GOUT

BY

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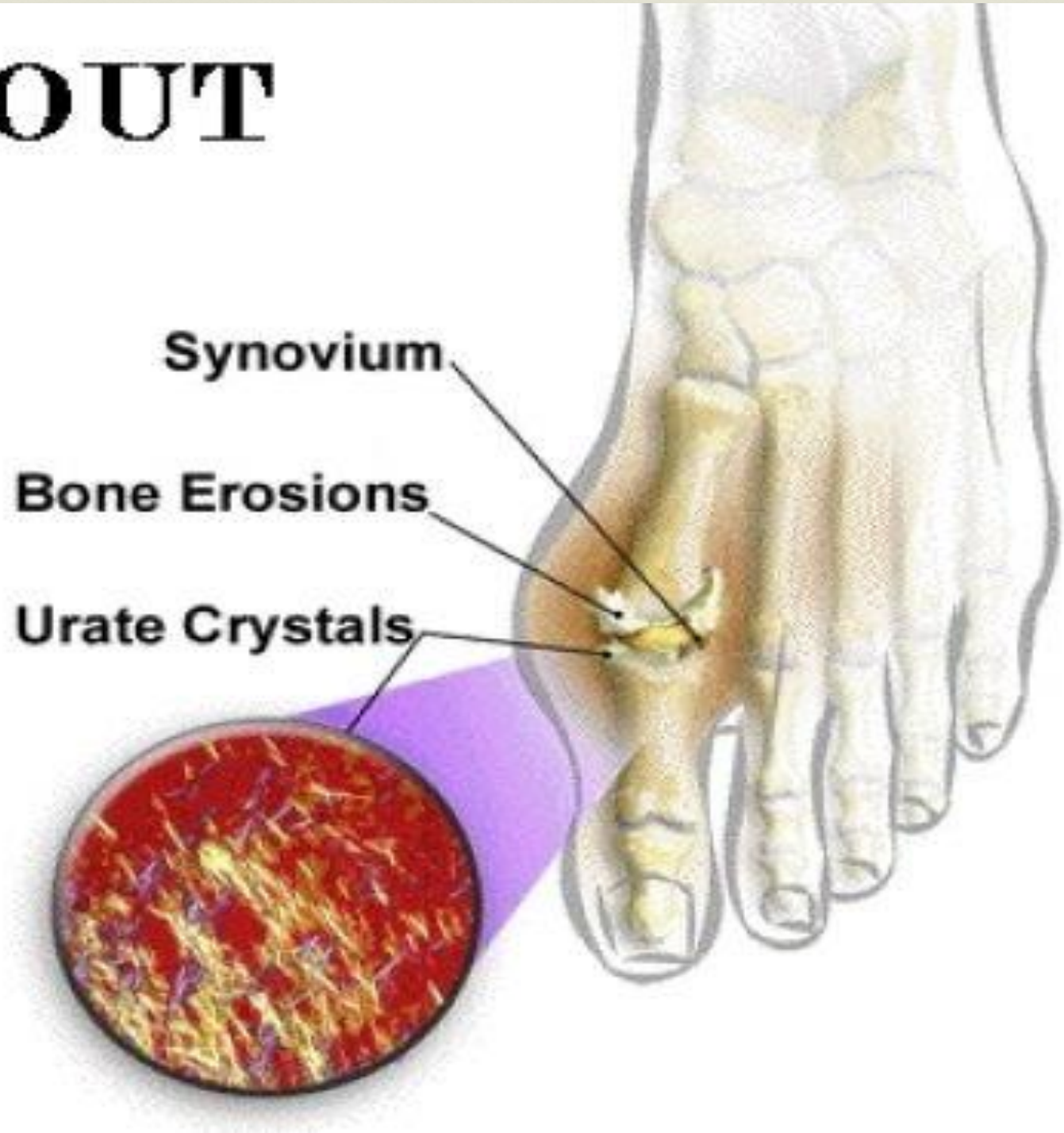
GOUT



- Gout is a disease that most commonly manifests as recurrent episodes of acute joint pain and inflammation secondary to the deposition of monosodium urate (MSU) crystals in the synovial fluid and lining

- It is the result of an increased body pool of urate with hyperuricemia.

- It is typically characterized by episodic acute and chronic arthritis

- **The term gout describes a disease spectrum including**
  - **Hyperuricemia,**
  - **Recurrent attacks of acute arthritis associated with monosodium urate crystals in leukocytes found in synovial fluid,**
  - **Deposits of monosodium urate crystals in tissues,**
  - **Interstitial renal disease, and**
  - **Uric acid nephrolithiasis.**

- A urate concentration > 7.0 mg/dL is abnormal and associated with an increased risk for gout.

- Hyperuricemia and gout are not always concurrently present.

- Sustained elevation of serum urate is virtually essential for the development of gout

- However, hyperuricemia does not always lead to gout, and most patients with hyperuricemia remain asymptomatic.

