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PD-EXP Henry William Bunbury, Origin of the Gout

CRYSTAL MEDIATED ARTHRITIDIES

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Winter, 2011

University of Michigan Medical School

Disclosure

Takeda Pharmaceuticals

ACKNOWLEDGEMENT—Special Thanks to

Dr. Blake Roessler

Dr. Seetha Monrad

What's new with GOUT?

1—changing epidemiology

2—treating to Sua < 6.0

3—Newer treatments

Top 10?

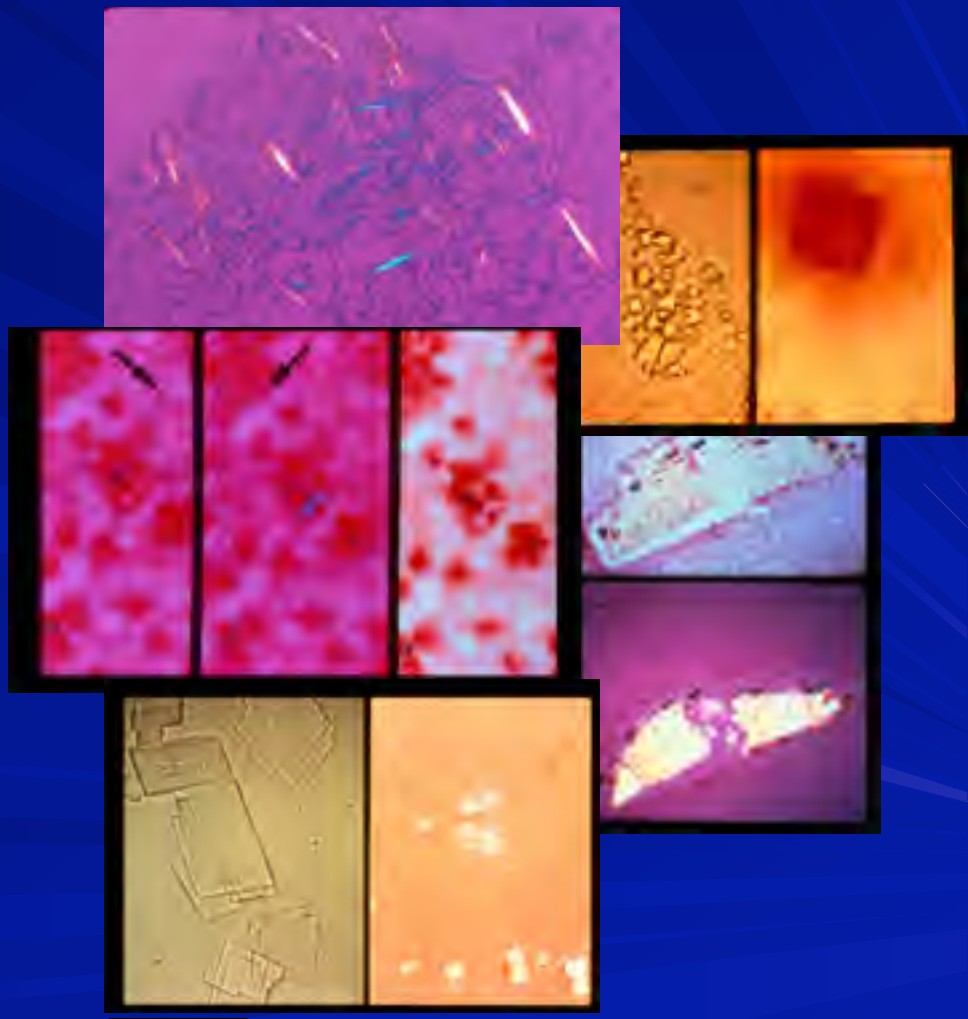
- Prevalence 2X incr
- Elderly
- OA/gout coexist
- Shorter prophy
- Persistent crystals
- UA < 6.0
- Newer XO inhib
- Chronicity
- Polycyclic
- Polyarticular
- Incr. tophi
- What initiates attacks?

OBJECTIVES

- The student will achieve:
- 1. An understanding of the clinical presentation of crystalline synovitis.
- 2. Understanding of the importance of polarizing microscopy in making the diagnosis.
- 3. Understanding of the diagnostic value of other clinical data (history , tophi, radiographs, therapeutic response)
- 4. Understanding of the therapeutic approaches to crystalline synovitis, including pharmacologic information.

Types of Crystalline Synovitis

- Gout (Monosodium urate)
- Pseudogout (Calcium Pyrophosphate)
- Hydroxyapatite
- Calcium Oxylate
- Miscellaneous



Differential Diagnosis

- Infectious
- Inflammatory
- Degenerative
- Traumatic
- Neoplastic

PD-EXP Henry William Bunbury, Origin of the Gout

Gout - Outline

- Definition
- History
- Epidemiology
- Diagnosis
- Clinical Presentation
- Associated Conditions
- Pathophysiology
- Pathology
- Therapy
  - Acute
  - Preventive
  - Chronic
  - Pharmacology
- Prognosis

“Gout” defined:

Gout: a metabolic condition characterized by excessive accumulation of uric acid in the blood stream which may lead to deposition of uric acid crystals in and around the joints, painful attacks of arthritis, impairment of renal function, and kidney stones.

Gout terminology

- Gout
- Gouty arthritis
- Acute gouty arthritis
- Podagra
- Monoarticular
- Monocyclic
- Chronic gouty arthritis
- Chronic tophaceous gout
- Polyarticular
- Polycyclic
- Tophus (plural, tophi)
- Inter-critical gout

- (others)
- Lesch-Nyhan Syndrome
- Kelley-Seegmiller Syndrome
- HGPRT deficiency
- PRPP synthetase superactivity
- Xanthine oxidase
- Allopurinol
- Uricosuric

Gout historic aspects

Famous Gout Sufferers

A.Martin Luther (1483-1546).

B.Francis Bacon (1561-1626).

C.Michelangelo (1475-1564).

D.Benjamin Franklin (1706-1790).

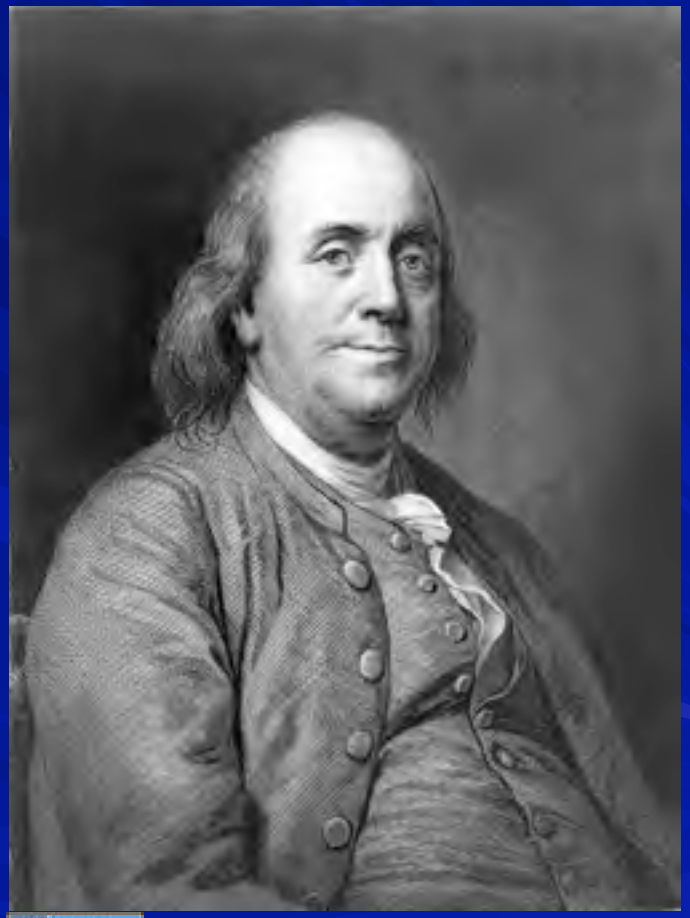
E.King James I (1566-1625).

F.Samuel Johnson (1709-1784).

G.William Pitt (1759-1806).

H.Charles Darwin (1809-1882).

I.Isaac Newton (1643-1727).



PD-EXP J.A. Duplessis, wikimedia commons

Clinical Aspects/Epidemiology

- Hyperuricemia w/o sxs (> 80 %)
- Acute gouty arthritis
- Chronic gouty arthritis (aka, tophaceous gout)
- Associated conditions (obesity, DM, hyperlipidemia, HTN, atherosclerosis, alcohol, acute illness, pregnancy, post-operative)
- Negative association (SLE, RA, amyloid, ?dialysis)
- Renal disease
  - urate nephropathy
  - acute uric acid nephropathy
  - calculi

PD-EXP Source Undetermined

Hyperuricemia (>7.0 mg/dl)

- Prevalence rate of 5-10% in adult men
- >80% of hyperuricemic individuals have no associated gout
- Hyperuricemia is associated with hypertension, cardiovascular, cerebrovascular, renal diseases and metabolic syndrome

Gout epidemiology

- Asymptomatic Hyperuricemia is common
- All patients with gout have hyperuricemia chronically
- Gout is caused by hyperuricemia
- Acute gouty arthritis patients may have hyperuricemia (80%)
- Prevalence of gout ~ 1% of men
- Estrogen is uricosuric

