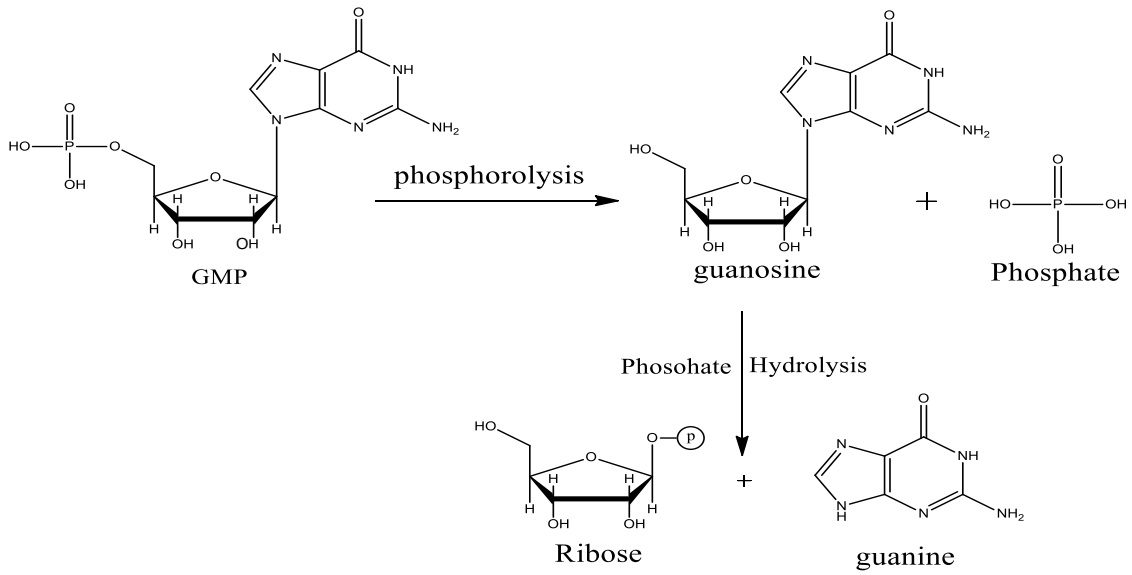
Purine and pyrimidine metabolism

1-Purine Catabolism

The end product of purine catabolism in human is **uric acid**. Other mammals have the enzyme **urate oxidase** and excrete the more soluble **allantoin** as the end product. Man does not have this enzyme so urate is the end product for us. Uric acid is formed primarily in the liver and excreted by the kidney into the urine.

Nucleotides to Bases

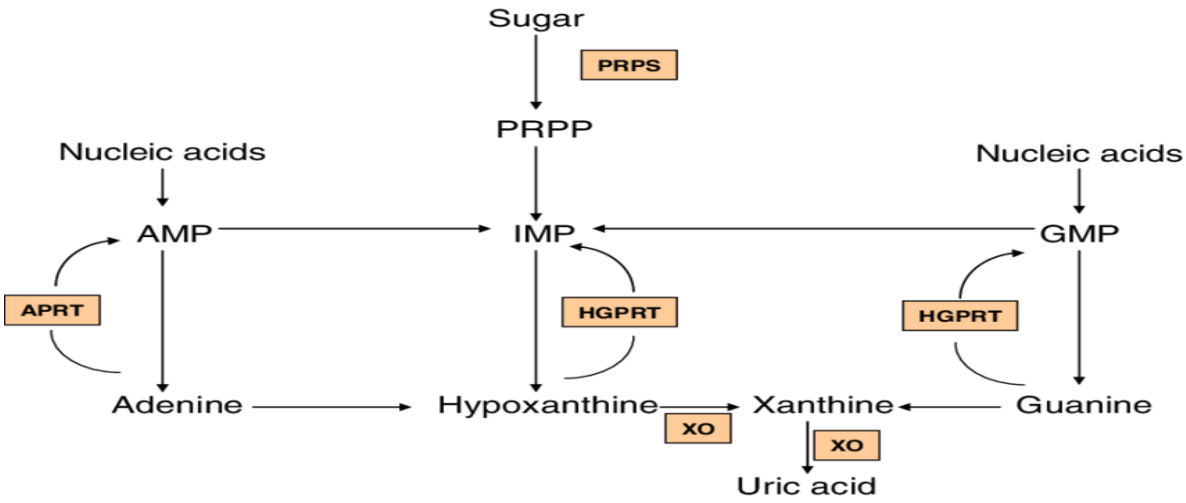
Guanine nucleotides are hydrolyzed to the nucleoside guanosine which undergoes phosphorolysis to **guanine** and **ribose 1-P**. human's intracellular nucleotidases are not very active toward AMP, however. Rather, AMP is deaminated by the enzyme adenylate (AMP) deaminase to IMP. In the catobilsm of purine nucleotides, IMP is further degraded by hydrolysis with nucleotidase to inosine and then phosphorolysis to hypoxanthine.



