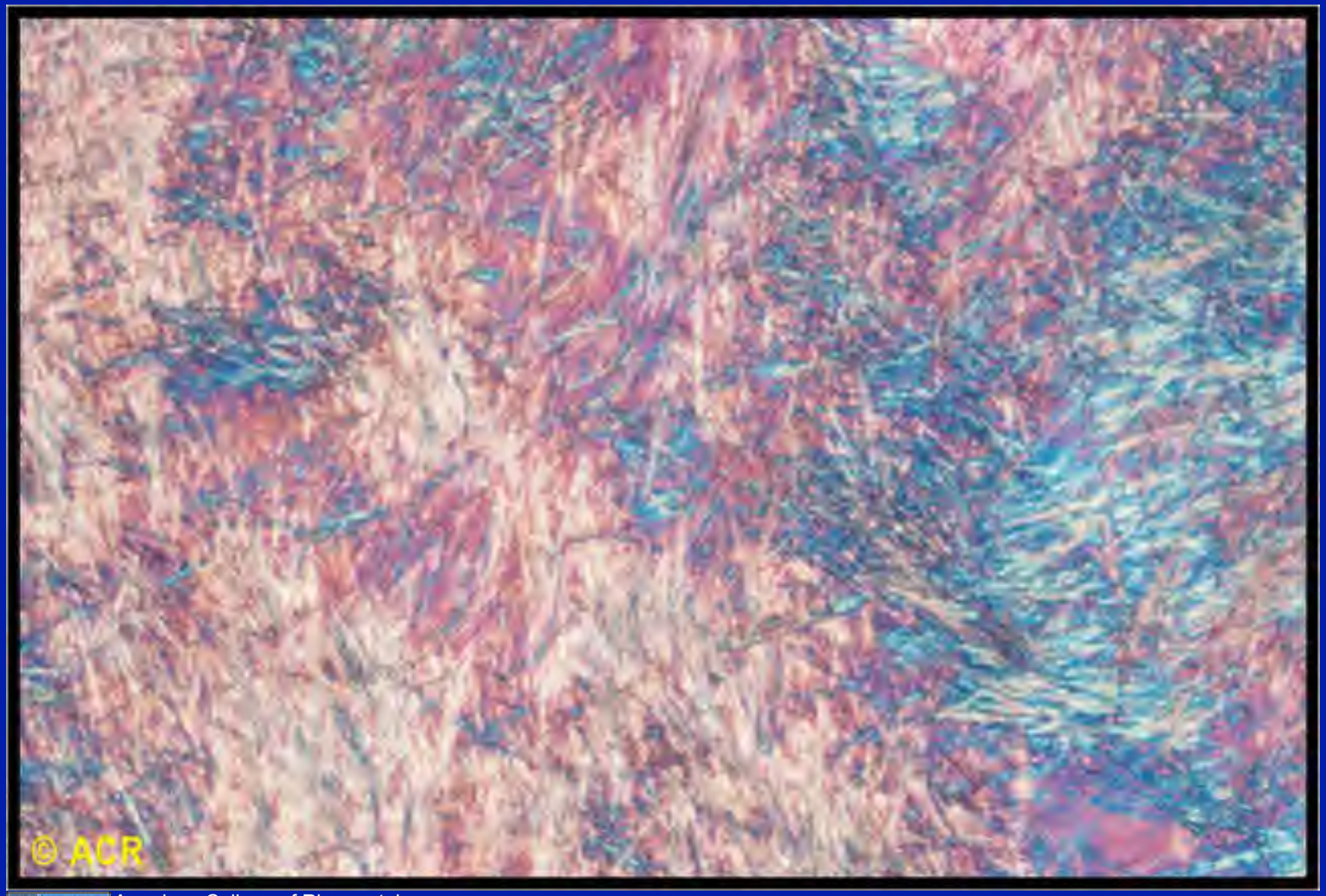




Serum uric acid

- If high, suggestive but not diagnostic
- Up to 1/3 of patients having an acute gout attack may have a uric acid <7
- 24 hour urine collections for uric acid
  - Difficult to perform
  - May be useful in select cases (young patient, history of urolithiasis)

