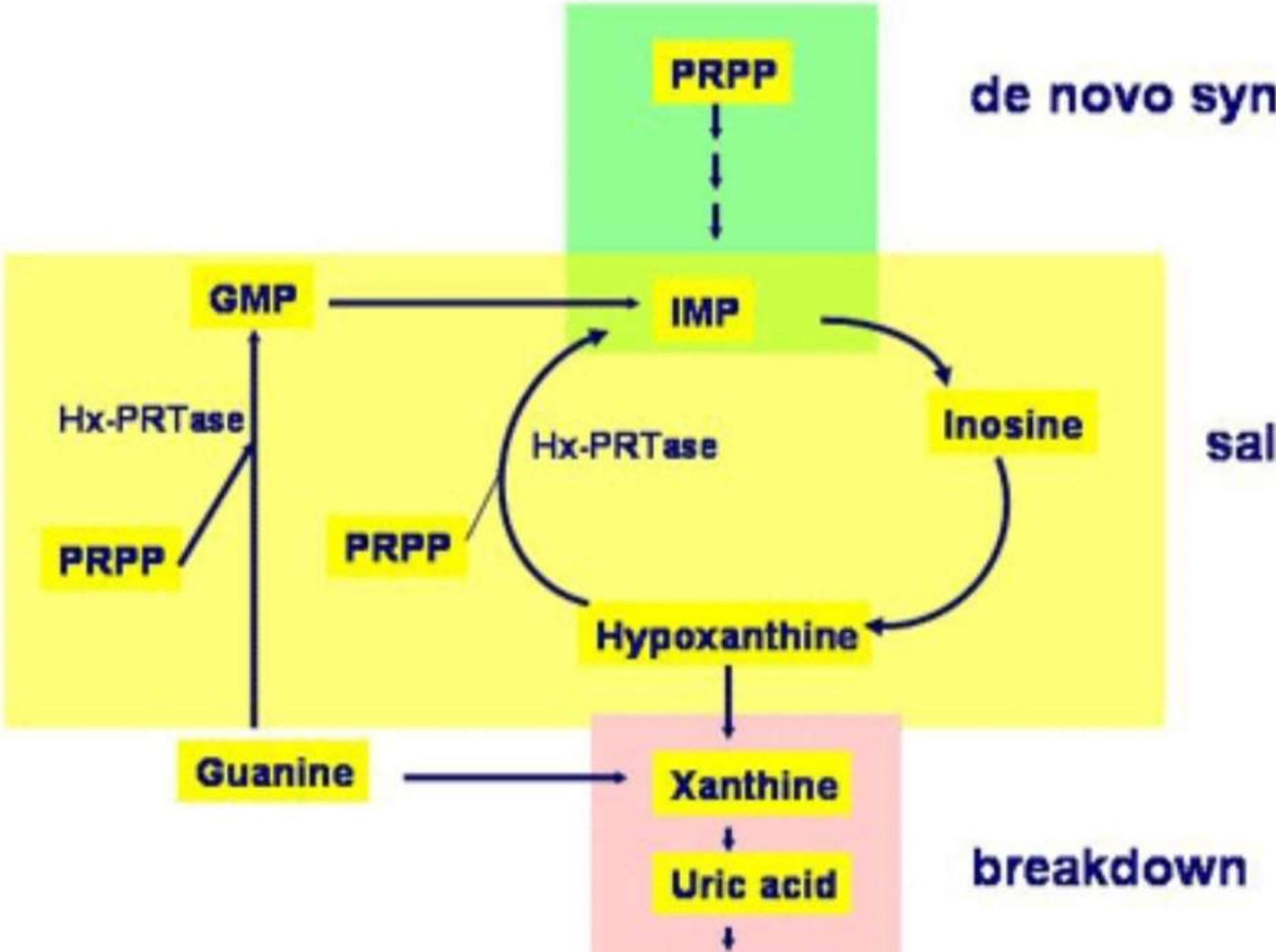
# PURINE METABOLISM II

By Anjum Sayyed
MIMER Medical College,
Talegaon (D)

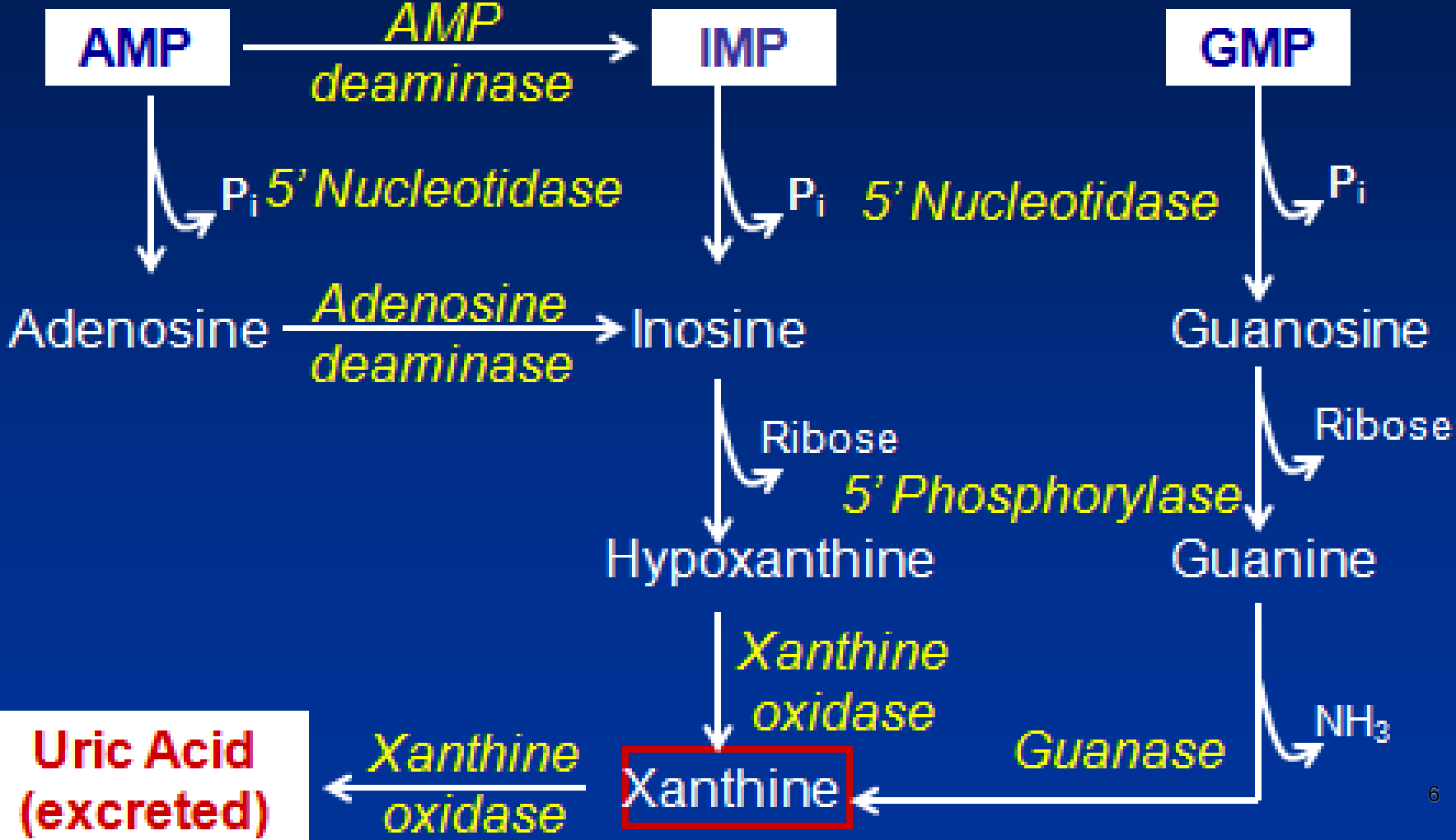
# Overview

- Catabolism of Purine
- Disorders of purine metabolism
- Pyrimidine Metabolism
- Disorders of Pyrimidine

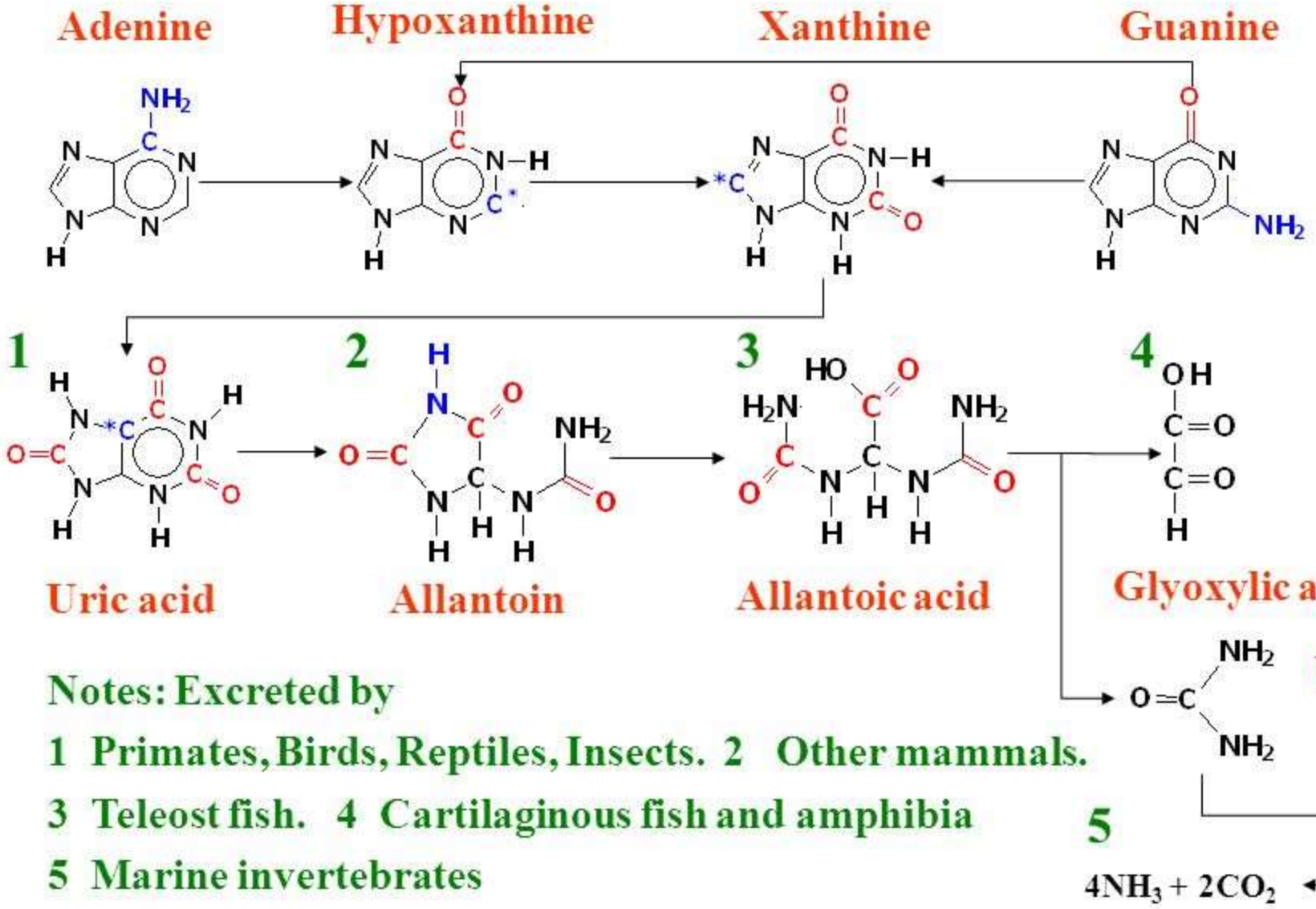

PRPP
de novo syn
GMP
IMP
Hx-PRTase
Inosine
sal
Hx-PRTase
PRPP
PRPP
Hypoxanthine
Guanine
Xanthine
Uric acid
breakdown

# DEGRADATION OF PURINE NUCLEOTIDES

# DEGRADATION OF PURINE NUCLEOTIDES



# The fate of uric acid in the various animals




Notes: Excreted by

1 Primates, Birds, Reptiles, Insects. 2 Other mammals.

3 Teleost fish. 4 Cartilaginous fish and amphibia

5 Marine invertebrates

# Uric acid ?

- The normal blood level of uric acid
- 2-6 mg/dl in females; 3-7 mg/dl in males.
- Nucleic acid content is more in non-vegetarian diet.
- Uric acid is sparingly soluble in water.
- Chemically it is alkaline – donate $H^+$ Uric acid.
- Antioxidant
- Hyperuricemia;
- serum uric acid concentration exceeding 6 mg/dl in female and 7 mg/dl in male
- Uricosuria;
- increased excretion of uric acid in urine.

