# Special aspects of renal metabolism

By
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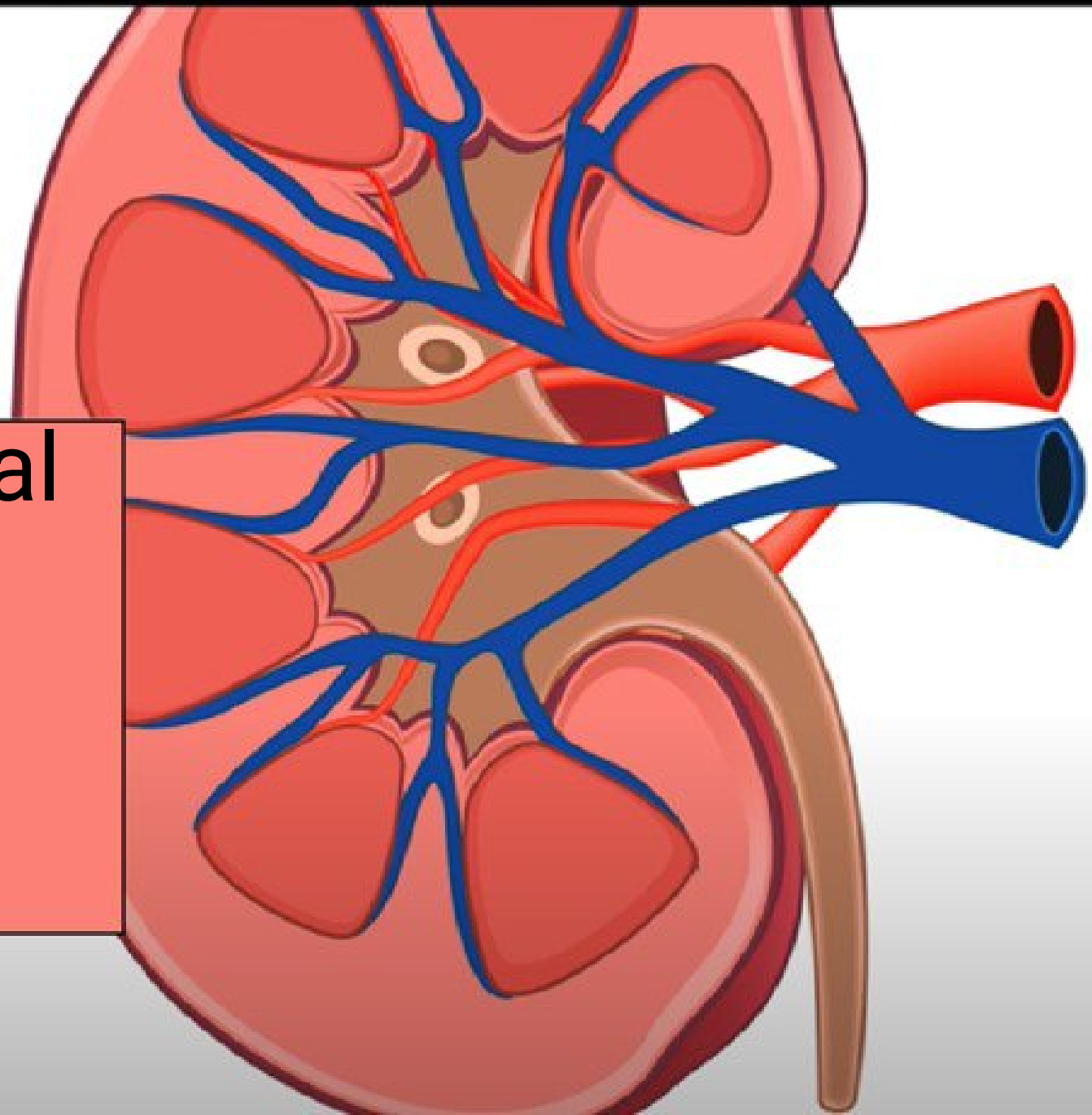


# Objectives

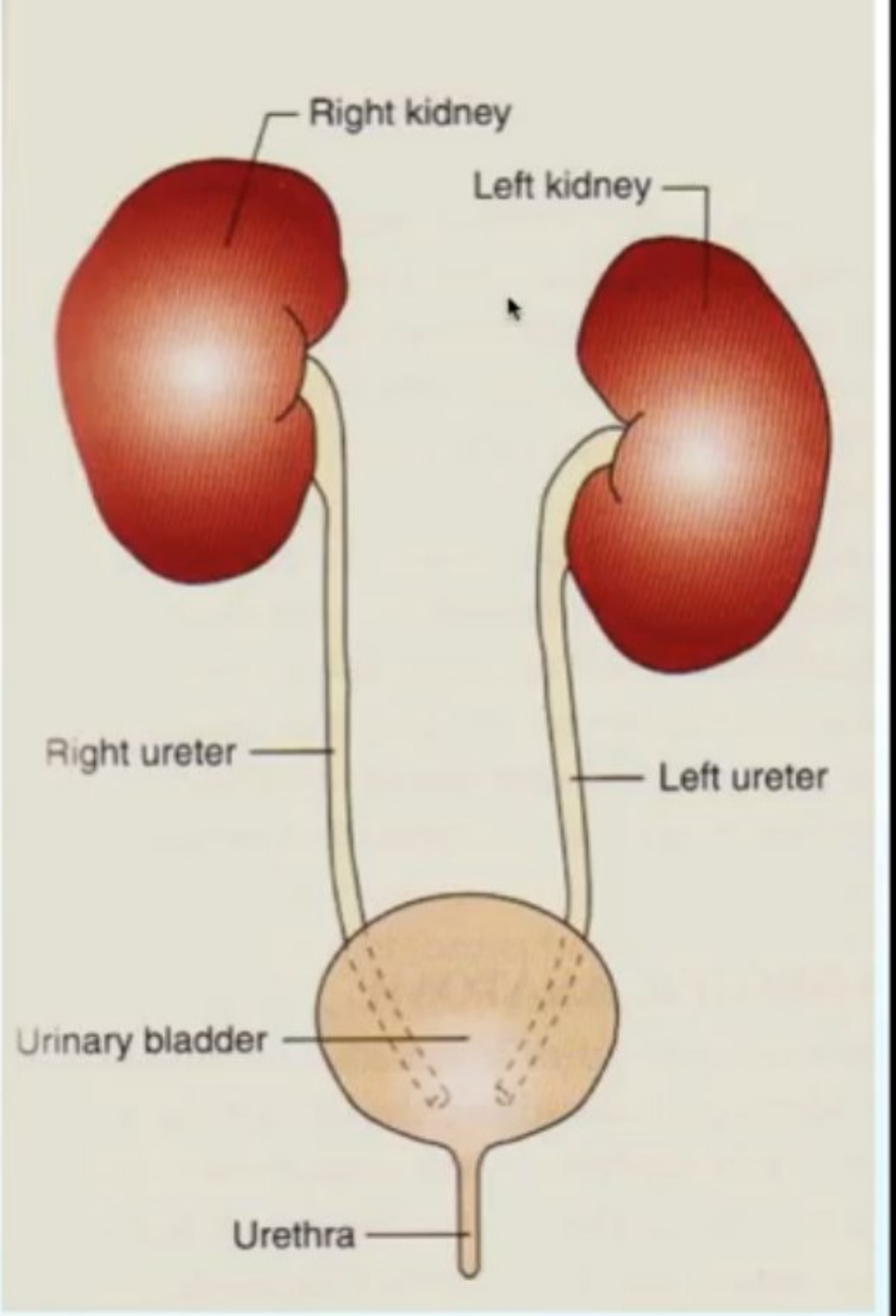
1. Basic renal function and morphology
2. Excretory function of the kidneys
   - Urine formation
   - Glomerulal filtration rate
   - Mechanism of resorption and factors affecting it
   - Normal composition and characteristics of urine
3. Homeostatic function of the kidneys
   - Acid-base balance
   - Electrolyte balance
4. Endocrinal function of the kidney
   - Calcitriol hormone synthesis
   - Erythropoietin hormone synthesis
   - Renin hormone synthesis
5. Metabolic function of the kidney
   - Renal gluconeogenesis
   - Role of the kidneys in amino acid metabolism

Part 1

# Renal Function and Morphology

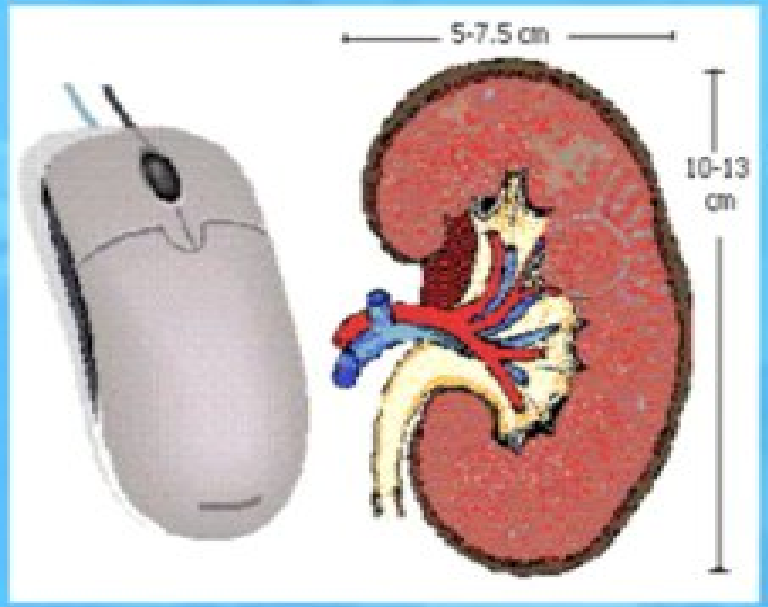
## Parts of the urinary system:

- **Kidneys**: contain the functional units to make urine
- **Ureters**: carry urine formed by the kidney to the urinary bladder
- **Urinary bladder**: store urine until released from the body
- **Urethra**: conduct urine outside the body



# The Human Kidney

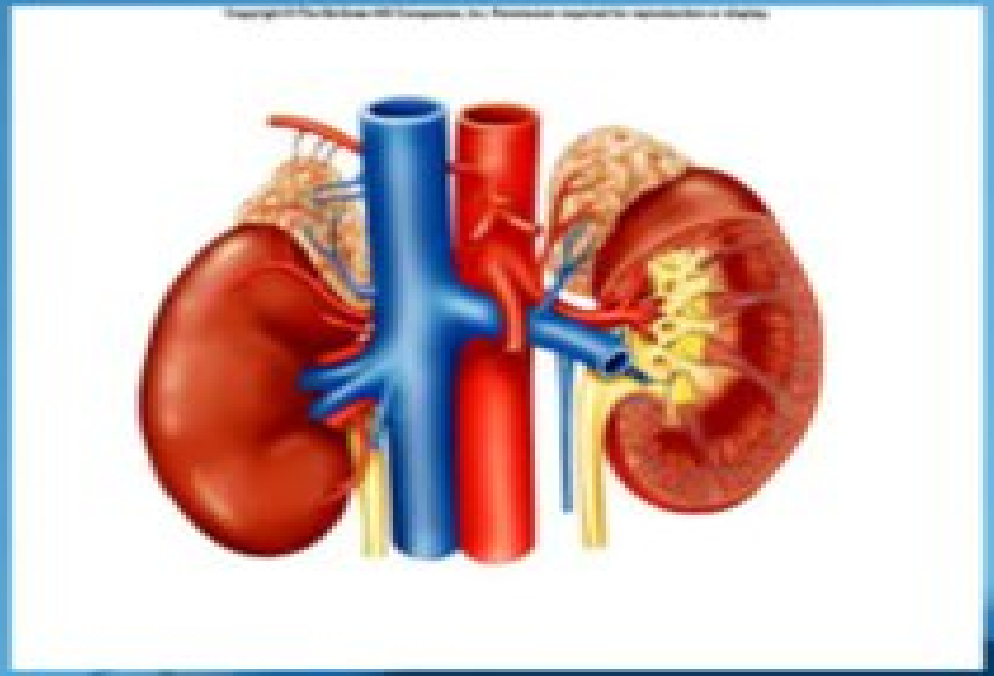
- bean shaped, reddish brown organs.
- about the size of your fist.
- It measures 10-12 cm long.
- covered by a tough capsule of fibrous connective tissue- renal capsule
- Adhering to the surface of each kidney-two layers of fat to help cushion them.



# Kidneys and their structures

- **The Renal Arteries**
  - transport oxygenated blood from the heart and aorta to kidneys for filtration

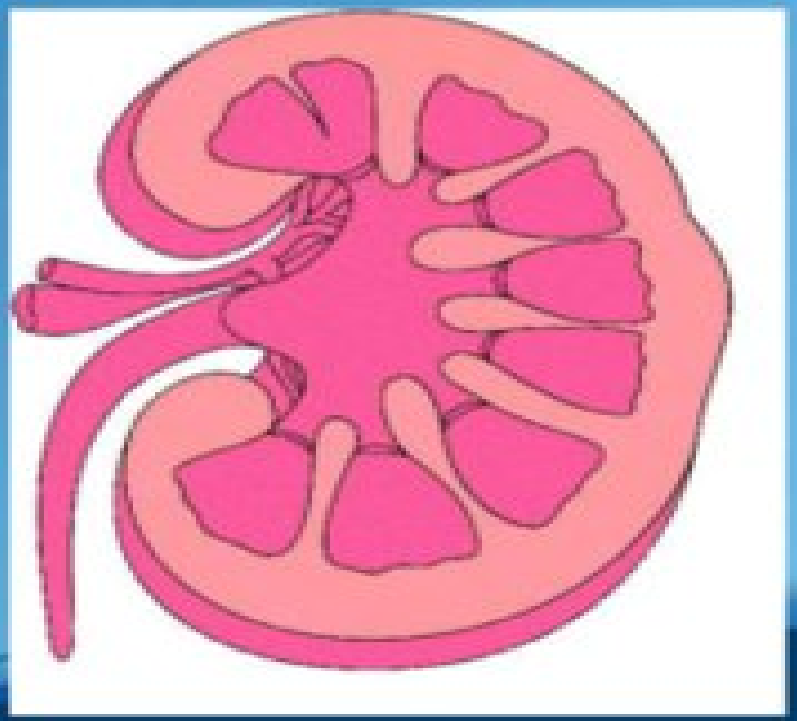
- **The Renal Veins**
  - Transport the filtered, deoxygenated blood from kidneys to the posterior vena cava and finally the heart



# Kidneys and their structures

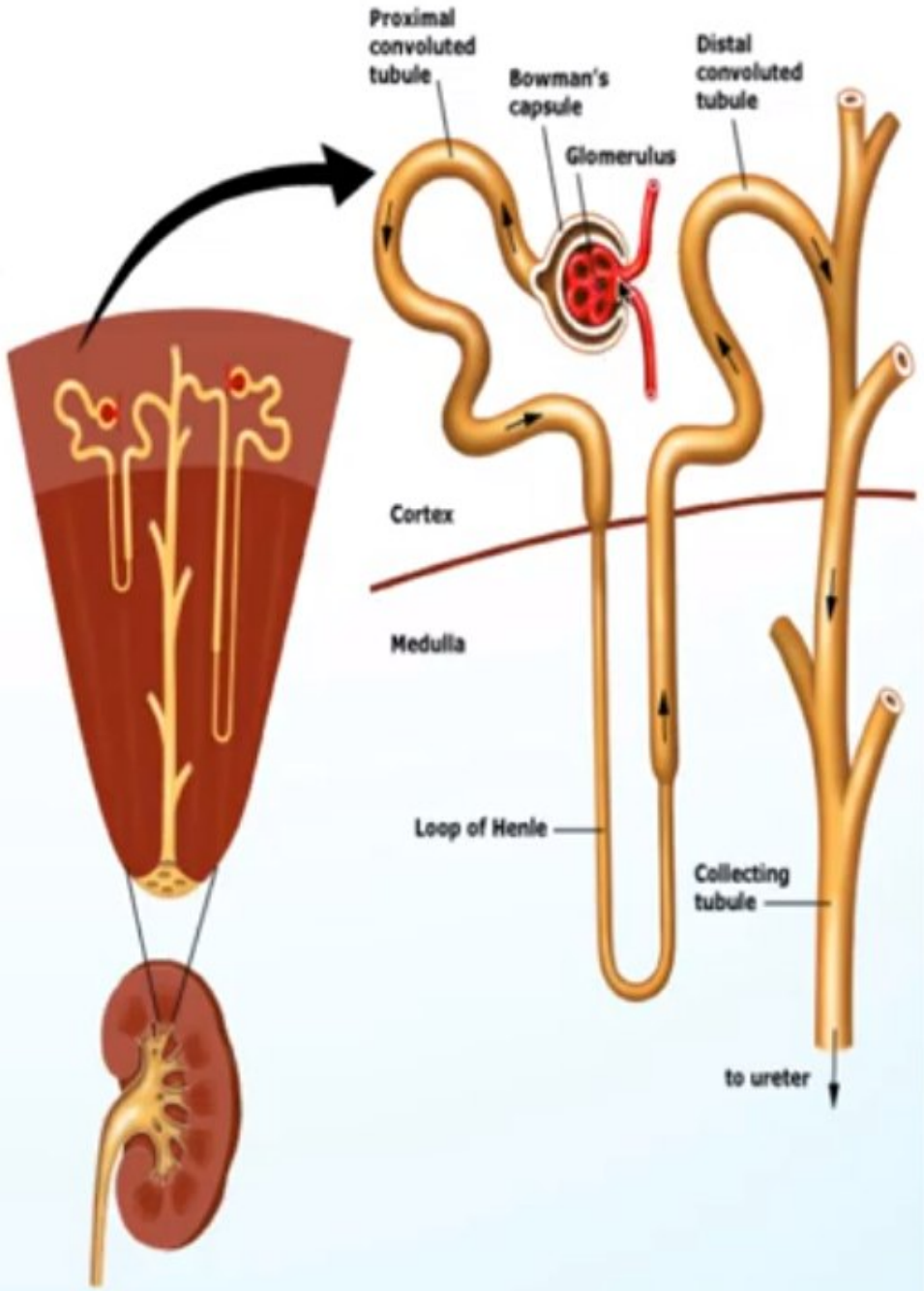
- **Renal Capsule**
  (inferior/superior)
  - Outer membrane which encloses and protects kidneys against infections and trauma.

- **The Renal Cortex**
  - Outer layer (granulated) of the kidney that contains most of the nephrons.



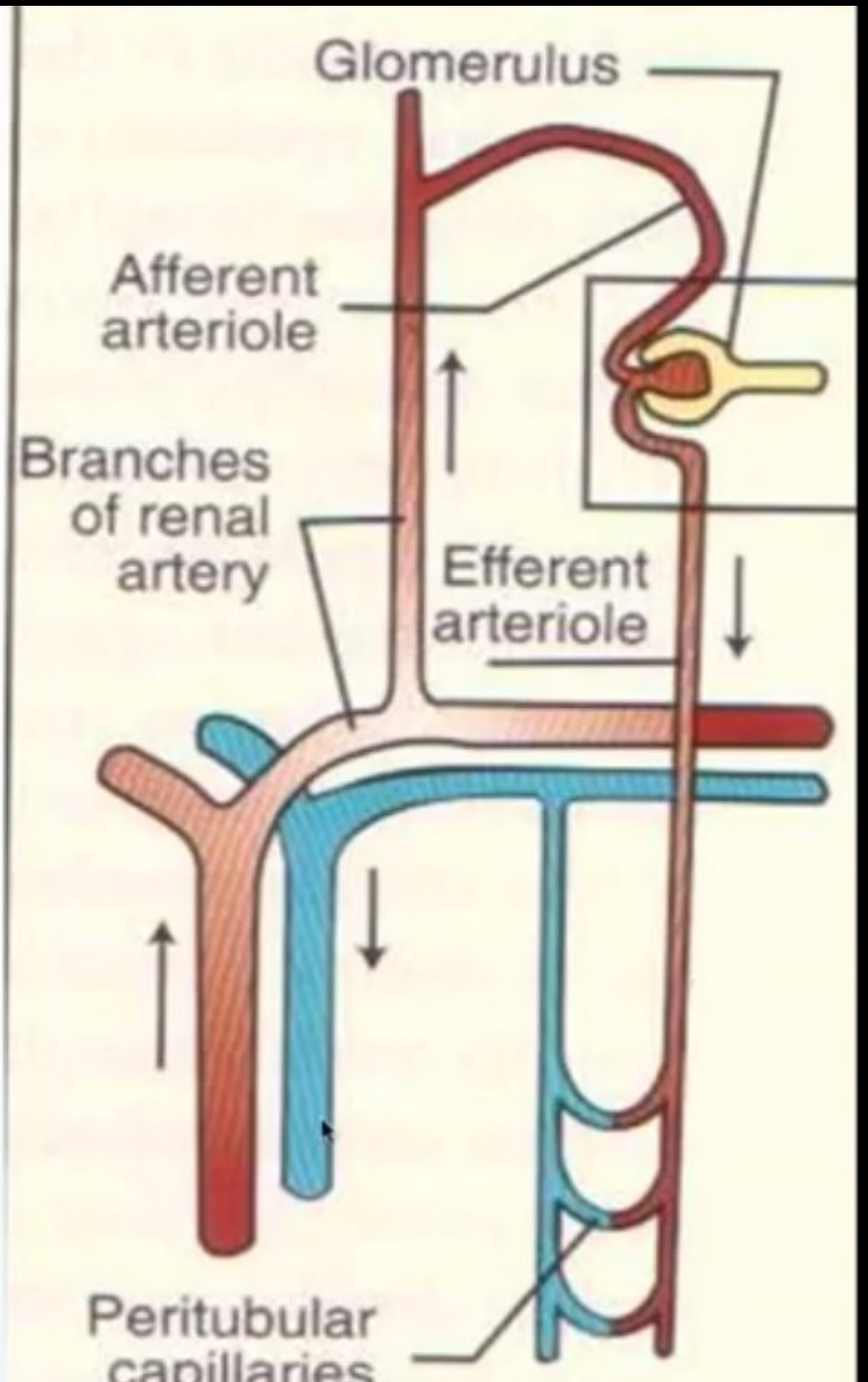
## Nephron: is functional units of kidneys

1. **Glomerulus:**
   - **Function:** filter blood into the first stage of urine formation
   - made up of network of branching and anastomosing glomerular capillaries which are encased in bowman's capsule
2. **Renal tubules:**
   - Process the glomerular filtrate into urine
   - Proximal convoluted tubule
   - Loop of henle: descending and ascending
   - Distal convoluted tubule
   - Collecting ducts



