The salvage pathway of purine synthesis

Purines that result from the normal turnover of cellular nucleic acids, or the small amount that is obtained from the diet and not degraded, can be converted to nucleoside triphosphate s and used by the body. This is referred to as the "salvage pathway" for purines.

Human body can recycle nucleotides and free nucleotide bases in circulation. This important process is termed the "purine salvage pathway". It is important because free purines are toxic, and because the liver, which synthesizes most nucleotides, releases the compounds as either free bases or free nucleosides.

Free purines are attached to the ribose ring (using PRPP as the base acceptor) by two enzymes. Adenine is attached by adenine phosphoribosyl transferase (APRT), while hypoxanthine and guanine are attached to the ribose ring by hypoxanthine guanine phosphoribosyl transferase (HGPRT).

The salvage pathway decreases the levels of PRPP, and therefore decreases the rate of purine synthesis. This is an important regulatory mechanism for purine metabolism. Overproduction of purines or lack of salvage of purines leads to significant disorders.

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.

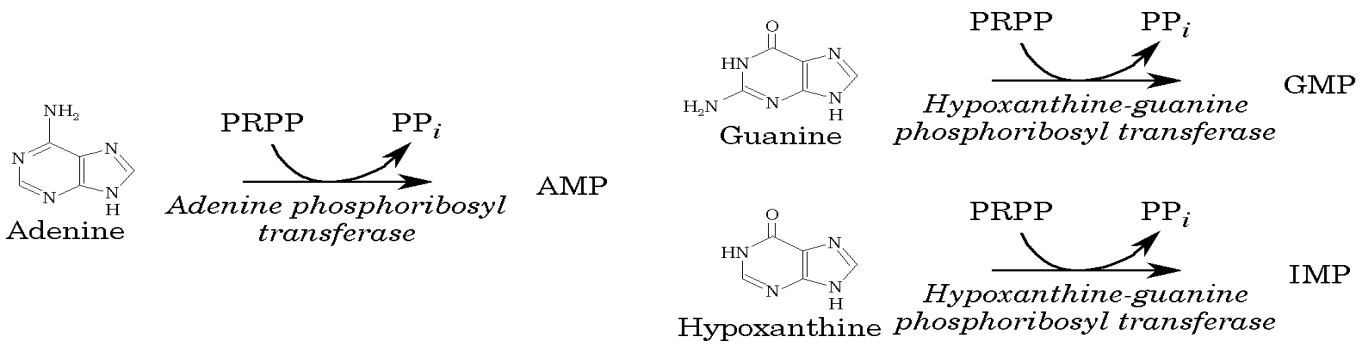


Figure 1: purines salvage pathway.

