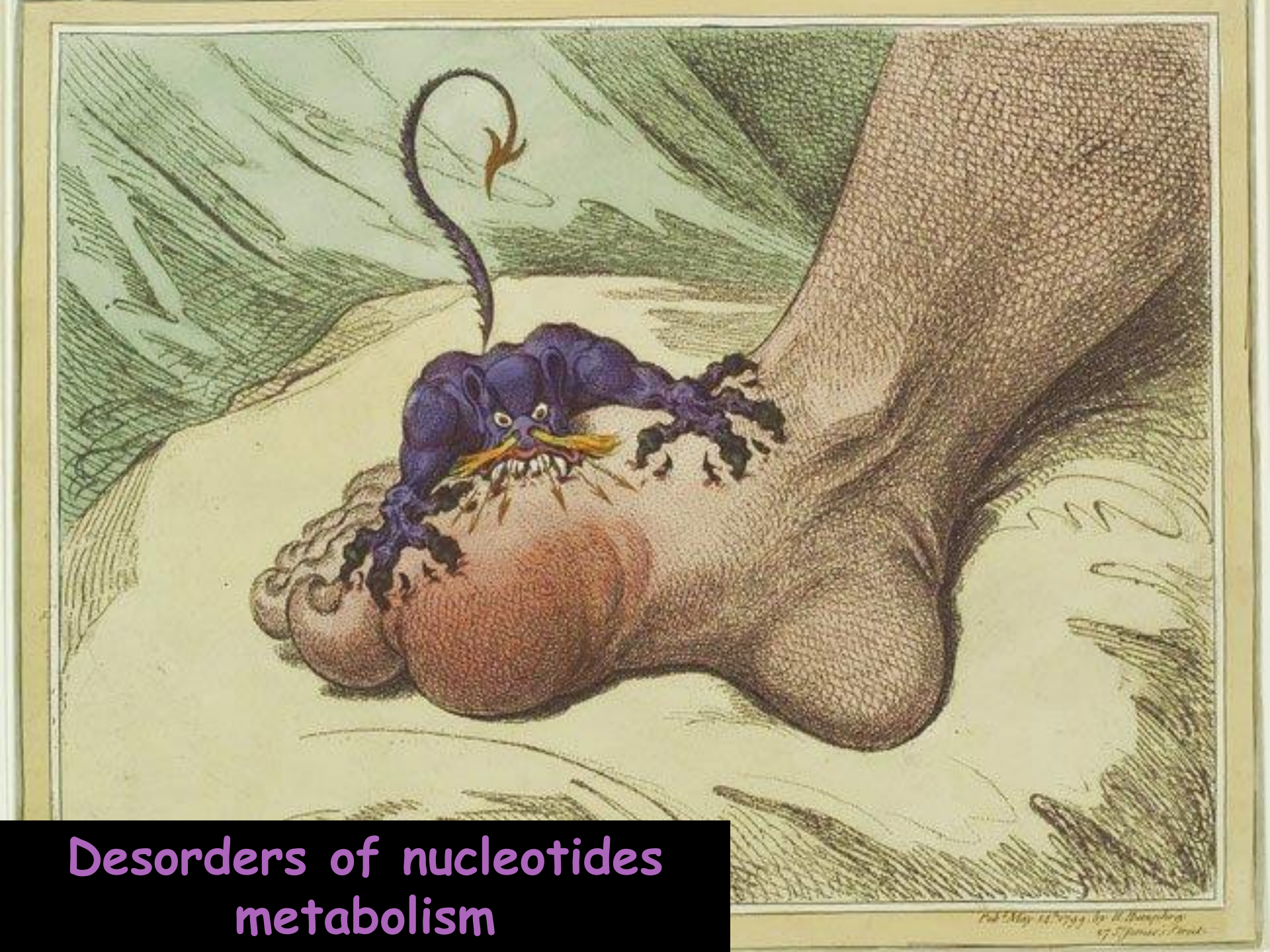


Desorders of nucleotides metabolism

Purine Metabolism

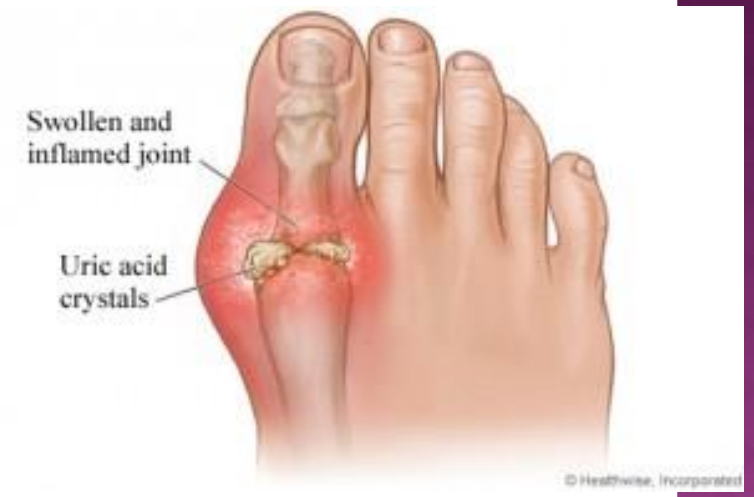
- **de novo pathway**
  - Phosphoribosylpyrophosphate (PRPP) synthetase superactivity,
- **Salvage pathway**
  - adenosine deaminase (ADA) deficiency
- **Catabolic pathway**
  - HGPRT deficiency

CASE

- 47 year old male
