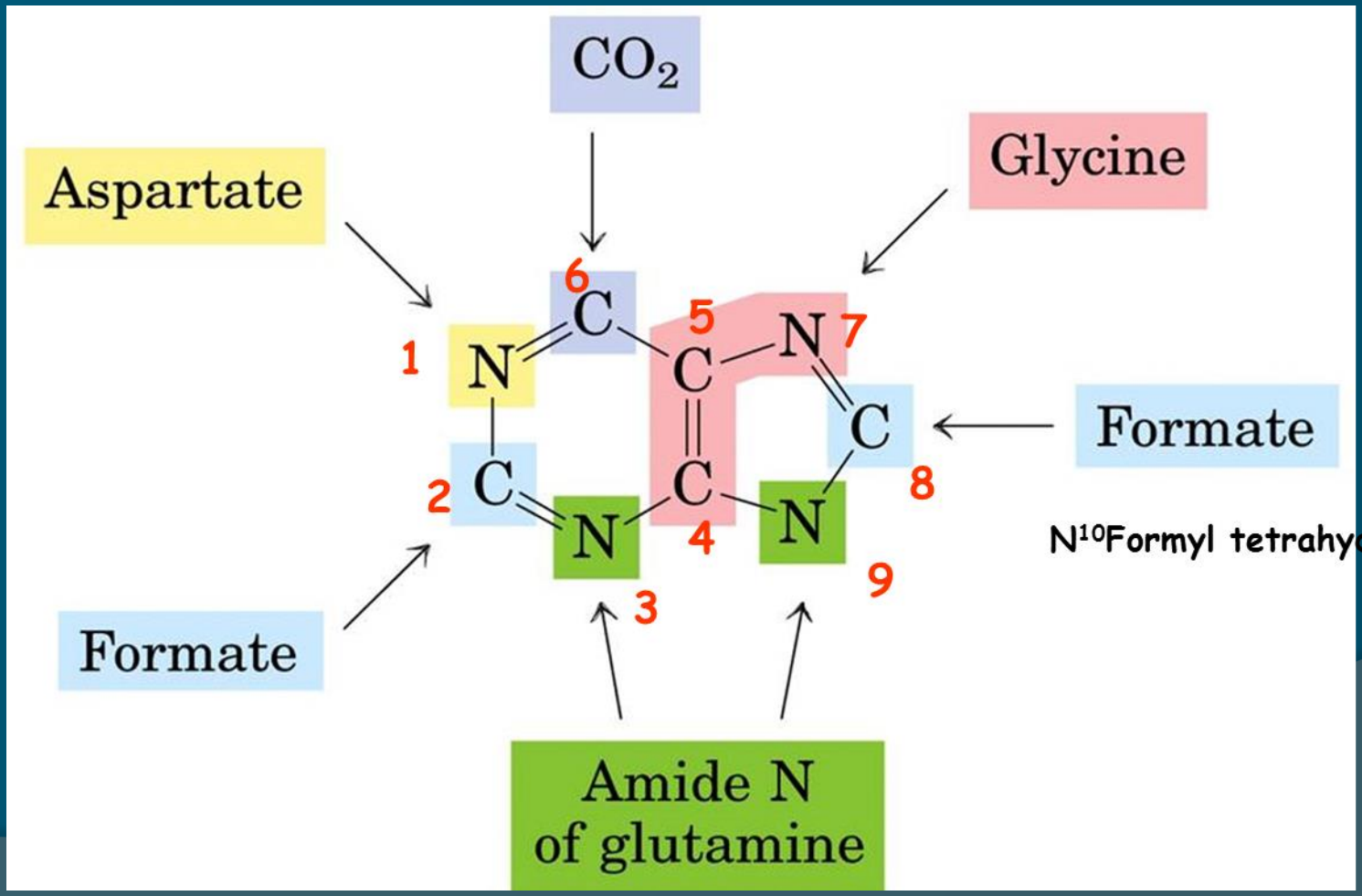
NUCLEOTIDES METABOLISM

Dr. ali al-bayati

Origin of the atoms in purine ring

The atoms of purine ring are from amino acids (aspartic acid, glycine and glutamine), CO_2 and tetrahydrofolate.



