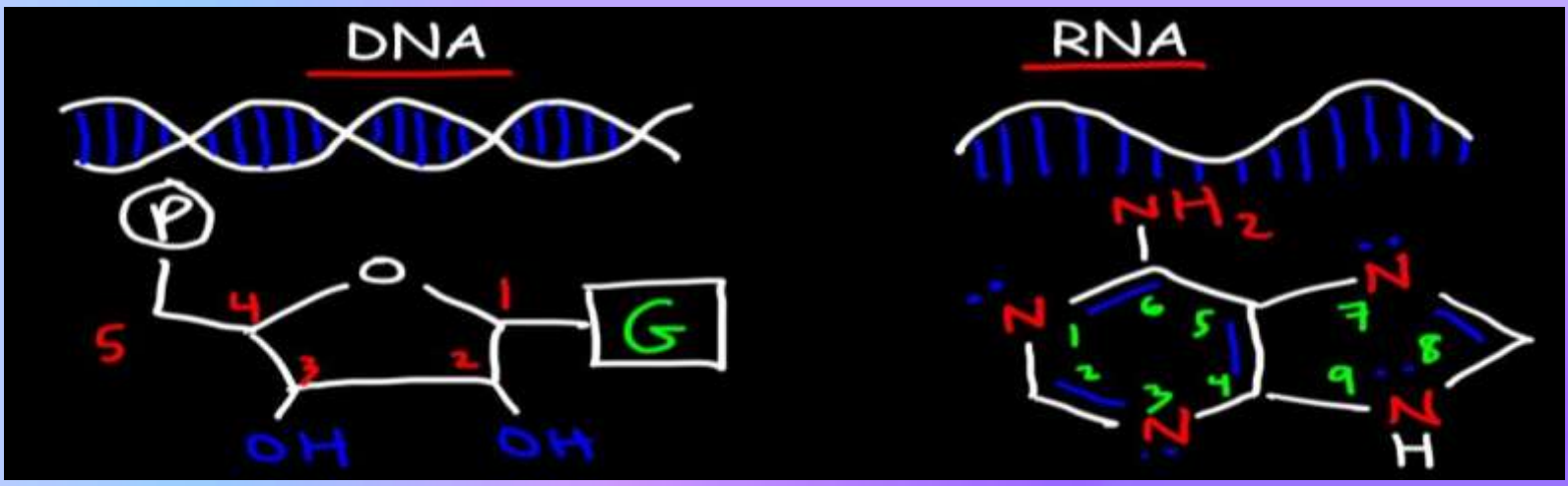
Metabolism of Nucleic acids



MOOHAMMAD SHAHRUKH

M.Sc. Medical Biochemistry

(Ph.D. Scholar)

BIOSYNTHESIS OF PURINE RIBONUCLEOTIDES

- Mammals and most of the lower vertebrates can synthesise purines and pyrimidines and are said to be prototrophic.

Many compounds contribute to the purine ring of the nucleotides .

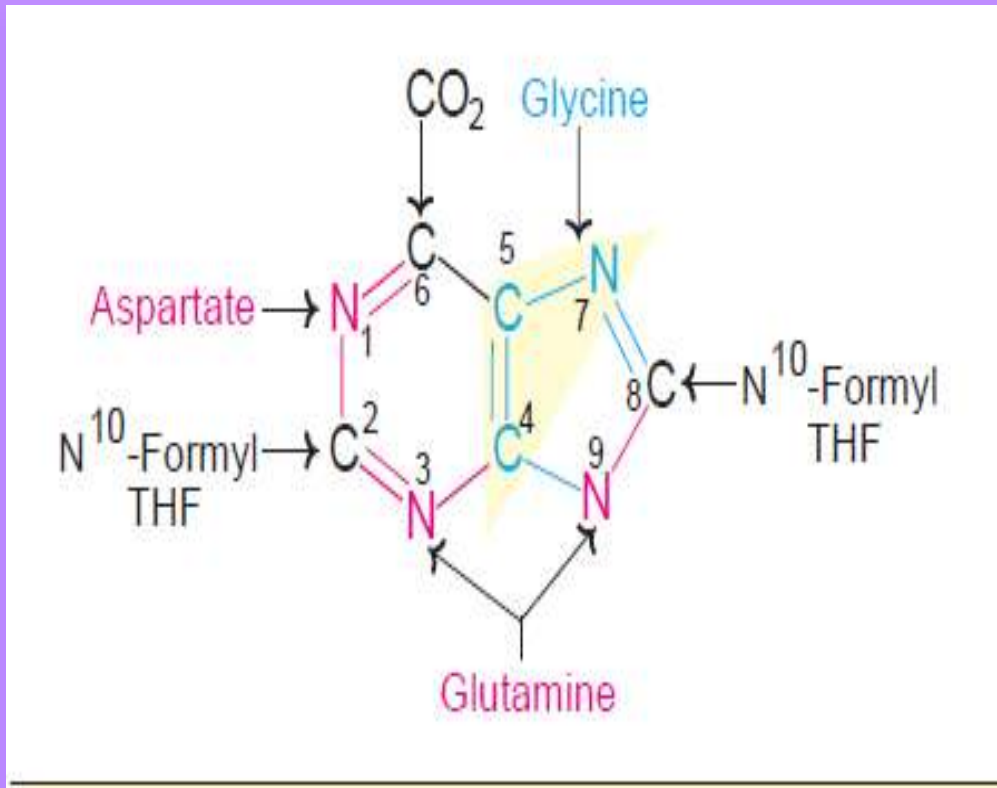
❖ N1 of purine is derived from amino group of aspartate.

❖ C2 and C8 arise from formate of N10- formyl THF.

❖ N3 and N9 are obtained from-amide group of glutamine.

❖ C4, C5 and N7 are contributed by glycine.

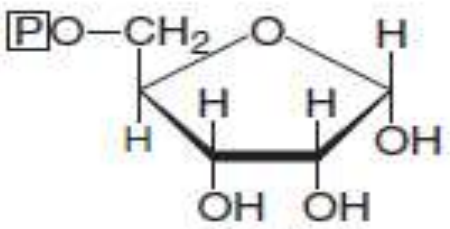
❖ C6 directly comes from CO2.



BIOSYNTHESIS OF PURINE RIBONUCLEOTIDES

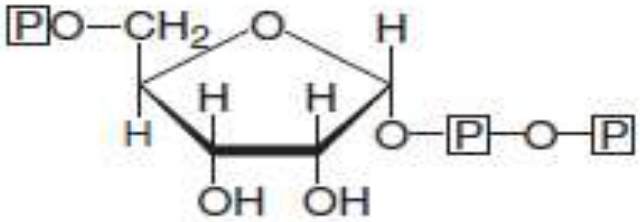
- **The purines are built upon a pre-existing ribose 5-phosphate.**
- **Liver is the** major site for purine nucleotide synthesis.
- Erythrocytes, polymorphonuclear leukocytes and brain cannot produce purines.

Synthesis of Inosine Monophosphate (IMP)