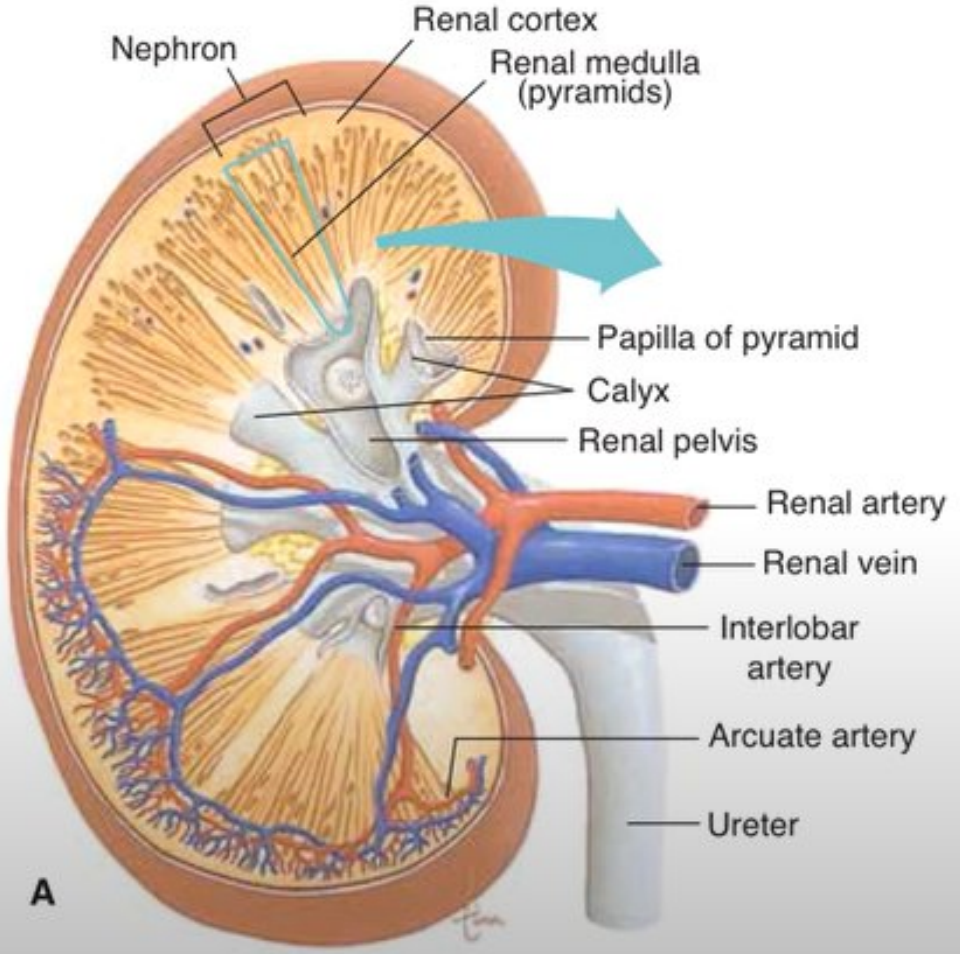
## Blood Supply:

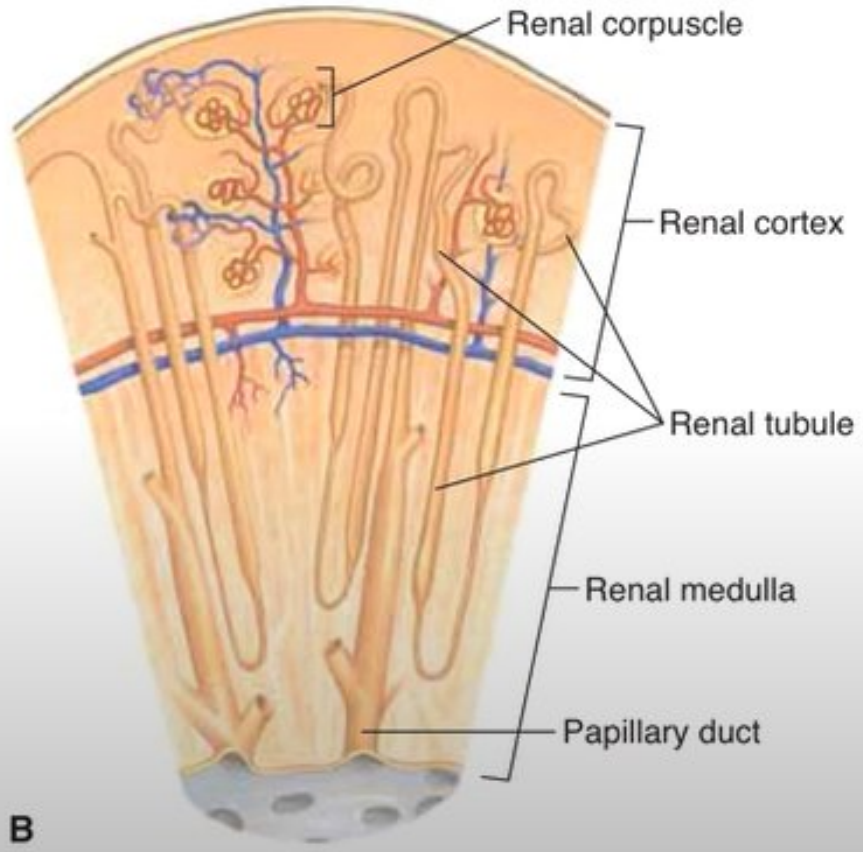
- **Renal artery:** Blood from the renal artery is delivered to the afferent arterioles.
- **Afferent arterioles** branches to form the glomerular capillaries which come together to form the efferent arterioles.
- **Efferent arterioles** divides to form the peritubular capillaries which give rise to the renal vein.



# Renal Morphology

**Nephrons** are the functional unit of the kidney



# Renal Function

## Excretory

Water excretion (body fluid regulation) and byproducts of metabolism (urea, creatinine)

## Endocrinal

Renin-angiotensin
Activation of Vitamin D
Erythropoietin formation

## Homeostasis

Acid-base and electrolyte balance

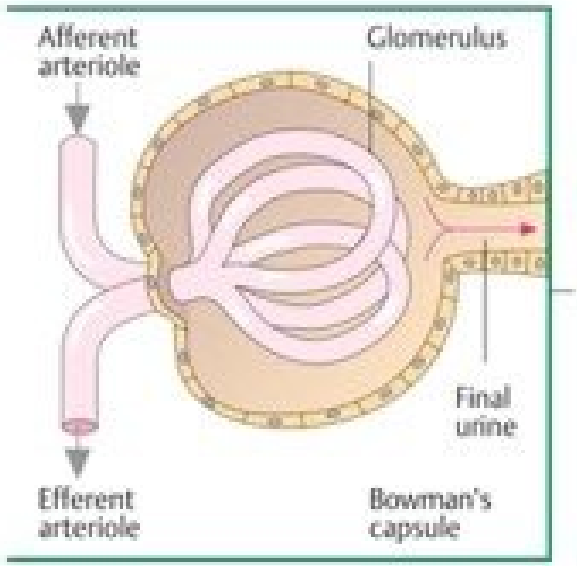
## Metabolic

Amino acid metabolism and carbohydrate metabolism (gluconeogenesis)

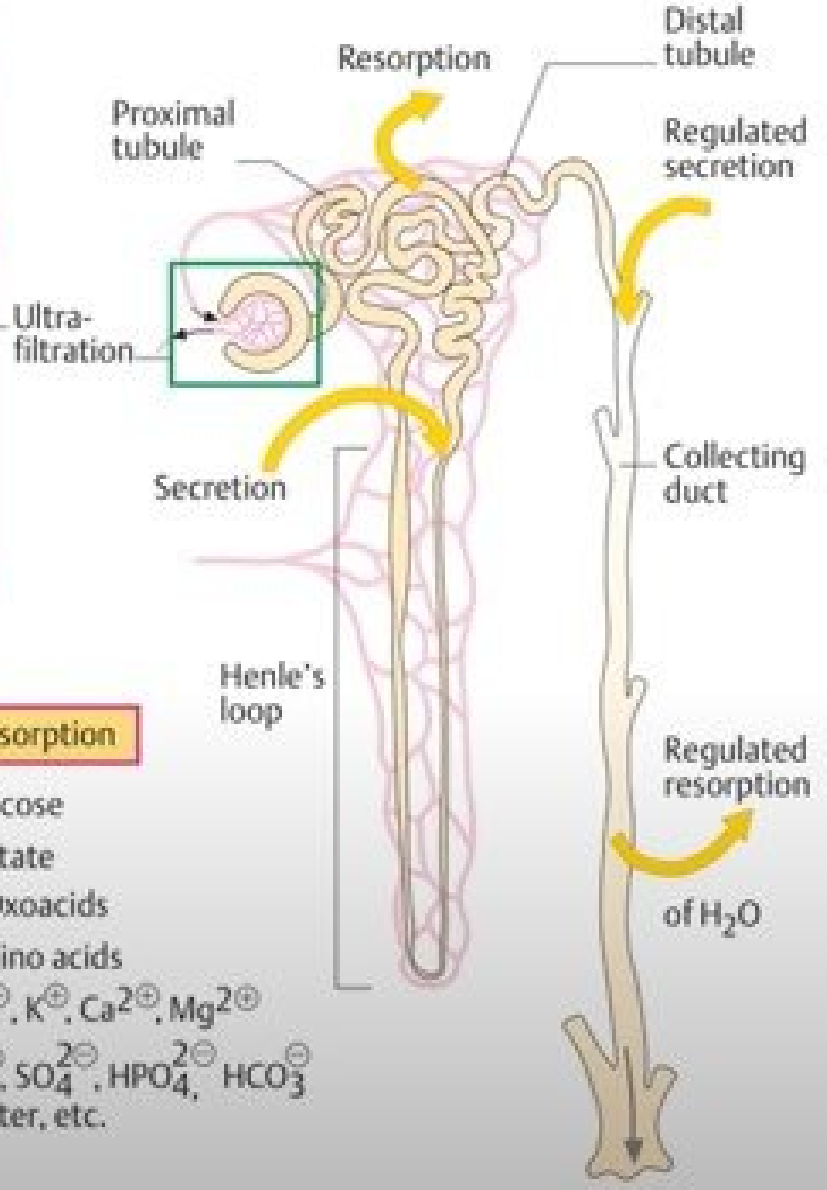
Part 2

# Excretory Function of the Kidneys

# Urine Formation




Renal corpuscle




| Ultrafiltration | Secretion | Resorption |
|---|---|---|
| All solute plasma components smaller than 3 nm = 65 kDa | $H^{\oplus}$ | Glucose |
| | $K^{\oplus}$ | Lactate |
| | Drugs | 2-Oxoacids |
| | Uric acid | Amino acids |
| | Creatinine | $Na^{\oplus}$, $K^{\oplus}$, $Ca^{2\oplus}$, $Mg^{2\oplus}$ |
| | | $Cl^{\ominus}$, $SO_4^{2\ominus}$, $HPO_4^{2\ominus}$, $HCO_3^{\ominus}$ |
| | | Water, etc. |

**Parts of the Nephron:**

1. Renal corpuscle (*bowman capsule* and glomerulus)
2. Proximal convoluted tubules
3. *Loop of Henle*
4. Distal convoluted tubules
5. Collecting duct

# Three Steps of Urine Formation

## [1] Ultrafiltration

In the **glomeruli**, blood plasma undergoes **ultrafiltration** to produce **primary urine (renal filtrate)**

## [2] Reabsorption

In the **proximal convoluted tubule,** the renal filtrate undergoes **reabsorption,** in which most (99%) molecules and compounds are reabsorbed back from the filtrate

## [3] Secretion

In the **distal convoluted tubules,** filtrate will be added with more compounds, and will then be excreted as the **final urine**

# Three Steps of Urine Formation

## [1] Ultrafiltration

In the **glomeruli**, blood plasma undergoes **ultrafiltration** to produce **primary urine (renal filtrate)**

**The ultrafiltration step is non-selective** and allows all compounds with a size < 65 kDa to pass through the glomeruli

***Glomerular filtration rate (GFR)*** marks the body's ability to excrete products, and is quantified by the amount of primary urine formed within a unit of time (eg: 1 minute). Normal values: 100-125 mL/minute

GFR can be measured by selecting a specific compound as a marker of filtration (eg: creatinine). An abnormal GFR may indicate loss or disturbance of renal function.

$$GFR = \frac{\text{urine concentration A} \times \text{volume}}{\text{plasma concentration A}}$$

$$CrCl = \frac{UCr \times \text{volume}}{PCr}$$

# Three Steps of Urine Formation

## [2] Reabsorption

In the **proximal convoluted tubule,** the renal filtrate undergoes **reabsorption,** in which most (99%) molecules and compounds are reabsorbed back from the filtrate

### Mechanisms of Reabsorption

**Active transport** for compounds such as glucose, amino acids, lactate, ketone bodies, calcium,$Na^+$, $K^+$
**Passive transport** for negative ions that passively follow the reabsorption of positive ions
**Osmosis** for water reabsorption
**Pynocytosis** for the reabsorption of large proteins

### Water Reabsorption

- Water reabsorption occur passively through the process osmosis
- Water reabsorption occurs within the collecting duct and is affected by ADH (antidiuretic hormone) which works to increase the volume of water reabsorbed
- ADH deficiency results in a condition called diabetes insipidus, in which urine formation can reach a volume of 30 L per

### Hormones Affecting Reabsorption

- ADH (antidiuretic hormone): increases water reabsorption
- PTH (parathyroid hormone): increases calcium reabsorption
- Aldosterone: increases $Na^+$ reabsorption and $K^+$ excretion
- ANP (atrial natriuretic peptide): reduces reabsorption of $Na^+$

# Three Steps of Urine Formation

| Characteristic | Description |
|---|---|
| Amount | 1–2 liters per 24 hours; highly variable depending on fluid intake and water loss through the skin and GI tract |
| Color | Straw or amber; darker means more concentrated; should be clear, not cloudy |
| Specific gravity | 1.010–1.025; a measure of the dissolved material in urine; the lower the value, the more dilute the urine |
| pH | Average 6; range 4.6–8.0; diet has the greatest effect on urine pH |
| Composition | 95% water; 5% salts and waste products |
| Nitrogenous wastes | Urea—from amino acid metabolism<br>Creatinine—from muscle metabolism<br>Uric acid—from nucleic acid metabolism |

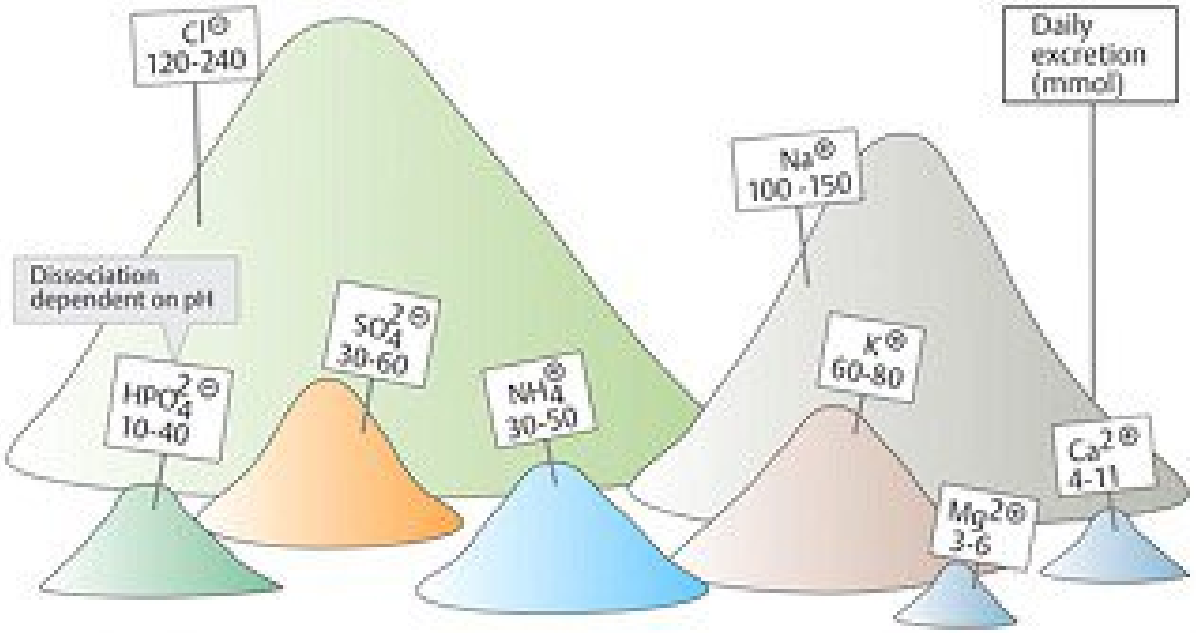
## [3] Secretion

In the **distal convoluted tubules,** filtrate will be added with more compounds, and will then be excreted as the **final urine**

# Normal Urine Composition

## Inorganic Compounds

**Cation:** $Na^+$, $K^+$, $Ca^{2+}$, $Mg^{2+}$ and $NH_4^+$
**Anion:** $Cl^-$ , $SO_4^{2-}$ and $HPO_4^{2-}$
$Na^+$ dan $Cl^-$ makes up 2/3 of electrolytes in the final urine



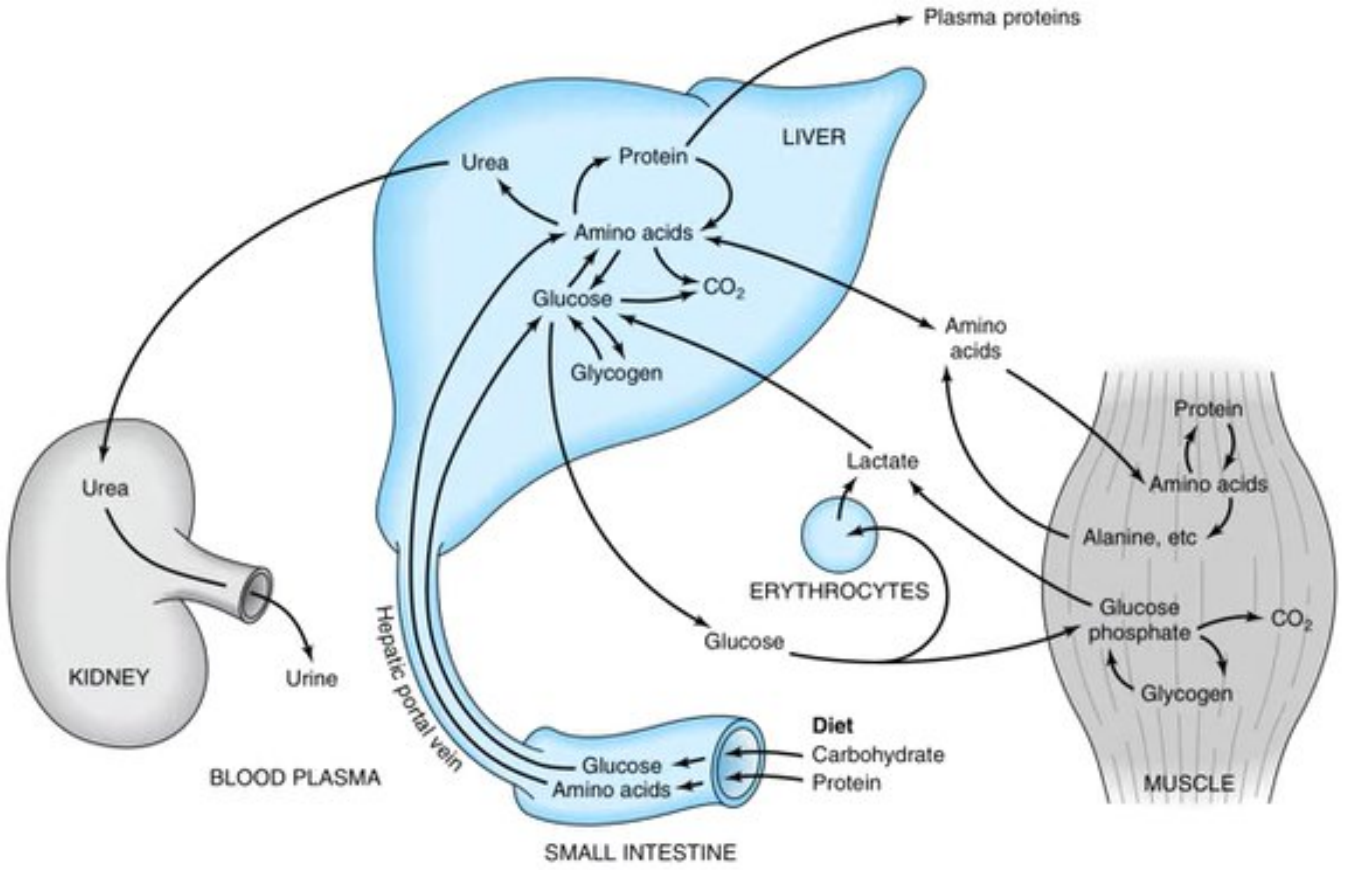

## Organic Compounds

**Metabolic waste products:**
Urea: 20-35 g
Uric acid: 0.3-2 g
Creatinine: 0.05-0.1 g

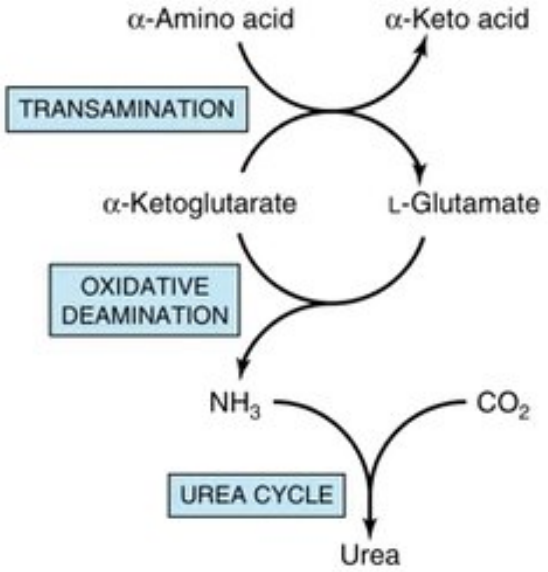
**Other physiologic compounds:**
Glucose: Normal <0.16 g
Ketone bodies: Normal < 3 g
Protein: Normal <0.15 g