Need to Know de novo purine synthesis

1. That sulfonamides inhibit purine synthesis in bacteria by interfering with folate synthesis.
2. That methotrexate inhibits purine synthesis by inhibiting dihydrofolate reductase.
3. That IMP is the end product of *de novo* purine synthesis.
4. AMP, GMP, and IMP inhibit the reaction. PRPP is an activator.
5. Rate limiting step of the pathway and source of atoms for the purine ring

Control of purine biosynthesis

- Purine Nucleotide Biosynthesis Is Regulated by Feedback Control

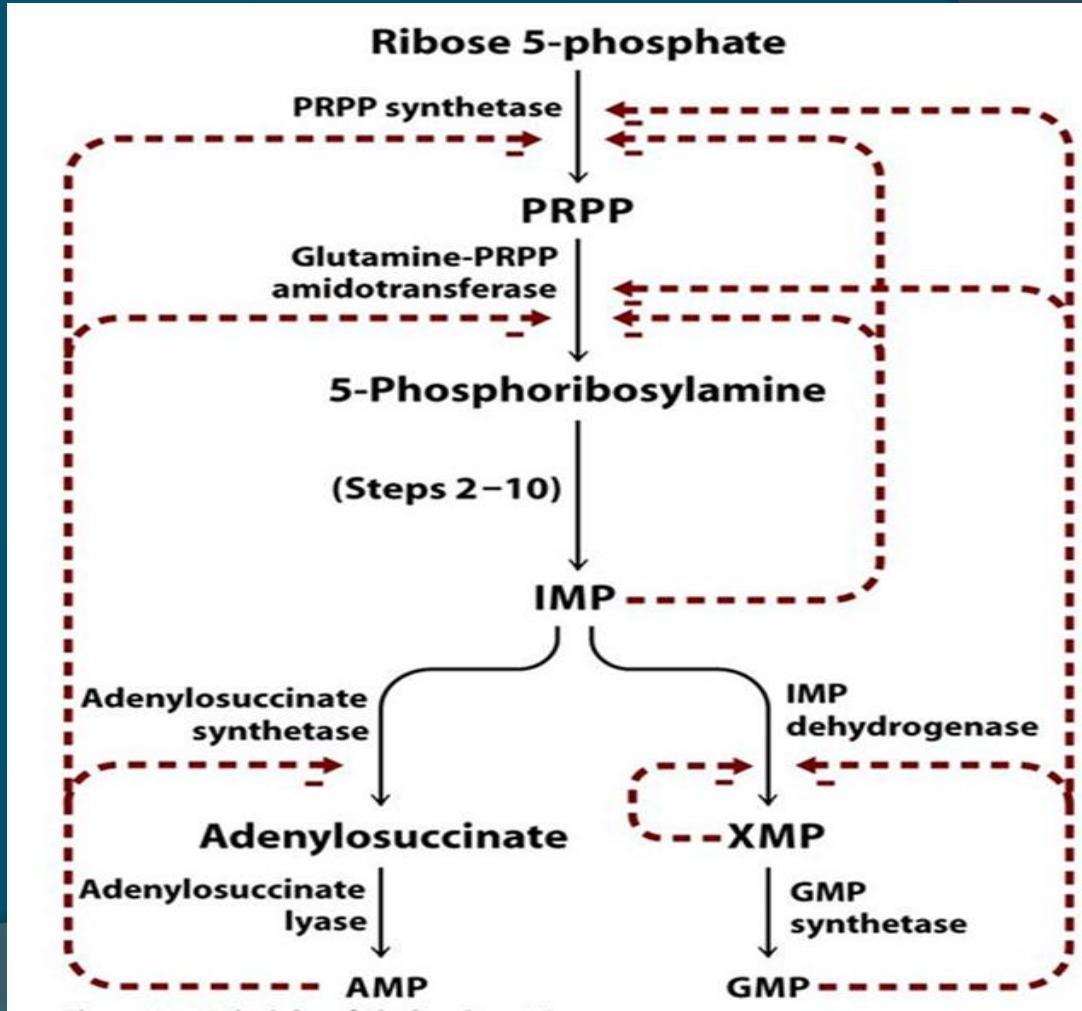
Three major feedback mechanisms are regulating the rate of de novo purine synthesis:

1. first reaction that is the transfer of an amino group to PRPP to form 5-phosphoribosylamine. allosteric enzyme glutamine-PRPP amidotransferase, which is inhibited by the end products IMP, AMP, and GMP

2. an excess of GMP in the cell inhibits formation of xanthine from inosinate by IMP dehydrogenase

3. GTP is required in the conversion of IMP to AMP, whereas ATP is required to form GMP from IMP, a reciprocal arrangement

balance synthesis of the two ribonucleotides.



purine salvage pathway.