Treatment

Asymptomatic hyperuricemia → No treatment

Acute gout → Antiinflammatory

Preventative

Chronic gout → Uric acid lowering therapy

Acute treatment

- NSAIDs
- Steroids
  - Intraarticular
  - Oral/IV
- ACTH
- Anakinra

- Colchicine
  - Never IV
  - Used prophylactically in intercritical periods
  - Toxicities: diarrhea (common), neuromyopathy, bone marrow suppression, hematologic abnormalities
  - Not dialyzable

Lowering uric acid

- Adjust offending medications (ex. diuretics)
- Weight loss
- Dietary adjustments
  - Less meat, seafood
  - Less alcohol (particularly beer)
  - Less fructose containing soft drinks
  - ?More dairy

- Purine rich foods
  - Beer, other alcoholic beverages.
  - Anchovies, sardines in oil, fish roes, herring
  - Yeast
  - Organ meat (liver, kidneys, sweetbreads)
  - Meat extracts, consomme, gravies

  - Mushrooms, spinach, asparagus, cauliflower, legumes (dried beans, peas) less associated with gout

Indications for uric acid lowering medication

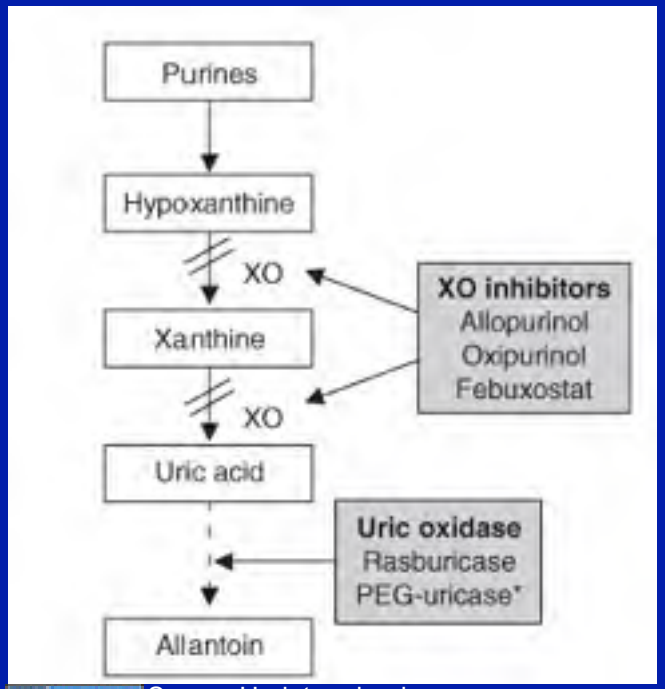
- Tophaceous gout
- Erosive gout
- Unacceptably frequent attacks (>3-4/year)
- Nephrolithiasis
- Serum uric acid >12 with other risk factors for gout or nephrolithiasis

- Goals: lower serum urate <6.0 (<5.0 if tophi)
- Should not be initiated during an acute flare

Treating undersecretion: uricosurics

- Suppress URAT1 -> decreases tubular reabsorption
- Probenecid
- (sulfinpyrazone, benzbromarone)
- Others: losartan, fenofibrate
- Limitations:
  - Require adequate GFR
  - Increases risk of uric acid stone formation/ urinary crystallization
  - Numerous drug-drug interactions (ampicillin, salicylates, indomethacin, heparin, etc.)

Treating overproduction



Allopurinol

- Purine analog of xanthine
- Competitive xanthine oxidase inhibitor
- Active metabolite = oxypurinol
- Potentiates azathioprine and warfarin
- Side effects:
  - Rash/toxic epidermolysis/Stevens Johnson syndrome
  - GI intolerance/liver enzyme elevation
  - Cytopenia

Allopurinol hypersensitivity syndrome

- Idiosyncratic; usually develops within first 3 months of initiation
- Fever, rash, hepatitis, interstitial nephritis, myocarditis, rhabdomyolysis, eosinophilia
- Incidence ~0.4%, mortality 25%
- Arellano, et al. 1993: ~75% of patients developing syndrome were receiving allopurinol for asymptomatic hyperuricemia

Renal dosing?