Bases to Uric Acid

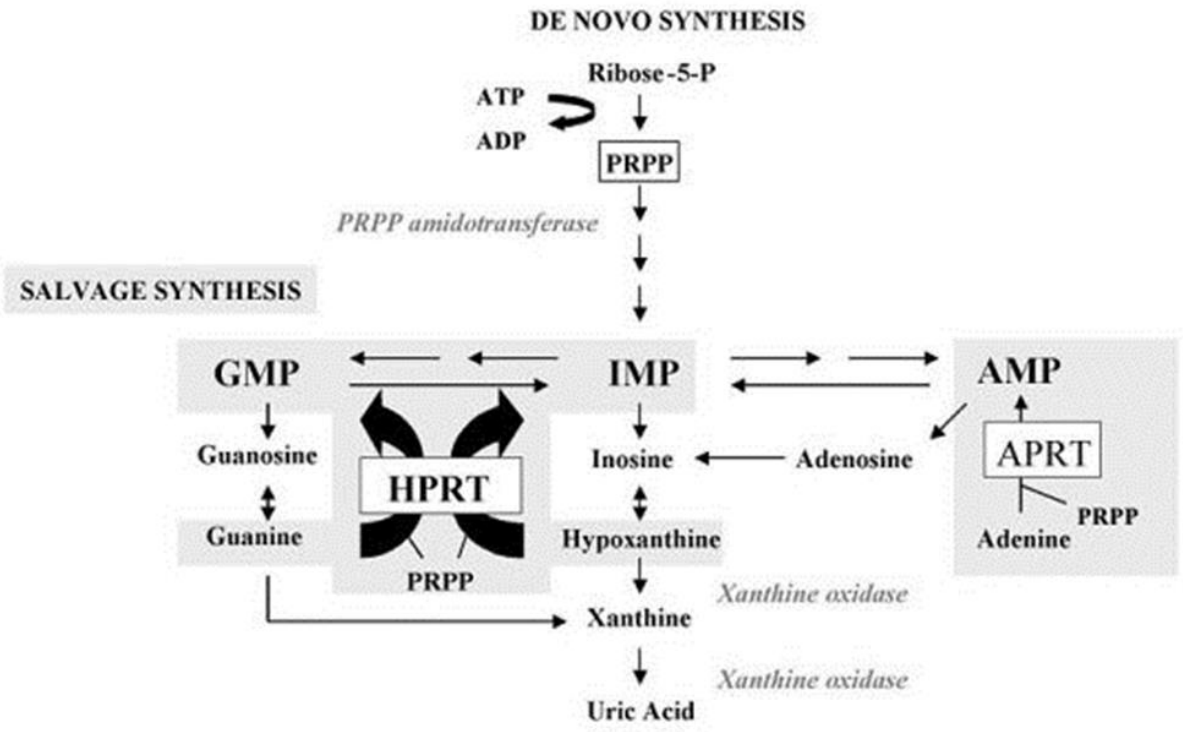
Both adenine and guanine nucleotides converge at the common intermediate xanthine. Hypoxanthine, representing the original adenine, is oxidized to xanthine by the enzyme xanthine oxidase. Guanine is deaminated, with the amino group released as ammonia, to xanthine. If this process is occurring in tissues other than liver, most of the ammonia will be transported to the liver as glutamine for ultimate excretion as urea.