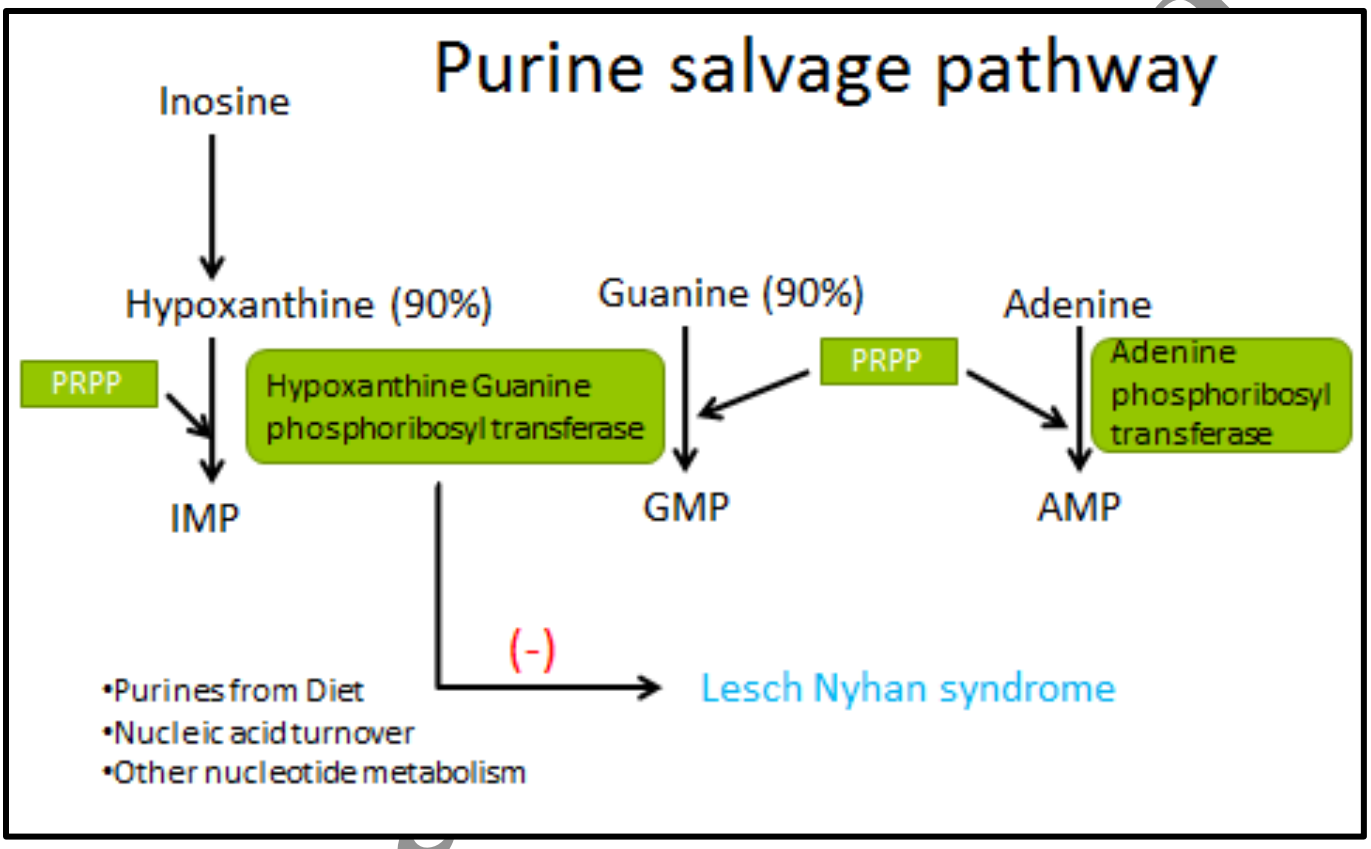


Figure 2: purines salvage pathway.

Disorder of salvage pathway of purines biosynthesis

Lesch-Nyhan syndrome:

Lesch-Nyhan is a rare, X-linked recessive disorder associated with a virtually complete deficiency of HGPRT. The deficiency results in an inability to salvage hypoxanthine or guanine, from which excessive amounts of uric acid, the end product of purine degradation, are then produced (as we will see later). In addition, the lack of this salvage pathway causes increased PRPP levels and decreased IMP and GMP levels. As a result, glutamine: phosphoribosyl pyrophosphate amidotransferase (the regulated step in purine synthesis) has

excess substrate and decreased inhibitors available, and *de novo* purine synthesis is increased. The combination of **decreased purine reutilization and increased purine synthesis results in increased degradation of purines and the production of large amounts of uric acid**, making Lesch-Nyhan a heritable cause of hyperuricemia. In patients with Lesch-Nyhan syndrome, the hyperuricemia frequently results in the formation of uric acid stones in the kidneys (urolithiasis) and the deposition of urate crystals in the joints (gouty arthritis) and soft tissues. In addition, the syndrome is characterized by motor dysfunction, cognitive deficits, and behavioral disturbances that include self-mutilation (for example, biting of lips and fingers)