- ✓ **Uric acid is the final metabolite of endogenous and dietary purine metabolism.**

- ✓ **At a physiological pH of 7·4 in the extracellular compartment, 98% of uric acid is in the ionised form of urate.**

- ✓ **Because of the high concentration of sodium in the extracellular compartment, urate is largely present as monosodium urate, with a low solubility limit of about 380 µmol/L.**

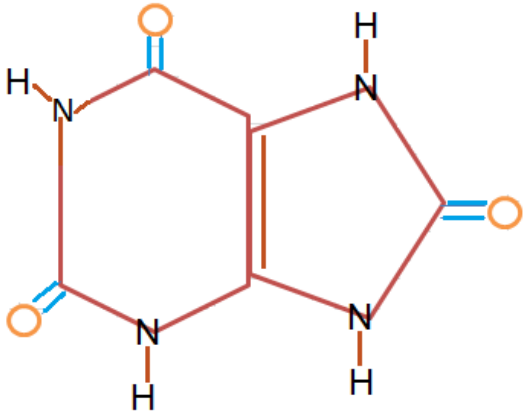
- ☙ **MSU Crystals forms in synovial fluid when its solubility limit exceeded**

- MSU solubility varies directly with temperature.

- The solubility of urate in physiologic saline is 6.8 mg per dL (400 µmol/L) at 37°C but only 4.5 mg per dL (270 µmol/L) at 30°C.

- Joint temperatures decrease distally. The average temperature of the knee is 33°C; that of the ankle is 29°C.

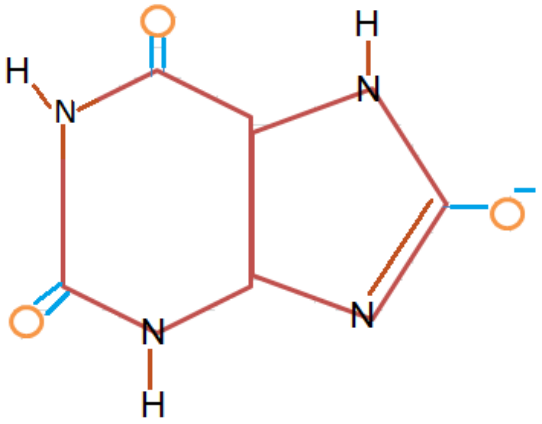
Crystal Formation



URIC ACID

Pka = 5.75

H^+



URATE ION

Types of gout

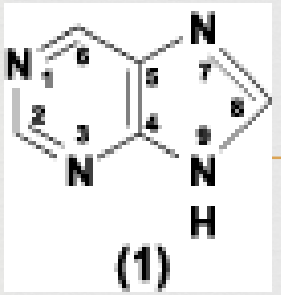
- Primary
- Secondary

RISK FACTORS OF GOUT

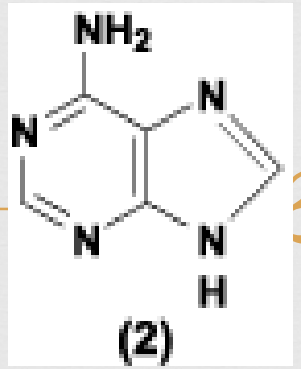
- Heredity
- Dehydration.
- Obesity
- Excessive alcohol consumption, and purines rich foods.
- Gender & Age
- Medications can also be causes of gout. Diuretics especially.
- Abnormal Kidney function

Etiopathogenesis

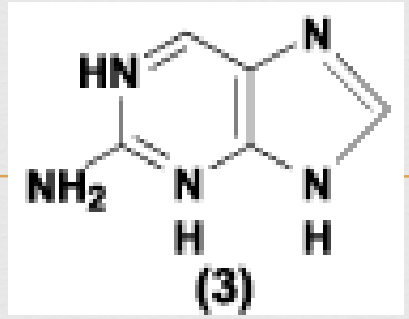
Purines



Purine



Adenine



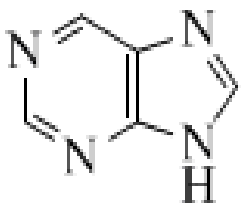
Guanine

- **Purine is a Hetrocyclic compound.**

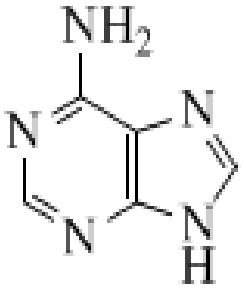
- **Sources**
  - **Dietary purine,**
  - **Conversion of tissue nucleic acid to purine nucleotides,**
  - **De novo synthesis of purine bases**

