NUCLEIC ACID METABOLISM AND RELATED DISEASES II

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Advance Clinical Biochemistry II (MA 406)

Summer Semester

Week two

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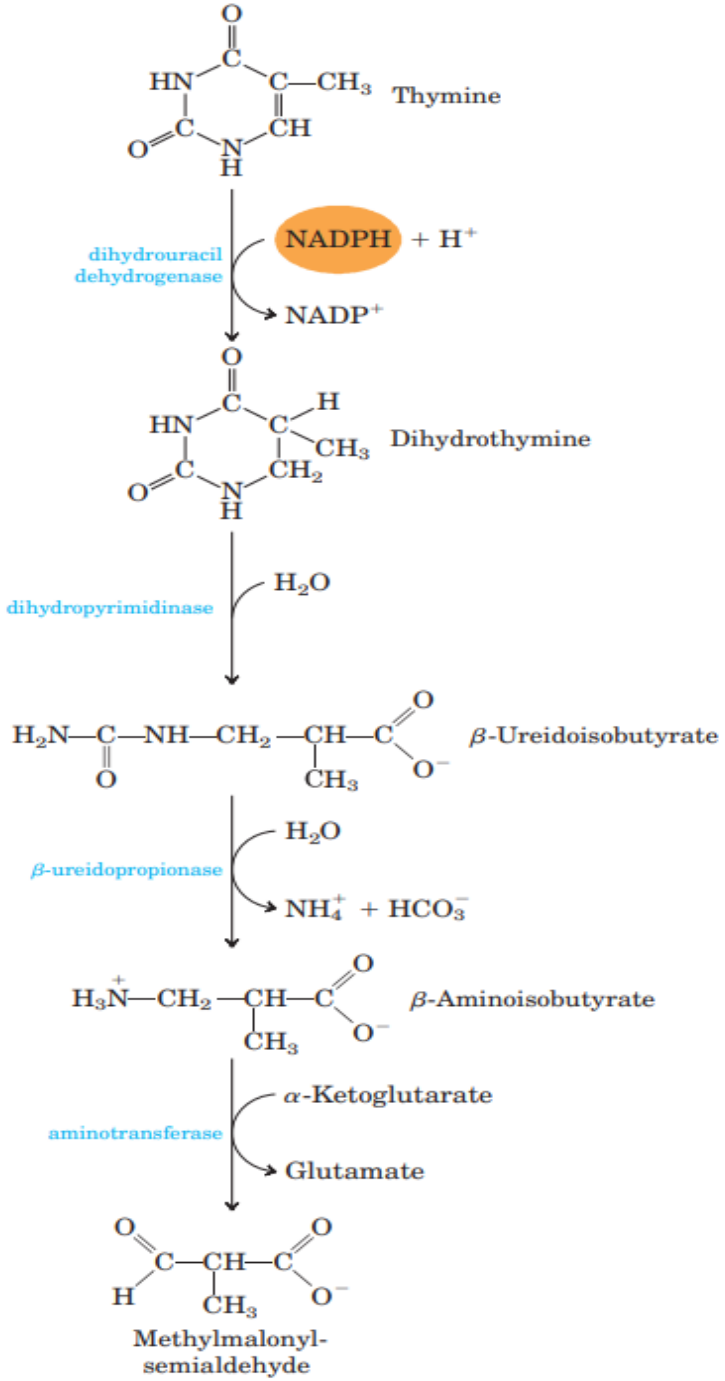
Outlines

- Objectives
- Pyrimidine catabolism
- Defect in purine metabolic enzyme
- Salvage pathway and Lesch Nyhan syndrome.
- Uric acid and gout diseases
- Summary
- Activities

