GOUT: DIAGNOSIS AND TREATMENT

DISEASE OF THE KINGS AND THE QUEEN OF DISEASES

PHYSIOLOGIE DU GOUT,

OU

MÉDITATIONS DE GASTRONOMIE TRANSCENDANTE;

OUVRAGE THÉORIQUE, HISTORIQUE ET A L'ORDRE DU JOUR,

Dédié aux Gastronomes parisiens,

PAR UN PROFESSEUR,

MEMBRE DE PLUSIEURS SOCIÉTÉS LITTÉRAIRES ET SAVANTES

TOME PREMIER.

PARIS,

CHEZ A. SAUTELET ET Cie LIBRAIRES,

PLACE DE LA BOURSE [illegible], PRÈS LA RUE FEYDEAU.

1826.

A MATTER OF "COURSE."

Eminent German Specialist. "VAT VATERS 'AVE YOU BEEN IN ZE 'ABIT OF TAKING?"

English Gouty Patient. "WATER! HAVEN'T TOUCHED A DROP, EXCEPT WITH MY TEA, FOR THE LAST THIRTY YEARS!"

[Upon which a mild course of Homburg, Kissengen, Marienbad, and Karlsbad is at once prescribed.

DEFINITION

- **Gout** is a clinical syndrome, a result of inflammatory response to monosodium urate monohydrate a (MSUM) crystals that can form in people with hyperuricemia.

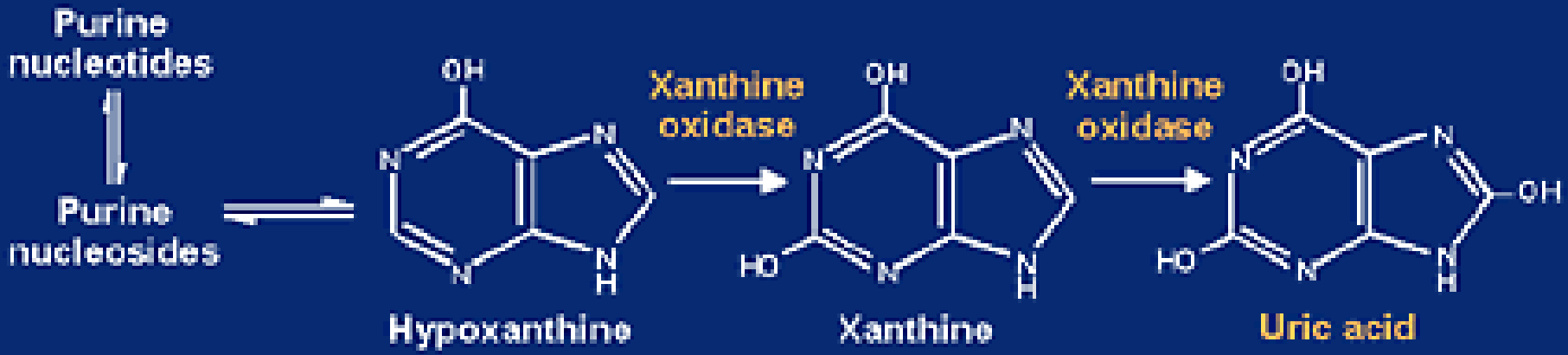
Uric Acid, Hyperuricemia, and Gout

- Uric acid (urate) is the end product of purine degradation in humans
- Hyperuricemia is a serum urate concentration in excess of urate solubility (≥6.8 mg/dL)
  - Results from overproduction and/or underexcretion of uric acid
  - Is a common serum abnormality but does not result in gout without crystal deposition
- Gout is the disease state resulting from deposition of monosodium urate crystals in tissues

From lecture by H.R. Schumaher

Purine Degradation to Uric Acid

- **Xanthine oxidase** catalyzes the final conversions to uric acid



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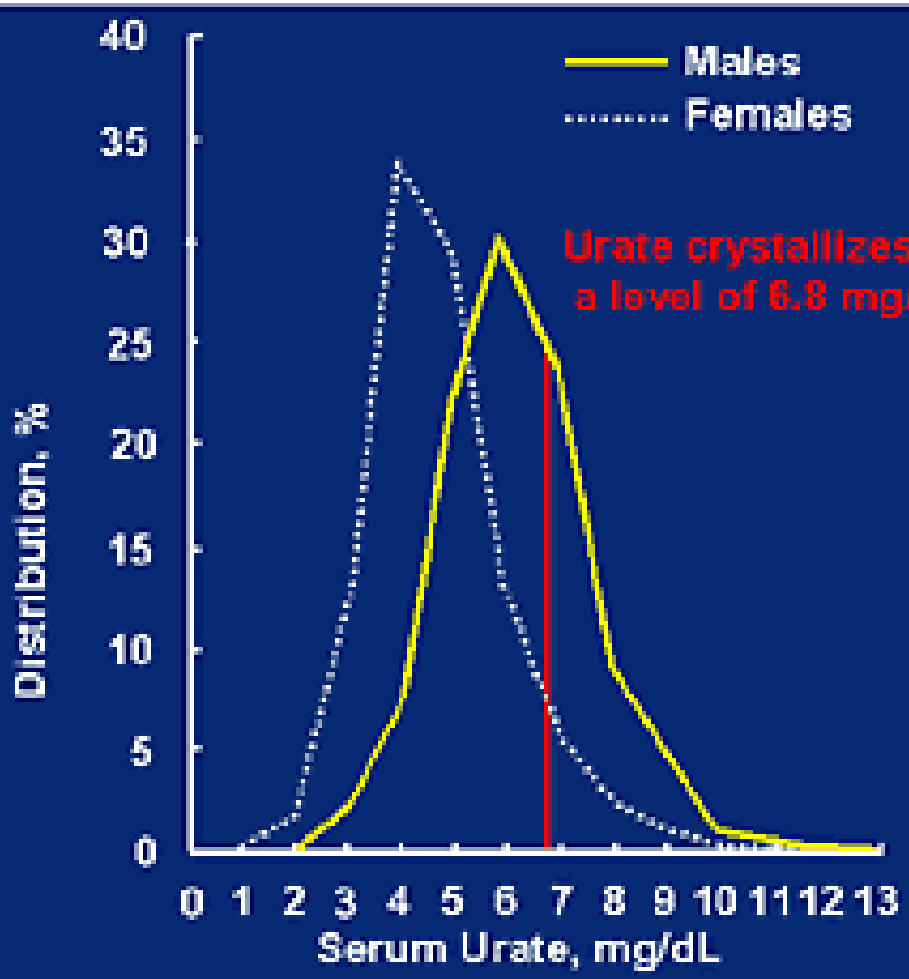
Distribution of Serum Urate Values

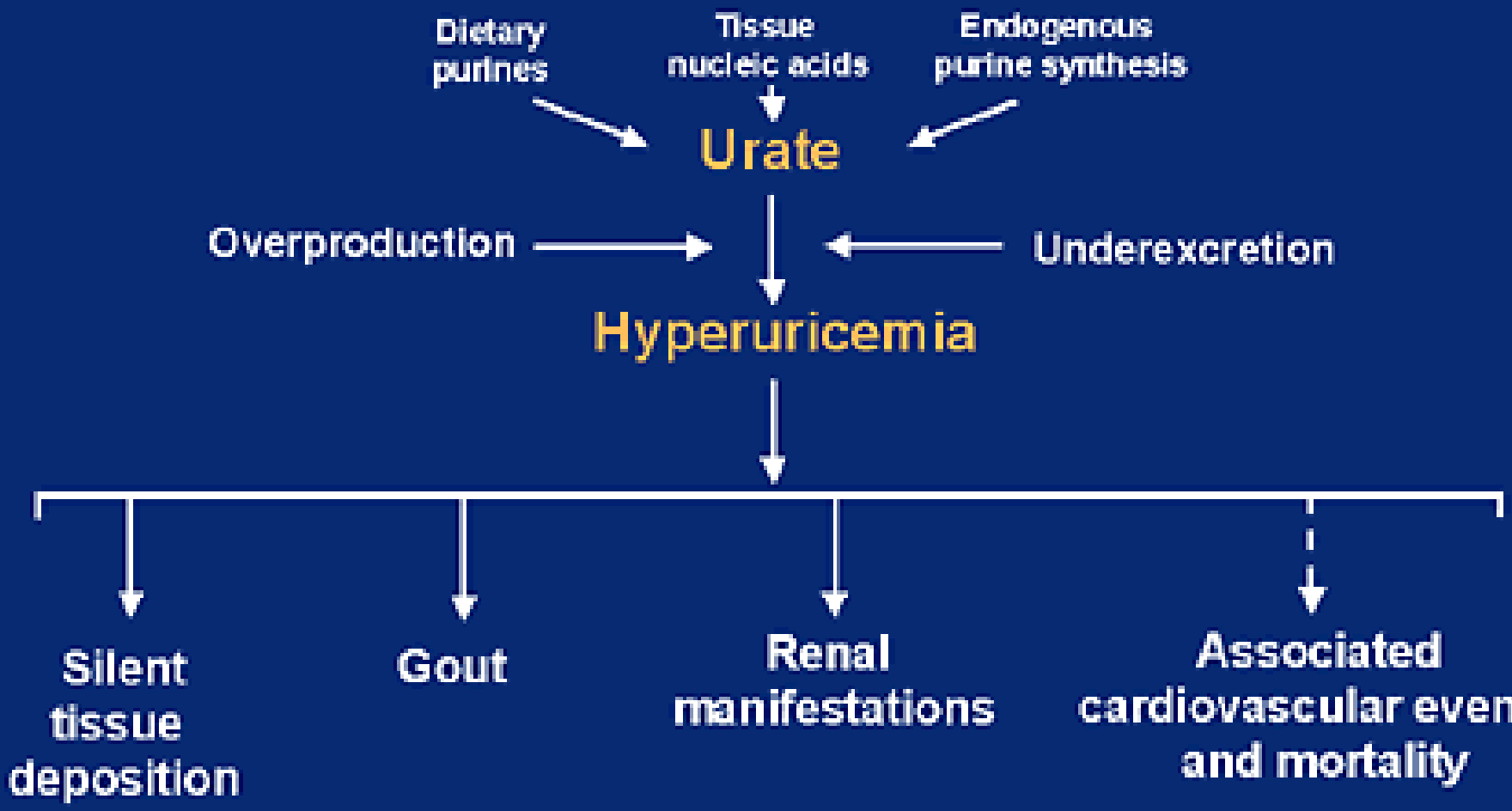


Serum urate levels in 1515 men and 1670 women aged ?30 in Taiwan 1991-1992

Lin et al. *J Rheumatol.* 2000;27(4):1045-1050.

From lecture by H.R. Schumaher

The Hyperuricemia Cascade



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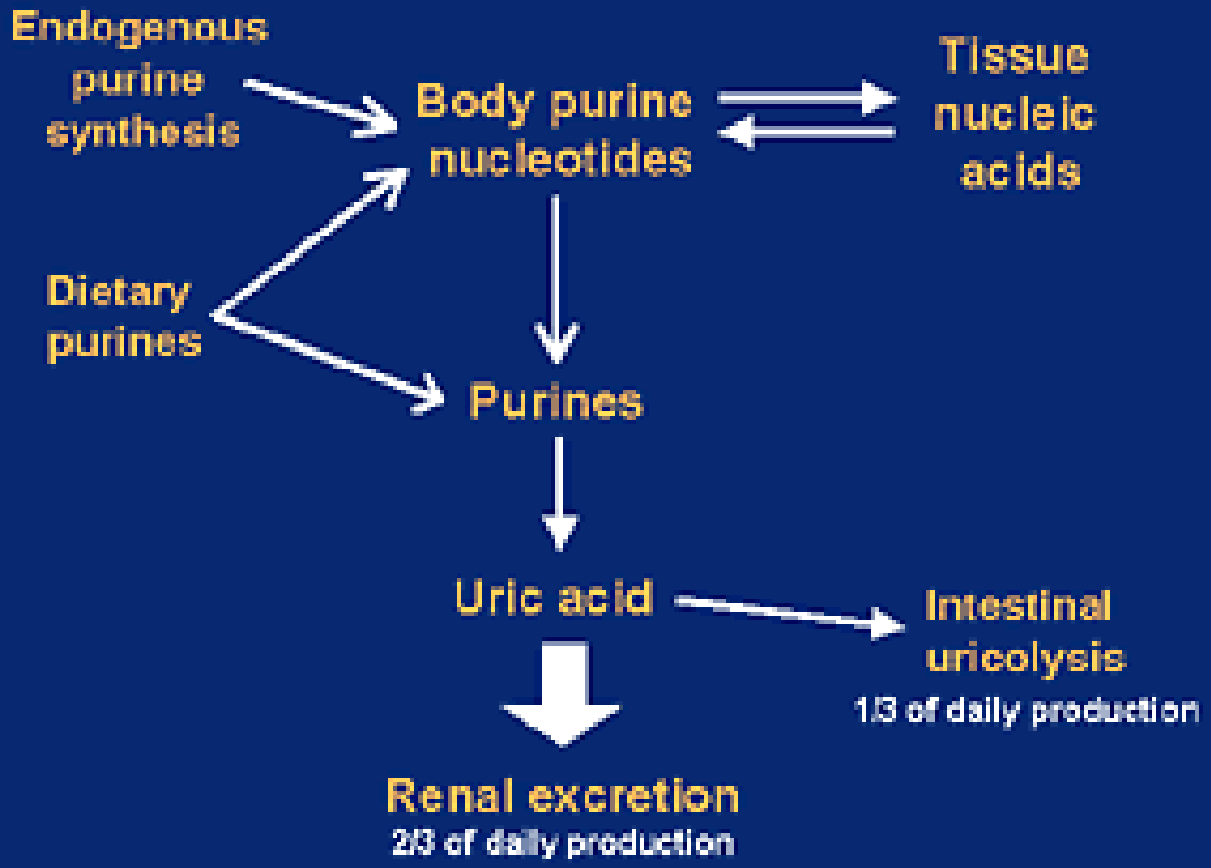
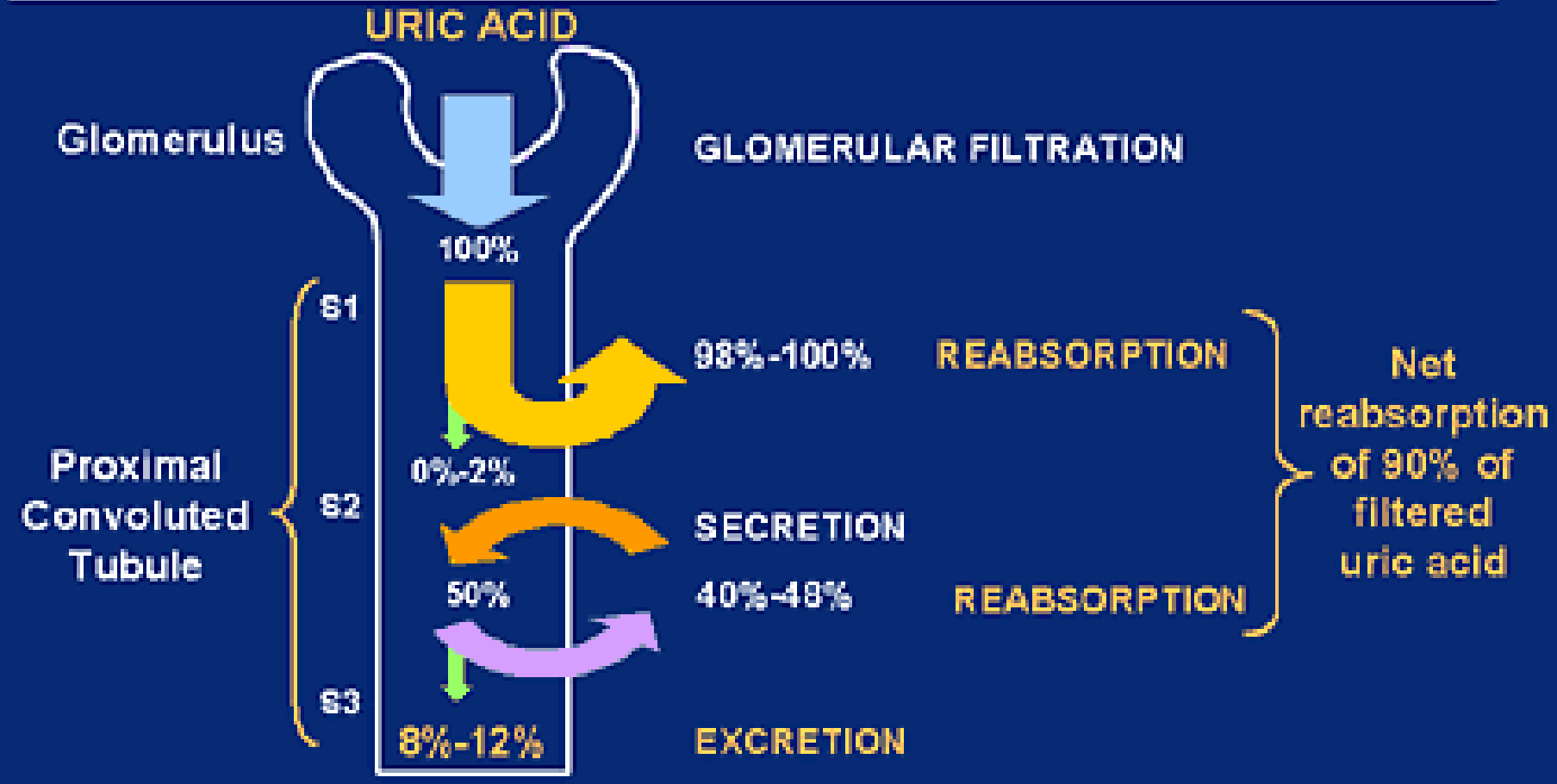
Schematic Overview of the Production and Elimination of Uric Acid



Koopman, ed. In: *Arthritis and Allied Conditions*. 14th ed. Lippincott, Williams and Wilkins; 2001:2283.

Renal Elimination of Uric Acid

Operationally Defined 4 Component Model of Renal Uric Acid Handling



The multiple reabsorptive and secretory mechanisms may be regulated by a recently identified gene product of URAT-1 (Enomoto et al., Nature, 2002)

Incidence of Gout

- High incidence[1]
  - 8.6% cumulative incidence in US white men for all gout
  - 5.9% for primary gout (gout without a history of diuretic use)
- Increasing incidence of primary gout[2]
  - 1977-1978 - age and sex-adjusted annual incidence rate for primary gout 20.2/100,000
  - 1995-1996 - age and sex-adjusted annual incidence rate for primary gout 45.9/100,000
  - A greater than 2-fold increase in the rate of primary gout

1. Roubenoff et al. *JAMA.* 1991;266:3004-3007.
2. Arromdee et al. *J Rheumatol.* 2002;29(11):2403-2406.

Why the Increased Prevalence of Gout and Subsets of Refractory Disease?

Increased Prevalence of Contributory Factors

- Longevity
- Hypertension
- Obesity
- Metabolic syndrome
- End-stage renal disease
- Diuretic use
- Low-dose aspirin
- Major organ transplantation

Bieber et al. *Arthritis Rheum.* 2004;50(8):2400-2414.

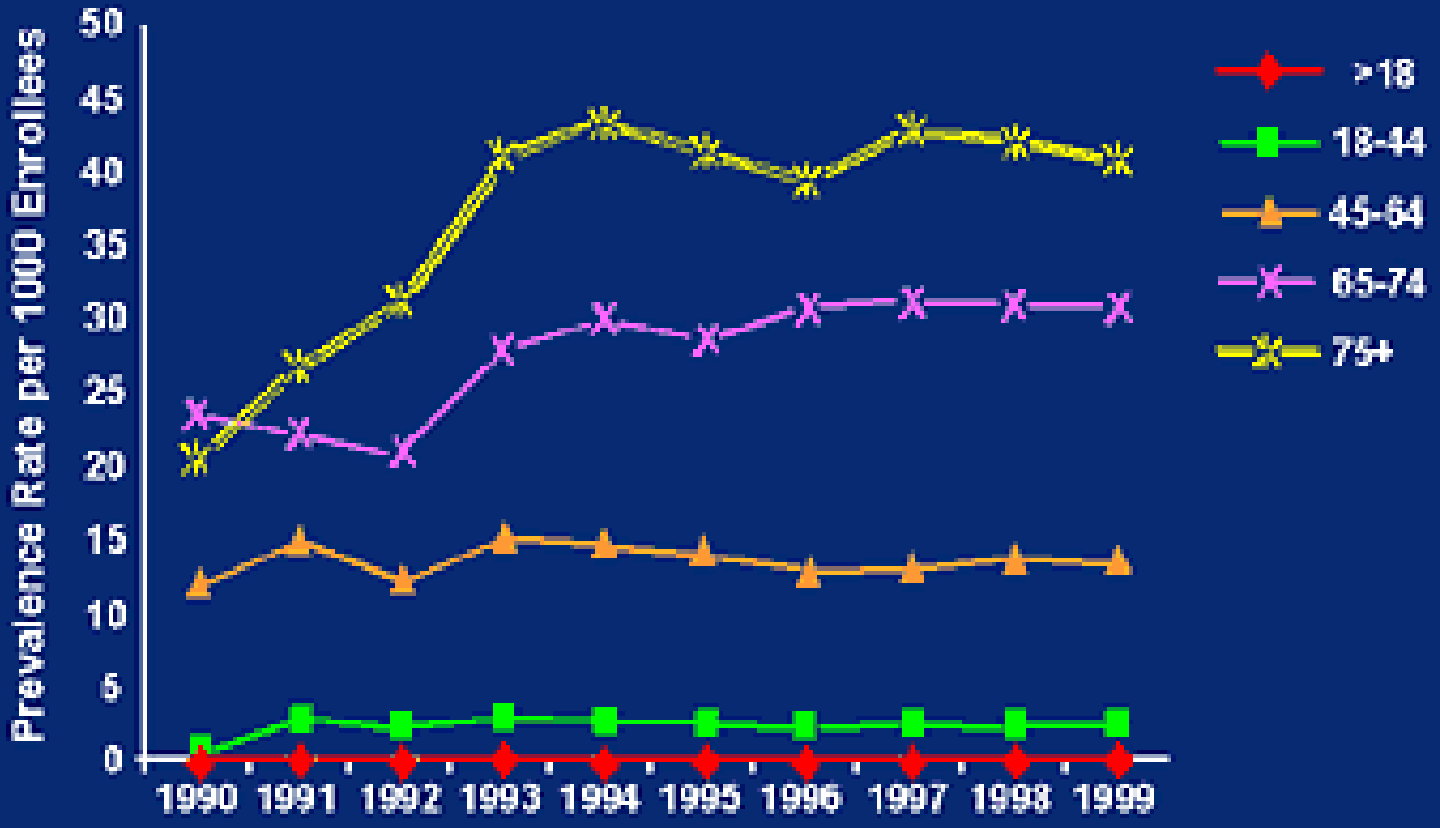
Risk Factors for the Development of Gout
Gender

- Men
  - Have higher serum urate levels
  - In younger patients, gout overwhelmingly in men
- Women
  - Increased risk after menopause
    - Decreased estrogen may diminish the renal excretion of uric acid
    - Of gout patients older than 60, half are women
  - The declining use of estrogen replacement therapy may promote a higher frequency of gout and an earlier age at onset[1]

1. Bieber et al. *Arthritis Rheum.* 2004;50(8):2400-2414.

Risk Factors for the Development of Gout
Aging

Higher prevalence of gout and clinically significant hyperuricemia in higher age groups



Wallace et al. *J Rheum.* 2004;31(8):1582-1587.

CAUSES OF HYPERURICEMIA

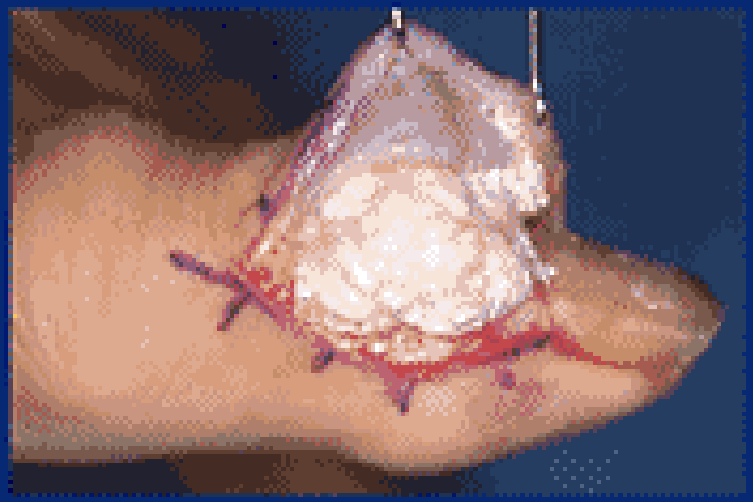
I. Hyperproduction	
Nutritional	Use of purines (meat, seafood) Alcohol (Beer) Fruit fructose
Hemopoietics	Myeloproliferative disorders Policitemia, infectious mononucleosis leukaemia
Rheumatic diseases	Psoriasis
Medication	Cytotoxic agents, nicotinic acid

CAUSES OF HYPERURICEMIA

II. Hypoexcretion	
Nutritional	Alchool
Renal/vascular	Kidney diseases (of any etiology) Low urine volume <1 ml/min Decrease of plasma volume Hypertension
Medication	Aspirin (low doses), phenylbutazone (low doses), thiazid diuretics, furosemide (increased uric acid reabsorption), etacrynic acid, etambutol, pyrazinamide, nicotinic acid.
Metabolites/ Hormones	Vazopresin, lactic acidosis, ketosis, angiotensin
Others	Mixedema, respiratory acidosis, gestosis, acute myocardial infarction, hyperparathyroidism

Monosodium Urate Crystal Formation From Hyperuricemia

- High levels of urate in extracellular fluids
- Crystals precipitate in joints and soft tissues



1

From lecture by H.R. Schumaher

1. http://www.eatonhand.com.