- Guidelines for dose adjustment in patients with renal insufficiency to minimize toxicity
- However,
  - Unclear if this is successful
  - Results in significant undertreatment of gout
- Recommend carefully advancing allopurinol as high as needed to lower serum urate

Other urate lowering therapies

- Febuxostat
  - Non-purine selective xanthine oxidase inhibitor
  - Hepatically metabolized -> ?safer in renal insufficiency
  - Side effects: transaminitis
- Uricase
  - Converts uric acid to allantoin
  - Prevents/manages tumor lysis syndrome
  - Infusion reactions; anti-uricase antibodies

Special instances of gout

- Organ transplant patients on cyclosporine
  - More likely to develop rapidly, be tophaceous, involve atypical joints
  - Steroid use may mask acute attacks despite accumulation of total body urate load
- Gout in young men (<25) or premenopausal women: likely genetic

CPPD disease

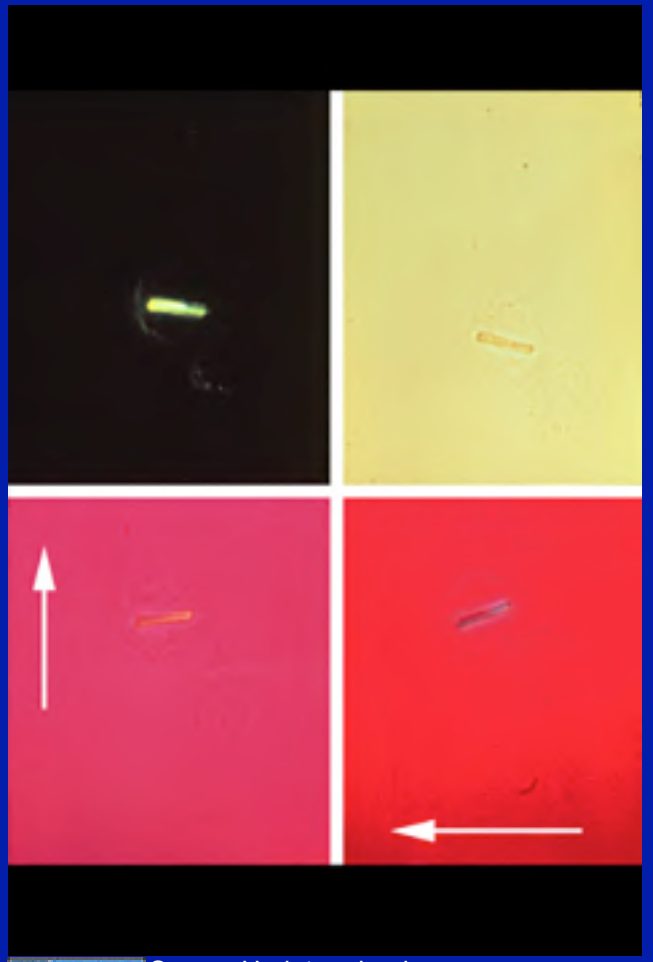
- Calcium pyrophosphate deposition disease
  - Pseudogout
  - Also pseudo-septic, pseudo-RA, pseudo-OA
- Associated with aging
- Also associated with
  - Hemochromatosis
  - Hyperparathyroidism
  - Hypomagnesemia/hypophosphatemia
  - Gout
  - Trauma
  - Hypothyroidism