Objectives

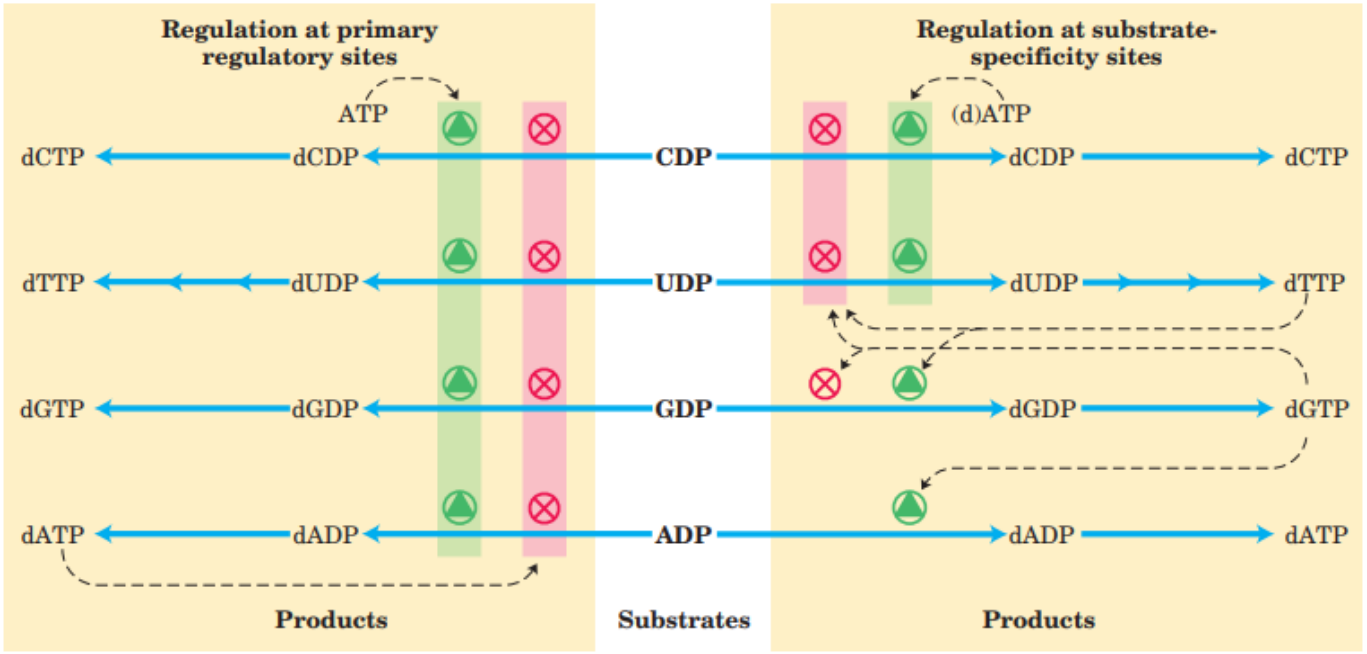
- **At the end of this lesson, the students should be able to:**

- Understand the catabolic process of pyrimidines.
- Understand the impact of genetic defect on certain enzymes.
- Be acquainted with the knowledge of salvage pathway.
- Understand the biochemical basis of gout disease development and possible treatment approaches.



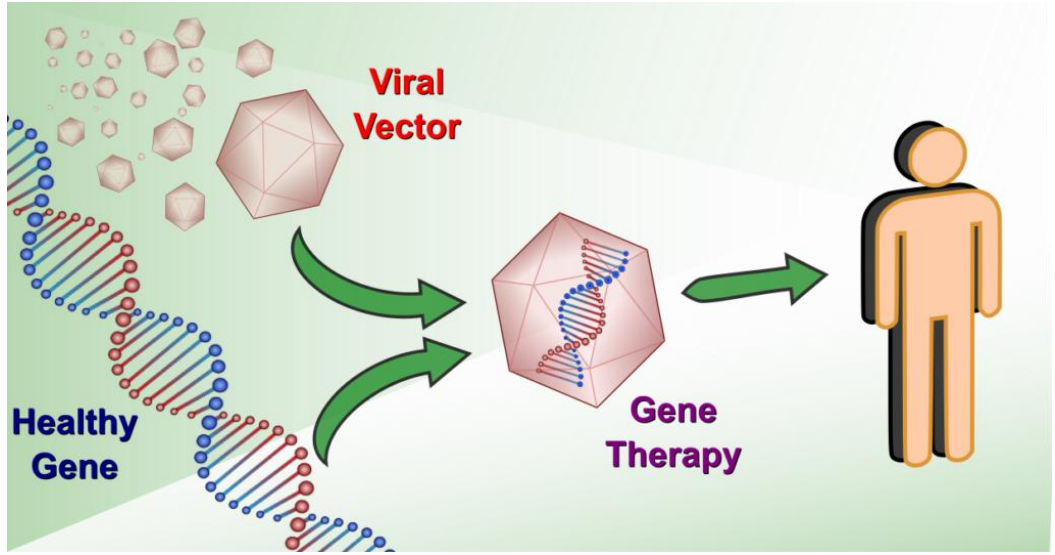
Catabolism of pyrimidines

- The pathways for degradation of pyrimidines generally lead to NH_4 production.
- Since NH_4 cannot be removed from the human body, urea is produced.
- Thymine, for example, is degraded to methyl malonyl semialdehyde (Figure) an intermediate of valine catabolism.
- It is further degraded through propionyl-CoA and methyl malonyl-CoA to succinyl-CoA



