

## Metabolism of Nucleic acid

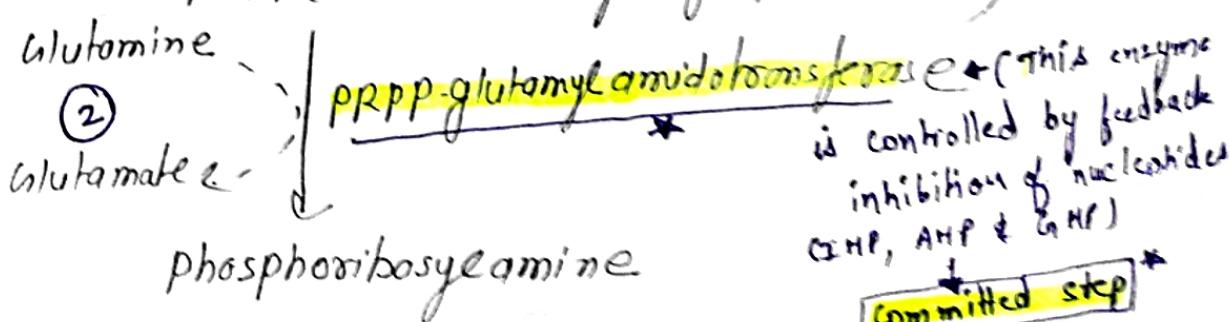
### Biosynthesis of purine Ribonucleotides

- 2 Purine bases are not synthesized as such, but they are formed as ribonucleotides.
- 2 Purine are built upon a pre-existing ribose-5-phosphate
- 2 Liver is the major site for purine nucleotide synthesis
- 2 RBC, brain & Leucocyte can't produce purine
- 2 The pathway for the synthesis of IMP (Inosine Monophosphate)

Re: Ribose-5-phosphate (HMP pathway)