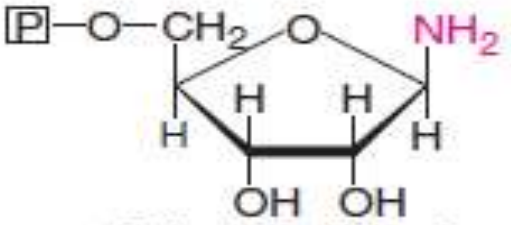
α-D-Ribose-5-phosphate

ATP → AMP — PRPP synthetase

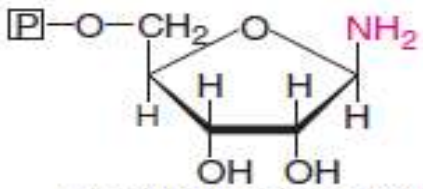


5-Phosphoribosyl α-pyrophosphate

Glutamine + H_2O → Glutamate + PPi — PRPP glutamyl amidotransferase

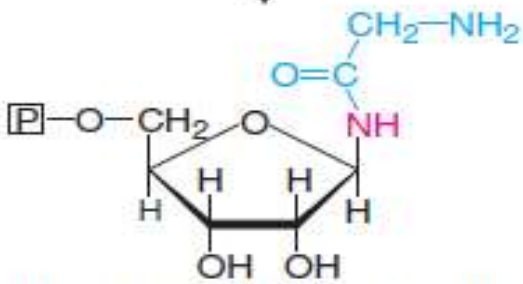


β-5-Phosphoribosylamine



β-5-Phosphoribosylamine

Glycine + ATP → ADP + Pi — Synthetase



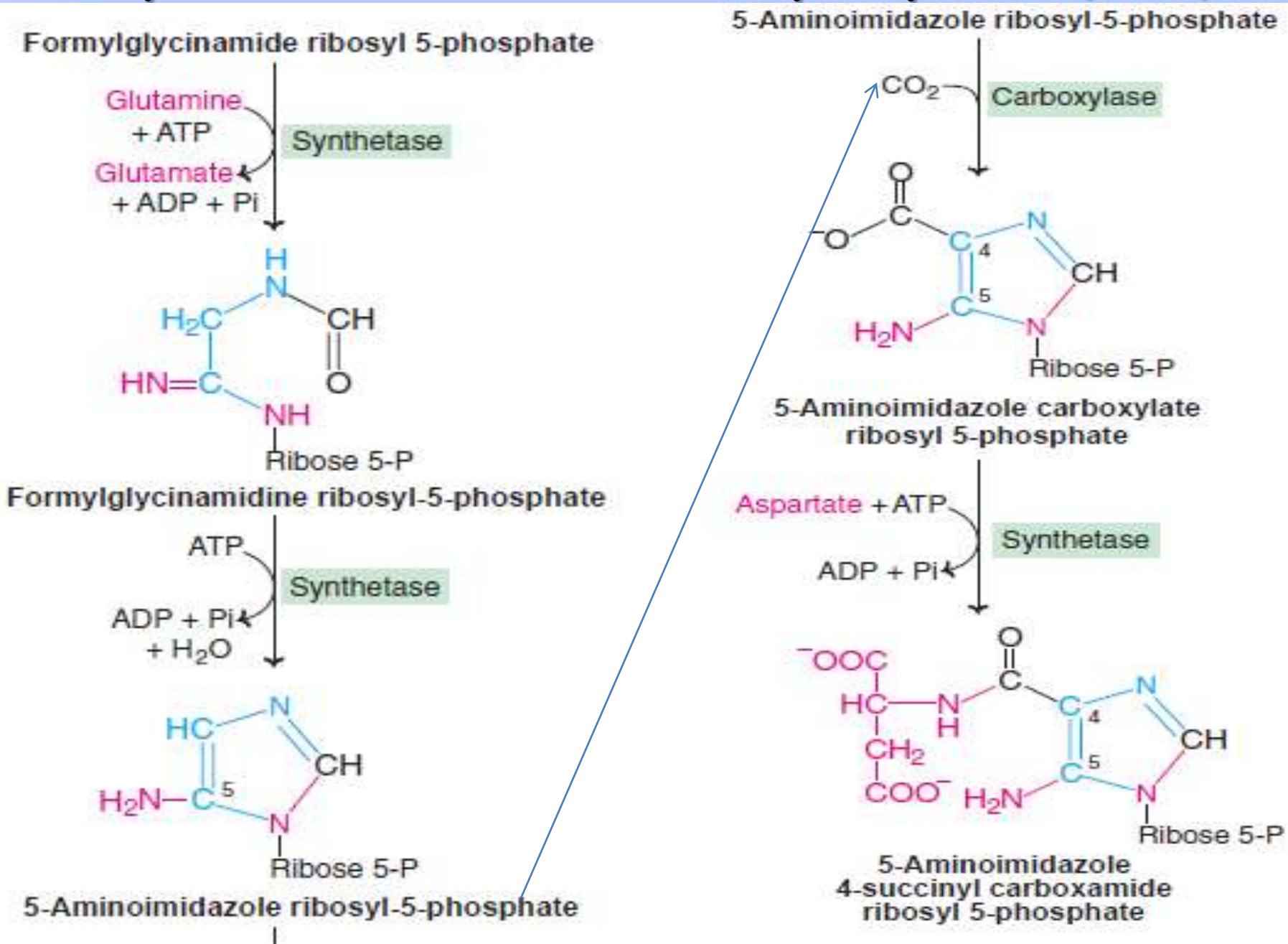
Glycinamide ribosyl 5-phosphate

N^{10}-Formyl THF → THF — Formyltransferase

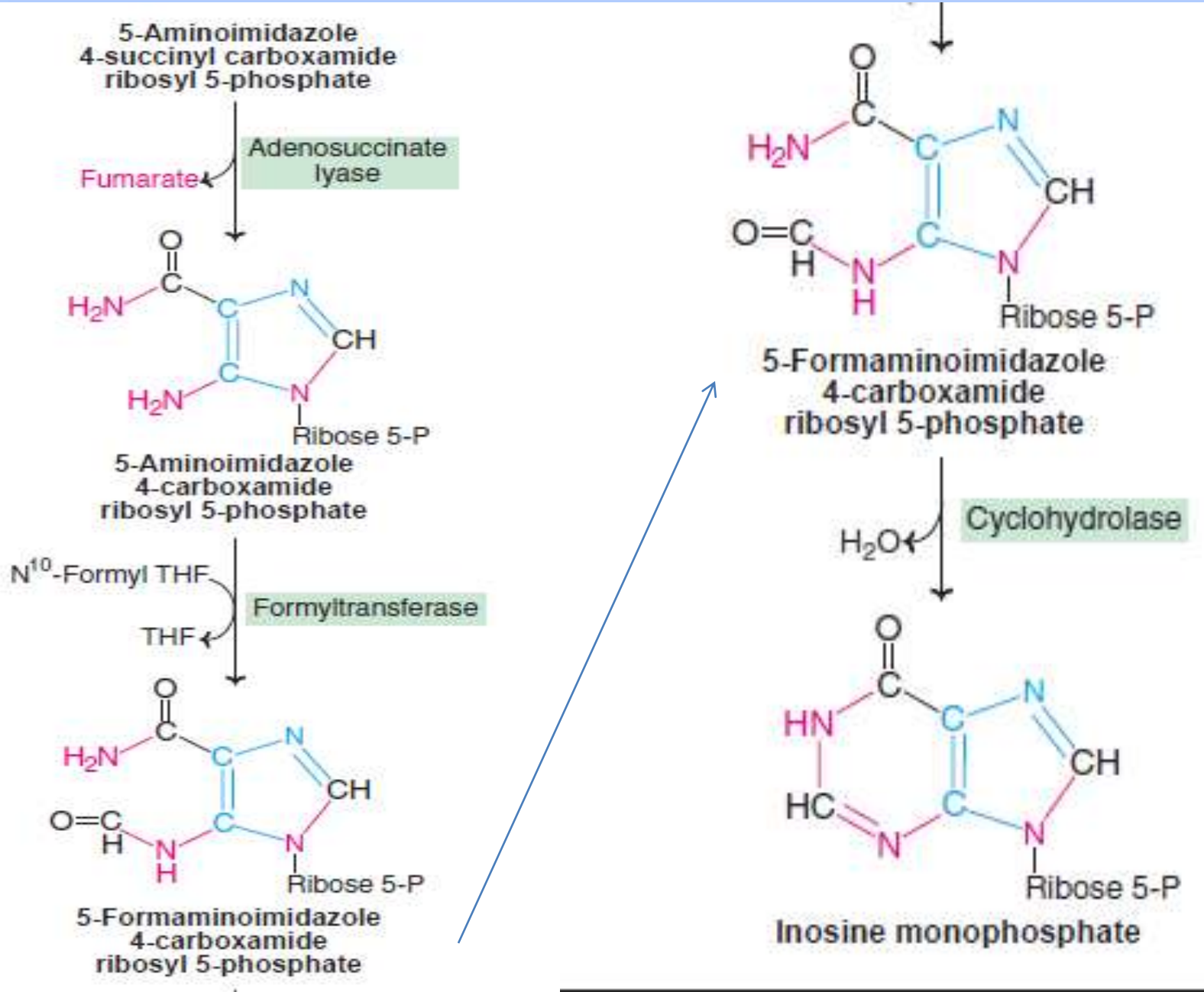
Ribose 5-P

Formylglycinamide ribosyl 5-phosphate

Synthesis of Inosine Monophosphate (IMP)



