

PART II
BONE &
CONNECTIVE TISSUE
DISORDERS

GOUT & HYPERURICEMIA

INTRODUCTION

- ◉ Gout is a condition characterized by the deposition of monosodium urate crystals in the joints or soft tissue.
- ◉ Early theories indicate that gout was only the problem of the elite social class & was caused by overindulgence in food, wine.
- ◉ The four phases of gout include asymptomatic hyperuricemia, acute gouty arthritis, intercritical gout and chronic tophaceous gout.
- ◉ The peak incidence occurs in patients 30 to 50 years old, and the condition is much more common in men than in women.

INTRODUCTION

- Patients with asymptomatic hyperuricemia do not require treatment, but efforts should be made to lower their urate levels by encouraging them to make changes in diet or lifestyle.
- Acute gout most commonly affects the first metatarsal joint of the foot, but other joints are also commonly involved.

INTRODUCTION

- Definitive diagnosis requires joint aspiration with demonstration of birefringent crystals in the synovial fluid under a polarized light microscope.
- Gout may be primary or secondary.

INTRODUCTION

- Treatment includes nonsteroidal anti-inflammatory drugs (NSAIDs), colchicine, corticosteroids and analgesics.
- In patients without complications, NSAID therapy is preferred.

EPIDEMIOLOGY

- Gouty arthritis is the most common form of inflammatory joint disease in men older than 40 years.
- The National Health Survey (1983 to 1985) determined the prevalence rate of self-reported gout to be 13.6 cases per 1,000 men and 6.4 cases per 1,000 women.

EPIDEMIOLOGY

- ⦿ These numbers reflect an approximate three fold increase in the prevalence of gout since 1969.
- ⦿ In contrast, cases of physician-diagnosed gout suggest a consistently lower prevalence rate--5.0 to 6.6 cases per 1,000 men and 1.0 to 3.0 cases per 1,000 women.

CLINICAL FEATURES

- **Asymptomatic Hyperuricemia**

Asymptomatic hyperuricemia is the term for an abnormally high serum urate level, without gouty arthritis or nephrolithiasis.

- Hyperuricemia is defined as a serum urate concentration greater than 7 mg per dL (416 μmol per L), the approximate level at which urate is supersaturated in plasma.

CLINICAL FEATURES

- Although gouty arthritis characteristically occurs in patients with hyperuricemia, it is incorrect to equate hyperuricemia with clinical gout.
- Researchers from the Normative Aging Study followed 2,046 initially healthy men for 15 years by taking serial measurements of serum urate levels.

CLINICAL FEATURES

- The five-year cumulative incidence rates of gouty arthritis were 2.0 percent for a serum urate level of 8.0 mg per dL (475 μ mol per L) or lower, 19.8 percent for urate levels from 9.0 to 10.0 mg per dL (535 to 595 μ mol per L) and 30 percent for a serum urate level higher than 10 mg per dL (595 μ mol per L).

CLINICAL FEATURES

- Hyperuricemia predisposes patients to both gout and nephrolithiasis, but therapy is generally not warranted in the asymptomatic patient.
- Recognizing hyperuricemia in the asymptomatic patient, however, provides the physician with an opportunity to modify or correct underlying acquired causes of hyperuricemia.

ACQUIRED CAUSES OF HYPERURICEMIA

Increased urate production

Nutritional	Excess purine, ethanol, fructose consumption
Hematologic	Myeloproliferative and lymphoproliferative disorders, polycythemia
Drugs	Ethanol, cytotoxic drugs, vitamin B ₁₂ (treatment of pernicious anemia)
Miscellaneous	Obesity, psoriasis, hypertriglyceridemia

Decreased renal excretion of urate

Drugs	Ethanol, cyclosporine (Sandimmune), thiazides, furosemide (Lasix) and other loop diuretics, ethambutol (Myambutol), pyrazinamide, aspirin (low-dose), levodopa (Larodopa), nicotinic acid (Nicolar)
Renal	Hypertension, polycystic kidney disease, chronic renal failure (any etiology)
Metabolic/endocrine	Dehydration, lactic acidosis, ketosis, hypothyroidism, hyperparathyroidism
Miscellaneous	Obesity, sarcoidosis, toxemia of pregnancy

CLINICAL FEATURES

- ◉ **Acute Gout**

Acute gout is characterized by the sudden onset of pain, erythema, limited range of motion and swelling of the involved joint.