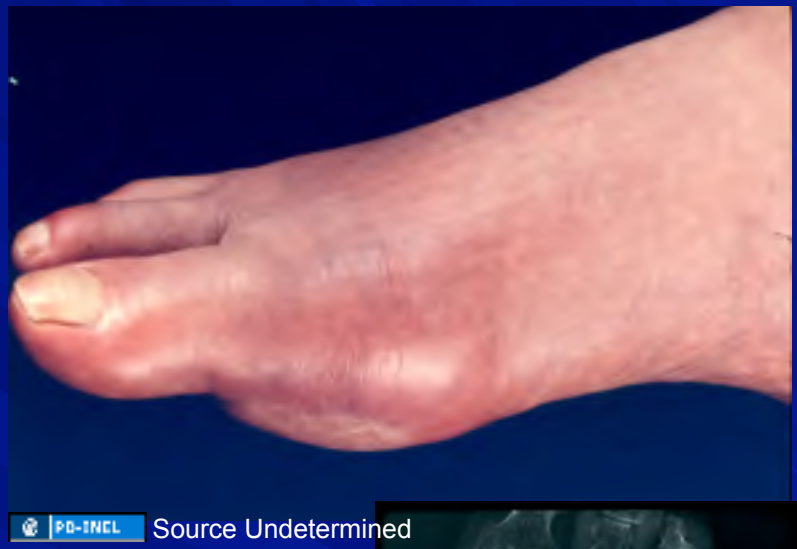
Hyperuricemia Causes

- Under-excretion (90% of cases)
- dehydration, starvation, ketosis (post-op)
- renal abnormality (RTA)
- drugs: diuretics low-dose aspirin
- toxins, ethanol, lead
- hypothyroidism

- Over-production (10% of cases)
- ethanol
- HGPRT or G6PD deficiency
- PRPP synthetase superactivity
- myeloproliferative disorders
- psoriasis

Acute Gouty Arthritis

- Abrupt onset, often at night
- Subsides completely
  - 3-5 days (with Rx);
  - 10-14 days (with no Rx)
- 75% in the first MTP joint
- Urate crystals in WBCs in synovial fluid
- May have hyperuricemia (80%)
- Usually monoarticular and monocyclic



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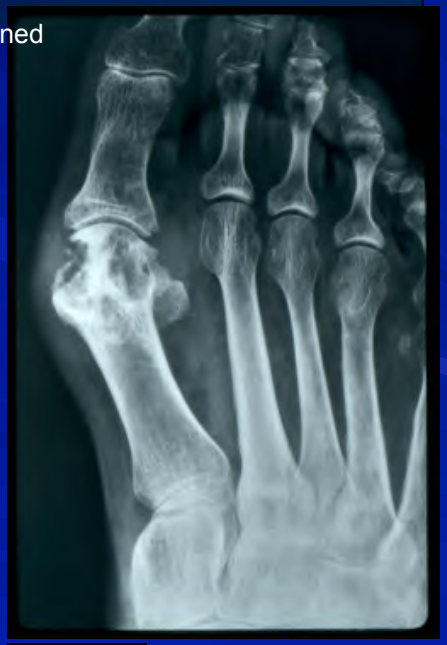

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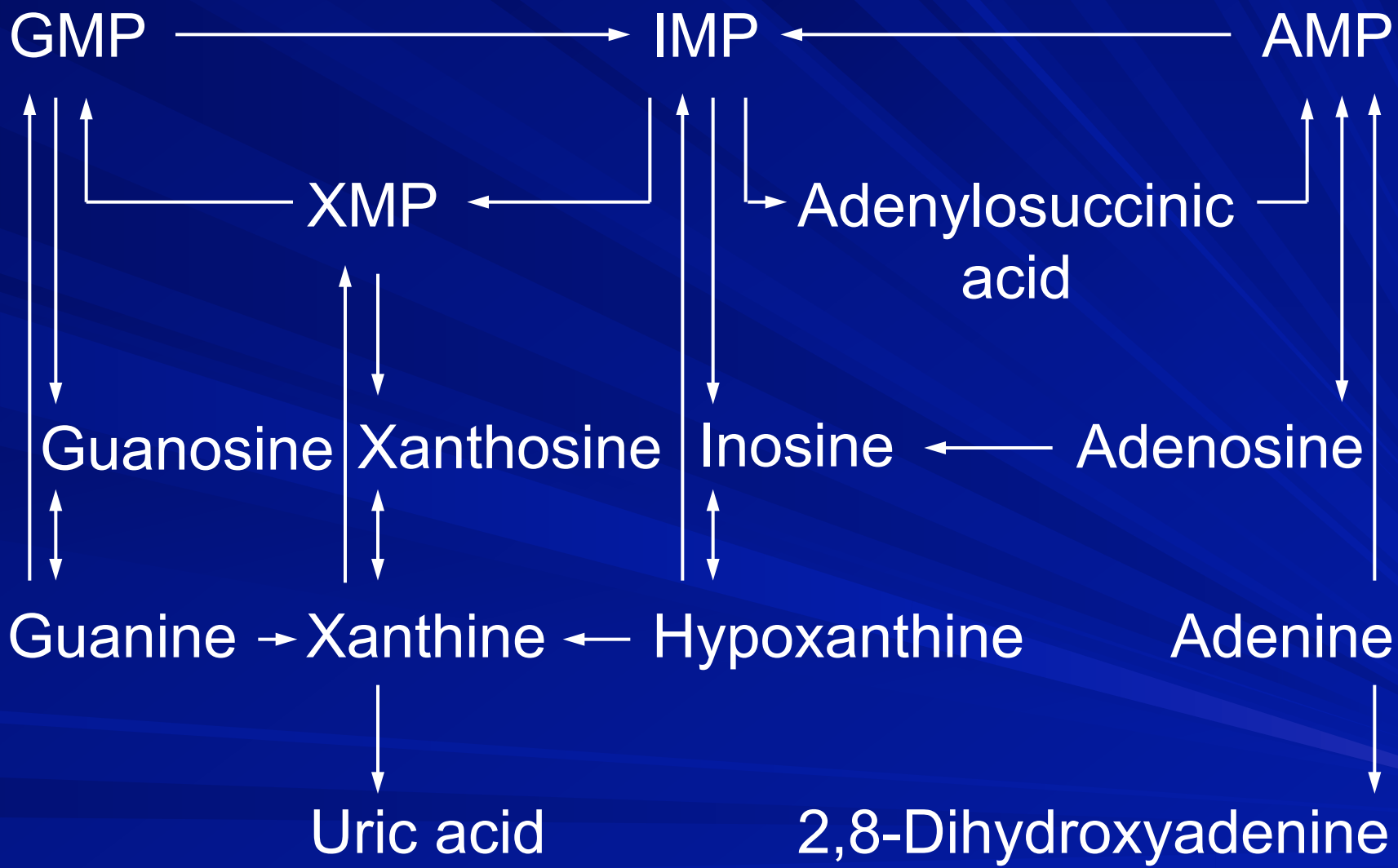
Purine Catabolic Pathway



(Becker & Roessler, "Hyperuricemia and Gout", in The Metabolic and Molecular Bases of Inherited Disease, McGraw-Hill 1995.)

How does this fit together?

- Xanthine oxidase =XO
- Conversion of hypoxanthine to xanthine and xanthine to uric acid
- Allopurinol inhibits XO (competitive inhibitor)
- XO has Multiple sites of action
- Competes with 6MP and azathioprine

Metabolic basis of hyperuricemia

- Only 1:200 cases of gout has identifiable enzymatic defect
- HGPRT deficiency
  - Complete=
  - Partial=
- PRPP synthetase superactivity
- Others?

- Numerous mutations characterized
- Lesch-Nyhan Syndrome
- Kelley-Seegmiller Syndrome

Lesch-Nyhan Syndrome

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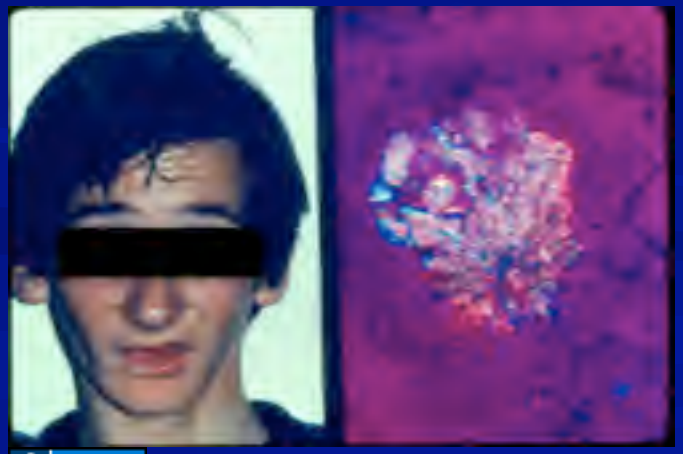