# Normal Urine Composition

## Metabolic Waste Product: [1] Urea




- Urea is the end product of amino acid metabolism
- Urea synthesis occurs in the liver, with the aim of converting toxic end-products (ammonia) into a non-toxic product (urea)
- Urea formed in the liver exits into the bloodstream, and is then filtered and excreted by the kidneys
- Urea excretion in the urine is affected by: diet, protein metabolism, and the kidney's capability of reabsorbing and filtrating urea
- Patients with kidney failure often struggle to excrete urea, therefore experiencing increased systemic urea levels in the blood (uremia)



# Normal Urine Composition

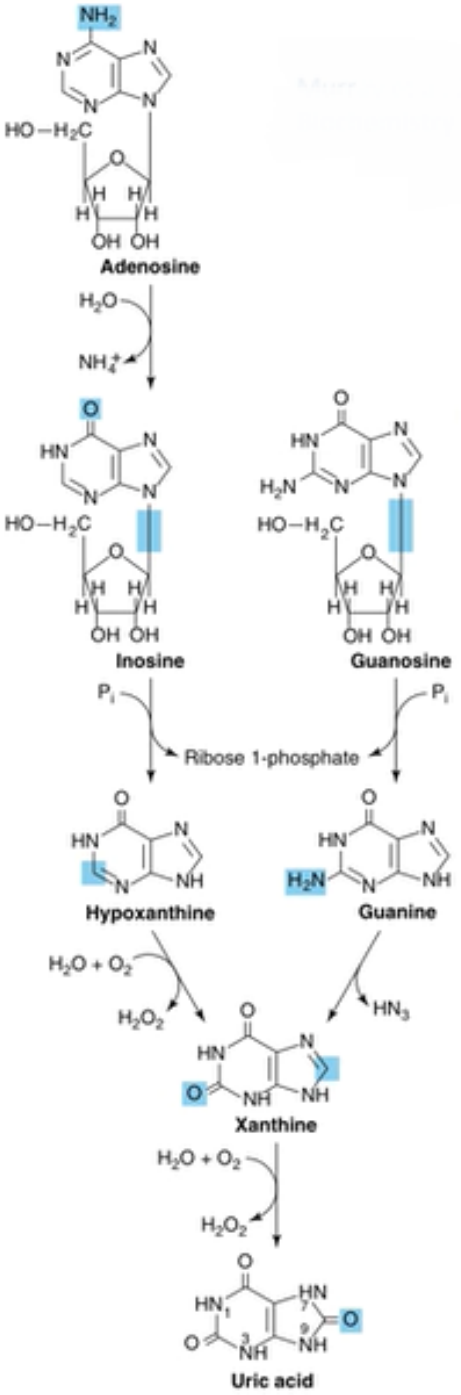
## Metabolic Waste Product: [2] Uric Acid

**Uric acid** is the end product of **purine catabolisme**, and it **does not dissolve in water**

Both adenosine and guanosine are purines that are converted into xanthine. Conversion of xanthine into uric acid requires the enzyme *xanthine oxidase*

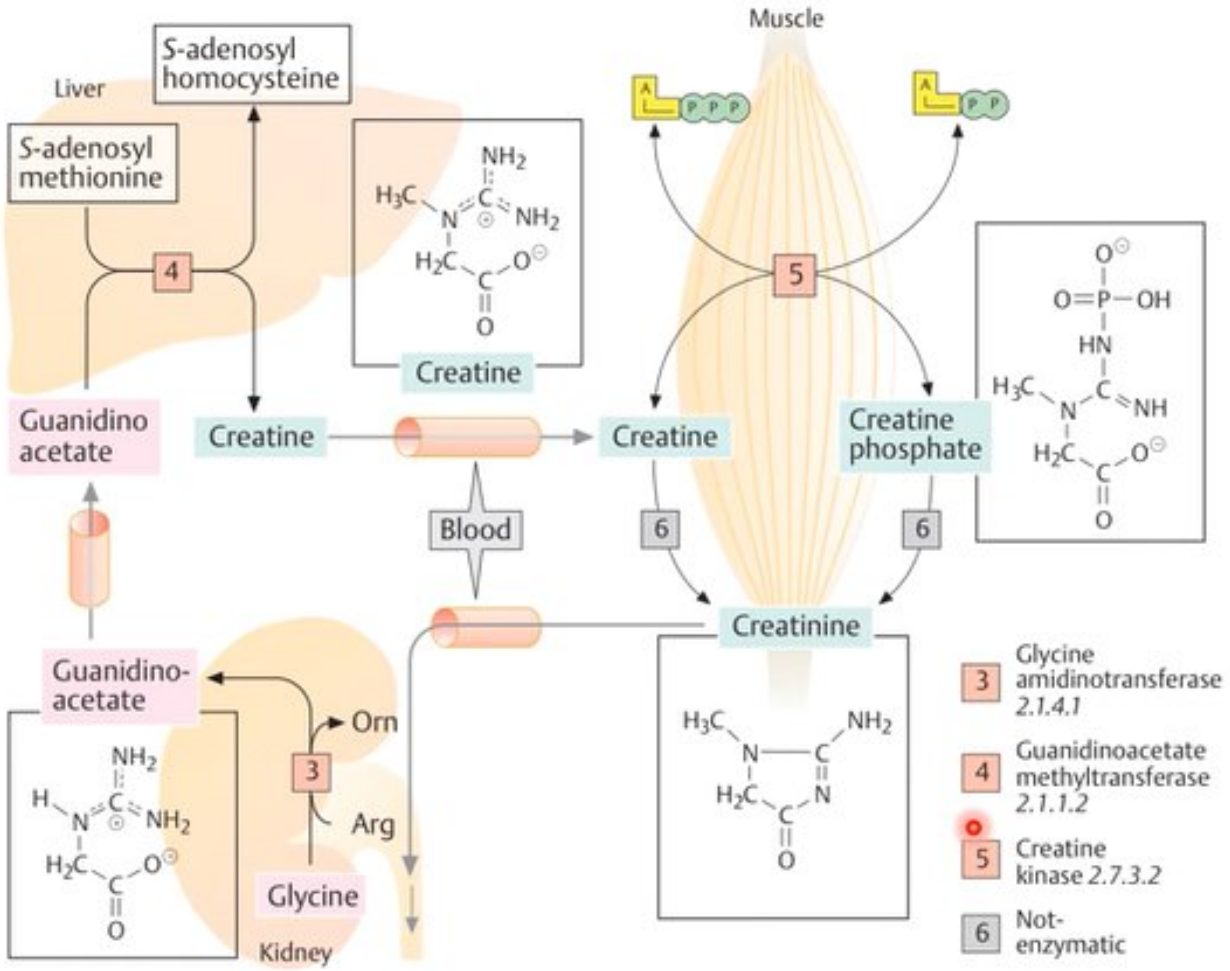
The amount of uric acid excreted in urine is affected by diet, and hence can not be used to reflect the GFR

In urine, uric acid can precipitate into crystals that turn into kidney stones. Increased plasma uric acid levels (hyperuricaemia) and urine uric acid levels occur in high-purine diets



# Normal Urine Composition

## Metabolic Waste Product: [3] Creatinine




**Creatinine** is the end product of muscle energy metabolism, from the cycling of creatine and creatine phosphate

Because the amount of creatinine excreted is relatively constant towards muscle mass, it can be used as a reliable marker for measuring GFR

# Abnormal Urine Composition

## Glycosuria

- Excess glucose in the urine
- Often found in patients with diabetes mellitus

## Proteinuria

- Excess protein in the urine
- Indicates an increase in glomeruli permeability

## Hematuria

- Excess erythrocytes in the urine
- May be caused by increased glomerular permeability or can also indicate a urinary tract infection (UTI) or kidney stones

## Ketonuria

- Excess ketone bodies in the urine
- Indicates increase utilization of fats and proteins as energy source in the body. Eg: in diabetes mellitus or in high-protein or ketogenic diets

## Bacteriuria

- Excess bacteria in the urine, often accompanied with WBCs
- Indicates a UTI

# Renal Calculi

- Renal calculi (kidney stones) are formed from through the precipitation of excess minerals in the urine
- Main cause is calcium, but can also be caused by other compunds such as uric acid
- Risk factors include lack of fluid consumption or excess consumption of minerals (eg: from dietary supplements)
- Formation of renal calculi often begins in the renal pelvis, but will create colicky pain and bleeding when it enters ureters.
- The blockage of urinary flow due to renal calculi often results in backward urine flow and hence damaging the kidneys (hydronephrosis)

Part 3

# Homeostatic Function of the Kidneys

# Renal Regulation of Acid-Base Balance

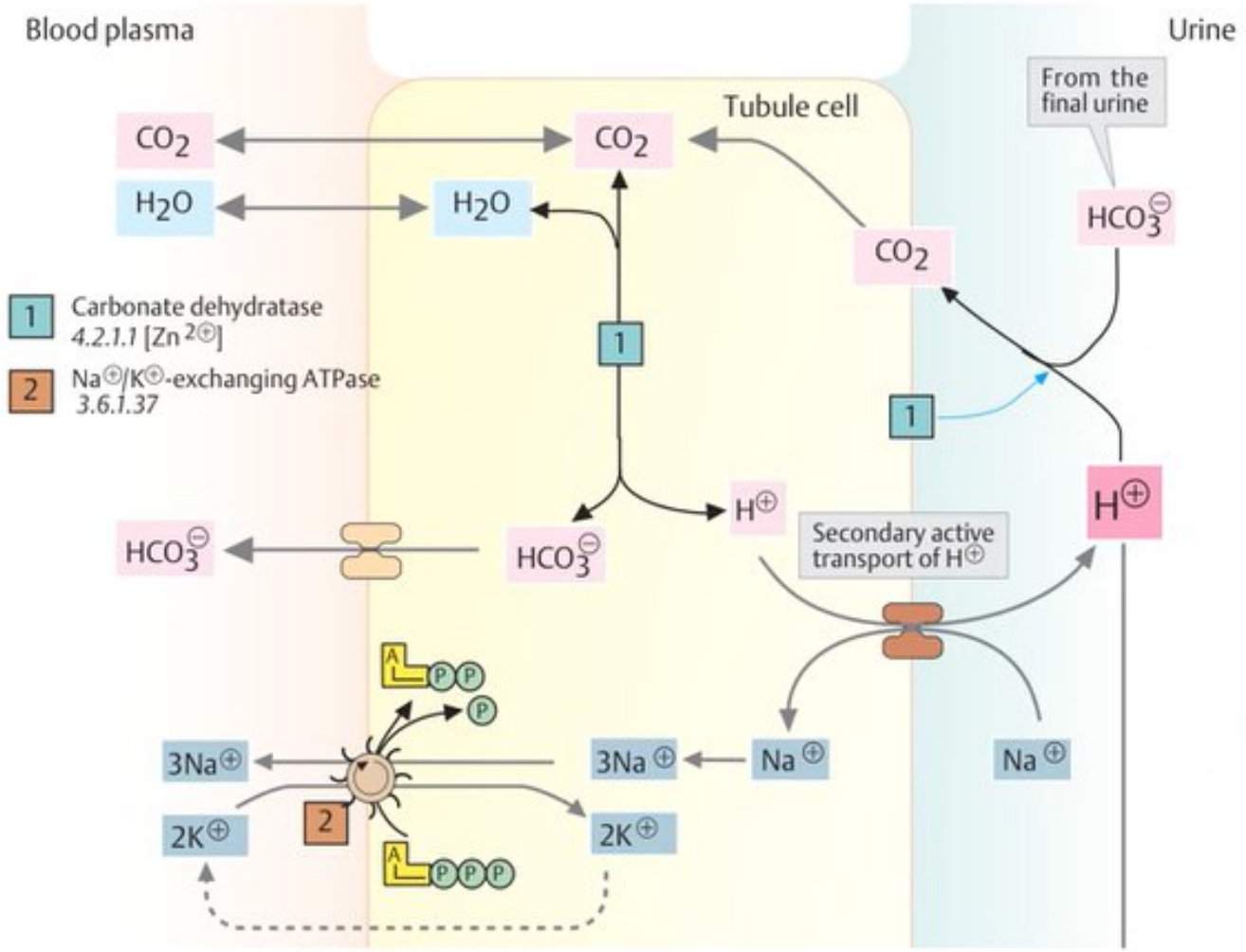
The kidneys hold an important role in maintaining acid-base balance

Renal regulation of acid-base balance is more time intensive and permanent (initiated within a few days-weeks) compared to the respiratory regulation of acid base balance (initiated within 1-3 minutes)

There are three buffer mechanisms of renal acid-base balance:

1. Proton $H^+$ excretion and carbonate ($HCO_3^-$) reabsorption
2. Protein buffer
3. Phosphate buffer

# Renal Regulation of Acid-Base Balance




## [1] Regulation of proton $H^+$ excretion and an carbonate reabsorption

The renal tubules can either increase the secretion of $H^+$ during acidosis or can increase the conservation of $H^+$ during alkalosis

**<u>An example of renal compensation during acidosis</u>:**

$CO_2$ from plasma combines with $H_2O$ to form carbonate ($HCO_3^-$) and $H^+$ through the enzyme *carbonate dehydratase*

↓

Carbonate then enters the plasma to increase plasma alkalinity

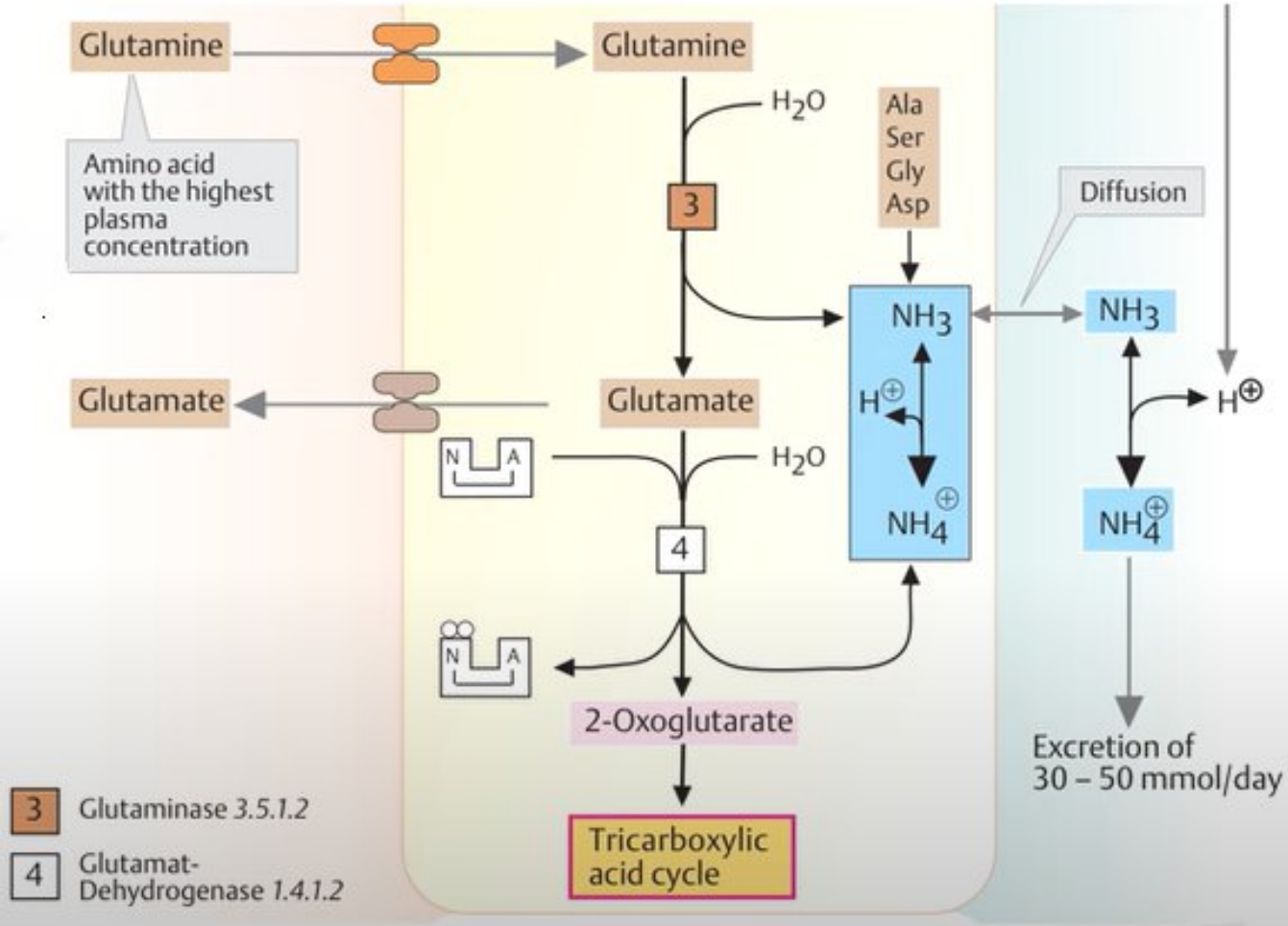
↓

$H^+$ protons exits into the urine via active transport accompanied with $Na^+$ exchange

↓

In the urine $H^+$ can either be excreted or can bind with $HCO_3^-$ pada therefore resulting in additional $HCO_3^-$ reabsorption in the form of $CO_2$

# Renal Regulation of Acid-Base Balance




## [2] Protein Buffer System

**<u>An example of renal compensation during acidosis</u>:**

In the renal tubules glutamine undergoes deamination to produce glutamate and ammonia ($NH_3$)

$NH_3$ diffuses freely into urine via the membrane of the tubules

$NH_3$ binds to $H^+$ to form ammonium ($NH_4^+$)

Ammonium that has been formed is unable to re-enter the tubules and must be excreted

The protein buffer system hence results in the reduction of the body $H^+$ content

# Renal Regulation of Acid-Base Balance

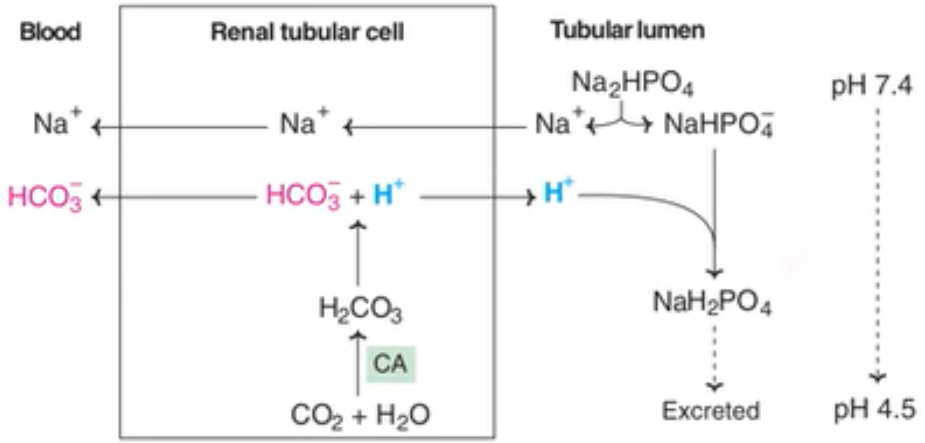



***Fig. 21.7 :*** *Renal regulation of blood pH–Excretion of titratable acid by phosphate buffer mechanism (CA–Carbonic anhydrase).*

## [3] Phosphate Buffer System

**<u>An example of renal compensation during acidosis</u>:**

Recall that renal tubules excrete excess $H^+$ through an exchange mechanism with $Na^+$

In the phosphate buffer system, $Na^+$ originates from **disodium** hydrogen phosphate ($Na_2HPO_4$)

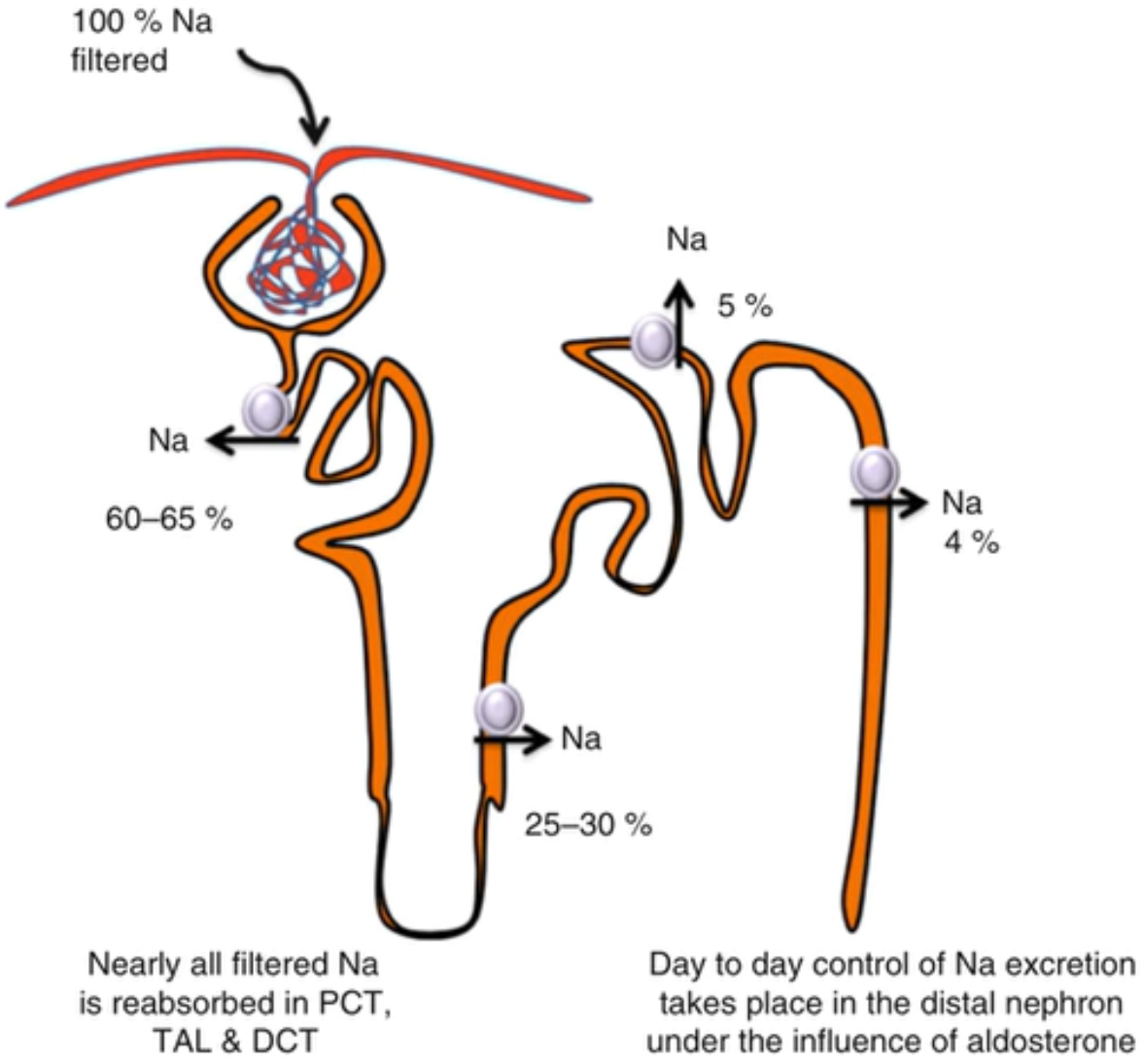
The excreted $H^+$ then binds with **sodium** hydrogen phosphate ($NaHPO_4^-$) to form natrium **dihydrogen** phosphate ($NaH_2PO_4^-$) that can then be excreted in the final urine

# Renal Regulation of Electrolyte Balance

## Sodium Balance

**Reabsorption of $Na^+$** occurs through active transport in the proximal convoluted tubule (65%), *Loop of Henle* (25%), distal convoluted tubule (5%) and collecting duct (5%).