# DISEASES ASSOCIATED WITH DEFECTS IN PURINE METABOLISM

- HYPERURICEMIA
- GOUT
- LESCH-NYHAN SYNDROME
- KIDNEY STONES
- SEVERE COMBINED IMMUNODEFECIENCY (SCID)

# HYPERURICEMIA

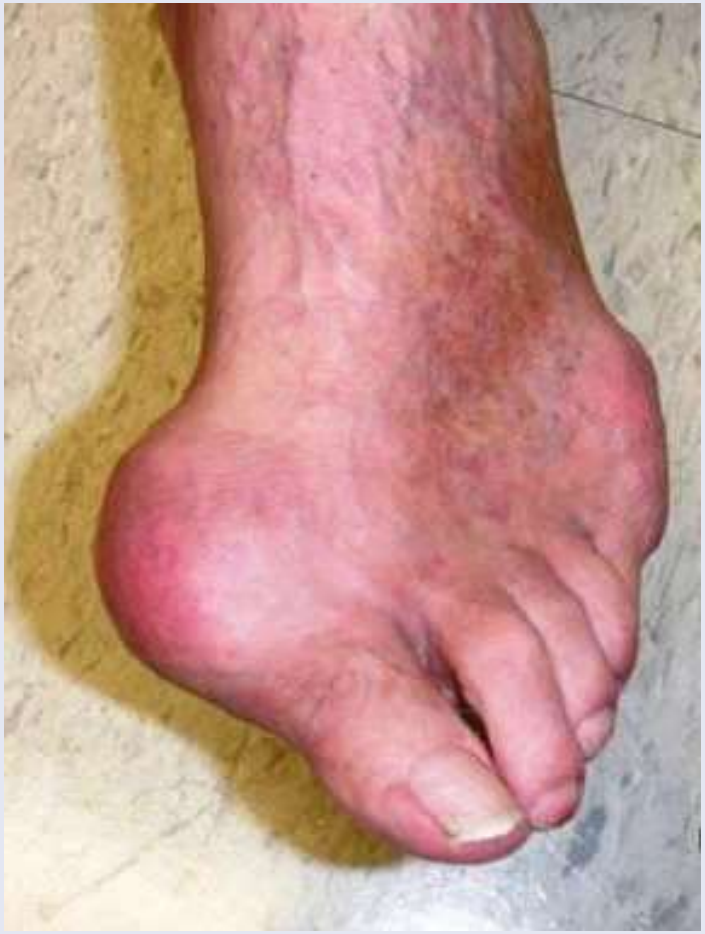
- **Primary Hyperuricemia**: an innate defect in purine metabolism and/or uric acid excretion

- **Secondary Hyperuricemia**: increased availability of purines due to medications/ medical conditions or through diet.

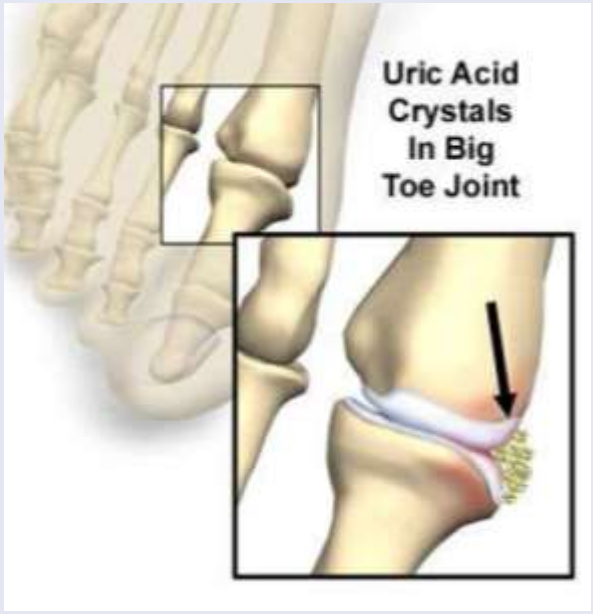
# Hyperuricemia & Gout

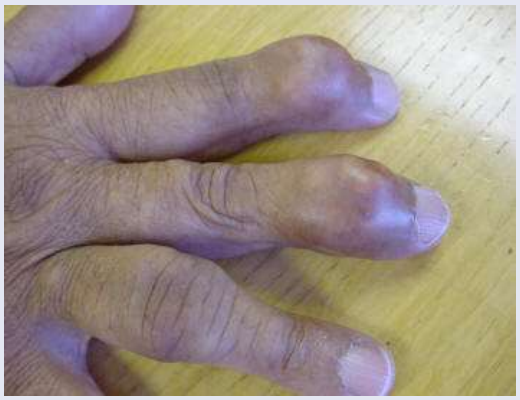
- Gout is the result of uric acid crystallization happens outside the bloodstream, mainly in the synovial fluid or interstitial fluid around the body.
- Conventional definition of hyperuricemia is high concentration of uric acid in the blood, serum but in a broad aspect, hyperuricemia represent high uric levels in the body as a whole.

# GOUT



Gout is caused by precipitation of sodium urate crystals in the joints resulting in inflammation and pain.



# Gout & Clinical Findings of Gout

It is due to accumulation of urate crystals in the synovial fluid resulting in inflammation leading to acute arthritis.

Uric acid is deposited to cause tophi; seen in distal joints of foot

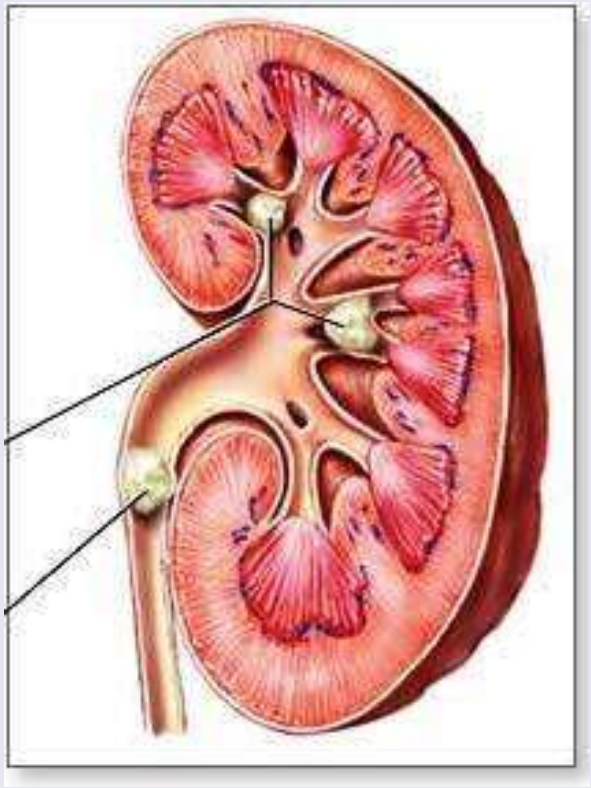
Increased excretion of uric acid may cause deposition of uric acid crystals in the urinary tract; leading to calculi or stone formation with renal damage.

Gouty attacks may be precipitated by high purine diet and increased intake of alcohol.

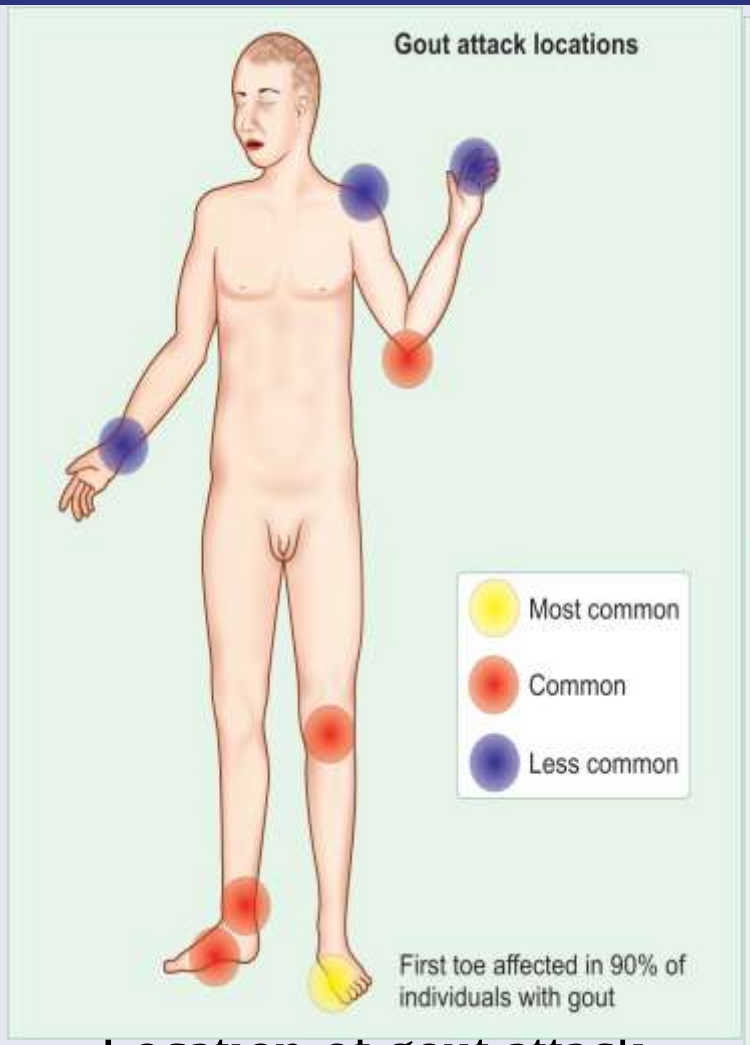
The typical gouty arthritis affects the first metatarsophalangeal joint (big toe), but other joints may also be affected.

The joints are extremely painful. Synovial fluid will show urate crystals.

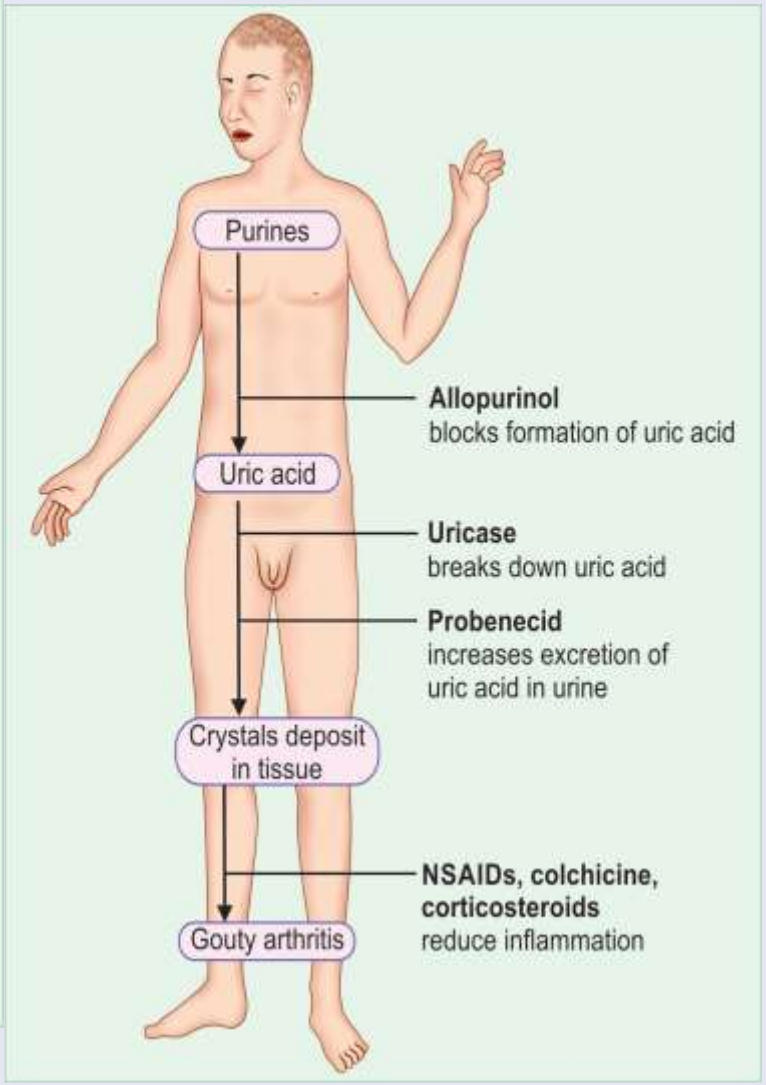
# KIDNEY STONES



When uric acid is present in high concentrations in the blood, it may precipitate as a salt in the kidneys. The salt can form stones, which can in turn cause pain, infection & kidney damage.




Location of gout attack.




Action of medicines in gout. NSAIDs: nonsteroidal anti-inflammatory drugs

# Progression of Hyperuricemia to Gout

Stage 1: Asymptomatic hyperuricemia.

At a serum urate concentration greater than 6.8 mg/dl, urate crystals may start to deposit in the joints. No evidence that treatment is required.

Stages 2 : Acute gout. If sufficient urate deposits develop around joints, and if the local environment or some trauma triggers the release of crystals into the joint space, an inflammatory response occurs. These flares can be self-resolving but are likely to recur.