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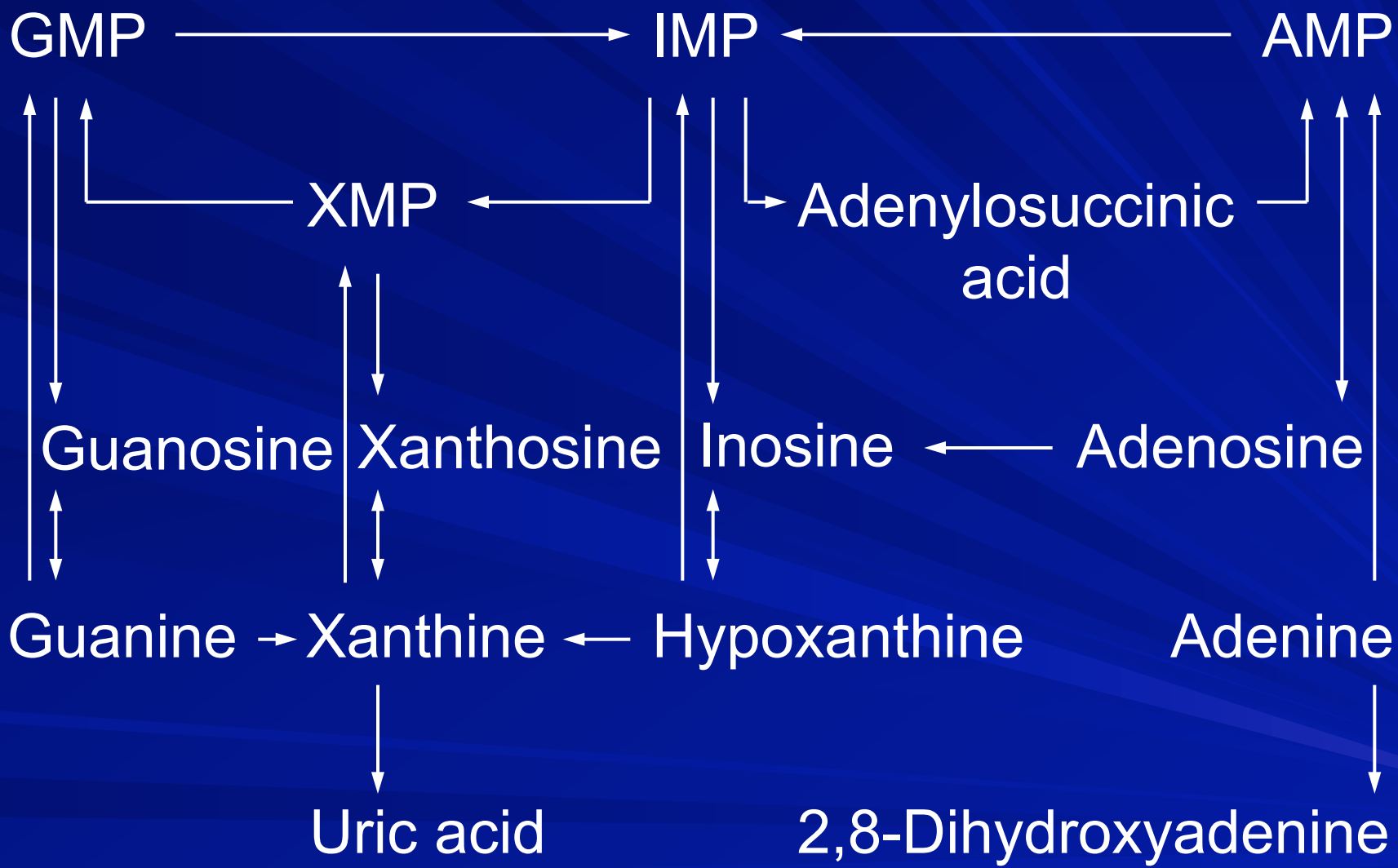
- HGPRT deficiency
- <1% protein expression
- UA Overproduction
- Mental retardation
- Microcephaly
- Compulsive Self-Mutilation
- Mutations/Gene Rx

Kelley-Seegmiller Syndrome

- Partial HGPRT Deficiency
- Early onset, severe gout
  - Arthritis
  - Renal calculi
- Intermediate PET scan appearance in basal ganglia 2,3-FDG utilization

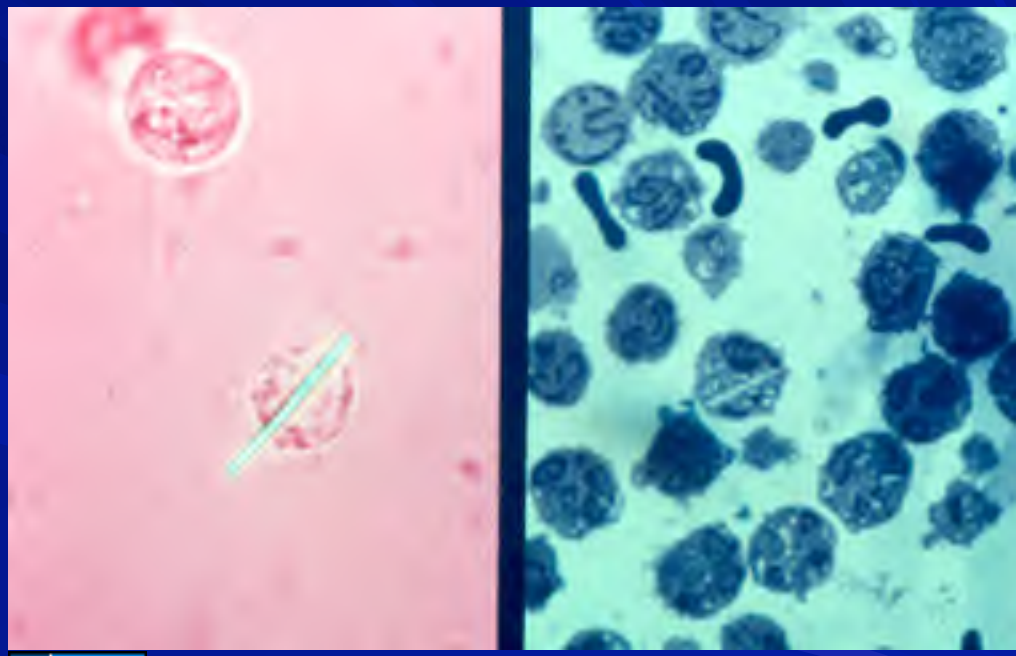
Purine Catabolic Pathway



(Becker & Roessler, "Hyperuricemia and Gout", in The Metabolic and Molecular Bases of Inherited Disease, McGraw-Hill 1995.)

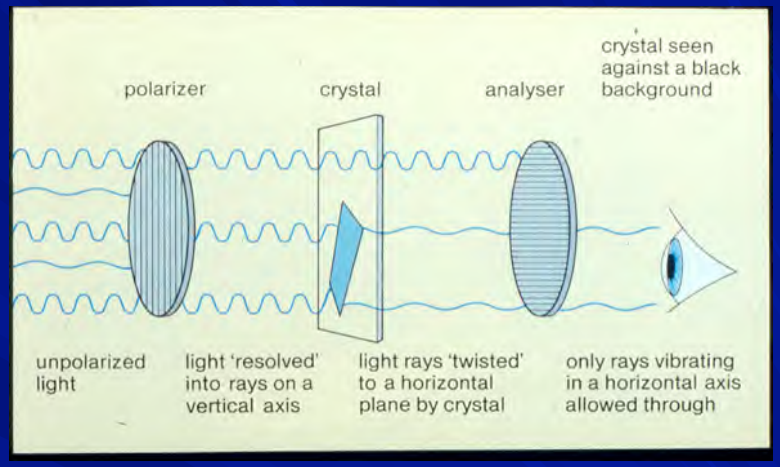
Acute Gout--Pathophysiology

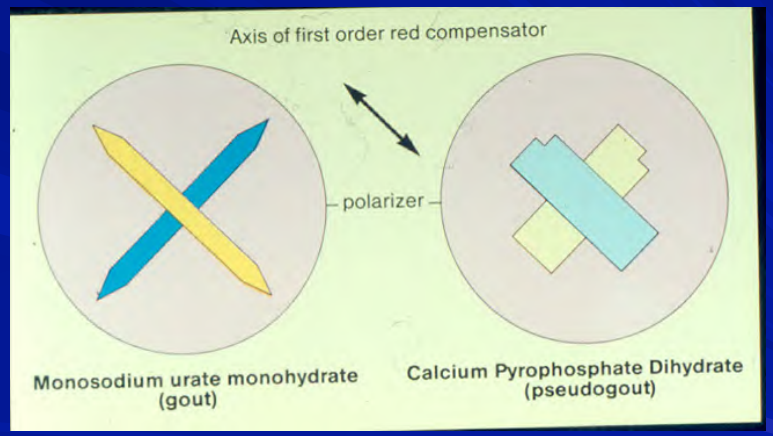
- role of crystals
- role of WBC's
- unexplained features:
  - initiation of attack
  - self-limited nature of attacks
  - joint distribution
  - role of trauma
  - Supersaturation is NOT sufficient explanation

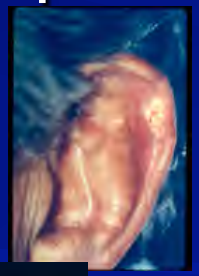


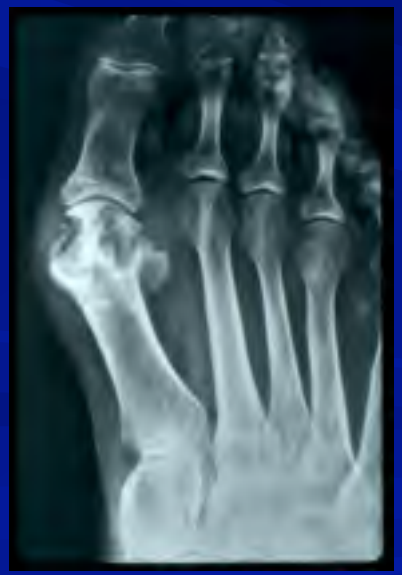
Diagnosis

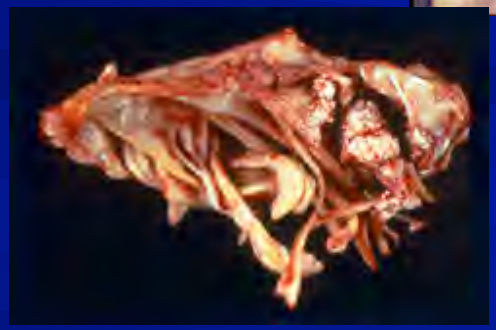
- "Clinical" Dx vs. "Pathological" Dx
- polarizing microscopy
- (response to therapy)
- Radiographs
- tophi