This active transport-mediated reabsorption process is **increased through aldosterone activity** and is **decreased through the activity of atrial natriuretic peptide (ANP)**



# Renal Regulation of Eletrolyte Balance

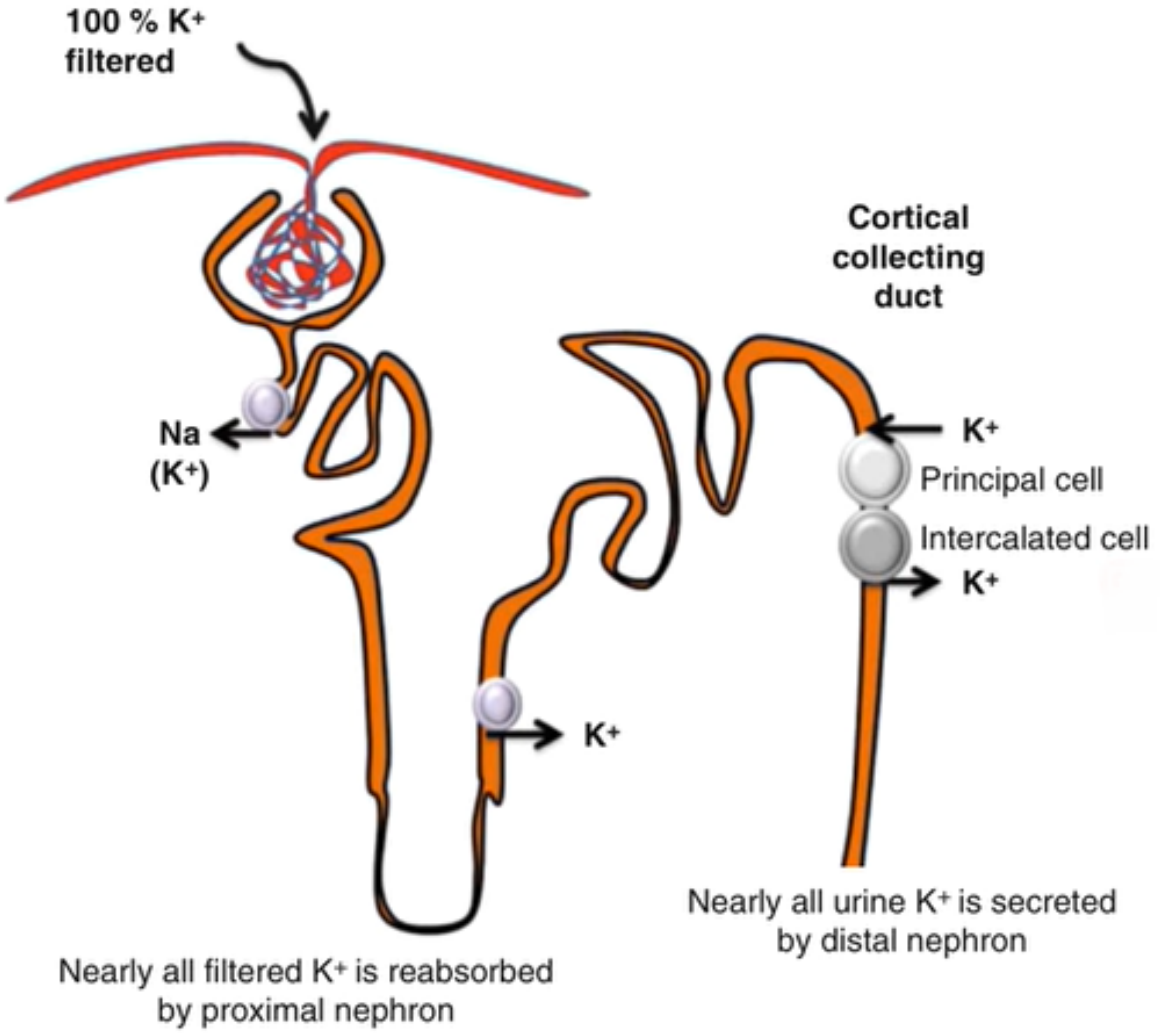
## Potassium Balance

Previously filtered $K^+$ can be reabsorbed either **passively following** $Na^+$ in the proximal convoluted tubules or **actively in the Loop of Henle.**

In hypokalemic conditions (low potassium level), **intercalated cells** in the collecting duct reabsorbs $K^+$.

$K^+$ is excreted by the **principal cell** of the collecting duct. Secretion of $K^+$ **increases through the activity of aldosterone**

**Aldosterone helps control the balance of water and salts in the kidney by keeping sodium in and releasing potassium from the body**



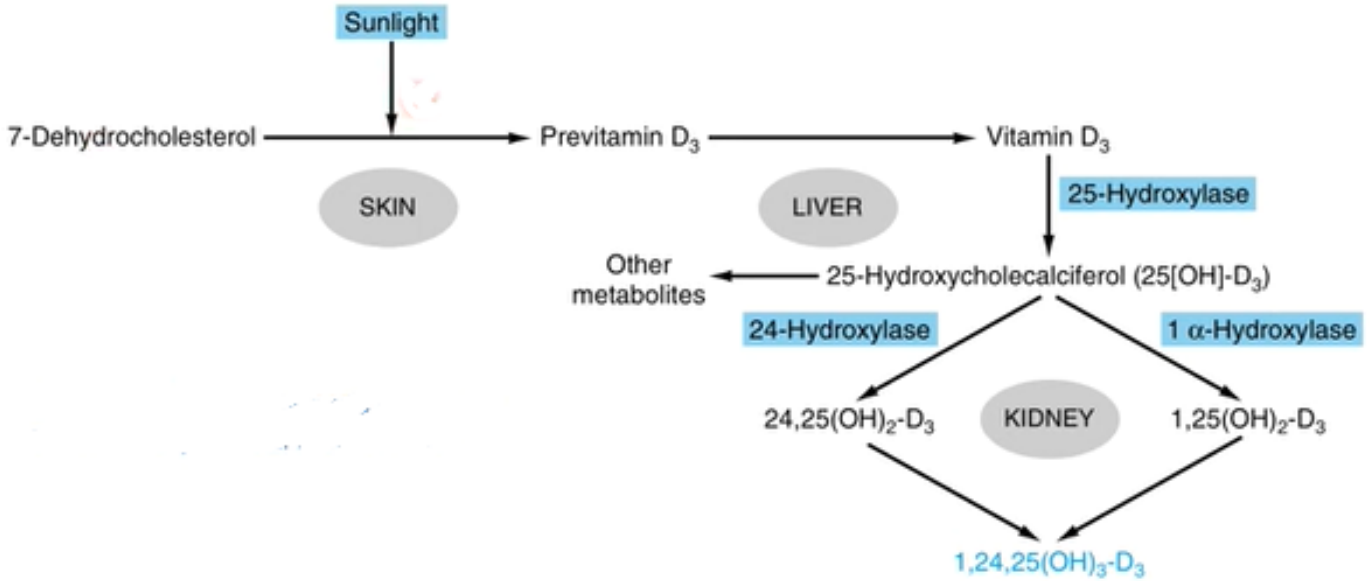
Part 4

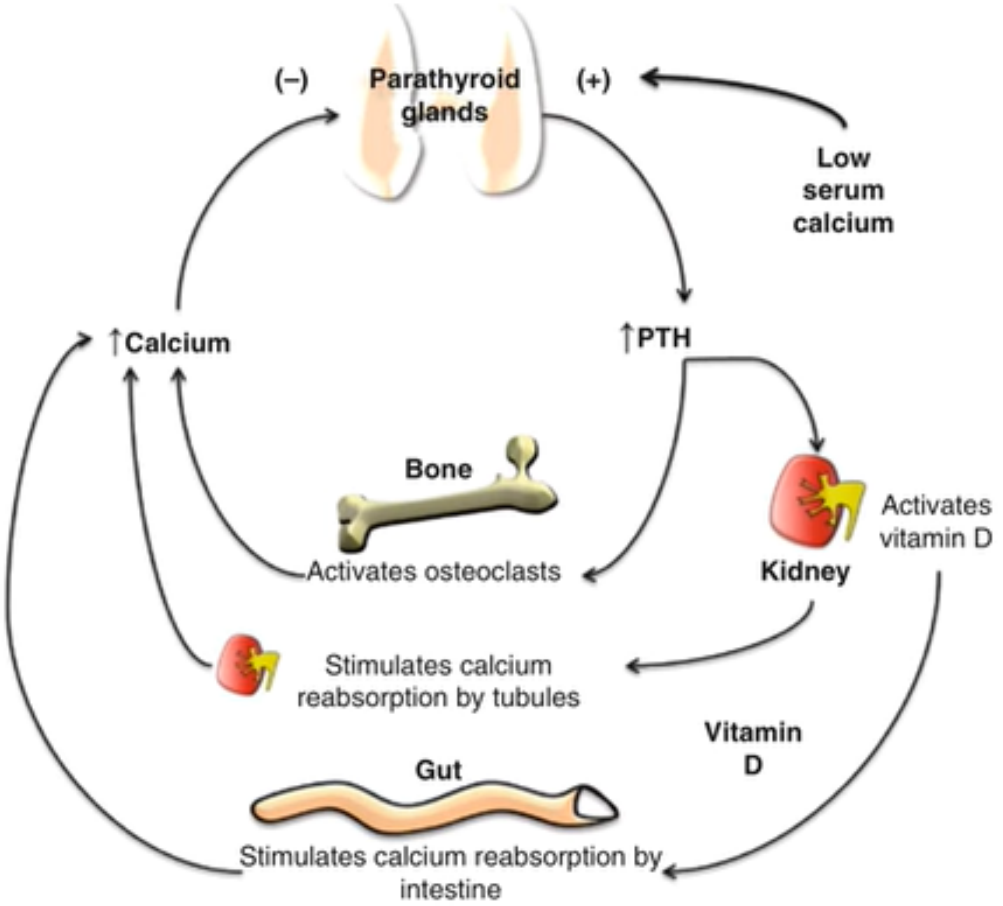
# Endocrinal Function of the Kidneys

# Formation of the Calcitriol Hormone

**Formation calcitriol (1,25-dihydroxycholecalciferol) in the kidneys:**

- Vitamin D (inactive form) can be obtained either from the diet or through a chemical process involving photolysis of 7-dehydrocholesterol in sunlight-exposed skin
- Within the kidneys, calcitriol (active vitamin D) is formed from inactive Vitamin D through a hydroxylation process mediated by the hormone **1-alfa-hydroxylase**. This hormone is upregulated by the parathyroid hormone (PTH)
- Calcitriol then works in conjunction with PTH to increase calcium uptake in the gut



# Formation of the Erythtropoietin (EPO) Hormone

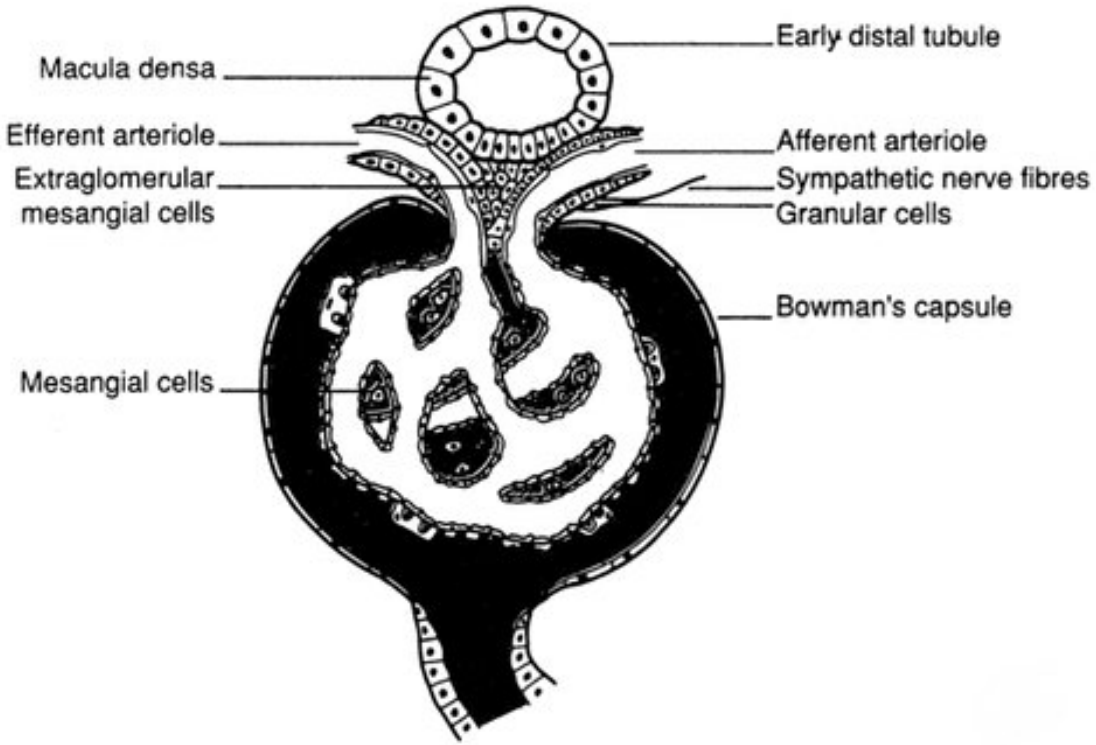



**Figure 2.6** The juxtaglomerular apparatus. The beginning of the distal tubule (i.e. where the loop of Henle re-enters the cortex) lies very close to the afferent and efferent arterioles, and the cells of both the afferent arteriole and the tubule show specialization. The cells of the afferent arteriole are thickened, granular (juxtaglomerular) cells and are innervated by sympathetic nerve fibres. The mesangial cells are irregularly shaped and contain filaments of contractile proteins. Identical cells are found just outside the glomerulus, and are termed extraglomerular mesangial cells or 'Goormaghtigh cells'.

Erythropoietin (EPO) is a glycoprotein responsible for erythropoiesis (formation of red blood cells)

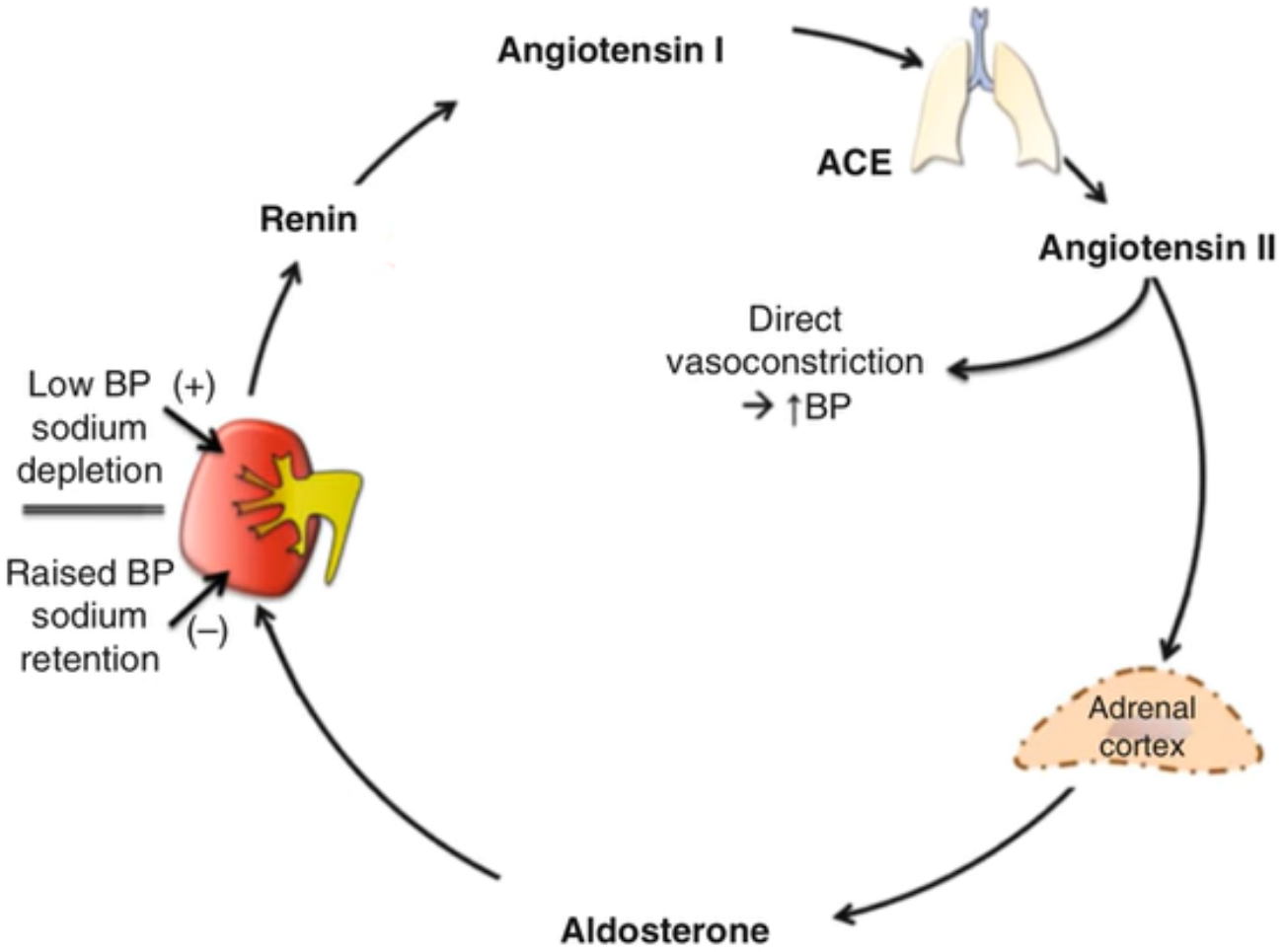
EPO works in the bone marrow by stimulating the differentiation of progenitor cells (stem cells) into erythrocytes

EPO is formed in the kidney as a response towards hypoxia (Low $PO_2$)

EPO synthesis occurs in the **mesangial cells** and the **renal tubular cells**

Patients with kidney failure often experience disturbed EPO synthesis and hence results in anemia

# Renin-Angiotensin




The renin-angiotensin system plays an important role in the regulation of blood pressure (BP)

The kidneys produce renin as a response towards low BP or from reduction in sodium levels

Once formed by the kidneys, renin enters the circulation to the convert angiotensinogen into angiotensin I. Angiotensin I is then converted into angiotensin II by the *angiotensin converting enzyme (ACE).*

Angiotensin II ultimately results in the increase of systemic BP.

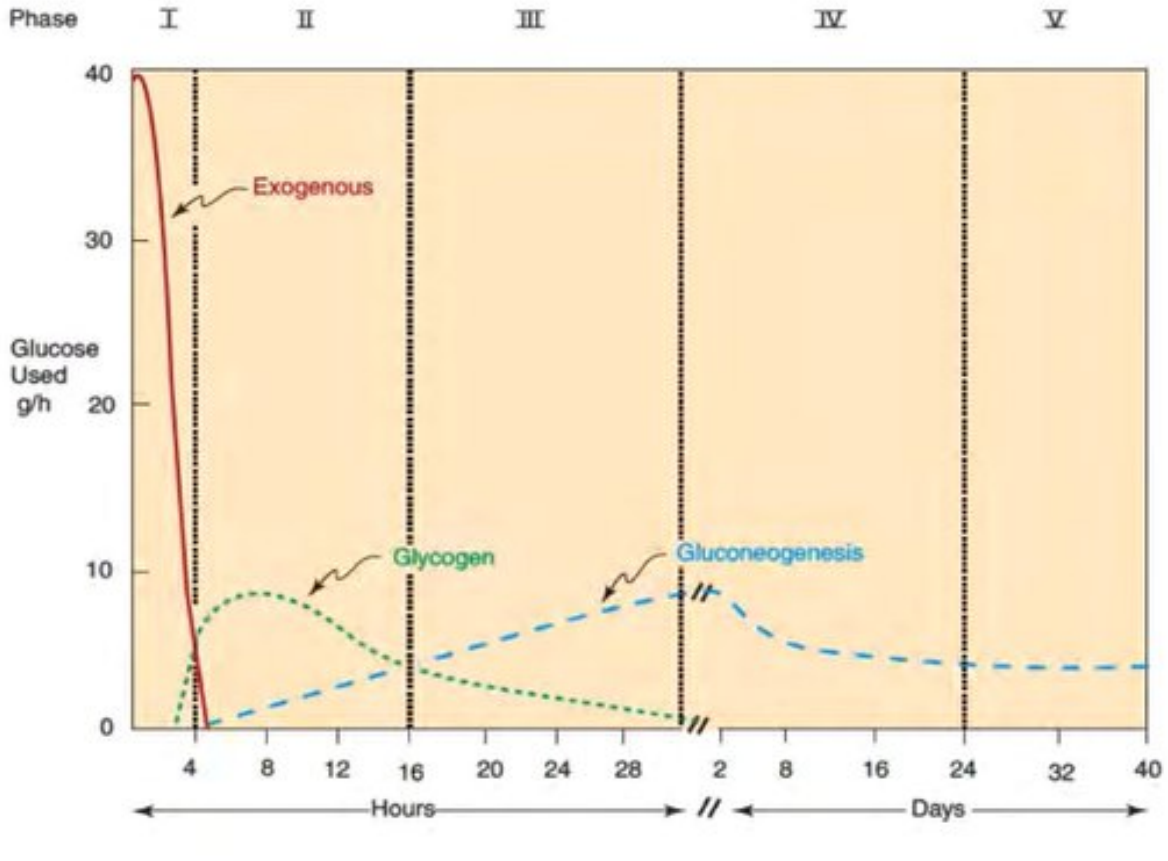
Part 5

# Metabolic Function of the Kidneys

# Renal Gluconeogenesis

- Besides the liver, the kidney is another organ capable of performing gluconeogenesis
- Renal gluconeogenesis occurs once the body is in the starvation state
- Substrates used as gluconeogenesis precursors in the kidneys include: glutamine, lactate, glycerol, and fructose

| Phase | ORIGIN OF BLOOD GLUCOSE | TISSUES USING GLUCOSE | MAJOR FUEL OF BRAIN |
|---|---|---|---|
| I | Exogenous | All | Glucose |
| II | Glycogen<br>Hepatic gluco–neogenesis | All except liver.<br>Muscle and adipose tissue at diminished rates | Glucose |
| III | Hepatic gluconeogenesis<br>Glycogen | All except liver.<br>Muscle and adipose tissue at rates intermediate between II and IV | Glucose |
| IV | Gluconeogenesis, hepatic and renal | Brain, RBCs, renal medulla. Small amount by muscle | Glucose, ketone bodies |
| V | Gluconeogenesis, hepatic and renal | Brain at a diminished rate, RBCs, renal medulla | Ketone bodies, glucose |



# Renal Metabolism of Amino Acids

Beside its role in amino acid degradation (catabolism), the kidney is also capable of various biosynthesis of amino acids (anabolic processes)

**Figure 21.7 Kidney and liver provide carnitine for other tissues.** Abbreviations: (TML), trimethyllysyl residues in protein molecules; TML, free trimethyllysine.