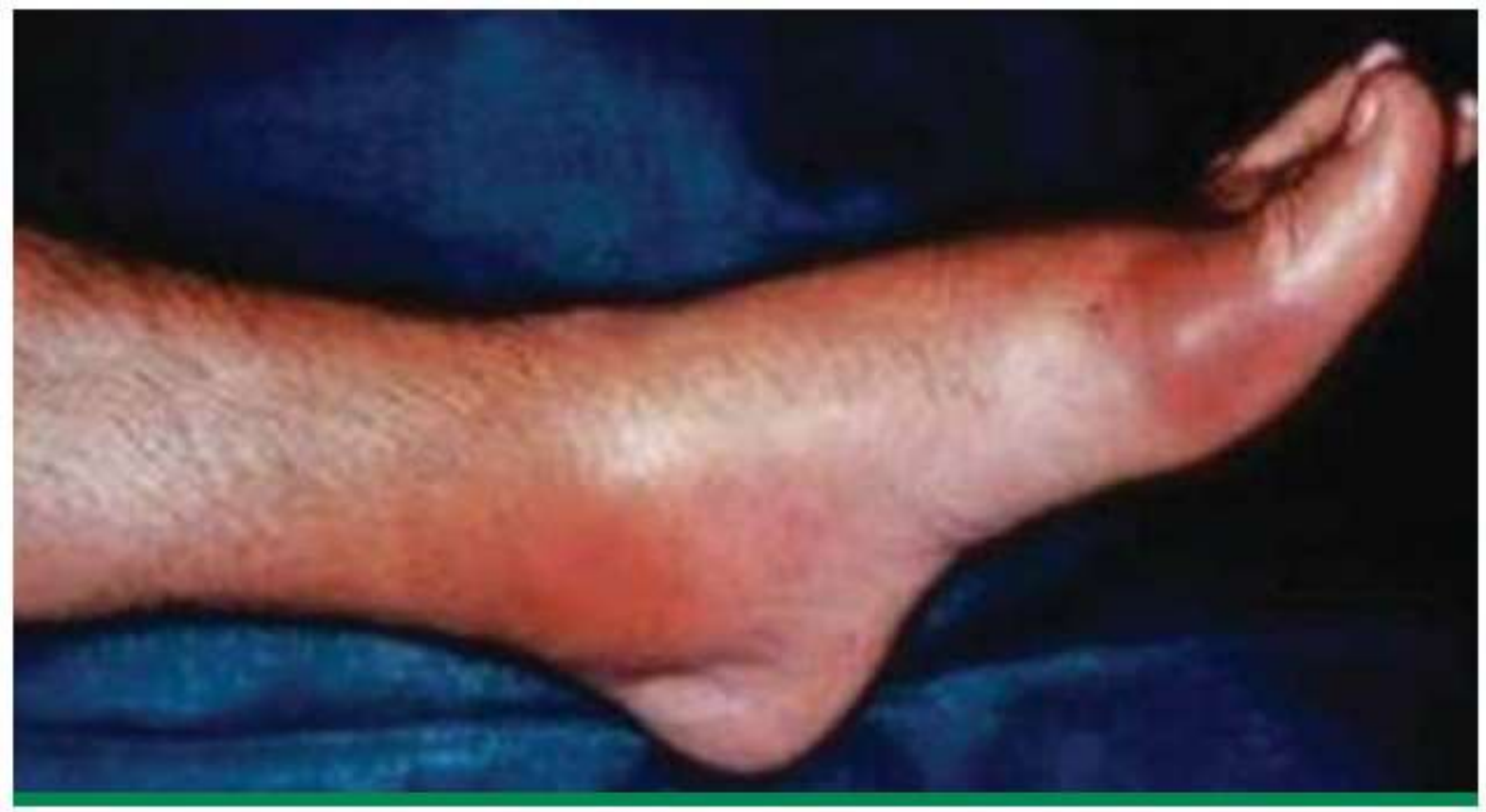
# Progression of Hyperuricemia to Gout

Stage 3: Intercritical periods:

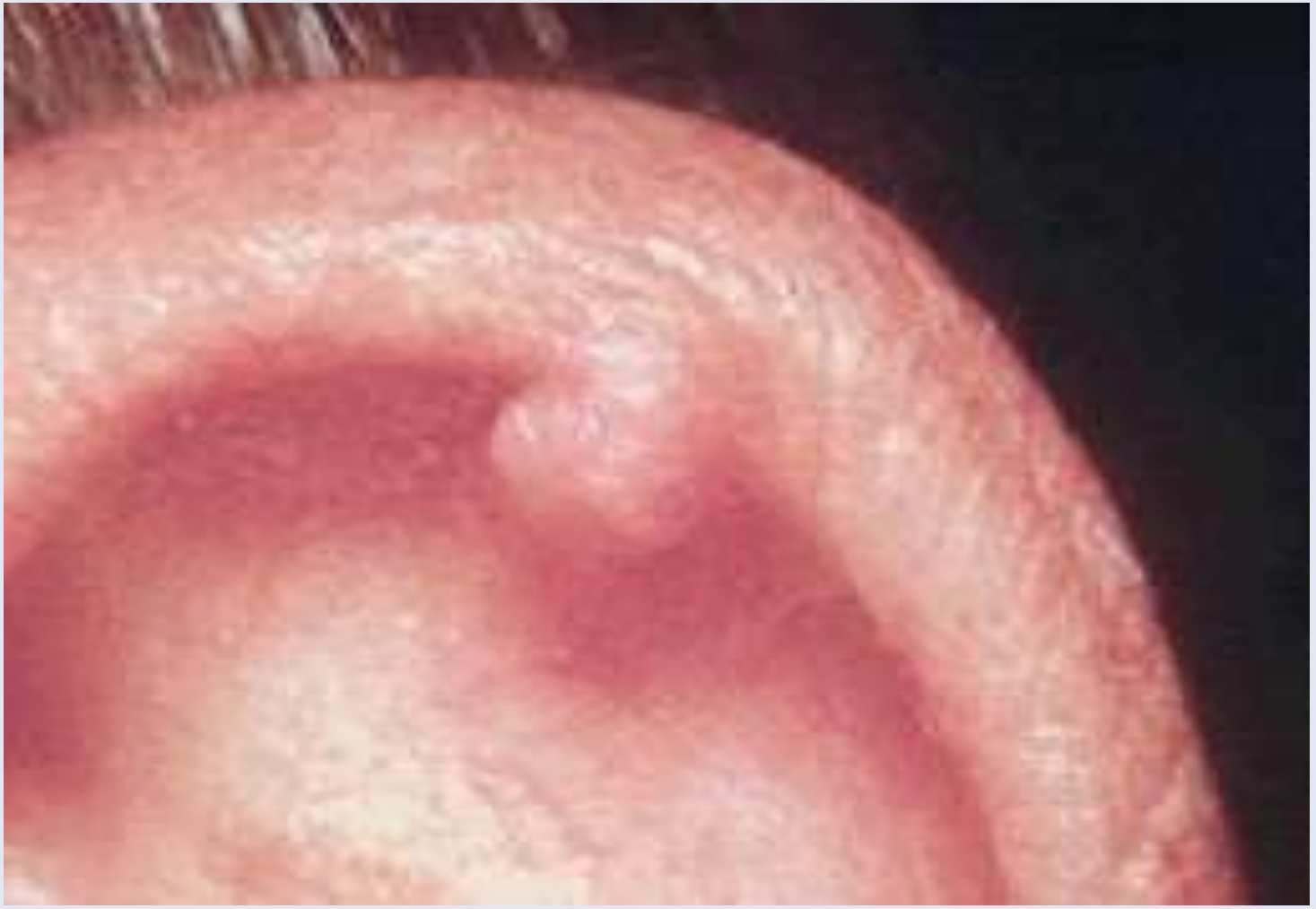
These are the intervals between attacks. During these periods, crystals may still be present at a low level in the synovial tissue & fluid resulting in future attacks.

Stage 4: Advanced gout: If crystal deposits continue to accumulate, patients may develop chronically stiff, swollen joints and tophi. This advanced stage of gout is relatively uncommon generally avoidable with therapy.

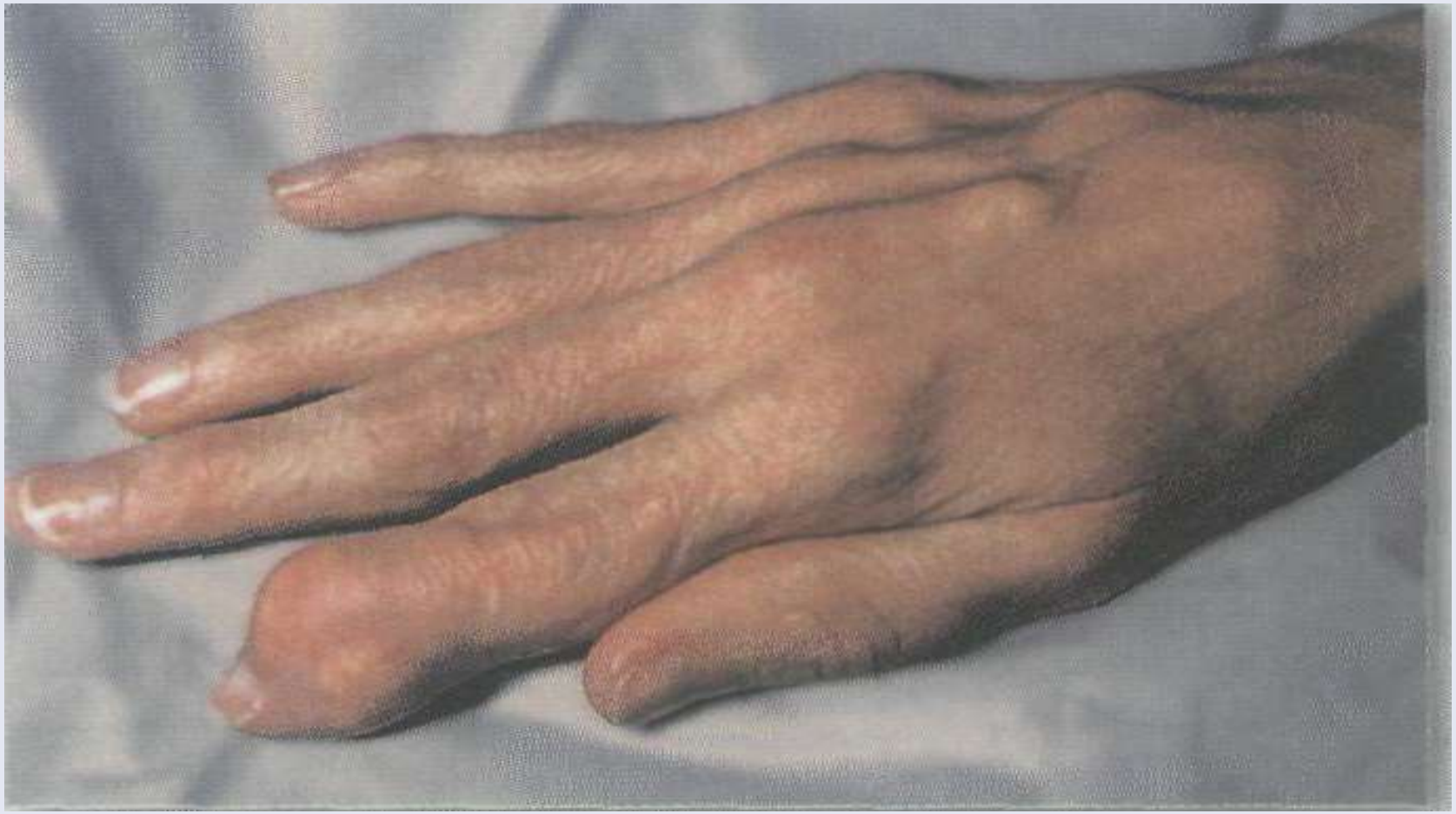
# Clinical features – Swollen MTP joint and ankle