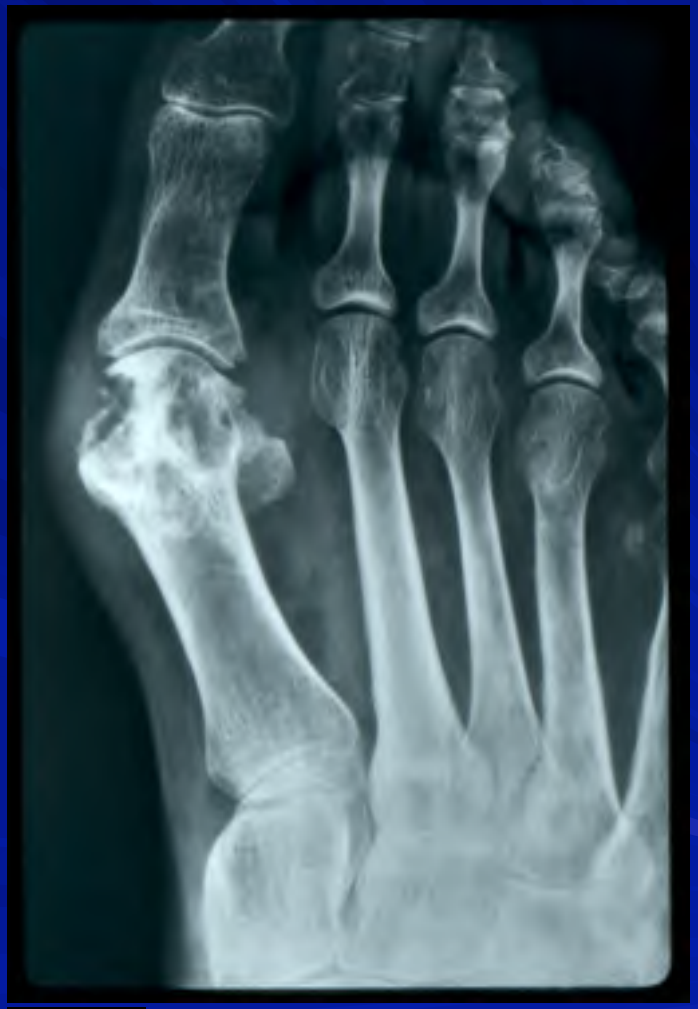


Diagnosis of Gout

- Synovial fluid aspiration and examination using polarizing microscopy
- DIY!
- Identification of intracellular monosodium urate crystals
- Needle-shaped, negative birefringence, yellow (parallel first order compensator)
- “parallel-yellow-uric acid” mnemonic

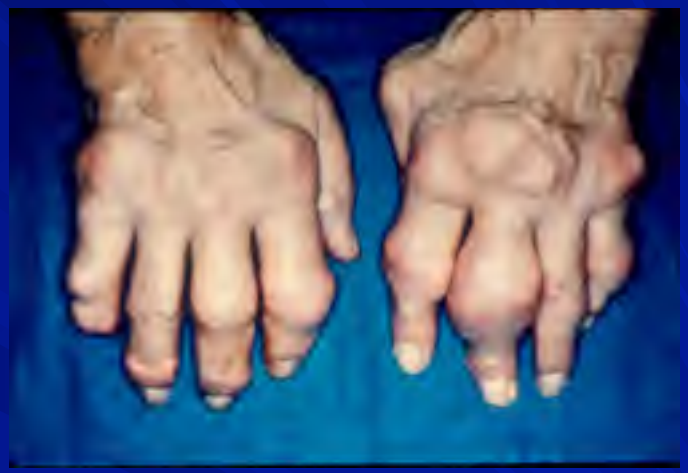
Radiologic findings in Gouty Arthritis

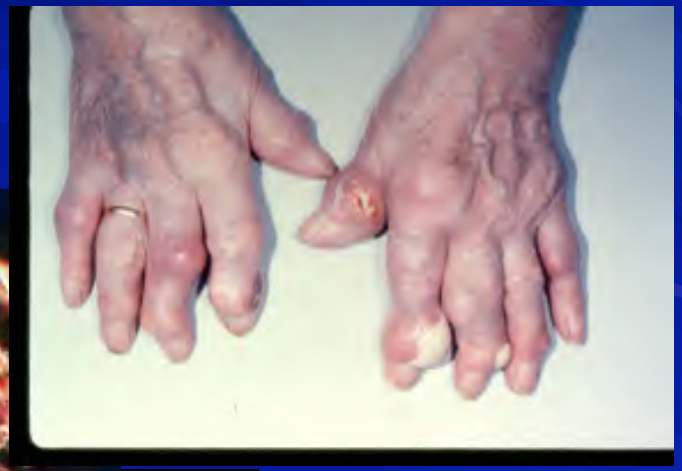
- Large punched-out lesions
- Overhanging edges
- Heterotopic bone growth
- Lucencies
- Quite different from OA, RA, psoriatic, etc.

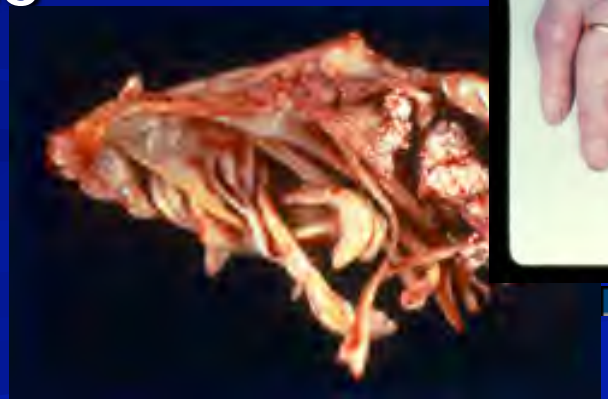


Tophi & Tophaceous gout

- Pure uric acid deposits
- Extensor surfaces
- Other locations
- Heberden's nodes
- Chronic drainage
- 2-5 yrs to reverse
- Allopurinol role







Hyperuricemia and gout

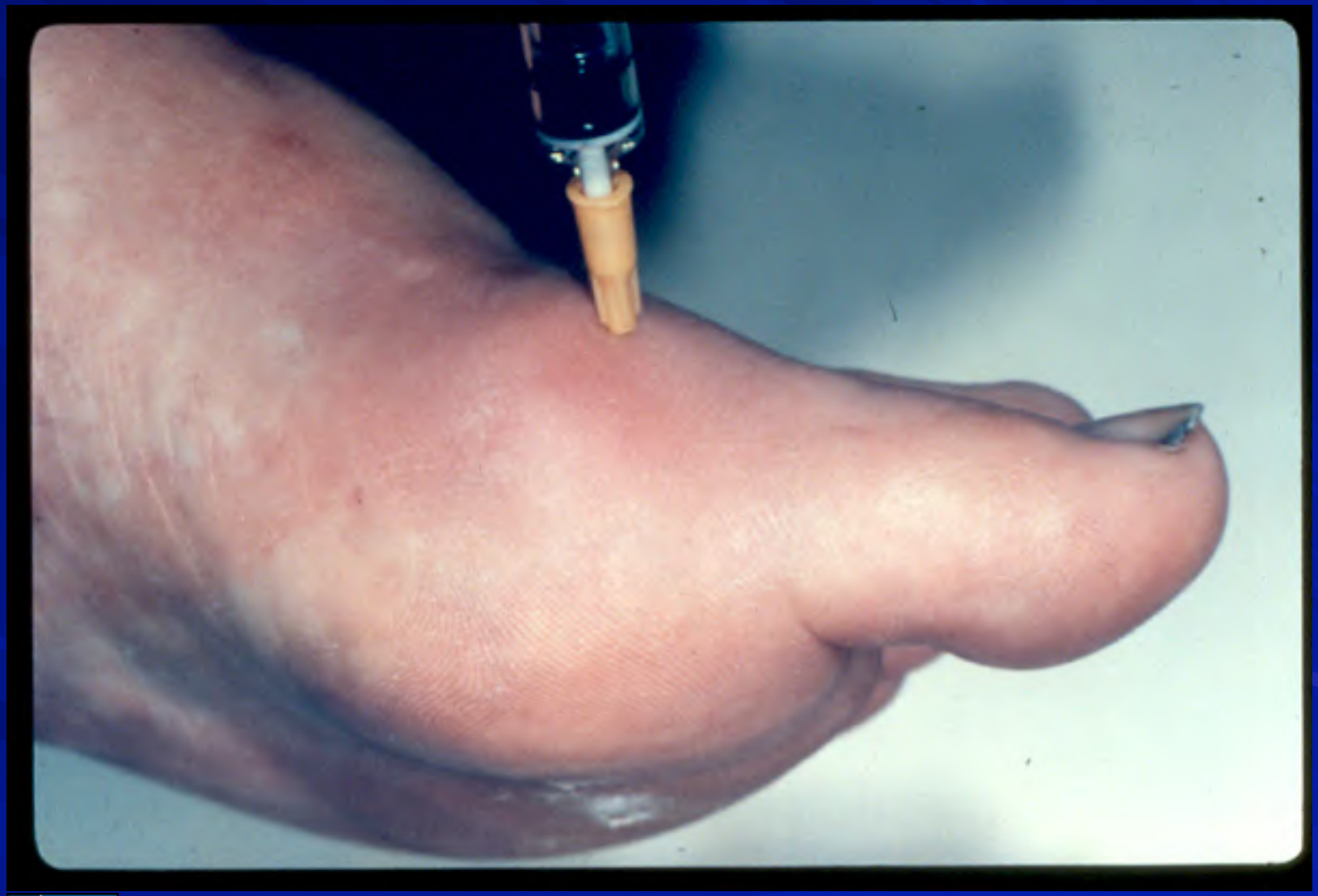
- >20% of patients with acute gout may be normo-uricemic
- ~1-2% of patients with tophaceous gout may be normo-uricemic
- Mean serum urate in tophaceous gout ~9 mg/dl