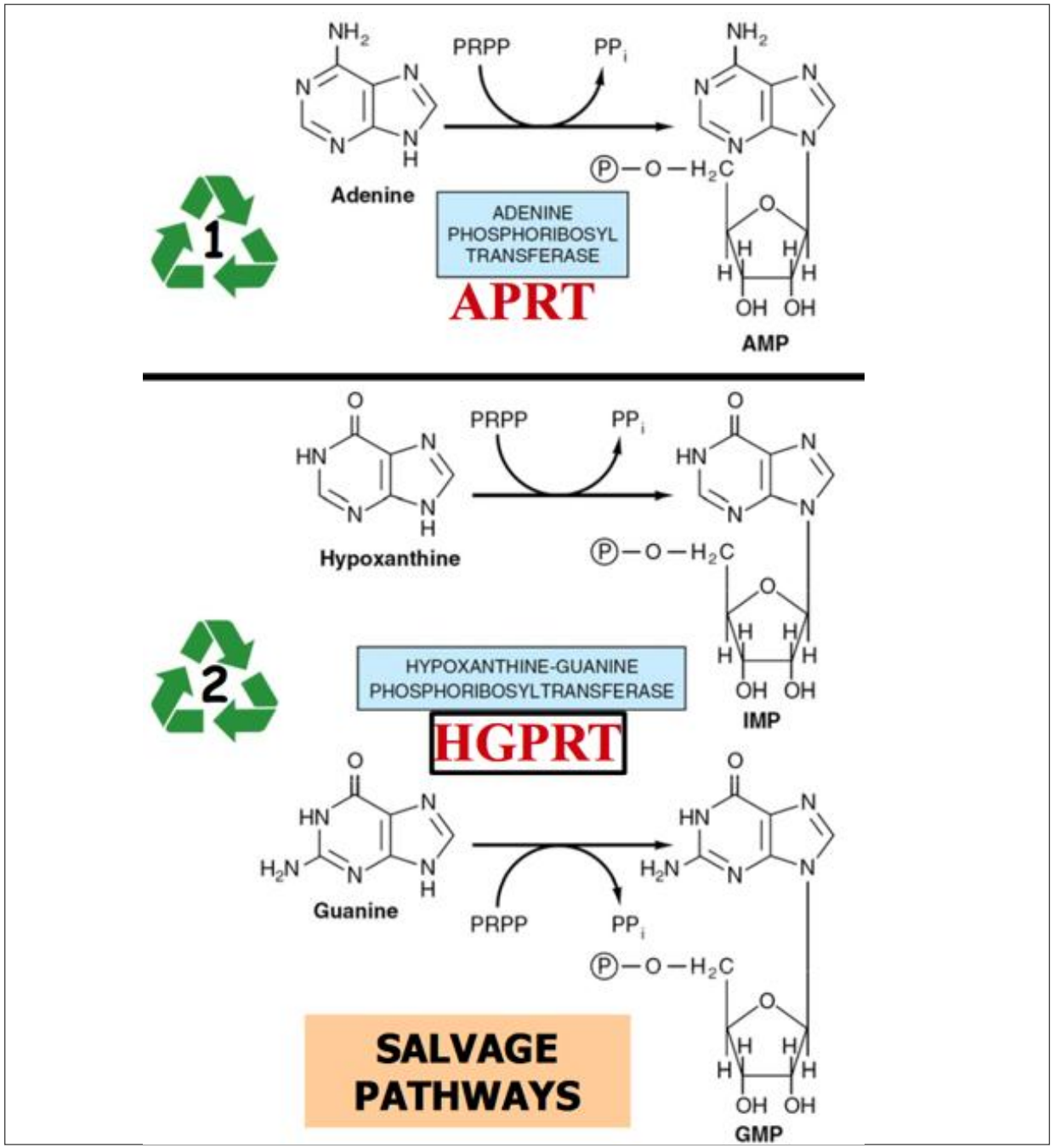
Defect in purine metabolism enzyme

- Genetic defects in human purine metab. have been found with consequences.
- E.g. Adenosine deaminase (ADA) deficiency leads to severe immunodeficiency disease in which T-lymphocytes and B lymphocytes do not develop properly.
- Lack of ADA leads to a 100-times increase in the cellular conc. of dATP, an inhibitor of ribonucleotide reductase.