- **Adenine and Guanine are the two principal purines found in both DNA & RNA.**

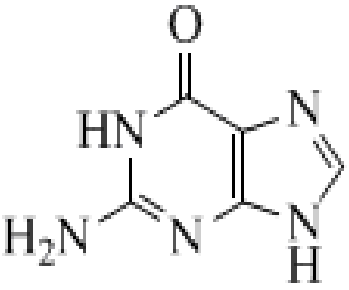
Purine Bases



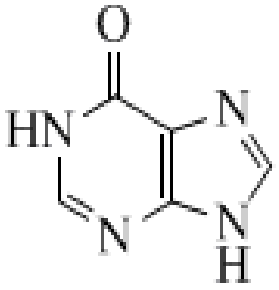
purine
1



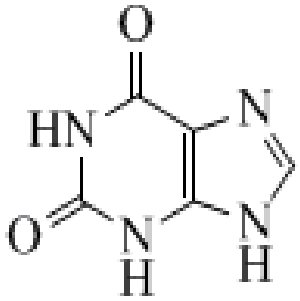
adenine
2



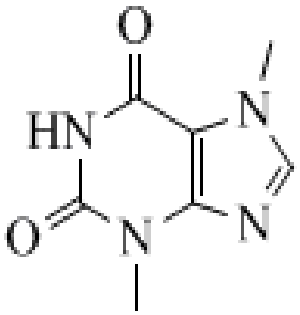
guanine
3



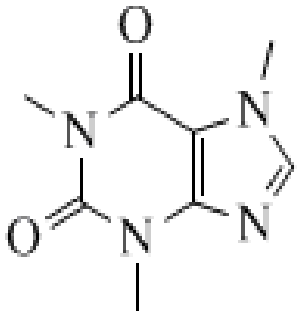
hypoxanthine
4



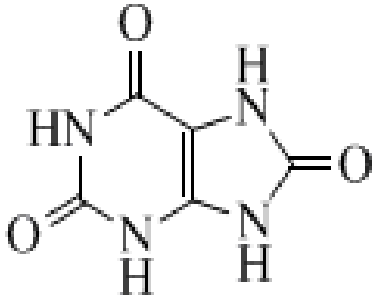
xanthine
5



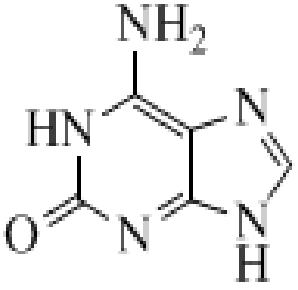
theobromine
6



caffeine
7



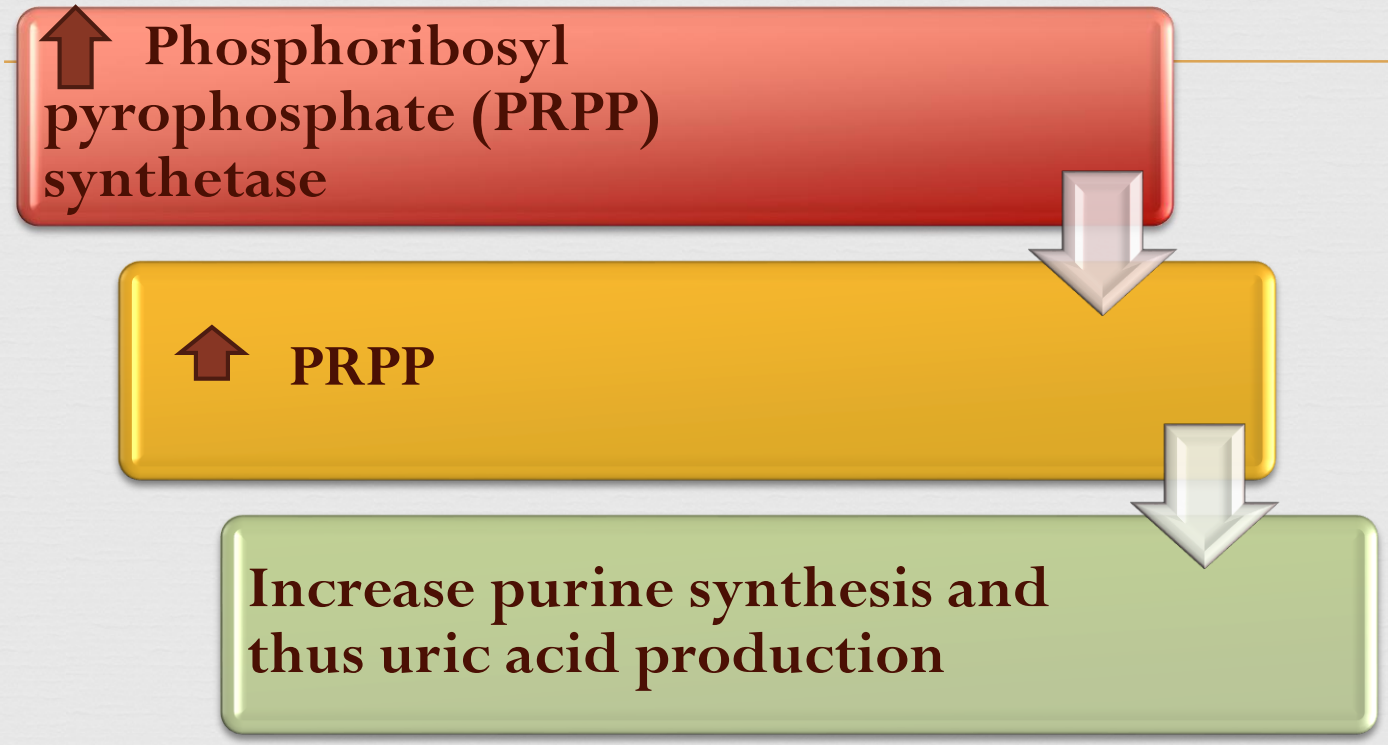
uric acid
8

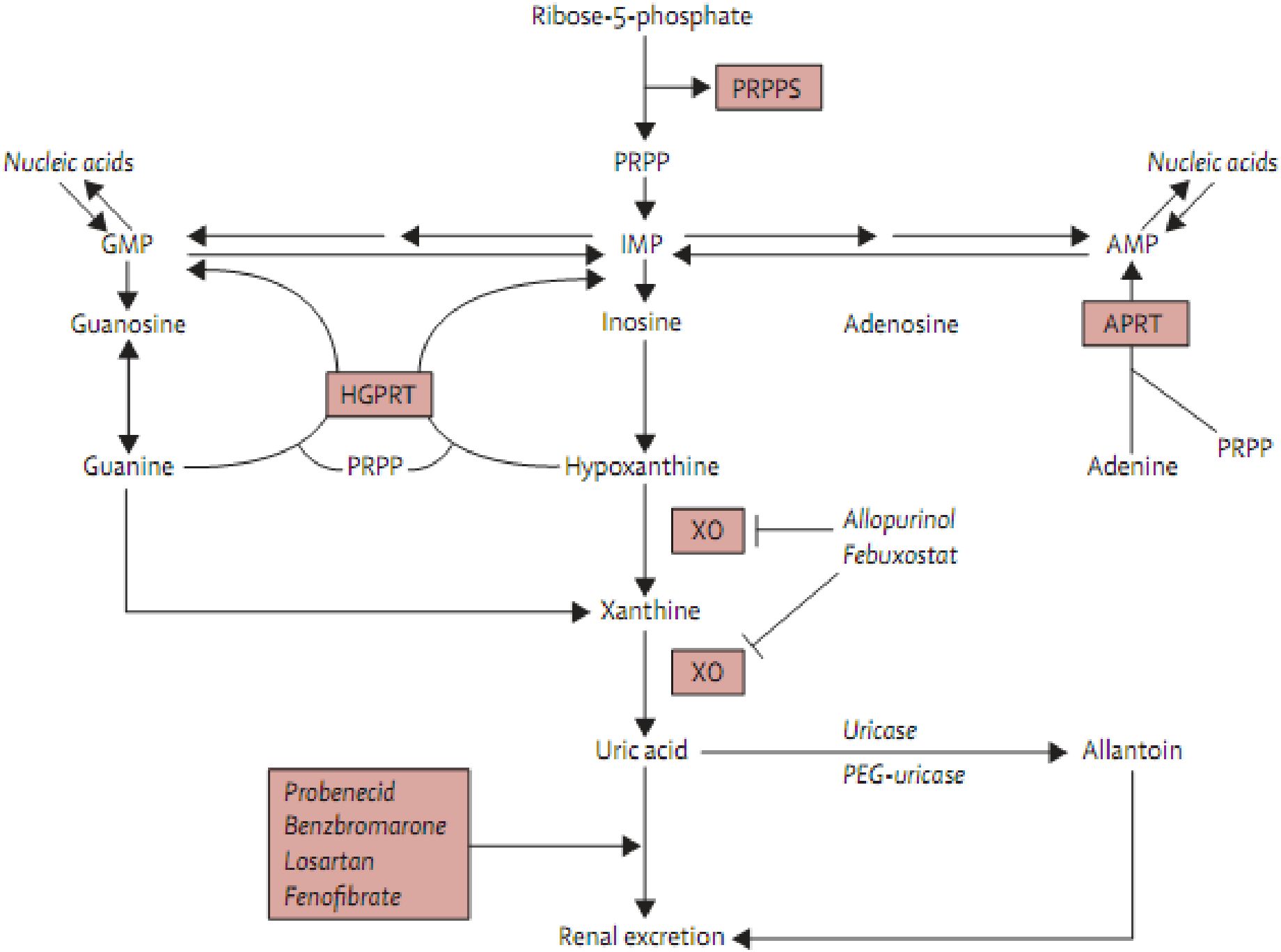


isoguanine
9

OVERPRODUCTION OF URIC ACID

1. PRPP




Ribose-5-phosphate
PRPPS
PRPP
Nucleic acids
Nucleic acids
GMP
IMP
AMP
Guanosine
Inosine
Adenosine
APRT
HGPRT
Guanine
PRPP
Hypoxanthine
Adenine
PRPP
XO
Allopurinol
Febuxostat
Xanthine
XO
Uric acid
Uricase
PEG-uricase
Allantoin
Probenecid
Benzbromarone
Losartan
Fenofibrate
Renal excretion

2. HGPRT

Deficiency of hypoxanthine–guanine phosphoribosyl transferase (HGPRT)

Overproduction 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.**

3. Myeloproliferative and lymphoproliferative disorders(breakdown of tissue nucleic acids).

&

Cytotoxic drugs (Lysis and breakdown of cellular matter).