- It is important because free purines are toxic,
- because the liver, releases purines as either free bases or free nucleosides.

Free purines are linked to the ribose ring (using PRPP as the base acceptor) by two enzymes.

1. adenine phosphoribosyl transferase (APRT)
2. hypoxanthine guanine phosphoribosyl transferase (HGPRT)

✓ The salvage pathway decreases the levels of PRPP, and therefore decreases the rate of purine synthesis.

✓ important regulatory mechanism for purine metabolism

Advantage of purine salvage pathway

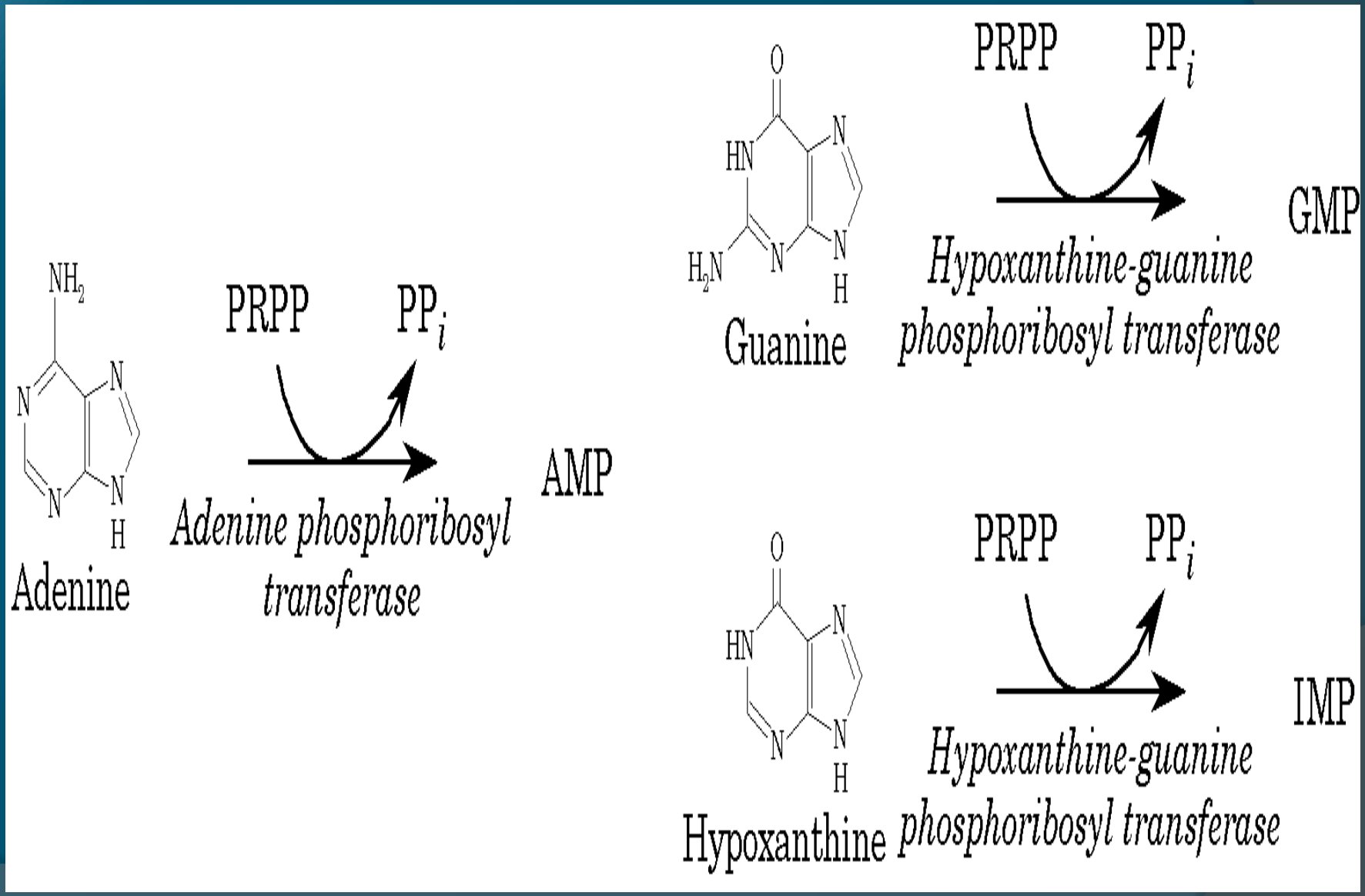
1. Reutilization of nucleotides

2. Prevents loss of ATPs which are required for de novo purine synthesis

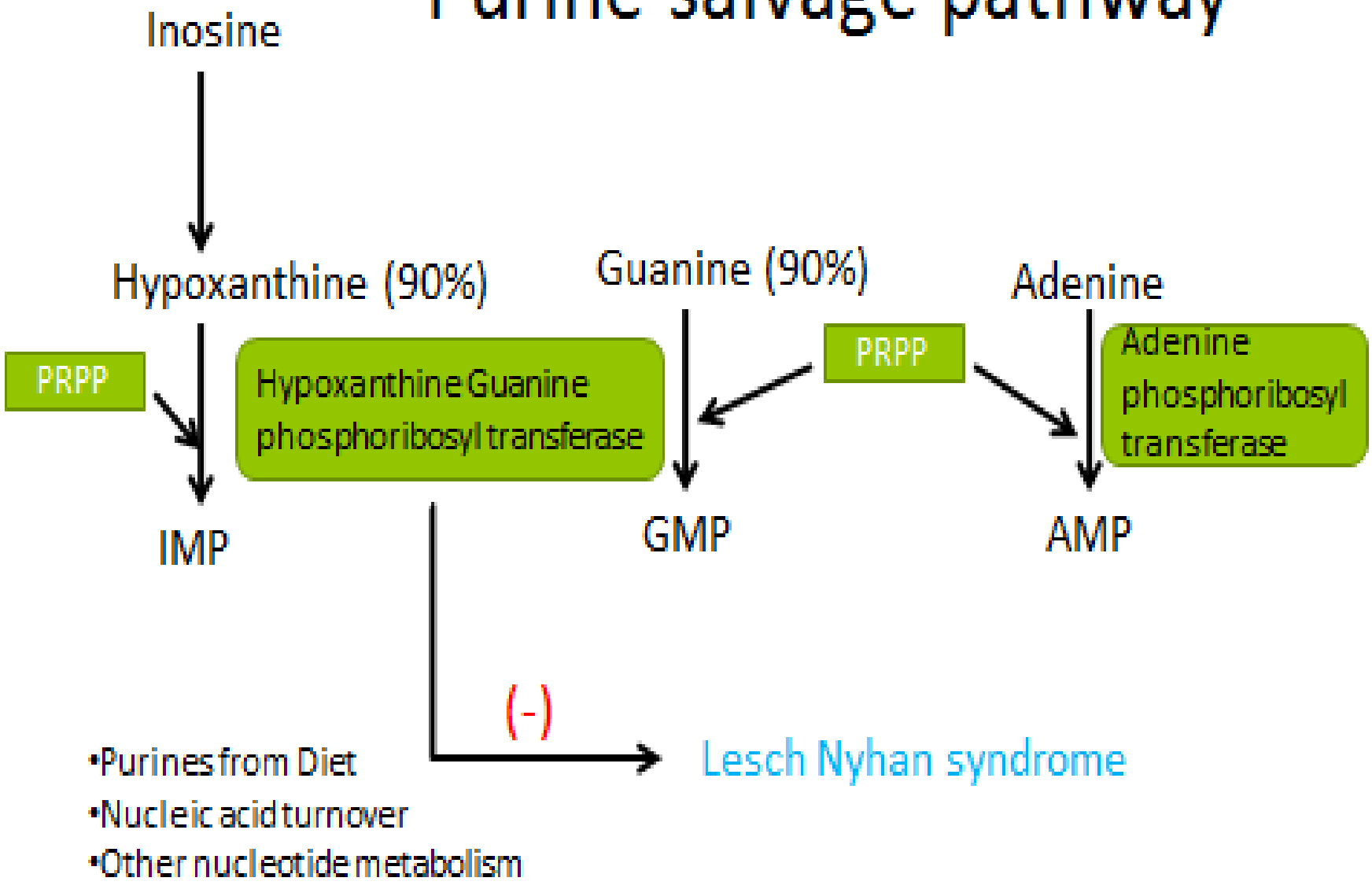
3. Nucleotides formed in the salvage pathway inhibits de novo pathway at the rate limiting step (improve Allosteric Controls).