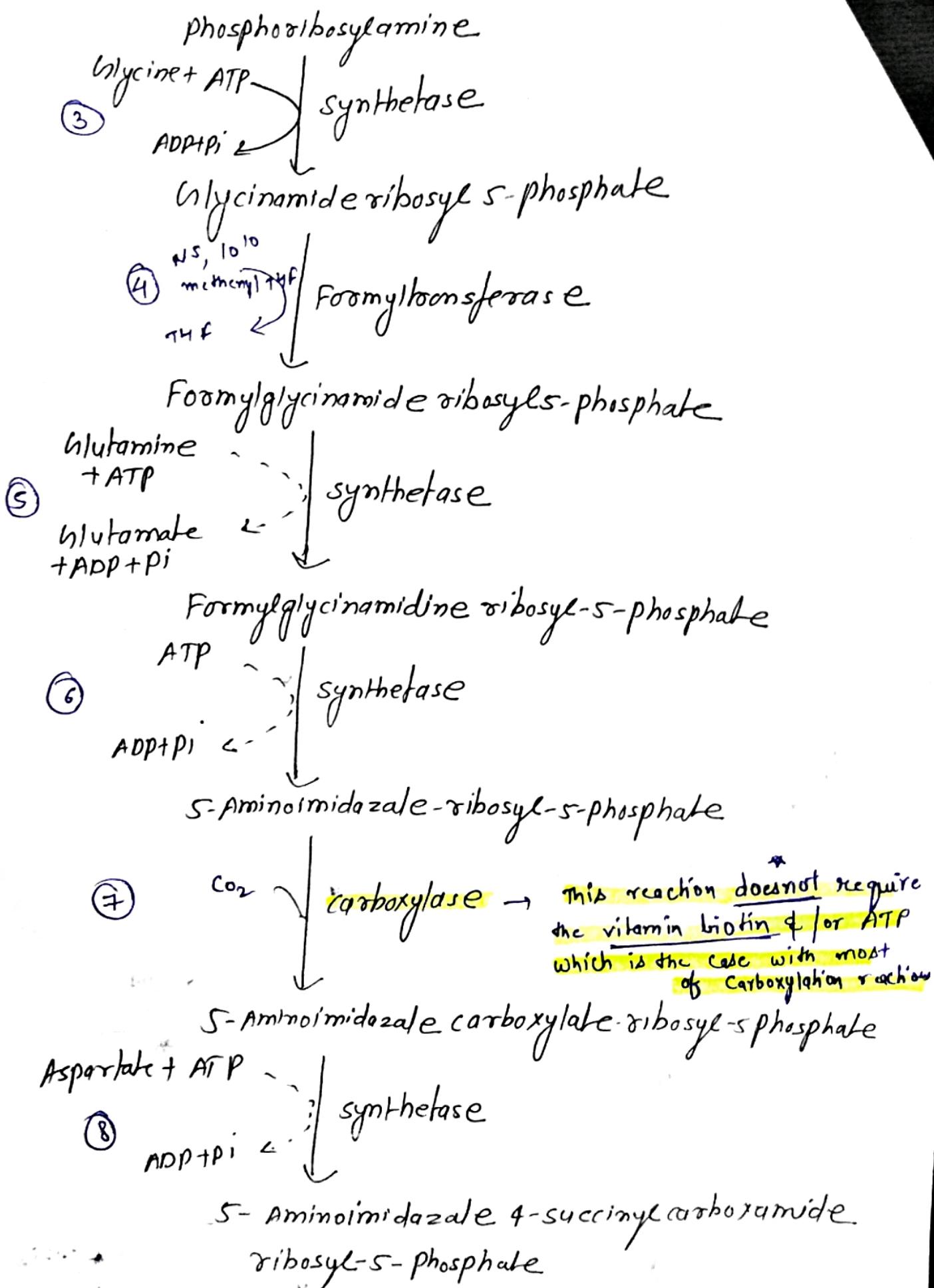


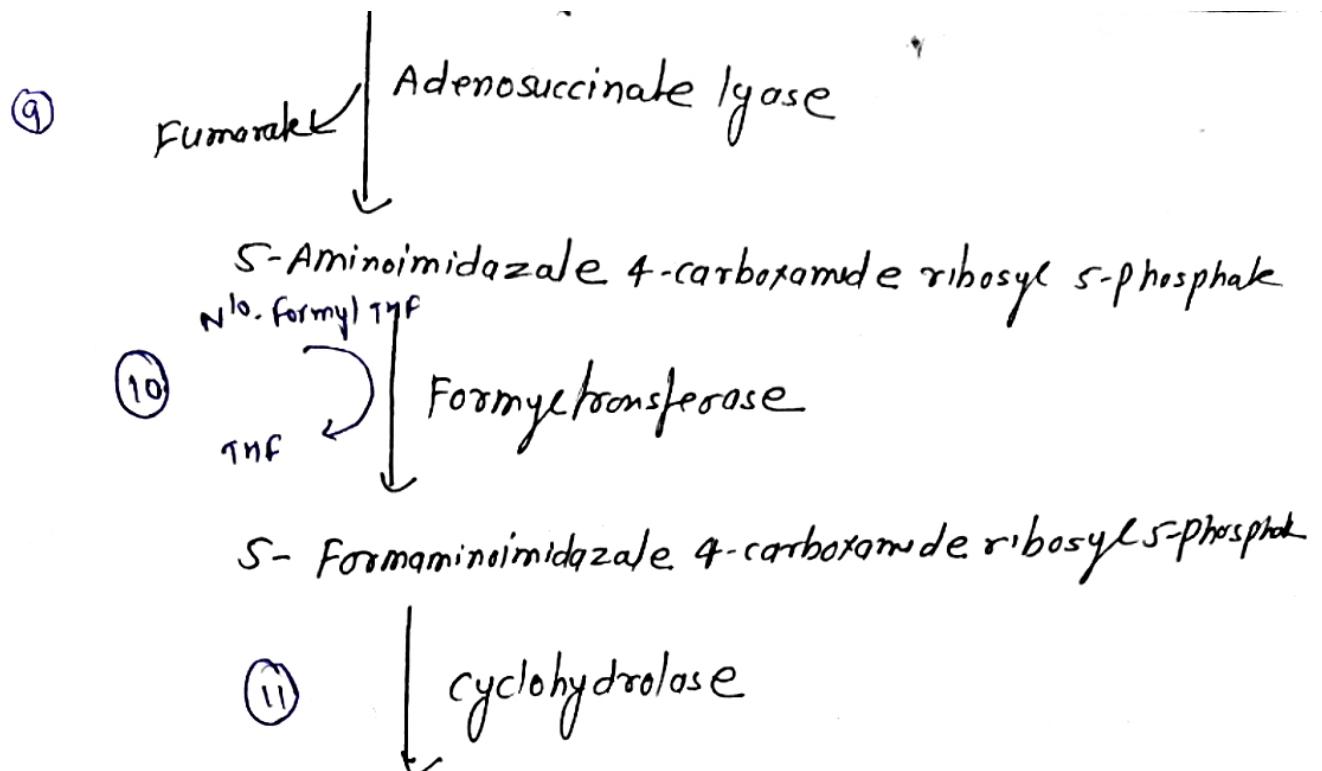
PRPP (Phosphoribosyl pyrophosphate)



phosphoribosylamine

↓  
**committed step**





Parent purine nucleotide from which other purine nucleotides can be synthesized.  $\leftarrow$  IMP (Inosine monophosphate)

### Inhibitors of purine synthesis

2 Folic acid (THF) is essential for synthesis of purine nucleotides. (reaction 4 & 10)  
(para-amino benzoic acid)

2) Sulphonamides are structural analogs of PABA. That can be used to inhibit the synthesis of folic acid by microorganism.

3) The structural analogs of folic acid (e.g. methotrexate) are used to control cancer.

## 2 synthesis of AMP and GMP from IMP

2 IMP is the immediate precursor for the formation of AMP & GMP

2 Aspartate condenses with ATP in the presence of GTP to produce adenylosuccinate

2 For the synthesis of GMP, IMP undergoes NAD<sup>+</sup> dependent dehydrogenation to form - xanthosine monophosphate (XMP) glutamine then transfer amide nitrogen to XMP to produce GMP

2 6-mercaptopurine is an inhibitor of the synthesis of AMP and GMP. It acts on the enzyme adenylylsuccinate and IMP dehydrogenase

### (a) Nucleoside Monophosphate

$\text{ATP} \rightarrow \text{AMP, GMP}$

$\text{ADP} \xrightarrow{\text{NMP kinase}}$

Nucleoside diphosphate  
 $(\text{ADP, GDP})$

$\text{ATP} \rightarrow$

$\text{ADP} \xrightarrow{\text{NDP kinase}}$

Nucleoside triphosphate  
 $(\text{ATP, GTP})$

### || Synthesis of AMP & GMP from IMP ||

$\text{Aspartate + GTP}$

$\text{GDP + Pi} \xrightarrow{\text{Adenylsuccinate synthetase}}$

IMP

It is inhibited by  
6-mercaptopurine \*

$\text{NAD}^+ + \text{H}_2\text{O} \xrightarrow{\text{IMP-dehydrogenase}}$

Xanthosine monophosphate  
(XMP)