Xanthine, like hypoxanthine, is oxidized by oxygen and xanthine oxidase with the production of hydrogen peroxide. In man, the urate is excreted and the hydrogen peroxide is degraded by catalase. Xanthine oxidase is present in significant concentration only in liver and intestine. The pathway to the nucleosides, possibly to the free bases, is present in many tissues.



AMP	Adenosine monophosphate
APRT	Adenine phosphoribosyl transferase
GMP	Guanosine monophosphate
HGPRT	Hypoxanthine-guanine phosphoribosyl transferase
IMP	Inosine monophosphate
PRPP	5-phosphoribosyl 1-pyrophosphate
PRPS	PRPP synthetase
XO	Xanthine-oxidase

In de novo pathway, **ribose -5-phosphate** works as the **starting material**. Then, it reacts with ATP and converts into phosphoribosyl pyrophosphate (PRPP). Next, glutamine donates its amide group to PRPP and converts it to 5-phosphoribosylamine. Thereafter, the 5-phosphoribosylamine reacts with glycine and becomes glycinamide ribosyl 5-phosphate, and later, it converts into formylglycinamide ribosyl 5-phosphate. Glutamine donates its amide group and converts formylglycinamide ribosyl 5-phosphate into formylglycinamideine ribosyl 5-phosphate. Then the imidazole ring of the purine completes its ring form. **Finally**, with the incorporation of CO2 and undergoing several further reactions, it becomes the **inosine monophosphate (IMP)**. IMP is the immediate **precursor molecule of the adenosine monophosphate (AMP) and guanosine monophosphate (GMP)**, which are purine nucleotides.



2-Pyrimidine Catabolism

In contrast to purines, pyrimidines undergo ring cleavage and the usual end products of catabolism are beta-amino acids plus ammonia and carbon dioxide. Pyrimidines from nucleic acids or the energy pool are acted upon by nucleotidases and pyrimidine nucleoside phosphorylase to yield the free bases. The 3-amino group of both cytosine and 5-methyl cytosine is released as ammonia.

Difference between De Novo and Salvage Pathway

The key difference between de novo and salvage pathway is that **de novo** synthesis of purine nucleotides refers to the process that utilizes small molecules such as phosphoribose, amino acids, CO_2 etc. as raw materials to produce purine nucleotides, while **salvage pathway** of purine synthesis refers to the process that utilizes purine bases and purine nucleosides in order to produce purine nucleotides.

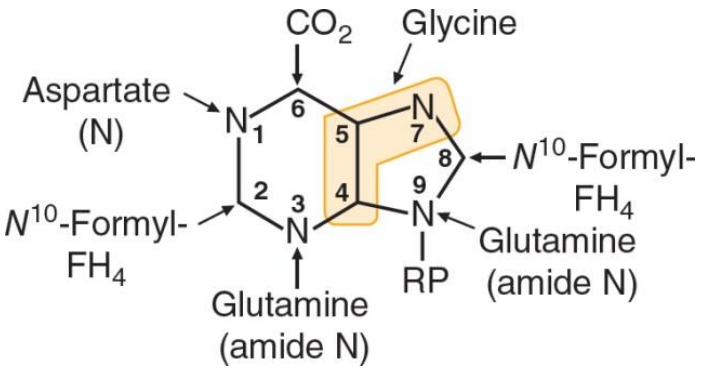
Anabolism of Nucleic acid

Nucleotides are the building blocks of nucleic acids. Moreover, some nucleotides, especially ATP, have an important role in energy transfer. Some work as secondary messengers as well. A nucleotide has three components: a **sugar**, a **nitrogen base** and a **phosphate group**.

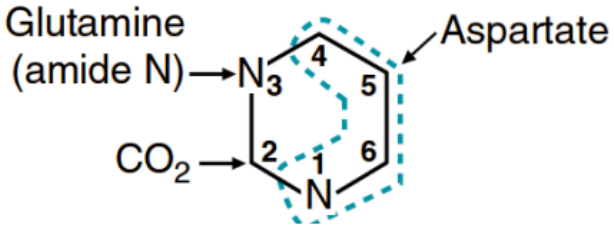
Synthesis of nucleotides takes place via different pathways. **De novo pathway** and **salvage pathway** are two main pathways of synthesis of **purine nucleotides**. De novo pathway acts as the main pathway while salvage pathway is important for purine nucleotide synthesis in the **brain**

and **bone marrow**. Therefore, the de novo pathway is a major pathway while salvage pathway is a minor pathway.