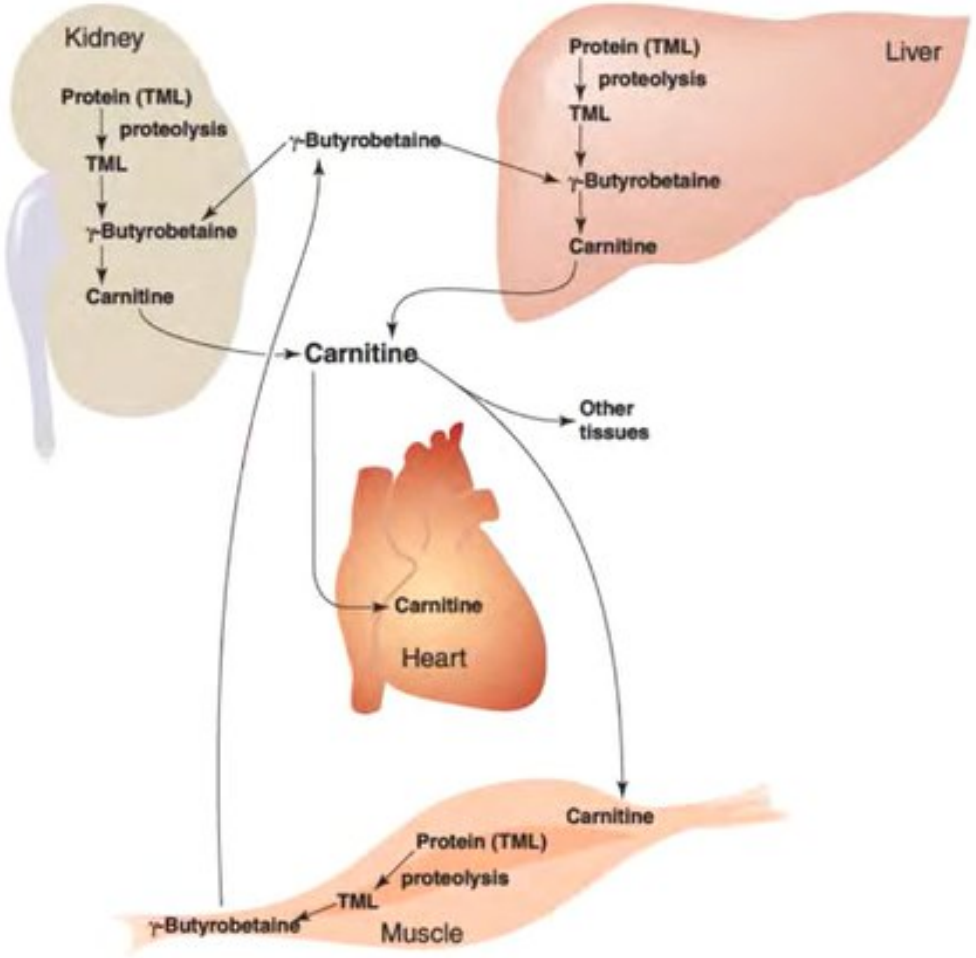
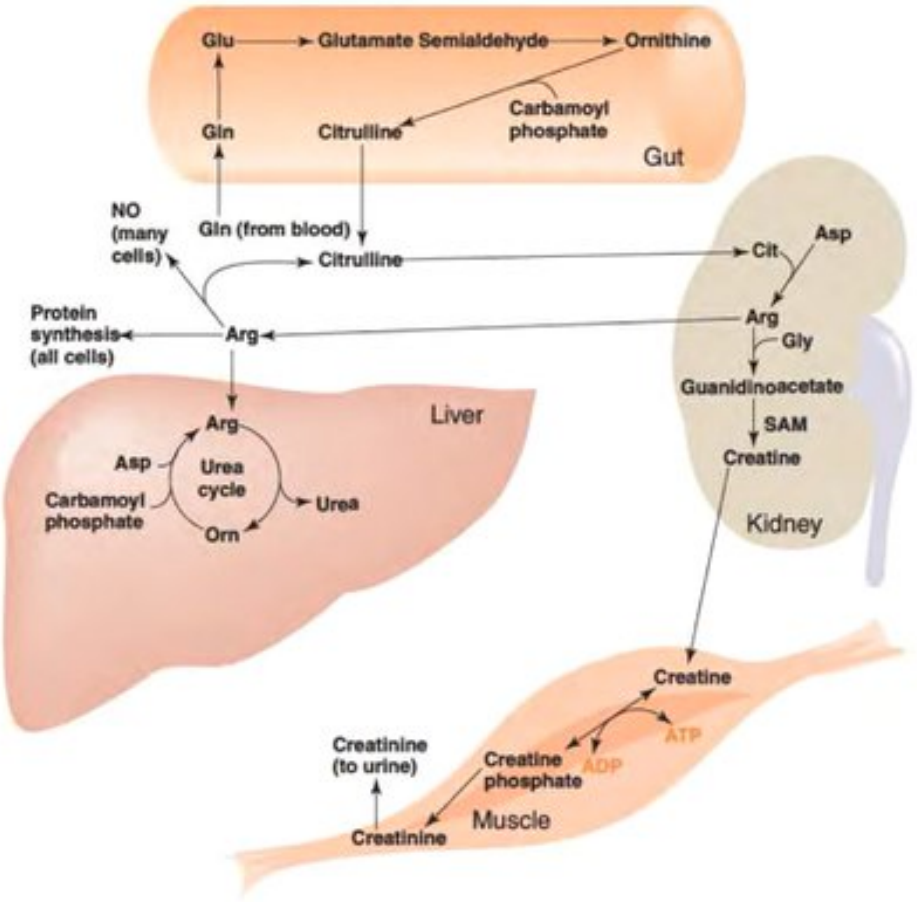



**Figure 21.6 Gut and kidney function together in synthesis of arginine from glutamine.** Abbreviations: Cit, citrulline; Arg, arginine; Asp, aspartate; Gln, glutamine; Glu, glutamate; NO, nitric oxide; Gly, glycine; Orn, ornithine; and SAM, *S*-adenosylmethionine.



# Conclusion

**Renal excretory function:**

- Renal production of urine occur in three steps: filtration, reabsorption, secretion
- The renal filtration ability can be measured with the GFR
- Renal reabsorption is affected by hormones such as PTH, Aldosterone, ANP, ADH
- Composition of excreted urine can be evaluated for the detection of pathological conditions. Kidney stones are an example of the consequence of chronic abnormalities in urine composition

**Renal homeostatic function:**

- The kidneys are long-term regulators of acid-base balance through three mechanisms: proton excretion and carbonate reabsorption, phosphate buffer, and protein buffer mechanism
- The kidneys also regulate electrolyte balance, examples include $Na^+$ and $K^+$ regulation, both affected by aldosterone

**Renal endocrinal function**

- The kidneys synthesize calcitriol, a hormone crucial for calcium homeostasis
- The kidneys synthesize EPO, a hormone crucial for erythropoiesis
- The kidneys synthesize renin, a hormone crucial for maintaining blood pressure through the renin-angiotensin system

**Renal metabolic function**

- The kidneys are involved in gluconeogenesis
- The kidneys are involved in amino acid metabolism

# PURINE & PYRIMIDINE METABOLISM & DISORDERS

By

Dr. Faten Allyan

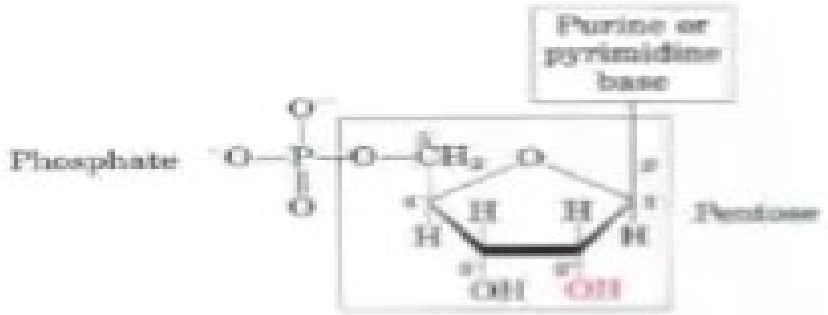
# INTRODUCTION

- Nucleotides are building blocks of nucleic acids.
- They are non-essential nutrients , because they can be synthesized in the body.
- Nucleic acids occur in the nucleoprotein.
- Nucleic acids are further digested in the small intestine to generate nucleotides.
- Nucleotides are absorbed into intestinal mucosa cells , where they are degraded to three components : base , pentose , phosphate.

  Pentose is absorbed but base is degraded and excreted

# What are Nucleotides?

- Nucleotides are the basic building blocks of nucleic acids (both DNA & RNA)
- Structurally, nucleotides have 3 components
  (1) a nitrogenous (nitrogen-containing) base,
  (2) a pentose,
  (3) a phosphate



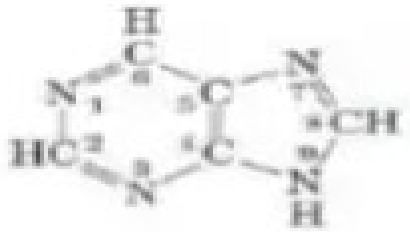

- The molecule without the phosphate group is called a **nucleoside.**

# Nucleotide Structure

**Nitrogenous bases**

- They are derivatives of two parent compounds, pyrimidine and purine.
- The bases are heterocyclic compounds.
- The carbon and nitrogen atoms in the parent structures are conventionally numbered to facilitate the naming and identification of the many derivative compounds.

Pyrimidine

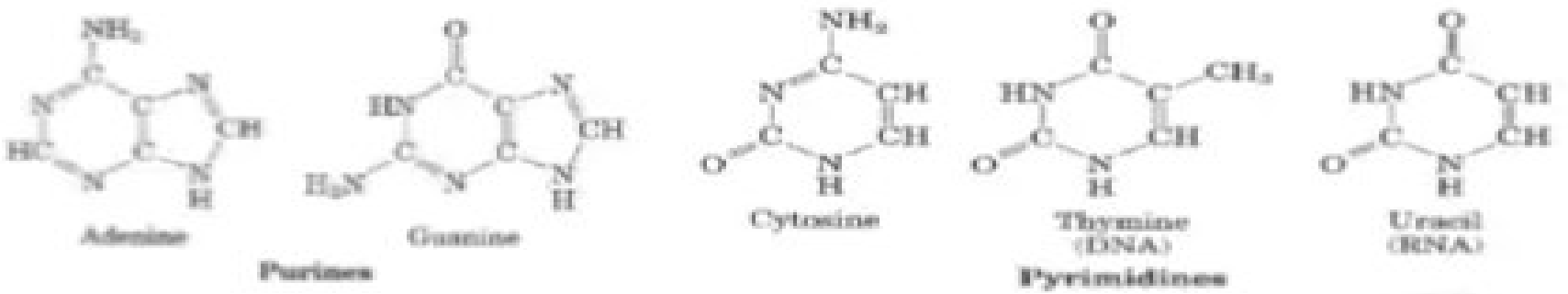


Purine

# Nitrogenous bases

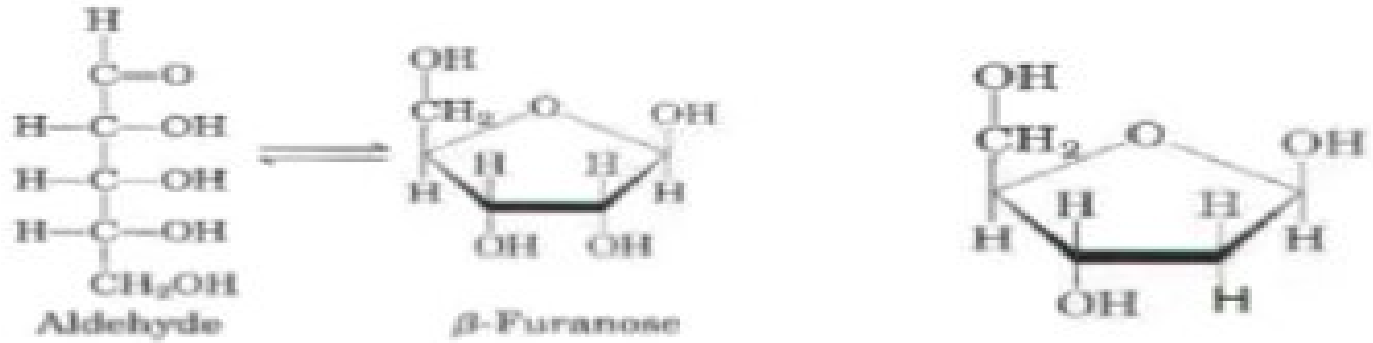
Both DNA and RNA contain

- two major purine bases, **adenine** (A) and **guanine** (G),
- and two major pyrimidines.
- In both DNA and RNA one of the pyrimidines is **cytosine** (C), but the second major pyrimidine **thymine** (T) in DNA and **uracil** (U) in RNA.



# Pentose sugar

- Nucleic acids have two kinds of pentoses.
- The recurring deoxyribonucleotide units of DNA contain 2 - deoxy-D-ribose, and
- The ribonucleotide units of RNA contain D-ribose.
- In nucleotides, both types of pentoses are in their β-furanose (closed five-membered ring) form.



# Functions of nucleotides

1. Nucleotides are **building block** of nucleic acid
2. Nucleotides serve as **carriers of activated intermediates** in the **synthesis** of some **carbohydrates**, **lipids**, and **proteins**.
3. They are **structural components** of **several essential coenzymes**

4. Nucleotides, such as **cyclic AMP** (CAMP) and **cyclic GMP** (CGMP), serve as **second messengers** in **signal transduction pathways.**

5. Nucleotides play an **important role** as "**energy currency" in the cell.**

6. Nucleotides are important **regulatory compounds** for **many pathways** of intermediary metabolism, **inhibiting or activating key enzymes**.

# Purine Nucleotide Metabolism
## Anabolism

- There are two pathways of synthesis of purine nucleotides :

  1.the De Novo synthesis pathway and the

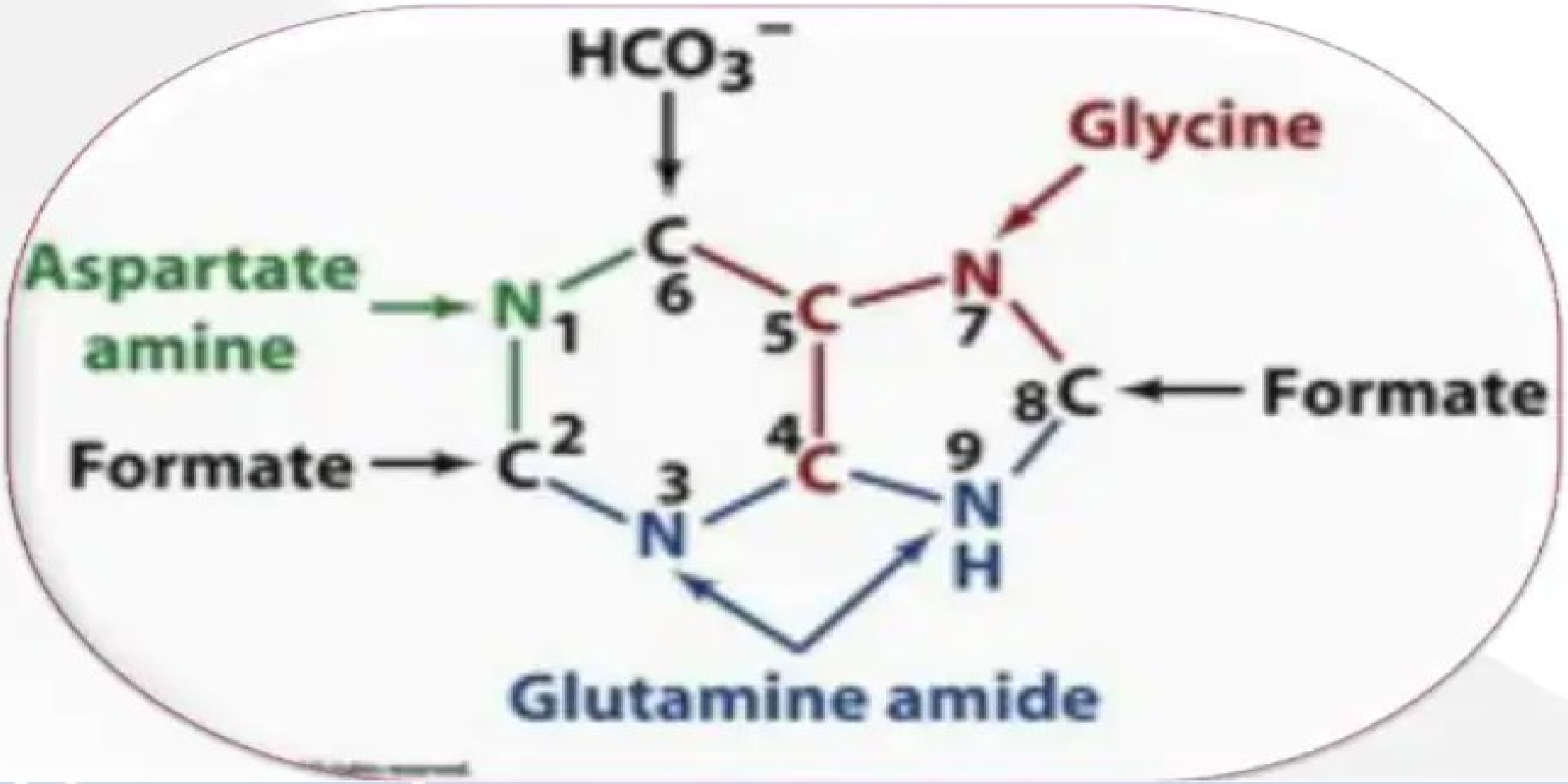
  2.Salvage pathway.

- The former is the main synthesis pathway of nucleotides , the latter is important one in brain and bone marrow.
- The de novo synthesis of purine nucleotide means using phosphoribose , amino acids , one carbon units and $CO_2$ as raw materials to synthesize purine nucleotide from the beginning.

# Formation of purine ring

- $N_1$ of purine is derived from amino group of aspartate.
- $C_2$ & $C_8$ from formate of $N^{10}$ - formyl THF.
- $N_3$ & $N_9$ are obtained from amide group of glutamine.
- $C_4$, $C_5$ & $N_7$ are contributed by glycine.
- $C_6$ directly comes from $CO_2$.

# Formation of purine ring



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

# Steps in Purine Biosynthesis

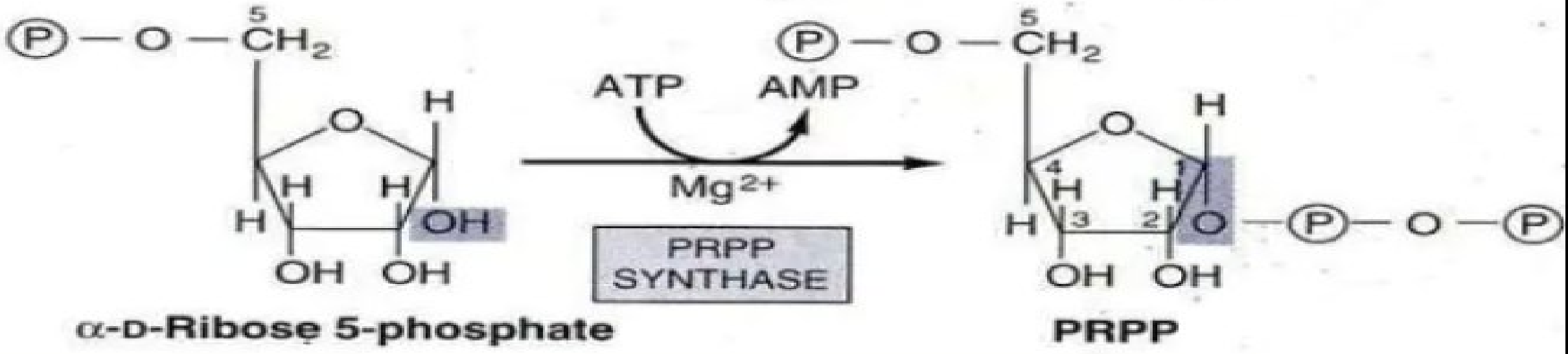
- Ribose 5-phosphate, of carbohydrate metabolism is the starting material for purine nucleotide synthesis.
- It reacts with ATP to form phosphoribosyl pyrophosphate (PRPP).
- Glutamine transfers its amide nitrogen to PRPP to replace pyrophosphate & produce 5-phosphoribosylamine.