Pseudogout

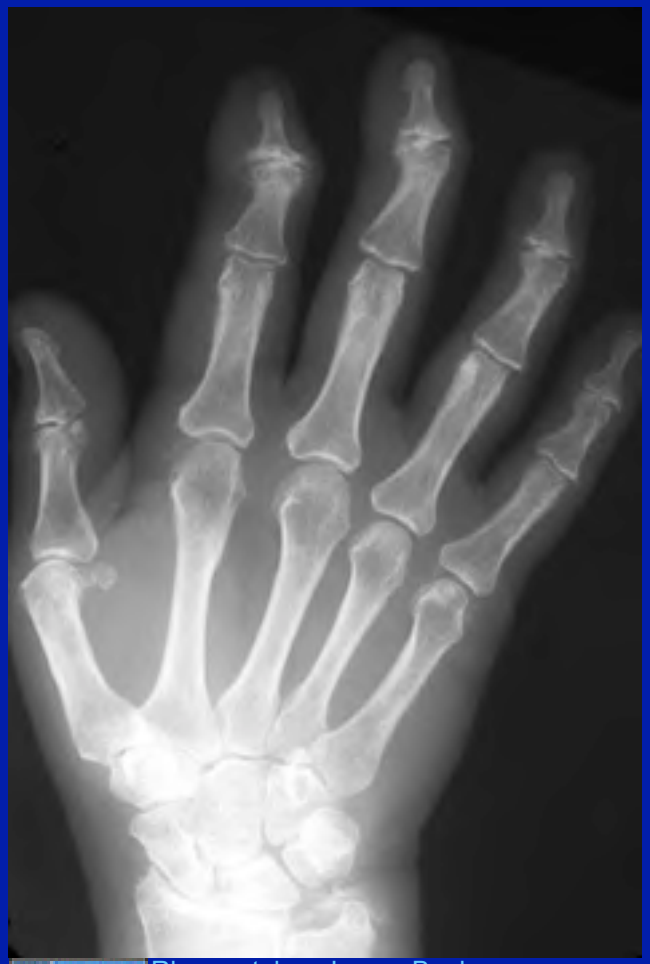
- Acute inflammatory attacks
- Asymptomatic in between
- Flares involve large joints: knees, shoulders, wrists, ankles
- Also can involve MCPs
- May take longer to reach peak intensity, longer to subside than gout
- Not due to uric acid

Diagnosis

- Joint aspiration
  - Crystals more rhomboid
  - Weakly positive birefringence



Chondrocalcinosis



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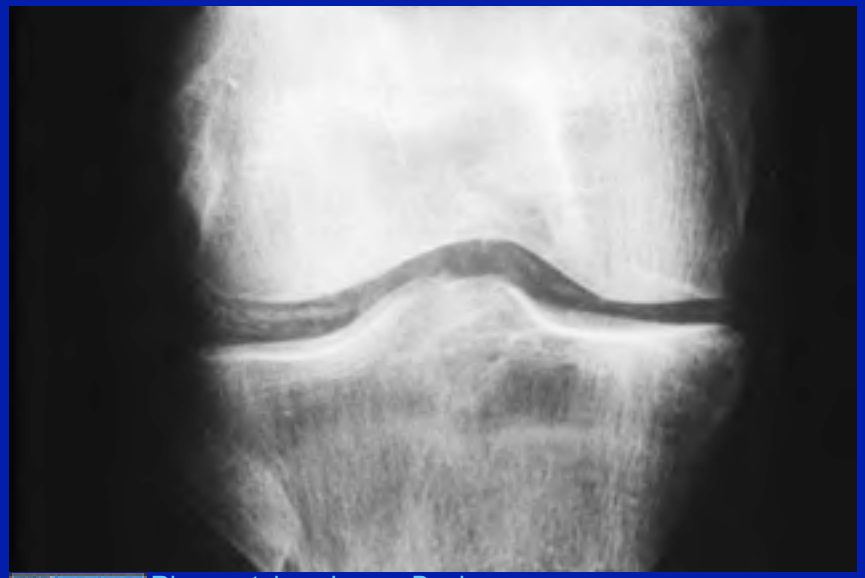