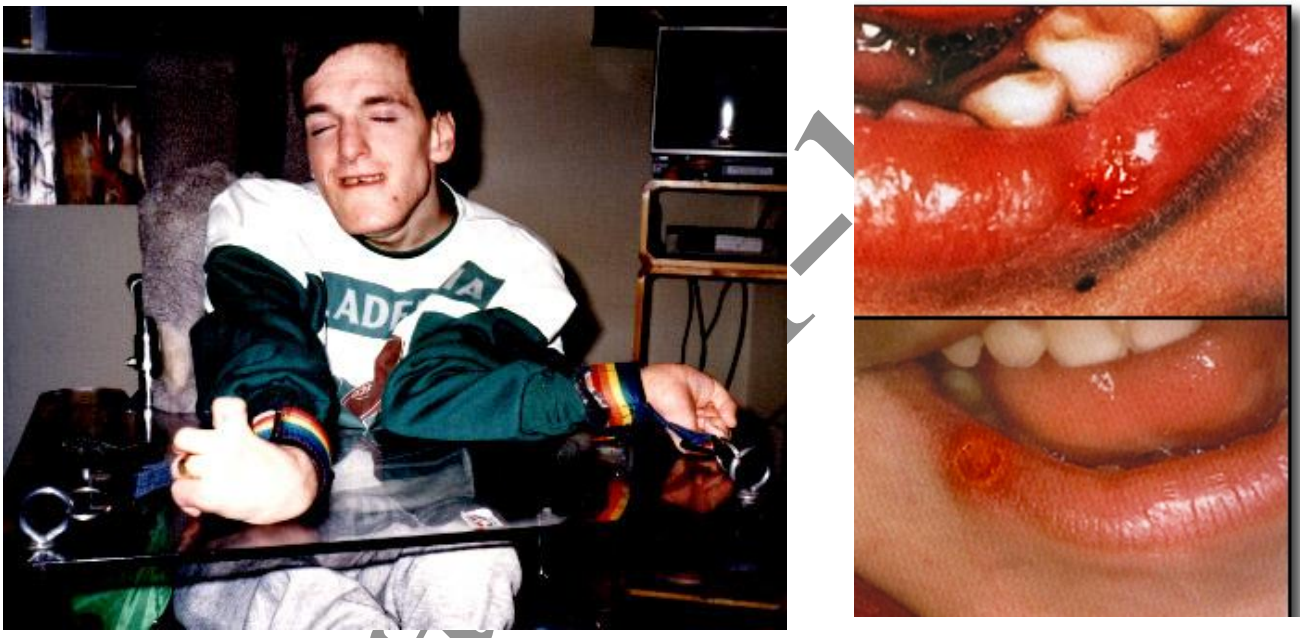


Figure 3: photographic pictues for Lesch-Nyhan with Les ions on the lips caused by self-mutilation.

Degradation of purine nucleotides

Degradation of dietary nucleic acids occurs in the small intestine, where a family of pancreatic enzymes hydrolyzes the nucleic acids to nucleotides. Inside the intestinal mucosal cells, purine nucleotides are sequentially degraded by specific enzymes to nucleosides and free bases.

Note: Purine nucleotides from *de novo* synthesis are degraded in the liver primarily. The free bases are sent out from liver and salvaged by peripheral tissues.

Dietary purine bases are not used to any appreciable extent for the synthesis of tissue nucleic acids. Instead, they are generally converted to uric acid in intestinal mucosal cells. Most of the uric acid enters the blood and is eventually excreted in the urine.