Gout

One Chronic Disease, Best Described by 4 Stages

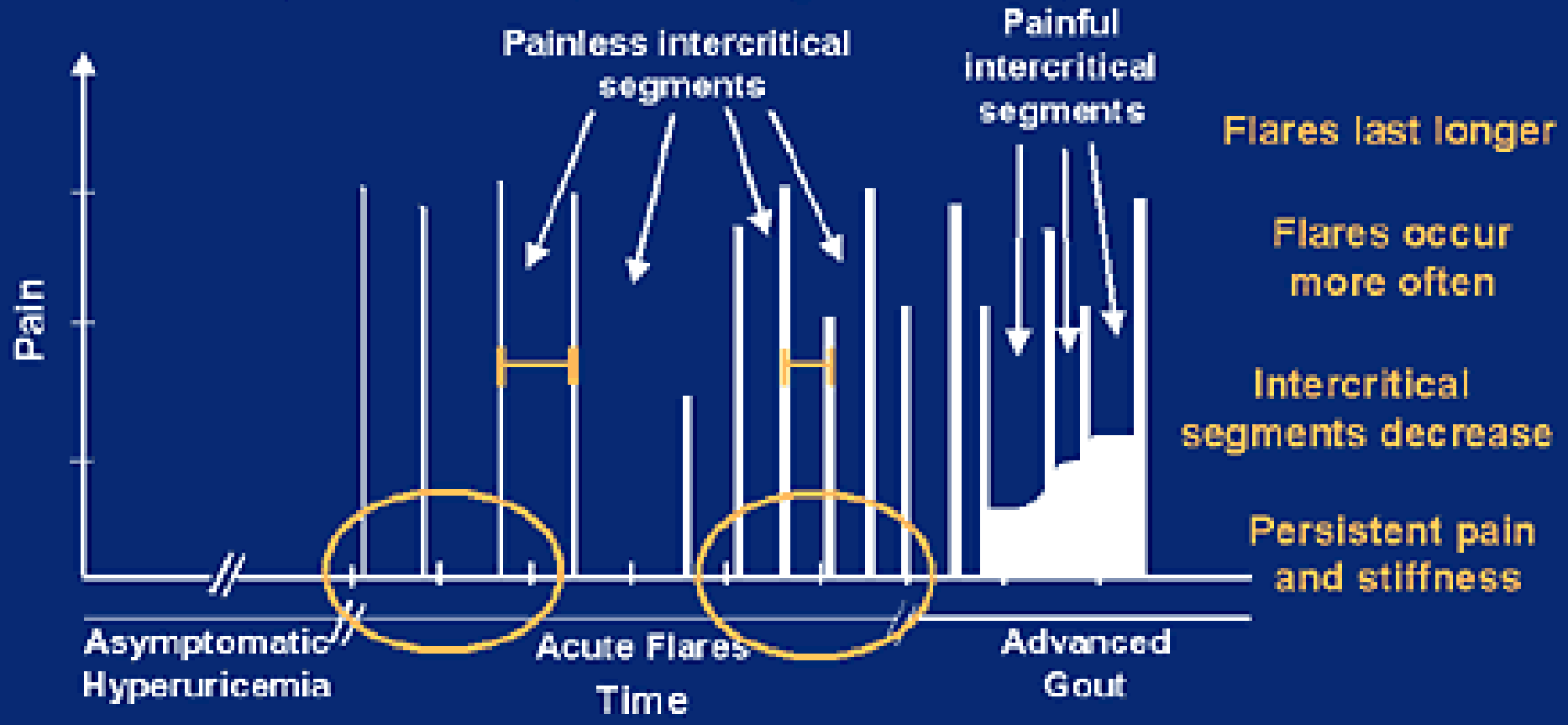
Asymptomatic Hyperuricemia	Acute Flares	Intercritical Segments	Advanced Gout
Elevated serum urate with no clinical manifestations of gout	Acute inflammation in the joint caused by urate crystallization	The intervals between acute flares	Long-term gouty complications of uncontrolled hyperuricemia

Uncontrolled Hyperuricemia

From lecture by H.R. Schumaher

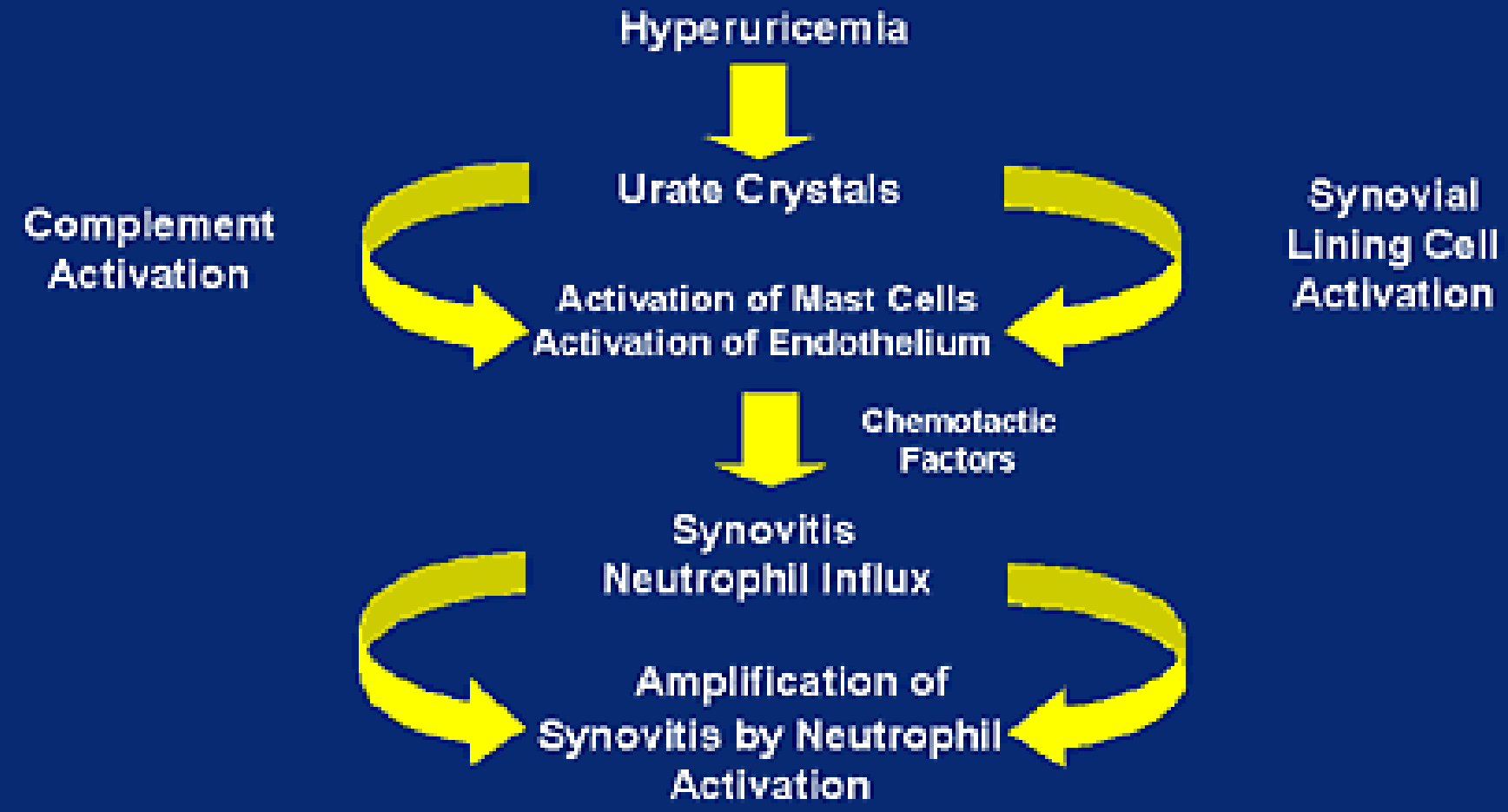
Evolution of Hyperuricemia and Gout

Over time, untreated, chronic hyperuricemia increases body urate stores, advancing the severity of the disease



Adapted from Klippel et al, eds. In: *Primer on the Rheumatic Diseases*. 12th ed. Arthritis Foundation; 2001:313.

Pathogenesis of Acute Gouty Inflammation



Tramontini et al. *Arthritis Rheum.* 2004;50:2633-2639.
Bieber et al. *Arthritis Rheum.* 2004;50:2400-2414.

Clinical features

- The evolution of gout goes through 4 distinctive stages: asymptomatic hyperuricemia, acute gout attack, gout in the intercritical period, chronic tofi gout

I. Asymptomatic hyperuricemia – represents the stage at which the serum level of uric acid is increased, but symptoms of gouty arthropathy still do not exist and no tofi or renal lithiasis have occurred.

It is not practically a disease but a modification of laboratory data and can be detected by chance.

Clinical features
Acute attack trigers

- Trauma: Microtraumas, surgery, joint trauma, intense exercise
- Food: alcohol use, excess food, hunger, obesity
- Some drugs, affecting the level of urates in serum (allopurinol, less than 1 gram aspirin, uricosuric agents)
- In the case of trauma, surgery, drugs that influence the level of urates in serum acute access may also occur on the background the normal level of urates in the serum

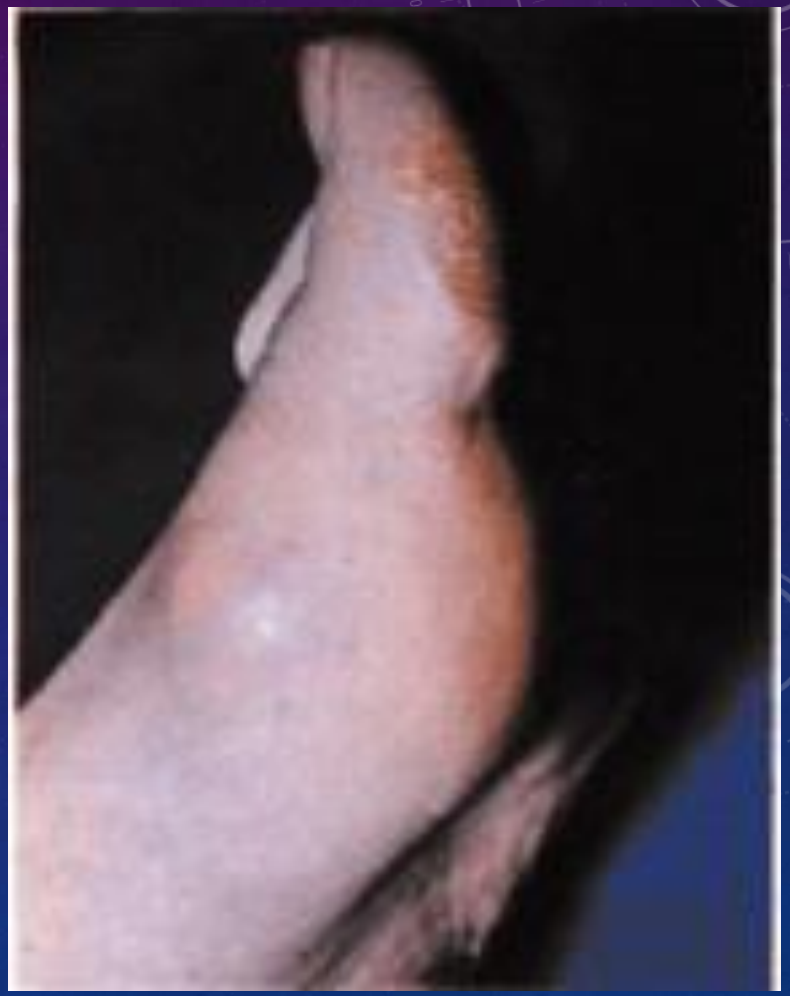
Clinical features

II. Acute gout attack – rapid development of pain, erythema, swelling and local fever in the affected joint.

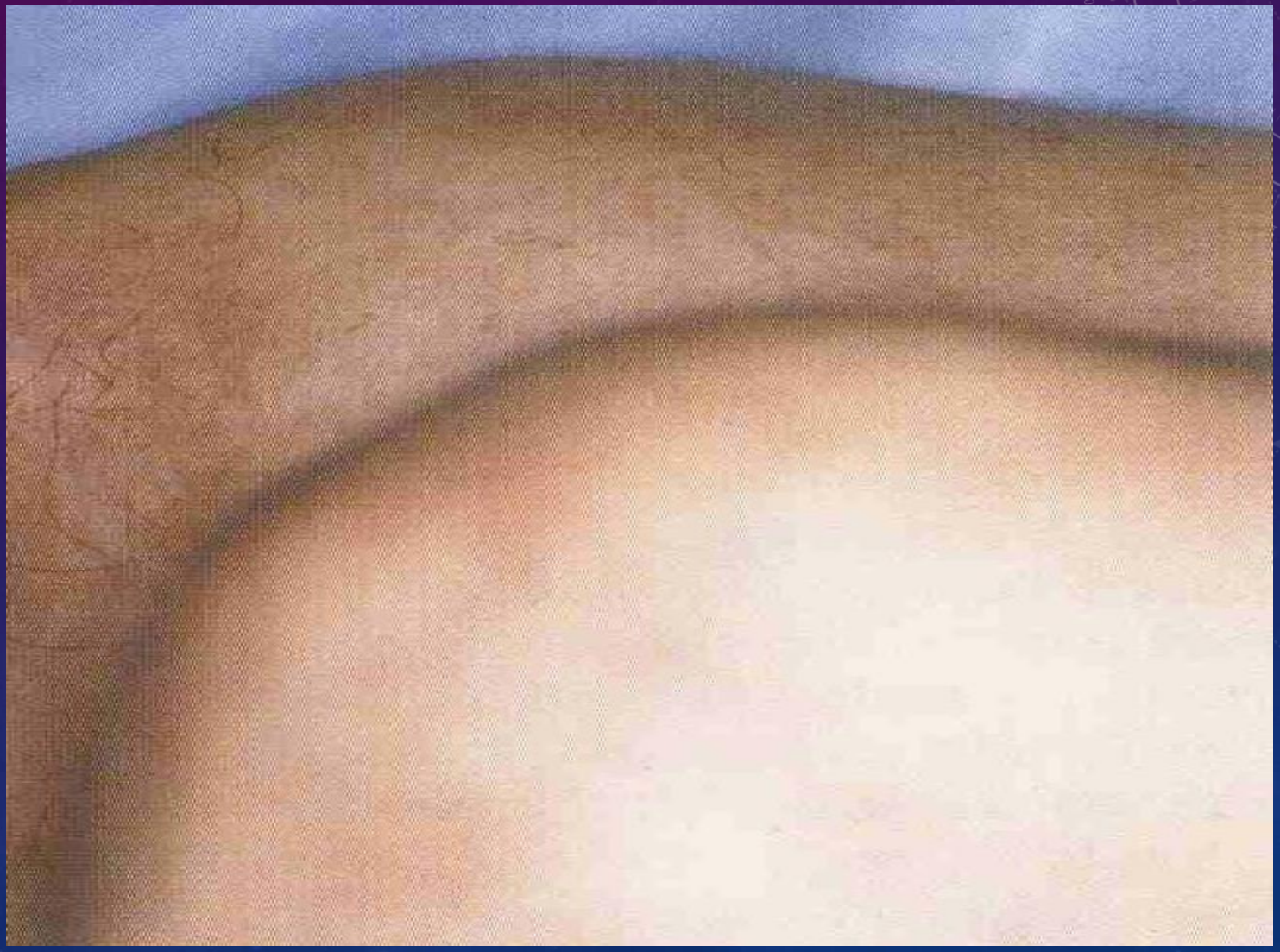
Affected joints: the initial attack is usually monoarticular and in most patients includes I MTP joint. Other joints that frequently are affect in gout: plantar joints, talo-crural, heel, knees, radiocarpals and elbows. Less often are affected shoulders, coxofemoral, spine, sacroiliac joints.

Clinical features

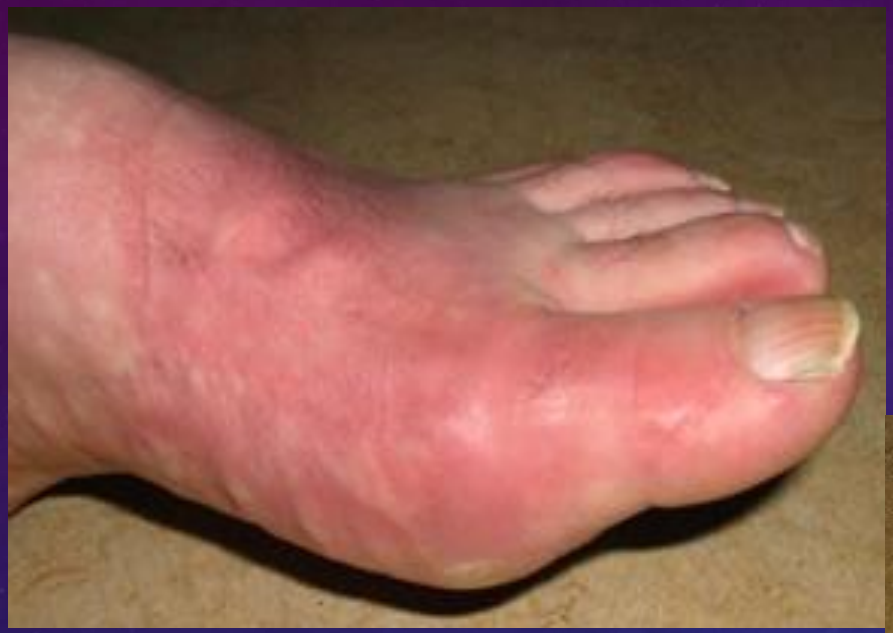
- **General symptoms:** fever, chills and general weakness may associate gout attack.
- **Polyarticular damage**: becomes much more common during the chronic phase.