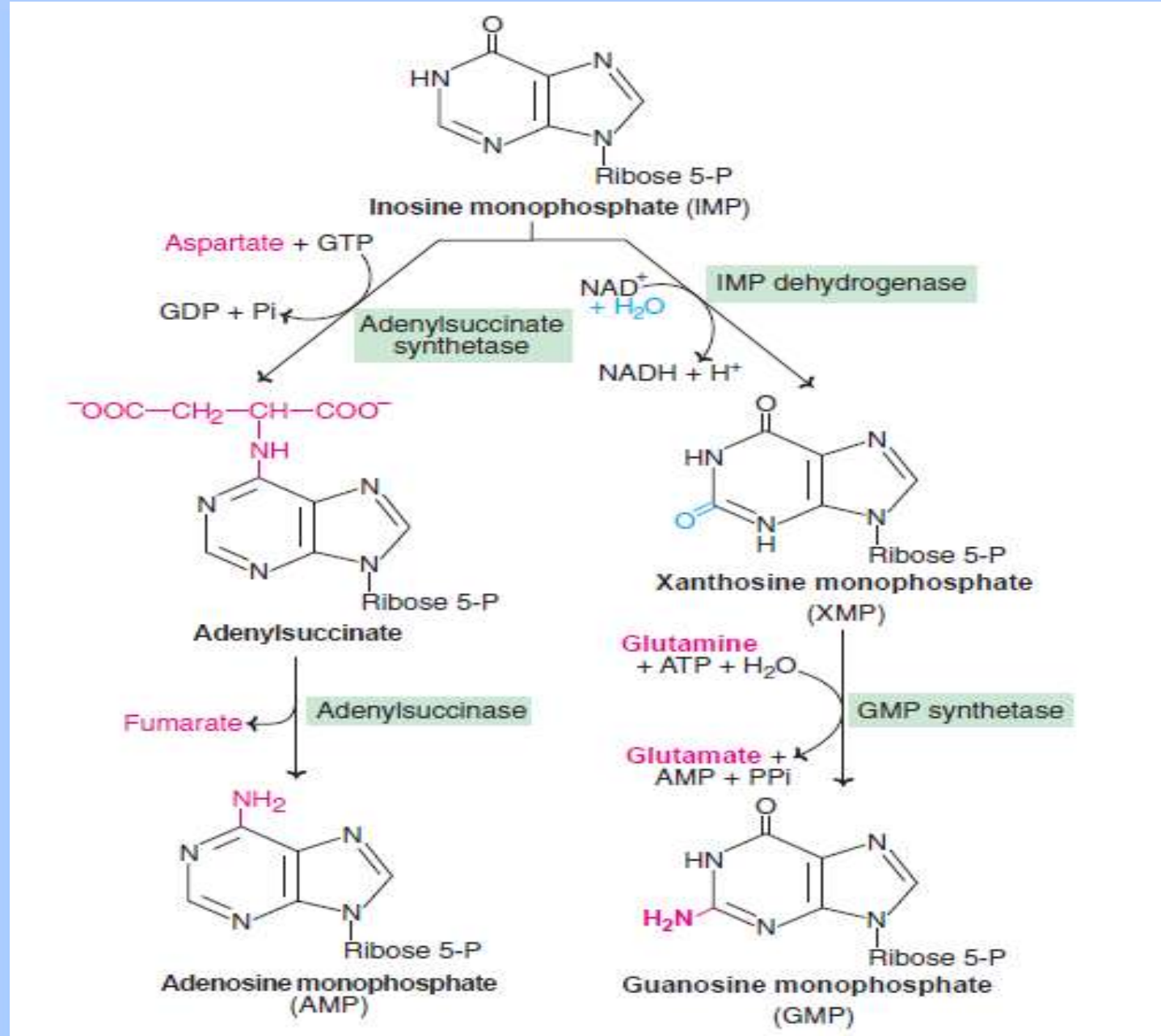
Synthesis of Inosine Monophosphate (IMP)



Inhibitors of purine synthesis

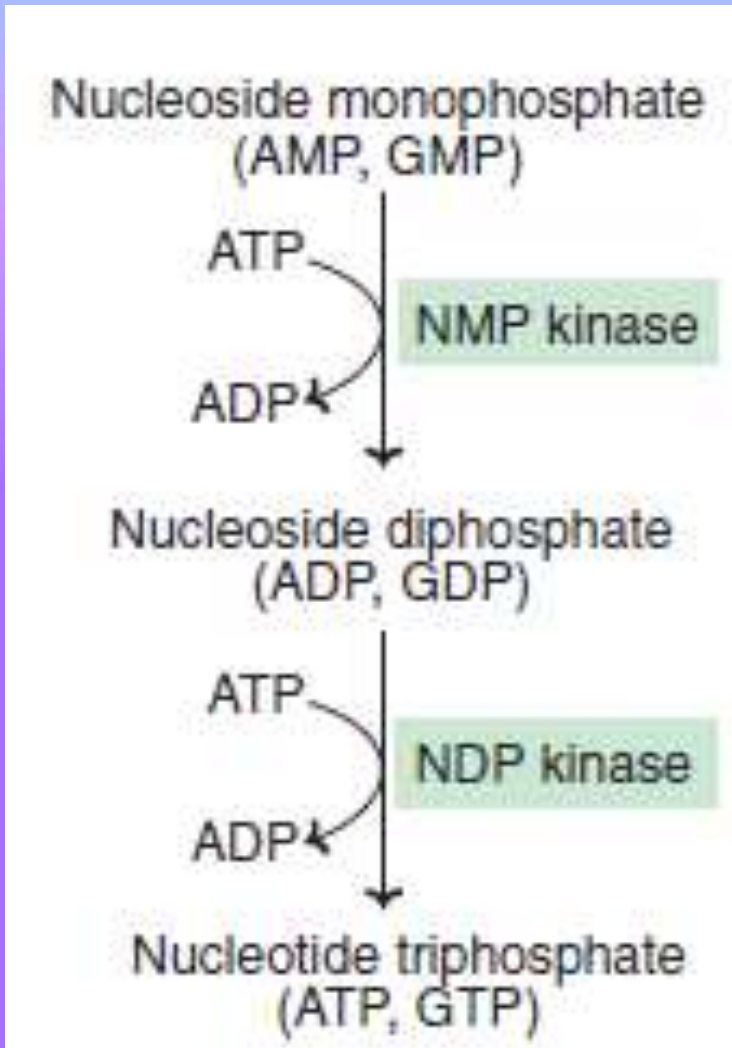
- Folic acid (THF) is essential for the synthesis of purine nucleotides.
- **Sulfonamides are the** structural analogs of paraaminobenzoic acid (PABA).
- These sulfa drugs can be used to **inhibit the synthesis of folic acid by microorganisms.**
- The structural **analogs of folic acid (e.g. methotrexate) are widely used to control cancer.**

Synthesis of AMP and GMP from IMP



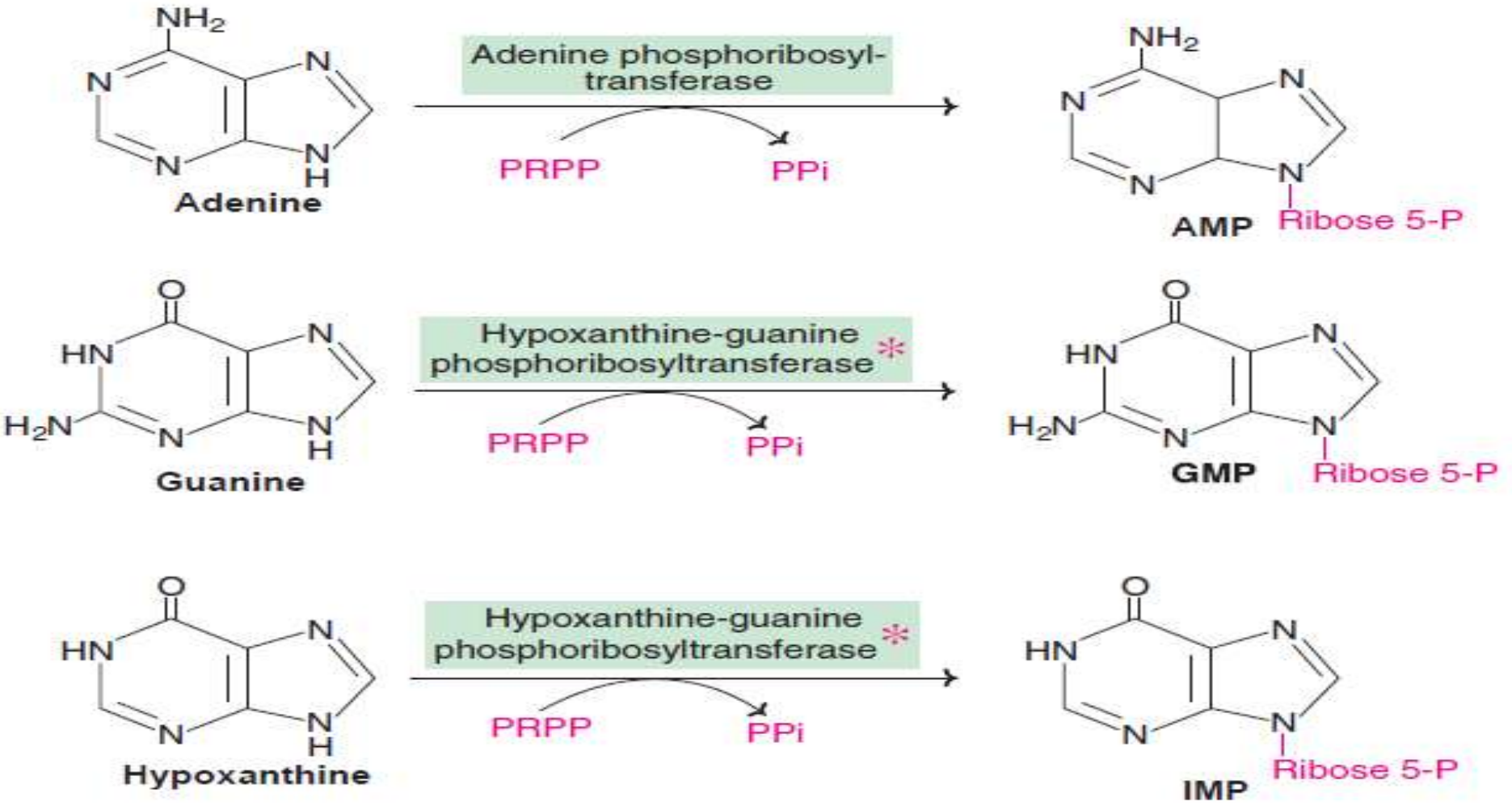
Formation of purine nucleoside diphosphates and triphosphates

- The AMP and GMP have to be converted to the corresponding di- and triphosphates to participate in most of the metabolic reactions.
- This is achieved by the transfer of phosphate group from ATP, catalysed by NMP and NDP kinases.