- ◉ Often quoted, the English physician Thomas Sydenham's classic description of his own gouty sufferings is as true today as it was in the 17th century:

CLINICAL FEATURES

- The victim goes to bed and sleeps in good health. About two 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 dislocation. . . . Then follows chills and shivers and a little fever.
- The pain, which was at first moderate, becomes more intense. . . . 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. . . ."

CLINICAL FEATURES

- The peak incidence of acute gout occurs between 30 and 50 years of age.
- Approximately 90 percent of first attacks are monoarticular.
- The attack may be precipitated by surgery, trauma, ds, alcohol or emotional stress.
- Acute gouty attacks usually resolve if untreated but may take 10-14 days to do so.

CLINICAL FEATURES

- In more than one half of patients with acute gout, the first metatarsophalangeal joint is the initial joint involved, a condition known as podagra.
- Joint involvement (in order of decreasing frequency) includes the metatarsophalangeal joint, the instep/forefoot, the ankle, the knee, the wrist and the fingers.

CLINICAL FEATURES

- ◉ Gout in women occurs exclusively after menopause since estrogens increase the renal excretion of uric acid.
- ◉ Women develop gout at an older age than men and have twice the prevalence of hypertension, renal insufficiency and exposure to diuretics.
- ◉ The onset of gout before age 30 in men or before menopause in women is atypical and raises concern about an associated inherited enzyme defect or renal disease.

CLINICAL FEATURES

- ◉ **Intercritical Gout**

Following recovery from acute gouty arthritis, the patient reenters an asymptomatic phase of the disease.

- ◉ This phase is referred to as "intercritical gout."

- ◉ It is during this intercritical phase that the physician should focus on secondary causes of hyperuricemia.

CLINICAL FEATURES

◉ **Intercritical Gout**

Medications should be assessed to identify those that may aggravate the patient's condition (e.g., diuretics) and dietary education regarding purine-rich foods (which contribute to higher serum uric acid levels) should be provided to the patient at this time.

- ◉ The patient should also be counseled about limiting alcohol consumption and gradually losing weight, if obese.

THE PURINE CONTENT OF FOODS AND BEVERAGES

High

Best to avoid:

Liver, kidney, anchovies, sardines, mussels, codfish, scallops, trout, , veal, turkey

Moderate

May eat occasionally:

Asparagus, beef, chicken, crab, duck, kidney beans, mushrooms, lobster, oysters, shrimp, spinach

Low

No limitation:

Carbonated beverages, coffee, fruits, breads, grains, macaroni, cheese, eggs, milk products, sugar, tomatoes and green vegetables



CLINICAL FEATURES

- ◉ **Recurrent Gouty Arthritis**

The frequency of subsequent acute attacks of gout usually increases over time.

- ◉ Approximately 60 percent of patients have a second attack within the first year, and 78 percent have a second attack within two years.

- ◉ Only 7 percent of patients do not have a recurrence within a 10-year period.¹⁰

CLINICAL FEATURES

- ◉ Polyarticular involvement also becomes more common over time and can often mimic other forms of arthritis.
- ◉ Gouty arthritis may mimic rheumatoid arthritis, with symmetric small-joint involvement and tophaceous deposits on extensor tendon surfaces that resemble rheumatoid nodules.
- ◉ As many as 30 percent of patients with tophaceous gout also have low titers of rheumatoid factor, adding to the diagnostic confusion.

CLINICAL FEATURES

- Postmenopausal women who are receiving diuretic therapy have a tendency to form tophi in osteoarthritic joints of the hands,¹² mimicking inflammatory "erosive osteoarthritis" .
- These clinical scenarios underscore the need for an accurate diagnosis when evaluating the patient with an acute arthritis.

CLINICAL FEATURES

- Analysis of synovial fluid is essential to identify monosodium urate crystals.
- Reliance on clinical presentation, serum hyperuricemia levels or response to NSAID therapy does not replace direct evaluation of synovial fluid and may lead to an inaccurate diagnosis.

CLINICAL FEATURES

⦿ **Chronic Tophaceous Gout**

Tophi are chalky deposits of sodium urate that are large enough to be seen on radiographs and may occur at virtually any site. The most common sites include the joints of the hands or feet. Articular tophaceous gout can result in a destructive arthropathy and chronic secondary osteoarthritis.