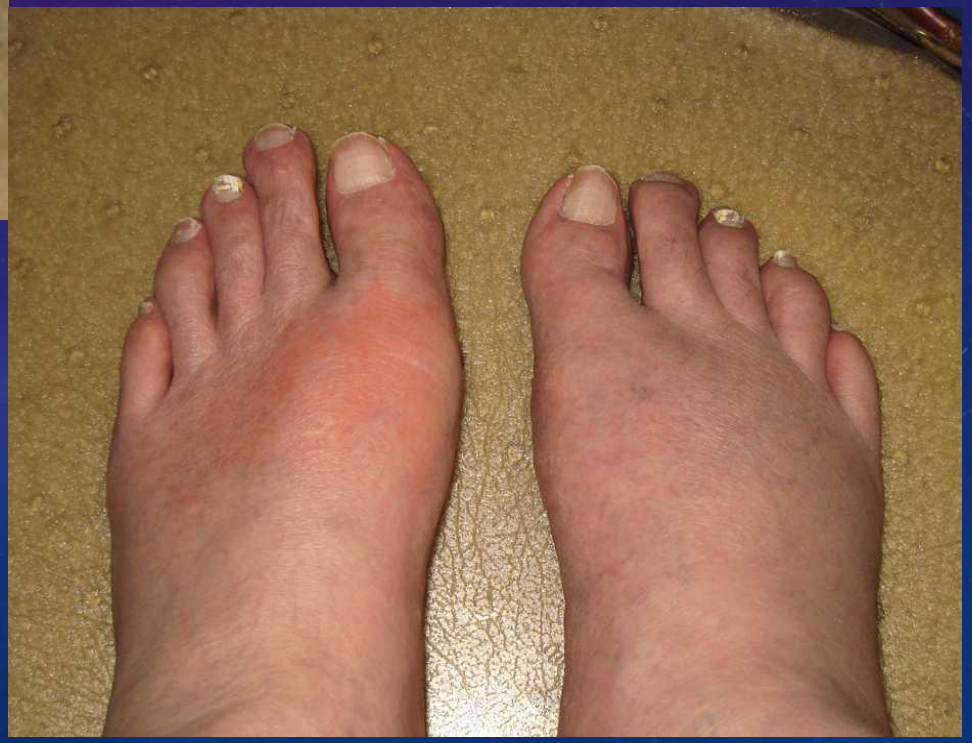


Clinical features

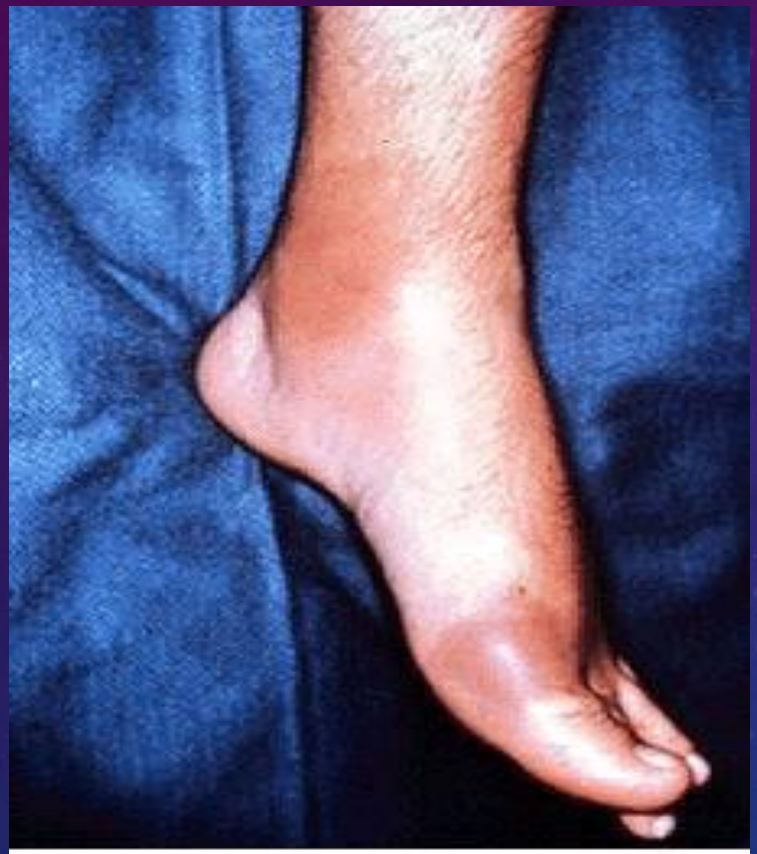


Clinical features





Clinical features



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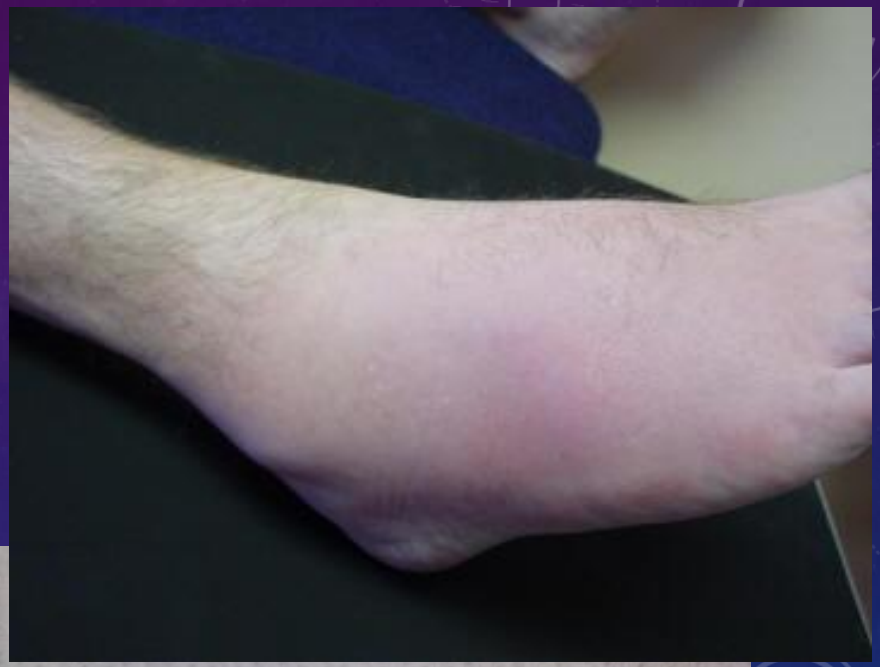
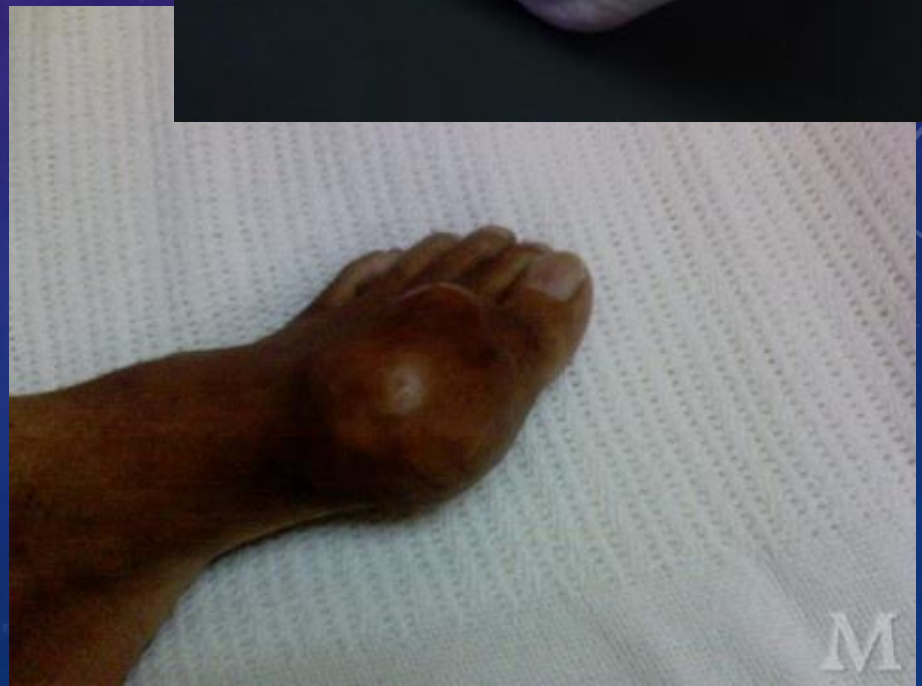
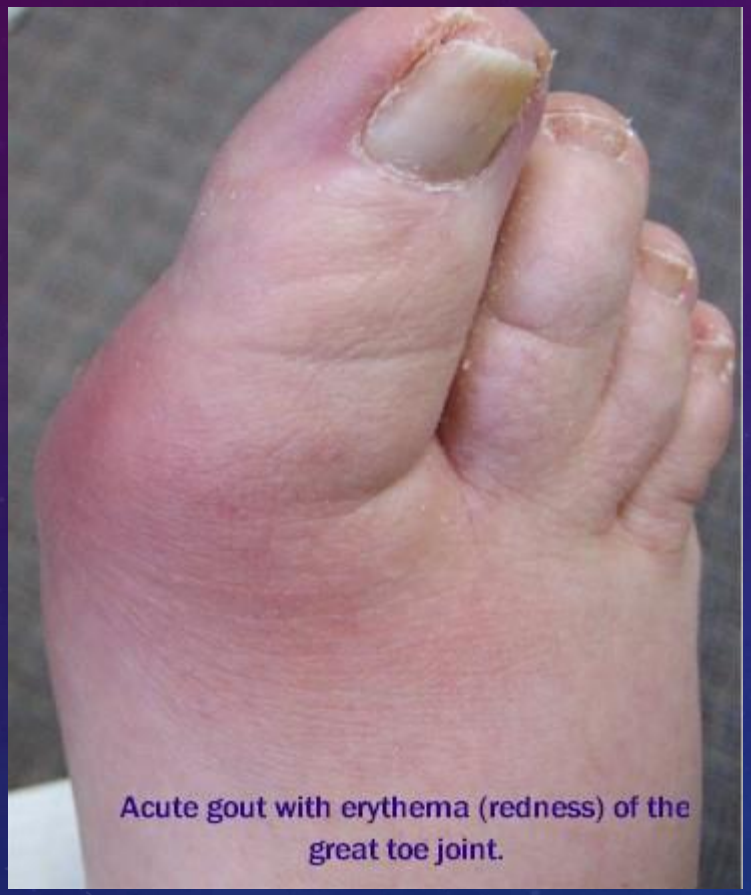
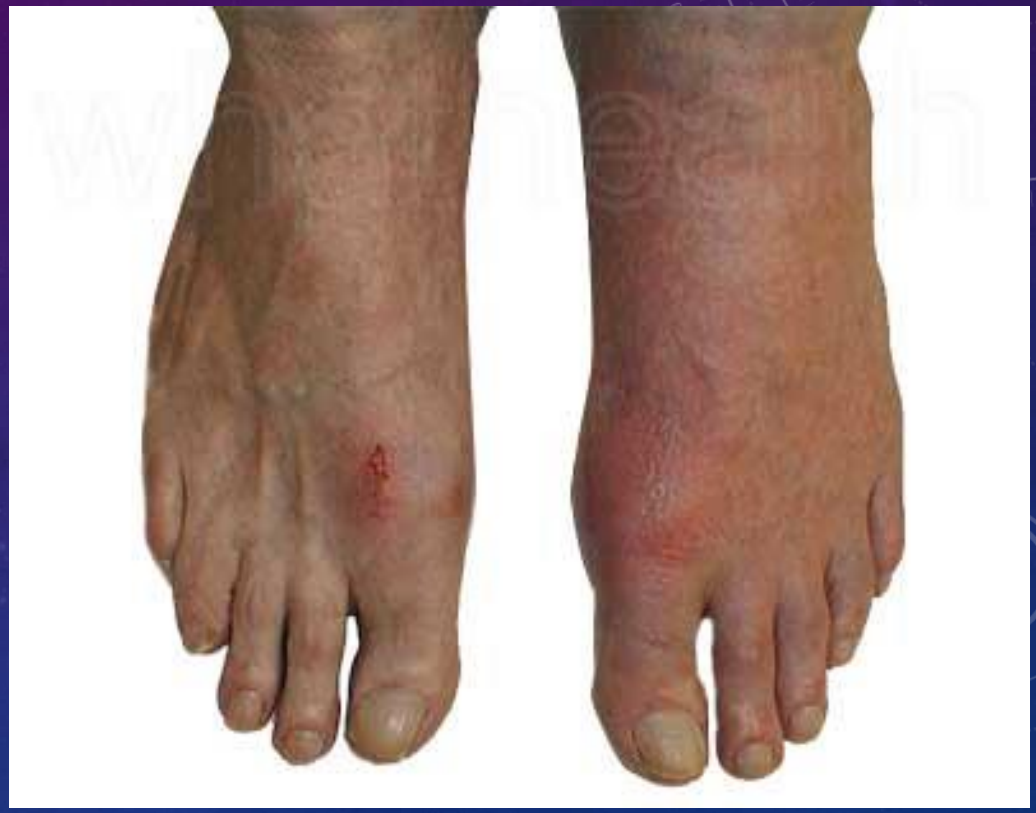




Clinical features


Acute gout with erythema (redness) of the great toe joint.



Aspects of an Acute Flare

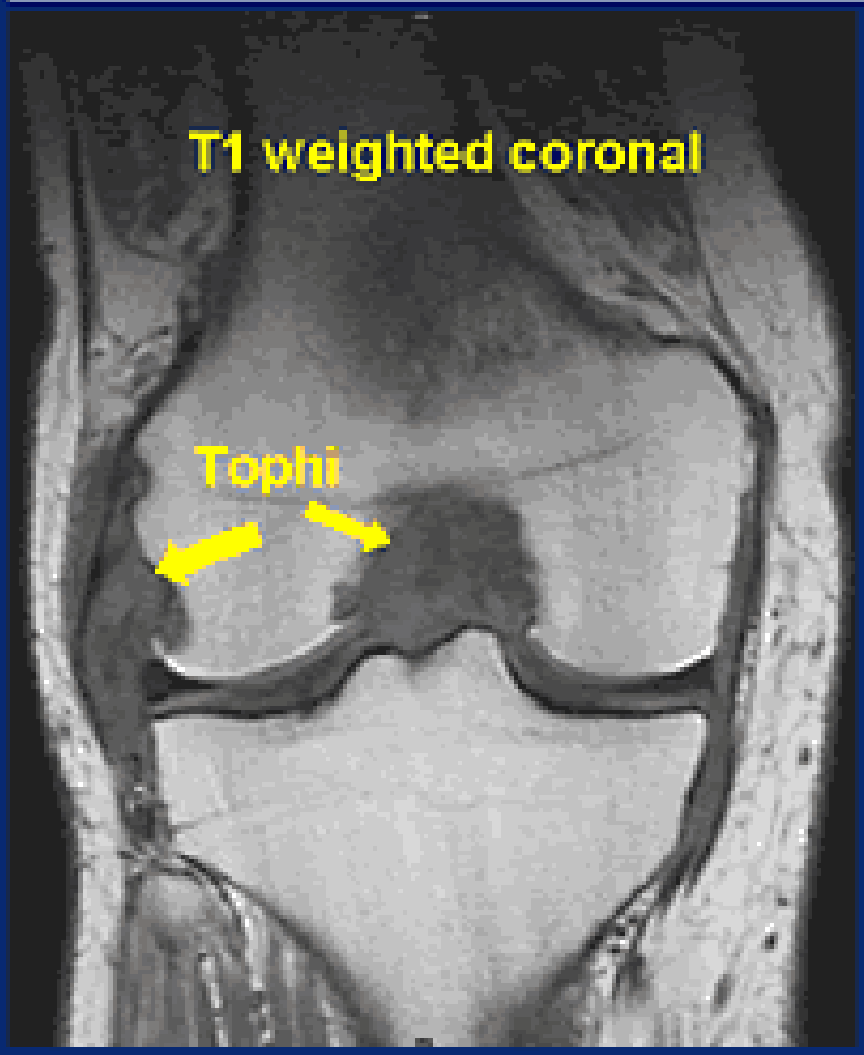
- Abrupt onset of severe joint inflammation, often at night
  - Warmth, swelling, erythema, pain
  - Fever, chills, and malaise may occur
- Untreated initial attacks subside over 3-10 days
- 90% first attacks monoarticular
  - 50% podagra

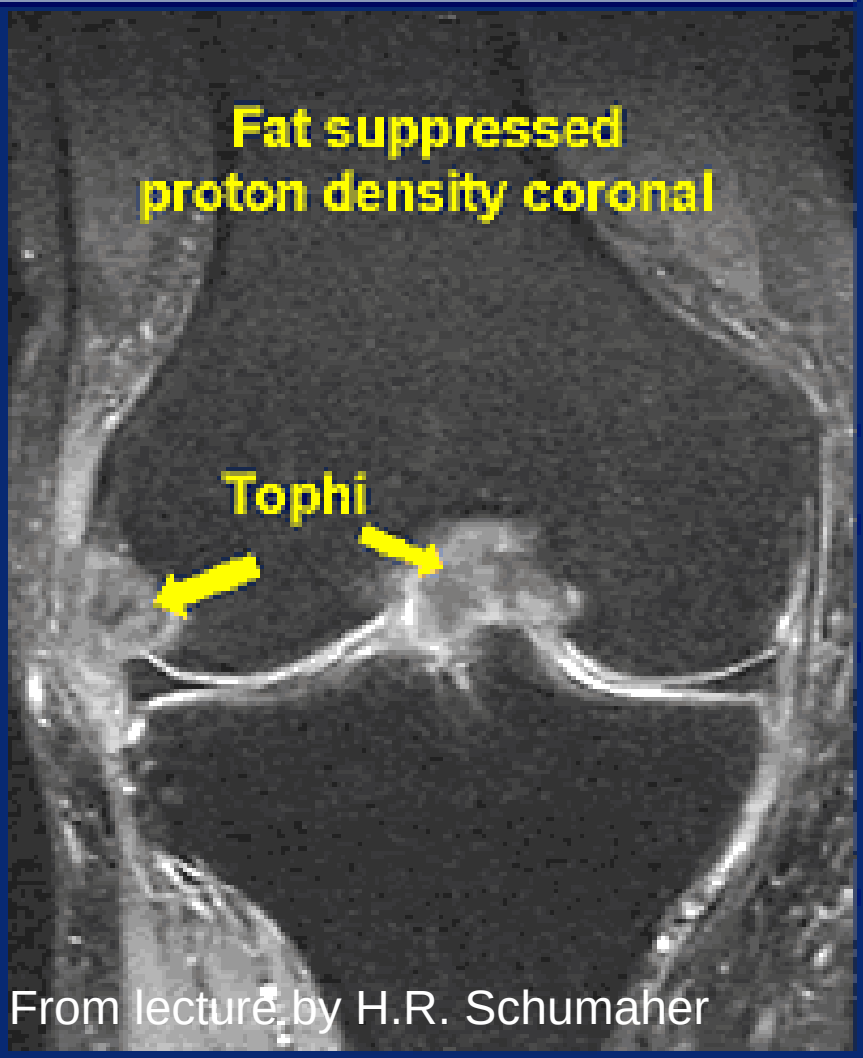
Clinical features

- After solving the acute attack gout follows the intercrtic period.
- The time between flares can vary from one week to a couple of years.

Intercritical Segments

Hidden Damage Can Occur





From lecture by H.R. Schumaher

Photos courtesy of Michael Recht, MD, Cleveland Clinic.

Clinical features

III.Chronic tofi gout :

A.The deposition of monosodium urate crystals at the level of articular and extraarticular structures causes a chronic destructive arthropathy, often with secondary degenerative phenomena.

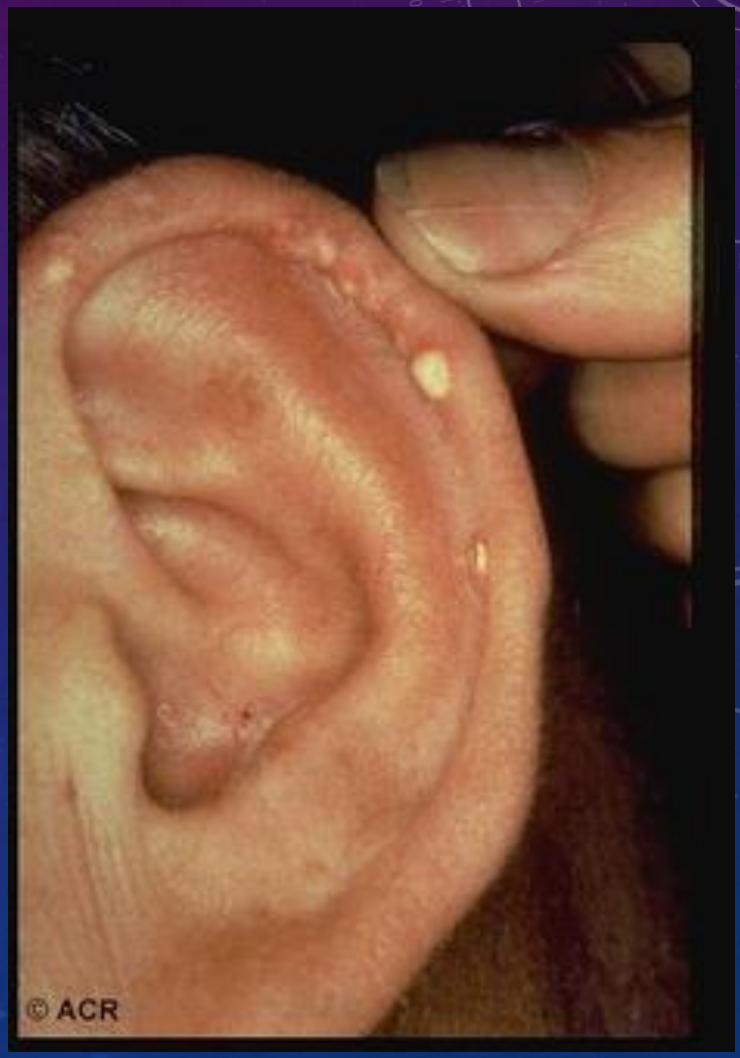
Clinical features

III. Chronic tofi gout :

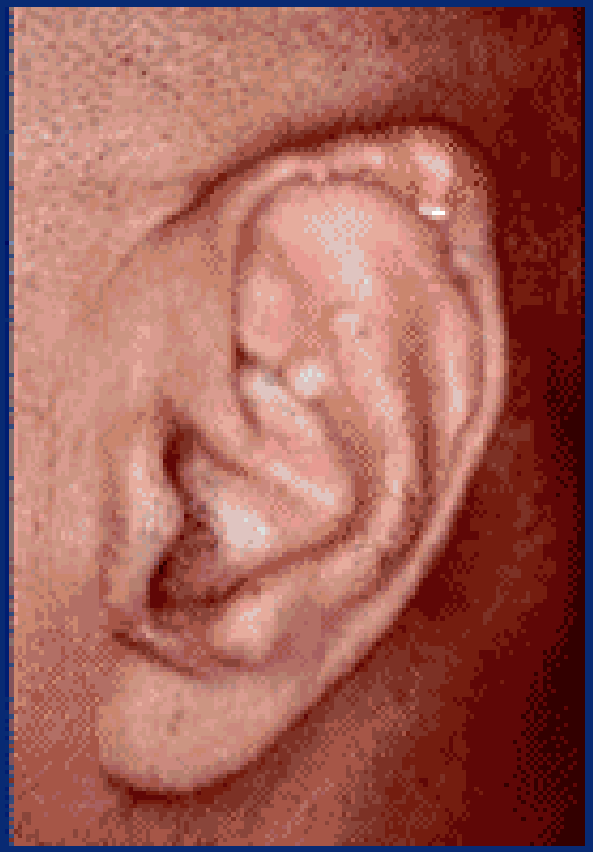
B. Develops over 10 or more years of intermittent acute gout. Affected joints become persistently uncomfortable and swollen, although the intensity of these symptoms is lower than during acute phase.

Clinical features

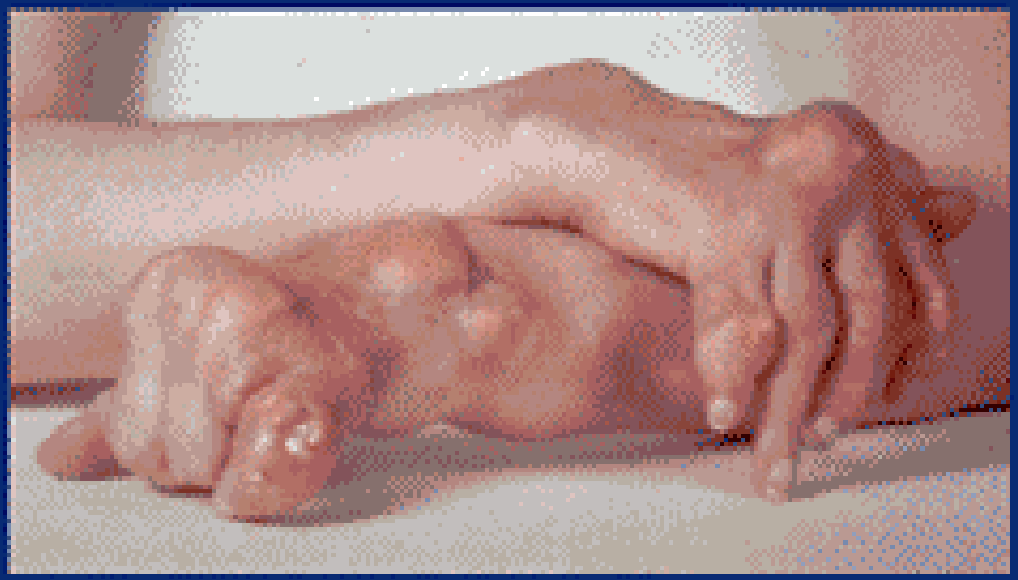
Tophi: – subcutaneous deposits of monosodium urate crystals can be detected during the first few years of chronic gout. They occur more frequently in the fingers, radio-carpal joints, ears, knees, the olecranon bursa and the Achilles tendon.



Advanced Gout
Typical Tophaceous Manifestations



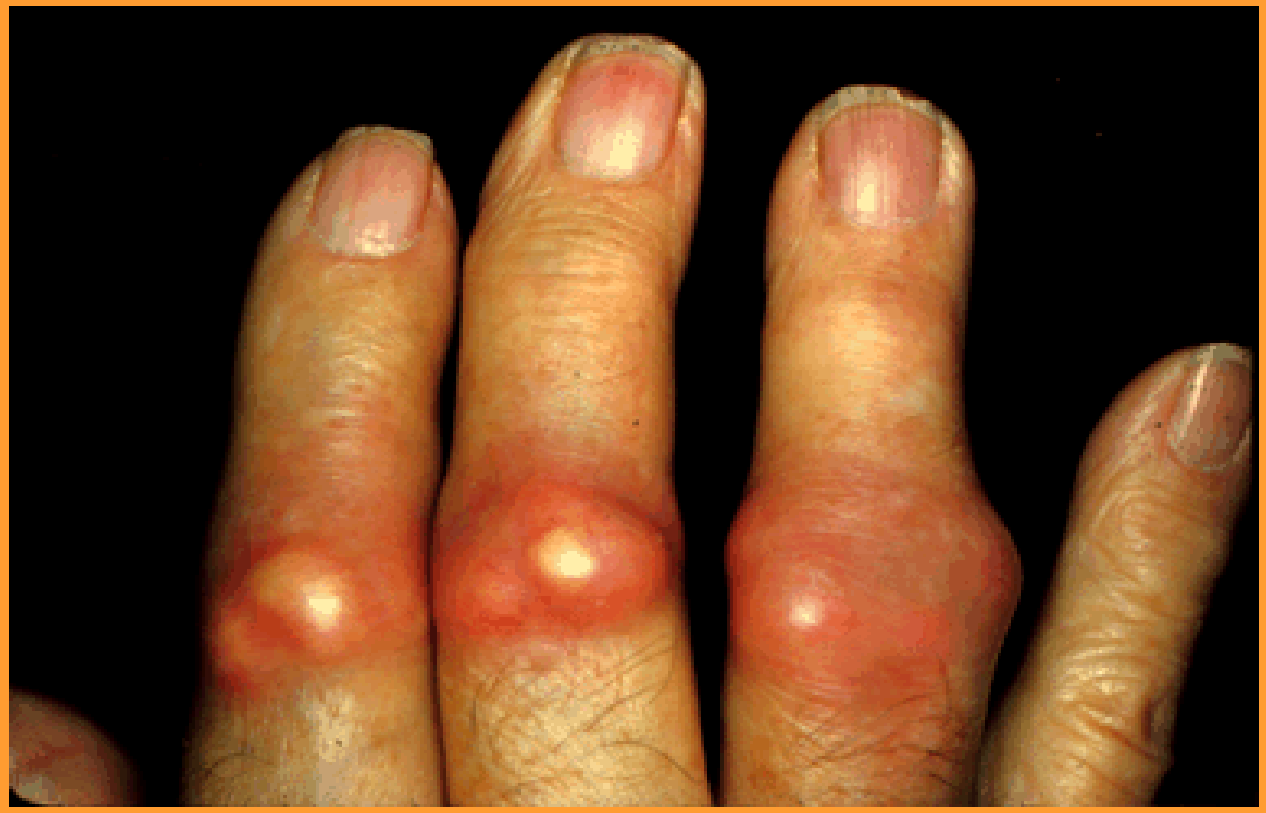
Helix of the ear



Hands, fingers, and wrists

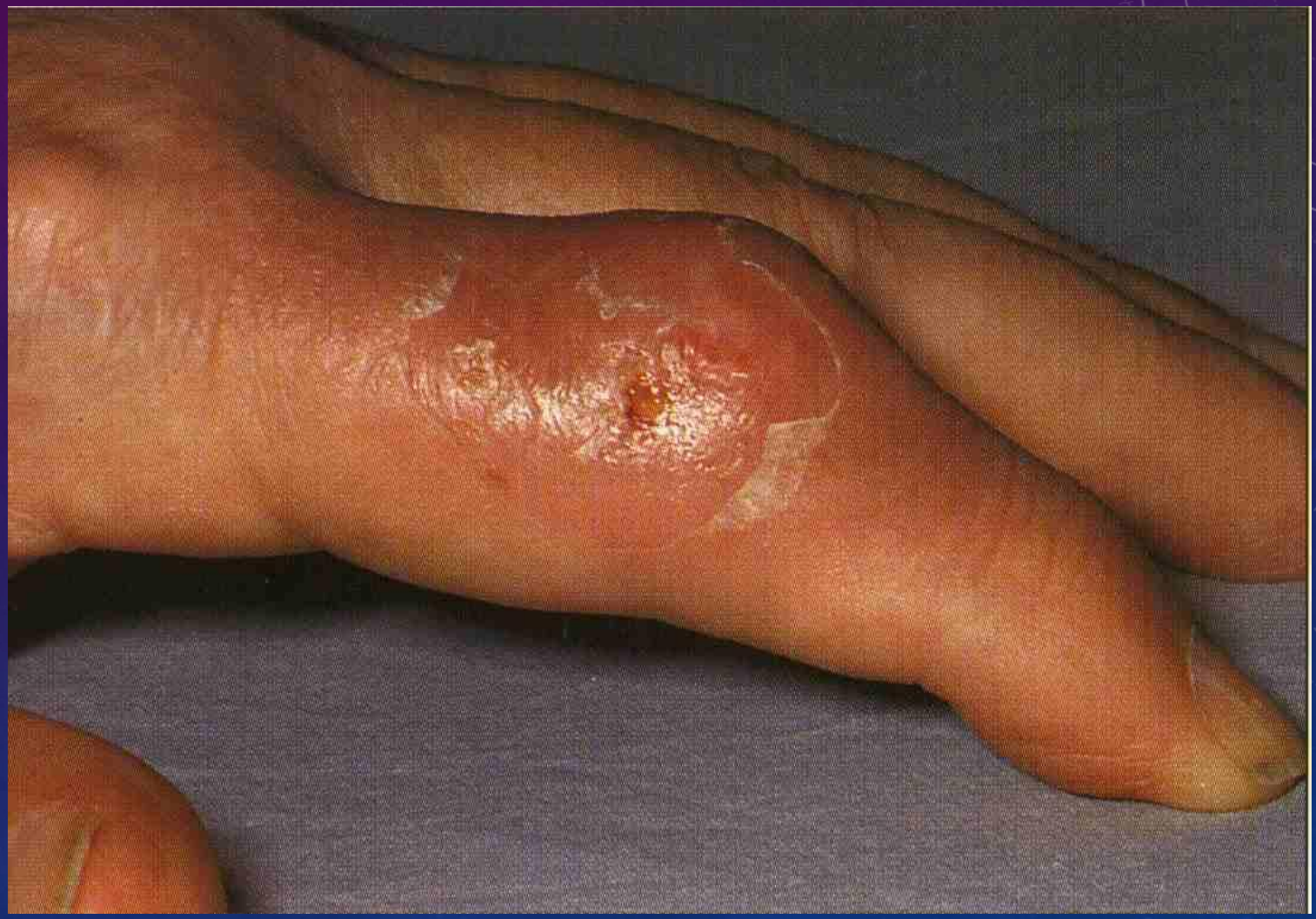
ACR Clinical Slide Collection on the Rheumatic Diseases, 1998.