Salvage pathway for purines

- The **purines** can be **directly converted to the corresponding nucleotides, and this process is known as** 'salvage pathway'.



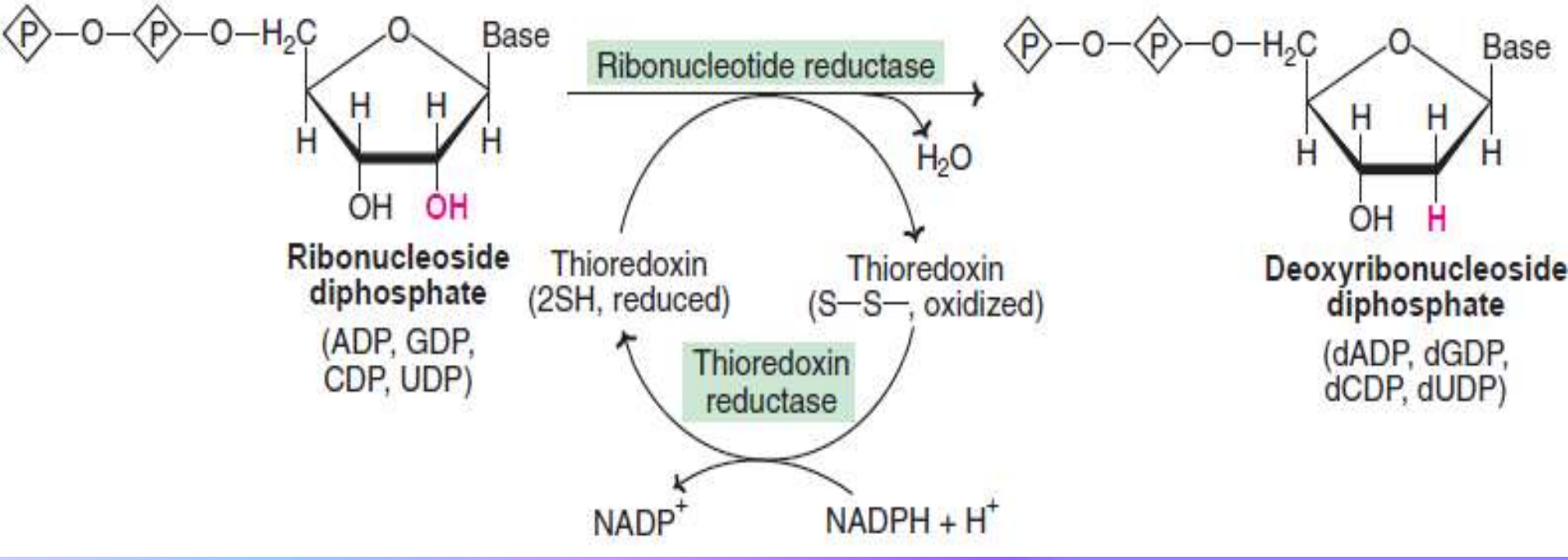
Salvage pathway for purines

- The salvage pathway is particularly important in certain tissues such as erythrocytes and brain where de novo (a new) synthesis of purine nucleotides is not operative.
- A **defect in the enzyme HGPRT causes Lesch- Nyhan syndrome**

Regulation of purine nucleotide biosynthesis

- The intracellular concentration of **PRPP regulates** purine synthesis to a large extent.
- This, in turn, is dependent on the availability of ribose 5-phosphate and the enzyme PRPP synthetase.
- PRPP glutamyl amidotransferase is controlled by a **feedback mechanism by purine nucleotides.**
- AMP inhibits adenylsuccinate synthetase while GMP inhibits IMP dehydrogenase. Thus, AMP and GMP control their respective synthesis from IMP by a feedback mechanism.

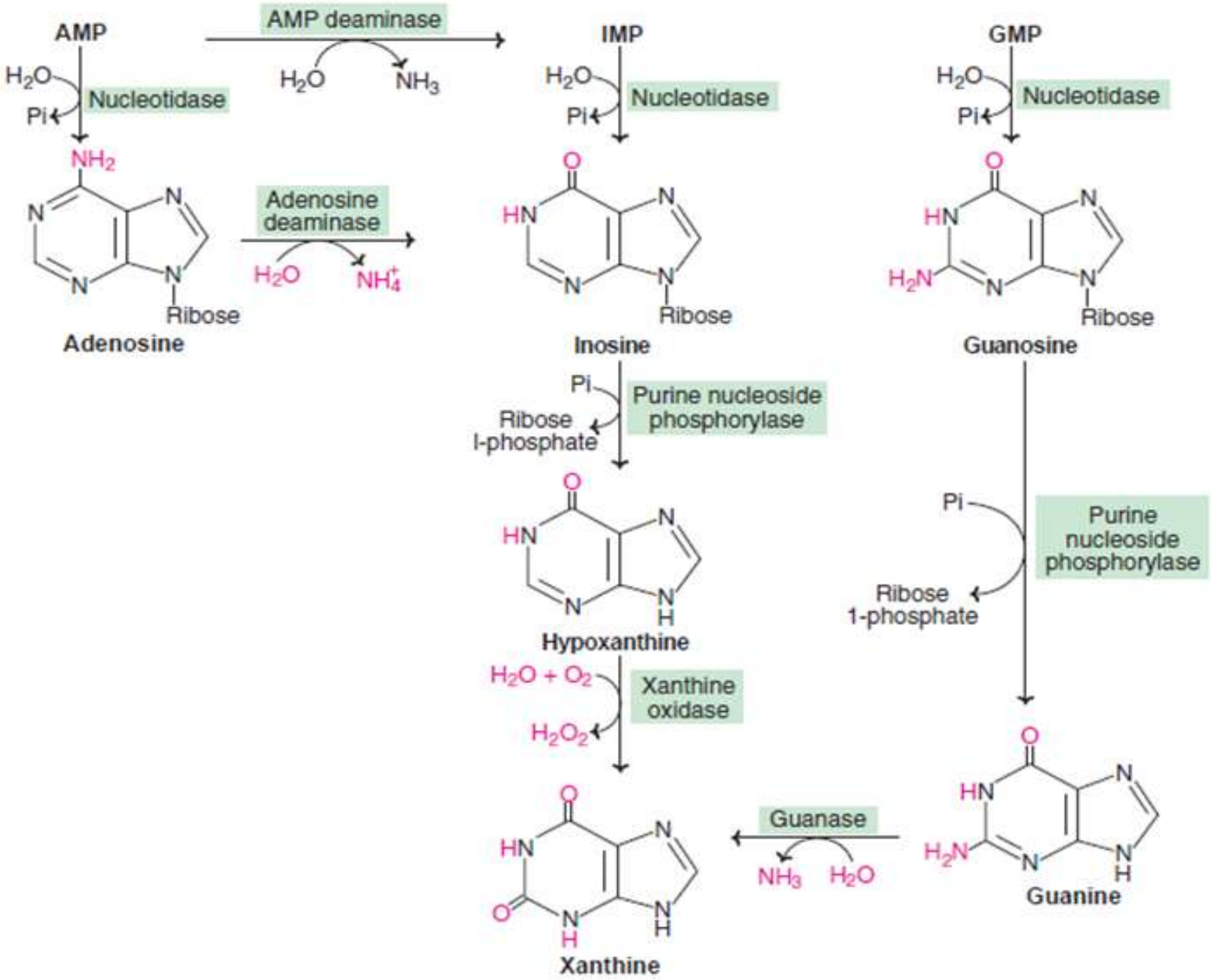
Conversion of ribonucleotides to deoxyribonucleotides

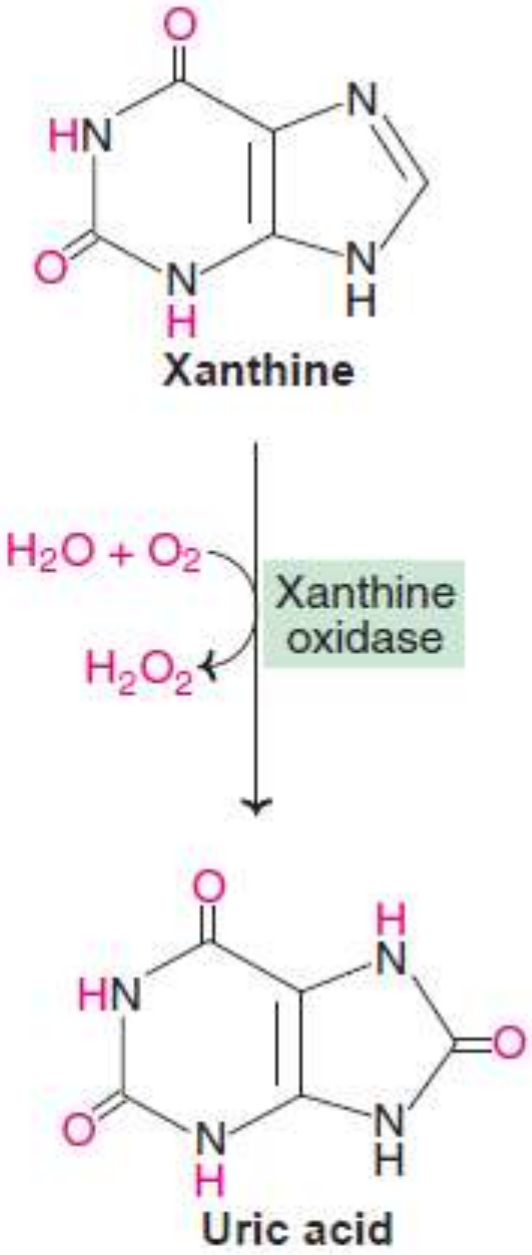


- The drug **hydroxyurea inhibits ribonucleotide** reductase by destroying free radicals required by this enzyme.
- Hydroxyurea is used in the **treatment of cancers such as chronic** myologenous leukemia.