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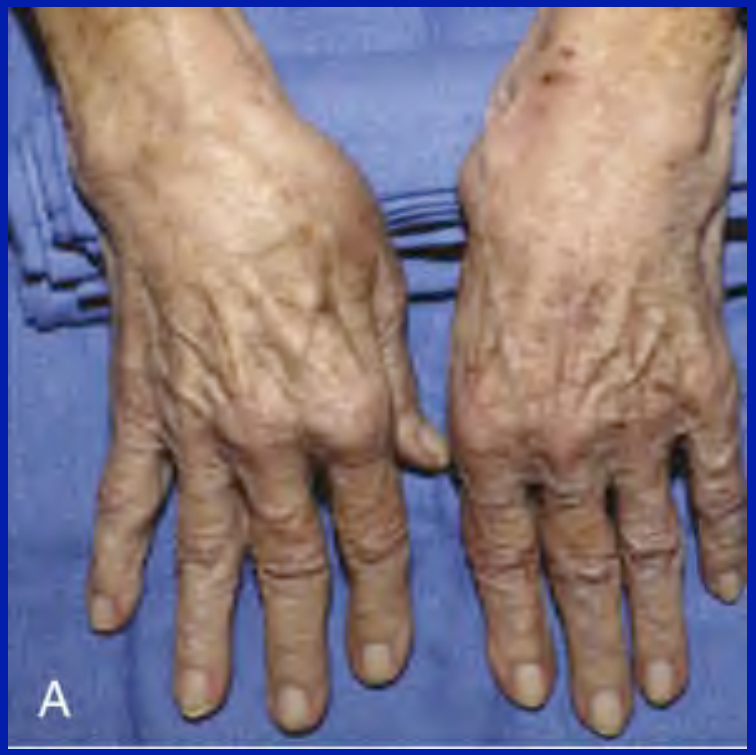