TOPHI



Inflamed tophaceous gout Three inflamed tophi over the proximal interphalangeal joints in a patient with chronic tophaceous gout. Several of the lesions ruptured spontaneously over the next three days, exuding a pasty material composed of urate crystals and inflammatory cells but no organisms. The inflammation largely subsided over one week after the administration of a nonsteroidal antiinflammatory drug. Courtesy of Michael A Becker, MD.

TOPHI



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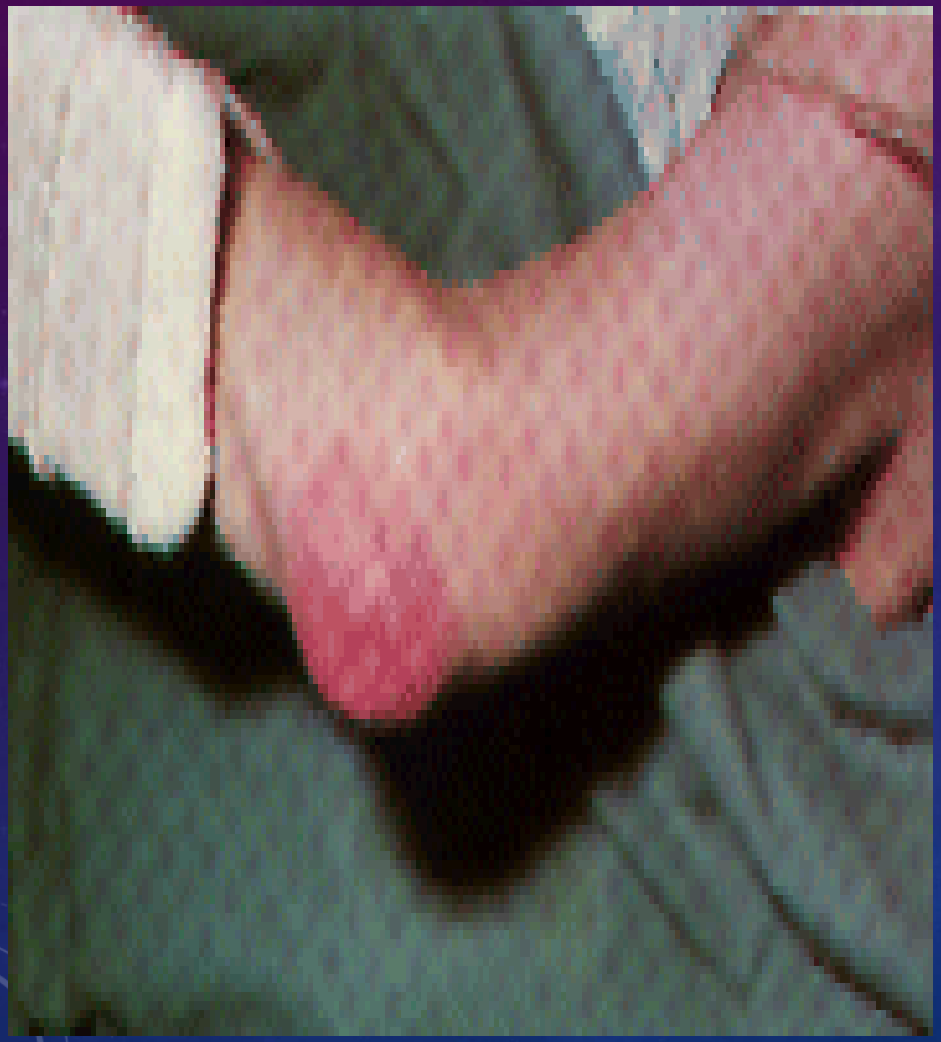

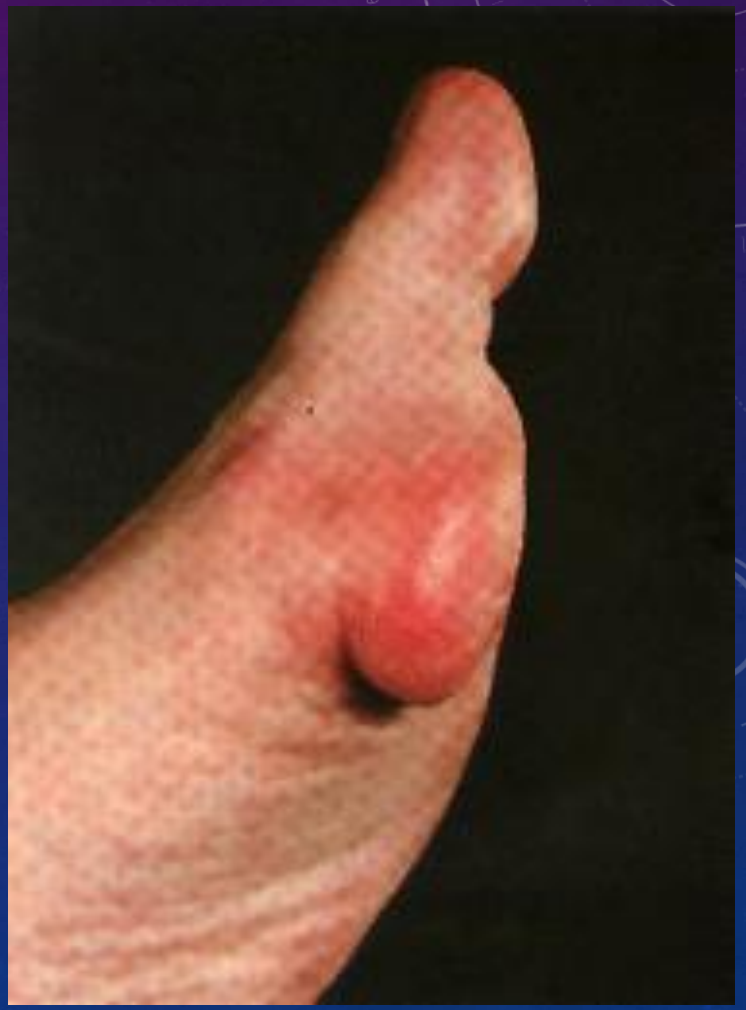

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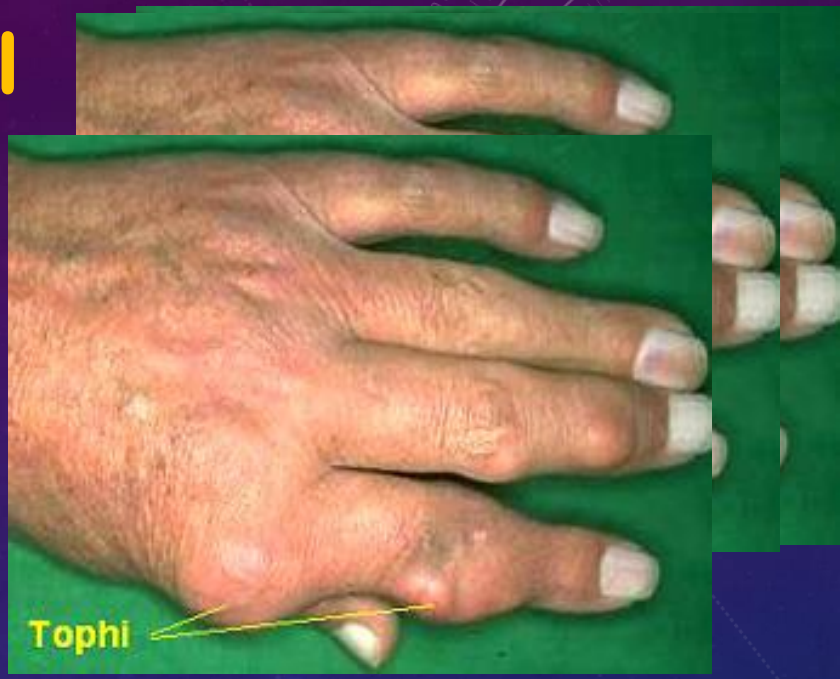
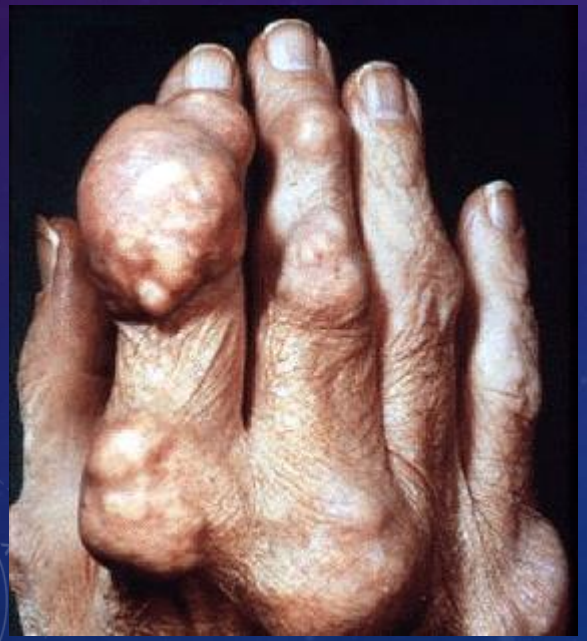
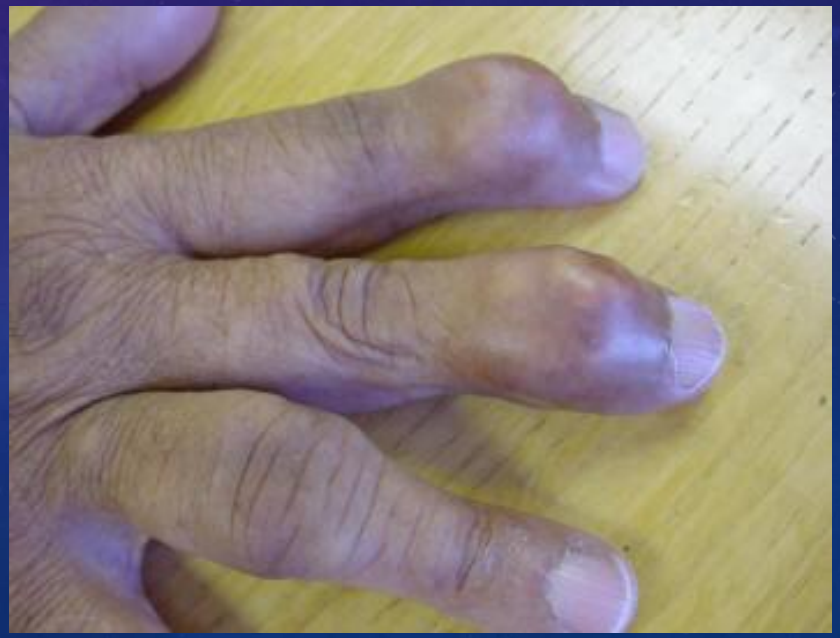
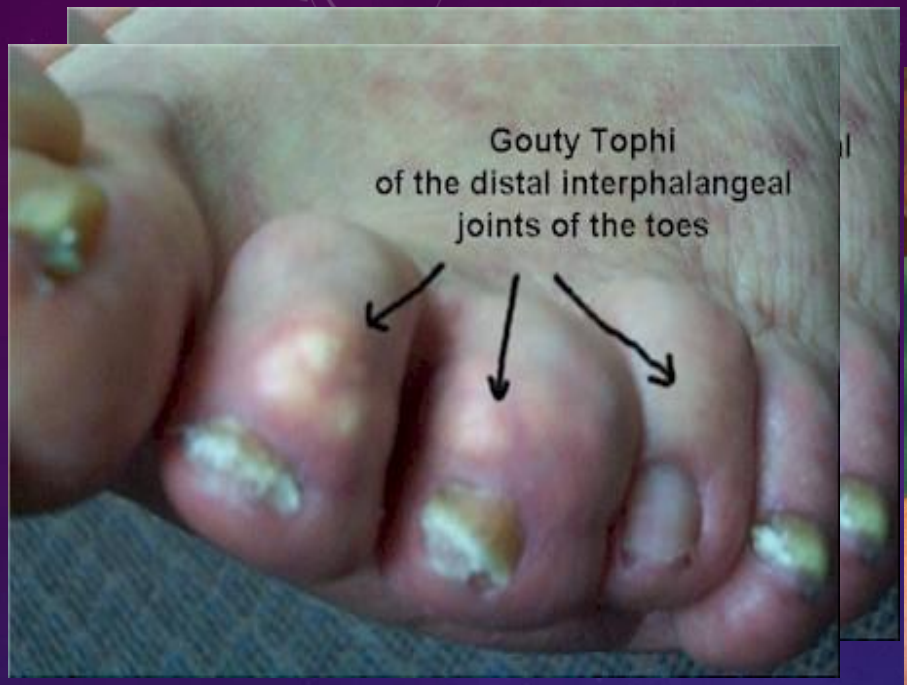
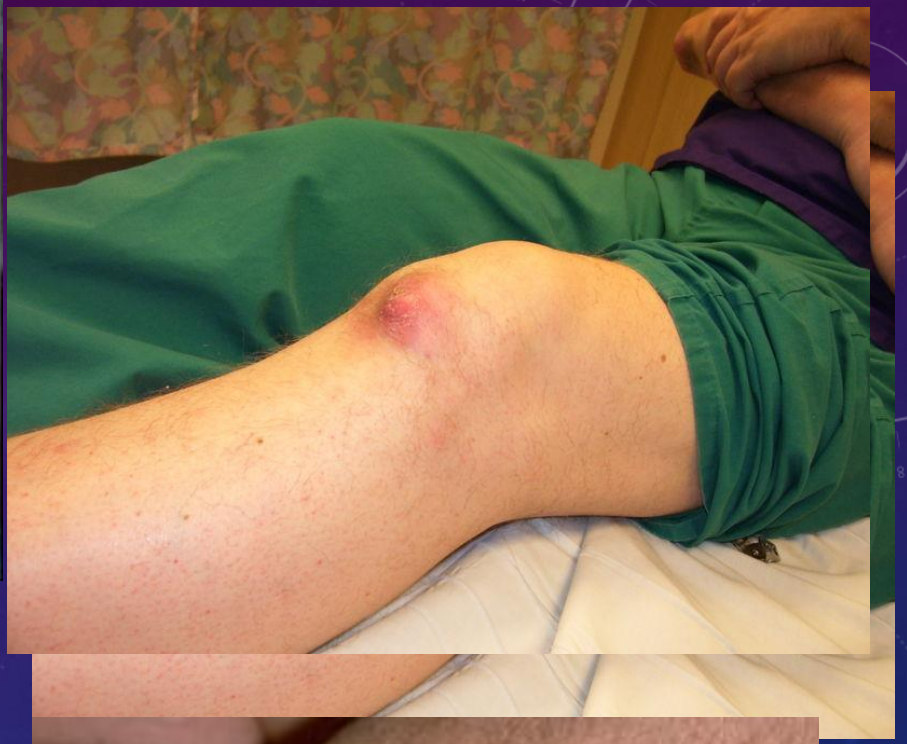
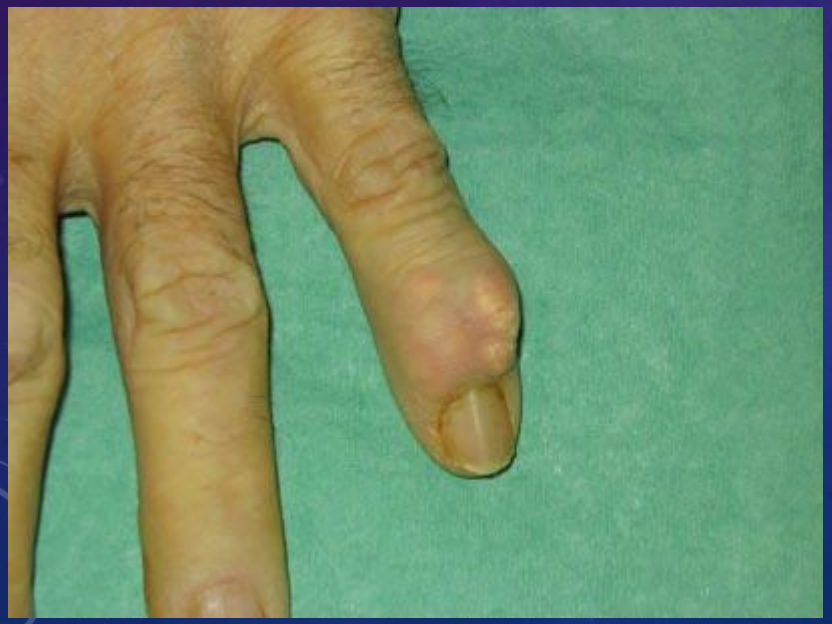


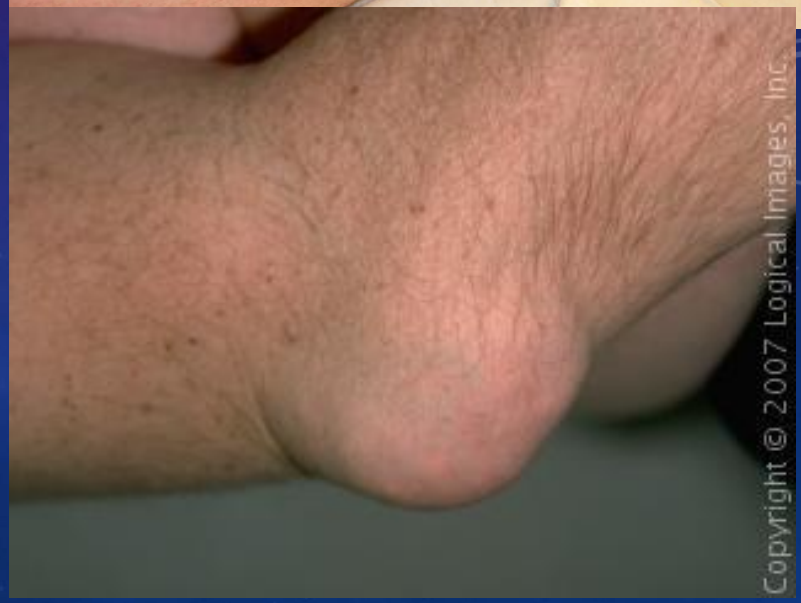





Gouty Tophi
of the distal interphalangeal
joints of the toes



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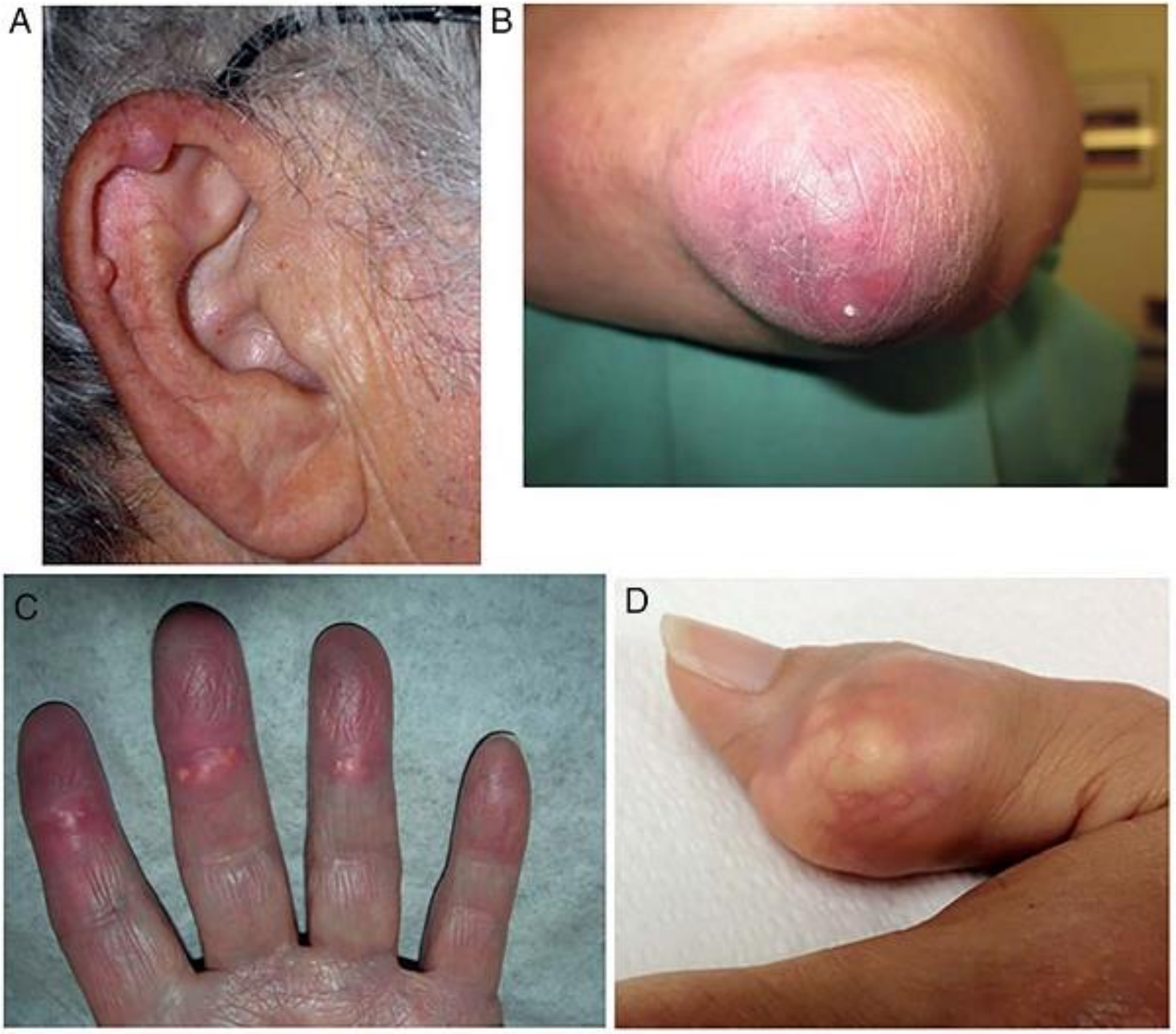
A
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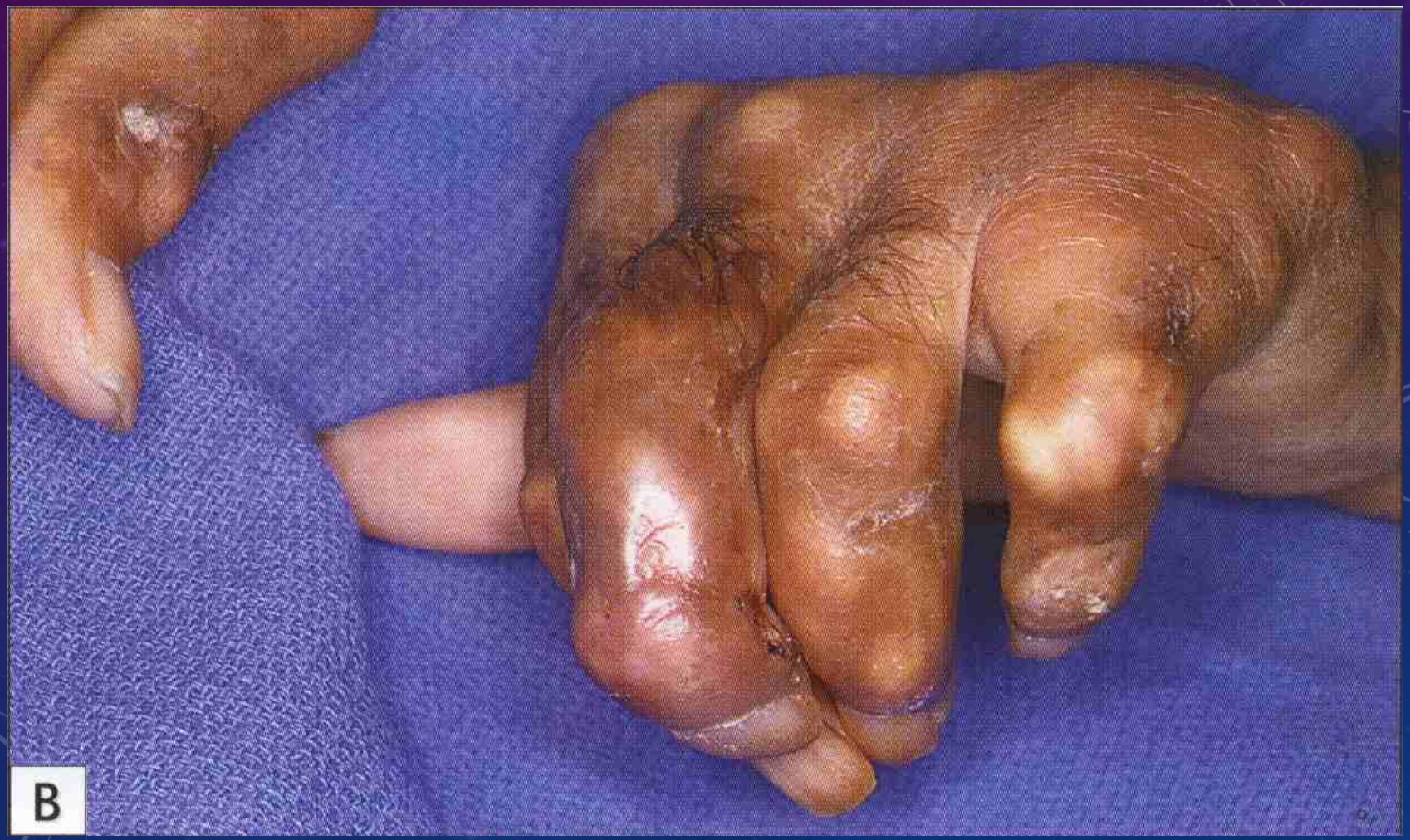
TOPHI, DEFORMED JOINTS