Source of Atom in Purine Ring



Sources of Atoms in Pyrimidine Ring

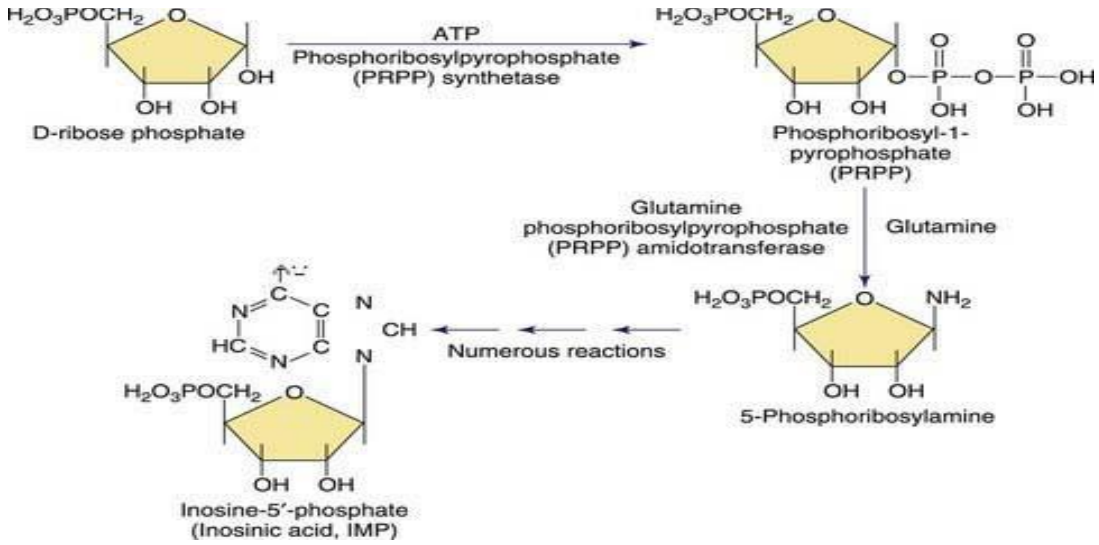


Disorders of Purine and Pyrimidine

The inherited disorders of purine and pyrimidine metabolism cover a broad spectrum of illnesses with various presentations. These include hyperuricemia, acute renal failure, renal stones, gout, unexplained neurologic deficits (seizures, muscle weakness, and dystonic movements), developmental disability, intellectual disability, compulsive self-injury and

aggression, autistic-like behavior, unexplained anemia, failure to thrive, susceptibility to recurrent infection (immune deficiency), and deafness. When such disorders are identified, all family members should be screened.

Purines are involved in all biologic processes; all cells require a balanced supply of purines for growth and survival. They provide the primary source of cellular energy through adenosine triphosphate (ATP) and, together with pyrimidines, provide the source for the RNA and DNA that stores, transcribes, and translates genetic information. Purines provide the basic coenzymes (NAD, NADH) for metabolic regulation and play a major role in signal transduction (GTP, cAMP, cGMP). Metabolically active nucleotides are formed from heterocyclic nitrogen-containing purine bases (guanine and adenine) and pyrimidine bases (cytosine, uridine, and thymine). The early steps in the biosynthesis of the purine ring are shown in Figure below



Uric acid is not a specific disease marker, so the cause of its elevation must be determined. The **level of uric acid** present at any time depends on the size of the purine nucleotide pool, which is derived from de novo purine

synthesis, catabolism of tissue nucleic acids, and increased turnover of preformed purines.

Increased production of uric acid is found in malignancy; Reye syndrome; Down syndrome; psoriasis; sickle cell anemia and gout.