Adenylyl succinate

$\text{fumarate} \xrightarrow{\text{Adenylyl succinase}}$

It is inhibited by  
6-mercaptopurine \*

AMP

Adenosine Monophosphate)

GMP

(Inosine Monophosphate)

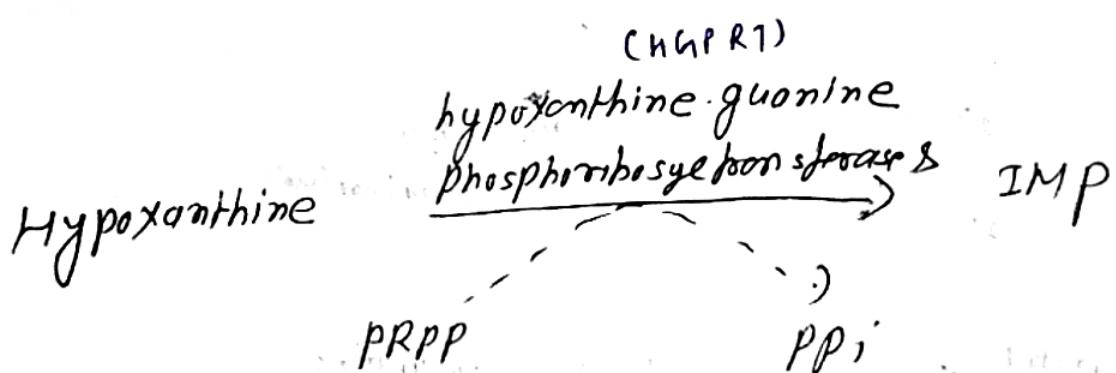
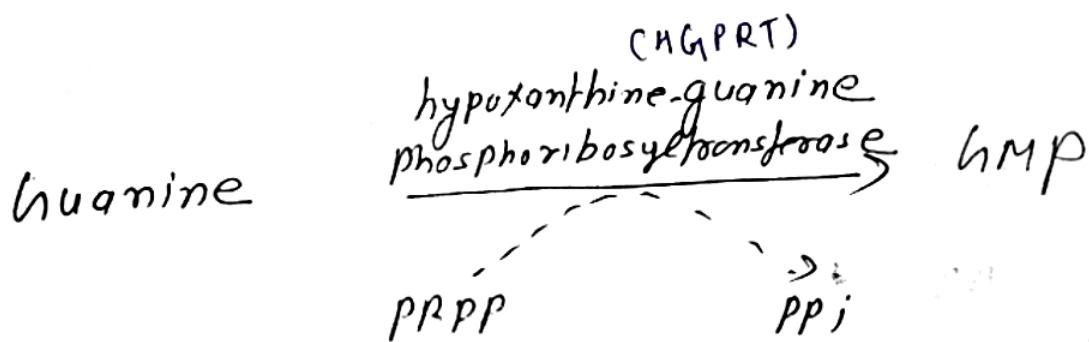
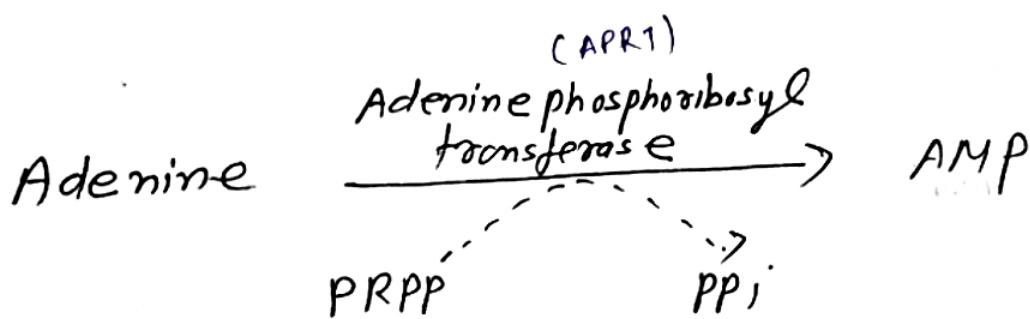
$\text{Glutamine + ATP} \xrightarrow{\text{GMP-synthetase}}$

$\text{Glutamate + AMP + Pi}$

## - Salvage-pathway for-purine

The free purine (adenine, guanine & hypoxanthine) are formed in the normal turnover of nucleic acids.