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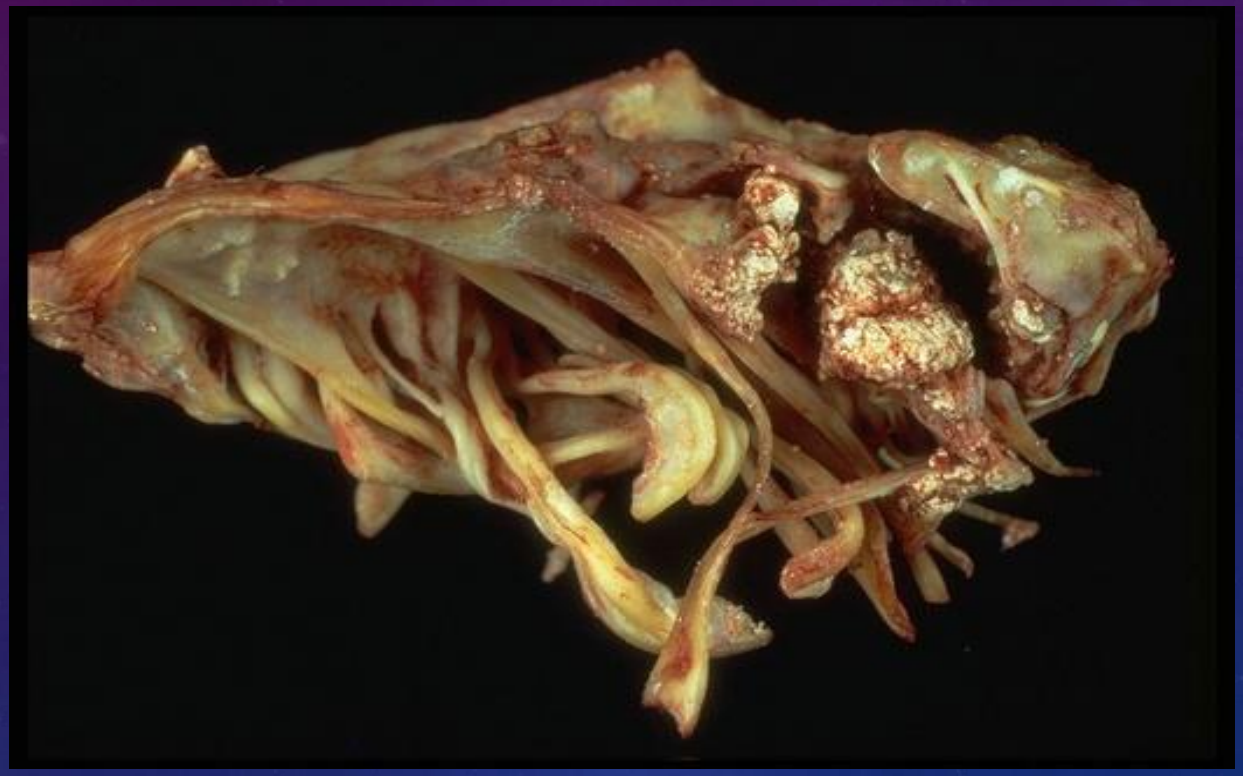
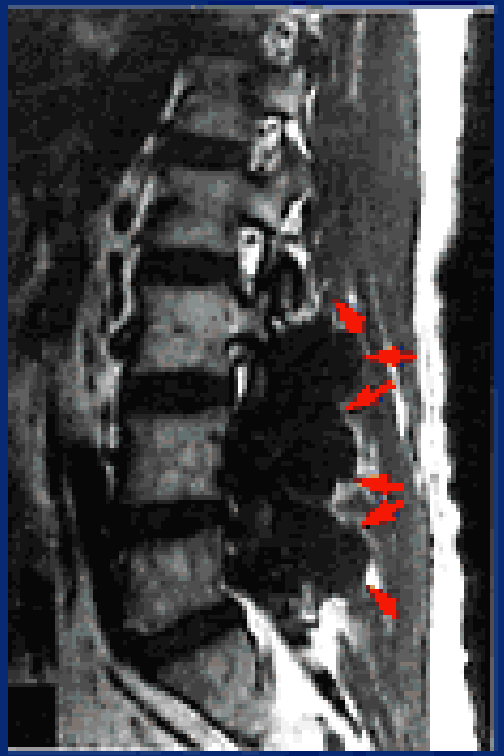


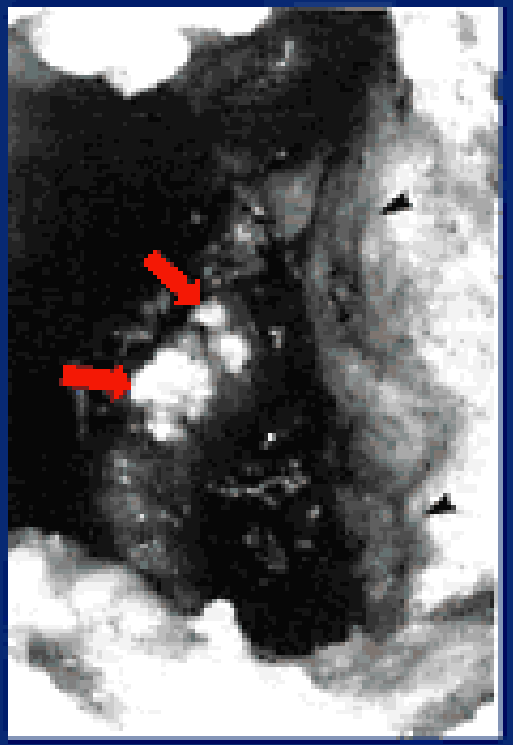
Tophi on mitral walve

Advanced Gout
Atypical Tophaceous Manifestations

Tophi in the spine in a patient with a 15-year history of gout



Irregular paraspinal mass between L3 and L5



Urate crystals found within the paravertebral muscle

Nakajima et al. *J Rheumatol.* 2004;31(7):1459-1460.

CLINICAL CLASSIFICATION OF GOUT

- **Acute gout**
- **Chronic intermittent gout**
- **Chronic tofi gout**

- **Acute joint access on (date) with joint involvement (name)**
- **Intercritical period**
- **Stage Ro I, II, III**
- **Insufficiency of joint function I, II, III**

- **Complications:**
- **Interstitial nephropathy, CKD (st)**
- **Secondary hypertension**

LABORATORY CHANGES

- ***Serum urate level*: relevant to the vast majority of patients with gout, but of limited value in diagnosis.**
- ***The level of urates in urine*: important for the detection of the type of hyperuricemia, the risk of development of urolithiasis, the choice of medication.**
- ***During acute attacks*:**

1. **VSH is elevated**
2. **Leukocytosis**
3. **Sometimes neutrophilia**

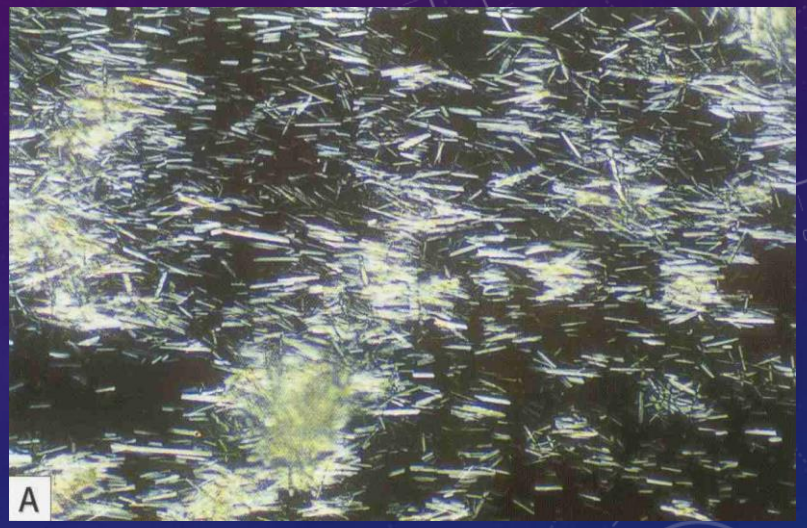
- ***Associated with gout***

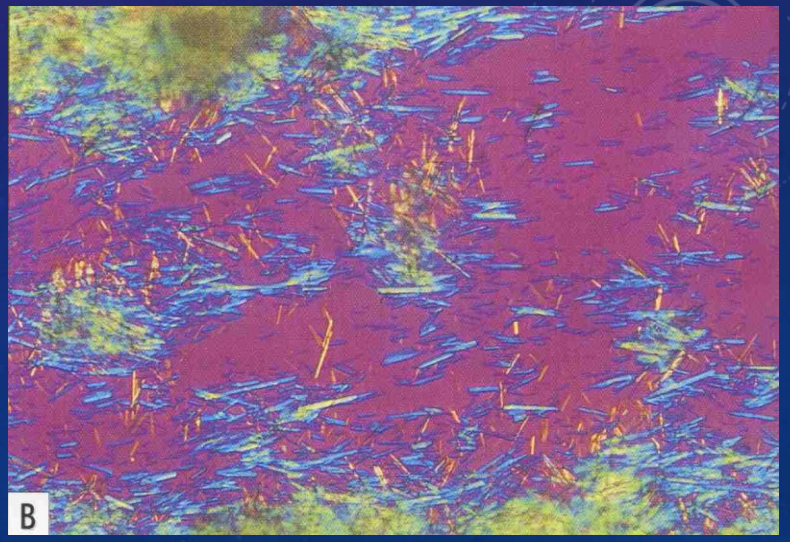
1. **Hyperglycaemia**
2. **Increased the level of total cholesterl, decreases HDL-cholesterol**
3. **Increased triglycerides**

SYNOVIAL FLUID ANALYSIS

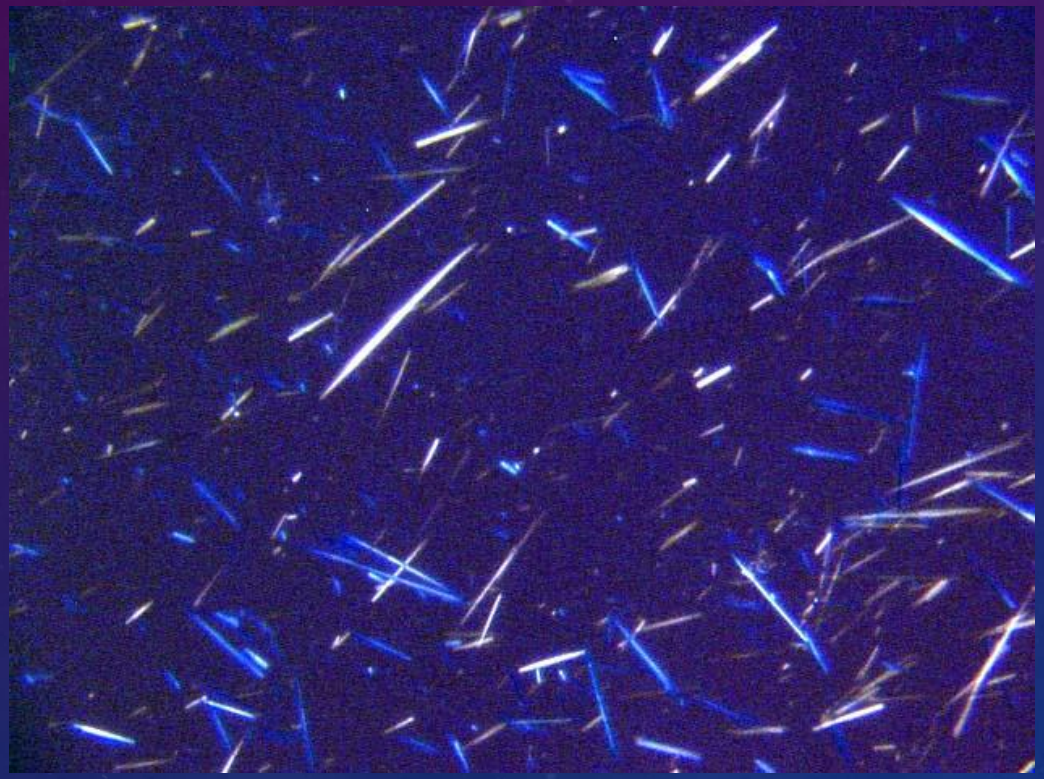
- **Monosodium urate crystals – usually have the form of sharp needles or canes. Under polarizing microscopy they appear as bright, birefrigent crystals.**
- **Number of leukocytes – relevant with approximate number between 15,000 and 20,000 cells/mm3. Neutrophiles predominate.**
- **Bacteriology – the aspirated liquid should be sent for the bacteriological testing if a septic process is suspected.**

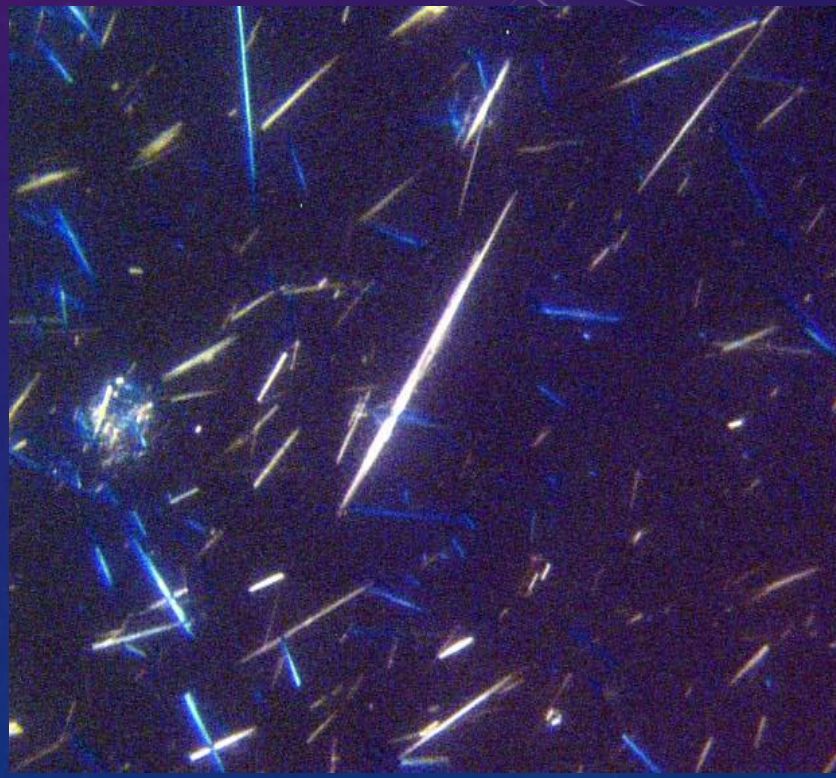
MONOHYDRAT SODIUM MONOURATE CRYSTALS





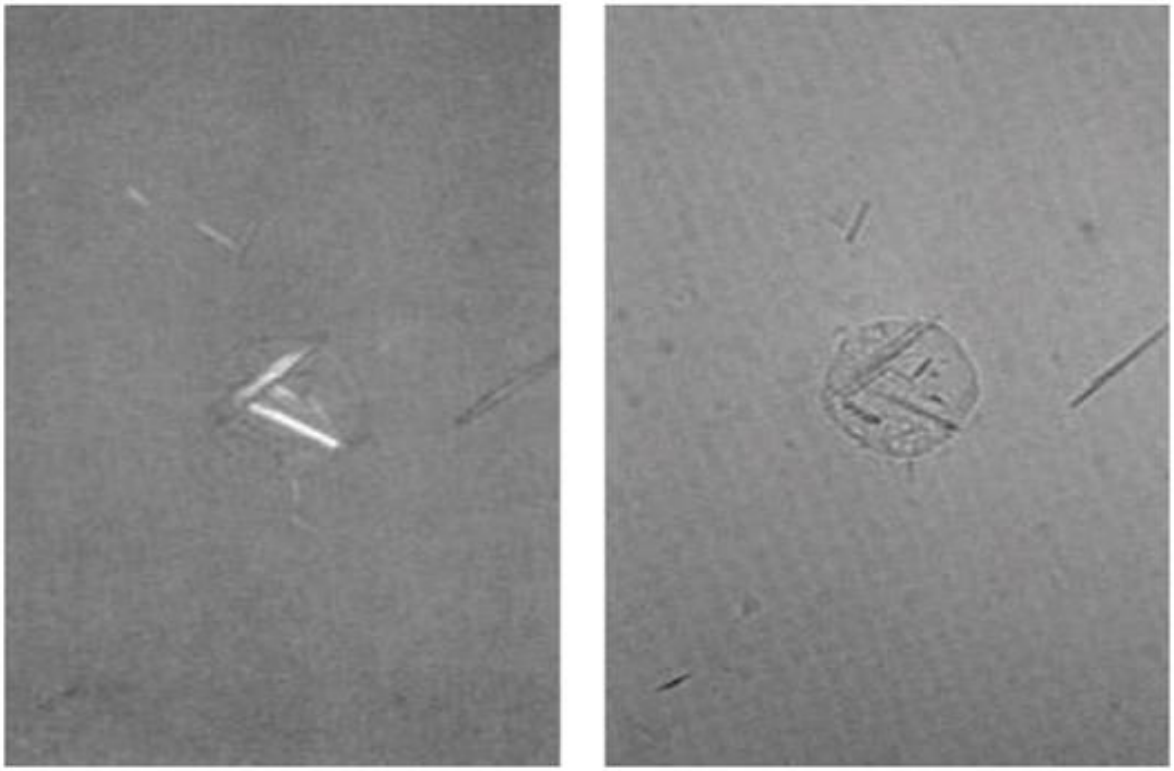
MONOHYDRAT SODIUM MONOURATE CRYSTALS





MONOHYDRAT SODIUM MONOURATE CRYSTALS

Figure. Intracellular and Extracellular MSU Crystals Under Polarized Light x400 (left) and Under Light Microscopy x4000 (right)



MSU indicates monosodium urate.
Source: Schumacher HR, Reginato AJ. *Atlas of Synovial Fluid Analysis and Crystal Identification.* 1st ed. Philadelphia, Pa: Lea and Febiger; 1991.

RADIOGRAPHIC PARTICULARITIES

***Early manifestations*: – radiographic manifestations of gout frequently are not noticed in the early period of the disease.**

***In the first attack* of acute gout, changes can be presented only by swelling of the tissues around the affected joint.**

***Late manifestations:* - round or oval radiotransparent bone defects, located near the joint extremity of the bone and surrounded by an osteosclerotic area, suggests gout.**

Radiographic peculiarities, M. Cohen et B. Emmerson, 1994

- **Soft tissues:**
  - Eccentric opacity, determined by tofus
- **Bones/articulations:**
  - Joint space is well presented
  - Juxtaarticular osteoporosis lacks
  - Erosions: geodes, marginal sclerosis, s-m "bread-free"