- Severe **pain** in right great toe – wore open toe sandals to clinic
- Began previous evening and kept him up through the night (**acute onset**)
- Taking **extra-strength acetaminophen** to keep the pain under control
- **Unable to bear weight** on his right foot
- No history of injury to right foot

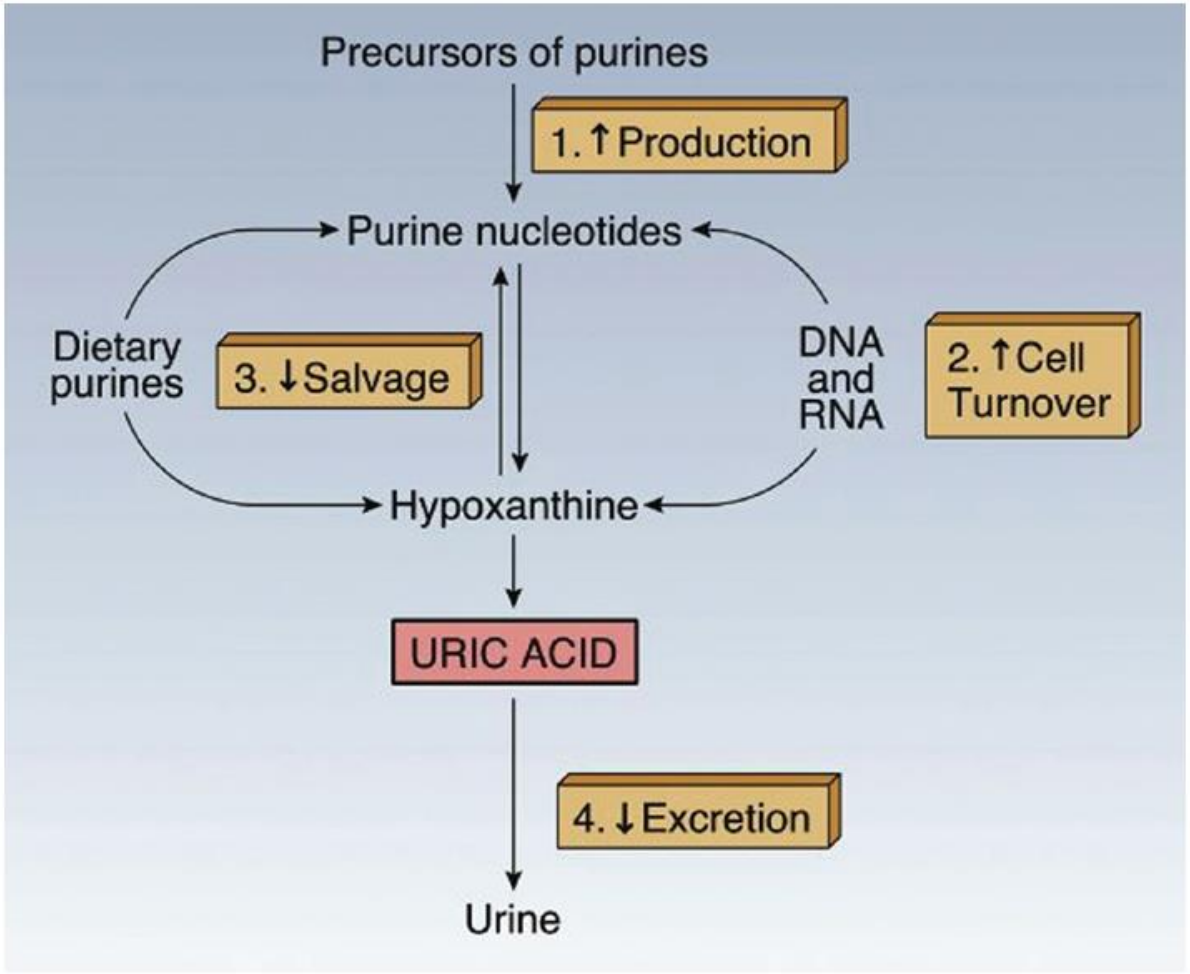
WHAT IS GOUT?