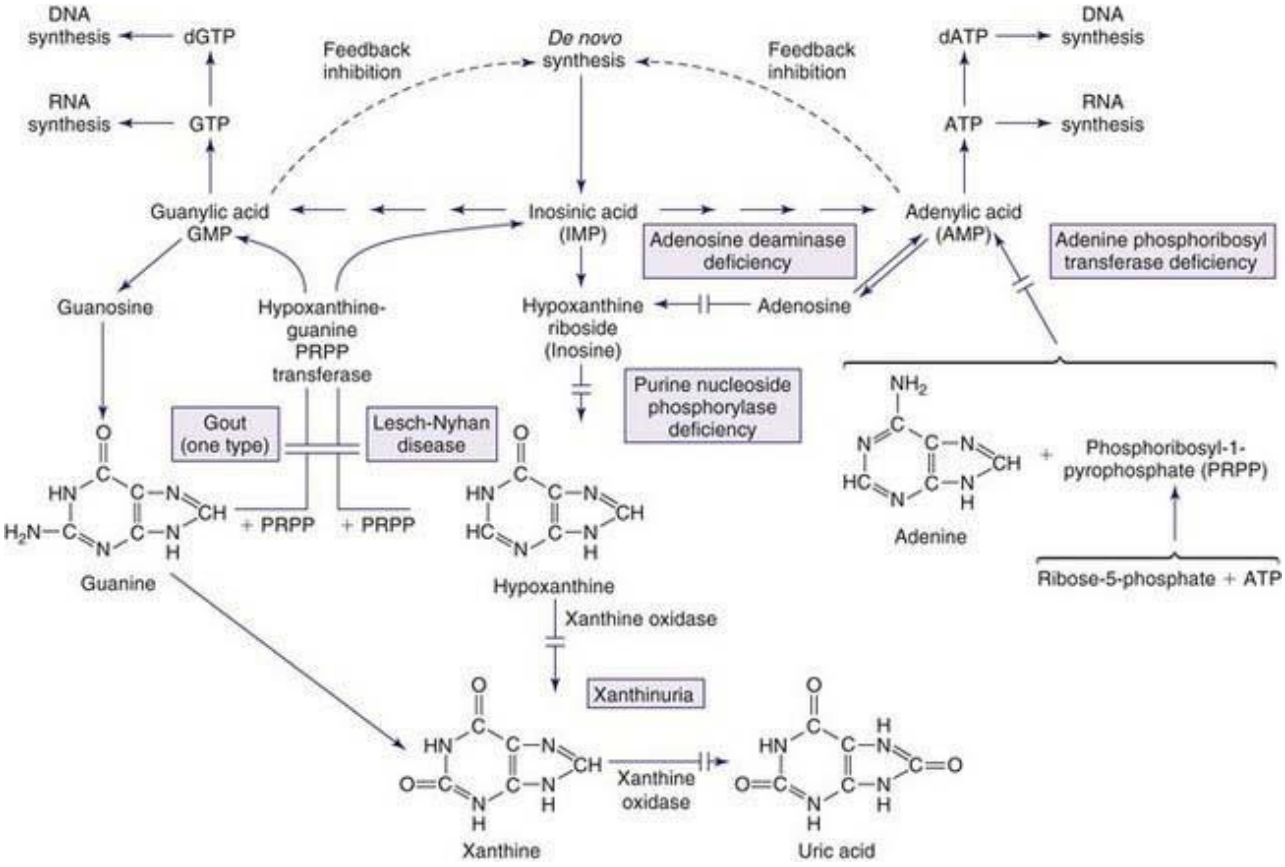
Inborn errors in the synthesis of purine nucleotides include: (1) phosphoribosylpyrophosphate synthetase superactivity, (2) adenylosuccinase deficiency, and (3) 5-amino-4-imidazolecarboxamide (AICA) riboside deficiency (AICA-ribosiduria).

Disorders resulting from abnormalities in purine catabolism include:

(1) muscle adenosine monophosphate (AMP) deaminase deficiency, (2) adenosine deaminase deficiency, (3) purine nucleoside phosphorylase deficiency, and (4) xanthine oxidoreductase deficiency.

Disorders resulting from the purine salvage pathway include:

(1) hypoxanthine-guanine phosphoribosyltransferase (HPRT) deficiency, and (2) adenine phosphoribosyltransferase (APRT) deficiency.



Pathways in purine metabolism and salvage