CLINICAL FEATURES

- The duration of time between the first gouty attack and recognizable tophaceous disease is highly variable and may range from three to 42 years (mean: 11.6 years).
- The rate of urate deposition and, consequently, the rate of tophi formation, correlate with the duration and severity of hyperuricemia.

CLINICAL FEATURS

- Tophaceous disease is more likely to occur in patients with the following: a polyarticular presentation, a serum urate level higher than 9.0 mg per dL (535 μ mol per L) and a younger age at disease onset (i.e., 40.5 years or younger).

PRESENTATION OF ACUTE GOUTY ARTHRITIS

GENERAL

Gout typically involves acute attacks of arthritis, nephrolithiasis, gouty nephropathy, and aggregated deposits of sodium urate (tophi) in cartilage, tendons, synovial membranes, and elsewhere.

SIGNS AND SYMPTOMS

Fever; intense pain, erythema, warmth, and swelling of involved joints

Excruciating pain, swelling, and inflammation involving one or more joints, most commonly starting in the great toe, but sometimes involving other joints of the extremities

LABORATORY TESTS

Elevated serum uric acid levels; leukocytosis

OTHER DIAGNOSTIC TESTS

None

PATHOPHYSIOLOGY

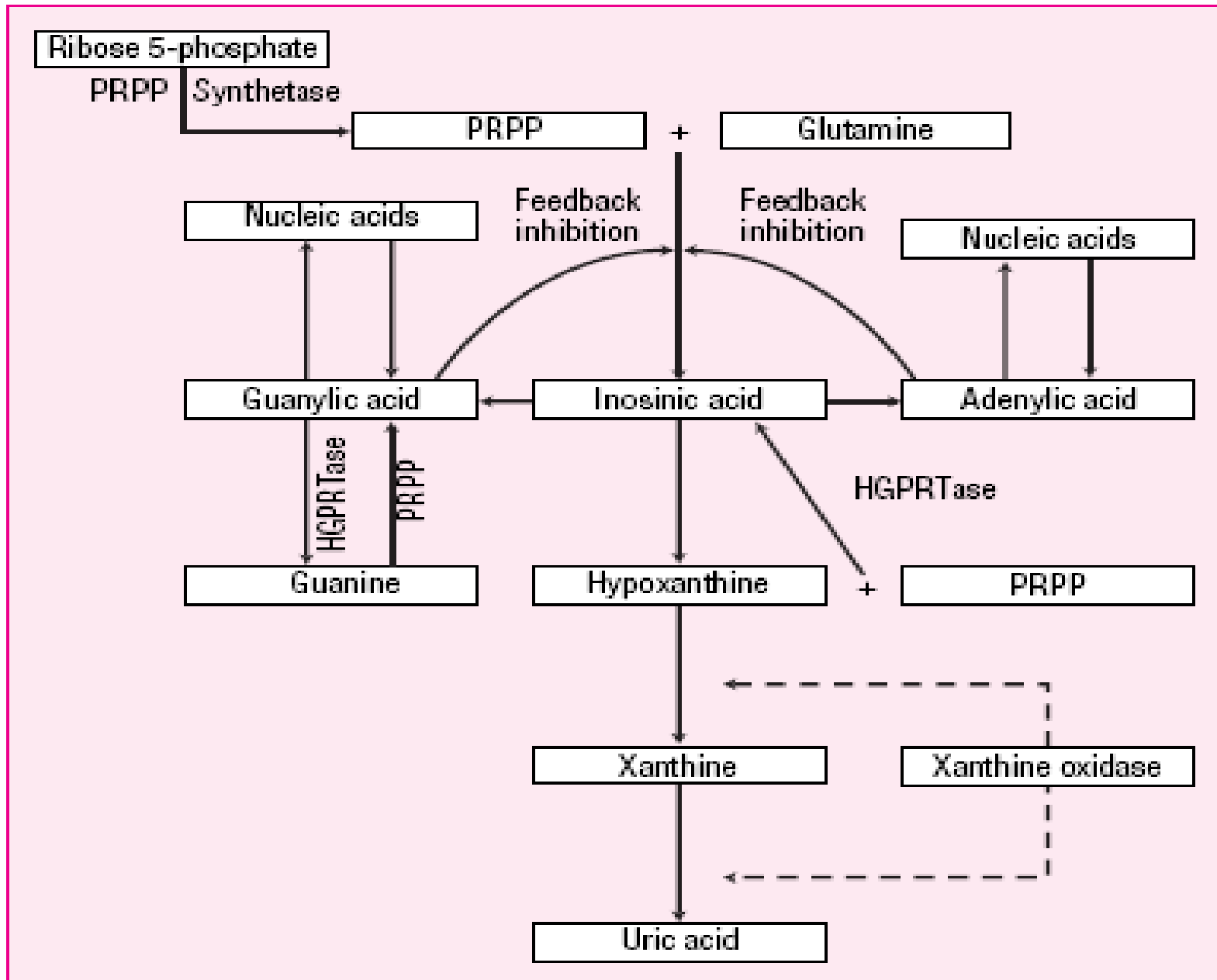


FIGURE 91-1. Purine metabolism.

PATHOPHYSIOLOGY

- In humans, uric acid is the end product of the degradation of purines. Uric acid serves no known physiologic purpose and therefore is regarded as a waste product.
- In lower animals, the enzyme uricase breaks down uric acid to the more soluble allantoin, and thus uric acid does not accumulate.

PATHOPHYSIOLOGY

- ◉ Gout occurs exclusively in humans in whom a miscible pool of uric acid exists.
- ◉ Under normal conditions, the amount of accumulated uric acid is about 1200 mg in men and about 600 mg in women.
- ◉ The size of the urate pool is increased severalfold in individuals with gout.
- ◉ This excess accumulation may result from either overproduction or underexcretion.

OVER PRODUCTION OF URIC ACID

- ⦿ The purines from which uric acid is produced originate from three sources:
 1. dietary purine,
 2. conversion of tissue nucleic acid to purine nucleotides,
 3. and de novo synthesis of purine bases.
- ⦿ The purines derived from these three sources enter a common metabolic pathway leading to the production of either nucleic acid or uric acid.

OVER PRODUCTION OF URIC ACID