- Mean CrCl = 90 +/- 30 ml/min
- Mean UrCl = 4.5 +/- 1.75 ml/min

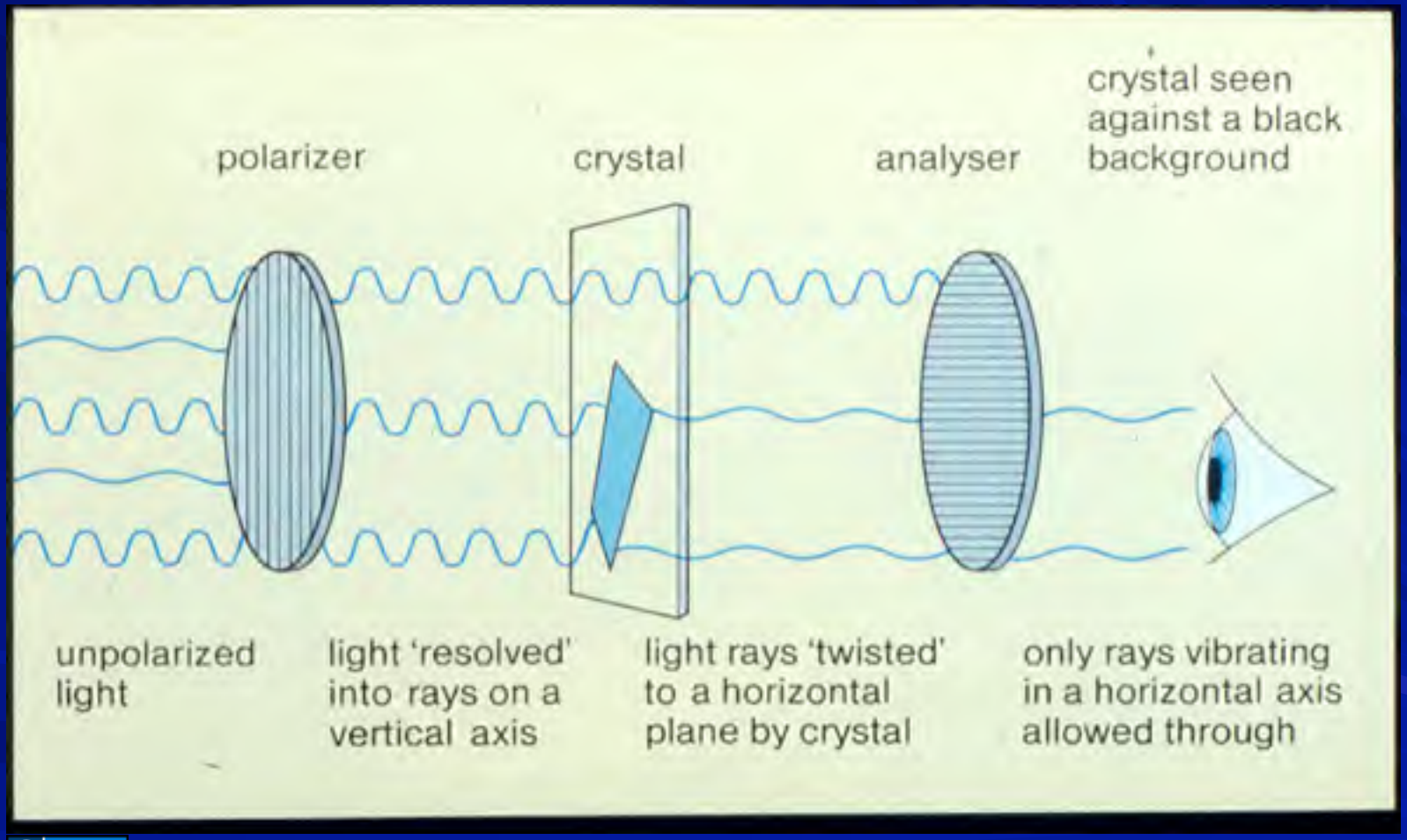
Acute Gouty Arthritis

- Historical Prevalence = 0.2%
- Current Prevalence = 0.4%
- Annual incidence > 0.02%
- Annual incidence rate correlates with mean serum urate levels
  - <7.0 = 0.1%
  - 7.0-9.0 = 0.5%
  - >9.0 = 5%

Diagnostic Arthrocentesis



Polarizing Microscopy



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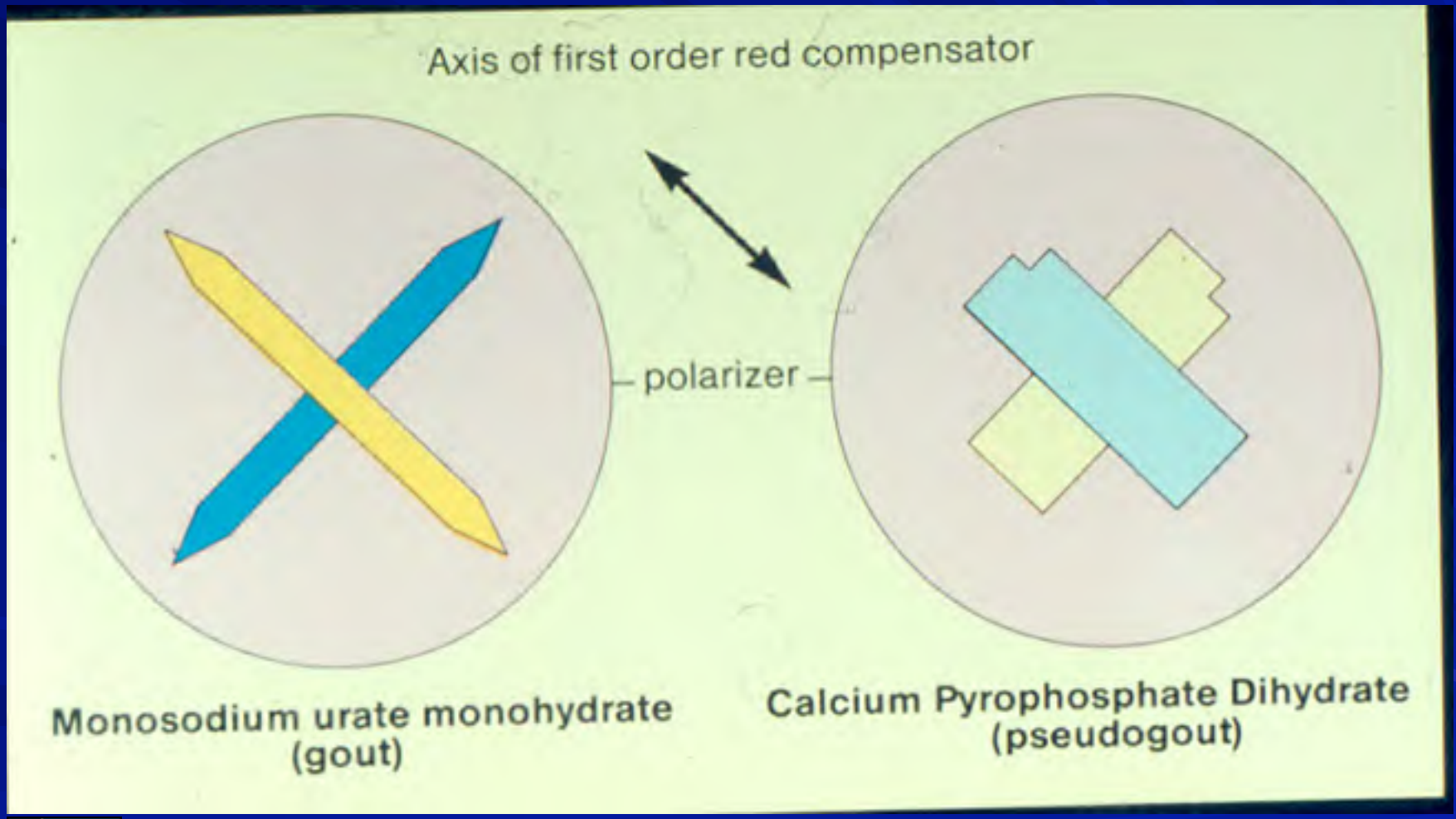
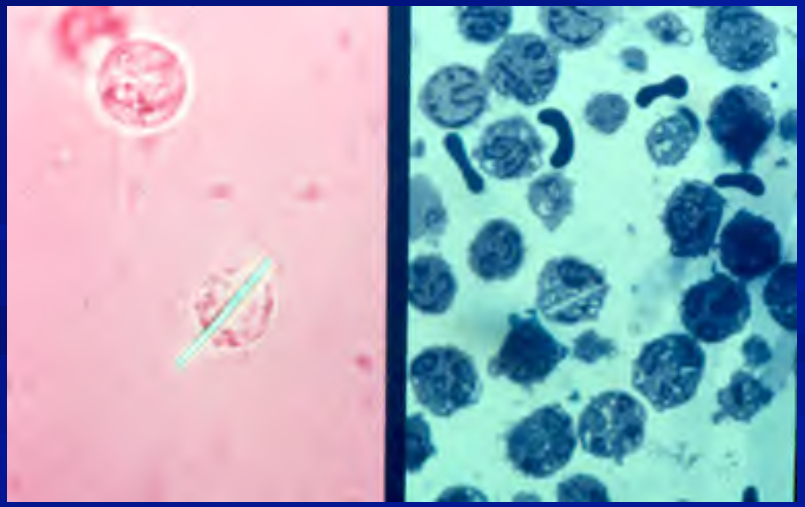
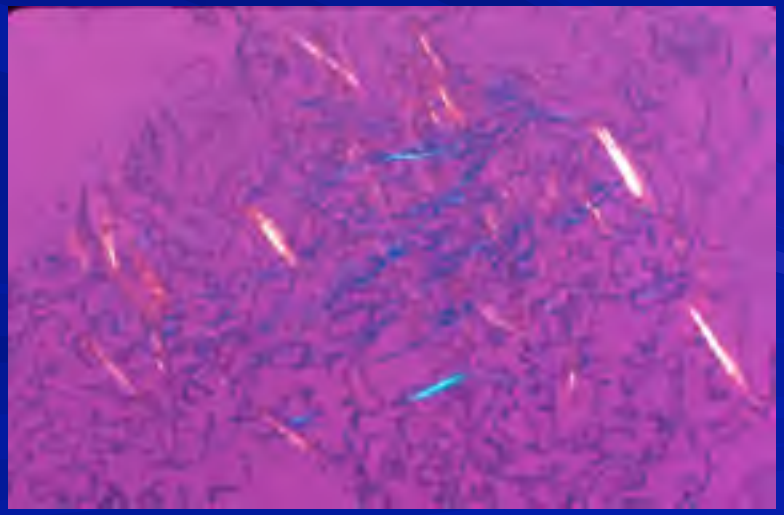
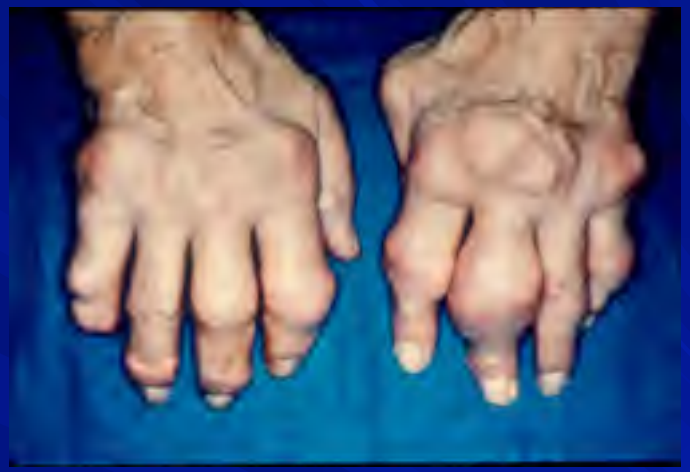