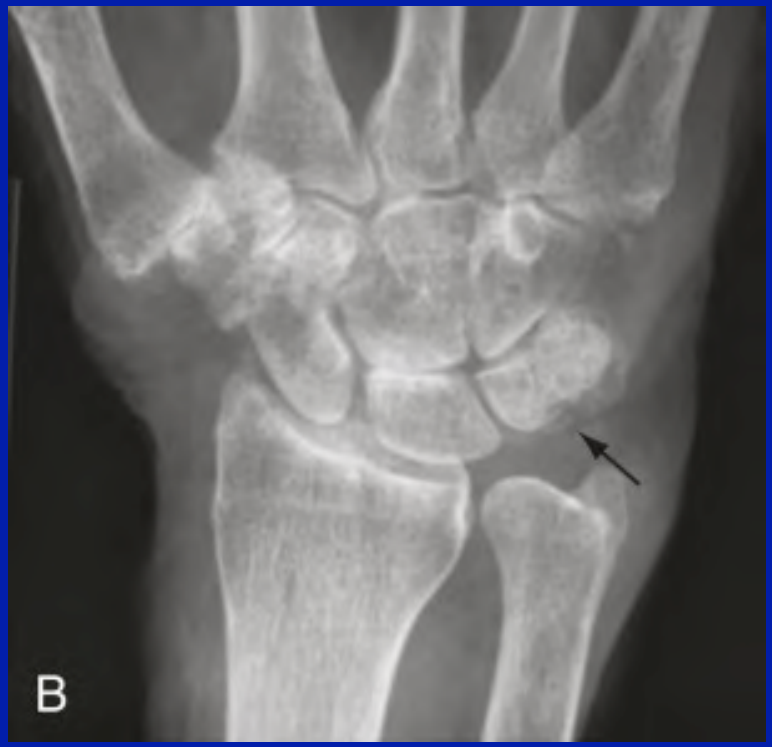
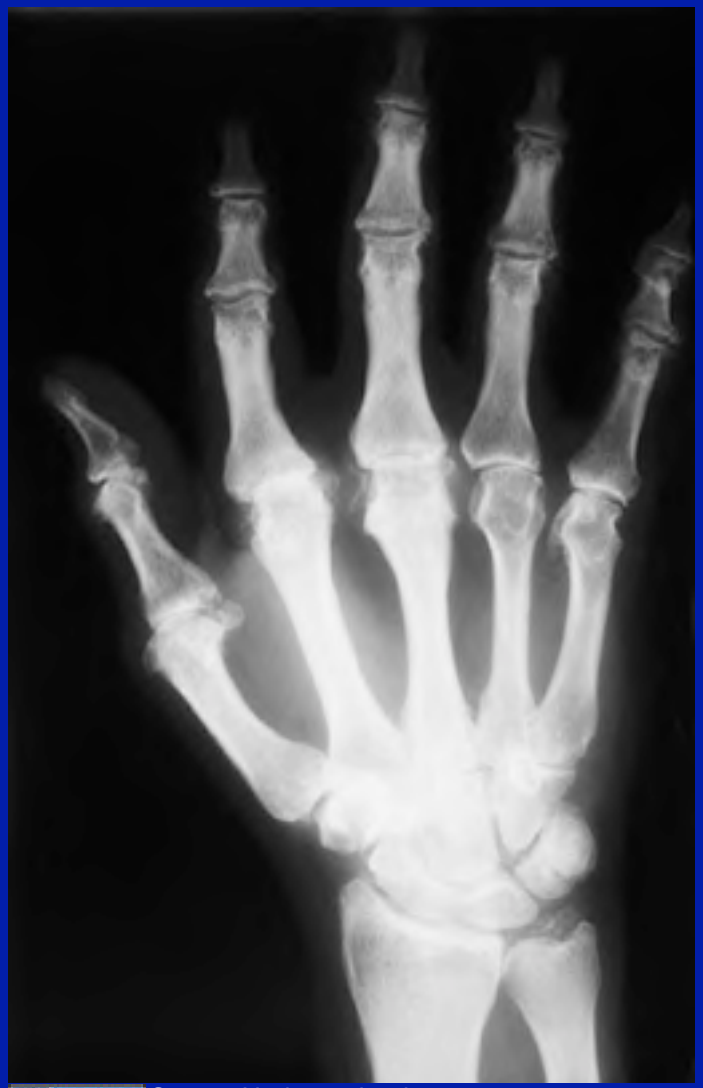
CPPD arthritis