# Biosynthesis of Purine Ribonucleotides

1. **Ribose 5-phosphate, produced in the hexose monophosphate shunt of carbohydrate metabolism is the starting material for purine nucleotide synthesis.**

   **It reacts with ATP to form phsophoribosyl pyrophosphate (PRPP).**

   **PRPP Synthetase is inhibited by PRPP**

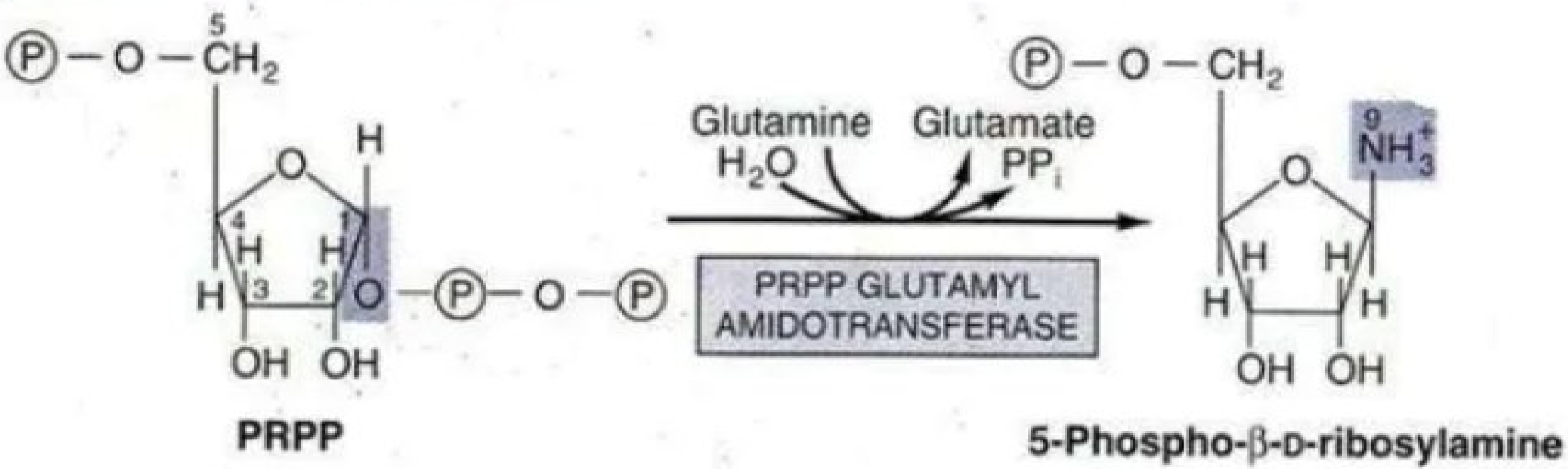



α-D-Ribose 5-phosphate

PRPP

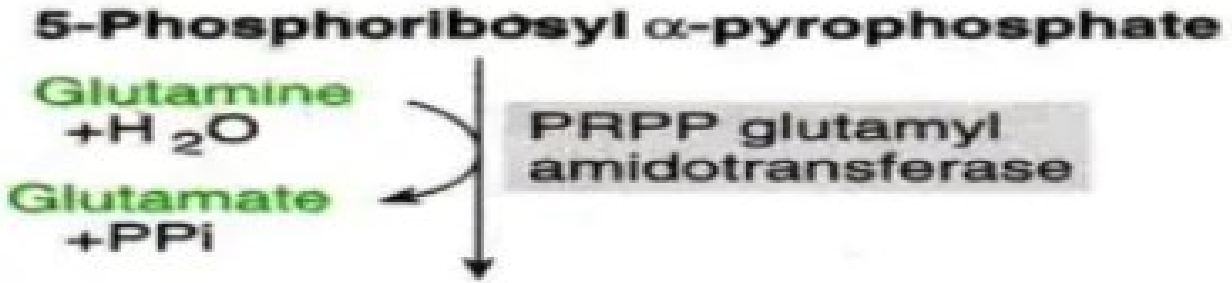
2. **Glutamine transfers it's amide nitrogen to PRPP to replace pyrophosphate and produce 5-phosphoribosylamine.**

**The enzyme PRPP glutamyl amidotransferase is controlled by feedback inhibition of nucleoltides (IMP, AMP and GMP,).**

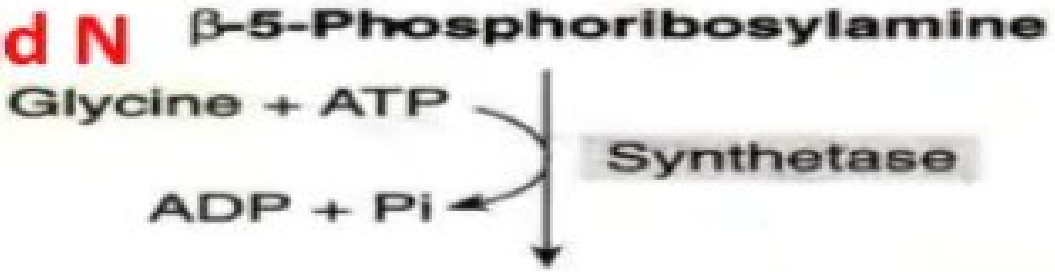


## Formation of PRPP


## Addition of N9




## Addition of C4 , C5 and N 7

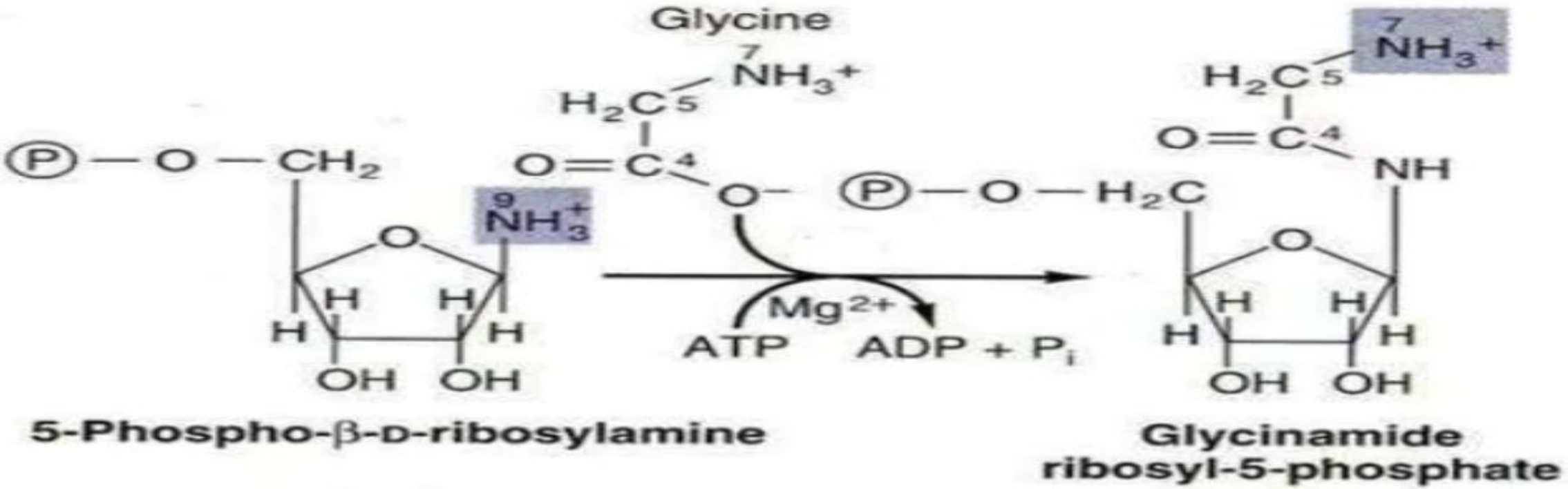



## Addition of C8


**Formylglycinamide ribosyl 5-phosphate**

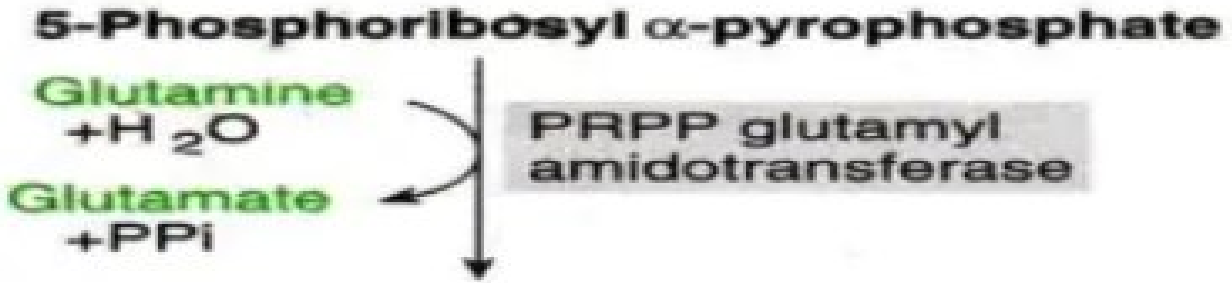
- PRPP glutamyl amidotransferase is controlled by feedback inhibition of nucleotides (IMP, AMP & GMP).
- This reaction is the 'committed.
- Phosphoribosylamine reacts with glycine in the presence of ATP to form glycinamide ribosyl 5-phosphate or glycinamide ribotide (GAR).
- Catalyzed by synthetase.

3. **Phosphoribosylamine reacts with glycine in the presence of ATP to form glycinamide ribosyl 5-phosphate or glycinamide ribotide (GAR).**

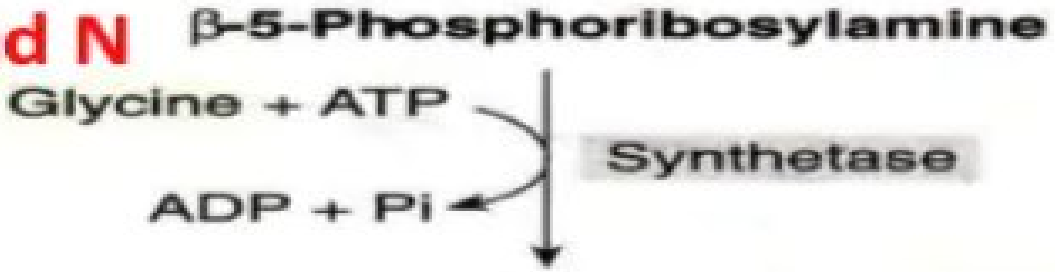


## Formation of PRPP


## Addition of N9




## Addition of C4 , C5 and N 7

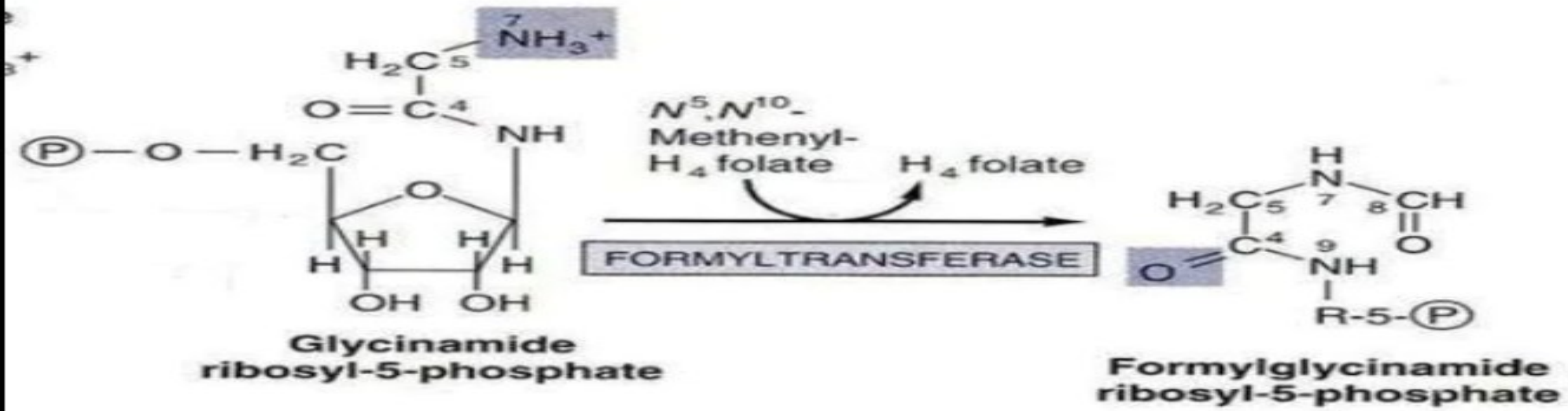



## Addition of C8

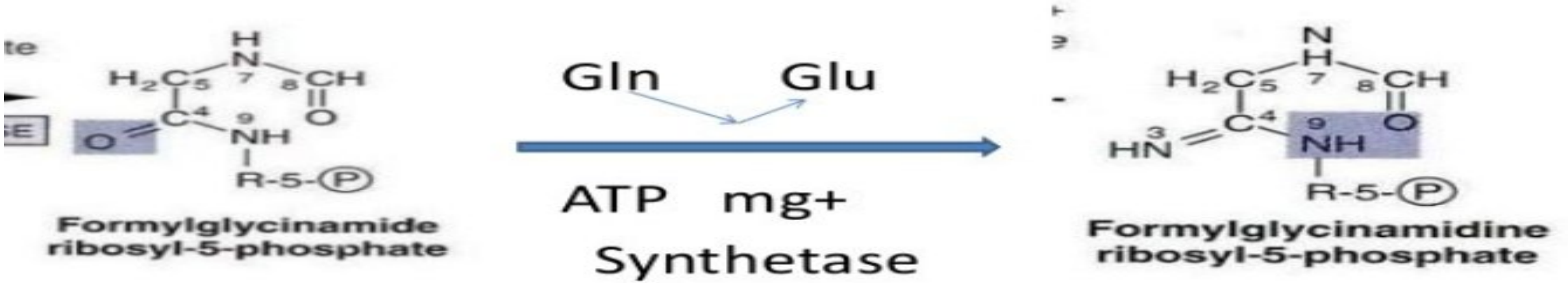

**Formylglycinamide ribosyl 5-phosphate**

- $N^{10}$-Formyl tetrahydrofolate donates the formyl group & the product formed is formylglycinamide ribosyl 5-phosphate.
- The reaction is catalyzed by formyltransferase.
- Glutamine transfers the second amido amino group to produce formylglycinamidine ribosyl 5-phosphate.
- The reaction is catalyzed by synthetase.

4. **N5,N¹⁰ formyl tetrahydrofolate donates the formyl group and the product formed is formylglycinamide ribosyl 5-phosphate.**

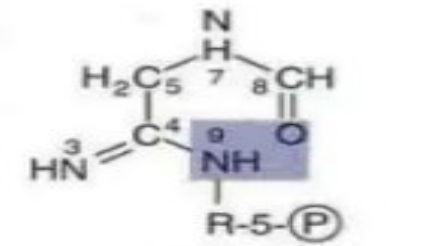


5. **Glutamine transfers the second amido amino group to produce formylglycinamideine ribosyl 5-phosphate.**

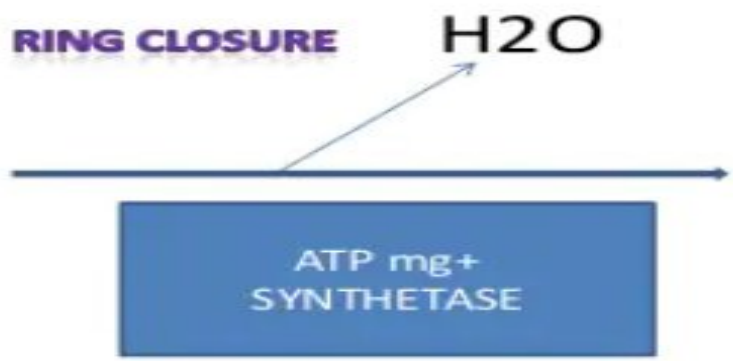


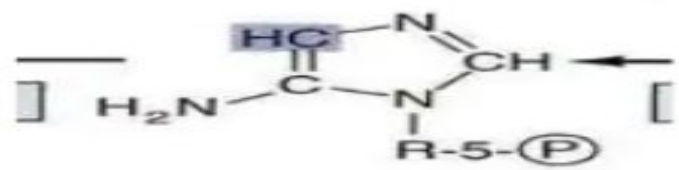
- The imidazole ring of the purine is closed in an ATP dependent reaction to yield 5-aminoimidazole ribosyl 5-phosphate.
- The reaction is catalyzed by synthetase.
- Incorporation of $CO_2$ (carboxylation) occurs to yield aminoimidazole carboxylate ribosyl 5-phosphate.
- The reaction is catalyzed by carboxylase.

6. **The imidazole ring of the purine is closed in an ATP dependent reaction to yield 5-aminoimidazole ribosyl 5-phosphate**




**Formylglycinamidine ribosyl-5-phosphate**

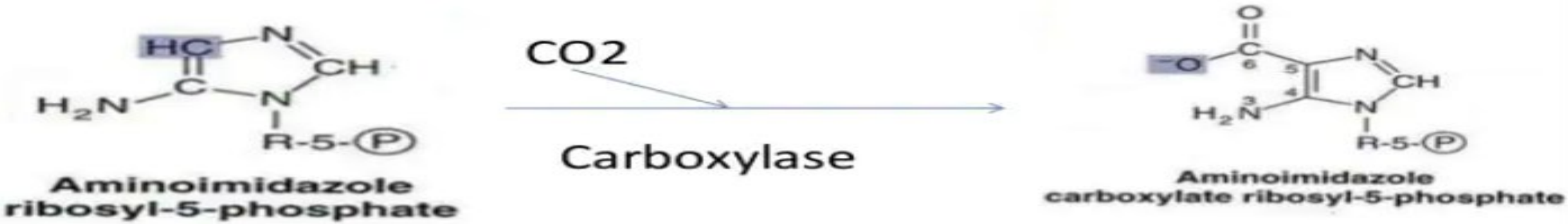



**Aminoimidazole ribosyl-5-phosphate**

7. **Incorporation of $CO_2$ (carboxylation) occurs to yield aminoimidazole carboxylate ribosyl 5-phosphate.**

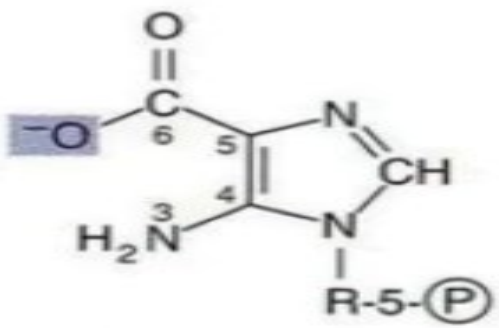
**This reaction does not require the vitamin biotin and /or ATP which is the case with most of the carboxylation reaction.**




**Aminoimidazole ribosyl-5-phosphate**

**Aminoimidazole carboxylate ribosyl-5-phosphate**

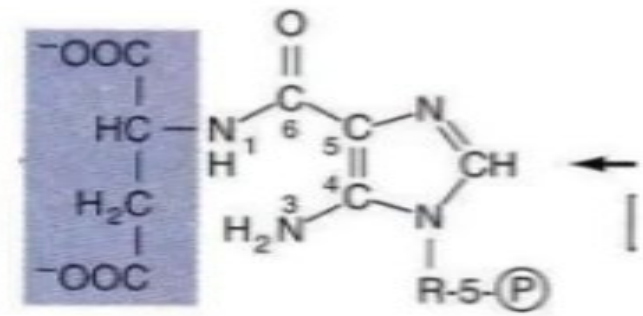
8. **Aspartate condenses with aminoimidazole carboxylate ribosyl 5-phosphate. to form aminoimidazole 4-succinyl carboxamide ribosyl 5-phosphate.**




**Aminoimidazole carboxylate ribosyl-5-phosphate**

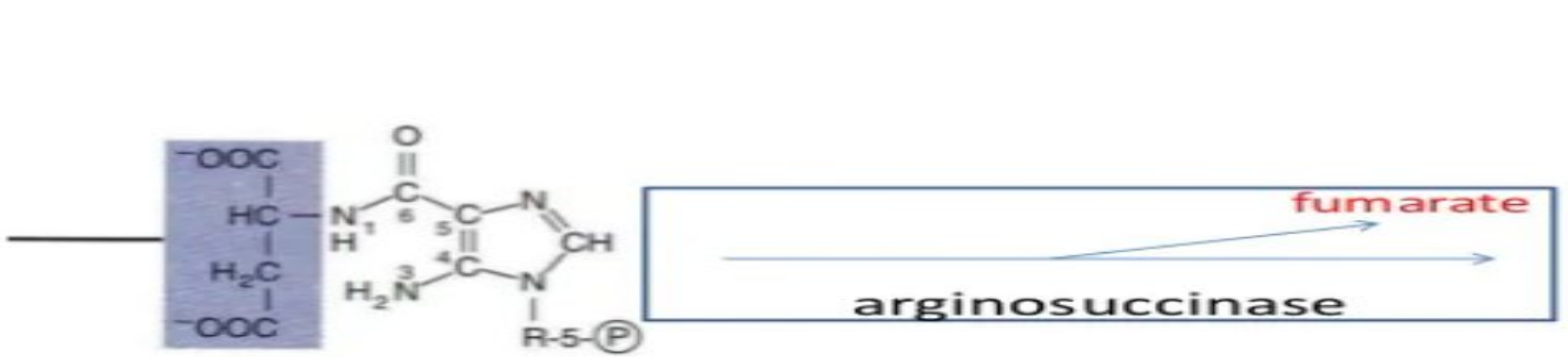
aspertate H2O

synthetase




**Aminoimidazole succinyl carboxamide ribosyl-5-phosphate**

9. **Adenosuccinase cleaves off fumarte and only the amino group of aspartate is retained to yield aminoimidazole 4-carboxamide ribosyl 5-phosphate.**