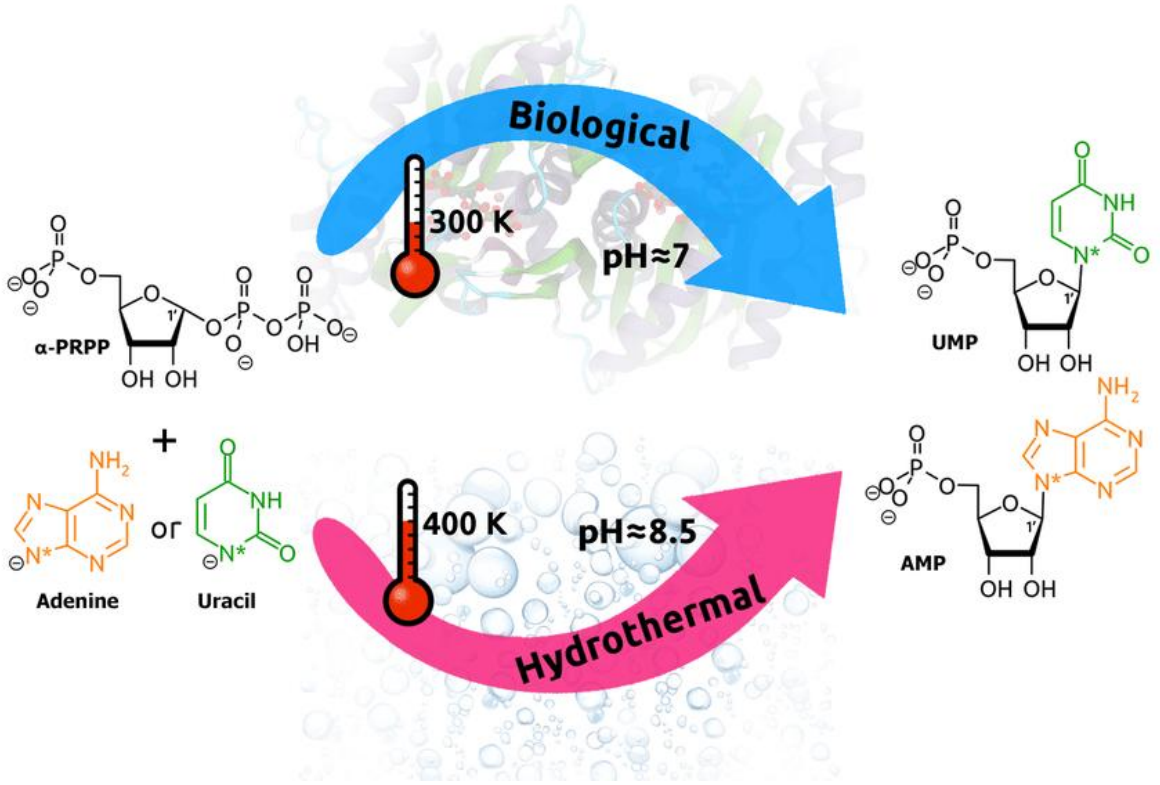
Cont.

- High levels of dATP produce a general deficiency of other dNTPs in T-lymphocytes.
- Individuals with ADA deficiency lack an effective immune system and **do not survive** unless isolated in a sterile environment.
- ADA deficiency is one of the first targets of human gene therapy trials.



Salvage (Recycle) Pathways for Purine and Pyrimidine Bases

- Free purine and pyrimidine bases are constantly released in cells during the metabolic degradation of nucleotides.
- Free purines are in large part salvaged and reused to make nucleotides, in a pathway much simpler than the de novo synthesis of purine nucleotides described earlier.



Salvage (Recycle) Pathways for Purine and Pyrimidine Bases

- One of the primary salvage pathways consists of a single reaction catalyzed by adenosine phosphoribosyl-transferase.
- Here, free adenine reacts with phosphoribosyl pyrophosphate (PRPP) to yield the corresponding adenine nucleotide:
- Adenine + PRPP → AMP PPi

48) Lesch Nyhan Syndrome

❖ Clinical features

- ✓ Self-injury (Most distinctive behavioral problem)
  - ▪ Fingers & mouth biting
  - ▪ Head banging
- ✓ Dystonia
- ✓ Chorea
- ✓ Hypotonia
- ✓ Ballismus
- ✓ Developmental delay

Pediatric On Squares

❖ Laboratory finding ?

- ✓ Hyperuricemia

❖ Complications :

- ✓ Gouty arthritis
- ✓ Kidney & bladder stones
- ✓ Renal failure

❖ Most common cause of death?

- ✓ Renal failure

❖ Mode of inheritance?

- ✓ X-linked recessive
- ✓ HPRT1 gene
- ✓ Defect in purine metabolism

❖ Treatment :

@OnSquares

- ✓ Allopurinol
- ✓ High fluid intake
- ✓ Behavioral therapy

Cont.