UNDEREXCRETION OF URIC ACID

Uric acid is eliminated in two ways.

- **Two-thirds production/day excreted in the urine.**

- **The rest is eliminated through the GI tract after enzymatic degradation by colonic bacteria**

- **A decline in the urinary excretion of uric acid to a level below the rate of production leads to hyperuricemia**

- Approximately **90% of filtered uric acid** is **reabsorbed** in the proximal tubule mediated by specific anion transporters, including **URAT1(active)**and **passive** transport mechanisms.

- The protein **GLUT9 (SLC2A9)** was reported to function as an **efflux transporter of urate** from tubular cells

- **Enhance sodium reabsorption** (e.g., dehydration) also lead to increased **uric acid reabsorption**

Genetic predisposition

- Polymorphisms in the GLUT9 (SLC2A9) gene
- Polymorphism in the URAT1 gene
- Two new loci have been identified—ABCG2 and SLC17A3—which also show an association with uric acid concentrations and risk of gout.

Drugs that decrease renal clearance of uric acid

(modification of filtered load or one of the tubular transport processes)

- Diuretics,
- Nicotinic acid,
- Salicylates (less than 2 g/day),
- Ethanol,
- Pyrazinamide,
- Levodopa,
- Ethambutol,
- Cyclosporine, and cytotoxic drugs

Deposition of urate crystals in synovial fluid

Inflammatory mediators activation like

Increased vascular permeability,

vasodilation,

complement activation,

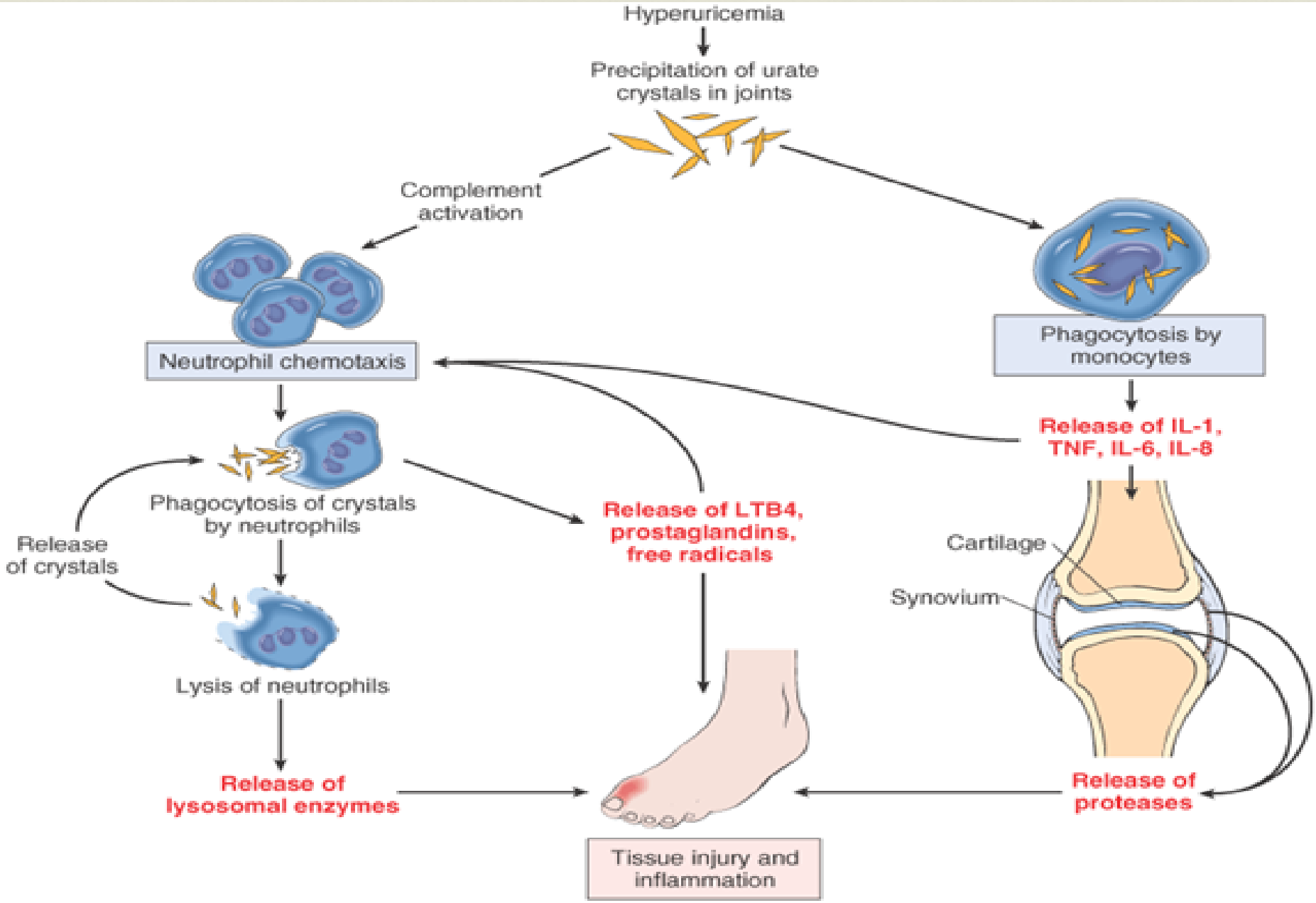
chemotactic activity for

polymorphonuclear leukocytes

Phagocytosis & discharge of proteolytic enzymes

Intense joint pain,

erythema, warmth, and swelling.