4. Decreases uric acid formation – end product of purine catabolism.

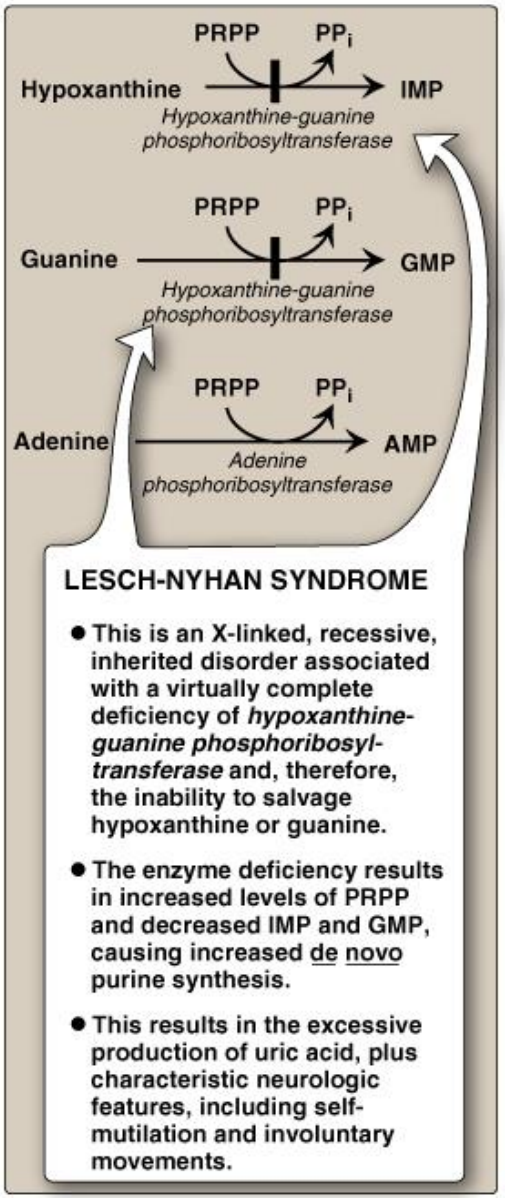
purines salvage pathway



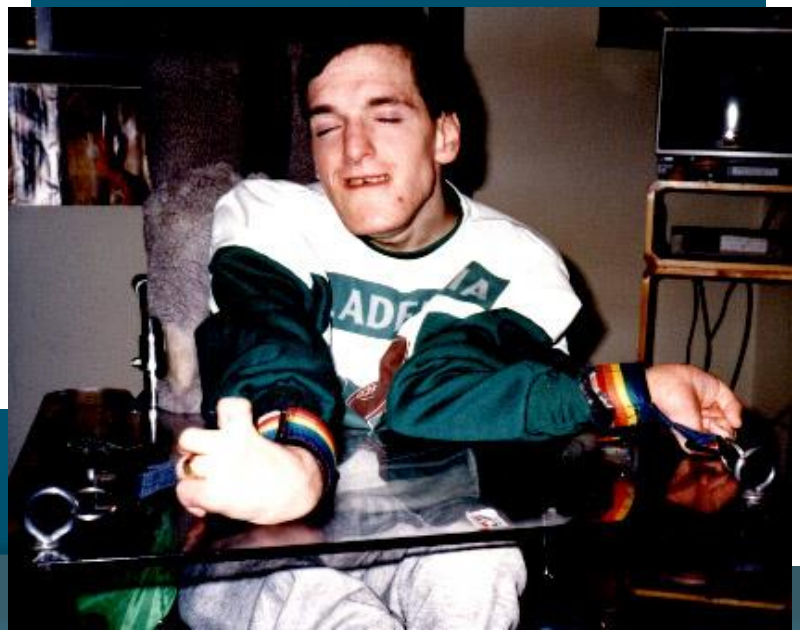
Purine salvage pathway



Lesch-Nyhan Syndrome



- X-linked recessive disorder
- complete deficiency of HGPRT
- Inability to use (salvage)of hypoxanthine and guanine
- Degradation of hypoxanthine and guanine results in increased uric acid
- Excess uric acid in urine often results in orange crystals in the diaper of affected children
- Severe mental retardation
- Self-mutilation
- Involuntary movements
- Gout