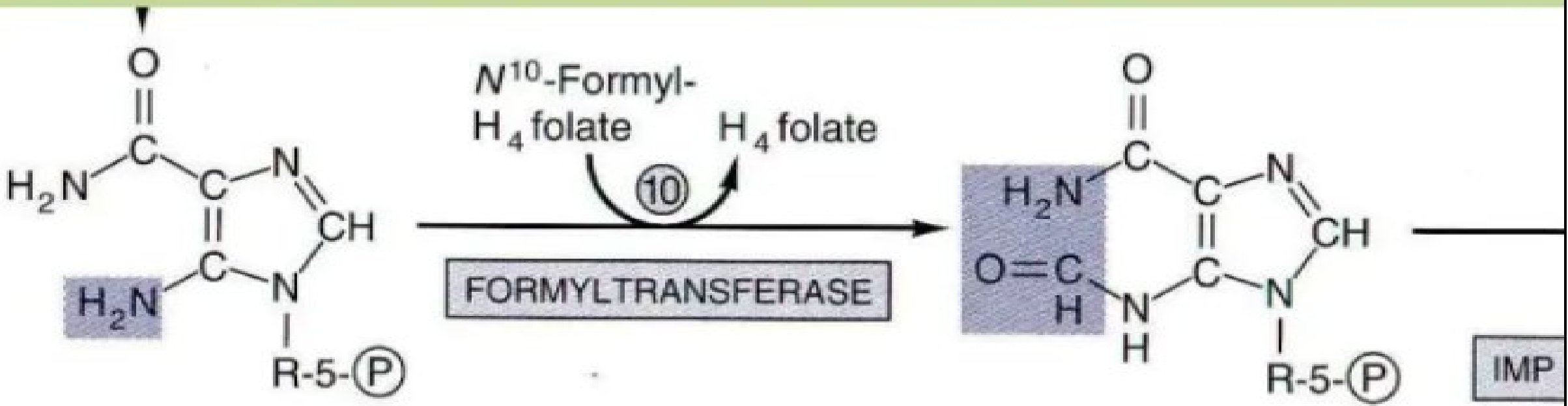



Aminoimidazole succinyl carboxamide ribosyl-5-phosphate

Aminoimidazole carboxamide ribosyl-5-phosphate

10. **$N^{10}$ formyl tetrahydrofolate donates a one-carbon moiety to produce formimidoimidazole 4-carboxamide ribosyl 5-phosphate.**

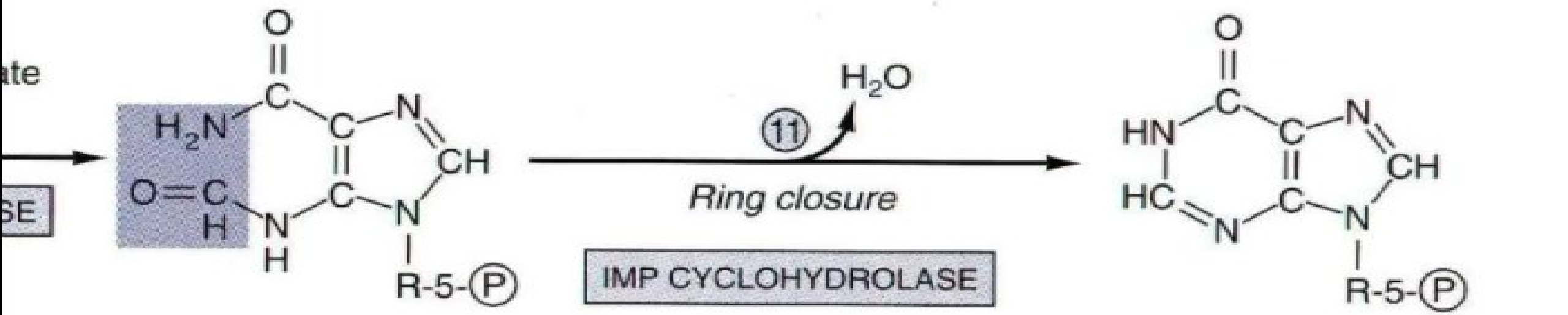
**With this reaction, all the carbon and nitrogen atoms of purine ring are contributed by the respective sources.**




**Aminoimidazole carboxamide ribosyl-5-phosphate**

**Formimidoimidazole carboxamide ribosyl-5-phosphate**

11. The final reaction catalysed by cyclohydrolase leads to ring closure with an elimination of water molecule from formimidoimidazole ribosyl-5-P by Inosine - monophosphate (IMP) cyclohydrolase forms IMP.



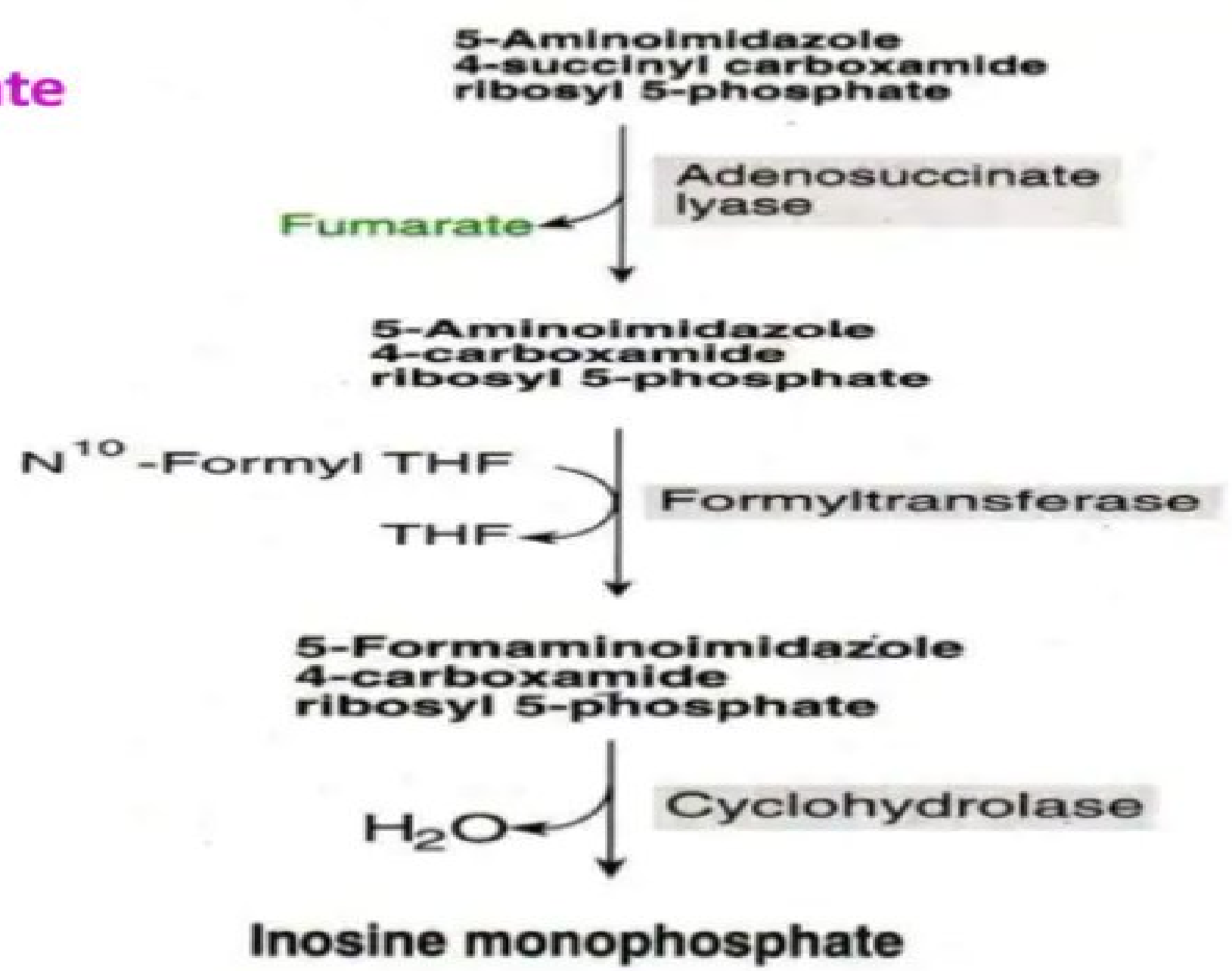

Formimidoimidazole carboxamide ribosyl-5-phosphate

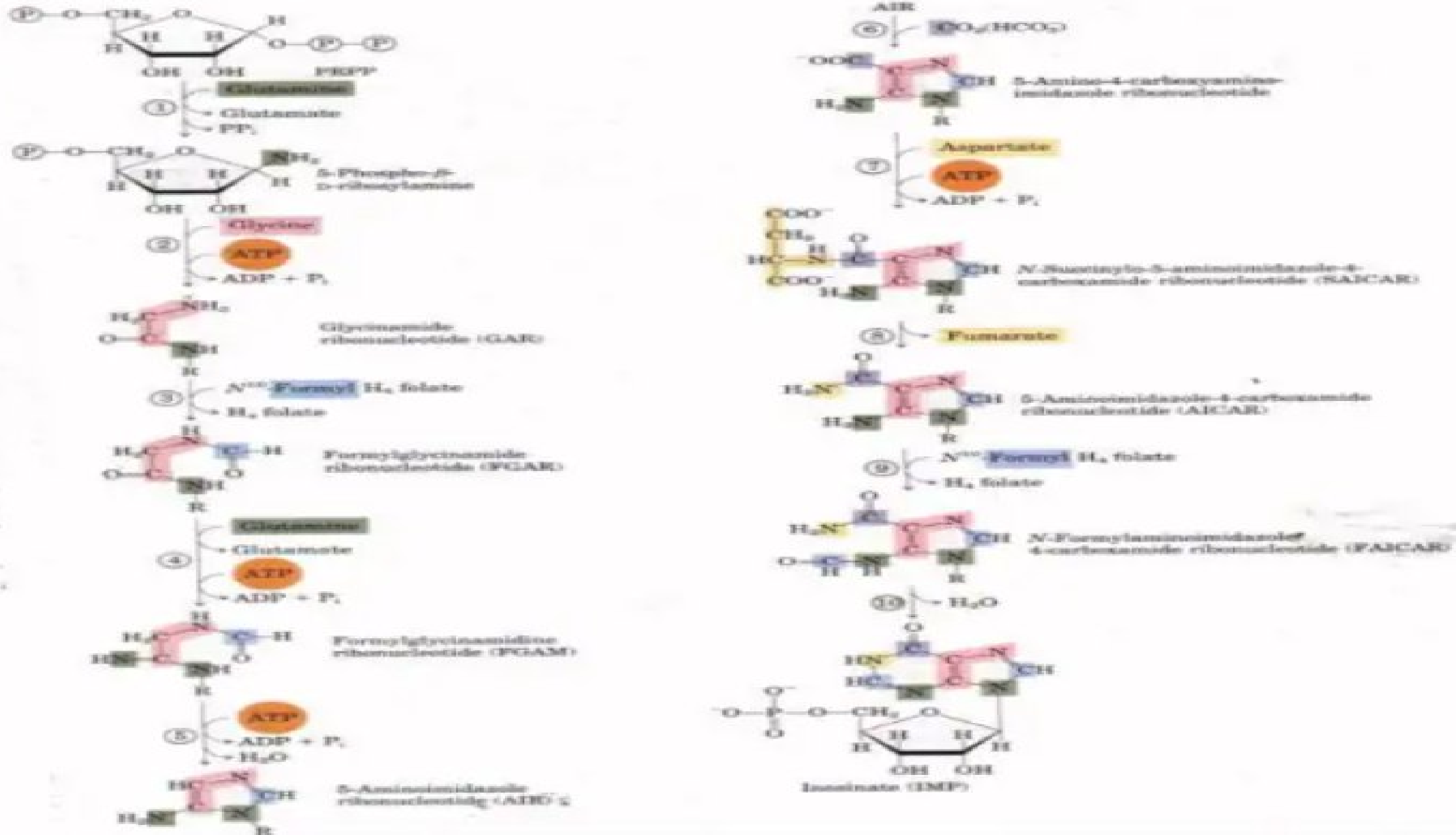
Inosine monophosphate (IMP) (XII)

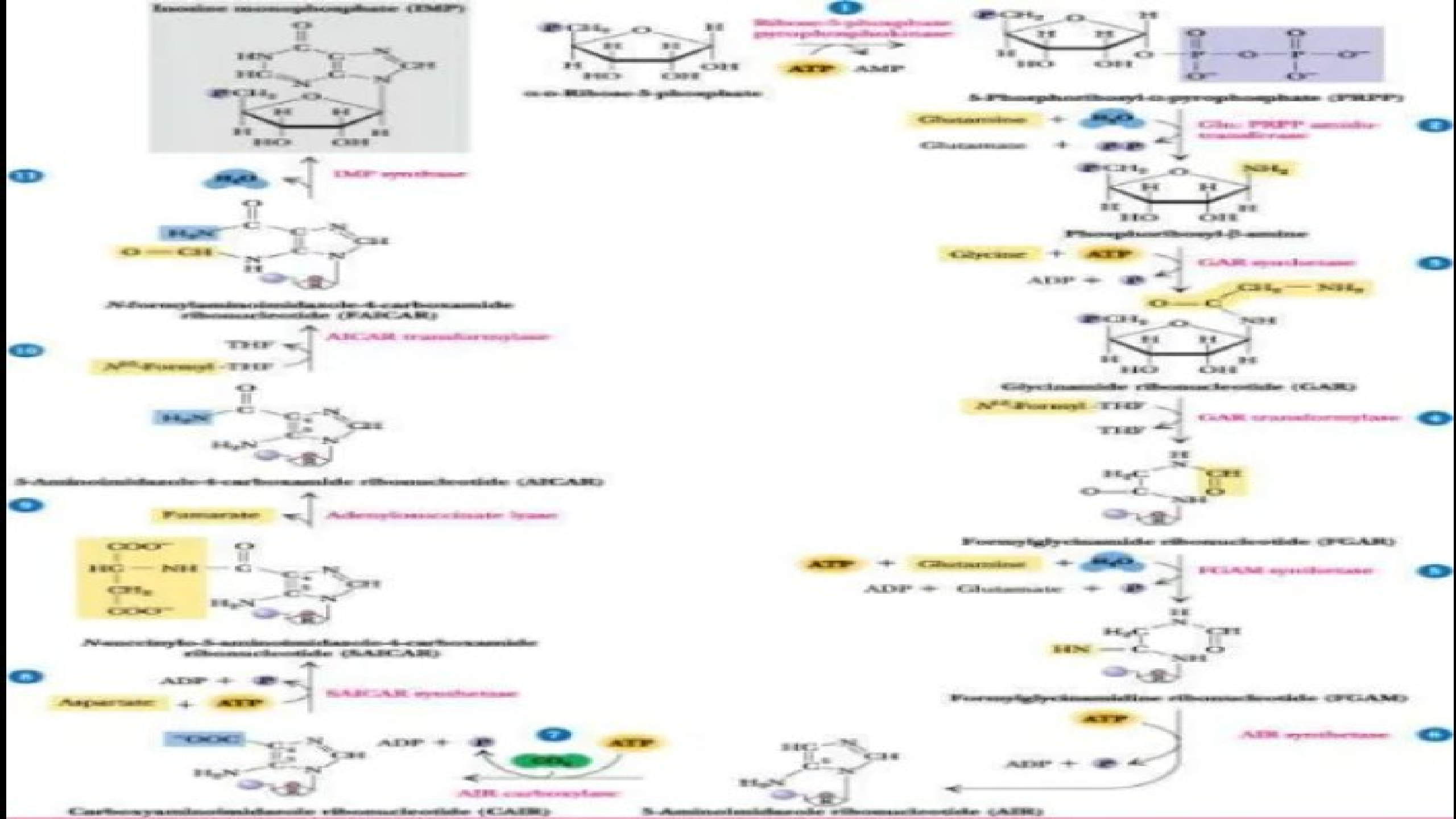
**Removal of fumarate**

**Addition of C 2**

**Cyclisation**



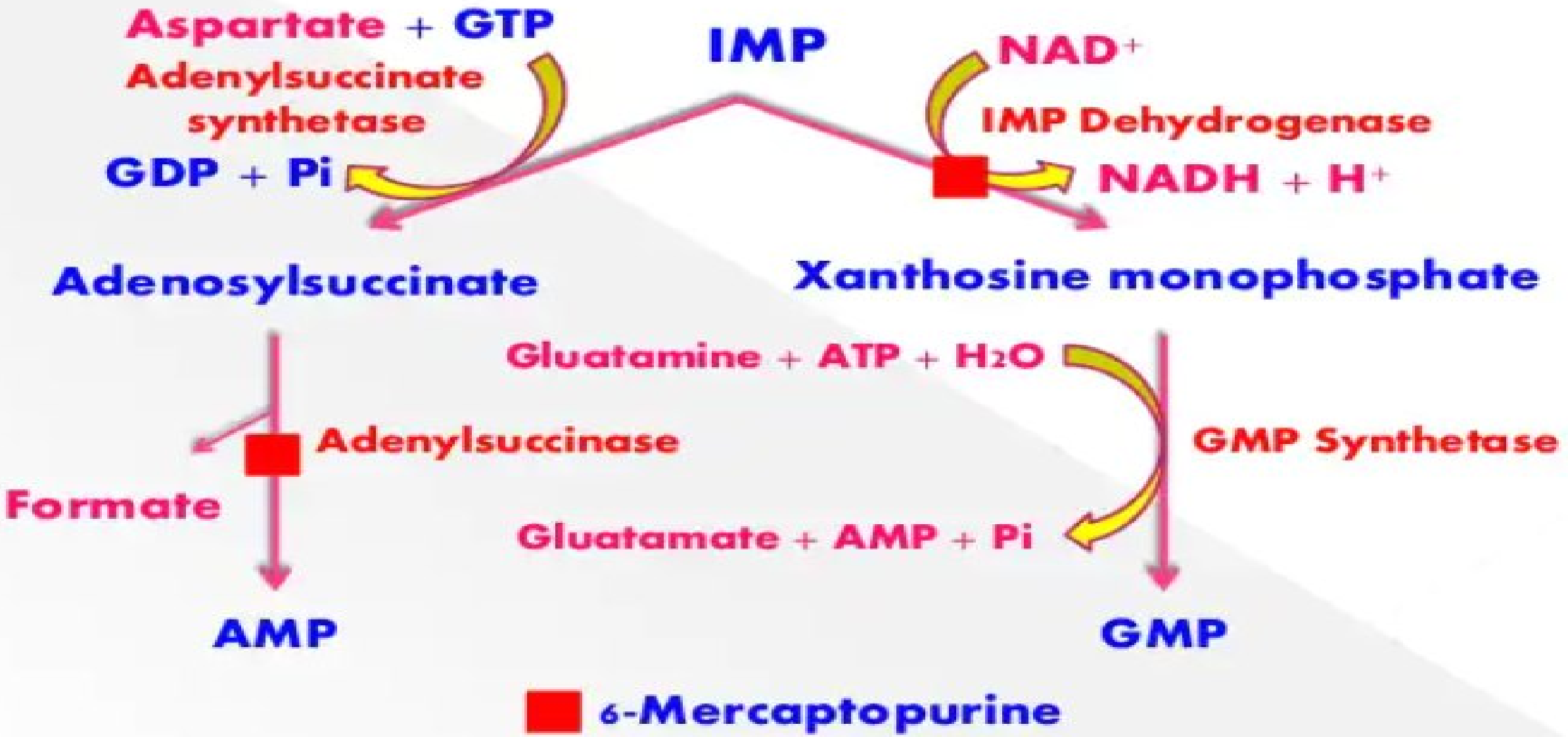

PRPP
Glutamine
Glutamate
5-Phospho-β-D-ribosylamine
Glycine
ATP
ADP + Pi
Glycinamide ribonucleotide (GAR)
N10-Formyl H4 folate
H4 folate
Formylglycinamide ribonucleotide (FGAR)
Glutamine
Glutamate
ATP
ADP + Pi
Formylglycinamidine ribonucleotide (FGAM)
ATP
ADP + Pi
H2O
5-Aminoimidazole ribonucleotide (AIR)
AIR
CO2 (HCO3-)
5-Amino-4-carboxyamino-imidazole ribonucleotide
Aspartate
ATP
ADP + Pi
N-Succinyl-5-aminoimidazole-4-carboxamide ribonucleotide (SAICAR)
Fumarate
5-Aminoimidazole-4-carboxamide ribonucleotide (AICAR)
N10-Formyl H4 folate
H4 folate
N-Formylaminoimidazole-4-carboxamide ribonucleotide (FAICAR)
H2O
Inosinate (IMP)


Inosine monophosphate (IMP)
IMP synthase
N-Formylaminoimidazole-4-carboxamide ribonucleotide (FAICAR)
AICAR transformylase
N10-Formyl-THF
5-Aminoimidazole-4-carboxamide ribonucleotide (AICAR)
Fumarate
Adenylosuccinate lyase
N-succinyl-5-aminoimidazole-4-carboxamide ribonucleotide (SAICAR)
SAICAR synthetase
Aspartate
ATP
AIR carboxylase
Carboxyaminoimidazole ribonucleotide (CAIR)
5-Aminoimidazole ribonucleotide (AIR)
AIR synthetase
N5-Formyl-THF
FGAM synthetase
Formylglycinamide ribonucleotide (FGAR)
GAR transformylase
Glycinamide ribonucleotide (GAR)
GAR synthetase
Glycine
Phosphoribosylamine
Glutamine
Glutamate
PRPP amidotransferase
5-Phosphoribosyl-α-pyrophosphate (PRPP)
PRPP synthetase
Ribose-5-phosphate pyrophosphokinase
α-D-Ribose-5-phosphate

# Synthesis of AMP & GMP from IMP

- **Synthesis of AMP:**
- **Ionosine monophosphate (IMP) is the immediate precursor for the formation of AMP & GMP.**
- **Aspartate condenses with IMP in the presence of GTP to produce adenylsuccinate which, on cleavage, forms AMP.**

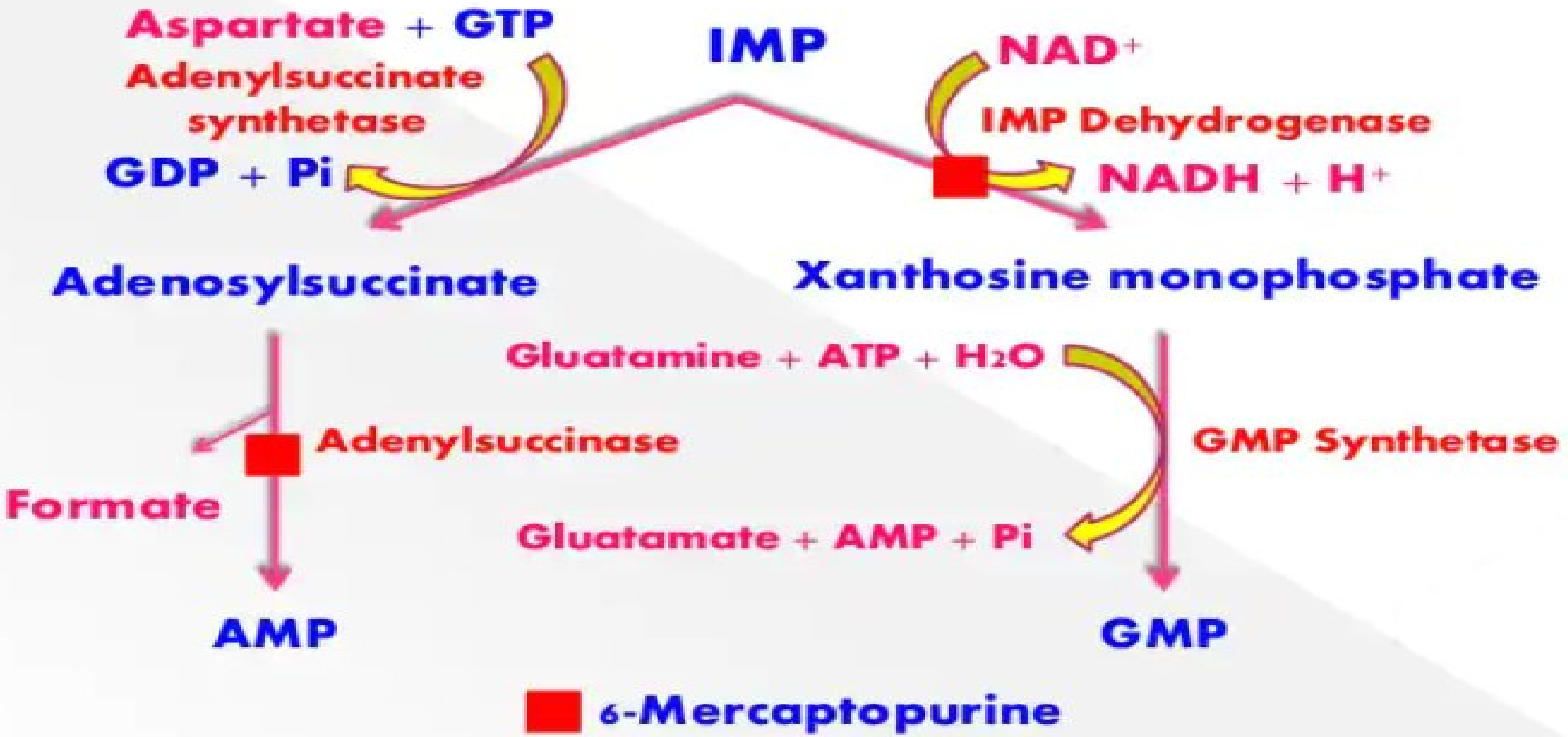
# Synthesis of AMP & GMP



- **Synthesis of GMP:**
- **IMP undergoes $NAD^+$ dependent dehydrogenation to form xanthosine monophosphate (XMP).**
- **Glutamine then transfers amide nitrogen to xanthosine monophosphate (XMP) to produce GMP.**

- 6-Mercaptopurine is an inhibitor of the synthesis of AMP & GMP.
- It acts on the enzyme adenylsuccinase (of AMP pathway).
- IMP dehydrogenase (of GMP pathway).