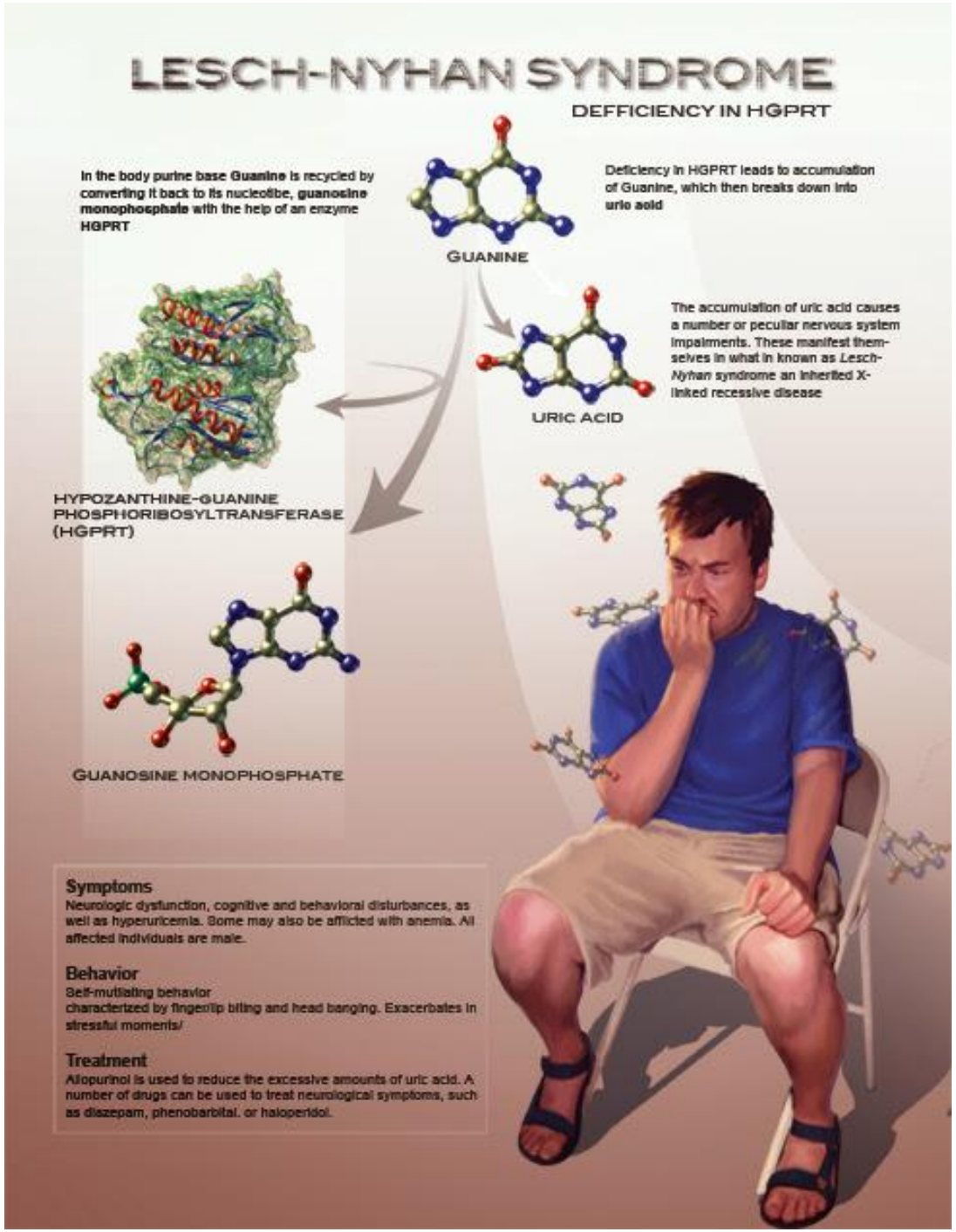
- Free guanine and hypoxanthine are salvaged in the same way by **hypoxanthine-guanine phosphoribosyl-transferase**.
- A genetic lack of that enzyme activity is seen almost exclusively in male children, resulting in a strange set of symptoms called **Lesch-Nyhan syndrome.**

Cont.

- **Lesch-Nyhan syndrome** usually manifests in children of 2 years.
- The victims sometimes become poorly coordinated and mentally retarded.
- In addition, they are extremely hostile and show compulsive self-destructive tendencies.
- They mutilate themselves by biting off their fingers, toes, and lips.

Cont.

- The devastating effects of **Lesch-Nyhan syndrome** illustrate the importance of the salvage pathways.
- Hypoxanthine and guanine arise constantly from the breakdown of nucleic acids in the absence of **the enzyme.**
- PRPP levels rise, and purines are overproduced by the de novo pathway.