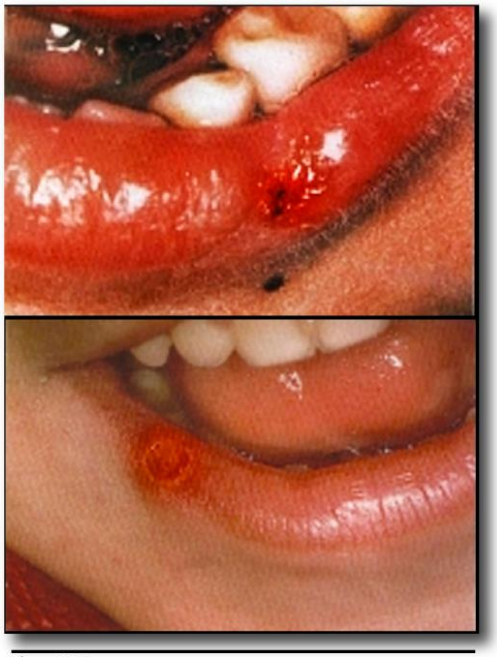
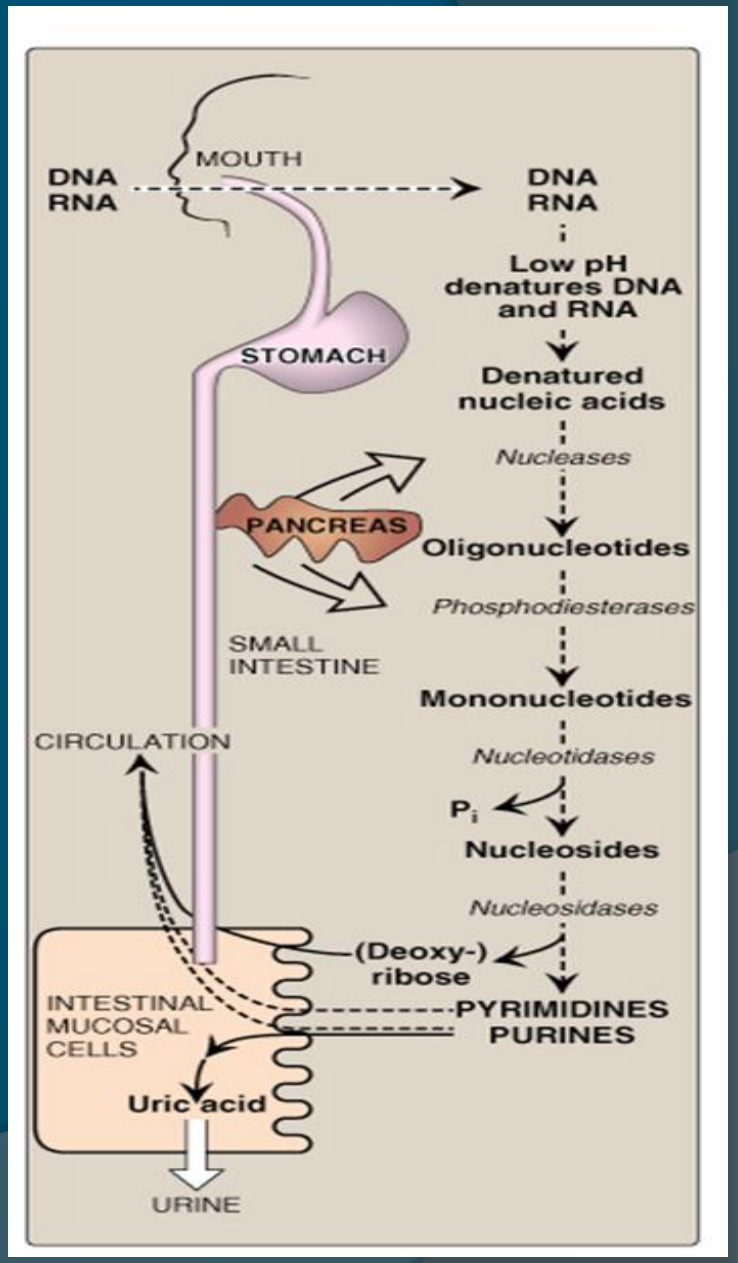