- Under normal circumstances, uric acid may accumulate excessively if production exceeds excretion.
- The average human produces about 600 to 800 mg of uric acid each day.
- 1st a supersaturation of urate occurs in plasma and body fluids followed by a deposition into and around the joints.

OVER PRODUCTION OF URIC ACID

- Several enzyme systems regulate purine metabolism.
- Abnormalities in these regulatory systems can result in overproduction of uric acid.
- Uric acid also may be overproduced as a consequence of increased breakdown of tissue nucleic acids, as with myeloproliferative and lymphoproliferative disorders.

OVER PRODUCTION OF URIC ACID

- Dietary purines play an unimportant role in the generation of hyperuricemia in the absence of some derangement in purine metabolism or elimination.

OVER PRODUCTION OF URIC ACID

- Two enzyme abnormalities resulting in an overproduction of uric acid have been well described.
- The first is an increase in the activity of phosphoribosyl pyrophosphate (PRPP) synthetase, which leads to an increased concentration of PRPP.
- PRPP is a key determinant of purine synthesis and thus uric acid production.
- The second is a deficiency of hypoxanthine guanine phosphoribosyl transferase (HGPRT).

OVER PRODUCTION OF URIC ACID

- HGPRT is responsible for the conversion of guanine to guanylic acid and hypoxanthine to inosinic acid.
- These two conversions require PRPP as the cosubstrate and are important reutilization reactions involved in the synthesis of nucleic acids.
- A deficiency in the HGPRT enzyme leads to increased metabolism of guanine and hypoxanthine to uric acid, and more PRPP to interact with glutamine in the first step of the purine pathway.

OVER PRODUCTION OF URIC ACID

- Complete absence of HGPRT results in the childhood Lesch-Nyhan syndrome, characterized by choreoathetosis, spasticity, mental retardation, and markedly excessive production of uric acid.
- A partial deficiency of the enzyme may be responsible for marked hyperuricemia in otherwise normal, healthy individuals.

UNDER EXCRETION OF URIC ACID

- Uric acid does not accumulate as long as uric acid production is balanced with elimination.
- Uric acid is eliminated in two ways:
 1. About two-thirds of the uric acid produced each day is excreted in the urine.
 2. The rest is eliminated through the gastrointestinal tract after enzymatic degradation by colonic bacteria.