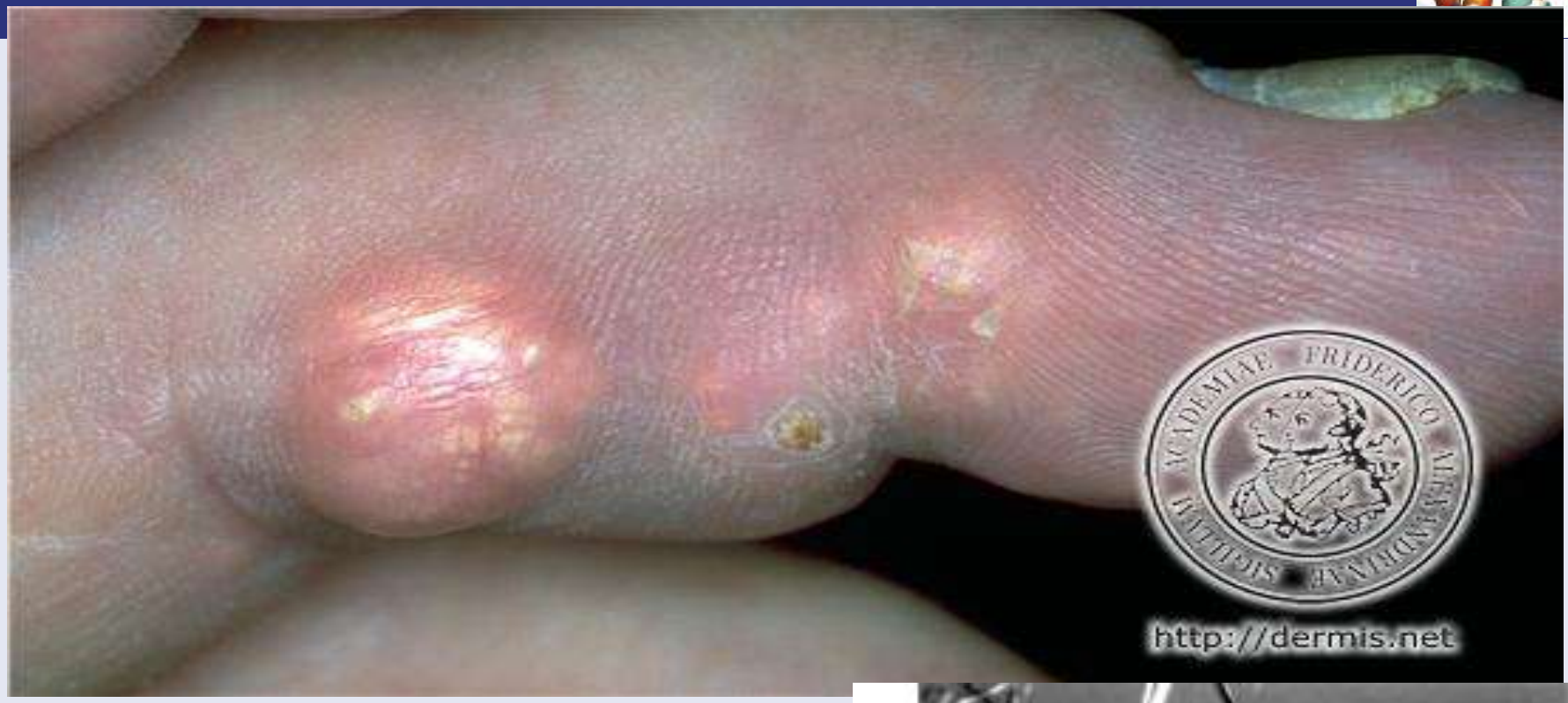


# Clinical features - tophaceous deposits in left ear

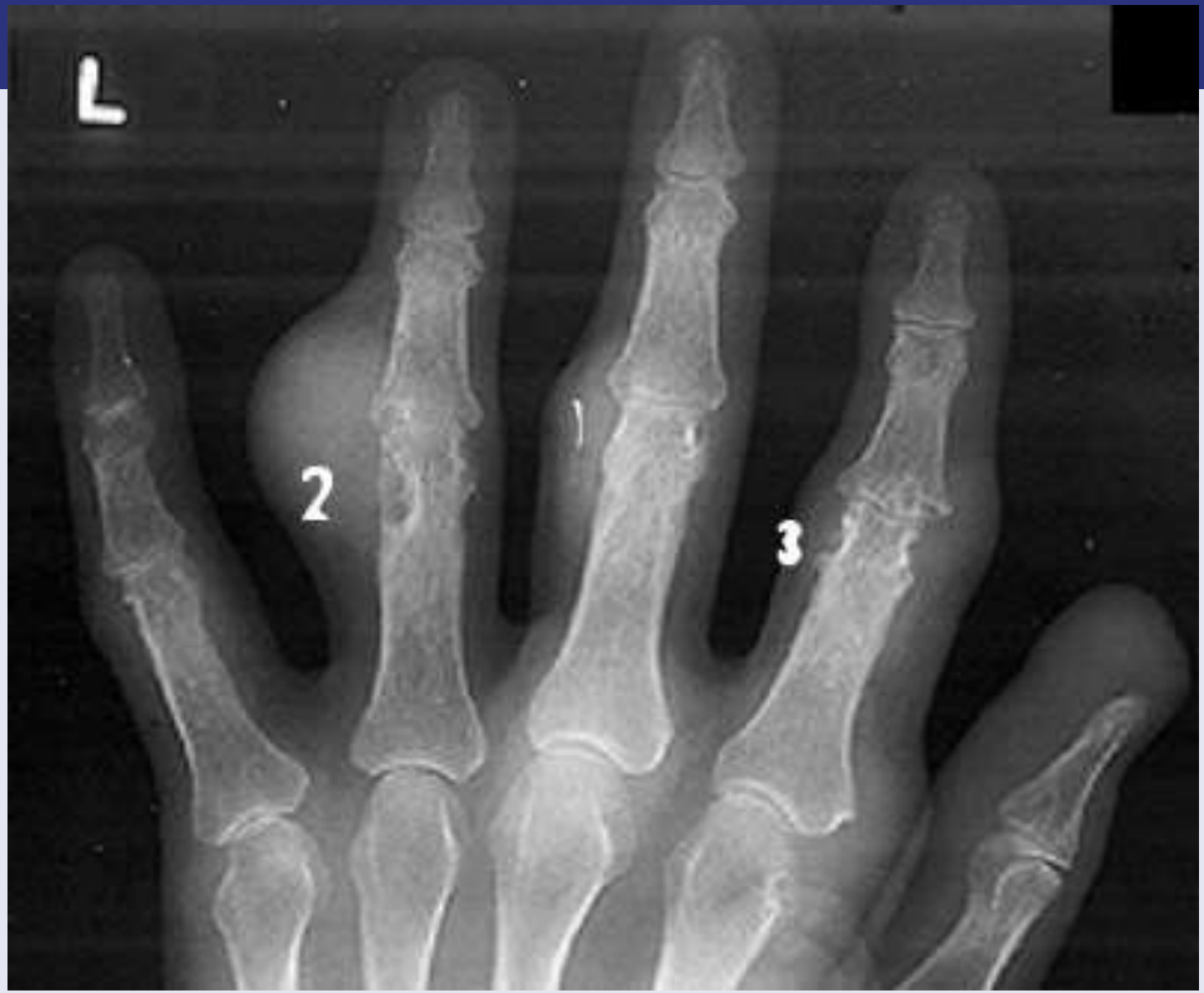


# Clinical features - tophaceous deposits in index finger






Sodium Urate Crystals


L
2
3

# GOUT - Causes

- Primary gout-

1. Abnormal PRPP synthesis: overproduction of PRPP = increased purine synthesis = increased purine degradation = increased uric acid production.

2. Abnormal Amidotransferase:-

3. Def. of HGPRT:- ↓ /partial HGPRT activity

   1) Deficiency of HGPRT ase= ↑HX and G

   2) Deficiency of HGPRTase = accumulation of PRPP = ↑ purine synthesis = ↑ uric acid levels.

   3) Deficiency of HGPRTase = ↓ IMP & GMP = ↓ inhibitors for purine synthesis.

# Gout - Causes

4.Glu – 6- phosphatase deficiency.

Glu – 6- phosphatas accumulates---↑ HMP shunt --- ↑Ribose 5 Phosphate --- PRPP.

5. Glutathione reductase variant.

Generates more $NADP^+$ which is utilised by HMP shunt , ↑Ribose 5 Phosphate --- PRPP.

# Secondary Gout

- Increased production of uric acid
- It may be due to enhanced turnover rate of nucleic acids as seen in rapidly growing malignant tissues, e.g.
- leukemias,
- lymphomas,
- polycythemia
- Psoriasis
- Chronic renal failure
- Diuretics (thiazide)
- Alcohol

# Lesch-Nyhan syndrome

- X-linked recessive disorder. Incidence is 1:10,000 males.
- Complete deficiency of **HGPRTase**
- Causes increase in PRPP level & decrease IMP & GMP stimulate purine biosynthesis so increase in uric acid.
- Characterized by mental retardation, aggression, self-destructive behavior, characterized by lip & finger biting.
- Symptoms – hyperuricemia, gout, urolithiasis, neurological symptoms motor dysfuction, behavioral disturbances, self mutilation.
- Allopurinol decreases uric acid formation.

# Lesch-Nyhan syndrome

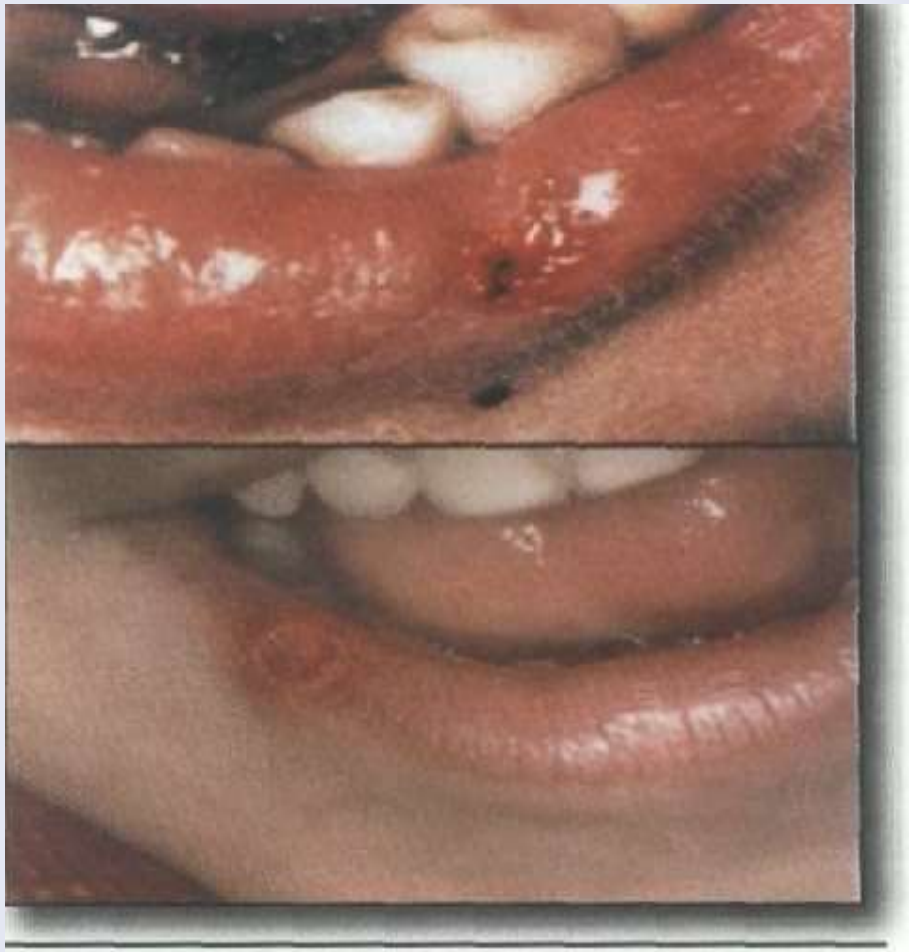
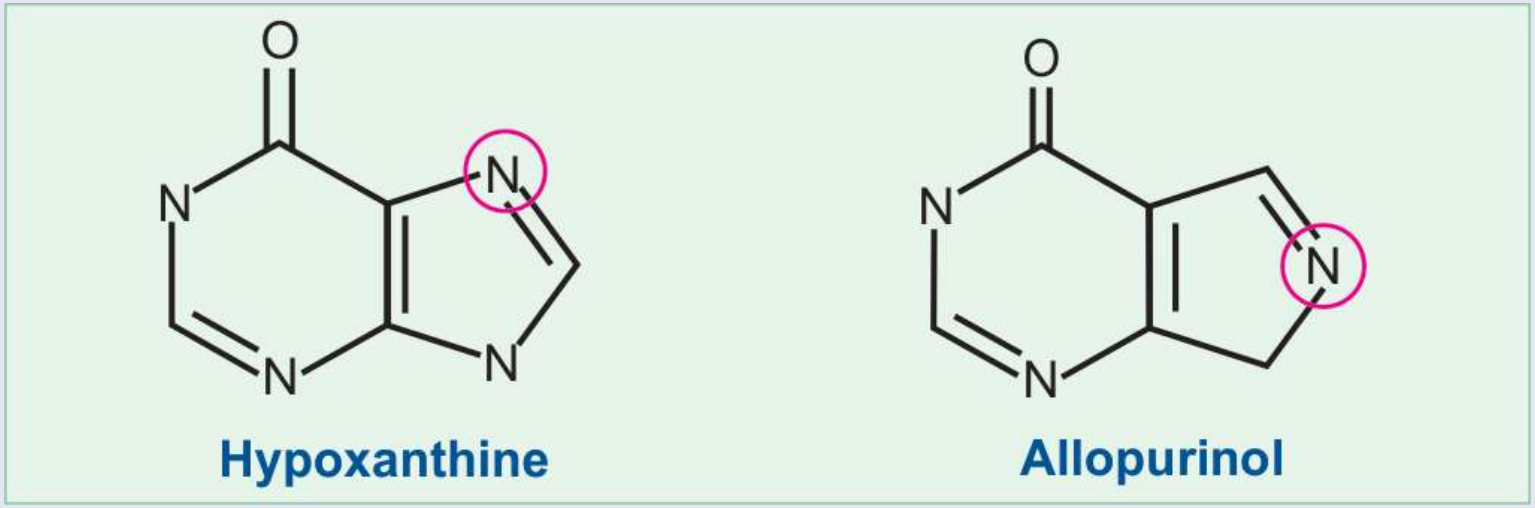


**Figure 22.11**
Lesions on the lips of Lesch-Nyhan patients caused by self-mutilation.

# GOUT - Treatment

- Low purine diet - Foods that are high in purine include: Seafood shellfish, sardines,mackerel
  - Red meat and organ meats (eg. liver)
  - Yeasts and yeast extracts (eg. beer and alcoholic beverages).
  - Asparagus, spinach, beans, peas, lentils, oatmeal, cauliflower & mushrooms.
  - Allopurinol – inhibits uric acid synthesis
- Colchicine –reduces inflammation
- Uricosuric agents – increase renal excretion of uric acid (probenecid)
- Avoid caffeine and alcohol
- Keep hydrated.




Allopurinol inhibits xanthine oxidase; an example of competitive inhibition.

# Hypouricemia

- Serum Uric Acid level  < 2mg/dl …. Hypouricemia
- Causes.

Congenital Xanthine Oxidase Deficiency

Clinical features.

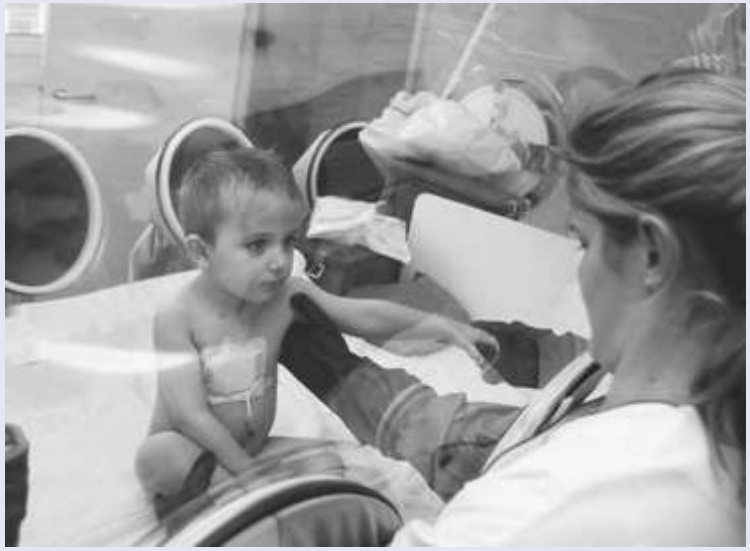
- Xanthinuria
- Xanthine Stones etc

# ***Adenosine deaminase deficiency***

- AR inheritance. Defective breakdown of purine nucleotides.. to to hypouricemia . Purine nucleoside phosphorylase deficiency
- Manifest as severe immunodeficiency.
- In the absence of ADA lymphocytes are destroyed.
- Deoxyadenosine is not destroyed, is converted to dAMP & then into dATP.
- dATP is a potent feedback inhibitor of deoxynucleotide biosynthesis.
- Treatment: ADA (blood for 1 – 2 weeks).
- Gene therapy: Replacing the gene that is missing or defective.