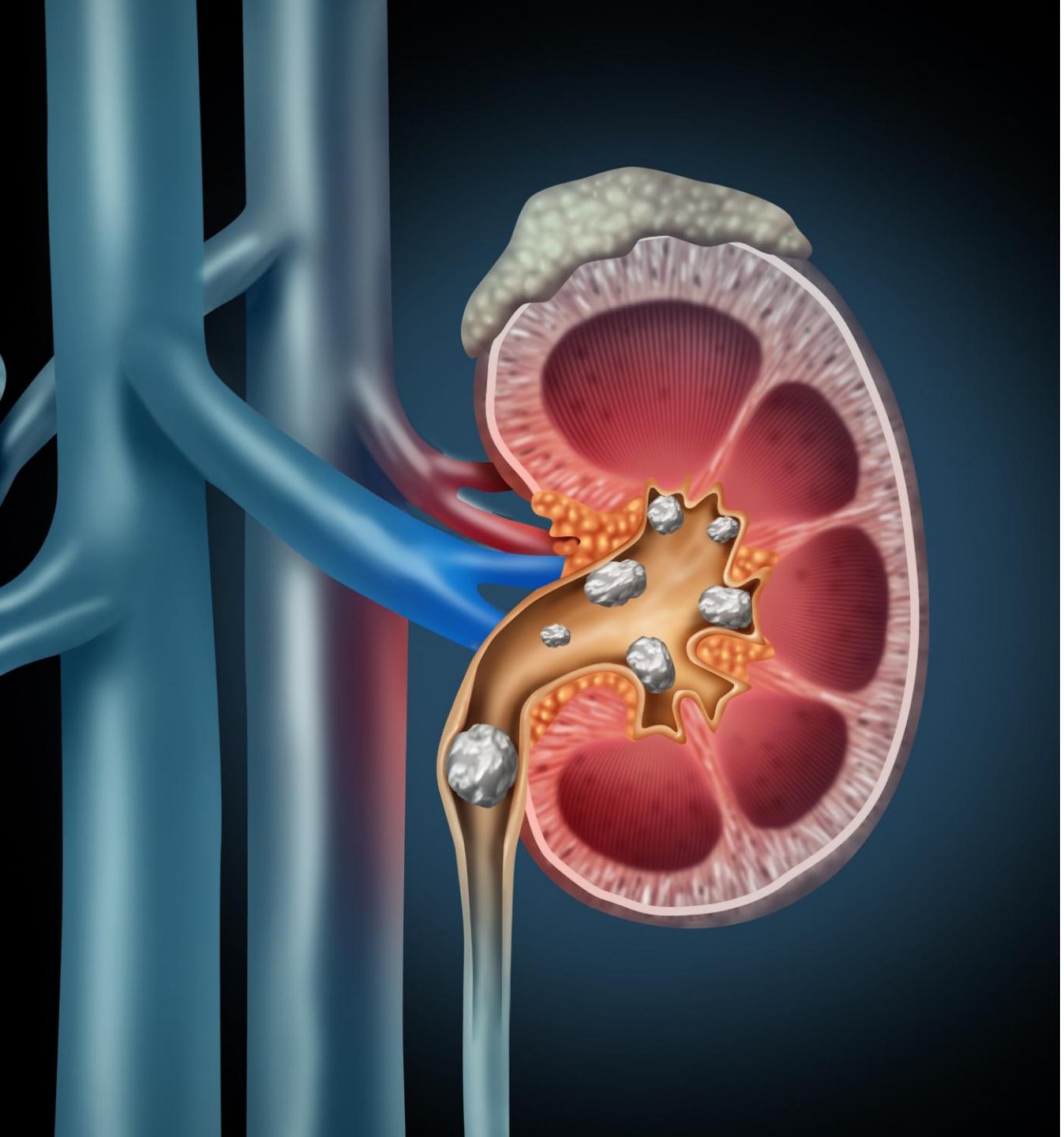


Cont.

- Resulting in high levels of uric acid production and gout-like damage to tissue.
- The brain is especially dependent on the salvage pathways, and this may account for the central nervous system damage in children with Lesch-Nyhan syndrome.
- This syndrome is another target of early trials in gene therapy.

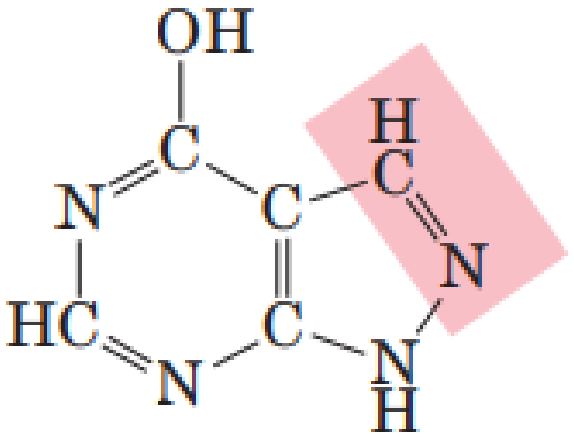
Excess Uric Acid Causes Gout

- Long thought, erroneously, to be due to “high living.”
- Gout is a disease of the joints caused by an elevated concentration of uric acid in the blood and tissues.
- The joints become inflamed, painful, and arthritic, owing to the abnormal deposition of sodium urate crystals.