The purines can be directly converted to the corresponding nucleotide and this process is known as salvage pathway.



salvage-pathway → RBC, Brain

- 2 Deficiency of HGPRT causes - Lesch-Nyhan-syndrome
- 2 The salvage pathway is low in RBC & brain where de novo synthesis of purine nucleotide is not operative

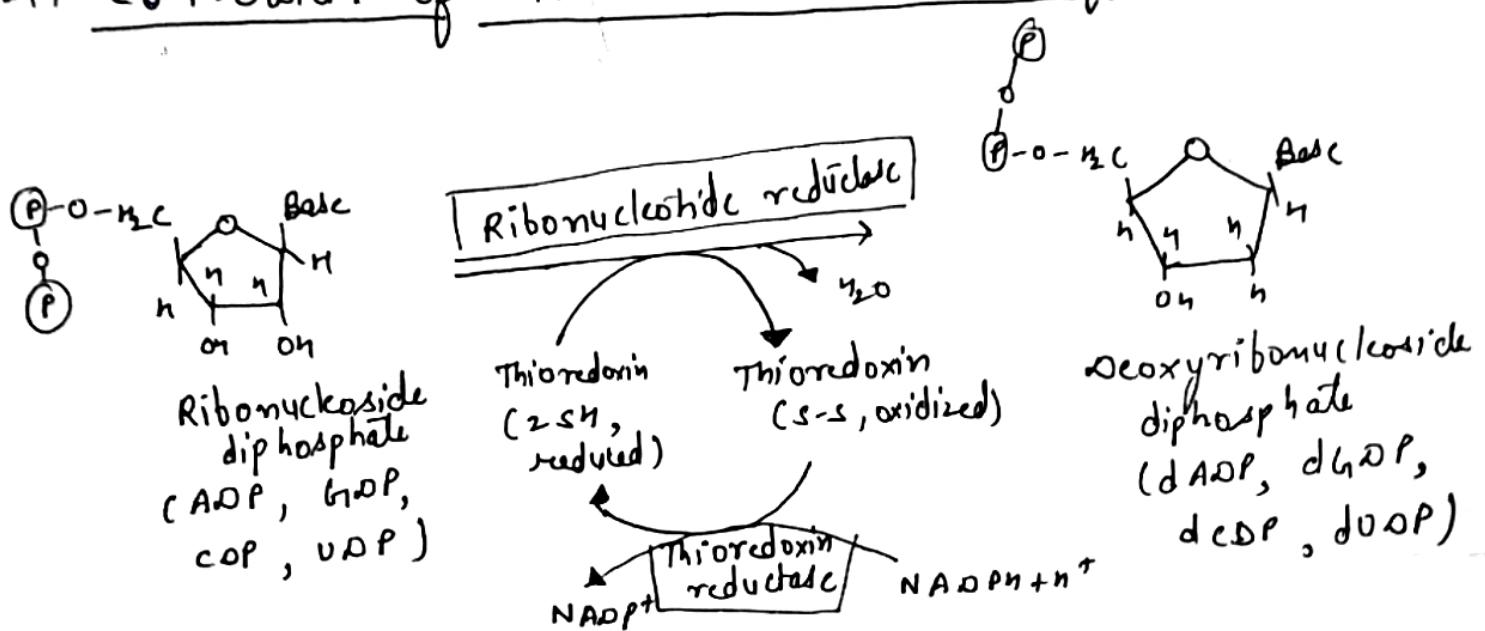
## Regulation of purine nucleotide biosynthesis.

① PRPP regulates purine synthesis

↓  
dependent on the availability of → ribose 5 phosphate  
→ PRPP synthetase

② PRPP glutamyl amidotransferase is controlled by  
feedback mechanism  
\* if

# Conversion of ribonucleotides to deoxyribonucleotides



① → Reduction at C<sub>2</sub> of ribose moiety.

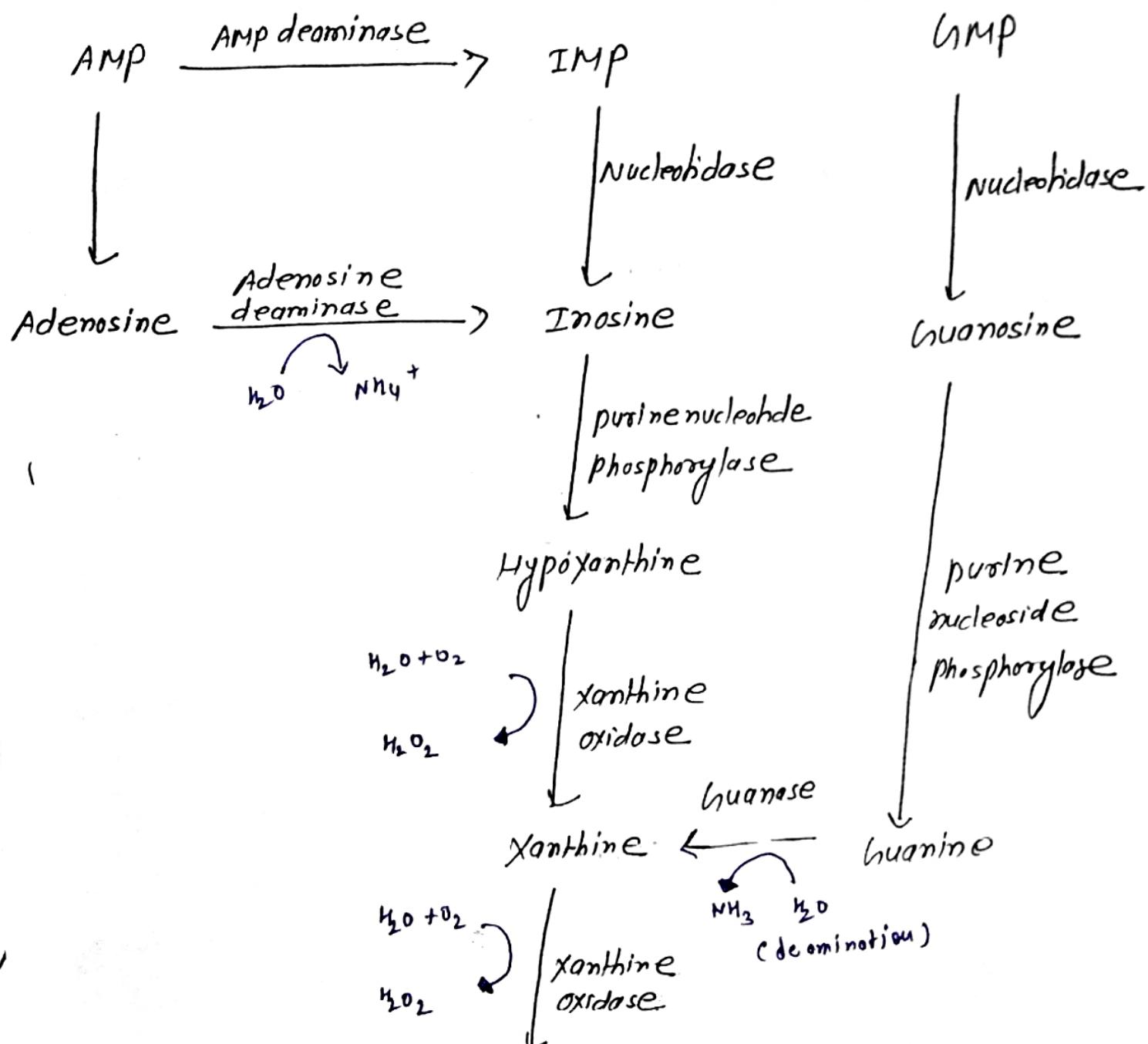
② → Thioredoxin serves as a protein cofactor in an enzymatic reaction.