CATABOLISM OF PURINE NUCLEOTIDES

- The excretory **end product of purine metabolism in** humans is **uric acid (2,6,8-trioxypurine).**
- Uric acid can serve as an important **antioxidant by getting itself converted (nonenzymatically)** to allantoin.
- Most animals (other than primates) however, oxidize uric acid by the enzyme uricase to allantoin, where the purine ring is cleaved.
- Allantoin is then converted to allantoic acid and excreted in some fishes.
- Further degradation of allantoic acid may occur to produce urea (in amphibians, most fishes and some molluscs) and, later, to ammonia (in marine invertebrates).


AMP
AMP deaminase
IMP
GMP
H_2O
Pi
Nucleotidase
NH_3
NH_2
Adenosine deaminase
NH_4^+
Ribose
Adenosine
Inosine
Guanosine
Pi
Ribose 1-phosphate
Purine nucleoside phosphorylase
Hypoxanthine
$H_2O + O_2$
H_2O_2
Xanthine oxidase
Guanase
Xanthine
Guanine


O
HN
N
O
N
H
N
H
Xanthine
$H_2O + O_2$
H_2O_2
Xanthine oxidase
O
HN
H
N
O
O
N
H
N
H
Uric acid

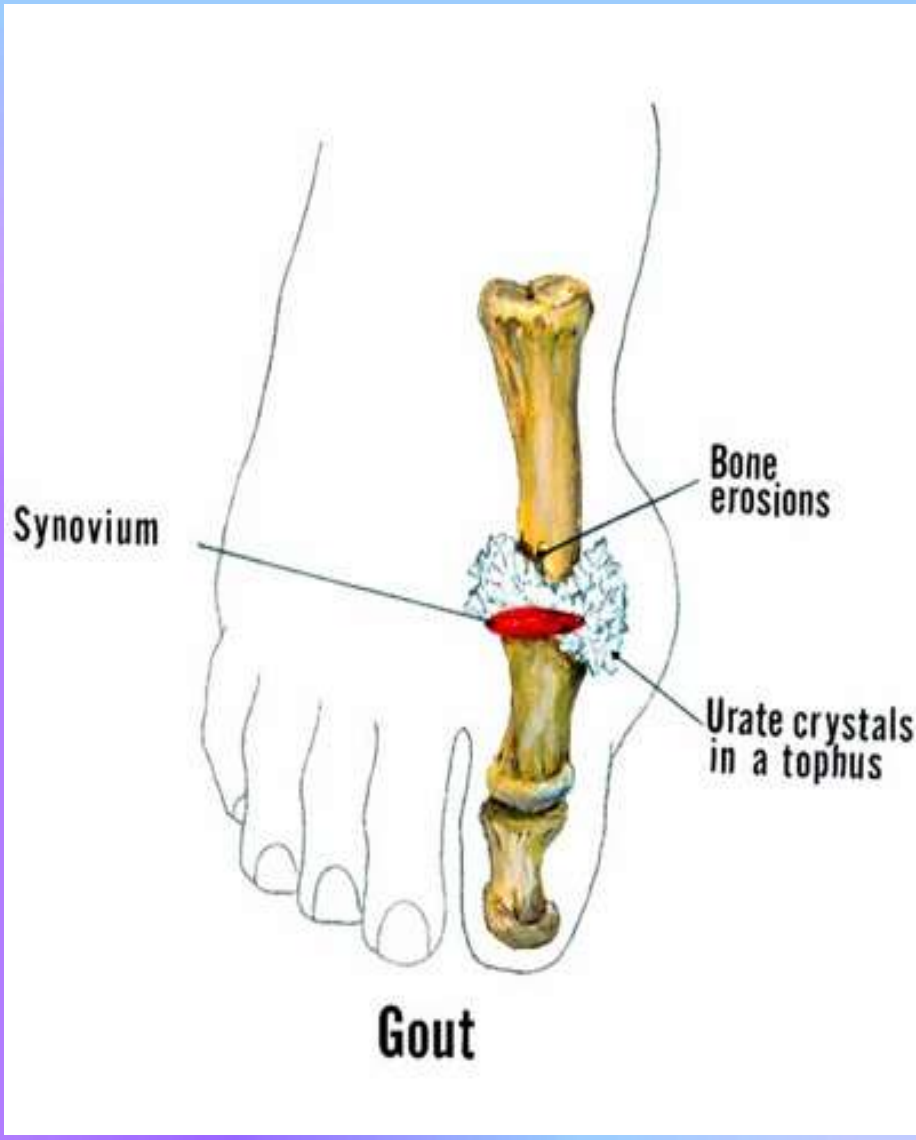
DISORDERS OF PURINE METABOLISM

HYPERURICEMIA AND GOUT

- The normal concentration of uric acid in the serum of adults is in the range of 3-7 mg/dl. In women, it is slightly lower (by about 1 mg) than in men. The daily excretion of uric acid is about 500-700 mg.
- Hyperuricemia refers to an **elevation in the serum uric acid concentration. This is sometimes** associated with increased uric acid excretion (uricosuria).

HYPERURICEMIA AND GOUT

- **Gout** is a metabolic disease associated with overproduction of uric acid.
- In severe hyperuricemia, crystals of sodium urate get deposited in the soft tissues, particularly in the joints, commonly known as **tophi.**
- This causes inflammation in the joints resulting in a painful gouty **arthritis.**
- **Sodium urate and/or uric acid** may also precipitate in kidneys and ureters that results in renal damage and stone formation.



GOUT

Gout is of two types—primary and secondary.

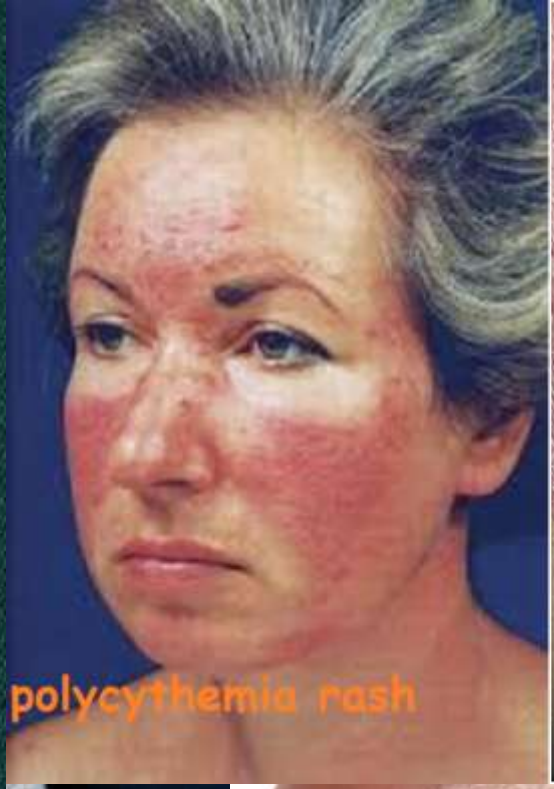
Primary gout : It is an inborn error of metabolism due to **overproduction of uric acid. This is** mostly related to increased synthesis of purine nucleotides. The following are the important metabolic defects (enzymes) associated with primary gout.