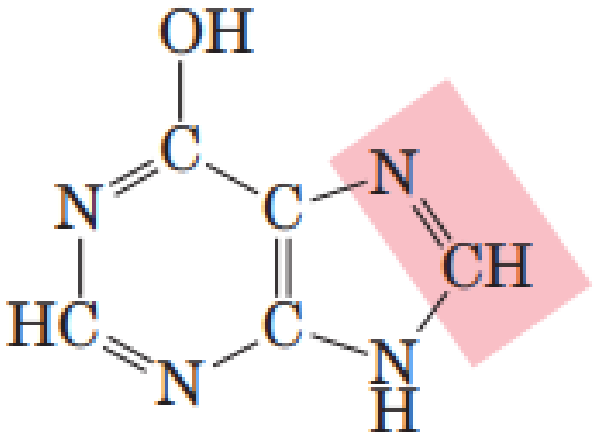


Excess uric acid causes gout

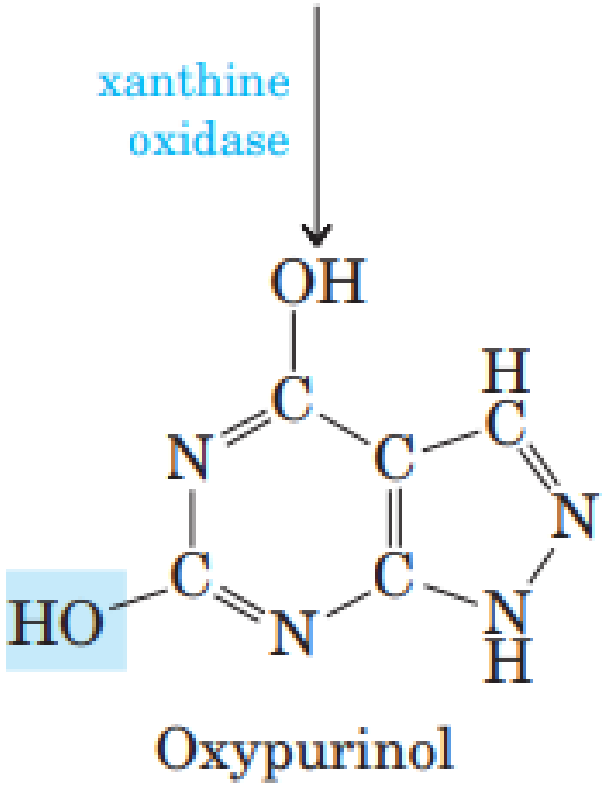
- The kidneys are also affected, as excess uric acid is deposited in the kidney tubules.
- Gout occurs predominantly in males. Its precise cause is not known, but it often involves an underexcretion of urate.
- A genetic deficiency of one or another enzyme of purine metabolism may also be a factor in some cases.



Allopurinol



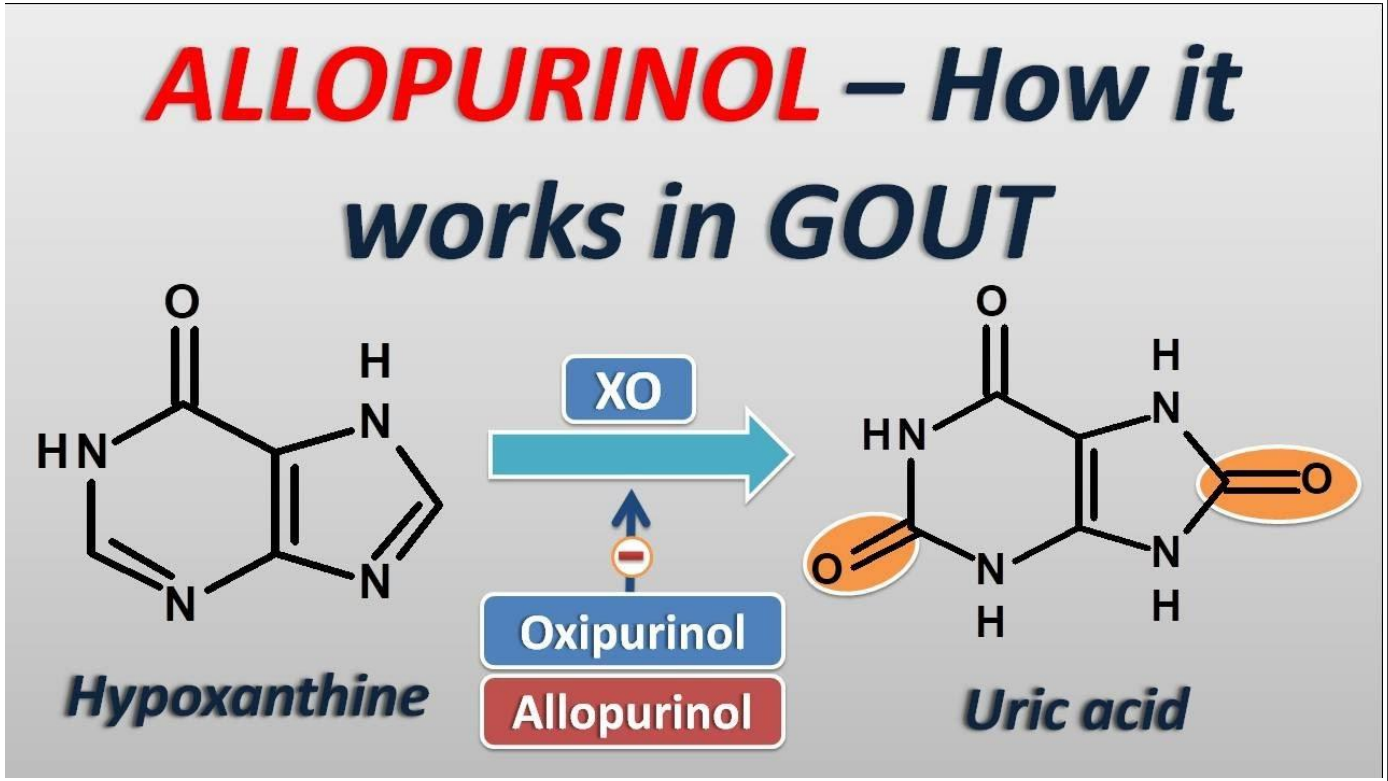
Hypoxanthine
(enol form)