③ → The drug hydroxyurea inhibits ribonucleotide reductase by destroying free radicals required by this enzyme.

④ → Hydroxyurea is used in the treatment of cancer chronic myelogenous leukemia.

## Degradation of purine metabolism

The end product of purine metabolism in human  
is uric acid

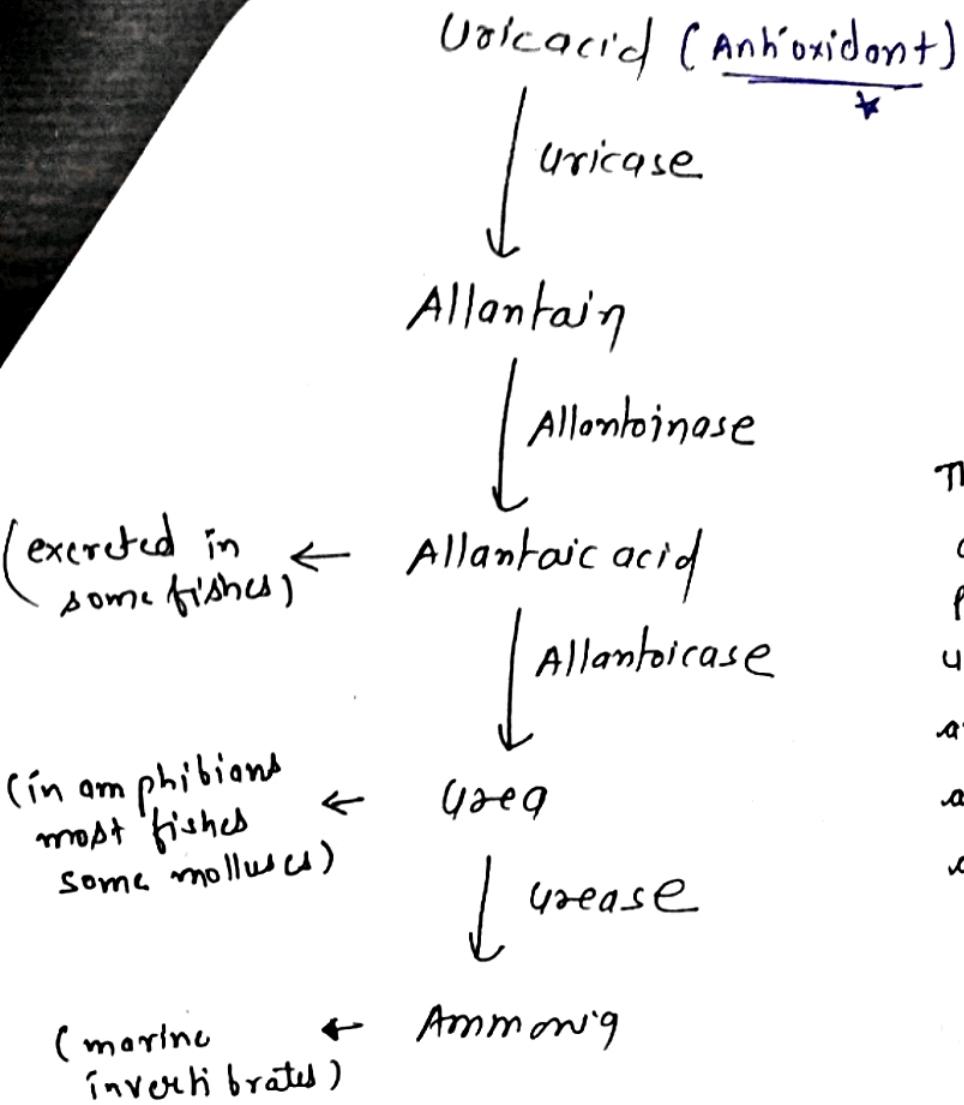


excretory product ← Uric acid (2,6,8 trioxypurine)

→ Xanthine oxidase contains FAD, Molybdenum & Iron (found in liver & small intestine)

↓ liberates H<sub>2</sub>O<sub>2</sub> which is harmful to the tissue

catalase cleaves H<sub>2</sub>O<sub>2</sub> to H<sub>2</sub>O & O<sub>2</sub>



The antioxidant role of ascorbic acid in primates is replaced by uric acid, since these animals have lost the ability to synthesize ascorbic acid.