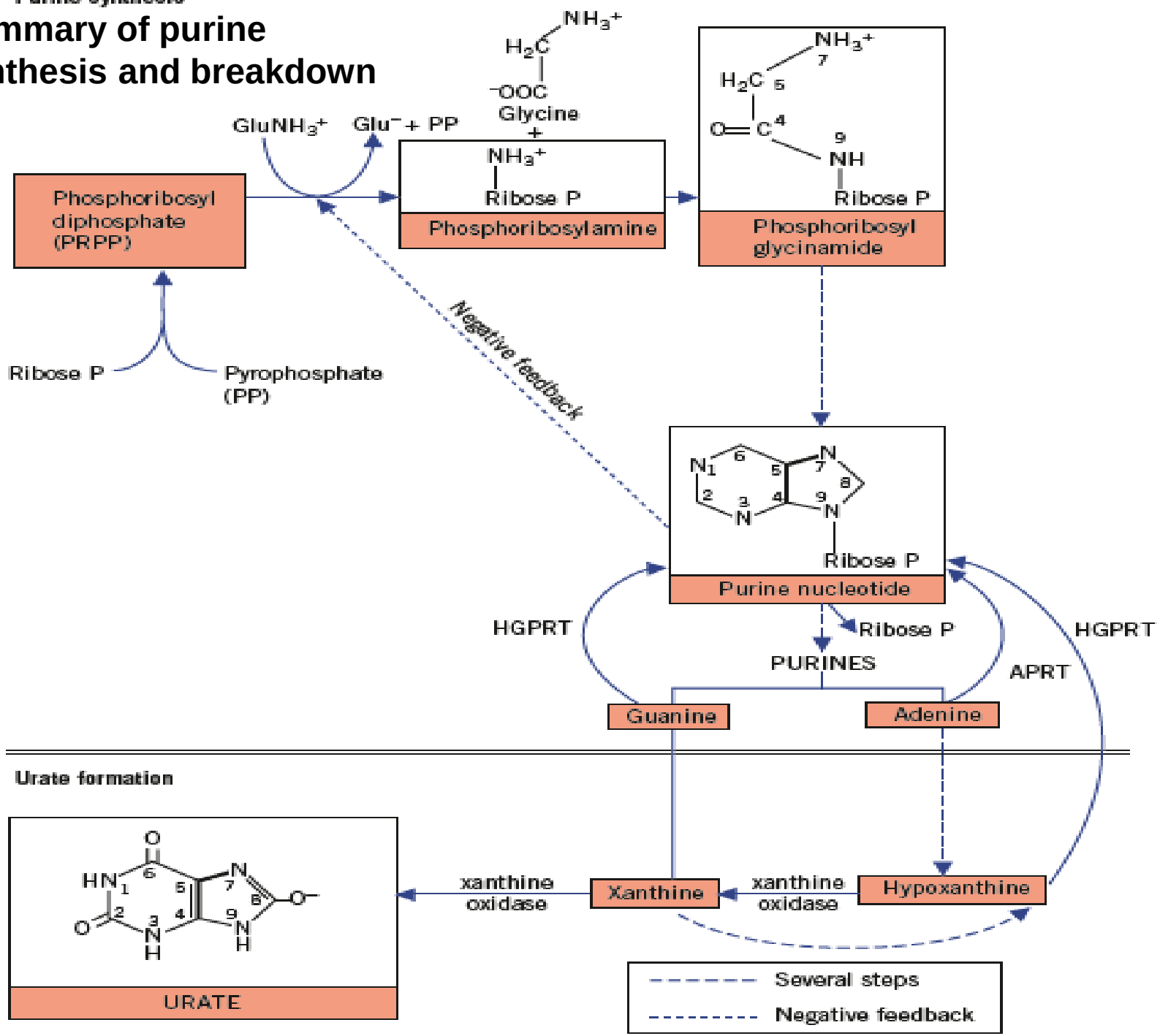
Figure 22.11
Lesions on the lips of Lesch-Nyhan patients caused by self-mutilation.

Degradation of purine nucleotides

- Degradation of dietary nucleic acids occurs in the small intestine
- pancreatic enzymes hydrolyzes the nucleic acids to nucleotides
- Inside intestinal cells, purine nucleotides degraded by specific enzymes to nucleosides and free bases.
- Purine from *de novo* degraded in liver primarily. The free bases are sent out from liver and salvaged by peripheral tissues.
- Dietary purines not used for the synthesis of tissue nucleic acids. Instead, they are generally converted to uric acid