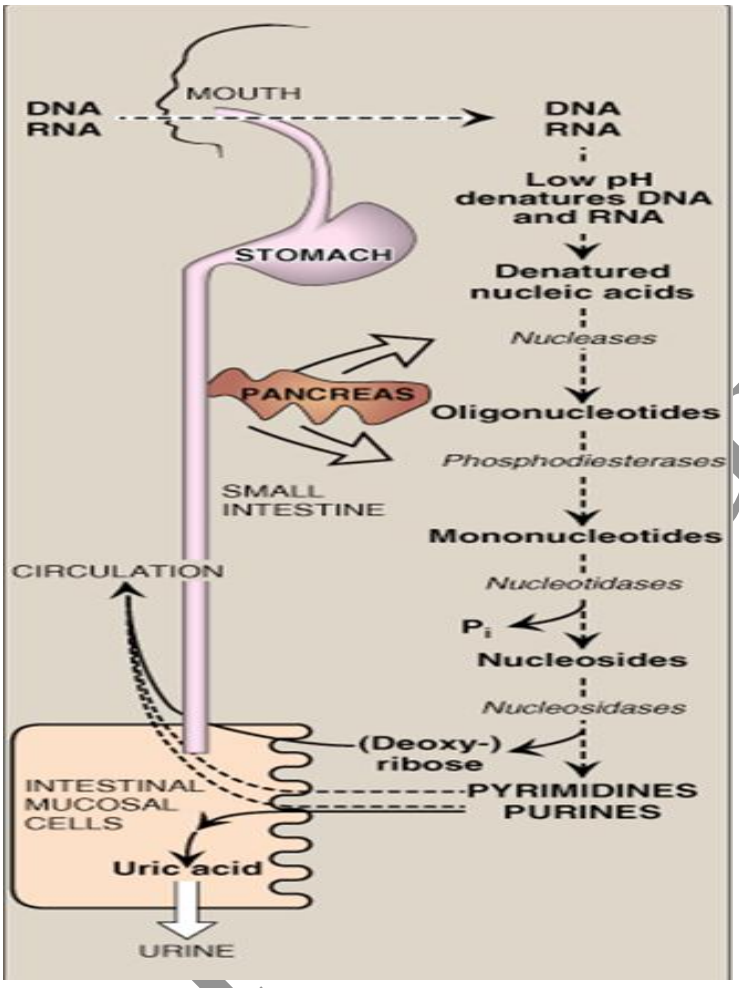


Figure 4: Digestion of dietary nucleic acids. [Note: Much of the metabolism of the mononucleotides occurs within the intestinal mucosal cells].

Fate of purines nucleotide

Each of the purine monophosphates (IMP, GMP and AMP) can be converted into their corresponding nucleosides by 5′-nucleotidase. The enzyme purine nucleoside phosphorylase then converts the nucleosides inosine or guanosine into the free purine bases hypoxanthine and guanine, and ribose-1-P.

Hypoxanthine is oxidized and guanine is deaminated to yield xanthine (Figure 5). Two other enzymes, **AMP deaminase** and **adenosine deaminase**, convert the amino group of AMP and adenosine into IMP and inosine, respectively, which are then converted to hypoxanthine.

In effect, guanine is directly converted to xanthine, while inosine and adenine are converted to hypoxanthine, then to xanthine.

Xanthine oxidase (XO), the final enzyme in this pathway, catalyzes a twostep oxidation reaction, converting hypoxanthine to xanthine, then xanthine to uric acid. Uric acid is the final metabolic product of purine catabolism in primates, birds, reptiles, and many insects. Other organisms, including most mammals, fish, amphibians and invertebrates, metabolize uric acid to more soluble products, such as allantoin (see Figure 5).