# SEVERE COMBINED IMMUNODEFICIENCY (SCID)

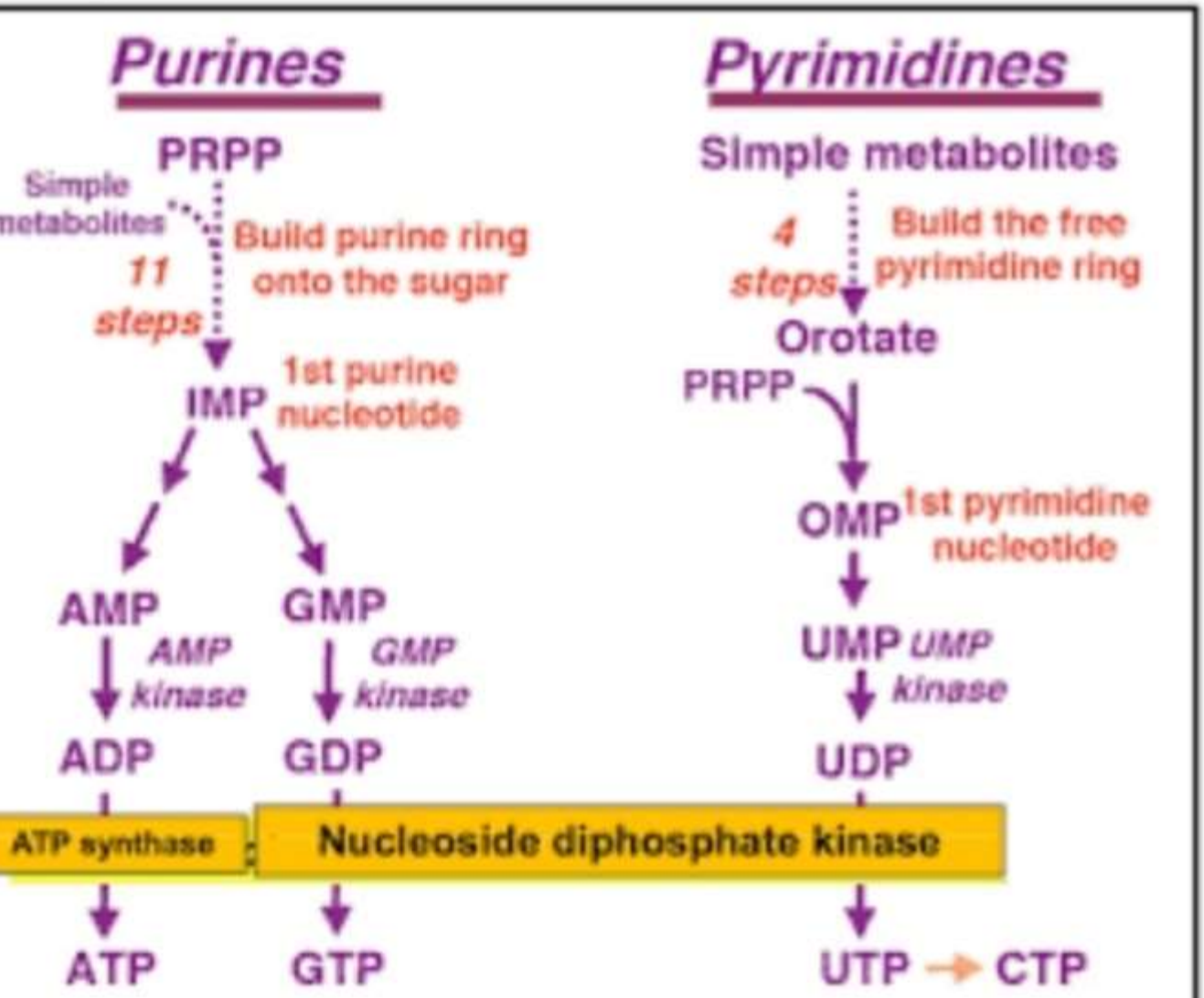
- Adenosine deaminase deficiency.
- Both T & B cells are deficient.
- Accumulation of dATP = inhibition of ribonucleotide reductase =B and T cells unable to divide.
- Infants have a high fatality rate due to infections.



# Pyrimidine Synthesis

# *De novo* synthesis of pyrimidine nucleotides

- Whereas the purine ring is built onto a sugar, the pyrimidine ring is first constructed and then converted into a nucleotide.

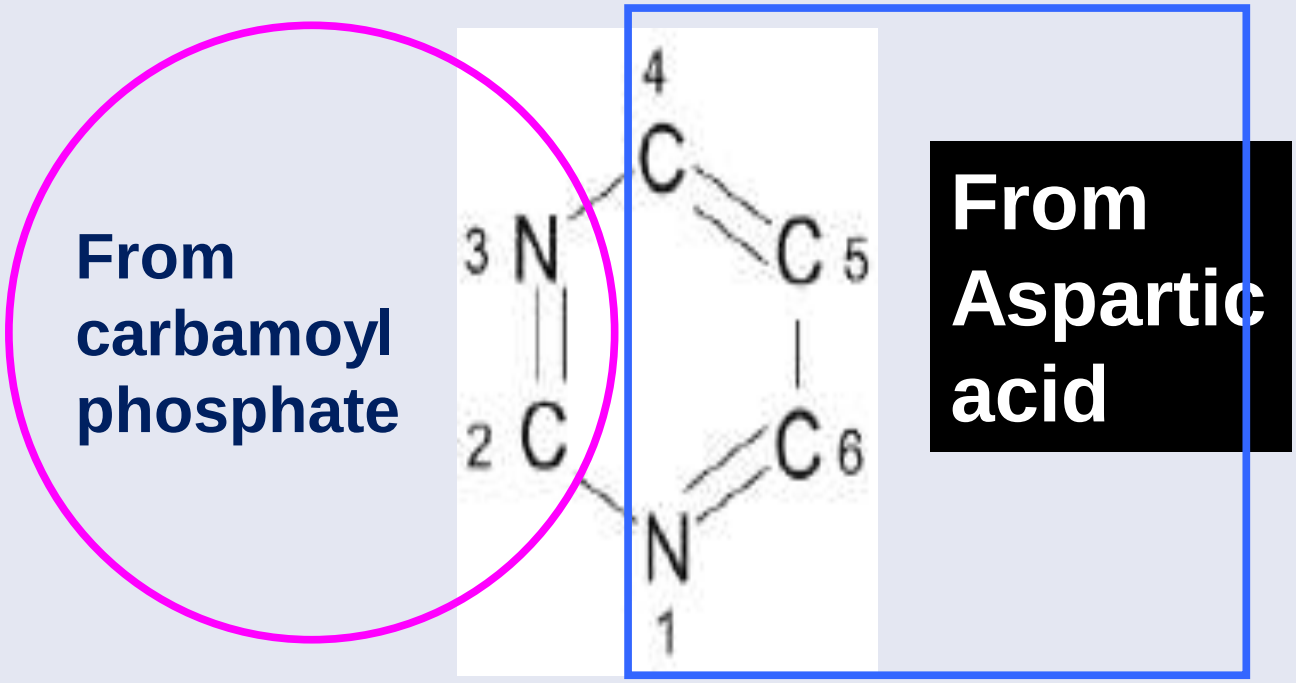



- (i) Fewer steps and fewer ATP molecules required.

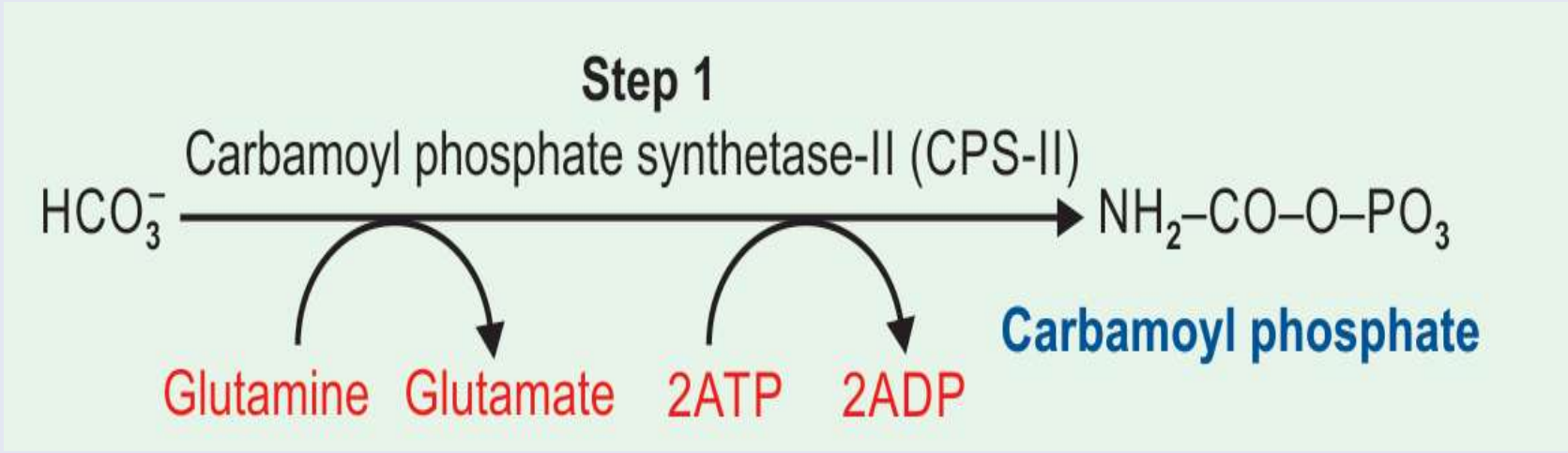
- (ii) Pyrimidine ring built and then linked to the sugar, but not built upon PRPP.

# De Novo Synthesis of Pyrimidine

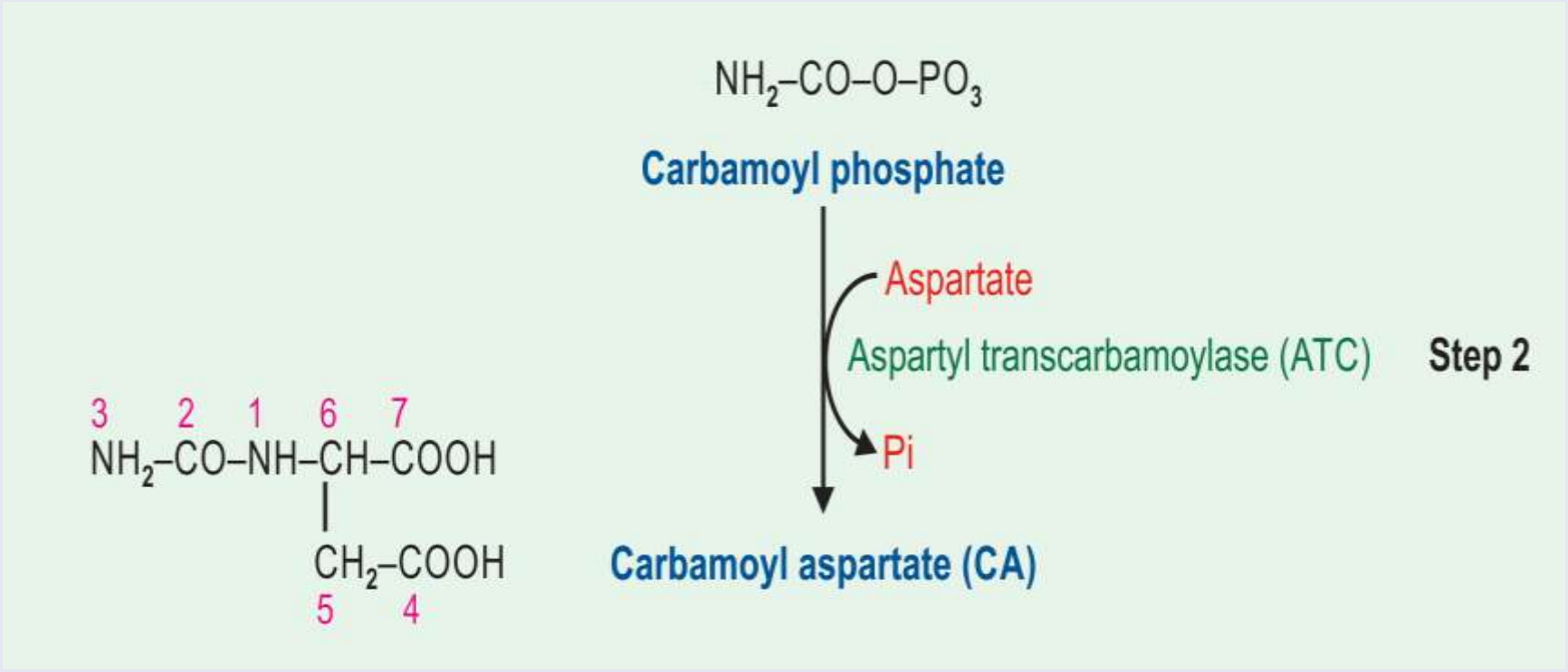
**The pyrimidine ring (unlike the purine) is synthesised as free pyrimidine and then it is incorporated into the nucleotide.**