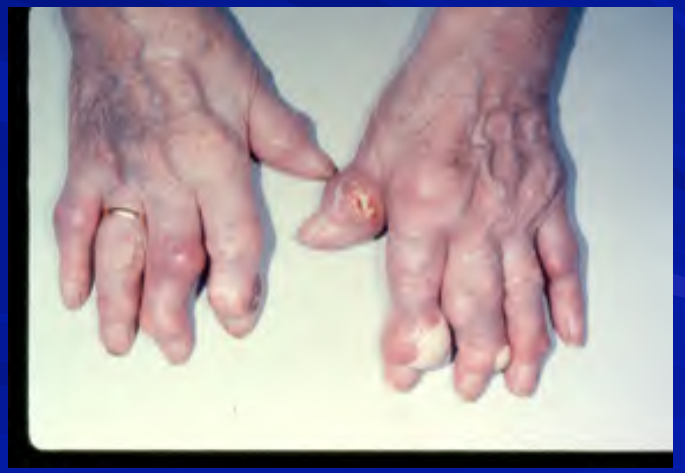
Polarizing Microscopy--examples





Diff Dx?





Diff Dx

- (you fill in the blanks here…)

Complications

- (you fill in the blanks here also)

Treatment

PD-EXP Hans-Simon Holtzbecker, wikimedia commons

- Historic vs. modern
- *Colchicum autumnale*
- Hippocratic writings
- Sydenham's treatise
- Exquisitely effective
- Matthei Botanical Gardens

3 Phases of Gout Treatment

- Acute
- Preventive
- Hyperuricemia control

PD-EXP Source Undetermined

Treatment--acute

- Indomethacin 25-50 mg qid, taper over 5 days
- colchicine 0.6 mg
  - one po per hour to max. of 12 in first 24 hours;
  - then no more than 0.6 mg po TID in the next 7 days
- ? IV colchicine - dangerous
- butazolidin
- IA steroids - other NSAID's
- IL-1 inhibition such as anakinra

Preventive

- indomethacin 25 mg po daily or BID
- colchicine 0.6 mg po daily or BID

Colchicine toxicity

- IV -- repeated doses are dangerous
- -- skin reactions
- Myelosuppression
- Muscle disease
- Neuropathy
- Aplastic anemia
- Thrombocytopenia
- Diarrhea

PD-DP Hans-Simon Holtzbecker, wikimedia commons

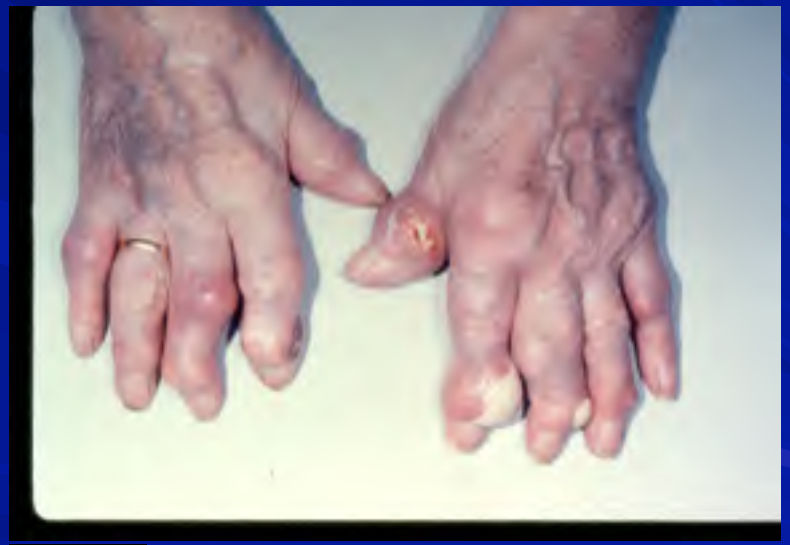
Long term anti-hyperuricemic Rx

- Allopurinol 300 mg po qd (decreases production)
- uricosuric
  - sulfinpyrazone 100 mg (titrate)
  - probenecid 500 mg qd-bid

  - NOTE: Uricosuric therapies require identification of 24 hour urinary uric acid excretion

Which patients need long term anti-hyperuricemic therapy?

- Frequency of attacks
- Severity
- Other circumstances



Uricosurics

- PRO
- ?safer than allopurinol?
- Putative role in decreasing atherogenesis
- Most people are eligible

- CON
- Patient education
- Renal stones
- Rashes
- Tolerability
- 24 hr urine collection to establish candidacy

Uricosuric Treatment

- Establish baseline CrCl and UrCl
- Probenecid: 250 mg bid, increase to 500-1000 mg bid
- Follow up CrCl and UrCl
- Change meds to secondary uricosurics

Primary Uricosurics

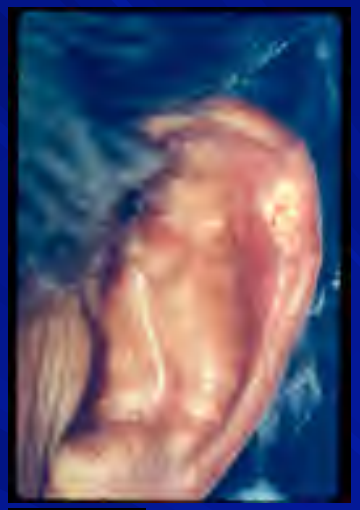
- Probenecid
- Sulfinpyrazone
- Benzbromarone
- EMD 336340

Secondary Uricosurics

- Fenofibrate
- Atorvastatin
- Losartan
- Ampicillin/β-lactams
- Valproic acid

Indications for allopurinol

- Tophi
- Renal insuff (CrCl <80)
- Renal stones (any type)
- Uric acid over-excretion
- Contraindications to uricosurics
- UA >13
- Induction chemotherapy



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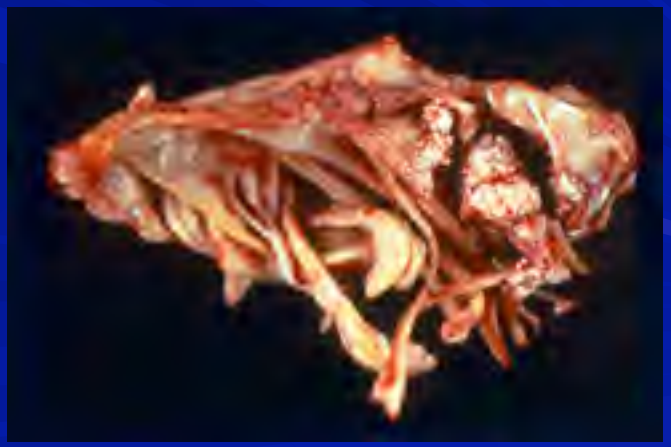

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Allopurinol Side Effects

- Hypersensitivity syndrome
  - Begins 2-12 weeks after treatment
  - Fever, often with maculopapular rash
  - Hepatitis, interstitial nephritis (ATN/ARF), myocarditis, rhabdomyolysis, eosinophilia
- Incidence rate of ~0.4%, mortality 25%
- Complex pathophysiology
  - Idiosyncratic, not related to dose or duration