RADIOLOGICAL IMAGE

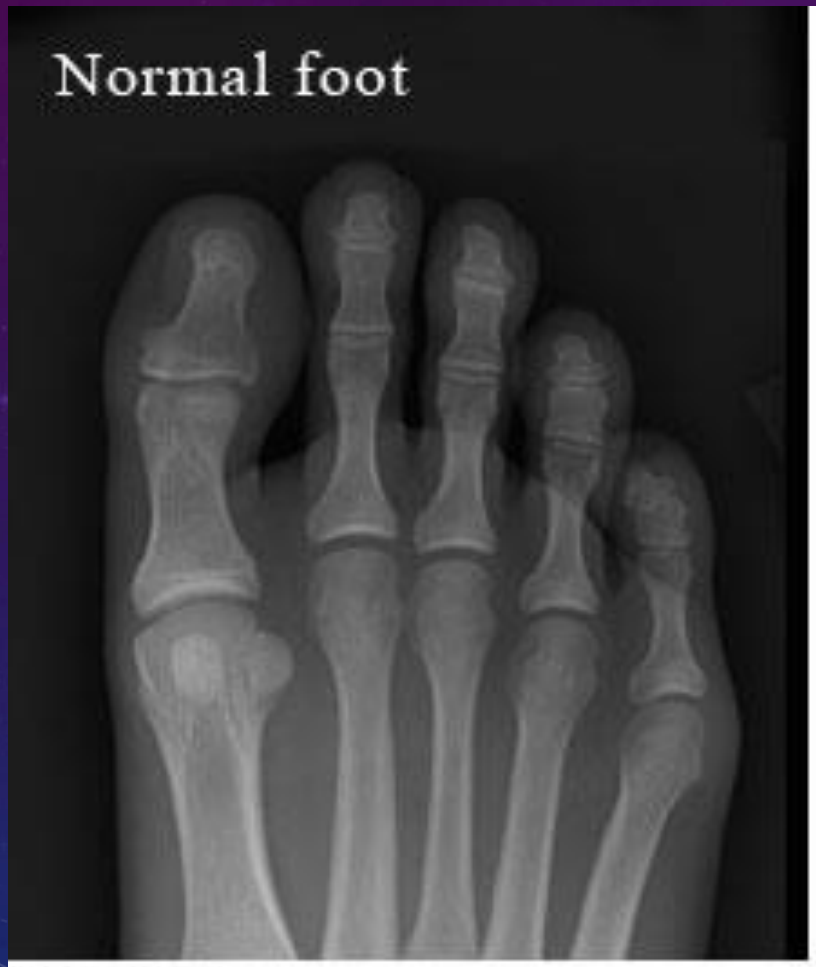


Figure 1

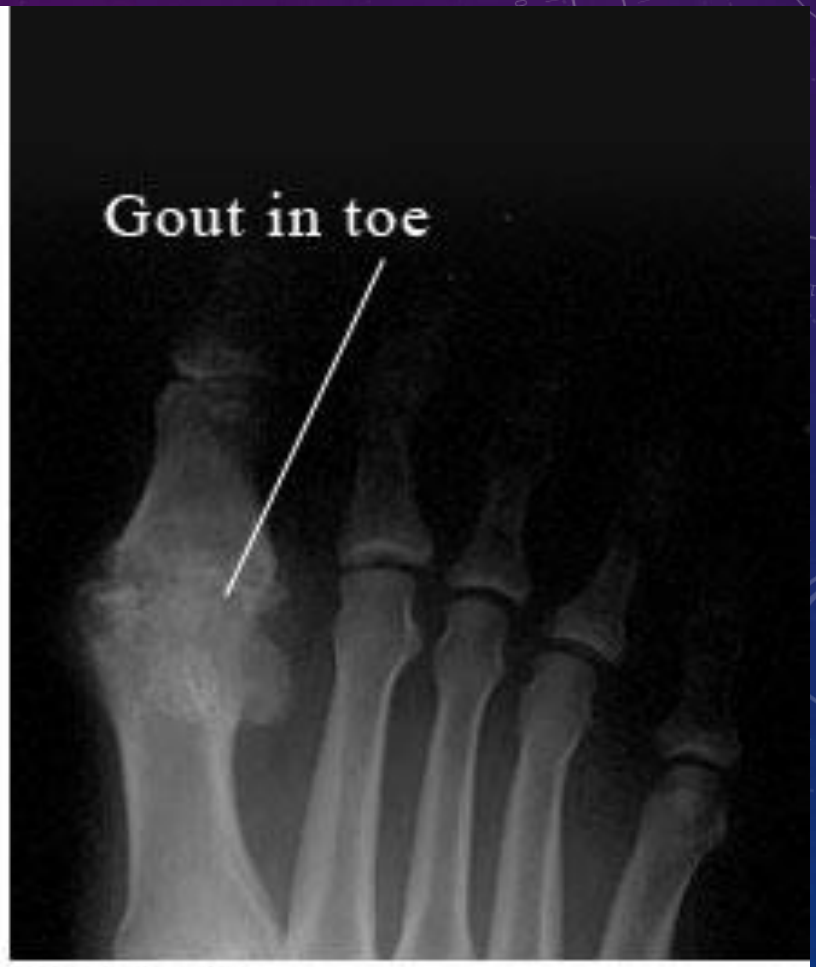


Figure 2

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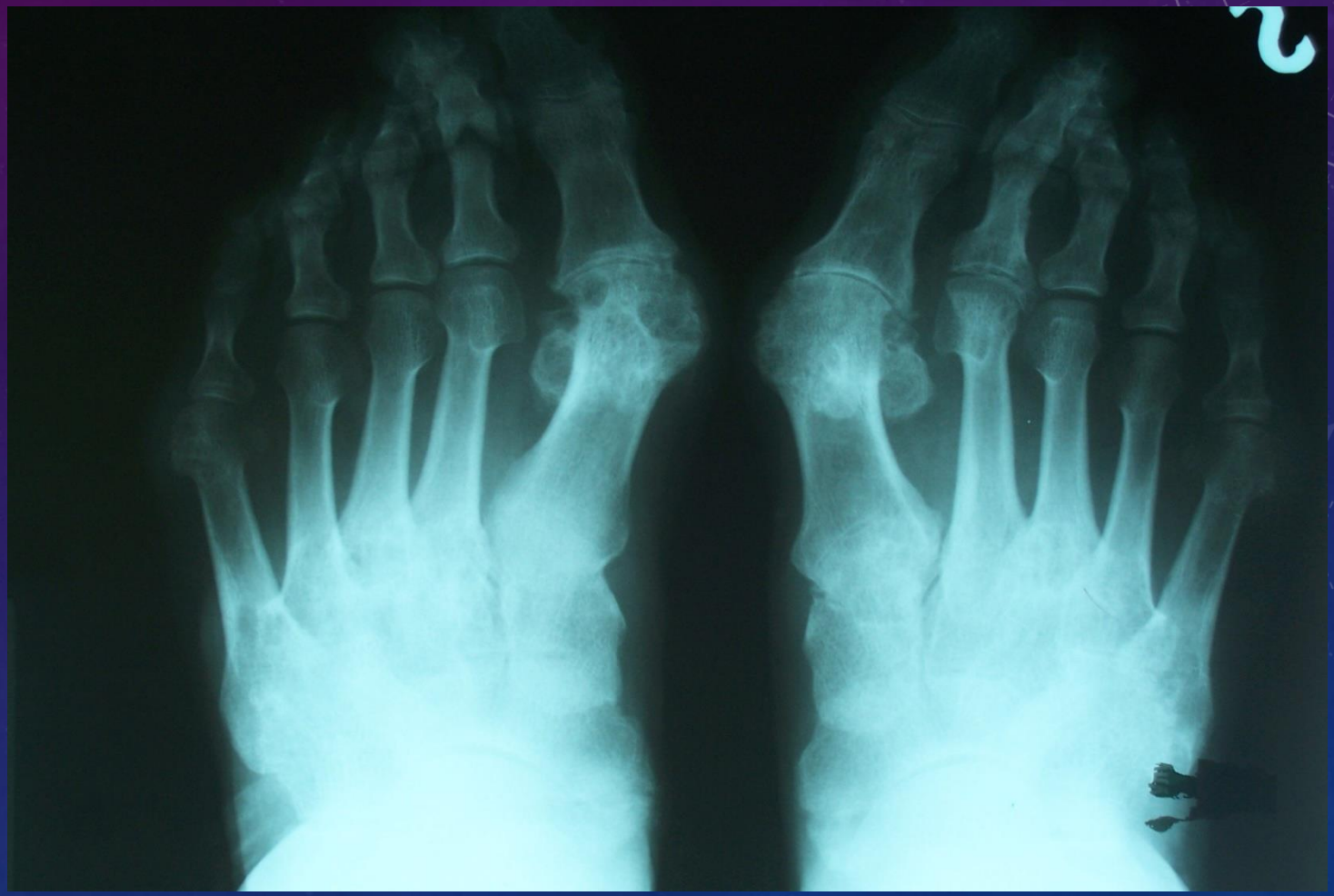

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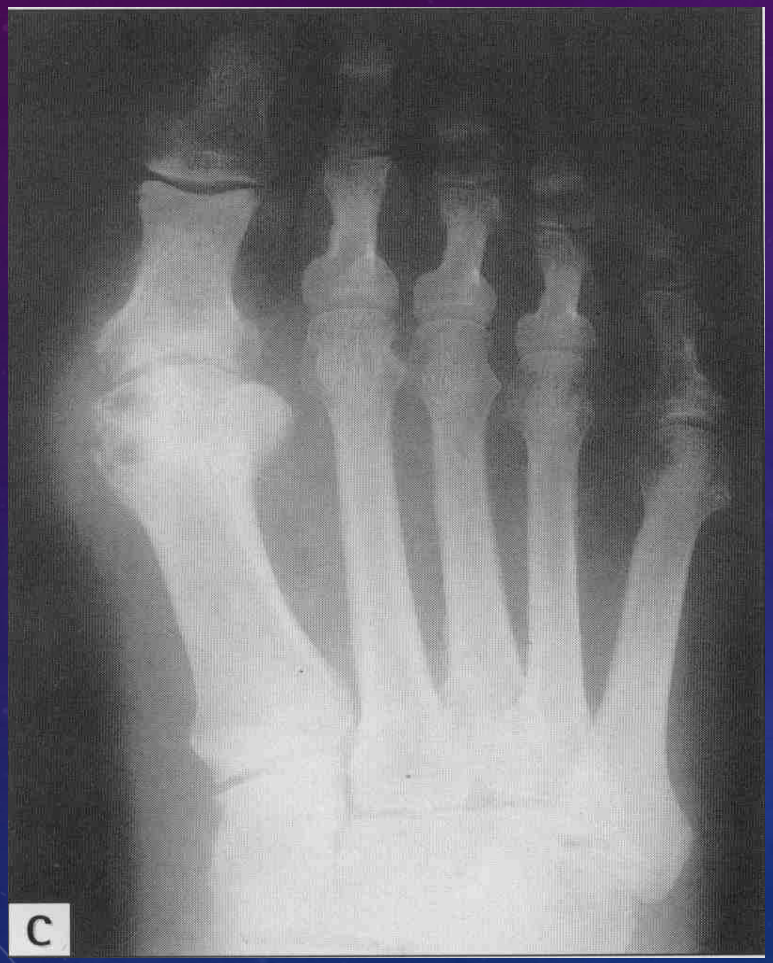

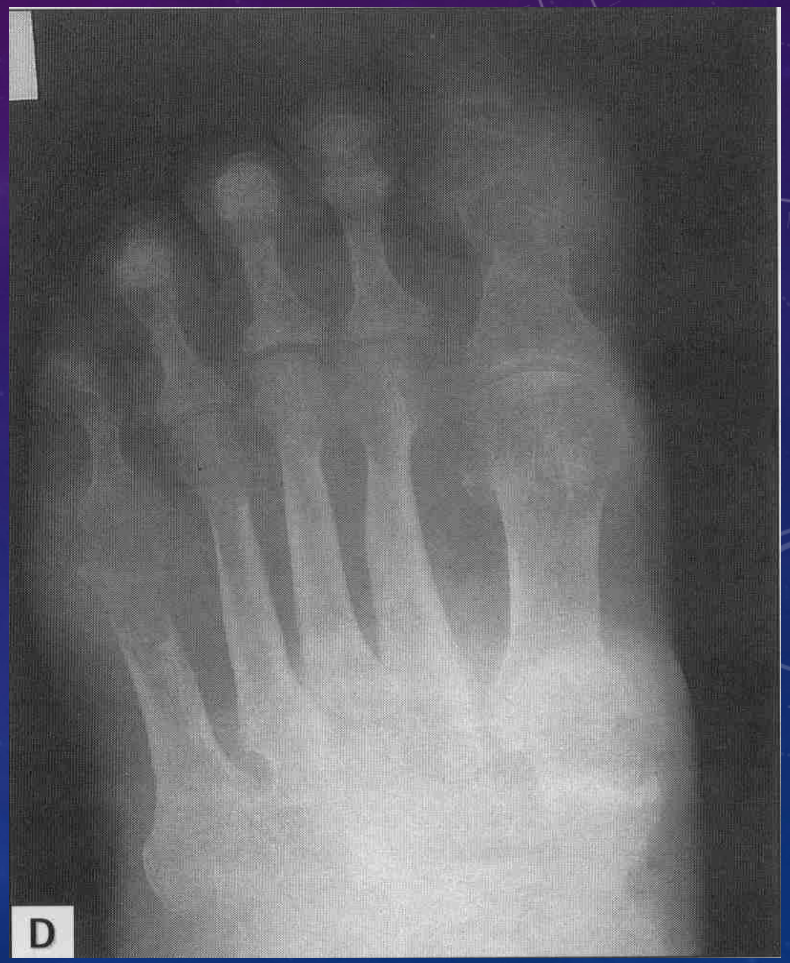

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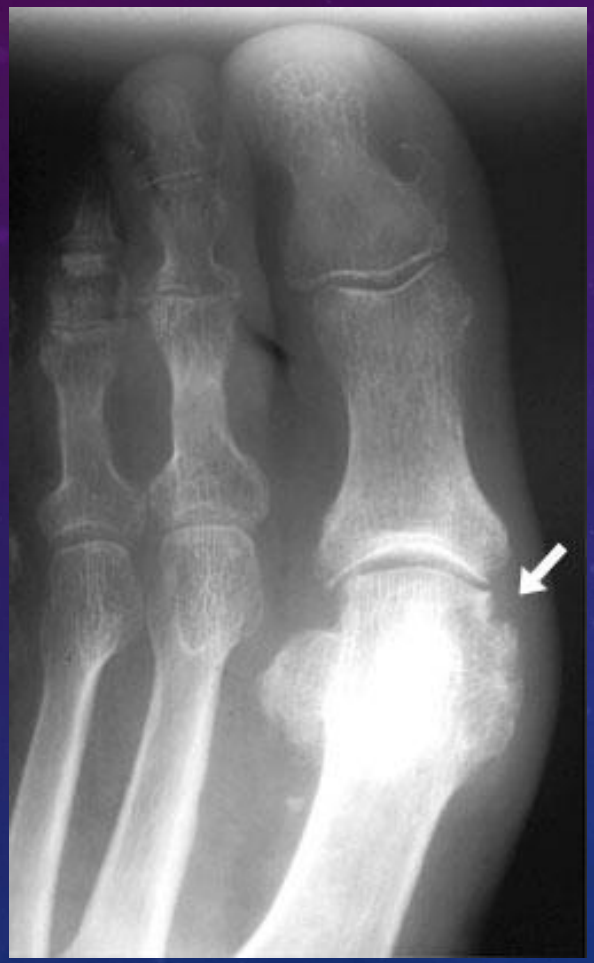

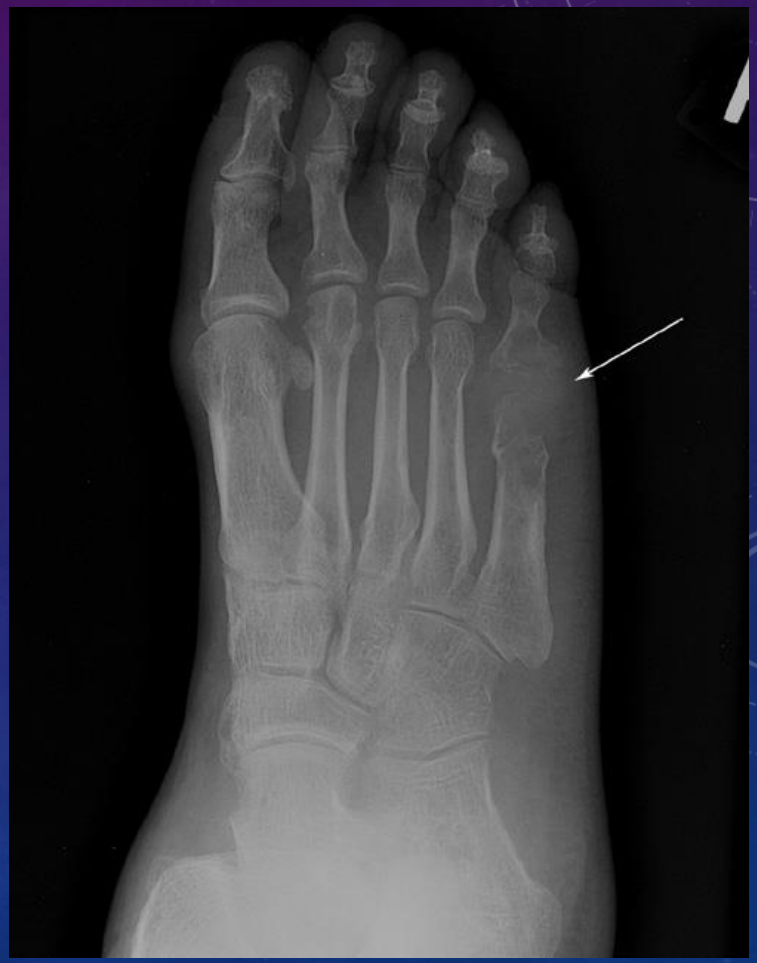

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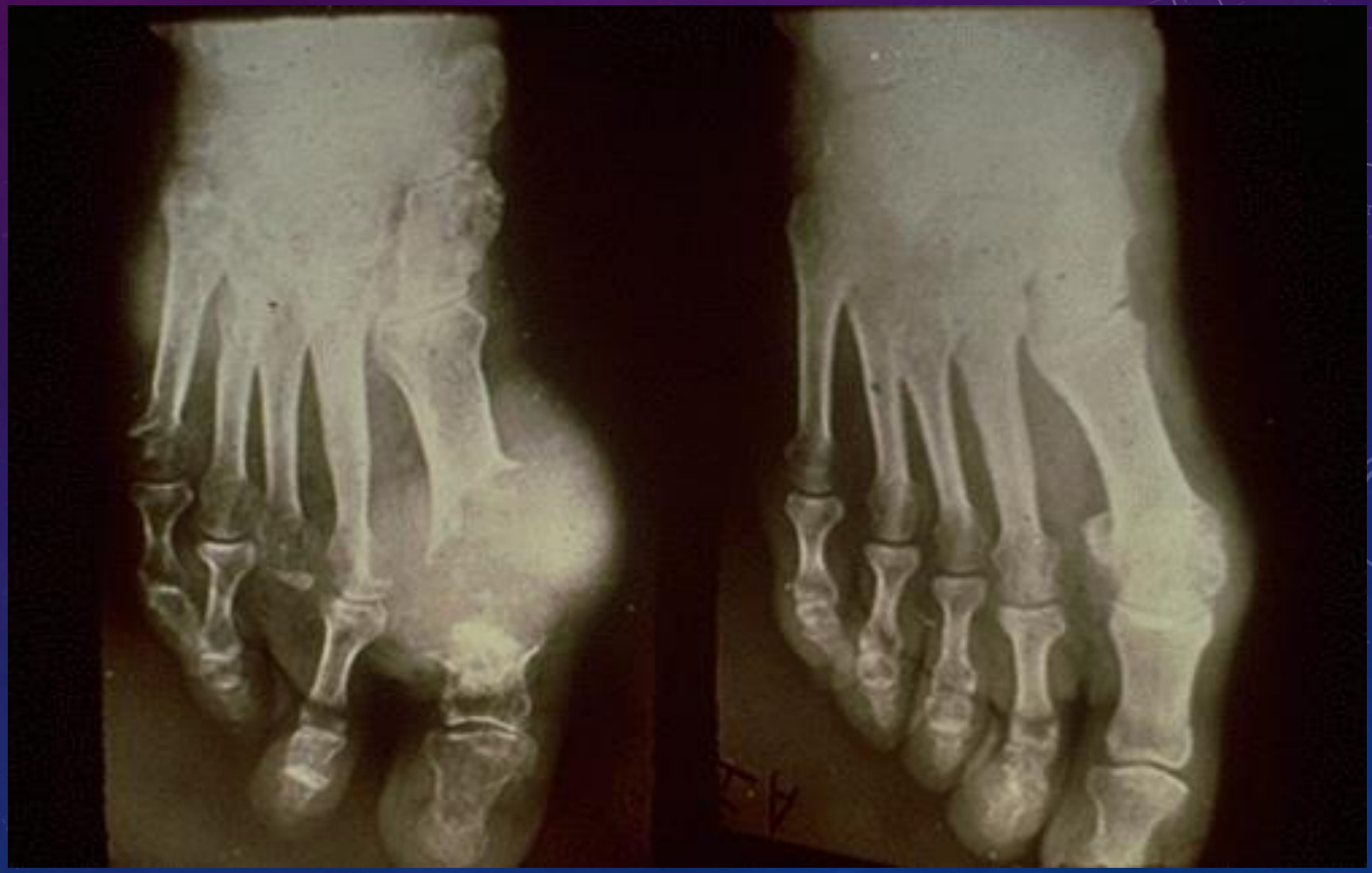

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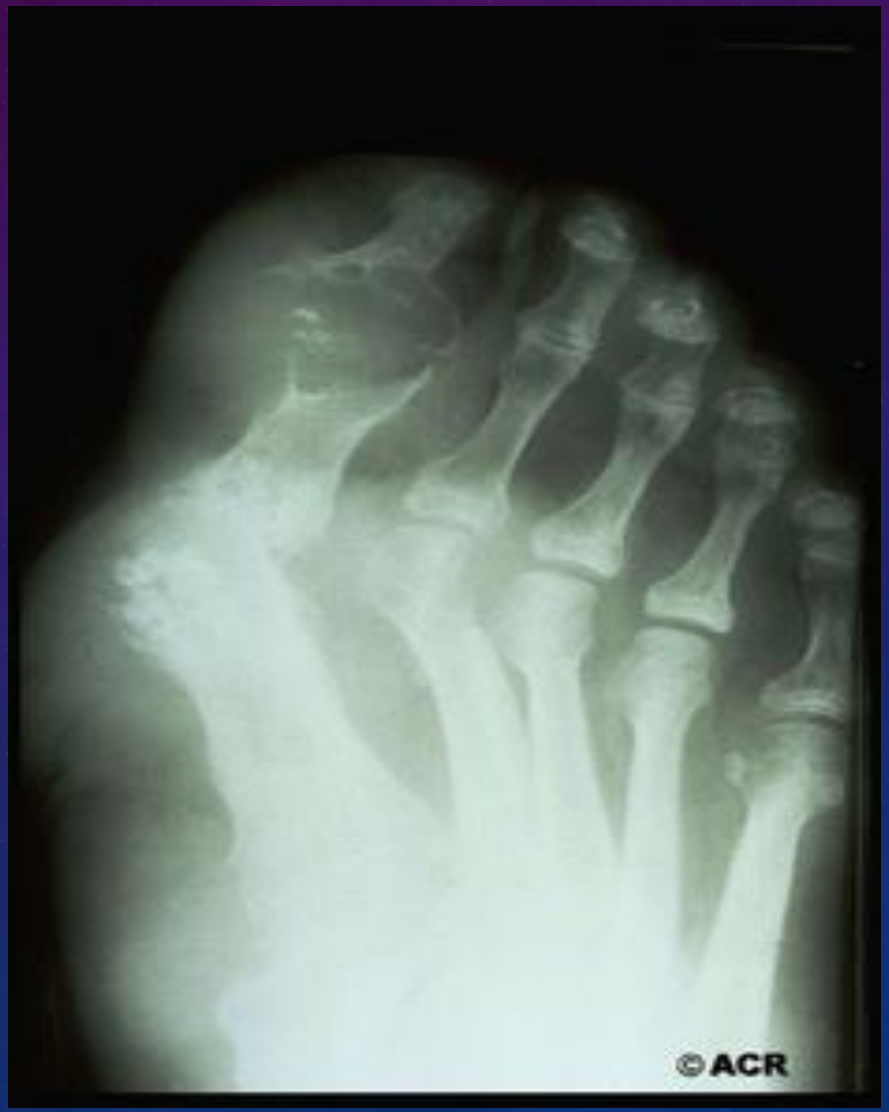

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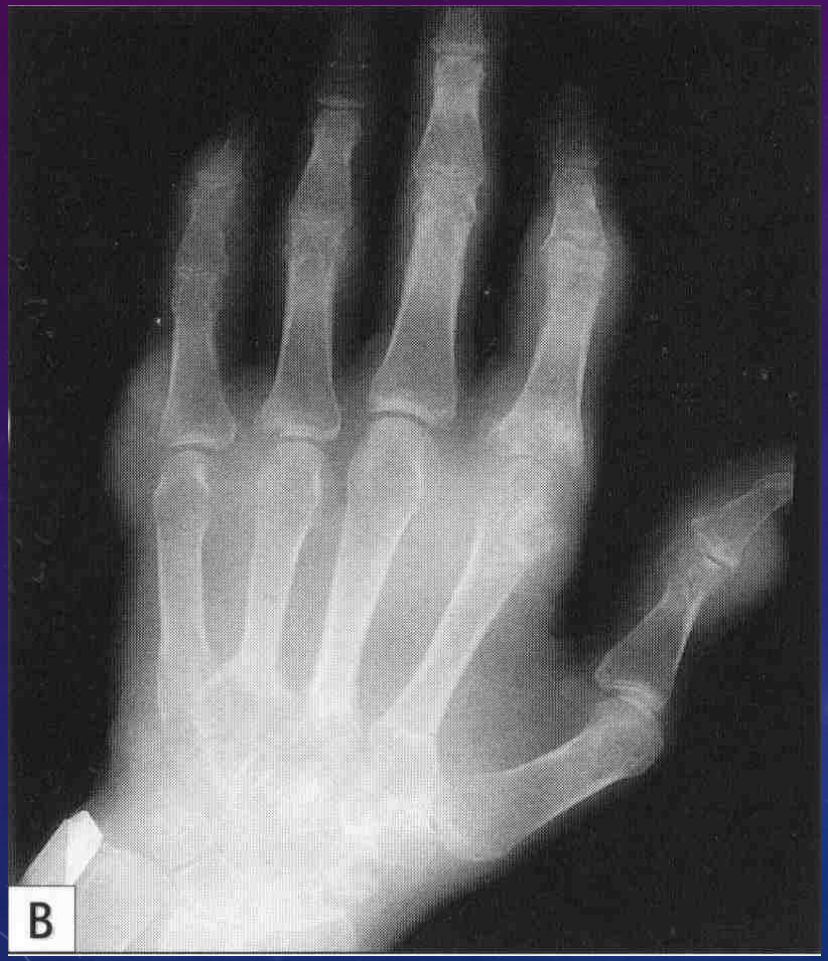