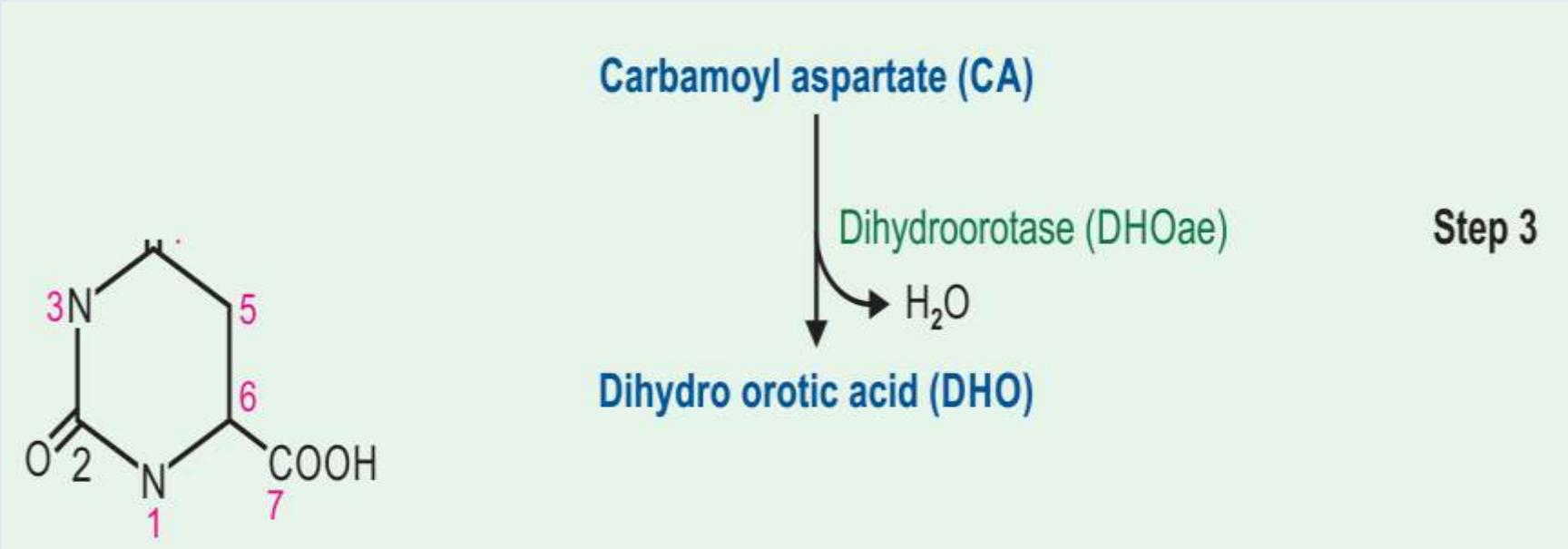

**Sources of C and N atoms of pyrimidine**



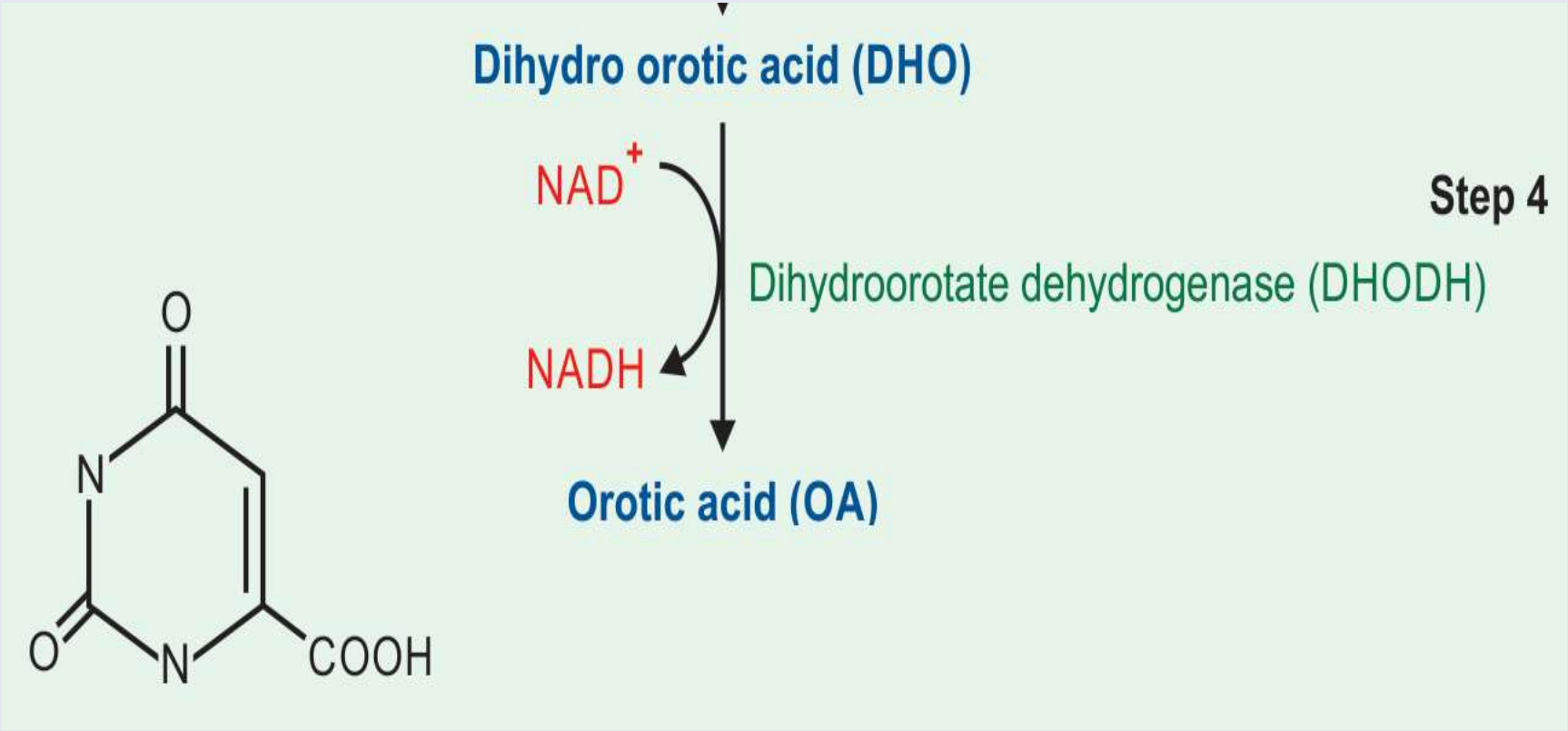

Step 1, de novo synthesis of pyrimidine,



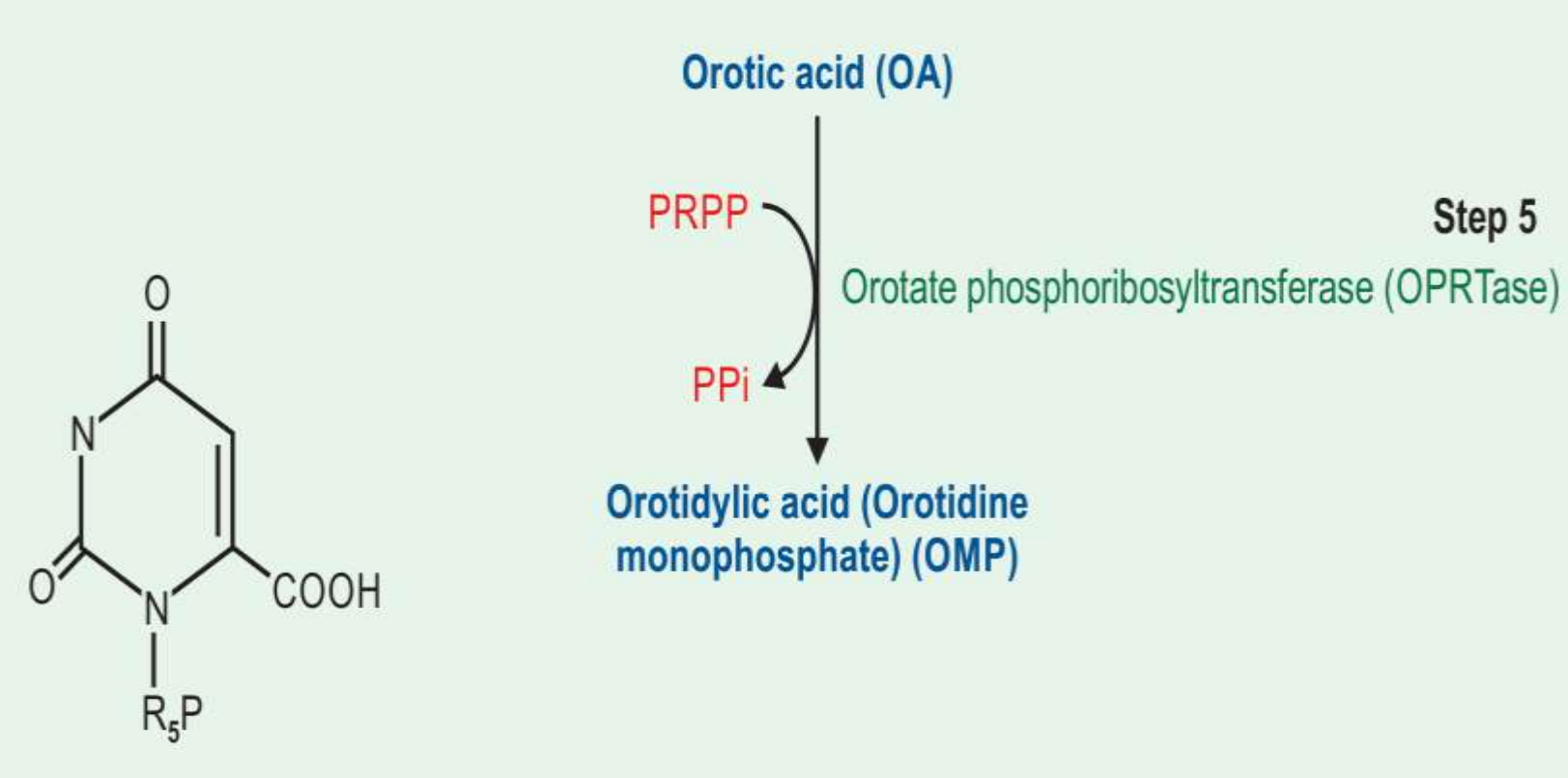

Step 2, de novo synthesis of pyrimidine,



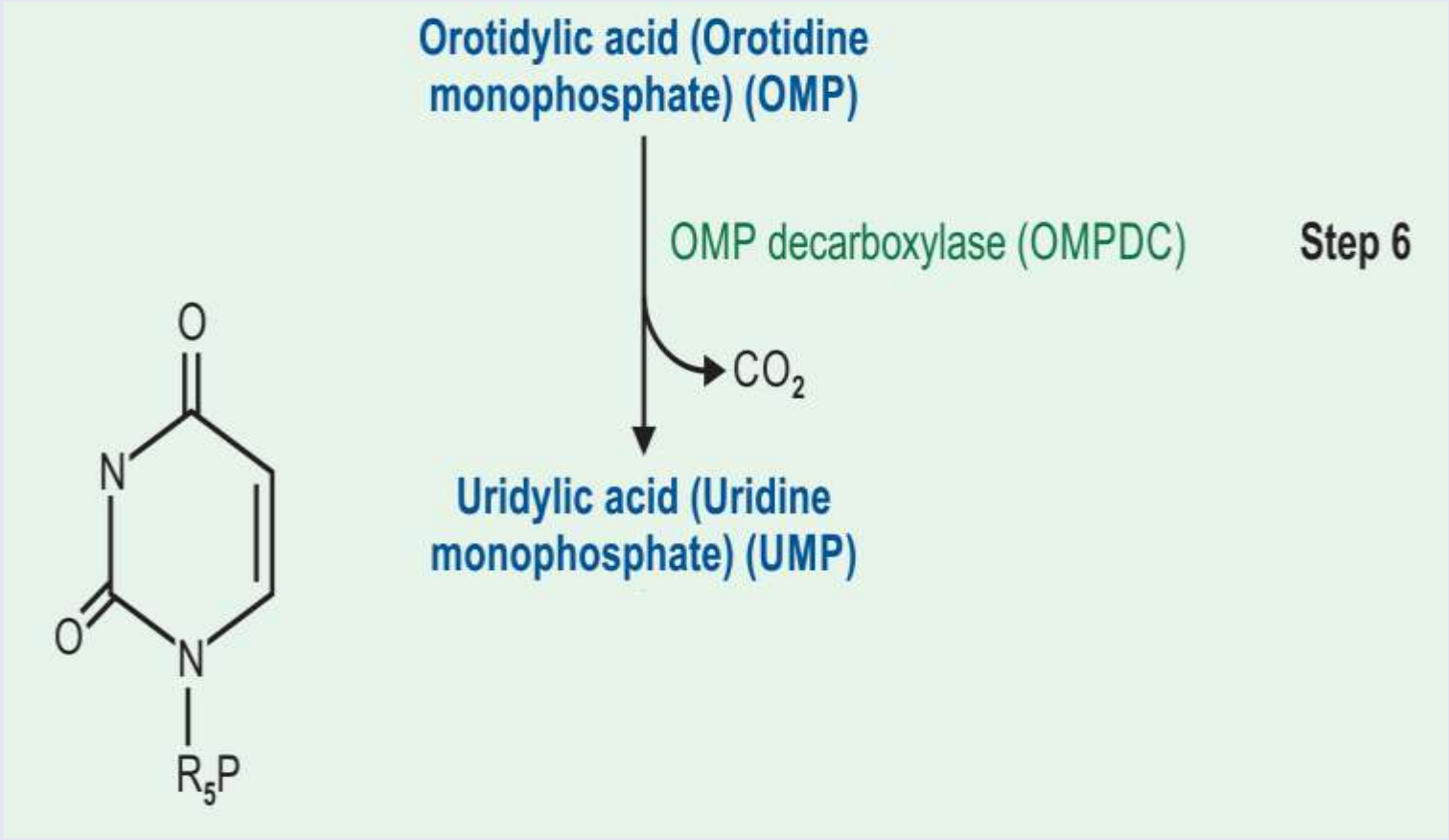