PD-INEL Kelley's Textbook of Rheumatology (Both Images)

CPPD arthritis

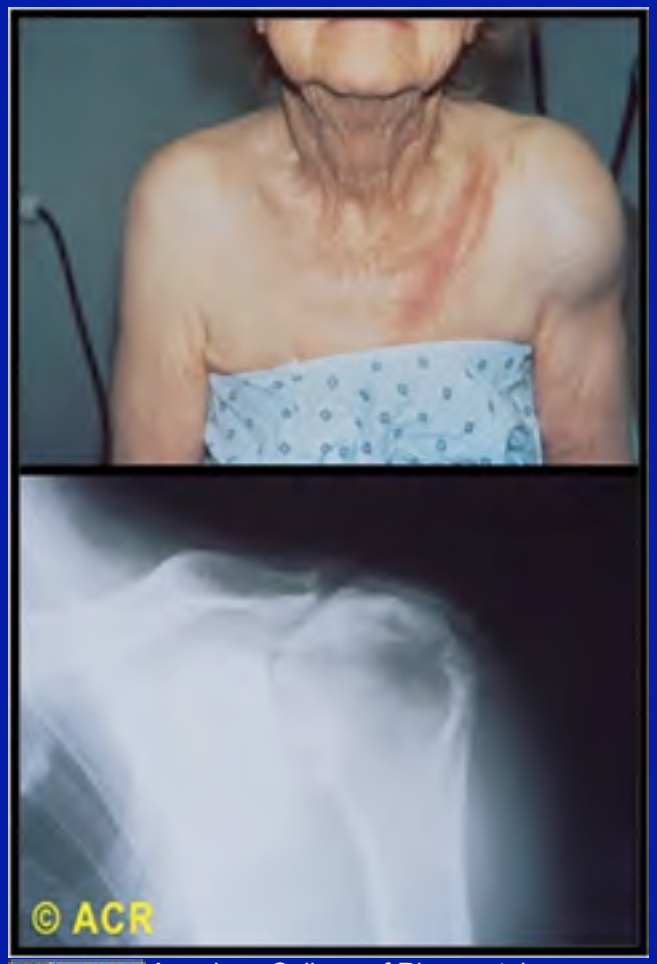


 Source Undetermined

Management of pseudogout

- NSAIDs
- Steroids
- ?Colchicine
- Treat associated disorders (hemachromatosis, hyperparathyroidism)

Other crystals: Hydroxyapatite



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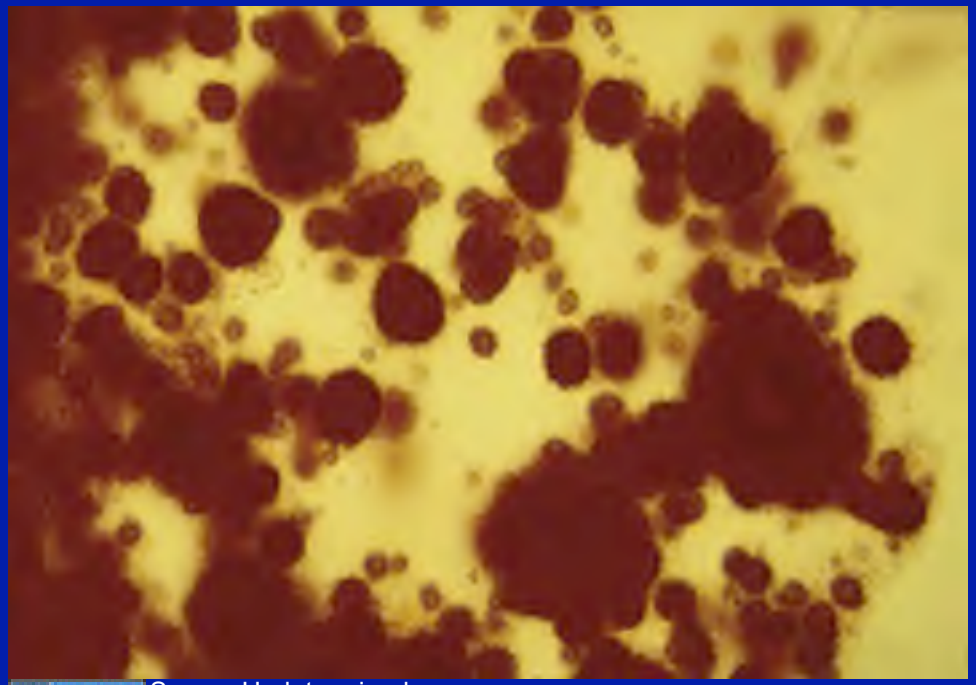

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Slide 5: Cecil Medicine, 23rd ed.

Slide 6: Seetha Monrad

Slide 7: Teng, Drugs, 2006

Slide 9: Cecil Medicine, 23rd ed.

Slide 12: Teng, 2006

Slide 13: Torpedo Extra IPA by Milletre, Flickr.com, http://www.flickr.com/photos/71781509@N00/3252864721

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Slide 24: Source Undetermined; Source Undetermined

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Slide 29: Source Undetermined

Slide 30: American College of Rheumatology; American College of Rheumatology

Slide 31: Source Undetermined; Source Undetermined; Source Undetermined

Slide 32: American College of Rheumatology

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Slide 47: Source Undetermined

Slide 48: Rheumatology Image Bank, http://images.rheumatology.org/

Slide 49: Kelley's Textbook of Rheumatology (Both Images)

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Slide 52: American College of Rheumatology; Source Undetermined