- Characterized by hyperuricemia (elevated plasmic uric acid concentrations) and severe, recurrent bouts of arthritis caused by monosodium urate (MSU) crystals deposited in the joint spaces.
- Syndrome of abnormal purine metabolism or excretion.



- Existed for over 2,000 years and used to be known as “disease of kings”
- Usually not life-threatening, but can be painful, chronic, and disabling.

PATHOPHYSIOLOGY



The greater the degree and duration of hyperuricemia, the greater is the likelihood of gout and the more severe are the symptoms.

Urate levels can be elevated because of:

- Decreased excretion.
- Increased production.
- Increased purine intake.

Pathophysiology

There are two types of gout :

- 1- **Primary gout .**
- 2- **Secondary gout , due to other diseases eg cancer ,** renal dysfunction , Metabolic syndrome (the combination of hypertension, diabetes, dyslipidemia, truncal obesity, increased cardiovascular disease risk).

PRIMARY GOUT

- It is caused by an excessive formation of uric acid due to inborn defect in enzymes.
- Molecular basis :

1- Mutations in PRPP synthetase (hyperactive)

2- Partial deficiency of HGPRT enzyme .

3- Glycogen storage disease type I .

- PRPP synthetase Hyperactivity: increased production of PRPP causes increased synthesis of purines.
- HGPRT deficiency: Decreased salvage leads to increased breakdown of purines. Also, there is reduced feedback inhibition of de novo pathway causing increased production.
- G6PD deficiency: Increased G6P is diverted to purine synthesis

SECONDARY GOUT

- Diet: Increased purine intake
- Rapid cell turnover: Leukemias, Chemotherapy, Hemolysis, Rhabdomyolysis
- Reduced excretion of uric acid:
  - Renal failure, Htn, DM, Lactic acidosis
- Alcohol:
  - Increased breakdown of ATP causes increased uric acid production
  - Also causes increased lactic acid, reducing excretion of uric acid

CLINICAL FEATURES

Gout usually presents as recurrent attacks of **acute inflammatory arthritis** (red tender, hot, swollen joint).

The joint that is most commonly affected is the **first metatarsalphalangeal joint** at the base of the big toe.