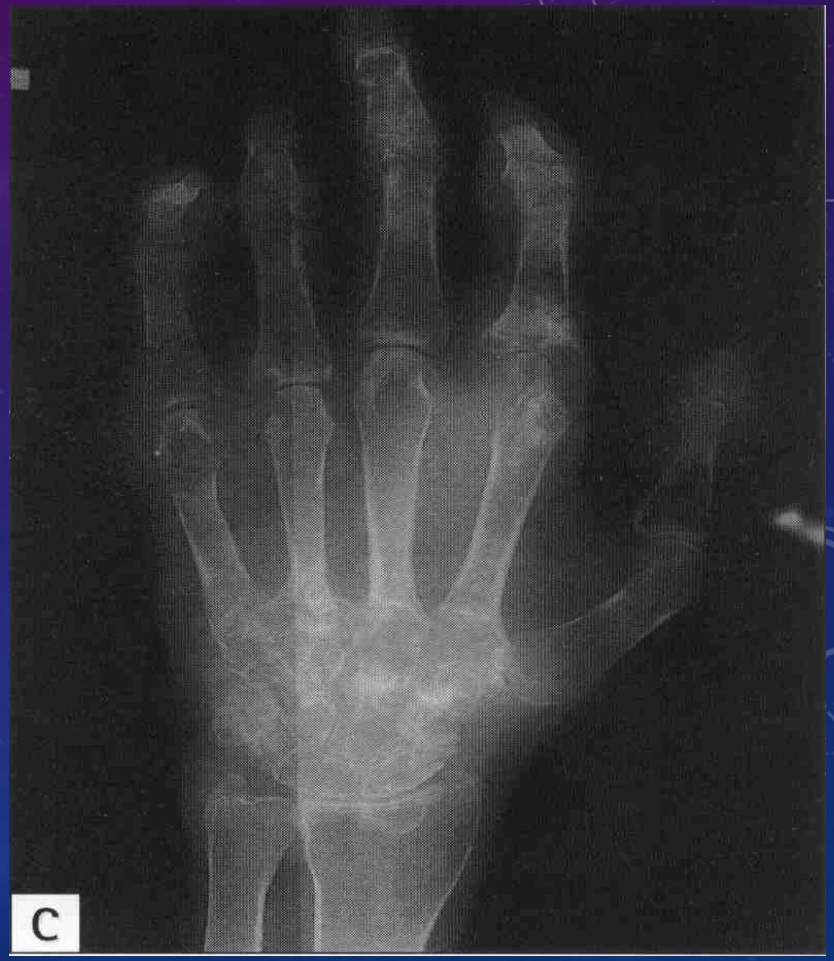

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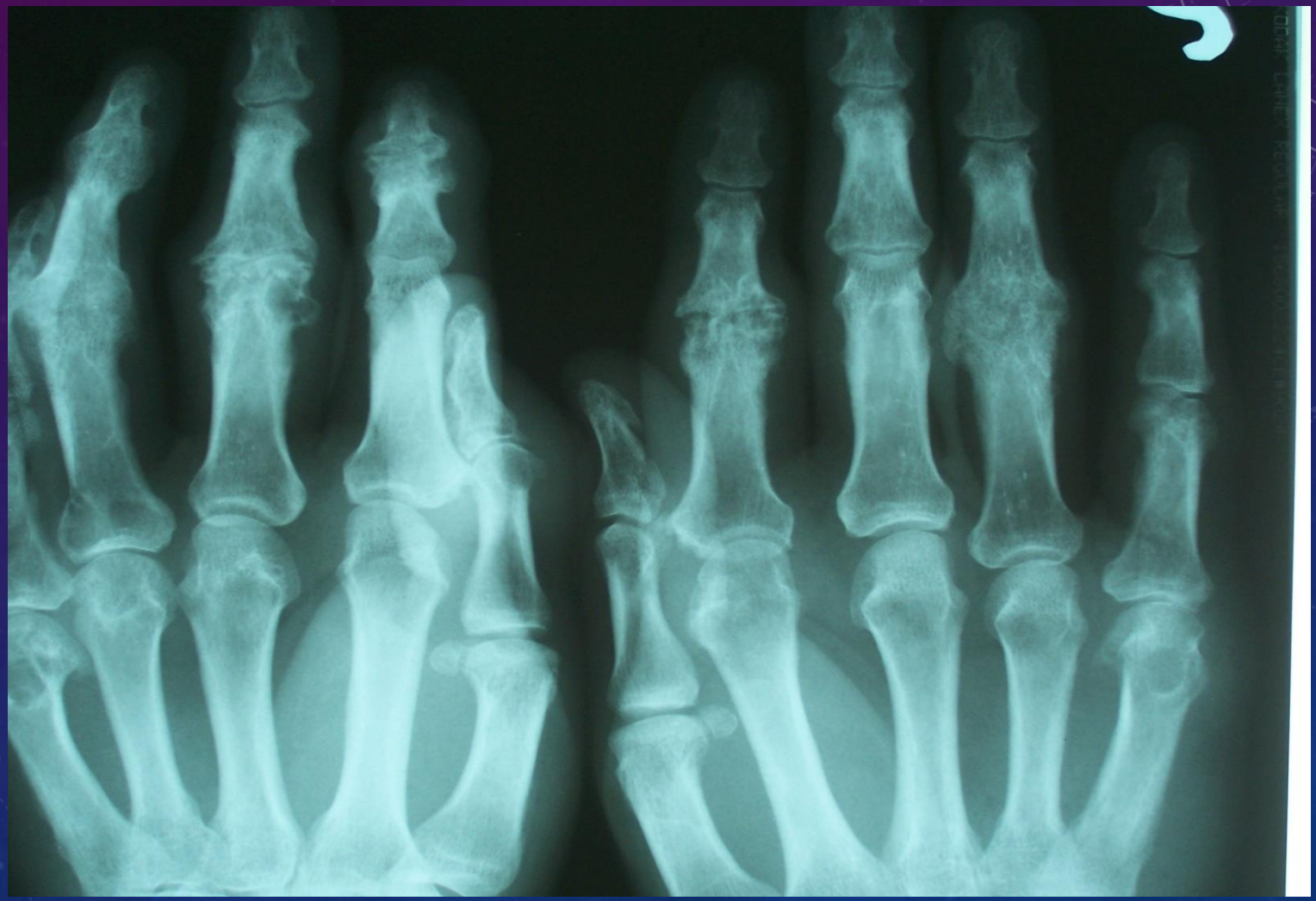

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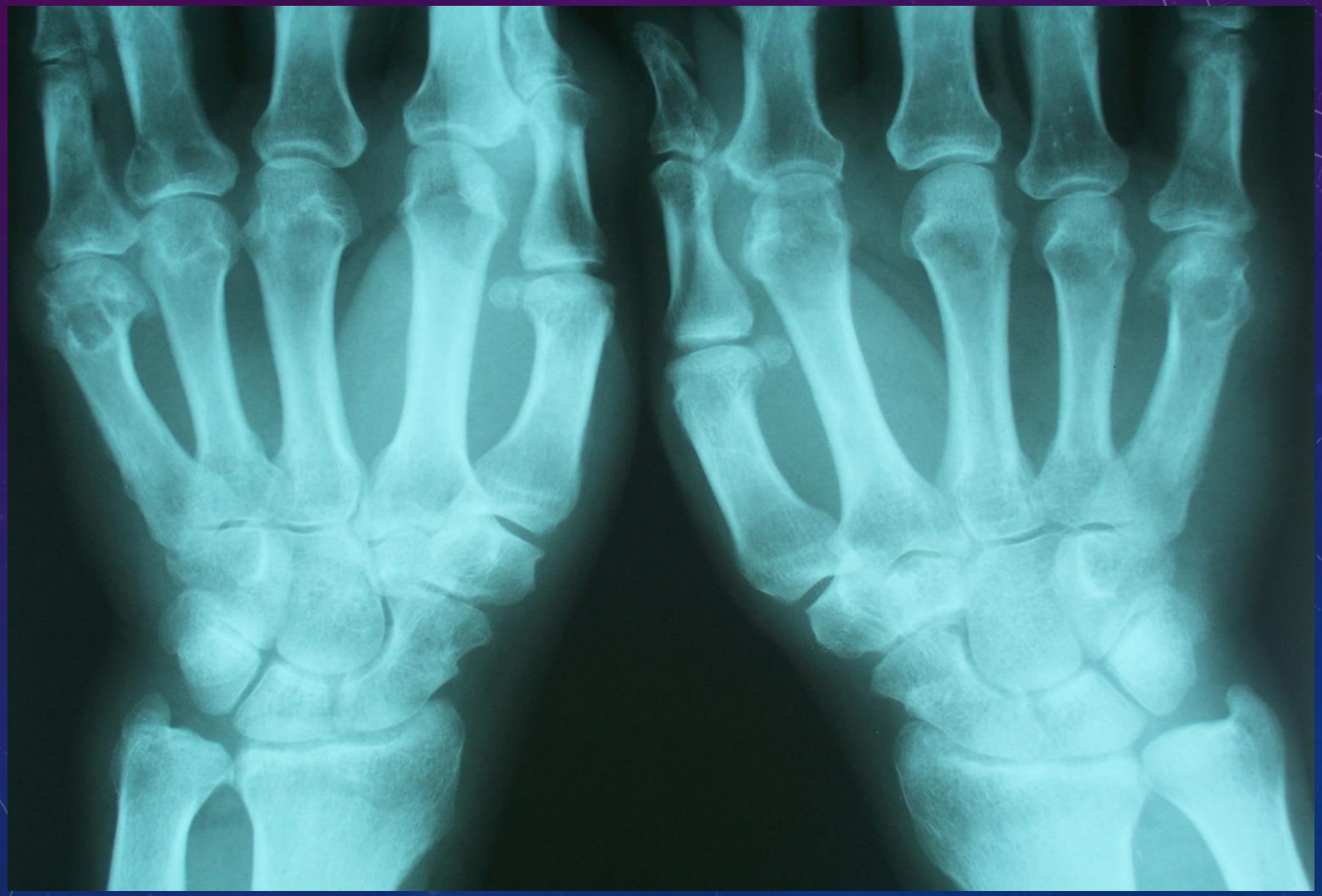

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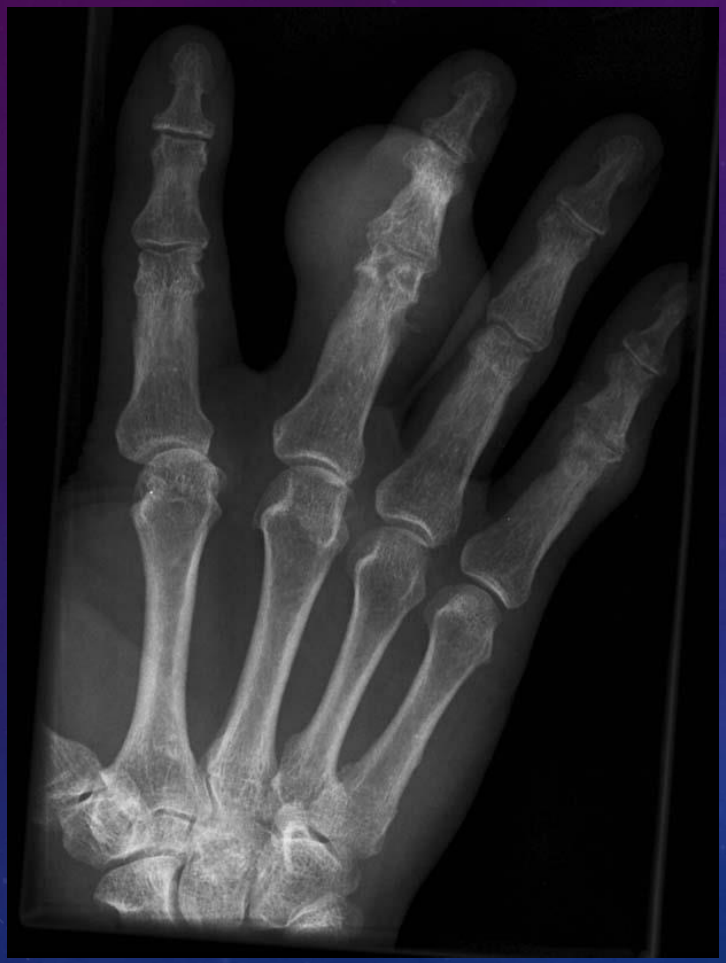

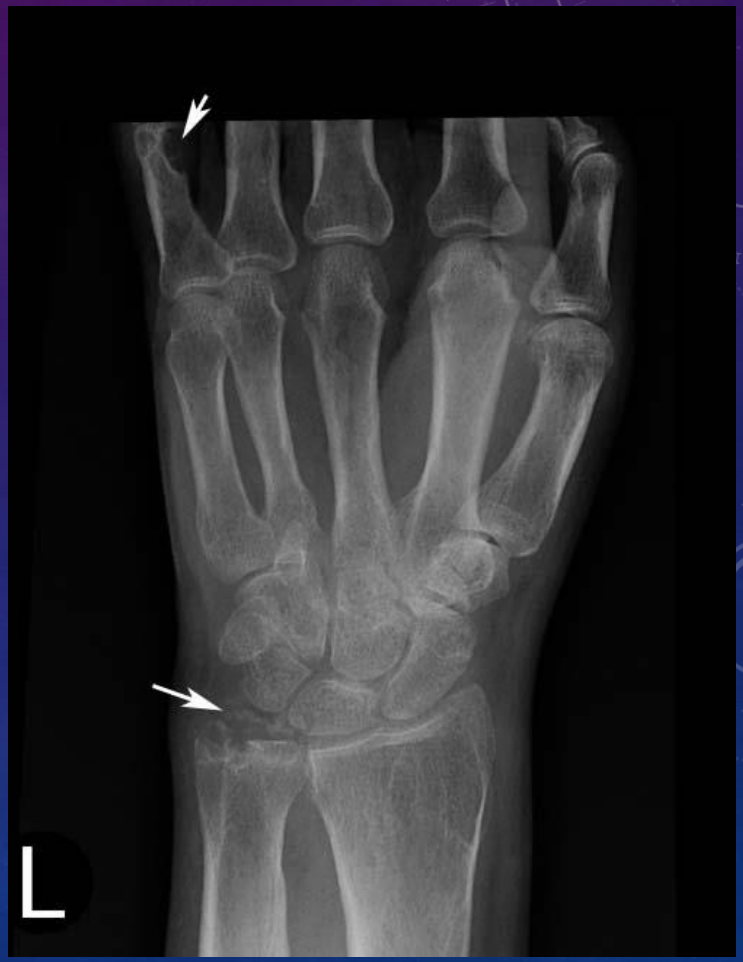

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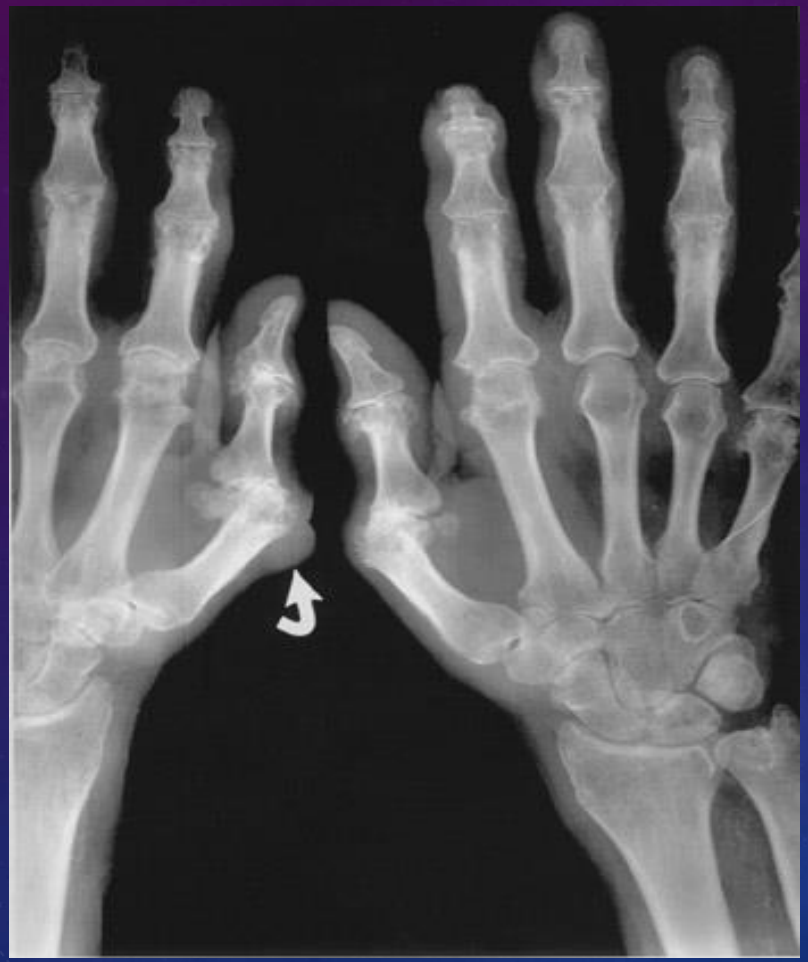

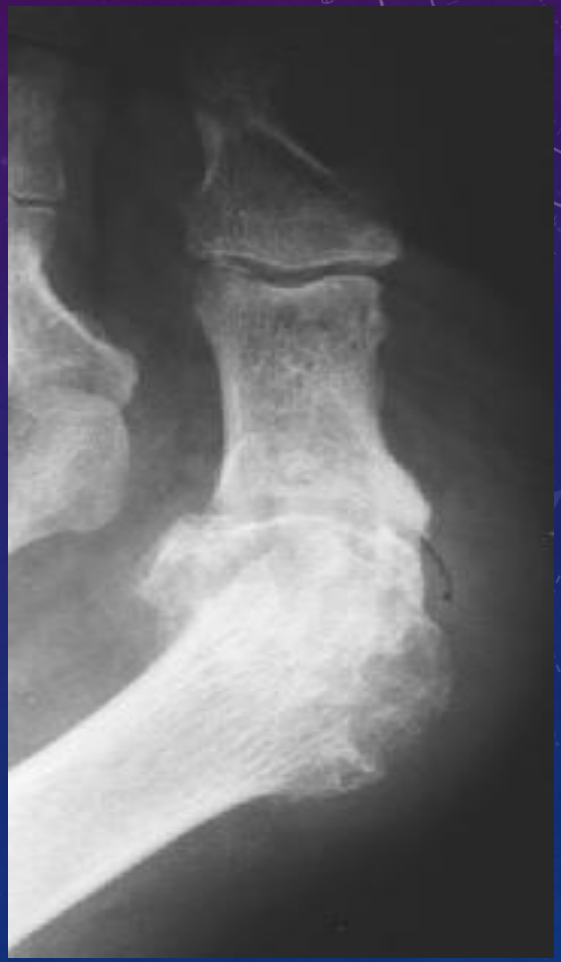

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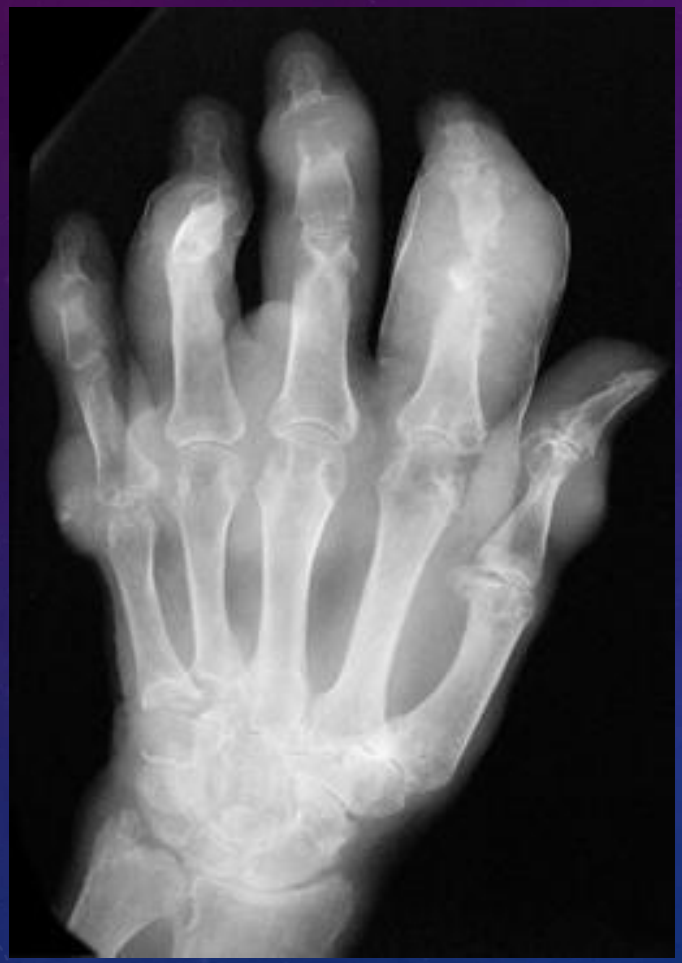

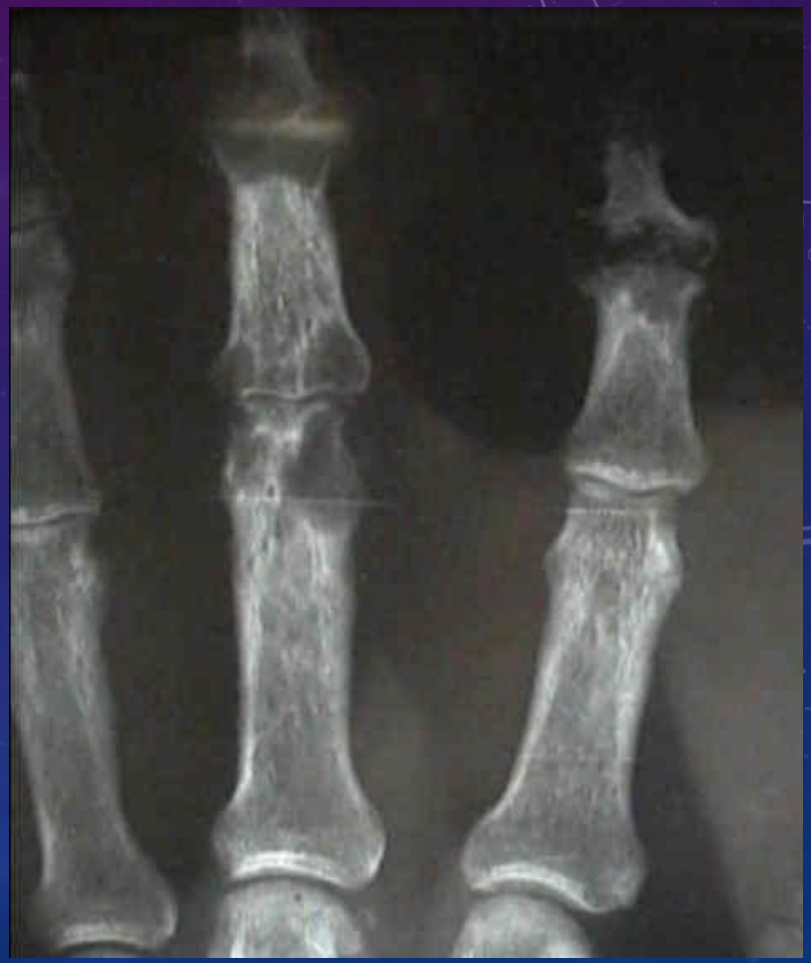

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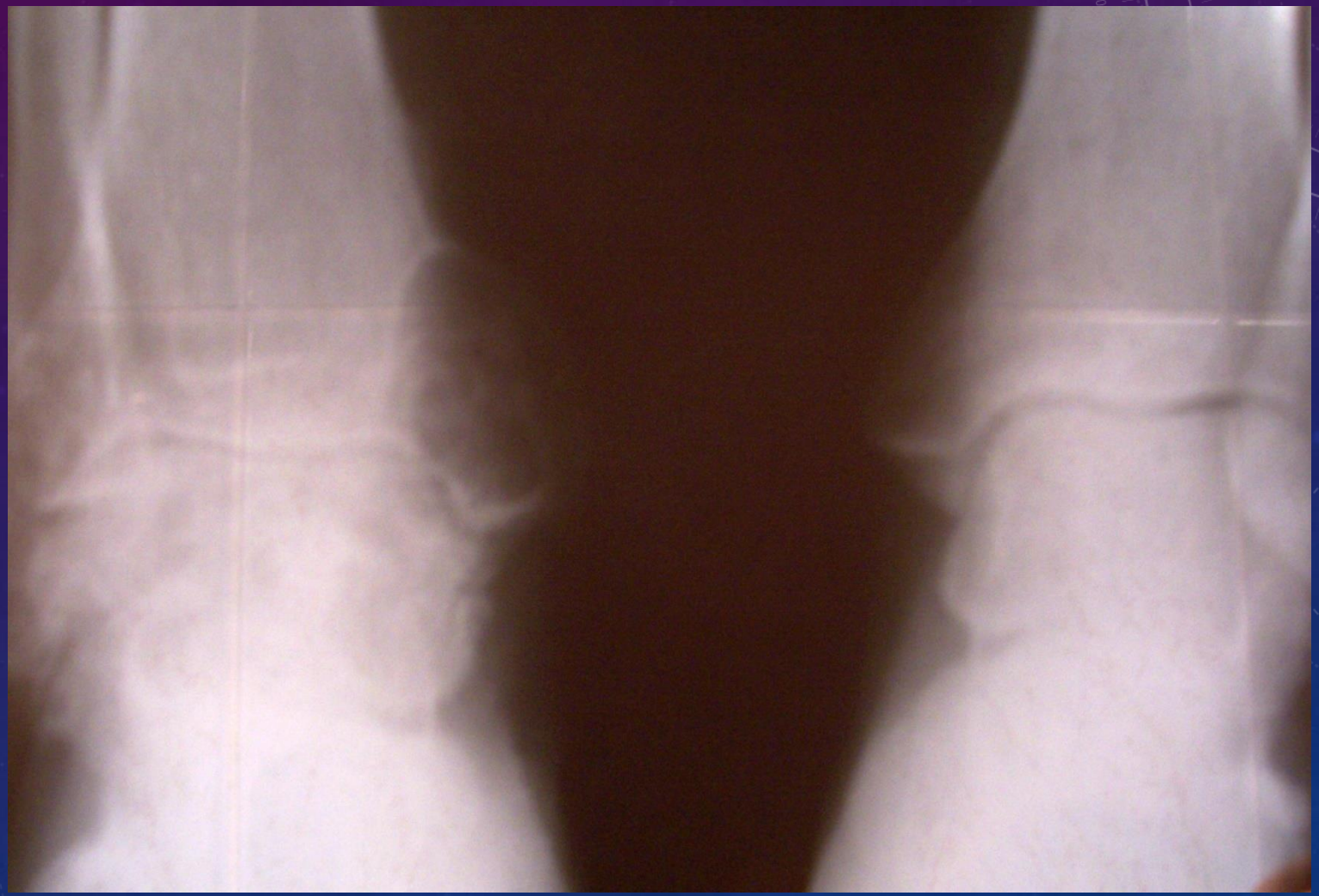