Pathogenesis of acute gouty arthritis

Clinical presentation

PHASES OF GOUT

- **Acute gouty arthritis** — Attacks of gout usually involve a single joint, most often the big toe or knee. This attack is known as acute gouty arthritis

- **Intercritical period** — The time between gout attacks is known as the intercritical period. A second attack typically occurs within two years, and additional attacks may occur thereafter.

- **Chronic tophaceous gout** — People who have **repeated attacks** of gout over **many years** can develop **tophaceous gout**.
- **Tophi** accumulation of large numbers of urate crystals in masses

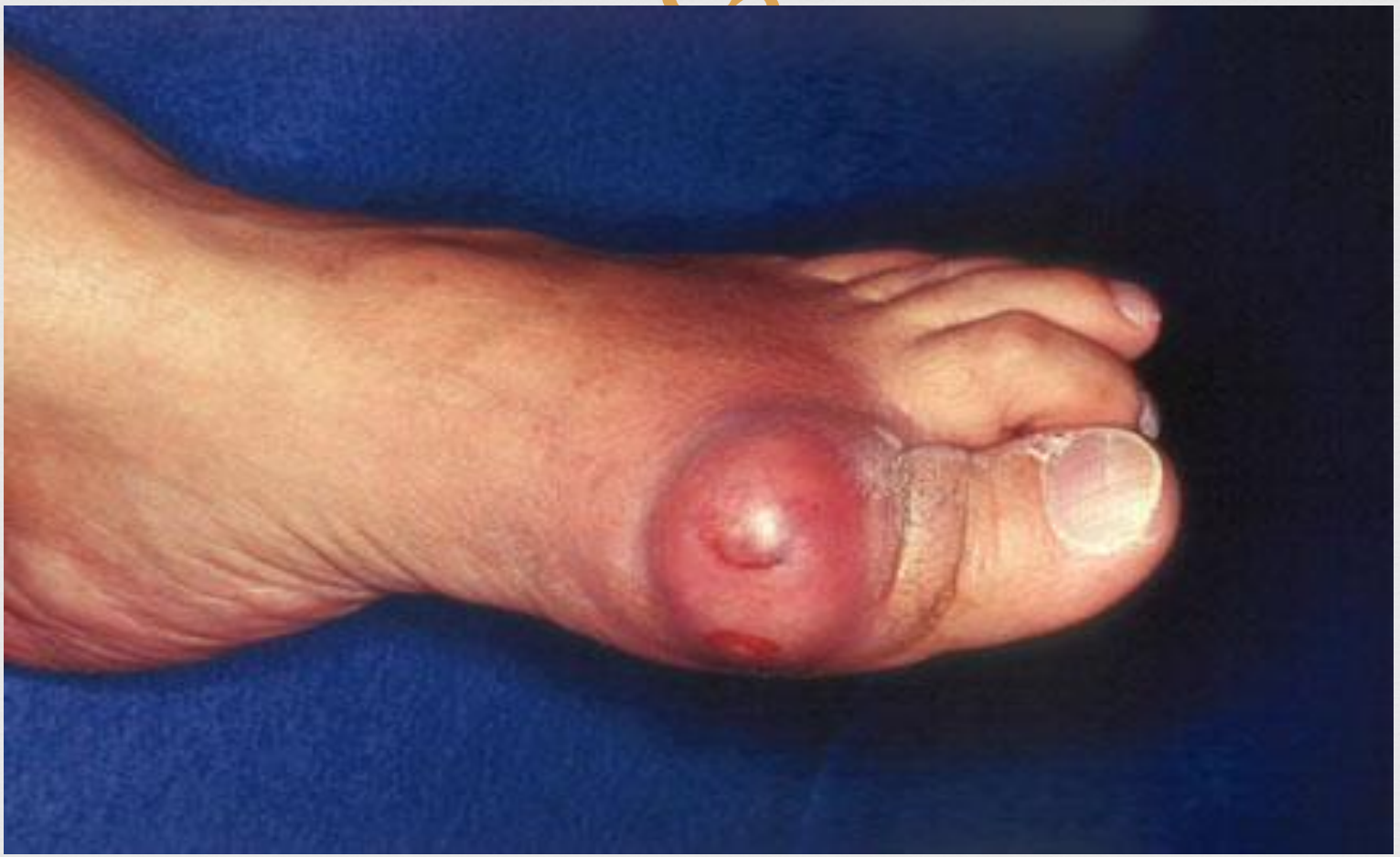
- Tophi may **cause erosion** of the bone and eventually joint damage and deformity.