Step 3, de novo synthesis of pyrimidine



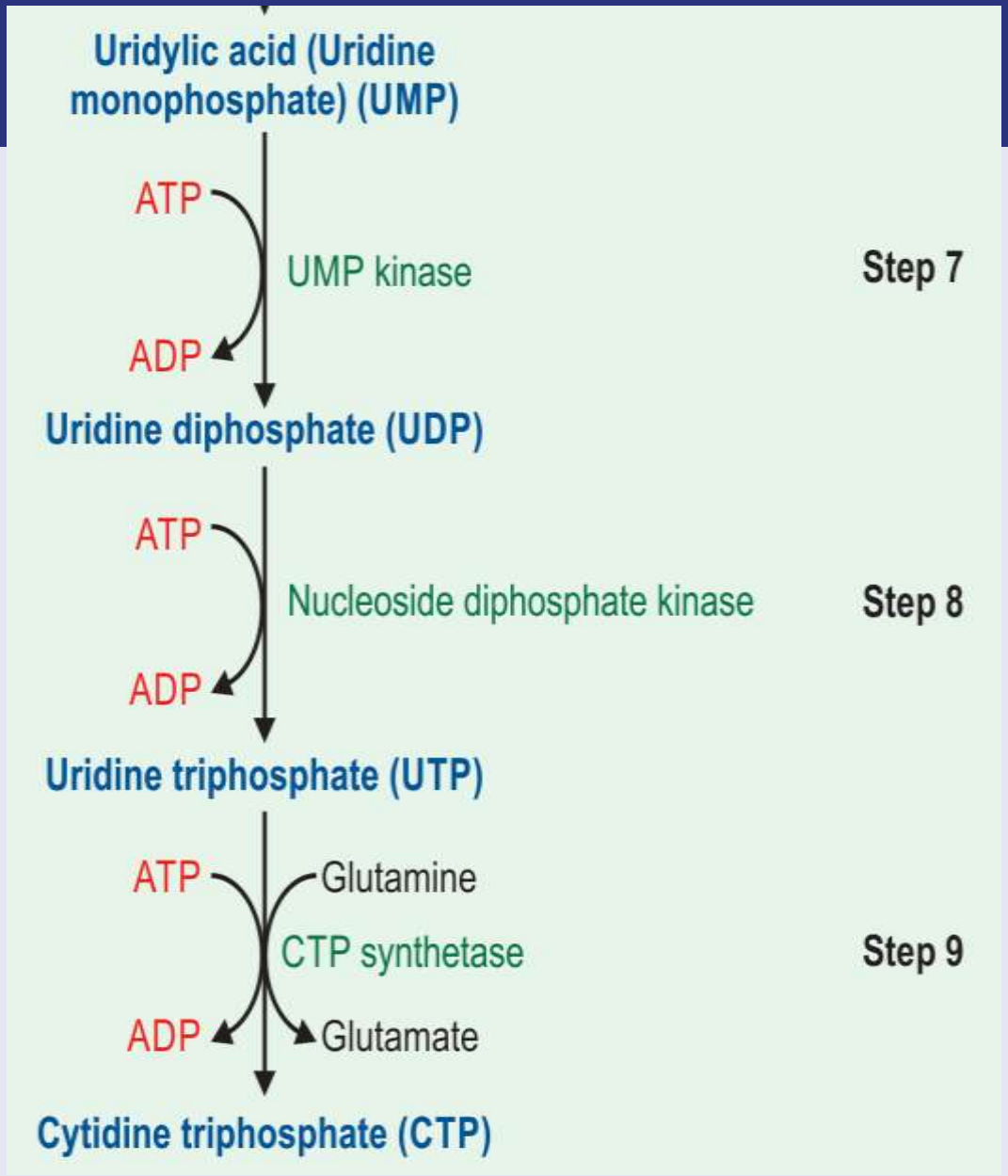

Step 4, de novo synthesis of pyrimidine.

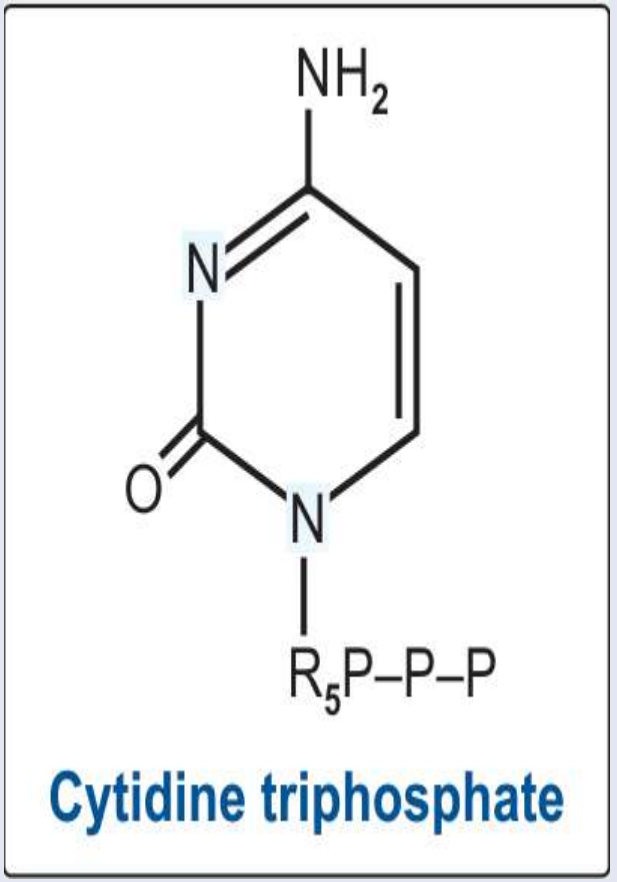



Step 5, de novo synthesis of pyrimidine.

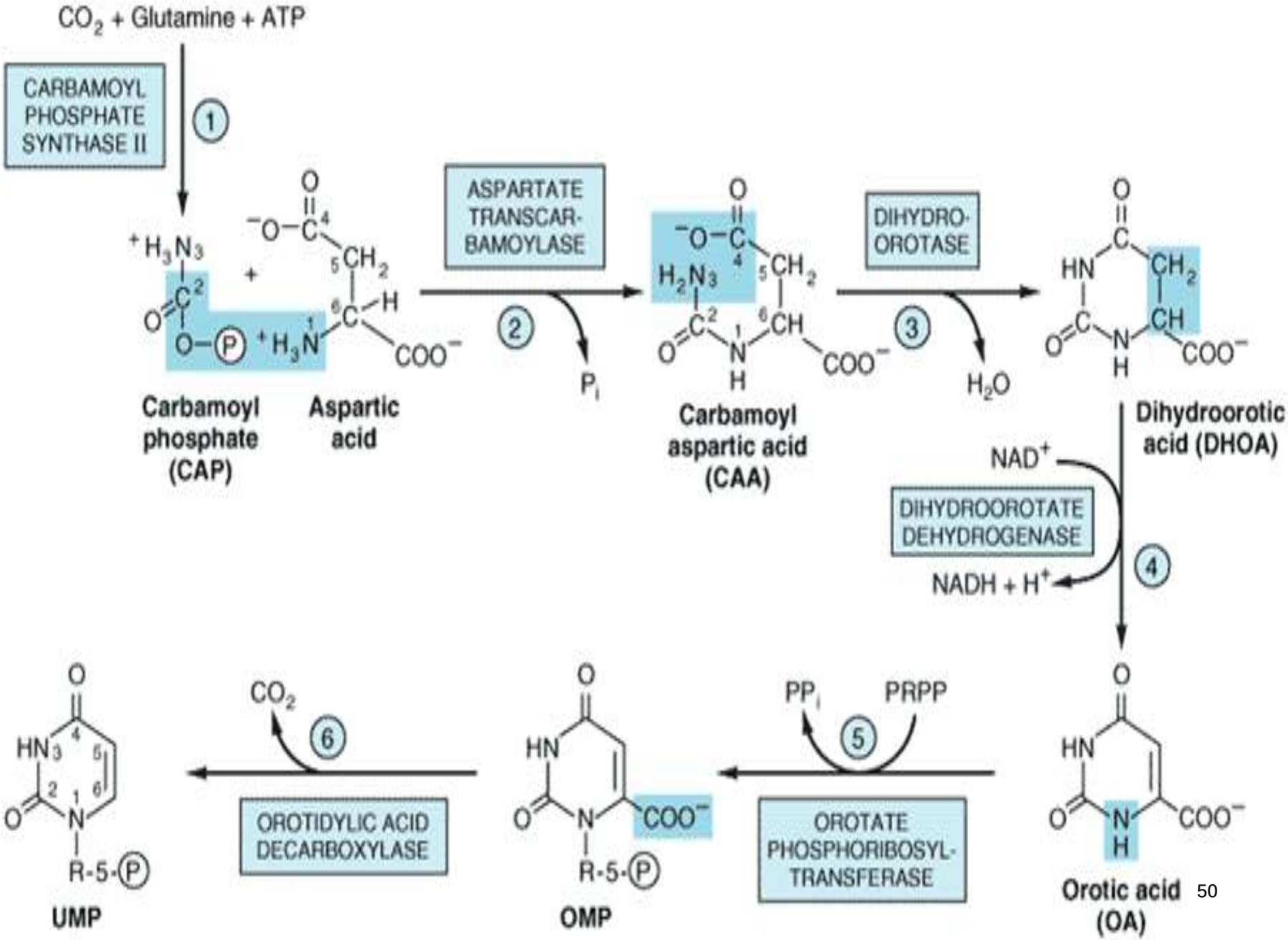


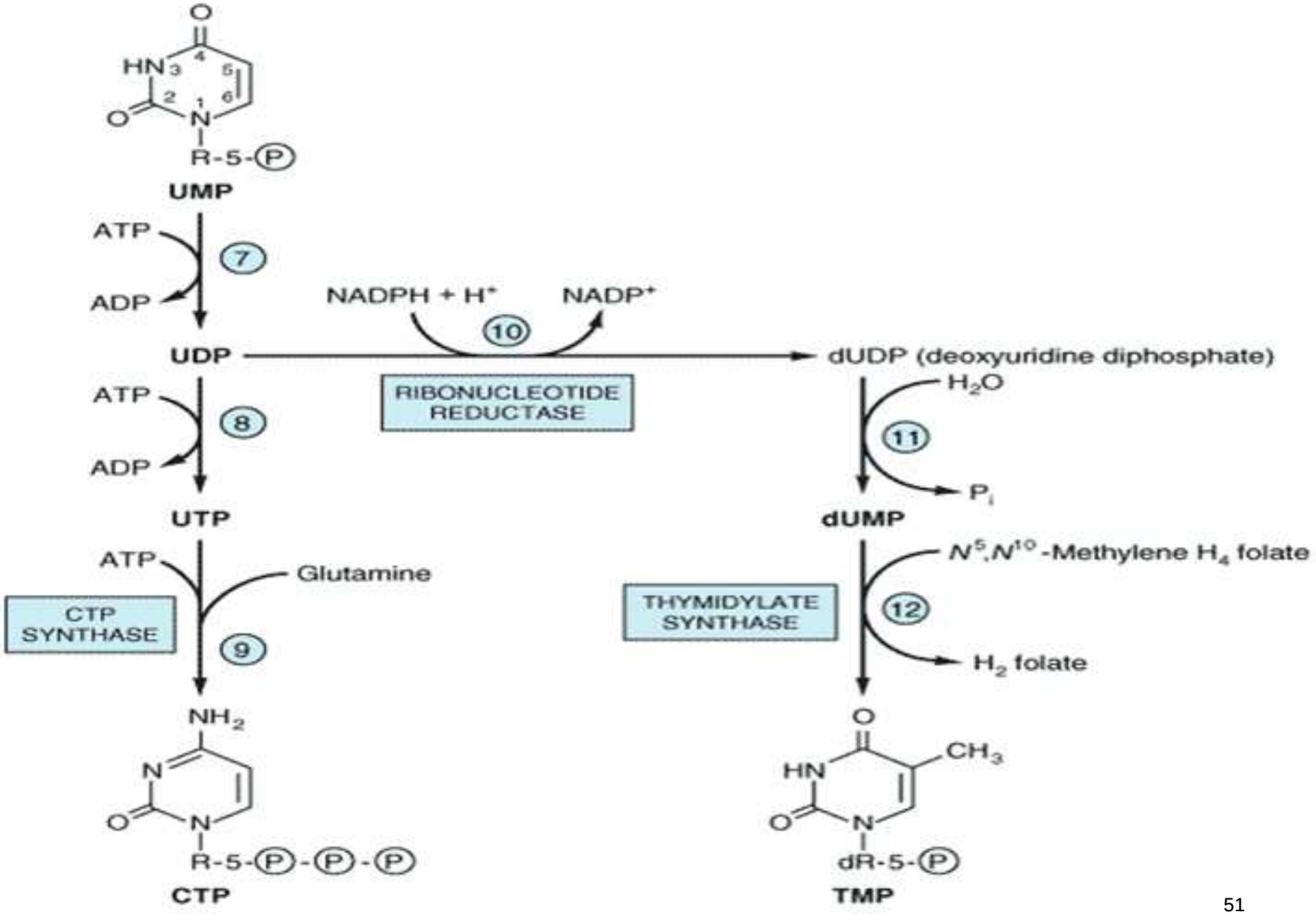

Step 6, de novo synthesis of pyrimidine.