## 2 Disorders of purine metabolism

Hyperuricemia and Gout

The normal conc. of uric acid in the serum of adult  $3-7 \text{ mg/dL}$   
The daily excretion of uric acid is about  $500-700 \text{ mg}$

Hyperuricemia may refer to an elevation in the serum uric acid concentration. In this crystals of sodium urate get deposited in soft tissues (joints) → known as tophi → this caused inflammation in joints. Gout is a metabolic disease associated with overproduction of uric acid. → painful gouty arthritis.

2. Habit is associated with overeating & Alcohol consumption  
(Historically)

Gout is of two(2) types.

1) primary gout : - It is an inborn error of metabolism due to over production of uric acid. This is mostly related to increase synthesis of purine-nucleotides.

2 The following are imp. metabolic defects (enzyme) are associated with - primary gout -

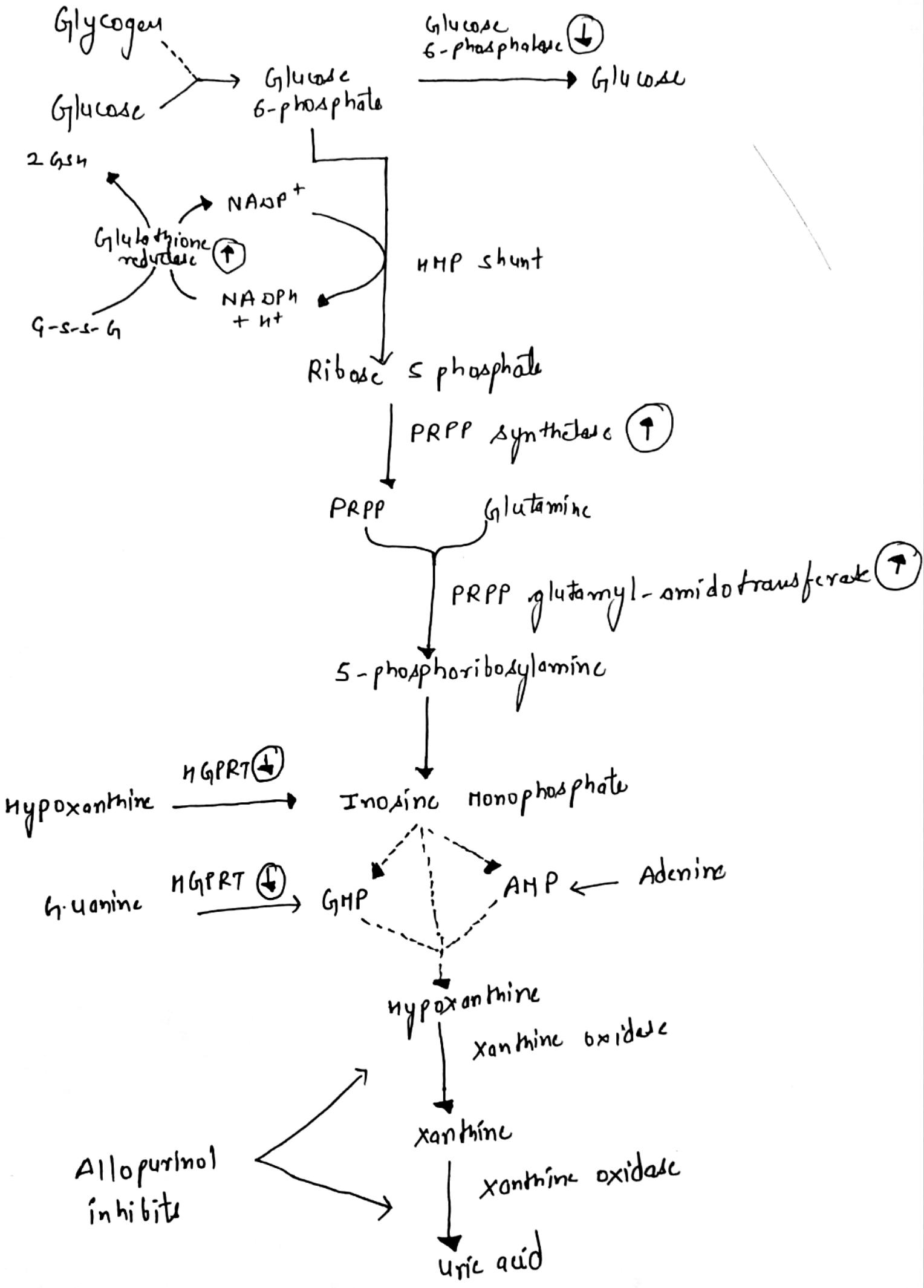
(1) PRPP synthetase : - This is related to increased production of purine