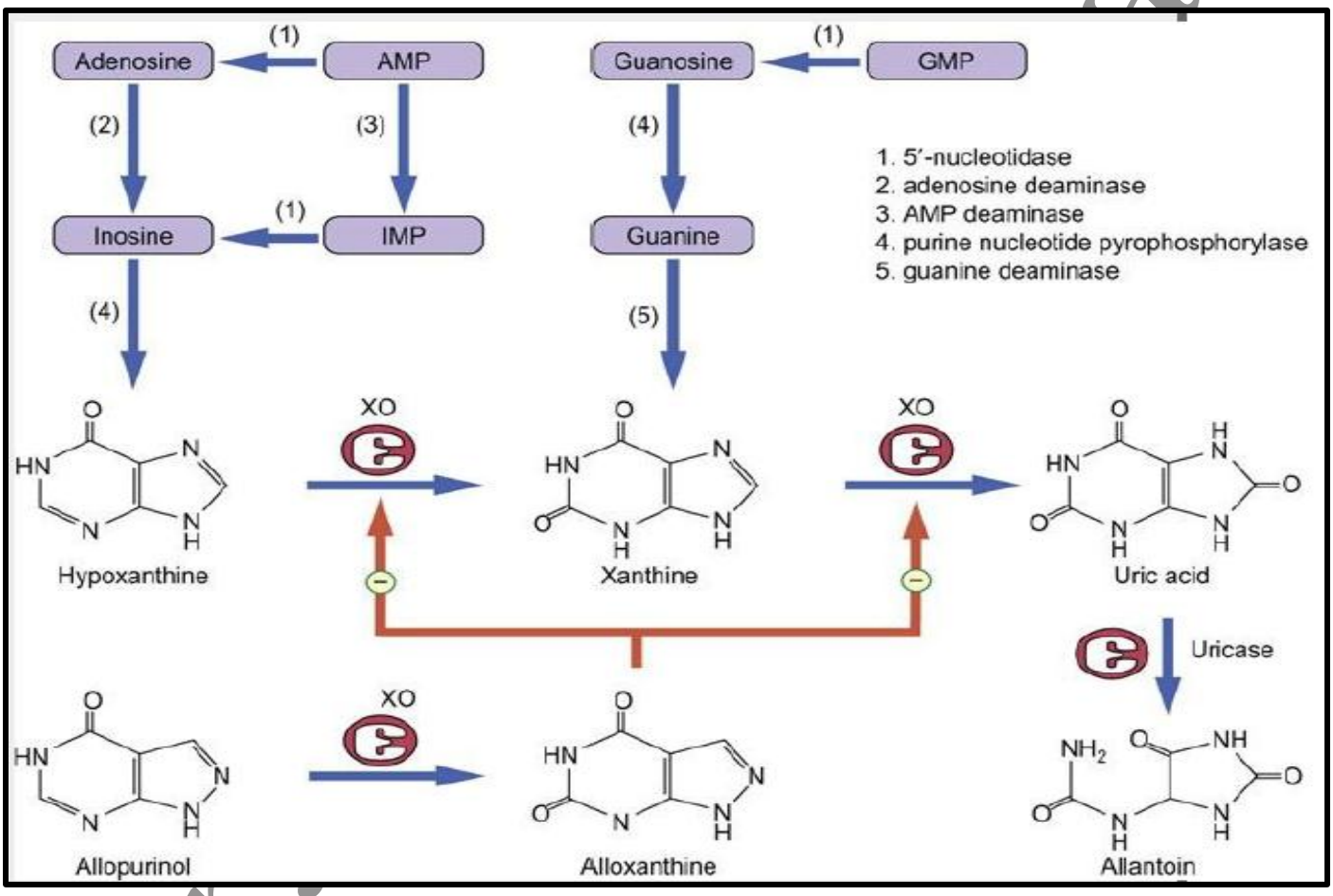


Figure 5: Degradation of purines and biochemical basis of uric acid formation.

Excretion of urate

Urate is filtered through the glomeruli and most is reabsorbed in the proximal tubules. **Urinary excretion is slightly lower in males than in females**, which may contribute to the **higher incidence of hyperuricaemia in men.** Renal secretion may be **enhanced by uricosuric drugs (e.g. probenecid or sulfinpyrazone),** which block tubular urate reabsorption. **Tubular secretion of urates is inhibited by organic acids, such as lactic and**

oxoacids, and by ketones and thiazide diuretics. **75% of urate leaving the body is in urine**. The remaining **25 % passes into the intestinal** lumen, where it is broken down by intestinal bacteria, the process being known as uricolysis.