- ✓ **PRPP synthetase increased**
- ✓ **PRPP glutamylamidotransferase increased**
- ✓ **HGPRT deficiency**
- ✓ **Glucose 6-phosphatase deficiency.**
- ✓ **Elevation of glutathione reductase.**

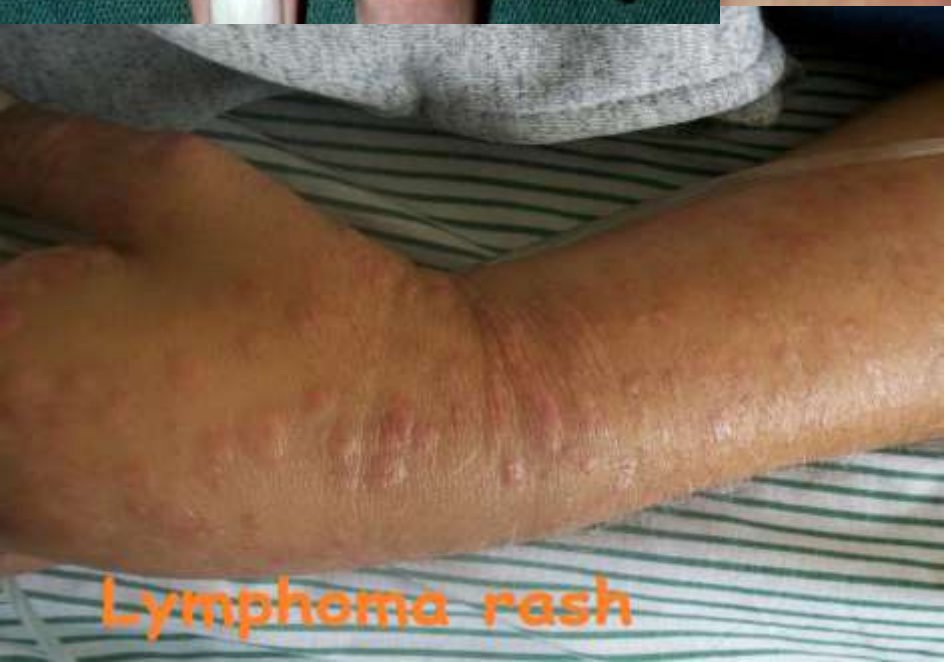
GOUT

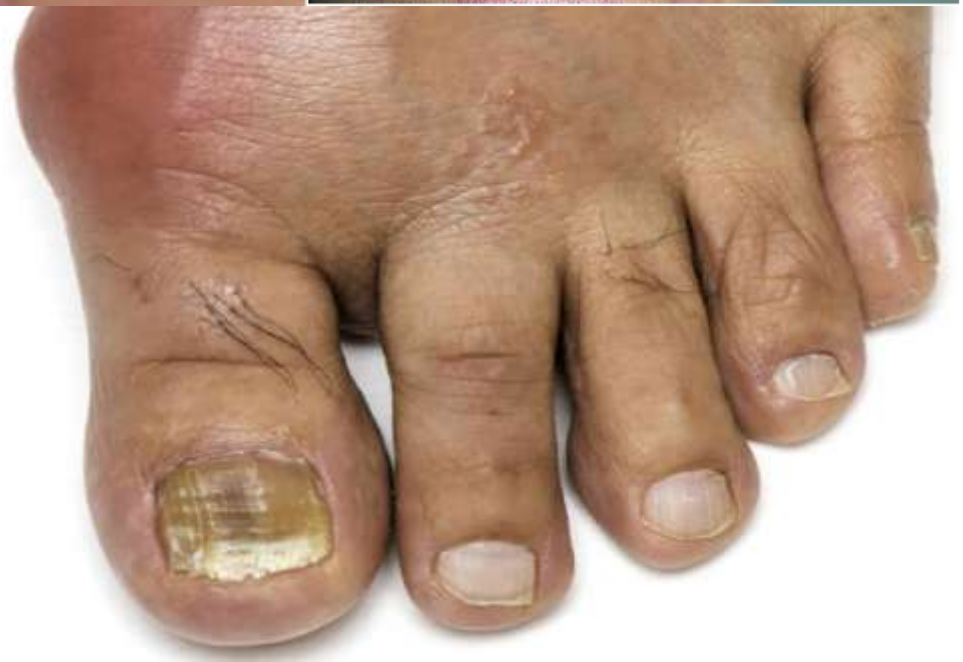
Secondary gout

- Secondary hyperuricemia is due to various diseases causing increased synthesis or decreased excretion of uric acid.
- Increased degradation of nucleic acids (hence more uric acid formation) is observed in various **cancers (leukemias, polycythemia, lymphomas,** etc.) **psoriasis and increased tissue breakdown** (trauma, starvation etc.).
- The disorders associated with impairment in renal function cause accumulation of uric acid which may lead to gout.


polycythemia rash


Psoriasis

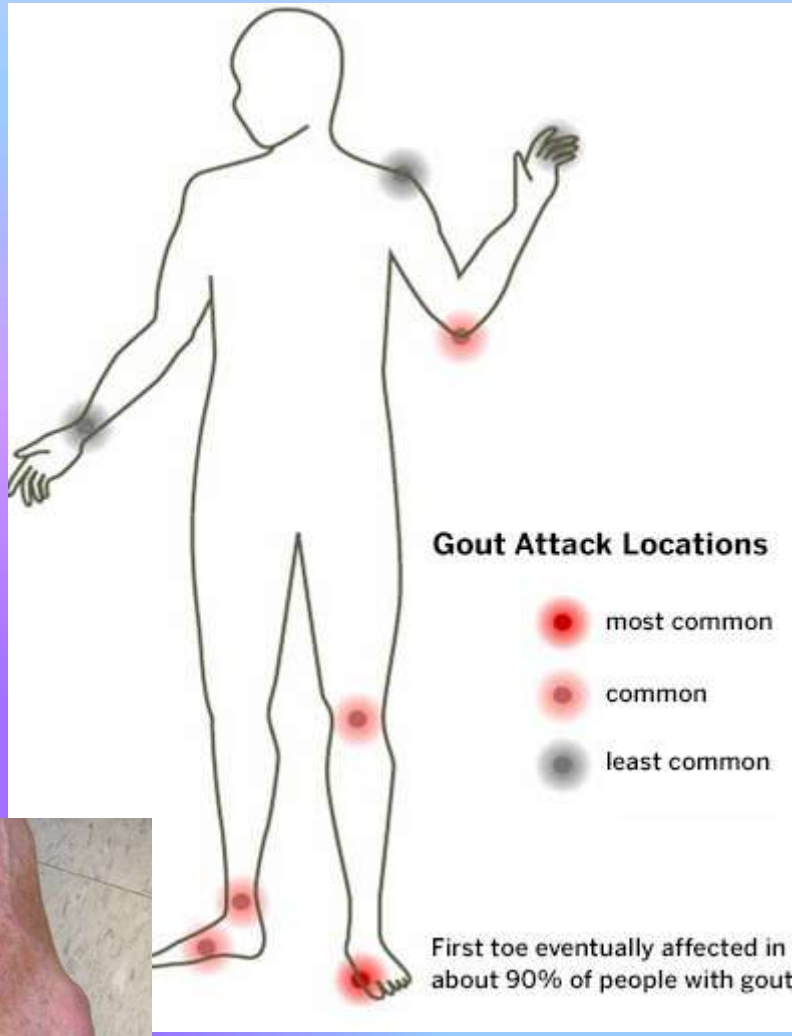

Lymphoma rash



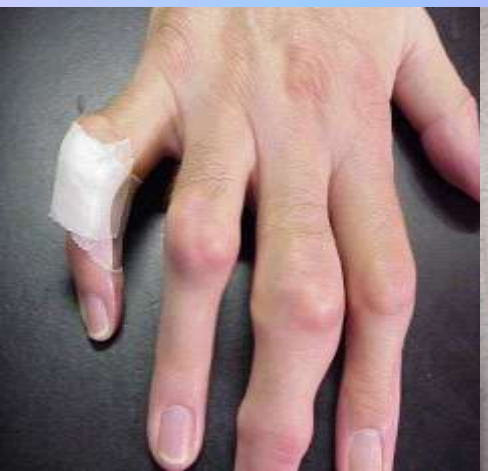
HYPERURICEMIA AND GOUT

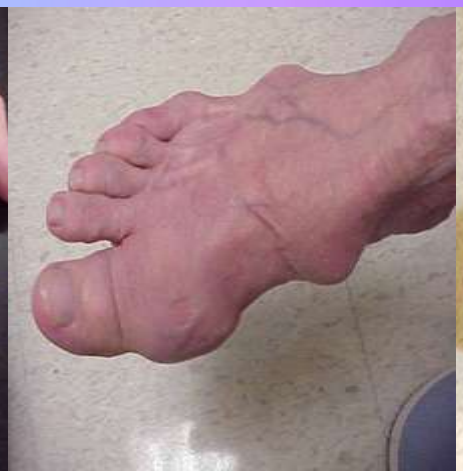
Causes:

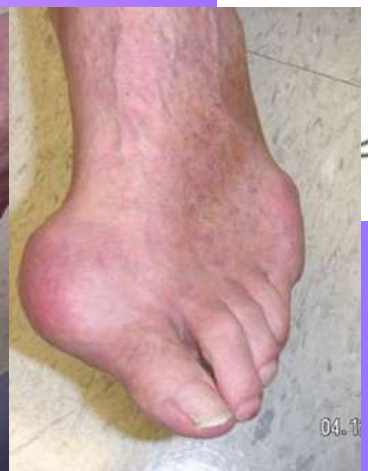
- ✓ high living,
- ✓ over-eating
- ✓ High protein diet (Non-Veg diet).
- ✓ **alcohol consumption**
- ✓ **Lead poisoning.**
- ✓ diet rich is **meat and seafoods**



Symptoms:



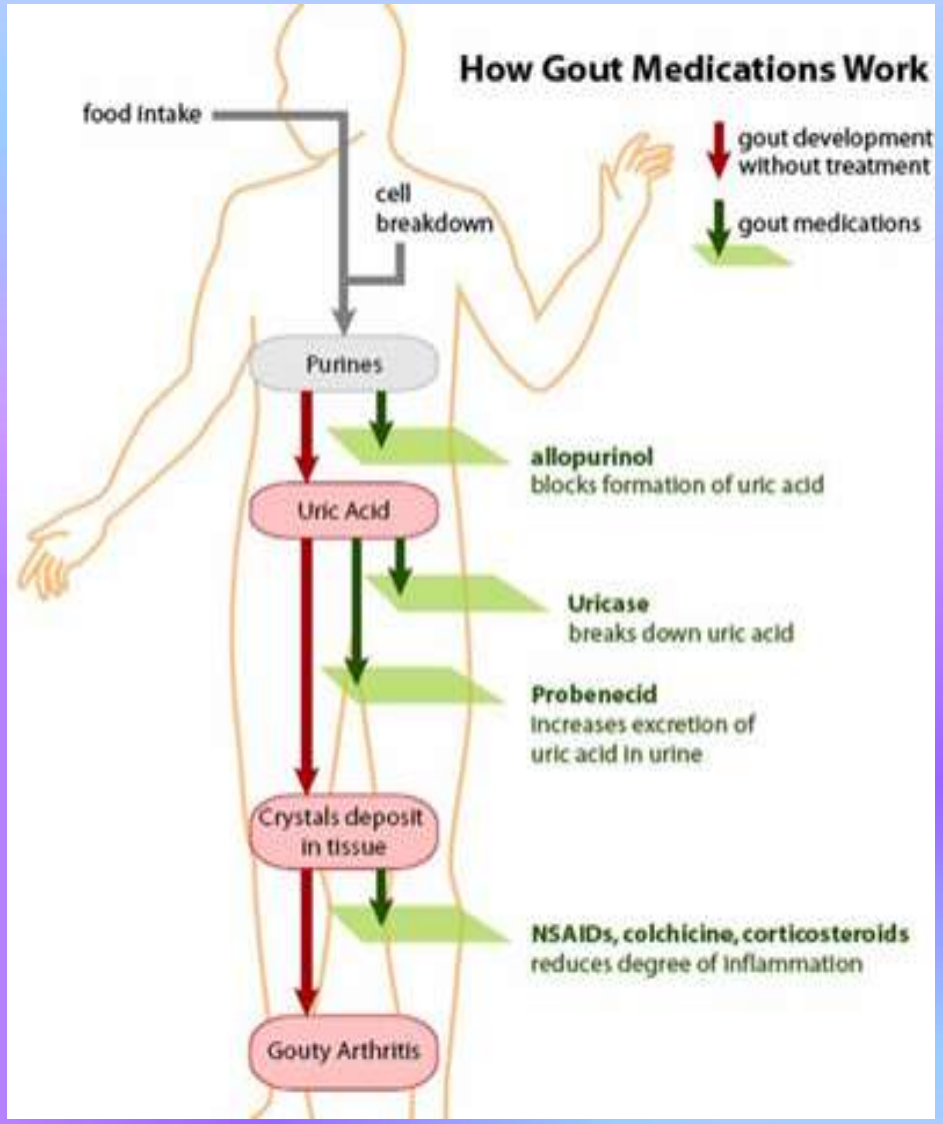




HYPERURICEMIA AND GOUT

Treatment:

- **Non-steroidal anti-inflammatory drugs (NSAIDs):** Naproxen 500mg twice daily, indomethacin 25mg three times daily. Example of COX-2 inhibitor.
- **Allopurinol:** This is a structural analog of hypoxanthine that competitively inhibits the enzyme **xanthine oxidase. Further,** allopurinol is oxidized to alloxanthine by xanthine oxidase Alloxanthine, in turn, is a more effective inhibitor of xanthine oxidase. This type of inhibition is referred to as **suicide inhibition.**



Treatment:

- Inhibition of xanthine oxidase by allopurinol leads to the accumulation of hypoxanthine and xanthine. These two compounds are more soluble than uric acid, hence easily excreted.
- The **anti-inflammatory drug colchicine is used** for the treatment of gouty arthritis. Other antiinflammatory drugs—such as phenylbutazone, indomethacin, oxyphenbutazone, corticosteroids are also useful.

Lesch-Nyhan syndrome

- It was first described in 1964 by Michael Lesch (a medical student) and William L. Nyhan (his teacher).
- This disorder is due to the deficiency of **hypoxanthine-guanine phosphoribosyltransferase** (HGPRT), an enzyme of purine salvage pathway.
- Lesch-Nyhan syndrome is a **sex-linked metabolic disorder since the structural gene for** HGPRT is located on the X-chromosome.
- It **affects only the males and is characterized by** excessive uric acid production (often gouty arthritis), and **neurological abnormalities such as** mental retardation, aggressive behavior, learning disability etc.

Immunodeficiency diseases

- The deficiency of adenosine deaminase (ADA) **causes severe combined immunodeficiency (SCID) involving T-cell and usually B-cell** dysfunction.
- It is explained that ADA deficiency results in the accumulation of dATP which is an inhibitor of ribonucleotide reductase and, therefore, DNA synthesis and cell replication.

Immunodeficiency diseases

- The deficiency of purine nucleotide phosphorylase is associated with impairment of T-cell function but has no effect on B-cell function.
- Uric acid synthesis is decreased and the tissue levels of purine nucleosides and nucleotides are higher.
- It is believed that dGTP inhibits the development of normal T-cells.

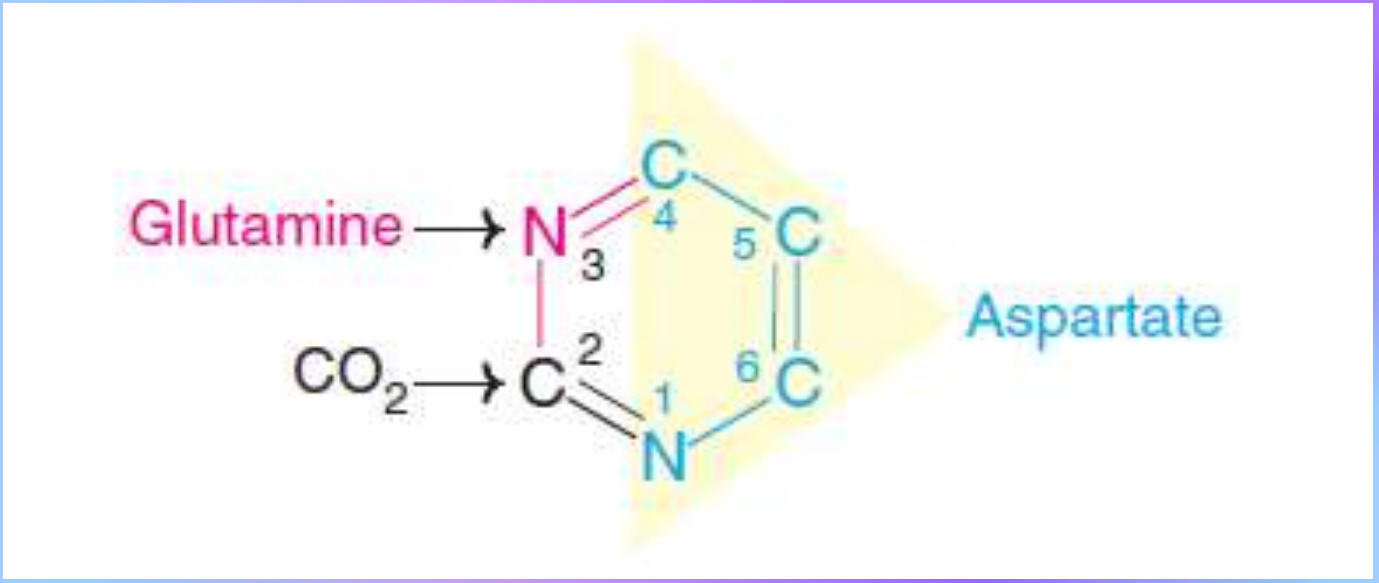
Hypouricemia

- Decreased uric acid levels in the serum (< 2 mg/dl) represent hypouricemia.
- This is mostly associated with a rare genetic defect in the enzyme xanthine oxidase.
- It leads to the increased excretion of xanthine and hypoxanthine.
- Xanthinuria frequently causes the formation of xanthine stones in the urinary tract.