Oxypurinol

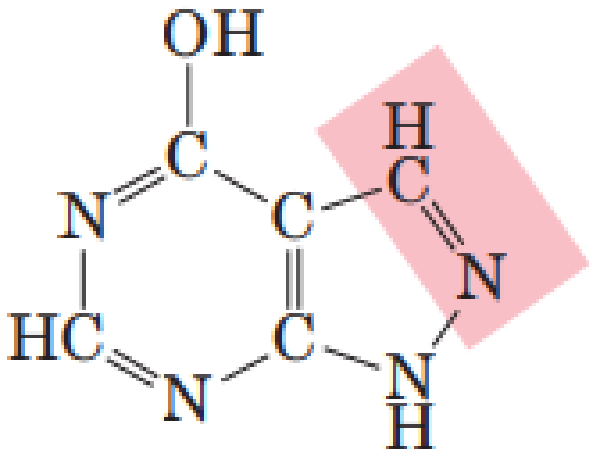
Cont.

- Gout is effectively treated by a combination of nutritional and drug therapies.
- Foods especially rich in nucleotides and nucleic acids, such as liver or glandular products, are suspended from the diet.
- Major alleviation of the symptoms is provided by the drug allopurinol.
- Allopurinol inhibits xanthine oxidase, the enzyme that catalyzes the conversion of purines to uric acid.

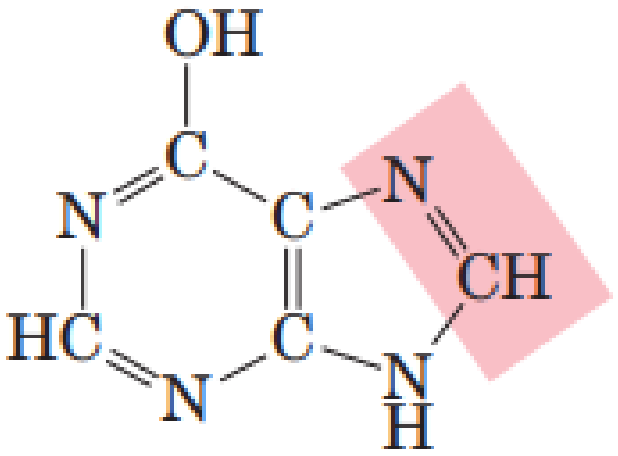


Cont.

- Allopurinol is a substrate of xanthine oxidase, which converts allopurinol to oxypurinol (alloxanthine).
- Oxypurinol inactivates the reduced form of the enzyme by remaining tightly bound in its active site.
- When xanthine oxidase is inhibited, the excreted products of purine metabolism are xanthine and hypoxanthine.
- They are more water-soluble than uric acid and less likely to form crystalline deposits.

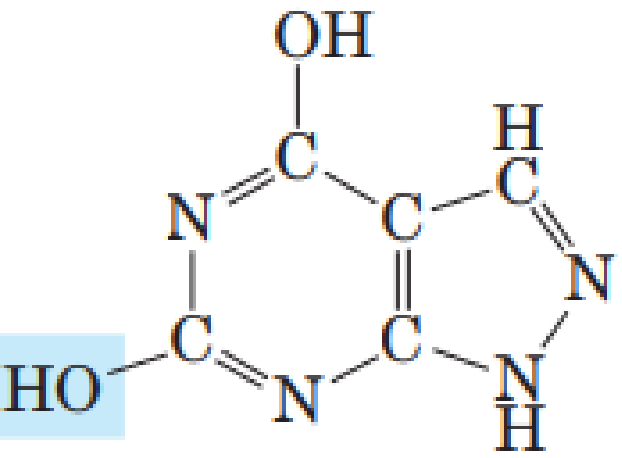


Allopurinol



Hypoxanthine
(enol form)

xanthine
oxidase



Oxypurinol

Treatment

- Allopurinol is an inhibitor of xanthine oxidase.
- Hypoxanthine is the normal substrate of xanthine oxidase.
- Only a slight change in the structure of hypoxanthine yields the medically effective enzyme inhibitor allopurinol.
- At the active site, allopurinol is converted to oxypurinol, a strong competitive inhibitor that remains tightly bound to the reduced form of the enzyme.

Summary

- Uric acid and urea are the end products of purine and pyrimidine degradation.
- Free purines can be salvaged and rebuilt into nucleotides.
- Genetic deficiencies in certain salvage enzymes cause serious disorders such as Lesch-Nyhan syndrome and ADA deficiency.
- Accumulation of uric acid crystals in the joints, possibly caused by another genetic deficiency, results in gout.
- Enzymes of the nucleotide biosynthetic pathways are targets for an array of chemotherapeutic agents used to treat cancer and other diseases.

Class activities

- The end product of Thyamine degradation is called _____
- Severe immunodeficiency disease could be caused by _____
- _____ leads to the underdevelopment of T- and B-lymphocytes.
- Differentiate between De novo and Salvage pathways.
- Discuss in detail the biochemical basis of the **Lesch Nyhan Syndrome** development.
- Describe the biochemical basis of gout disease development and its possible treatment.

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