(2) PRPP glutamylamidotransferase → Increased synthesis of purine

(3) HGPRT deficiency : - It is associated with increased synthesis (Lesch-Nyhan syndrome) of purine nucleotide by a two(2) fold mechanism : -

- i) Firstly decreased utilization of purines by salvage pathway
- ii) The defect in salvage pathway leads to decreased level of IMP & GMP

(4) Glucose-6-phosphatase deficiency : - In type-1 glycogen storage disease (Von-Hierkel's) glucose-6-phosphate cannot be converted to glucose due to deficiency of glucose-6-phosphate. This leads to increased utilization of G-6-P by HMP shunt resulting in elevated level of Ribose-5-phosphate & PRPP and ultimately purine-1 over production



### ② Elevation of glutathione reductase

Causes increased glutathione reductase generates more NADPH

Causes increase of ribose-5-phosphate & PRPP synthesis

Among the five(s) enzyme first three are directly involved in purine synthesis. Remaining two(s) indirectly regulate purine ~~met~~ production.

2) secondary gout: - It is due to various disease causing synthesis or decreased excretion of uric acid

Increase uric acid formation is observed in various conditions like gout & increased tissue breakdown (trauma, starvation)

Two disorders associated with impairment in renal function cause accumulation of uric acid which may leads to gout:

### 2) Treatment of Gout: -

The drug of choice for the treatment of primary gout is ~~allopurinol~~  
\* allopurinol \*, Allopurinol is oxidized to alloxanthine (considered as suicide inhibition)  
↳ competitively inhibits the enzyme xanthine oxidase.

Inhibition of xanthine oxidase by allopurinol

↓  
Accumulation of hypoxanthine & xanthine

more soluble & easily excreted  
→ uricosuric drugs → decrease renal reabsorption of uric acid & increase its excretion into urine

## 2 Pseudogout:

~~It is similar~~ The clinical manifestations are similar to gout. But this disorder is caused by the deposition of calcium-pyrophosphate crystals in joint but serum uric acid concentration is normal in pseudogout.

## 3 Lesch-Nyhan-syndrome

It's due to deficiency of HGPRT (Hypoxanthine-guanine phosphoribosyl transferase) an enzyme of purine-salvage pathway

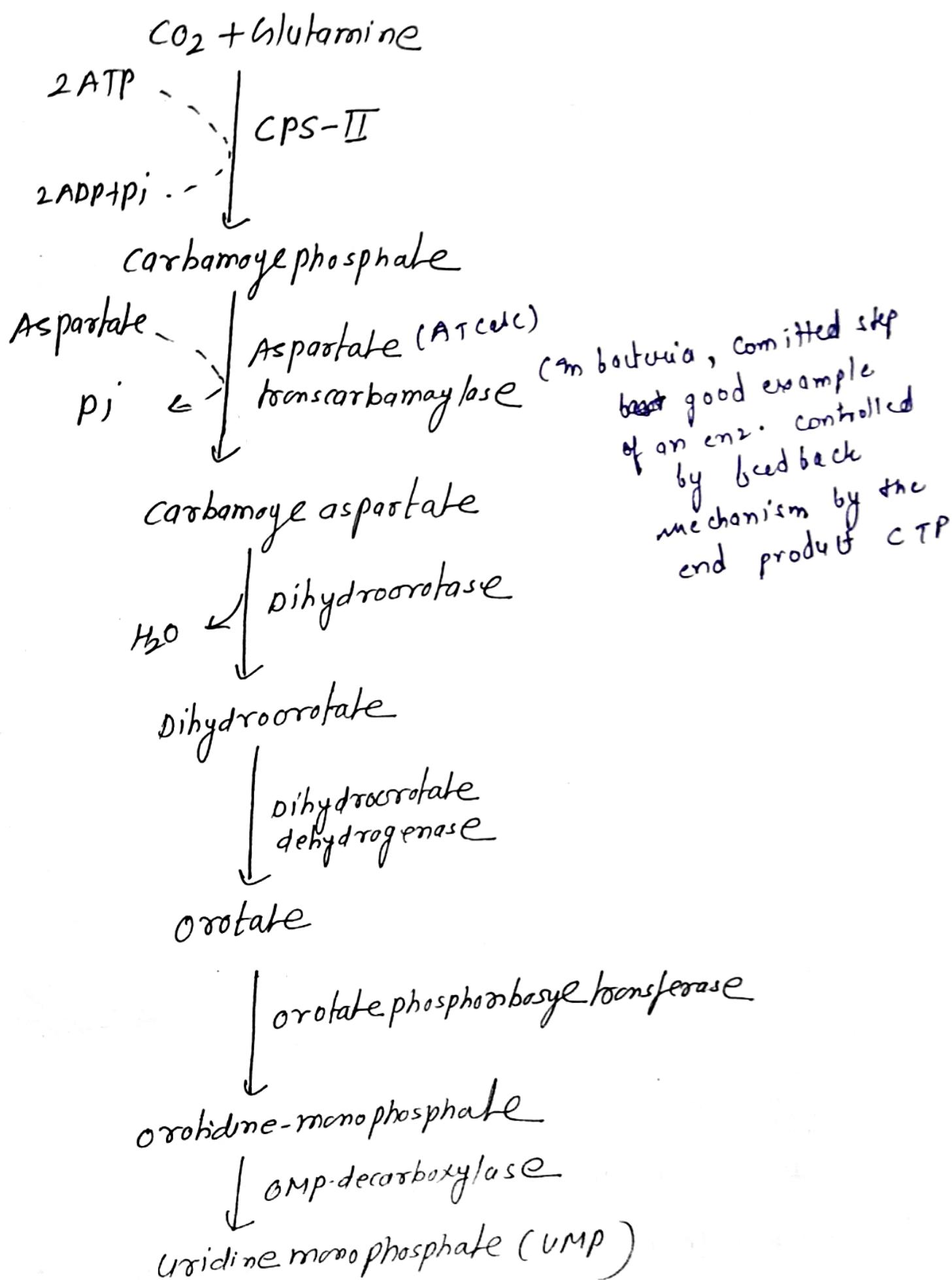
2 It's a sex-linked metabolic disorder. since the structural gene for HGPRT is located on the X-chromosome. It affects only the males & characterized by excessive uric acid production and neurological abnormalities