UNDER EXCRETION OF URIC ACID

- A decline in the urinary excretion of uric acid to a level below the rate of production leads to hyperuricemia and an increased miscible pool of sodium urate.
- Almost all the urate in plasma is freely filtered across the glomerulus.

UNDER EXCRETION OF URIC ACID

- The concentration of uric acid appearing in the urine is determined by multiple renal tubular transport processes in addition to the filtered load.
- Evidence favors a four-component model including:
 1. glomerular filtration,
 2. tubular reabsorption,
 3. tubular secretion,
 4. and postsecretory reabsorption.

UNDER EXCRETION OF URIC ACID

- Approximately 90% of filtered uric acid is reabsorbed in the proximal tubule, probably by both active and passive transport mechanisms.
- There is a close linkage between proximal tubular sodium reabsorption and uric acid reabsorption, so states that enhance sodium reabsorption (e.g., dehydration) also lead to increased uric acid reabsorption.

UNDER EXCRETION OF URIC ACID

- The exact site of tubular secretion of uric acid has not been determined; this too appears to involve an active transport process.
- Postsecretory reabsorption occurs somewhere distal to the secretory site.

PATHOPHYSIOLOGY

- Factors that decrease uric acid clearance or increase its production will result in an increase in serum urate concentration.
- Drugs that decrease renal clearance of uric acid through modification of filtered load or one of the tubular transport processes are listed in Table.
- By enhancing renal urate reabsorption, insulin resistance is also associated with gout.

PATHOPHYSIOLOGY

- The pathophysiologic approach to the evaluation of hyperuricemia requires determining whether the patient is overproducing or underexcreting uric acid. This can be accomplished by placing the patient on a purine-free diet for 3 to 5 days and then measuring the amount of uric acid excreted in the urine in 24 hours.

PATHOPHYSIOLOGY

- ⦿ Normal individuals produce 600 to 800 mg of uric acid daily and excrete less than 600 mg in urine.
- ⦿ Individuals who excrete more than 600 mg on a purine-free diet may be considered overproducers.

PATHOPHYSIOLOGY

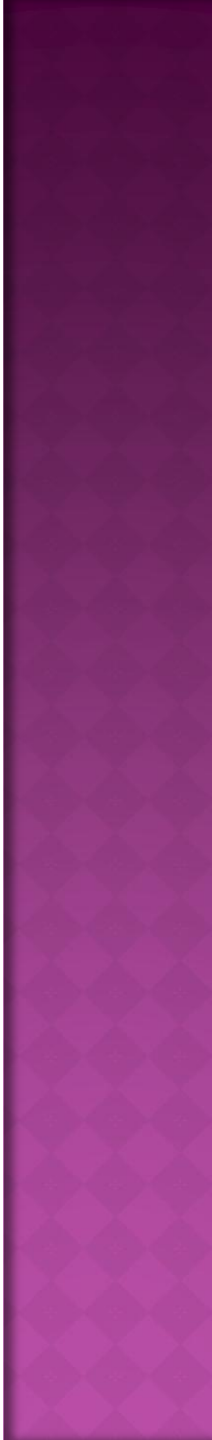
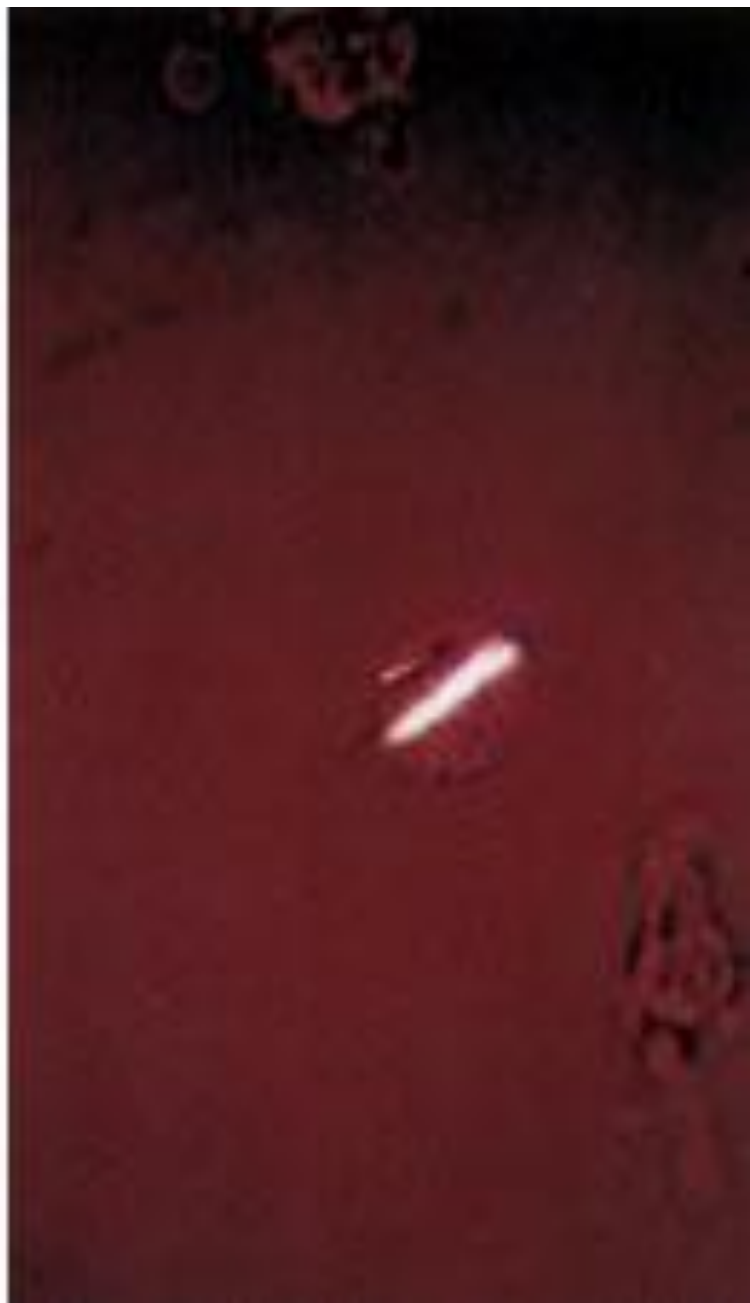
- Hyperuricemic individuals who excrete less than 600 mg of uric acid per 24 hours on a purine-free diet may be classified as underexcretors of uric acid.
- However, it is very difficult in clinical practice to maintain someone on a purine-free diet for several days.
- On a regular diet, excretion of greater than 1000 mg per 24 hours reflects overproduction; less than this is probably normal.