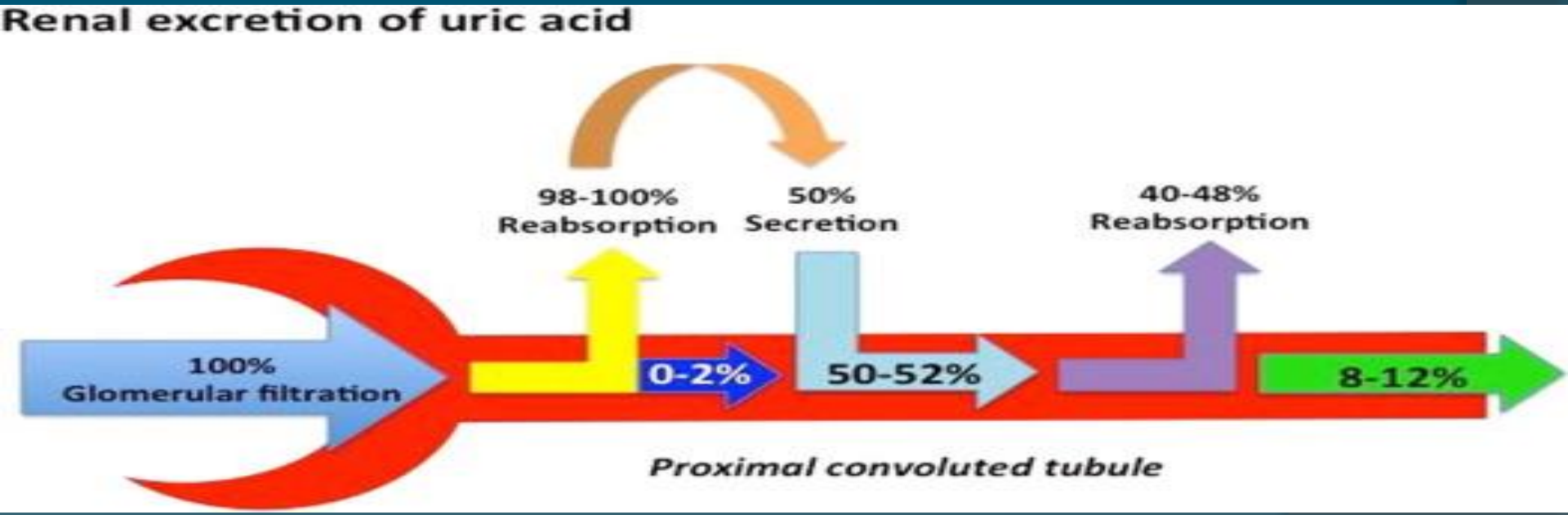


Summary of purine synthesis and breakdown



Excretion of uric acid

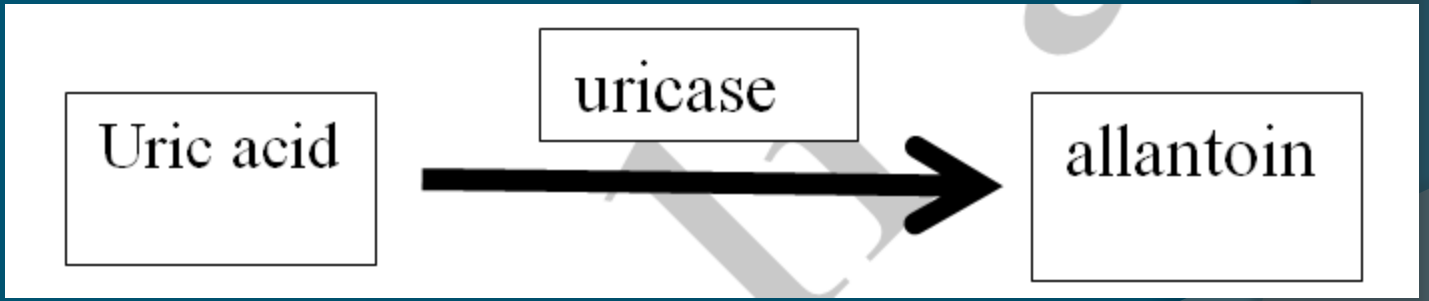
- 75% of urate leaving the body is in urine.
- 25 % passes into the intestinal lumen
- Urinary excretion is slightly lower in males than in females
- Renal secretion enhanced by uricosuric drugs (e.g. probenecid or sulfinpyrazone), block tubular urate reabsorption
- Tubular secretion of urates is inhibited by organic acids, such as lactic and oxoacids, and by ketones and thiazide diuretics.



Uric acid

- end product of purine metabolism in humans
- weak acid, uric acid circulates in plasma (pH 7.4) predominantly (98%) in the form of a monosodium urate salt.
- reach plasma saturation in the concentration of 6.4 mg/dL
- uric acid has excellent antioxidant capacity, and it can be responsible for 2/3 of total plasma antioxidant capacity.

In animals



during evolution a mutation making uricase not functional.

- antioxidant and in the defense against tumor and long lifespan .
- ability to retain sodium and raise blood pressure beneficial in food shortage.

Thank You