Prolonged or acute elevation of blood urate leads to precipitation, as crystals of **sodium urate, in the synovial fluid of joints**. These precipitates cause inflammation.

People with long-standing hyperuricemia can have **tophi** (uric acid crystal deposits) in tissues. These are usually hard, non-painful deposits .

Elevated levels of urine uric acid can lead to uric-acid crystals precipitating in the kidneys which may form **kidney stones** and lead to urate nephrophathy.

URATE AND URIC ACID

- pKa of Uric acid: 5.7
- Serum pH: 7.2-7.4
- Urine pH: 5.8 and above
- Solubility of uric acid is very less, saturation at 7 mg/dl
- Normal Serum uric acid: 3-6 mg/dl

- As conc. of Uric Acid crosses 7, it precipitates
- In urine, ph decreases, Urate is formed.
- It combines with Sodium and forms MSU crystals
- These precipitate and form stones
- Diagnosis:
  - Serum urate levels
  - Synovial fluid analysis: Needle shaped negatively birefringent urate crystals

Treatment

Treatment with allopurinol, which inhibits xanthine oxidase .

Probenecid: Causes increased excretion of uric acid

Avoid purine rich foods:

red meat and organ meat (liver, kidneys)

high fluid intake

Alkalinization of urine

Anti-inflammatory drugs

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- A patient with acute lymphocytic leukemia is treated appropriately with anticancer drugs. Inhibition of which enzyme will help prevent side effects of this therapy?

- A 57 year old sales representative has a history of alcohol abuse and hyperuricemia. He attends an out of town conference and binges on meat rich foods. Next day, he develops a painful swelling in his big toe. Which things could have contributed to this episode.

- A 4 year old retarded child hurls himself into walls and bites his fingertips so severelt that they must be bandaged. The child most likely has a deficiency of:
- Cystathionine synthase
- Hexosaminidase A
- HGPRTase
- Phenylalanine hydroxylase

LESCH-NYHAN SYNDROME

- Due to severe or complete deficieny of Hypoxanthine

Guanine Phosphoribosyltransferase (HGPRT) .

- Recessive X-linked genetic disease .
- This disorder is an example for loss of normal feedback

inhibition .

- This disorder is characterized by :
- Choreoathetosis (movement disorder) .
- Severe neurologic disease, characterized by self-mutilating

behaviors such as lip and finger biting and/or head banging.

- A severe gouty arthritis .
- Early death may be due to kidney failure.

- A 6 years old girl presented with repeated episodes of respiratory infections since the age of 2 years. Frequency of such attacks were variable. However, minimum two such episodes were noticed per month. There was no specific time of occurrence or any weather predilection. There was no history of loose motions, skin lesions, anorexia, weight loss, contact with patient suffering from Tuberculosis or family history of asthma or allergy. Response to antibiotics and bronchodilators was temporary at best.

ADENOSINE DEAMINASE DEFICIENCY

- Severe combined immune deficiency

(SCID)

- Autosomal recessive disease .
- Both B and T lymphocytes are affected .
- Patients are susceptible, often fatally, to infectious diseases because of an inability to

mount an immune response to antigenic

chanllenge.

- Infants with this deficiency have a high fatality

rate due to infections .

TREATMENT OPTIONS:

- GERM FREE ENVIRONMENT
- BONE MARROW TRANSPLANT
- ROUTINE INJECTIONS OF ADENOSINE DEAMINASE ENZYME (ADA)
- GENE THERAPY USING SUBJECTS OWN CELLS (RETROVIRUS CONTAINING ADA TO "INFECT" SUBJECTS BONE MARROW STEM CELLS)

OROTIC ACIDURIA

- Excessive excretion of orotic acid in urine
- Autosomal recessive disorder
- Orotate phosphoribosyl transferase
- Orotidylate decarboxylase
- Presentation:
  - Growth failure
  - Developmental retardation
  - Megaloblastic anemia
  - Increased orotic acid in urine
- Treatment
  - Uridine supplementation