PATHOPHYSIOLOGY

- The uric acid crystals initiate a phagocytic response by leucocytes, and as the leucocytes ingest the urate crystals the responses of other inflammatory mechanisms are triggered.
- The inflammatory response may be influenced by the site and magnitude of uric acid crystal deposition.
- The inflammatory reaction may become self-propagating and self-enhancing because of the deposition of additional crystals from the serum.

DIAGNOSIS

- It is important to make an accurate diagnosis of gout before beginning therapeutic intervention.
- A definitive diagnosis requires aspiration & examination of synovial fluid to confirm the presence of monosodium urate crystals.
- Even the smallest amount of fluid obtained from the shaft or hub of the needle during aspiration can be examined for crystals.
- Monosodium urate crystals are identified by examination under polarized light microscopy.



DIAGNOSIS

- In order to demonstrate the characteristic birefringence, it is necessary to use a microscope with a first-order red compensator and a rotating stage.
- Urate crystals are bright (strongly birefringent), needle shaped and yellow.

DIAGNOSIS

- Even if a polarizing microscope is not available, the characteristic needle shape of the monosodium urate crystals, especially when found within white blood cells, can be identified with conventional light microscopy; in this case, they resemble a toothpick pierced through an olive.

DIAGNOSIS

- Confirmation of the presence of monosodium urate crystals is imperative so that patients with coincidental hyperuricemia and osteoarthritis are not incorrectly diagnosed with gout and unnecessarily treated with allopurinol (Zyloprim).
- Furthermore, rheumatoid arthritis, calcium pyrophosphate dihydrate deposition (pseudogout), spondyloarthropathies and osteoarthritis may also mimic gouty arthritis.

TREATMENT

- NSAIDs in hi doses to reduce acute inflammation of the joints then the dose is reduced gradually over the next few days
- Colchicine inhibit phagocytic leucocytes and produce a dramatic and rapid relief of symptoms.
- Probenecid and sulfinpyrazone are 2 commonly used uricosuric agents that inhance renal excretion of uric acid.
- Allopurinol blocks the formation of uric acid.