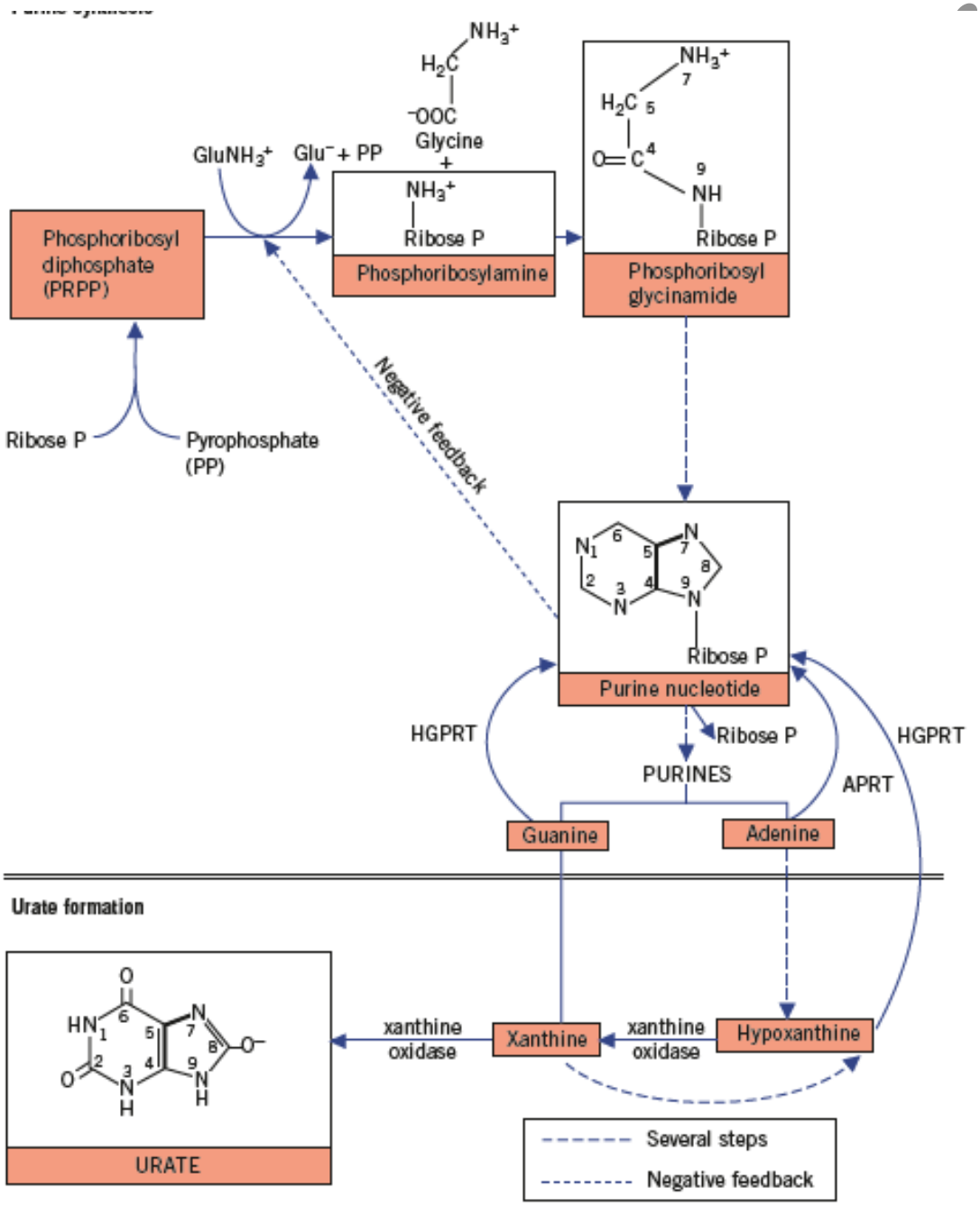


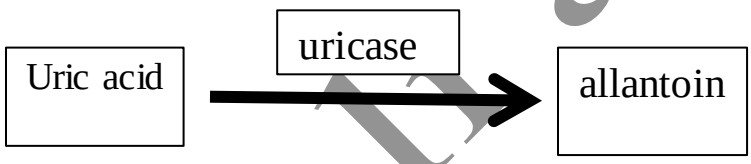
Figure 6: Summary of purine synthesis and breakdown, showing the steps of clinical importance.

Uric acid

Uric acid is an organic compound that is endogenously produced by animals as a purine metabolite. It is formed by the liver and mainly excreted by the kidneys (75%) and intestines (25%). Uric acid is the end product of purine metabolism in humans due to the loss of uricase activity, which led to humans having higher Uric acid levels than other mammals. Because it is a weak acid, uric acid circulates in plasma (pH 7.4) predominantly (98%) in the form of a monosodium urate salt. It shows low solubility in water (as well as in plasma), and it would theoretically reach plasma saturation in the concentration of 6.4 mg/dL, which may not occur because solubility increase is provided by its binding to proteins, namely albumin, which is its main transporter. Protein-bound uric acid shows plasma solubility that is 70% higher than in its free state

Due to its double bonds, uric acid has excellent antioxidant capacity, and it can be responsible for 2/3 of total plasma antioxidant capacity.

Uric acid is generated by the metabolism of purines in most mammals. In lower species, allantoin is degraded by an enzyme called liver uricase resulting in very low serum uric acid levels.



However, in humans, a mutation occurred during evolution making uricase not functional. It is believed that this selection has occurred because of the beneficial effects of uric acid as antioxidant and in the defense against tumor. Furthermore, the uric acid ability to retain sodium and raise blood pressure could be considered beneficial in situations of food shortage. However, with changing eating habits of the modern diet, rich in salt and uric acid precursors such as fructose, it has been observed that uric acid is associated with hypertension, coronary artery disease, peripheral vascular disease, renal failure and strokes. Therefore uric acid appears to play a dual role in oxidative stress: antioxidant in the extracellular space and pro-oxidant within the cell,

Men	**3.5-7.2 mg/dl**	**0.21-0.43 mmol/L**
Women	**1.5-6.0 mg/dl**	**0.09-0.36 mmol/L**
Pregnancy	**1.2-4.5**	**0.07-0.27 mmol/L**

Table 1: Normal Values of serum uric acid.

- **These are general values taken from a variety of sources. The actual normal values may vary from lab to lab and from one type of testing protocol to another.**