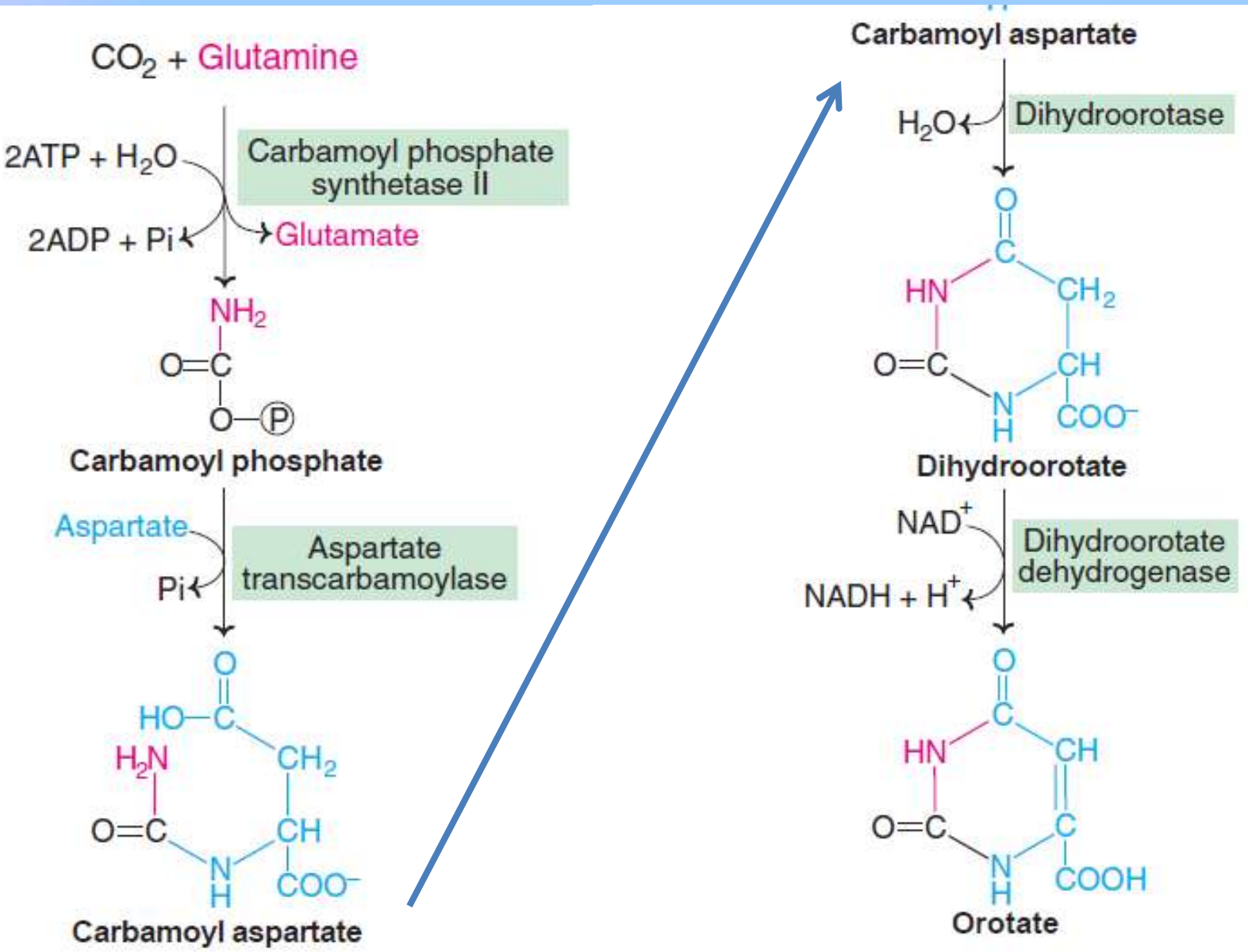

Thank
You

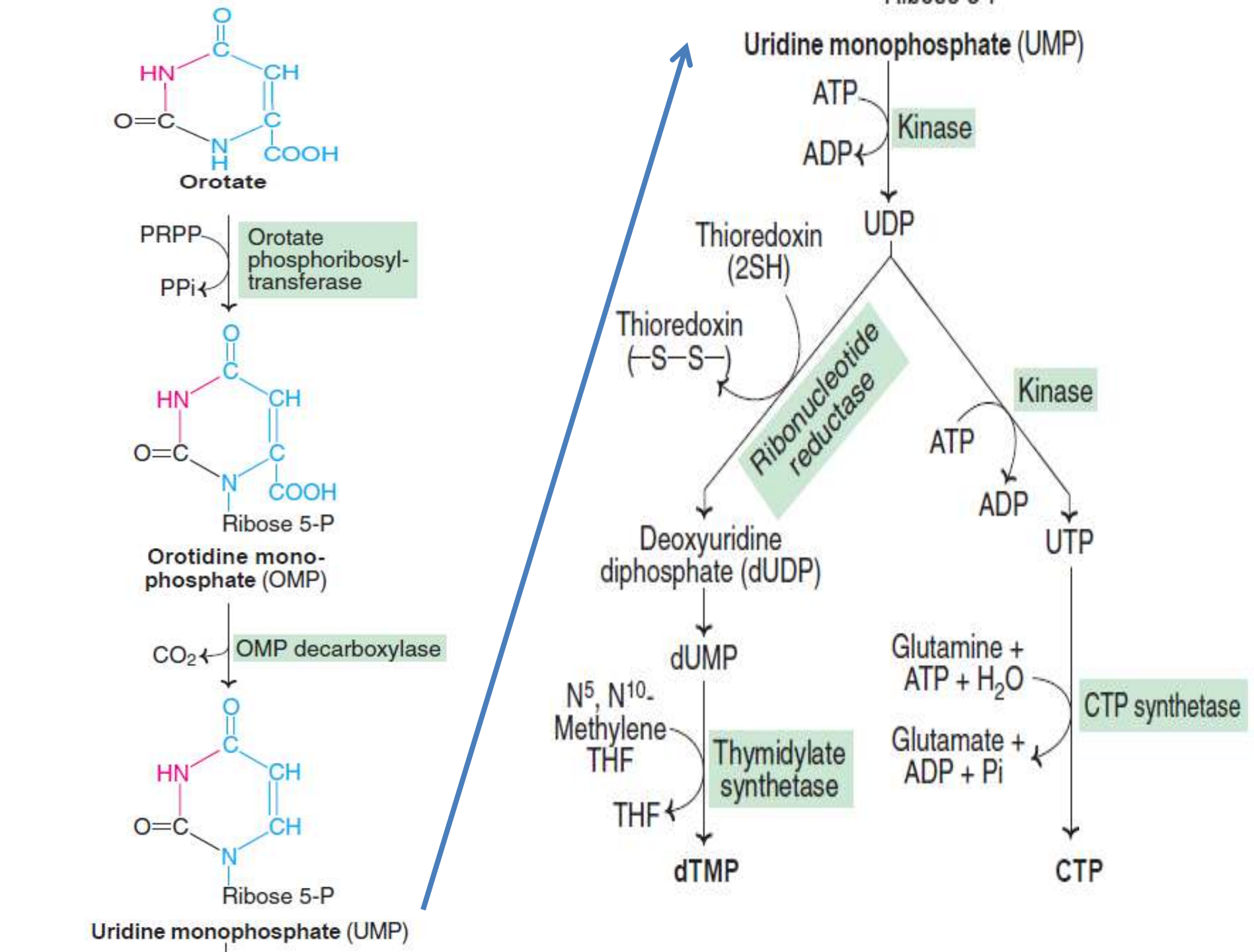
BIOSYNTHESIS OF PYRIMIDINE RIBONUCLEOTIDES

- Aspartate, glutamine (amide group) and CO2 contribute to atoms in the formation of pyrimidine ring



BIOSYNTHESIS OF PYRIMIDINE




Orotate
PRPP
PPi
Orotate phosphoribosyl-transferase
Ribose 5-P
Orotidine mono-phosphate (OMP)
CO_2
OMP decarboxylase
Ribose 5-P
Uridine monophosphate (UMP)
Uridine monophosphate (UMP)
ATP
ADP
Kinase
UDP
Thioredoxin (2SH)
Thioredoxin (–S–S–)
Ribonucleotide reductase
ATP
ADP
Kinase
UTP
Deoxyuridine diphosphate (dUDP)
dUMP
N^5, N^{10}-Methylene THF
THF
Thymidylate synthetase
dTMP
Glutamine + ATP + H_2O
Glutamate + ADP + Pi
CTP synthetase
CTP

Regulation of Pyrimidine Synthesis

- In bacteria, **aspartate transcarbamoylase** (ATCase) catalyses a **committed step in** pyrimidine biosynthesis.
- In certain bacteria, UTP also inhibits ATCase. ATP, however, stimulates ATCase activity.
- **Carbamoyl phosphate synthetase II (CPS II) is** the regulatory enzyme of pyrimidine synthesis in animals.
- It is activated by PRPP and ATP and inhibited by UDP and UTP. OMP decarboxylase, inhibited by UMP and CMP, also controls pyrimidine formation.

Degradation of pyrimidine nucleotides

- The pyrimidine nucleotides undergo similar reactions (dephosphorylation, deamination and cleavage of glycosidic bond) like that of purine nucleotides to liberate the nitrogenous bases- cytosine, uracil and thymine.
- The bases are then degraded to highly soluble products- β-**alanine** and β-**aminoisobutyrate.**
- **These are the amino** acids which undergo transamination and other reactions to finally produce acetyl CoA and succinyl CoA.

Disorders of pyrimidine metabolism

Orotic aciduria

- This is a rare metabolic disorder characterized by the excretion of orotic acid in urine, severe anemia and retarded growth.
- It is due to the deficiency of the enzymes orotate phosphoribosyl transferase and OMP decarboxylase of pyrimidine synthesis.
- Feeding diet rich in uridine and/or cytidine is an effective treatment for orotic aciduria.

Disorders of pyrimidine metabolism

Reye's syndrome

- This is considered as a secondary orotic aciduria.
- It is believed that a defect in ornithine transcarbamoylase (of urea cycle) causes the accumulation of carbamoyl phosphate.
- This is then diverted for the increased synthesis and excretion of orotic acid.


Thank
You