Allopurinol Side Effects

- Toxic epidermal necrolysis (TEN/ Stevens-Johnson syndrome)
- Incidence of ~ 0.5%
- High serum levels of oxypurinol may increase risk
- Azotemia may increase risk

Allopurinol Safety

- Potentiates azathioprine serum levels
- Potentiates warfarin effects
- ACE inhibitors increase risk of TEN
- Arellano & Sacristan, Ann Pharmacother 27:337-43;1993
  - 76/101 patients with hypersensitivity syndrome were receiving allopurinol for asymptomatic hyperuricemia

Allopurinol Safety

- Roujeau JC et. al, NEJM 333:1600-07;1995.
  - Case control study in 4 European countries to determine relative risk associated with meds and TEN-Stevens-Johnson syndrome
  - RR of allopurinol = 52 (16-167)
  - RR of phenytoin = 53 (11-infinity)
  - RR of pen = 7, ceph = 14

New Therapeutics

- Febuxostat; a specific and potent xanthine oxidase inhibitor with hepatic metabolism
  - US FDA approval 2/13/2009
- Rasburicase; (Recombinant Aspergillus)
  - Approved for tumor lysis syndrome
    - Potential for anaphylaxis
- Uricase-PEG20 (Recombinant Candida)
  - Approved Oct. 2009 “pegloticase” for IV use

Important drug interactions

- Azathioprine
- Mercaptopurine
- Cyclosporin

(another important "interaction" is shown: "Boston Tea Party")

PD-EXP The Boston Tea Party by Sarony and Major

Aspirin (ASA)

- Low dose (100-300 mg) ASA exhibits first-order pharmacokinetics and inhibits tubular secretion of UA
- High dose (>1.0 gm) ASA exhibits zero-order pharmacokinetics, is an effective uricosuric, and may be responsible for the historical observation that RA and gout do not co-exist

Cyclosporin

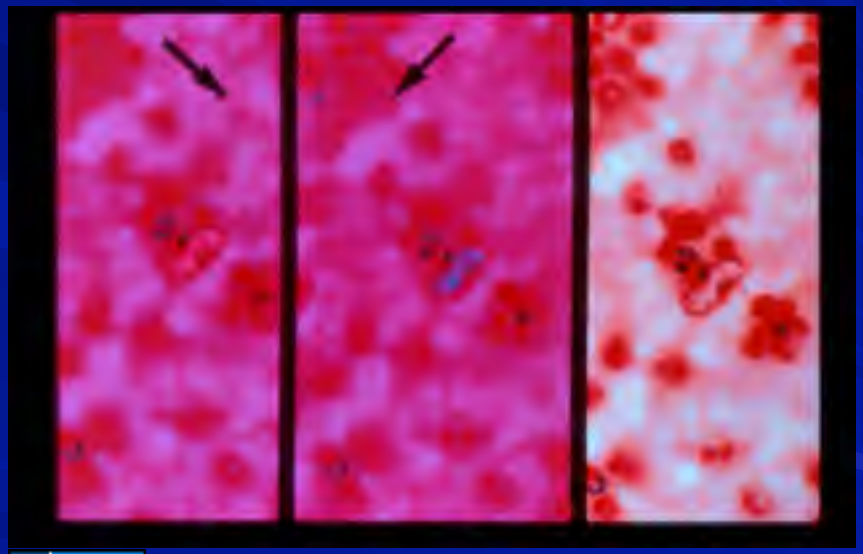
- Major cause of hyperuricemia in organ transplant patients
- Tacrolimus similar effects
- Complex pathophysiology
  - Reduced GFR
  - Reduced urate secretion from proximal tubule
  - Other effects on tubular function

Ethanol

- High dietary purines (beer)
- Ethanol -- acetate -- acetyl-CoA metabolism produces large amounts of AMP in liver
- If AMP production exceeds rates of ATP regeneration then excess AMP is metabolized to uric acid
- Ethanol inhibits UrCl (organic acids and dehydration)

Miscellaneous gout issues…

- What is the role of oxypurinol?
- Role of diet
- Co-existent gout and...
  - OA
  - CPPD
  - Septic arthritis



PD-INCL Source Undetermined

Co-existing conditions

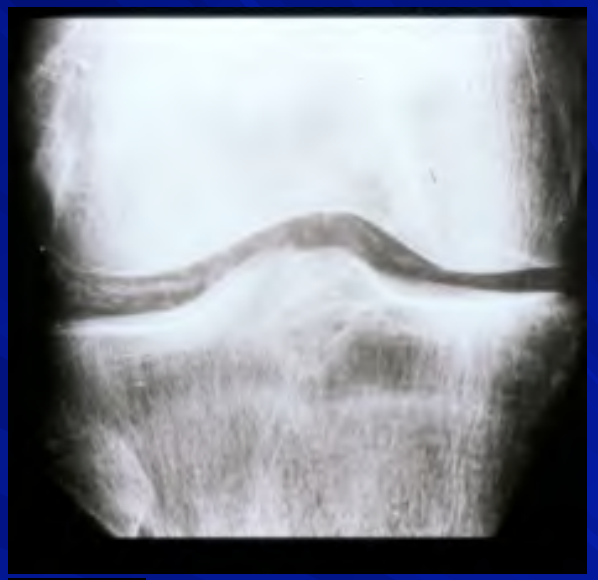
- Gout can occur with infectious arthritis, CPPD, psoriatic arthritis or rheumatoid arthritis
- Joint aspiration with cultures and crystal examination is optimal approach to diagnosis and management

Hyperuricemia and Gout

- Hyperuricemia is not a disease (?)
  - Feig et al. NEJM October 23, 2008
- Gout is diagnosed by examination of synovial fluid
- Allopurinol is not the only treatment

PSEUDOGOUT

- Clinical Syndromes associated with CPPD
  - Radiographic Dx ("Chondrocalcinosis")
  - Familial Clusters
  - Endocrinopathies
  - Intra-operative diagnosis (cause or effect?)
  - Pseudogout attacks
  - Polarizing Microscopy



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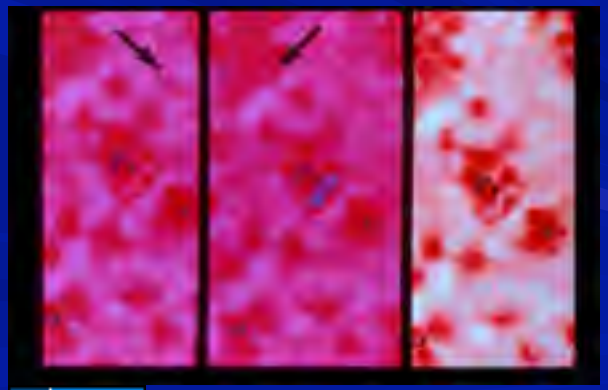

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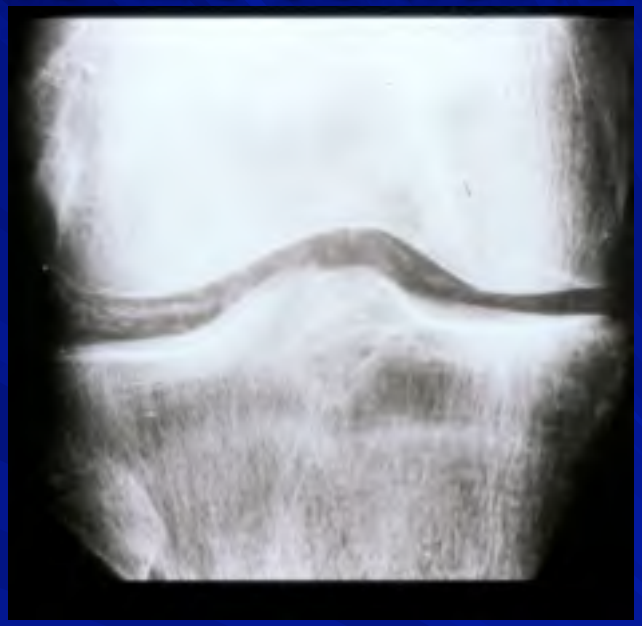
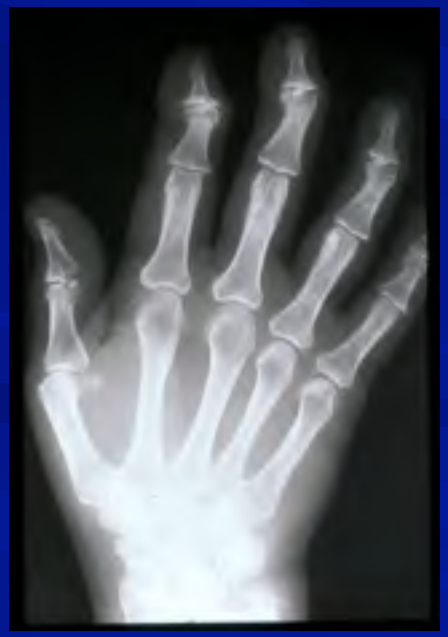
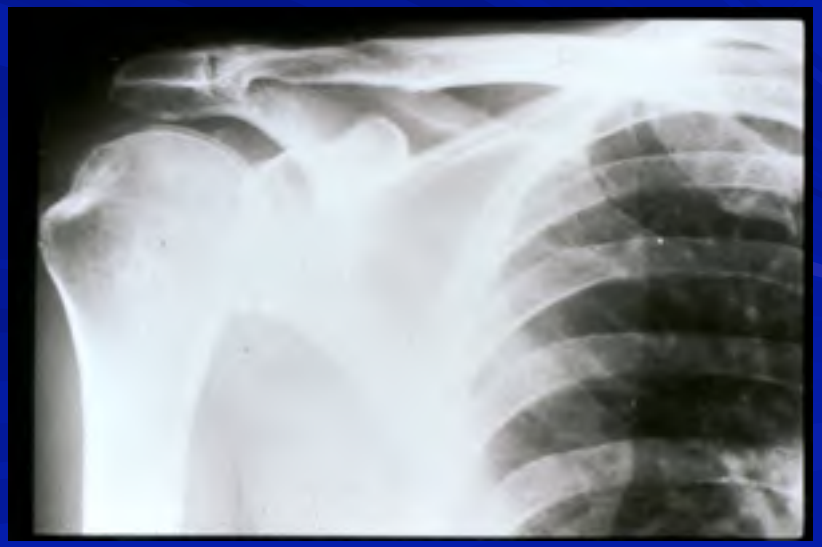
Chondrocalcinosis Locations