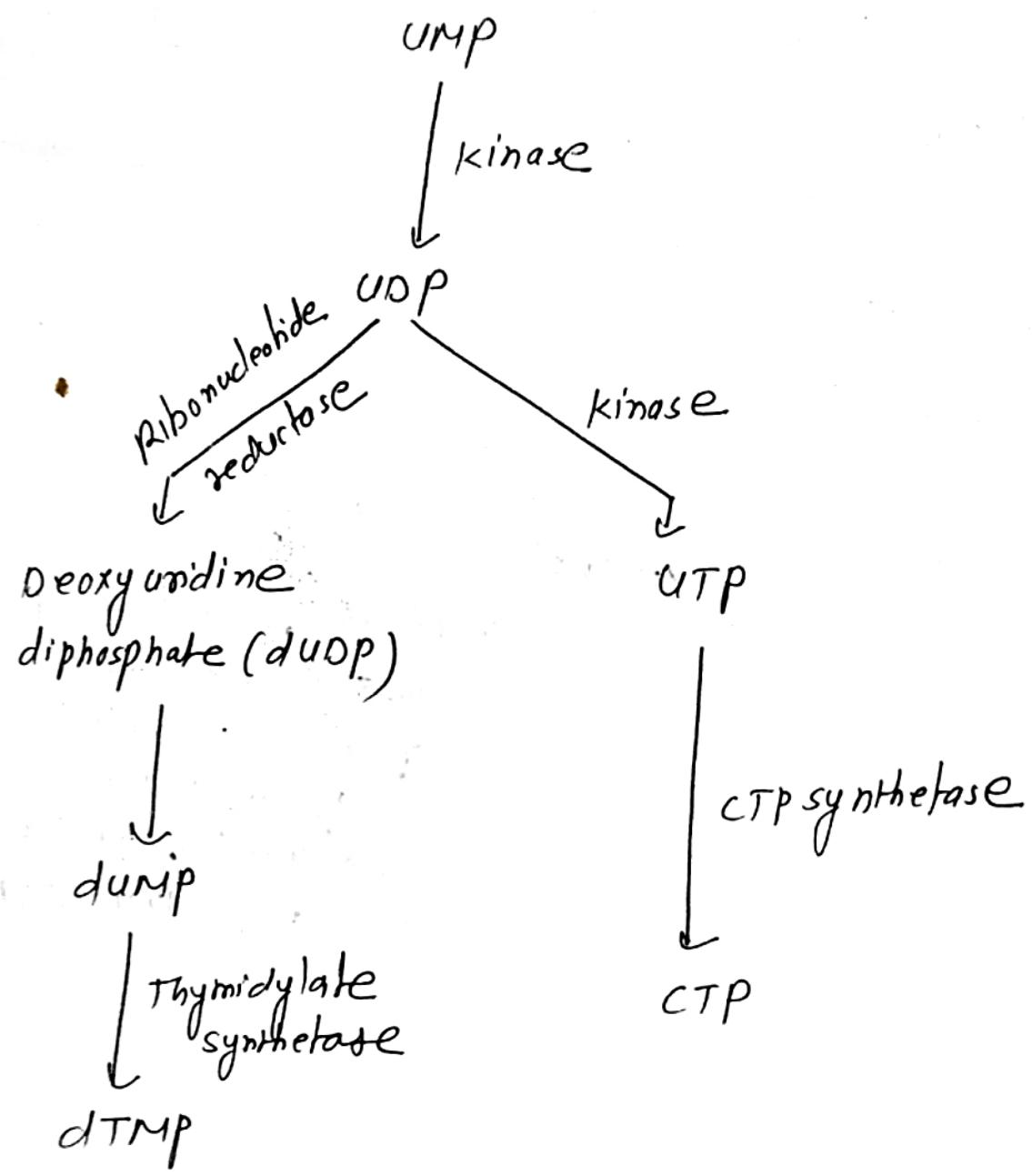
## 2 Immunodeficiency disease associated with purine metabolism

AMP \* (ADA)

It is due to enzyme-defects are adenosine deaminase and purine nucleoside phosphorylase involved in uric acid synthesis.

## Biosynthesis of pyrimidine ribonucleotides





metabolic pathway for the synthesis of pyrimidine nucleotides

## Regulation of pyrimidine synthesis

carbamoyl phosphate synthetase-II (CPS-II) is the regulatory enzyme of pyrimidine synthesis in animals.

### Disorders of pyrimidine metabolism

- ① orotic aciduria → it is due to the deficiency of the enzymes orotate phosphoribosyl transferase & OMP decarboxylase.