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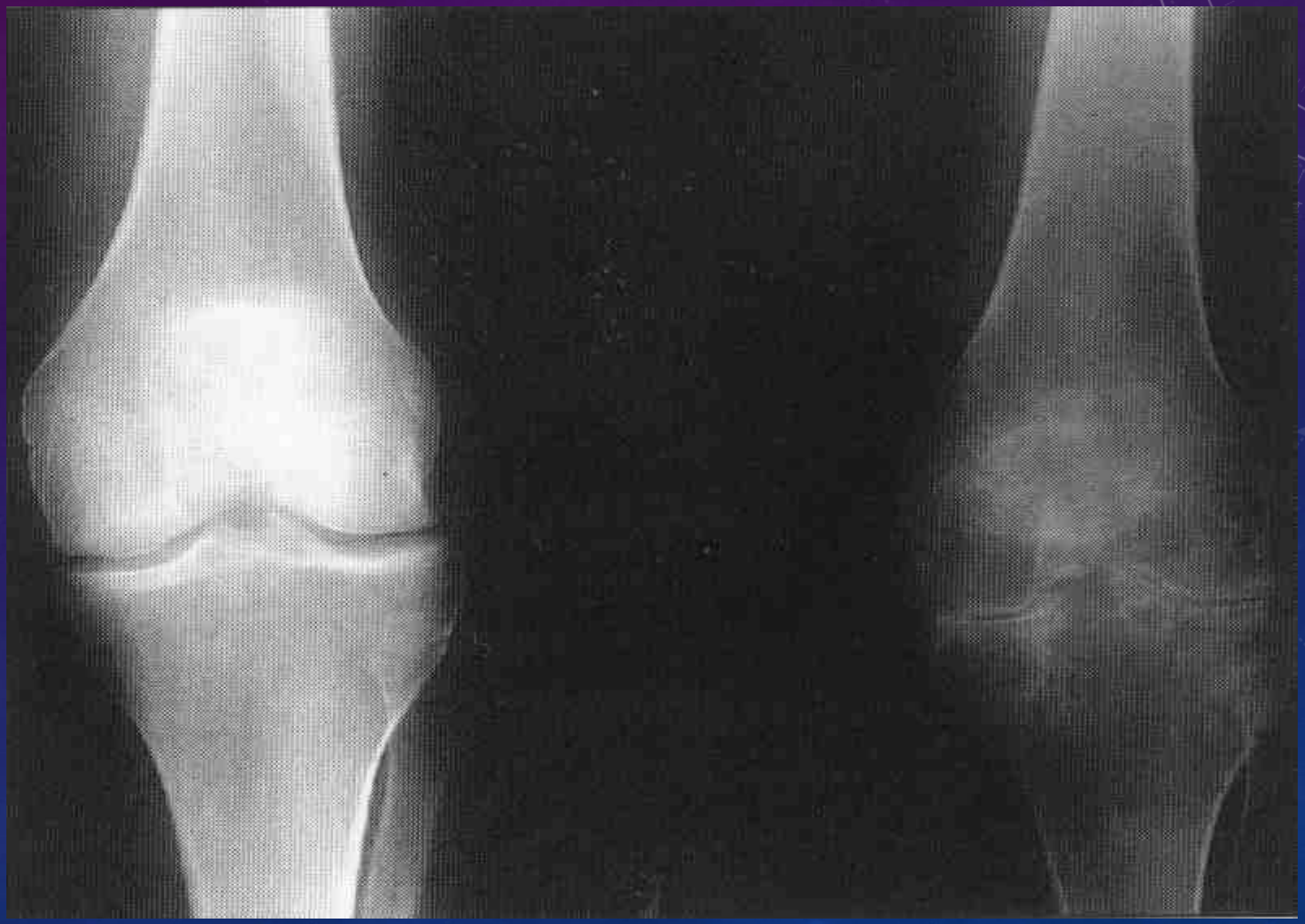


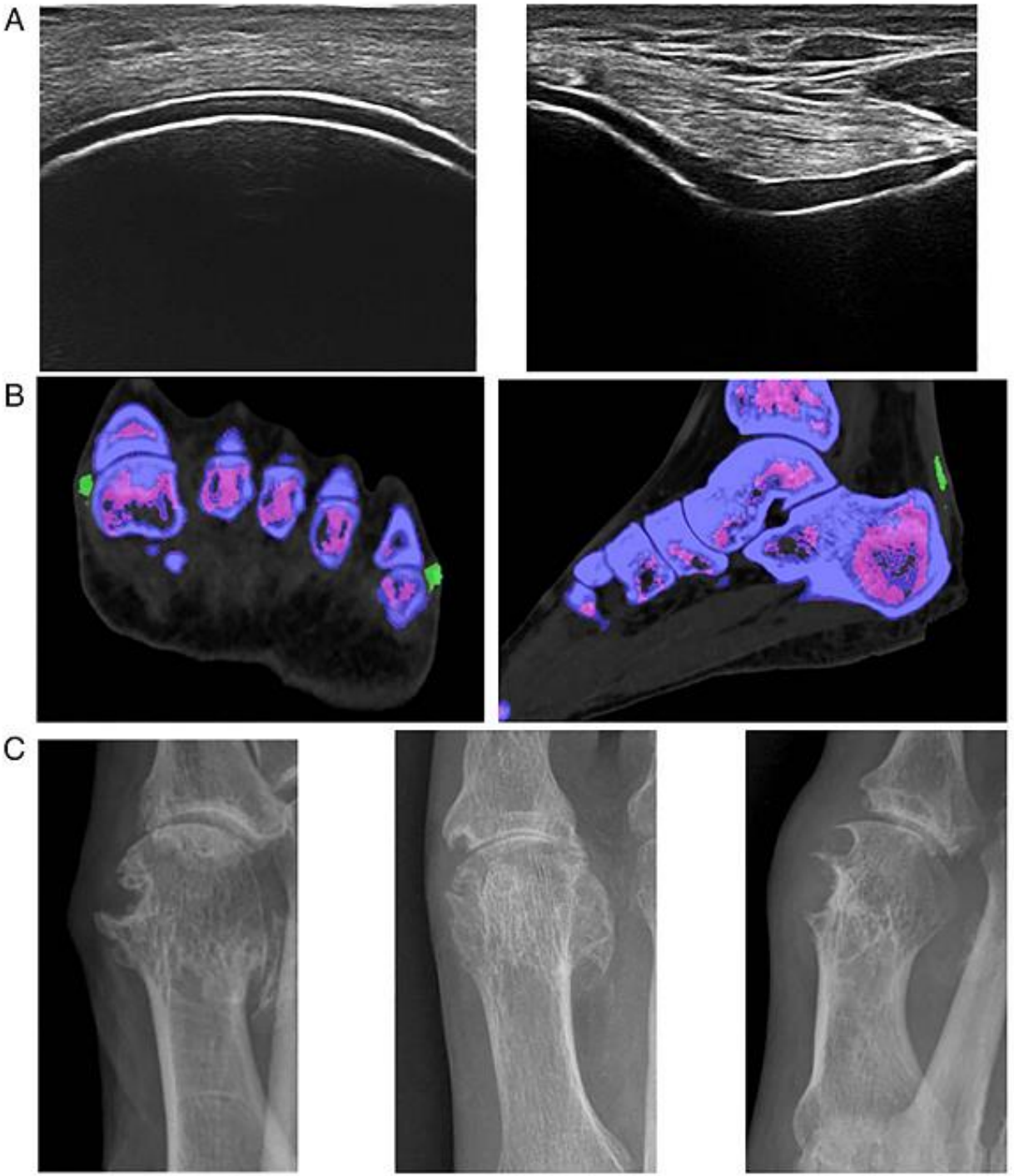
FOR DIAGNOSIS WE NEED DIAGNOSTIC CRITERIA

ACR/EULAR DIAGNOSTIC CRITERIA (OCTOBER 2015)

ENTRY CRITERION (only apply criteria below to those meeting this entry criterion)	At least 1 episode of swelling, pain, or tenderness in a peripheral joint or bursa
SUFFICIENT CRITERION (if met, can classify as gout without applying criteria below)	Presence of MSU crystals in a symptomatic joint or bursa (ie in synovial fluid) or tophus
CRITERIA (to be used if sufficient criterion not met)	***See in slide below*** ***≥8 points classifies an individual as having gout***

CLINICAL		
Pattern of joint/bursa involvement during symptomatic episode(s) ever	Ankle *or* mid-foot (as part of monoarticular or oligoarticular episode without involvement of the first metatarsophalangeal joint	1
	Involvement of the first metatarsophalangeal joint (as part of monoarticular or oligoarticular episode)	2
Characteristic of symptomatic episode(s) ever ➢Erythema overlying affected joint (patient-reported or physician-observed) ➢Can't bear touch or pressure to affected joint ➢Great difficulty with walking or inability to use affected joint	One characteristic	1
	Two characteristics	2
	Three characteristics	3
Time course of episode(s) ever *Presence (ever) of ≥2, irrespective of anti-inflammatory treatment:* ➢Time to maximal pain <24h ➢Resolution of symptoms ≤14 days ➢Complete resolution (to baseline level) between symptomatic episodes	One typical episode	1
	Recurrent typical episodes	2
Clinical evidence of tophus Draining or chalk-like subcutaneous nodule under transparent skin, often with overlying vascularity, located in typical locations: joints, ears, olecranon bursae, finger pads, tendons (eg. Achilles)	Present	4

LABORATORY		
Serum urate: Measured by the uricase method. Ideally should be scored at a time when the patient was not receiving urate-lowering treatment and it was >4 weeks from the start of an episode (ie, during the intercritical period); *if* practicable, retest under those conditions. The highest value irrespective of timing should be scored	<4 mg/dl (< 0.24 mmol/l)	-4
	6 – 8 mg/dl (0.36 – 0.48 mmol/l)	2
	8 – 10 mg/dl (0.48 – 0.60 mmol/l)	3
	≥ 10 mg/dl (≥ 0.60 mmol/l)	4
	Three characteristics	3
Synovial fluid analysis of a symptomatic (ever) joint or bursa (should be assessed by a trained observer	MSU negative	-2
IMAGING		
Imaging evidence of urate deposition in symptomatic (ever) joint or bursa: ultrasound evidence of double-contour sign *or* DECT demonstrating urate deposition	Present (either modality)	4
Imaging evidence of gout-related joint damage: conventional radiography of the hands and/or feet demonstrates at least 1 erosion	Present	4


A
B
C

Treatment

ASYMPTOMATIC HYPERURICEMIA

- **Most patients with asymptomatic hyperuricemia never develop gout or urolythiasis.**
- **Treatment for asymptomatic hyperuricemia carries some risk.**
- **It is not considered beneficial or cost-effective and, generally, is not recommended.**
- **The exception to this is an oncologic setting in which patients receiving cytolytic treatment may be treated prophylactically to prevent acute uric acid nephropathy.**

TREATMENT GOALS

1. **TO STOP THE ACUTE ATTACK AS QUICKLY AS POSSIBLE;**
2. **PREVENTION OF RECURRENT ATTACKS**
   - **Reduces the possibility of repeated crystal-induced inflammation**
3. **TREATMENT OF HYPERURICEMIA AND PREVENTION OF DISEASE PROGRESSION**
   - **Long-term correction of metabolic problems**
   - **Significant reduction in the level of body urates**

Differences Between Hyperuricemia Control and Acute Attack Treatment

- Remedies that treat acute gout attack usually do not influence uricemia levels

- Antihyperuric preparations, such as allopurinol, have no effect in the treatment of acute attack, vice versa – they can worsen the evolution of acute attack

Treatment of acute gout attack

- **Resolution of crystal-induced inflammation.**
  - DOES NOT treat gout
  - Only resolve symptoms
  - After resolving of the inflammation the crystals remain in the affected joint.
- **Medicines:**
  - Oral Colhicine
  - NSAIDs
  - Glucocorticosteroids Local
  - ACTH
  - Biological Therapy

Treatment of acute gout attack

- ***COLCHICINE:***
- 1st day Maximum dose 1.8 mg
- 2nd day and subsequently 0.6 mg per day during 6 months after acute attack
- Requires dose adjustment at ClCr <50 mL/min
- Decreases CV and overall mortality in gout patients.
- Monitoring of adverse effects*: neuropathy, rhabdomyolysis.*

Treatment of acute attack NSAIDs

Medicine	Dose
Diclofenac	75 mg every 8-12 hours with reduction to 25 mg every 8 hours
Nimesulide	100 mg 2 times a day with reduction to 100 mg a day
Ibuprofen	800 mg every 8 hours with a reduction of up to 400 mg every 6 hours
Dexketoprofen	25 mg every 8-12 hours with reduction to 12.5 mg every 8 hours

Treatment of acute gout attack

In the case of contraindications to NSAID and colhicine

Corticosteroid

- Intraarticular ++
- Parenteral administration is rare

(Werlen et al. Rev Rhum (Engl Ed) 1996; 63: 248-54)

ACTH

Biological therapy

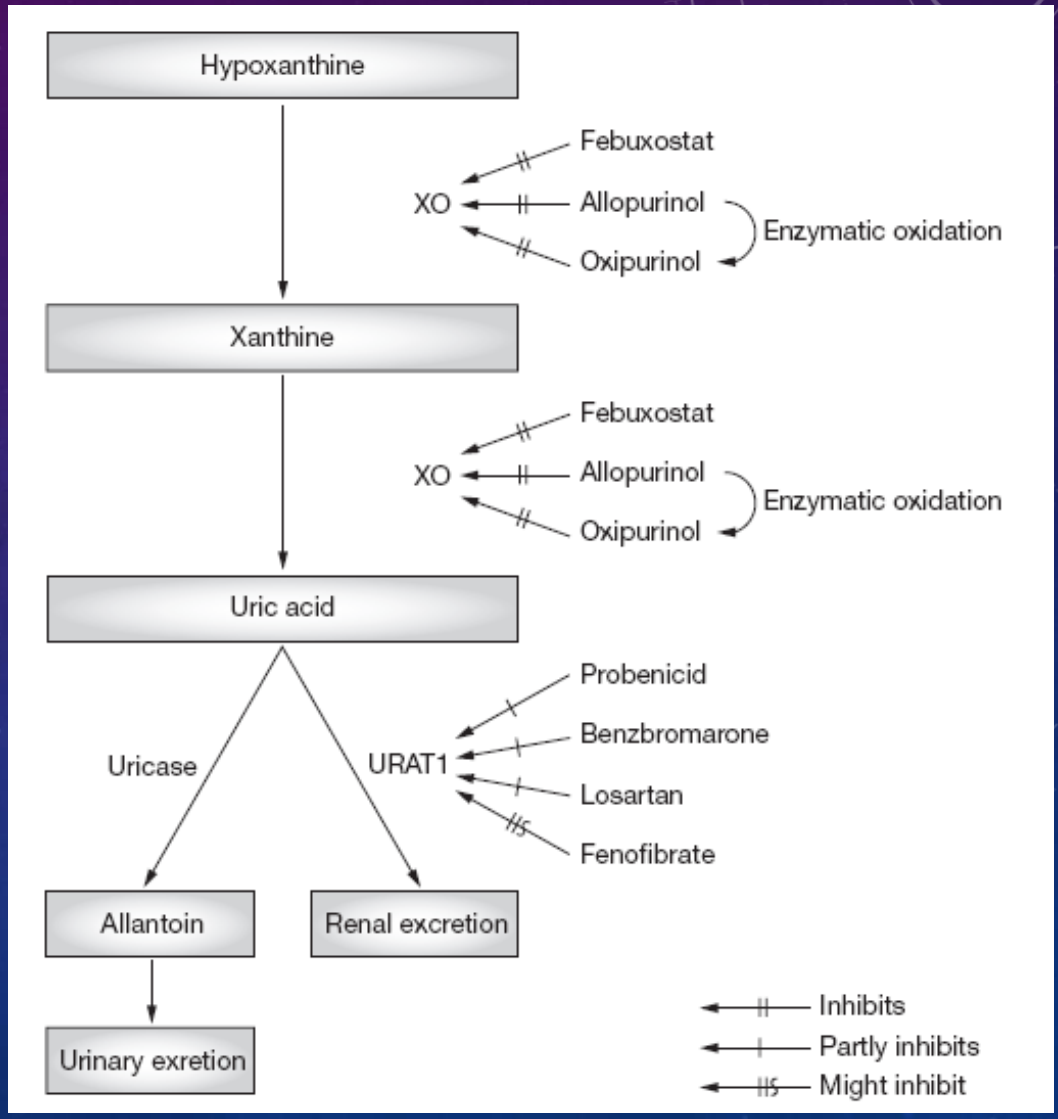
- Severe and resistant
- anti-TNF- or anti-IL-1 gout

BIOLOGICAL THERAPY (IL 1 INHIBITORS)

- Urate crystals can engage an intracellular pattern recognition receptor, the macromolecular NALP3 (cryopyrin) inflammasome complex.
- NALP3 inflammasome may result in interleukin 1 (IL-1) beta production, which, in turn, begins an inflammatory response.
- Inhibition of this pathway has been targeted as a treatment for hyperuricemia-induced crystal arthritis, with recent reports documenting the efficacy of the IL-1 inhibitors **CANAKINUMAB AND RILONACEPT** for preventing gout flares during the initiation of allopurinol therapy.

Hypouricemiant drugs: target < 6 mg/dl

1. Synthesis inhibitors
   - Allopurinol
   - Febuxostat
2. Uricozuric
   - Probenecid
   - Sulfinpyrazone
   - Benziodarrone
   - Benzbromarone
   - Fenofibrate
   - Losartan
   - Lenisurad
3. Urat oxidase



ALLOPURINOL

The ideal candidates for allopurinol treatment are as follows:

- Uric acid overproducers (24-h urinary uric acid excretion >800 mg on general diet or >600 mg on a purine-restricted diet)
- Patients with renal insufficiency, nephrolithiasis, or tophaceous gout
- Patients at risk for developing uric acid nephropathy
- Dosage varies from 100 mg to max. 800 mg once a day

Hypersensitivity syndrome to allopurinol

- ***Frequency : 0.4%***

✓Skin rash,

✓ fever,

✓Cytolysis of hepatocytes,

✓Leukocytosis and eosinophilia,

✓ Renal insufficiency

- ***Mortality: 20%***

FEBUXOSTAT

- A non purine selective inhibitor of xantine oxidase
- Relatively new medicine
- Indications are the same as for allopurinol plus allopurinol intolerance or allergy
- Dosages: 80 or 120 mg once a day

BENZBROMARONE

- **Increases the renal clearance of uric acid.**

  Action on the carrier of URAT1.

- **May cause urolithiasis (in patients with good renal function)**
- **Hepatotoxicity**
- **Limited administration but is available in European countries**
- **Adverse effects comparable to allopurinol or colhicine.**

  Jansen TL, Clin Exp Rheumatol 2004;22:651

- **Increases renal clearance of uric acid.**

BENZBROMARON

- **Dosage is started with 50 mg/24 hours . Dose increases up to 100 mg/24 hours Maximum dose – 200 mg/24 hours**

- **Contraindicated in hyperuraturia greater than 700 mg/24 hours.**

PROBENECIDE

- **Probenecid is a uricosuric drug**
- **Inhibits the tubular reabsorption of filtered and secreted urate, thereby increasing urate excretion.**
- **The ideal candidates for probenecid therapy:**
  - **those with a 24-hour urine uric acid excretion of less than 800 mg in 24 hours**
  - **no history of nephrolithiasis**
  - **good renal function (creatinine clearance >80 mL/min).**

PROBENECIDE

- **The starting dose for probenecid is 250 mg twice a day**
- **It can be increased gradually to a maximum daily dose of 3 g/d.**
- **Some degree of gastrointestinal irritation is experienced by approximately 2% of patients.**

LESINURAD (ZURAMPIC)

- **The first selective uric acid reabsorption inhibitor (SURI) approved by the FDA.**
- **It acts by inhibiting the urate transporter, URAT1, which is responsible for the majority of the renal reabsorption of uric acid.**
- **It also inhibits organic anion transporter 4 (OAT4), a uric acid transporter associated with diuretic-induced hyperuricemia.**

LESINURAD (ZURAMPIC)

- Lesinurad should be coadministered with a xanthine oxidase inhibitor and is indicated for hyperuricemia associated with gout in patients who have not achieved target serum uric acid levels with a xanthine oxidase inhibitor alone.
- Dosage 200 mg a day
- It is not approved for asymptomatic hyperuricemia and it is contraindicated for increased uric acid levels caused by tumor lysis syndrome or Lesch-Nyhan syndrome.

Urate oxidase

Rasburicase (Fasturtec*)

Indications: tumor lysis syndrome

High Cost Administration
i/v Relapsing
Severe Tofacee Gut

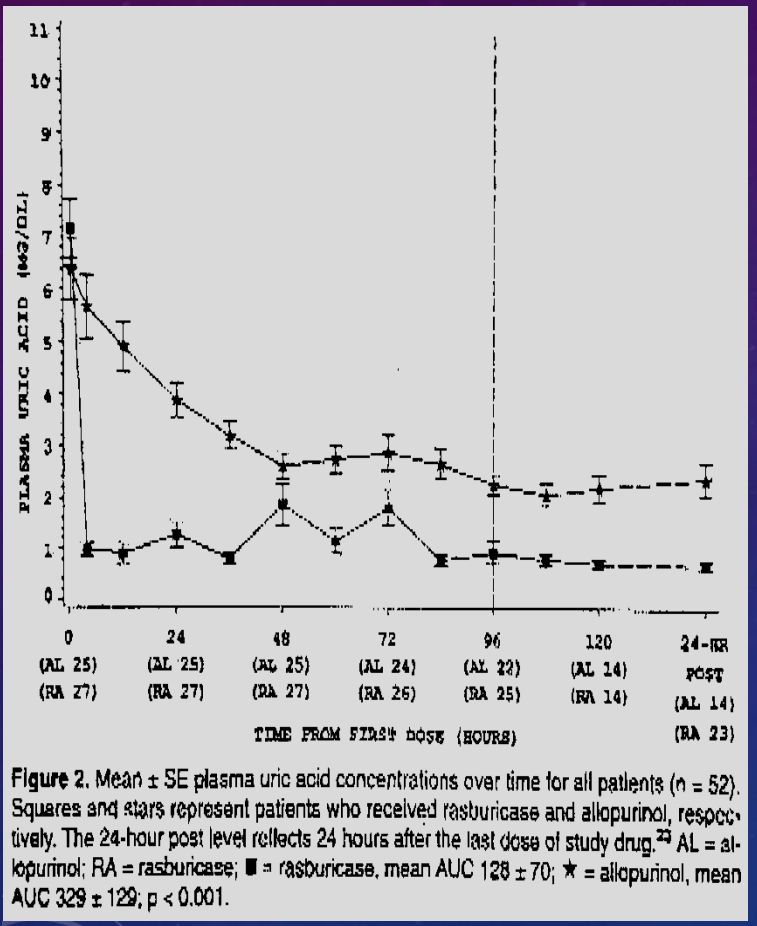


Figure 2. Mean ± SE plasma uric acid concentrations over time for all patients (n = 52). Squares and stars represent patients who received rasburicase and allopurinol, respectively. The 24-hour post level reflects 24 hours after the last dose of study drug.[23] AL = allopurinol; RA = rasburicase; ■ = rasburicase, mean AUC 128 ± 70; ★ = allopurinol, mean AUC 329 ± 129; p < 0.001.

B Yim et al. Ann Pharmacotherapy 2003; 37 : 1047

PEG uricasa

In clinical research

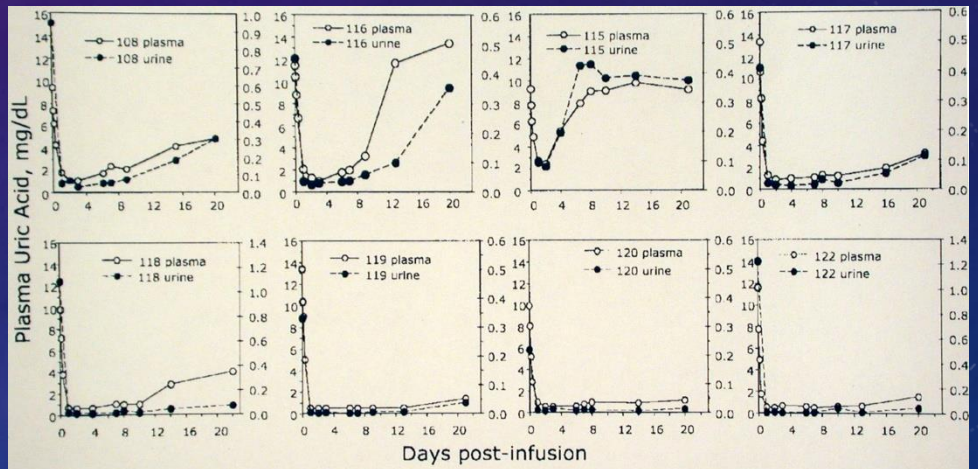


Figure 2. Relationship between the plasma uric acid concentration and the urine uric acid:creatinine ra Upper panels show data for individual patients who received IV infusions of 4 mg PEG-uricase; lower pa show data for subjects who received 8-mg infusions. See Figure 1 for definitions.

Sundy et al . Arthritis Rheum 2007; 56: 1021-8

PEGLOTICASE (KRYSTEXXA)

- **A recombinant, pegylated, uric acid–specific enzyme that catalyzes the oxidation of uric acid to allantoin.**
- **It is approved for use in adults with chronic gout that is refractory to conventional therapy.**
- **It is administered by intravenous infusion.**

Thank you