- Knee
- Shoulder
- Wrist
- Symphisis Pubis







Diagnosis of Pseudogout

- Synovial fluid aspiration and examination using polarizing microscopy
- DIY!
- Identification of intracellular CPPD crystals
- Rhomboid shaped, positive birefringence, blue (parallel first order compensator)

CPPD some more clinical facts

- “DISH” diffuse idiopathic skeletal hyperostosis is common
- CPPD is a common radiographic finding in the elderly
- Radiographs and symptoms do not always correlate
- Treatment is simpler than gouty arthritis therapies

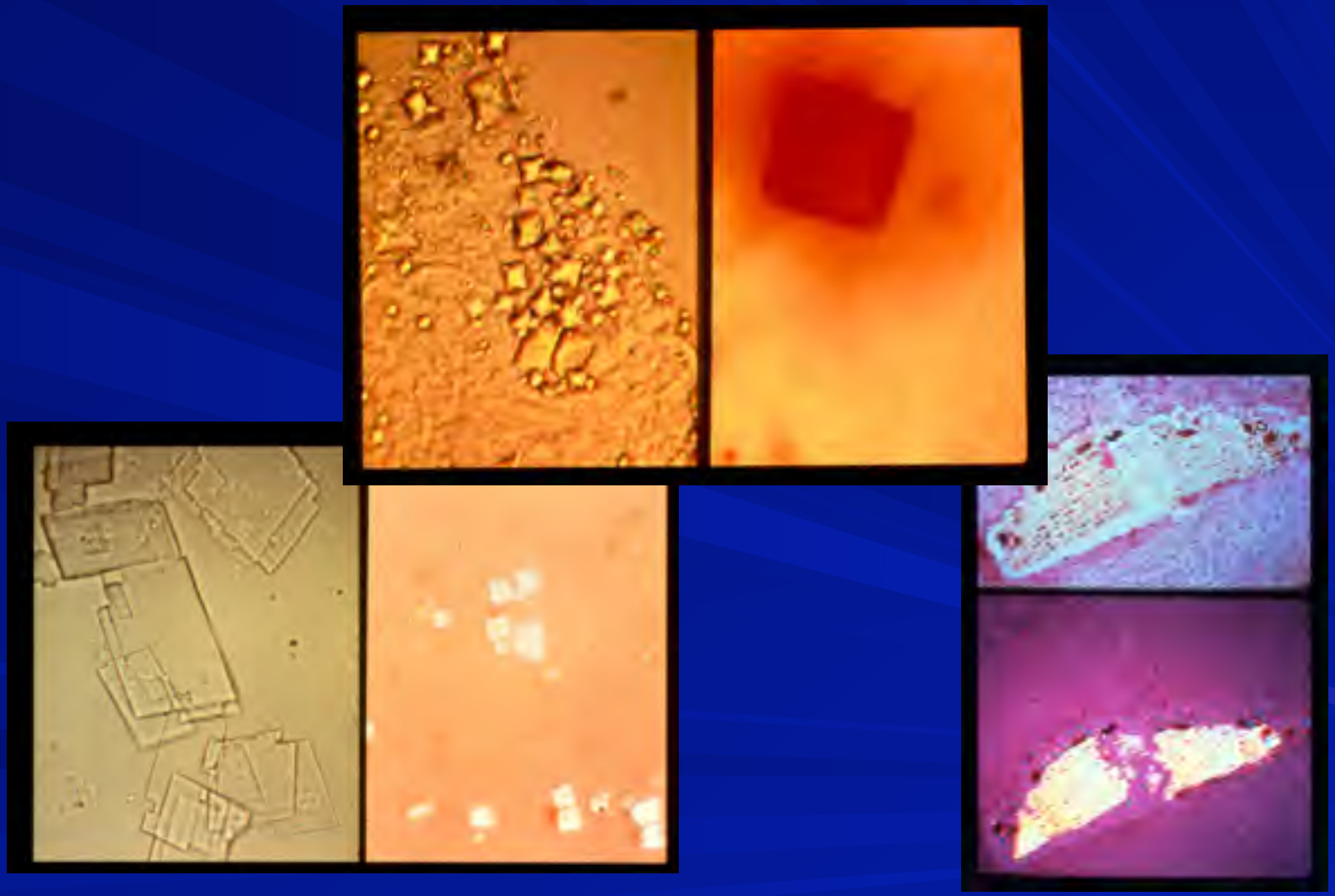
Pseudogout Treatment

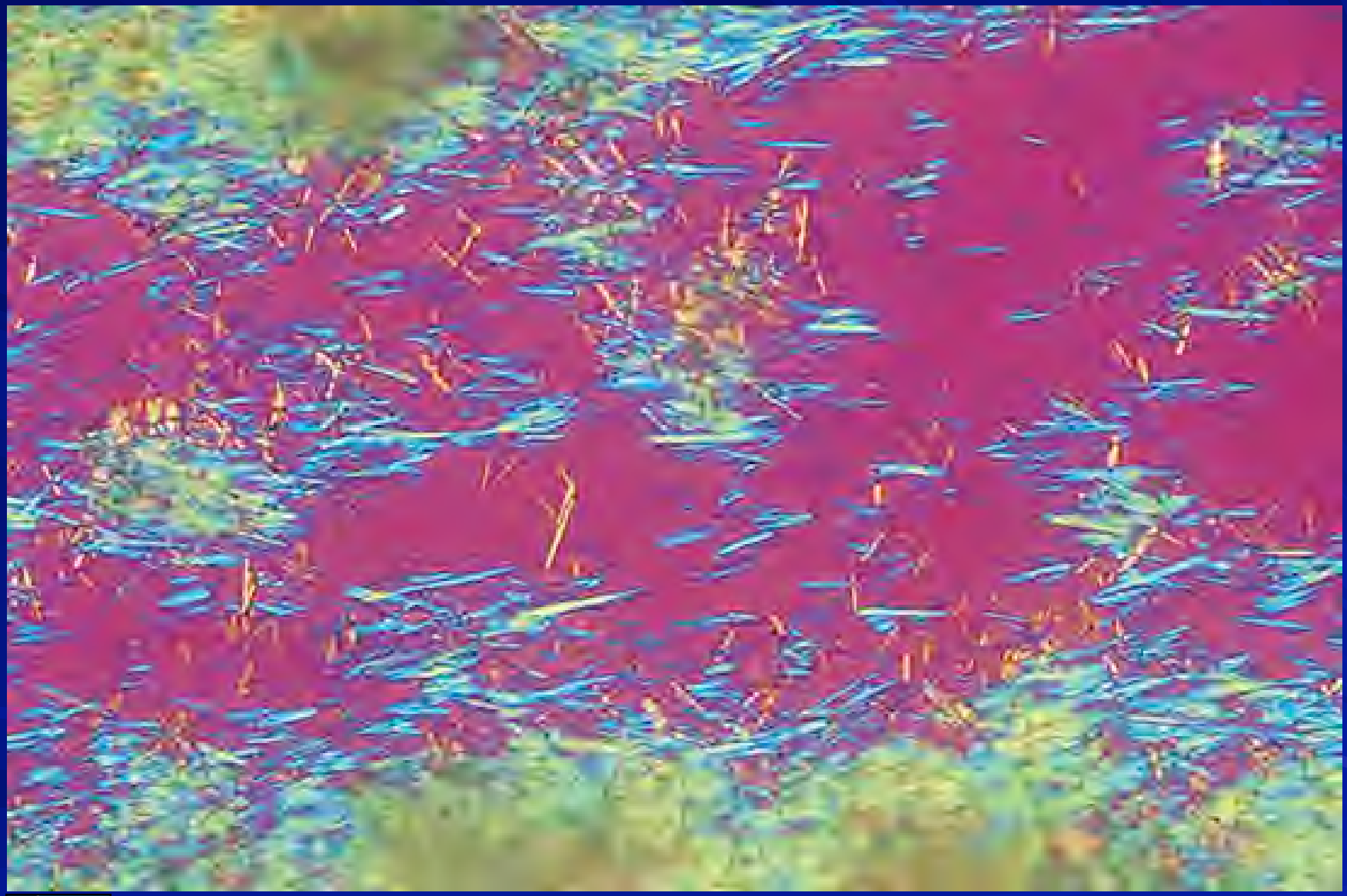
- Response to Indomethacin
- Response to Colchicine
- Monophasic treatment only
- Intra-articular steroids
- Epiphenomenon/ cause or effect?/ is treatment worthwhile?

CPPD Treatment

- Symptomatic
- NSAIDS
- Colchicine
- Intra-articular steroids
- Metabolic risk factors
  - Thyroid disease
  - Hyperparathyroidism
  - Hemachromatosis
  - DM

Miscellaneous Crystals





PD-INCL Source Undetermined

Thank you!
Questions?

Additional Source Information

for more information see: http://open.umich.edu/wiki/CitationPolicy

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