Steps 7,8,9, de novo synthesis of pyrimidine.

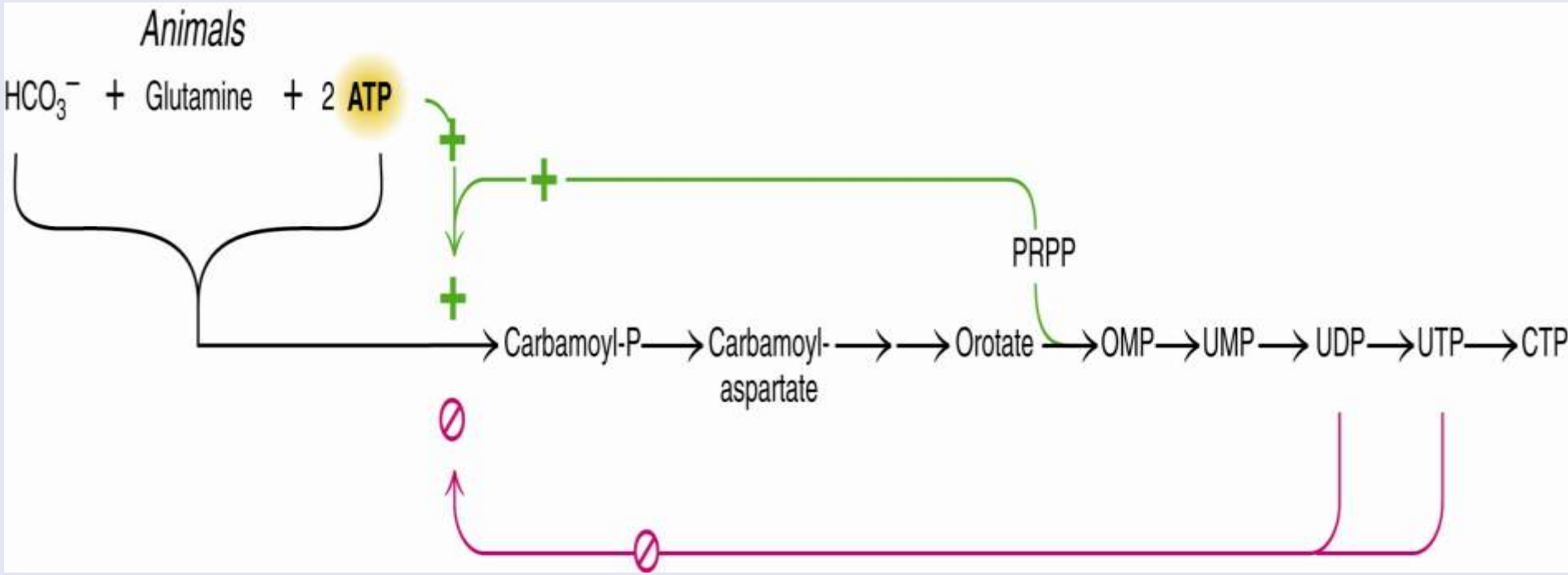

$CO_2$ + Glutamine + ATP
CARBAMOYL PHOSPHATE SYNTHASE II
1
Carbamoyl phosphate (CAP)
Aspartic acid
ASPARTATE TRANSCAR-BAMOYLASE
2
$P_i$
Carbamoyl aspartic acid (CAA)
DIHYDRO-OROTASE
3
$H_2O$
Dihydroorotic acid (DHOA)
$NAD^+$
DIHYDROOROTATE DEHYDROGENASE
$NADH + H^+$
4
Orotic acid (OA)
$PP_i$
PRPP
5
OROTATE PHOSPHORIBOSYL-TRANSFERASE
OMP
$CO_2$
6
OROTIDYLIC ACID DECARBOXYLASE
UMP



# Regulation

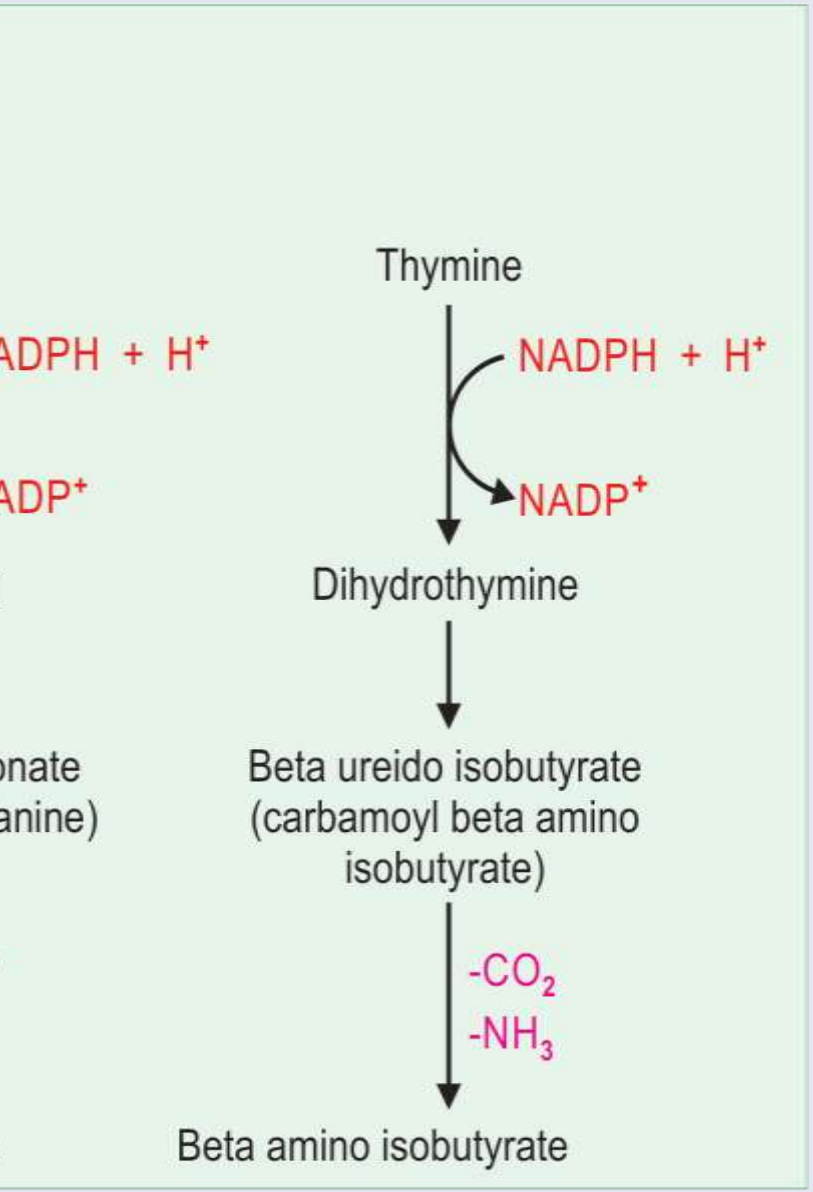
- In eukaryotes the1st Three enzymes CPS-II, ATC, DHOase present as multienzyme complex referred as CAD.
- Last 2 enzymes OPRTase & OMP decarboxylase – present as a single functional complex.
- Carbamoyl phosphate synthase II is inhibited by UTP & activated by PRPP.
- b. Aspartate transcarbamoylase is inhibited by CTP but activated by ATP.
- c. OMP decarboxylase is inhibited by UMP
- Purine & pyrimidine nucleotide biosynthesis are coordinately regulated.

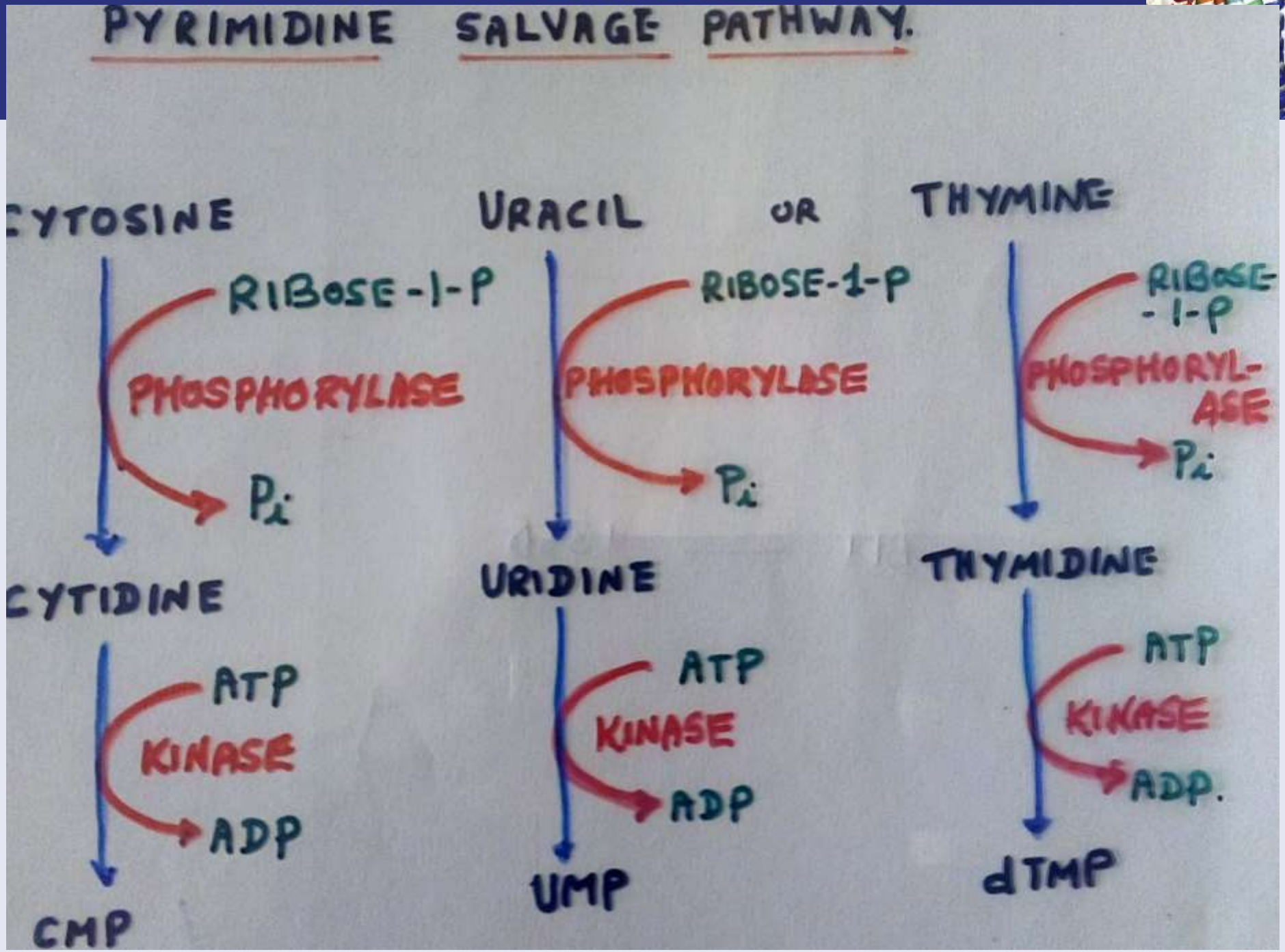
# Pyrimidine Biosynthesis is Regulation



| | CPS I | CPS II |
|---|---|---|
| Cellular location | Mitochondria | Cytosol |
| Pathway involved | Urea cycle | Pyrimidine synthesis |
| Source of nitrogen | Ammonia | γ-Amide group of glutamine |
| Regulators | Activator: N–acetyl-glutamate | Inhibitor: UTP<br>Activator: ATP; PRPP |

# Catabolism of Pyrimidines




PYRIMIDINE SALVAGE PATHWAY.
CYTOSINE
RIBOSE-1-P
PHOSPHORYLASE
Pi
CYTIDINE
ATP
KINASE
ADP
CMP
URACIL
OR
THYMINE
RIBOSE-1-P
PHOSPHORYLASE
Pi
URIDINE
ATP
KINASE
ADP
UMP
RIBOSE-1-P
PHOSPHORYL-ASE
Pi
THYMIDINE
ATP
KINASE
ADP.
dTMP

# Disorders of Pyrimidine Metabolism
# Orotic Aciduria

- Causes:
  - Absence of OPRTase or OMP decarboxylase
  - Inherited as autosomal recessive
  - **Clinical Features**
  - Retarded growth
  - Severe megaloblastic anaemia
  - Crystals excreted in urine
  - Cryslalluria may cause UTI
  - Rx– Feeding cytidine or Uridine

# Orotic aciduria

- **A. Type I orotic aciduria** reflects a deficiency of both orotate phosphoribosyl transferase & OMP decarboxylase .

- B. **type II orotic aciduria** is due to a deficiency only of OMP decarboxylase

# Reyes Syndrome

- Inability of severely damaged mitochondria to utilize carbamoyl phosphate, which then becomes available for cytosolic overproduction of orotic acid.

# THANK YOU