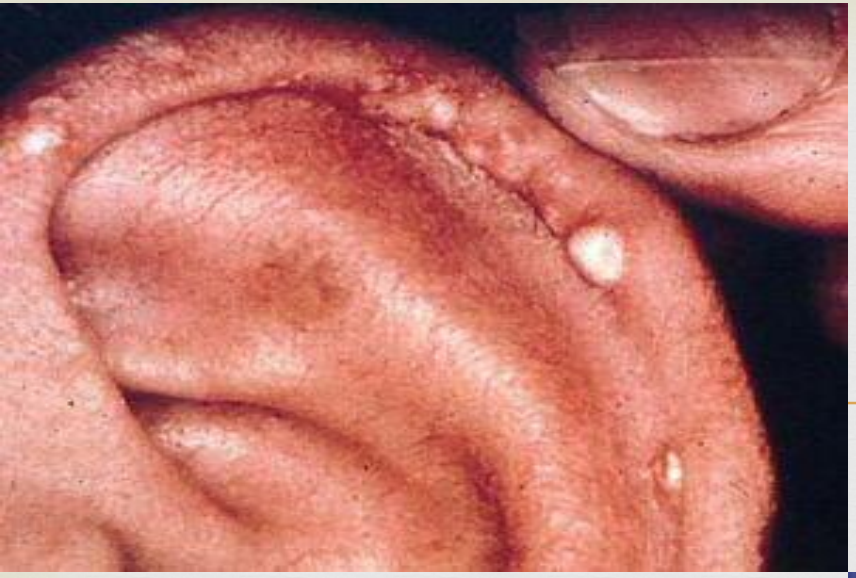

Uric Acid
Build up
Inflamed
Joint
Sharp Needle Like
Uric Acid Crystals

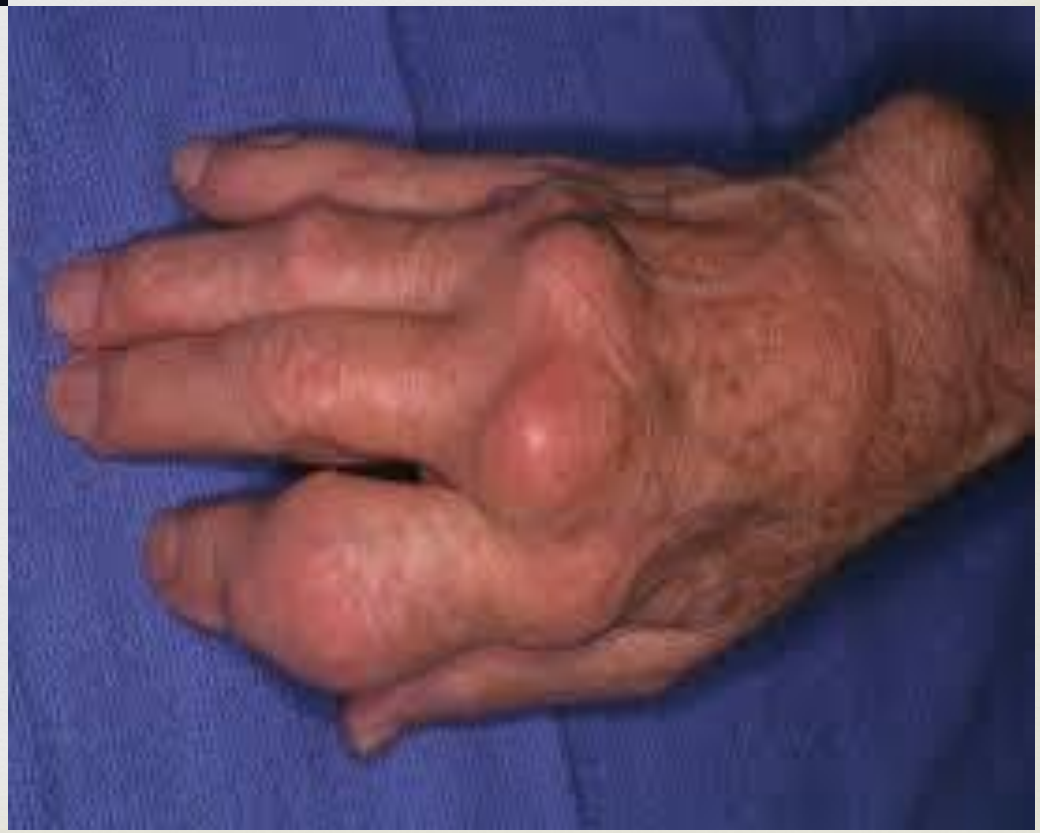
Clinical presentation

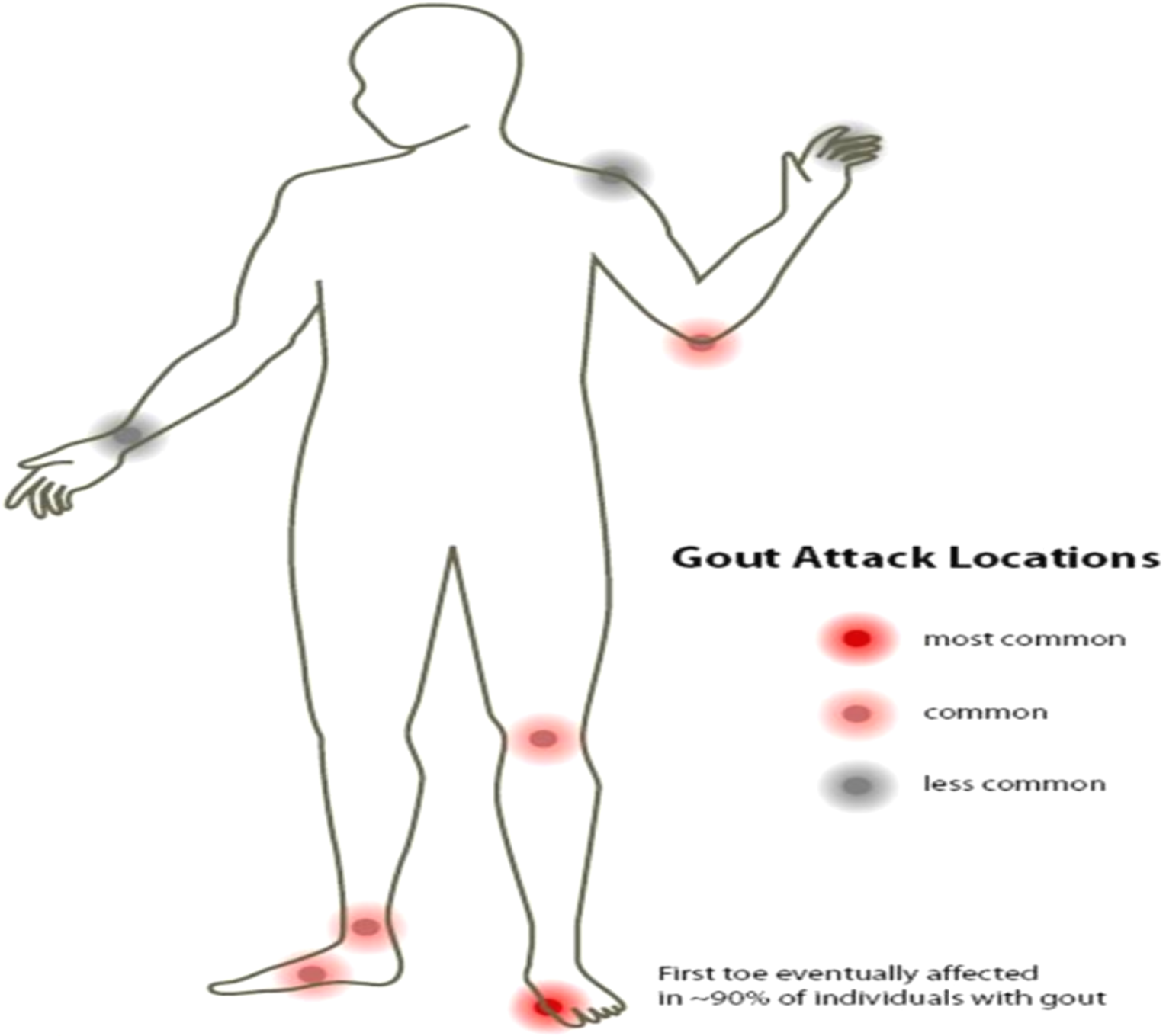
Classic acute gout ("podagra")	Monoarticular arthritis Frequently attacks the first metatarsophalangeal joint although other joints of the lower extremities are also frequently involved Affected joint is swollen, erythematous, and tender
Interval or intercritical gout	Asymptomatic period between attacks
Tophaceous gout	Deposits of monosodium urate crystals in soft tissues Complications include soft-tissue damage, deformity, joint destruction, and nerve compression syndromes such as carpal tunnel syndrome
Atypical gout	Polyarthritis affecting any joint, upper or lower extremity May be confused with rheumatoid arthritis or osteoarthritis
Renal effects	Nephrolithiasis Acute and chronic gouty nephropathy

The first metatarsophalangeal joint is affected, a condition known as podagra








Gout Attack Locations
most common
common
less common
First toe eventually affected
in ~90% of individuals with gout

Low Purine DIET GUIDE

Group I: Select from these Foods

Cheese	Fruits (except those in group III)
Eggs	Gelatine
Cereals/ cereal products	Milk
Bread	Coffee and tea
Butter/ margarine	Vegetables
Beverages	Syrups

Group II: Use in Moderation

Fish (expect those in group III)	Chicken (poultry products)
Legumes (beans)	Seafoods (crabs, shrimps, oysters)
Meat (meat soup and broth)	Vegetables (spinach, mushrooms, asparagus, cauliflowers)
Oatmeal	

Group III: Avoid these Foods

Gravies	Nuts-Peanuts, cashew nuts . . .
Mackerel/Sardines	Fruits (avocado)
Mussels	Sweet beans
Meat Extracts	Fish (Tuna)
Internal organs	
Yeast	

Thank you