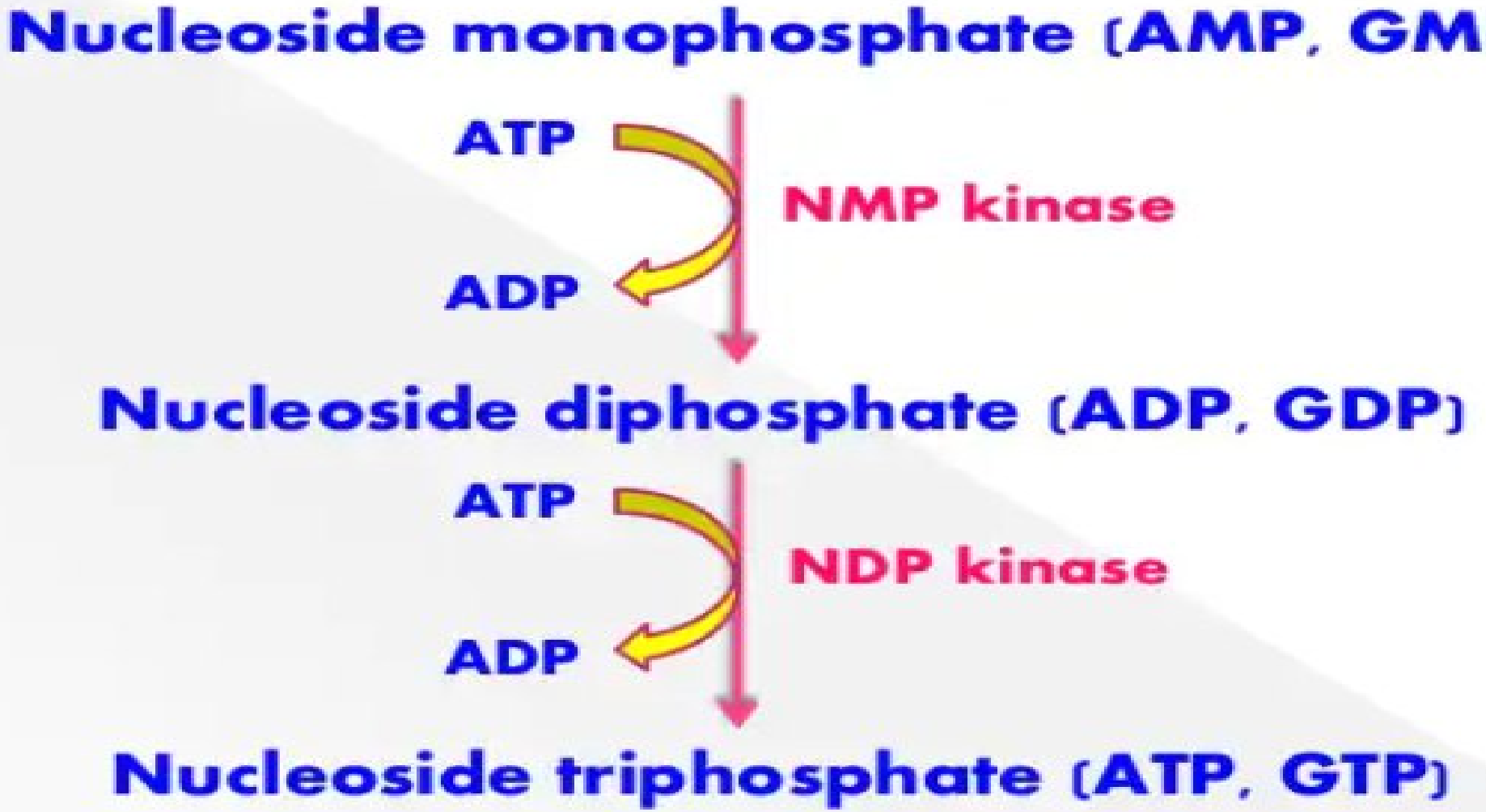
# Synthesis of AMP & GMP



# Formation of di & tri-phosphates

- The nucleoside monophosphates (AMP & GMP) converted to the corresponding di & triphosphates.
- This is achieved by the transfer of phosphate group from ATP, catalysed by nucleoside monophosphate (NMP) kinases & nucleoside diphosphate (NDP) kinases.

# Formation of di & tri-phosphates



# 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 inhibit the synthesis of folic acid by microorganisms.

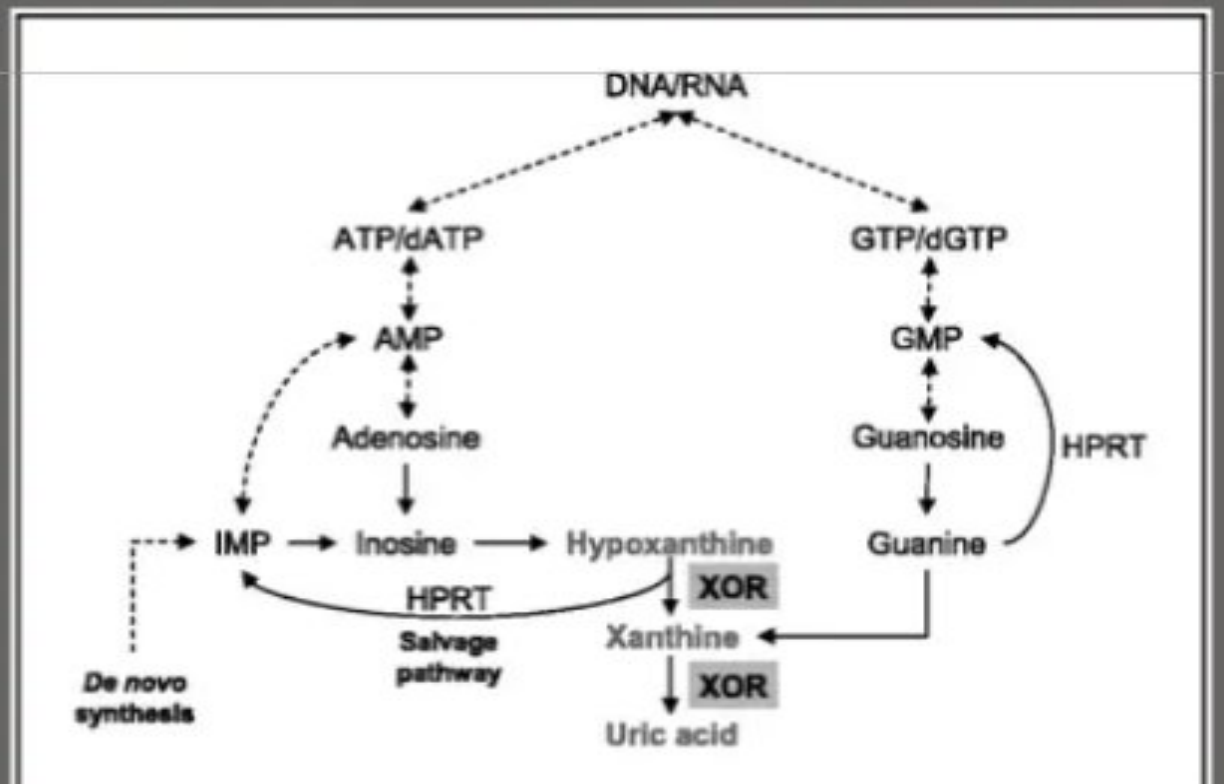
- This indirectly reduces the synthesis of purines & nucleic acids (DNA & RNA).
- The structural analogs of folic acid (e.g. methotrexate), used to control cancer.
- They inhibit the synthesis of purine nucleotides & nucleic acids.
- These inhibitors also affect the proliferation of normally growing cells.

- Azaserine (diazo acetyl-L-Serine) is a glutamine antagonist & inhibits reactions involving glutamine.
- Other synthetic nucleotide analogues used as anticancer agents are 6-thio guanine & 8-aza guanine.

# Salvage Pathway of Purine Nucleotides

- Many cells have mechanisms to retrieve purine bases and purine nucleosides. They are used to synthesize purine nucleotides.

  This is the salvage pathway.



# Contd.

- From Base to Nucleotides

APRT

- A + PRPP----------→AMP + ppi

HGPRT

- H + PRPP----------→ IMP + ppi

**HGPRT**

- G + PRPP----------→GMP + ppi

# Contnd.

- From Nucleoside to Nucleotide

AR kinase

- AR + ATP----------→ AMP + ADP

- In comparison to de novo pathway, salvage pathway is energy-saving.

- In brain and bone marrow tissues salvage pathway is the only pathway of nucleotide synthesis.

- Deficiency of HGPRT causes Lesch Nyhan syndrome

# Salvage pathway for purines

- This pathway ensures the recycling of purines formed by degradation of nucleotides.
- Nucleosides & deoxy-nucleosides can also be salvaged.
- The purines can be directly converted to the corresponding nucleotides & this process is known as 'salvage pathway'.

- PRPP is the starting material in this pathway.
- It is also a substrate for de novo synthesis.
- The free purines are salvaged by two different enzymes.

1. Adenine phospho ribosyl transferase (APRTase).
2. Hypoxanthine guanine phosphoribosyl transferase (HGPRTase).

- **Adenine phosphoribosyl transferase catalyses the formation of AMP from adenine.**
- **Hypoxanthine-guanine phosphoribosyl transferase (HGPRT) converts guanine & hypoxanthine to GMP & IMP.**
- **Phosphoribosyl pyrophosphate (PRPP) is the donor of ribose 5-phosphate in the salvage pathway.**

# Regulation of purine nucleotide synthesis

- The intracellular concentration of PRPP regulates purine synthesis.
- This is dependent on the availability of ribose 5-phosphate & the PRPP synthetase.
- PRPP glutamyl amidotransferase is controlled by a feedback mechanism by purine nucleotides.

- If AMP & GMP are available in adequate amounts, their synthesis is turned off at the amidotransferase reaction.
- Another important stage of regulation is in the conversion of IMP to AMP & GMP.
- AMP inhibits adenylsuccinate synthetase while GMP inhibits IMP dehydrogenase.
- AMP & GMP control their respective synthesis from IMP by a feedback mechanism.

# DEGREDATION OF PURINE NUCLEOTIDES

- The end product of purine metabolism in humans is uric acid.

1. The nucleotide monophosphates (AMP, IMP & GMP ) are converted to their respective nucleoside forms (adenosine,inosine & guanosine ) by the action of nucleosidase.

2. The amino group, either from AMP or adenosine, can be removed to produce IMP or inosine respectively.

3. Inosine & guanosine are, raspectively, converted to hypoxanthine & guanine (purine bases) by purine nucleoside phosphorylase.

4. Adenosine is not degreded by this enzyme, hence it has to be converted to inosine.

5. Guanine undergoes deamination by guanase to form xanthine.

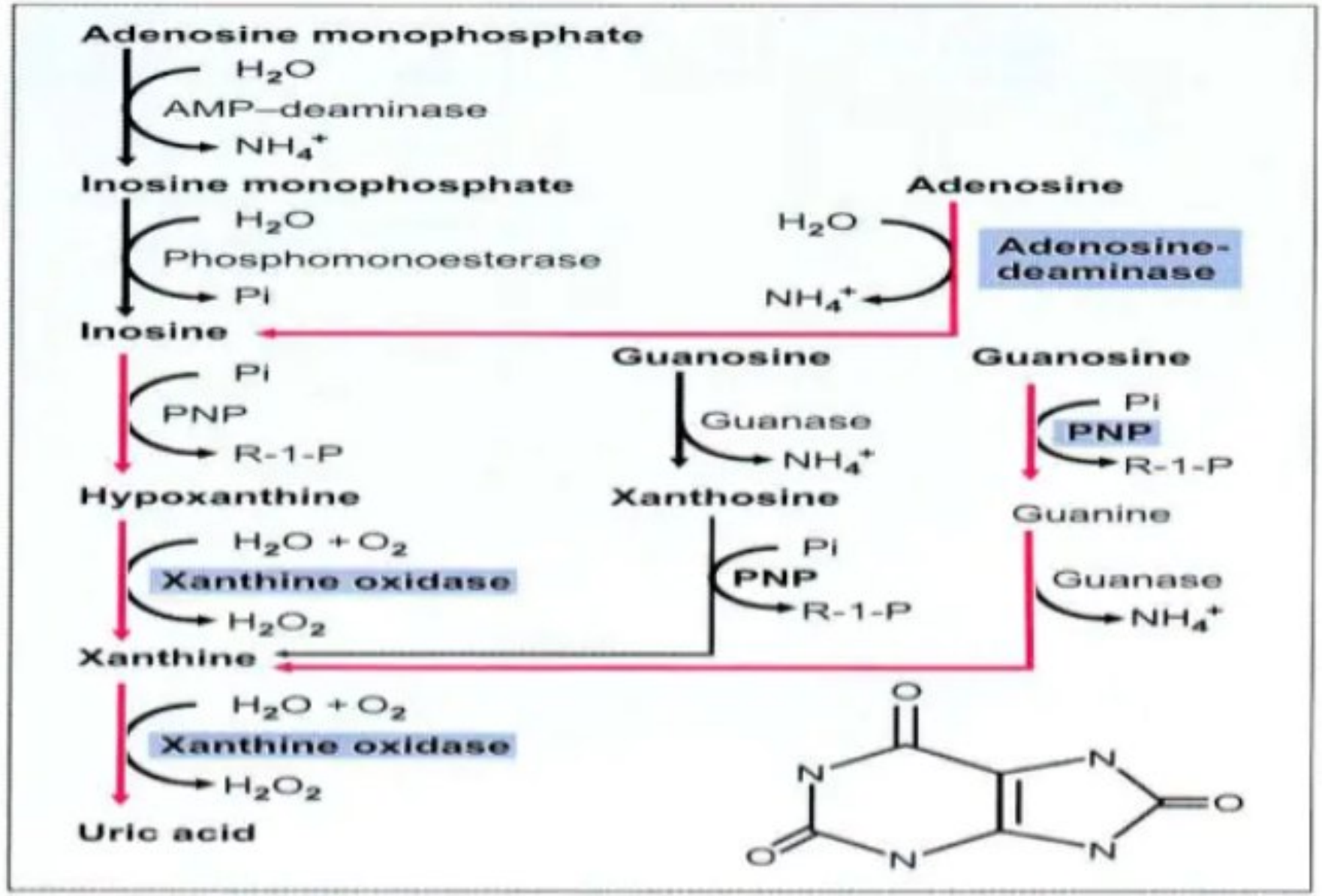



**Fig. 39.15.** Degradation of purine nucleotides. Main pathway is in red arrows. PNP = purine nucleoside phosphorylase; R-1-P = ribose-1-phosphate

- **Xanthine oxidase** is an important enzyme that converts hypoxanthine to xanthine, & xanthine to uric acid.

- This enzyme contains FAD, Molybdenum & Iron, & is exclusively found in liver & small intestine.

- Xanthine oxidase liberates $H_2O_2$ & $H_2O$ which is harmful to the tissues.

- Catlase cleaves $H_2O_2$ to $H_2O$ & $O_2$.

    - Uric acid ( 2,6,8-ttioxopurine ) is the final excretory product of purine metabolism in humans.

# DISORDERS OF PURINE METABOLISM

## 1. HYPERURICEMIA AND GOUT

Uric acid is the end product of purine metabolism in humans.

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 excreation 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 excreation ( Uricosuria)

- GOUT is metabolic disease associated with overproduction of uric acid.

- At the physiological pH, uric acid is found in a more soluble form as sodium urate.

- In severe hyperuricemia, crystals of sodium urate get deposited in the soft tissues, perticularly in the joints.

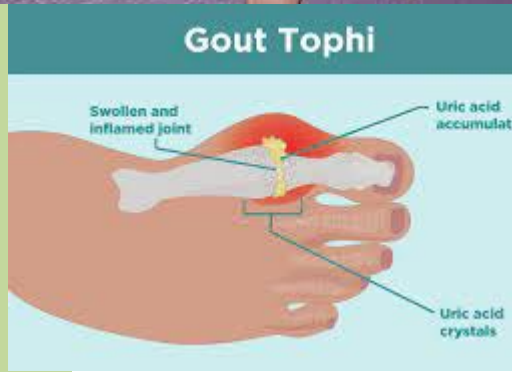
- Such deposits are commonly known as **tophi.**

- This causes inflammation in the joints resulting in a **painful gouty arthritis.** Typical gouty arthritis **affects first metatarsophalangeal joint.(GREAT TOE).**

- Sodium urate &/or uric acid may also precipitate in kidneys & ureters that result in renal damage & stone formation.

- Historically, gout was found to be often associated with **high living, over-eating & alcoho consumption.**

- The prevalence of gout is about 3 / 1,000 persons, mostly affecting males.



- **GOUT IS OF TWO TYPES**

1. **PRIMARY GOUT.**

   **It is an inborn error of metabolism due to overproduction of uric acid.**

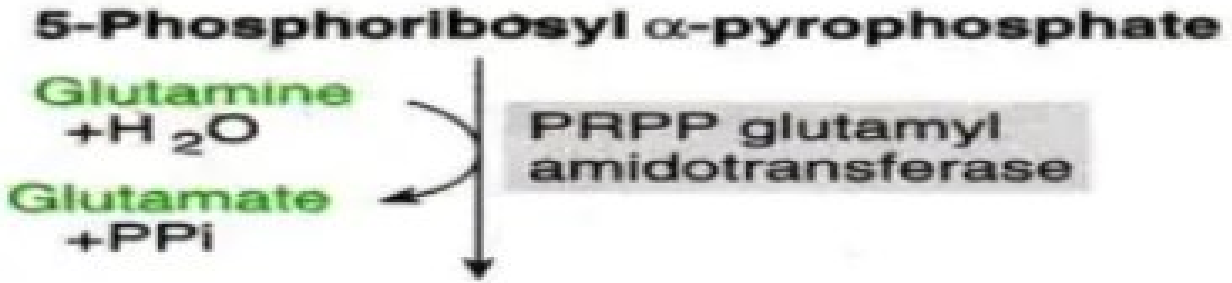
   **This is mostly related to over production of purine nucleotides.**

- ***PRPP synthetase*** **: in normal circumstances , PRPP synthetase is under feedback control by purine nucleotides ( ADP & GDP ).**

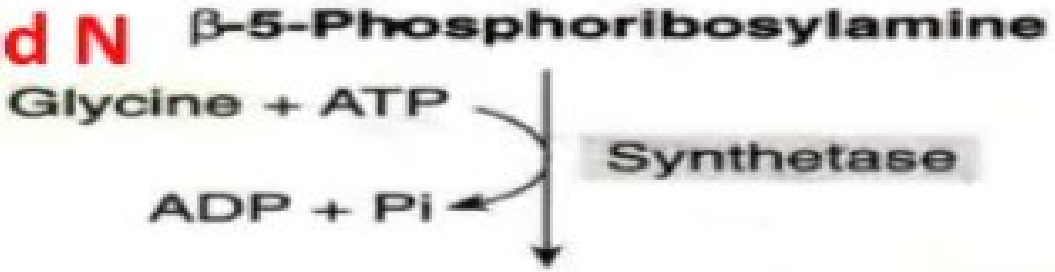
  **However, varient forms of PRPP synthetase-which are not subjected to feedback regulation-have been detected. This leades to increased production of purines.**

## Formation of PRPP


## Addition of N9




## Addition of C4 , C5 and N 7




## Addition of C8


**Formylglycinamide ribosyl 5-phosphate**

- **PRPP glutamylamidotransferse :**

  The lack of feedback control of this enzyme by purine nucleotides also leads to their elevated synthesis.

- **HGPRT deficiency :** This is an enzyme of purine salvage pathway, & its defect causes Lesch-Nyhan syndrome. This disorder is associated with increased synthesis of purine nucleotides by a two fold mechanism.

  Firstly, decreased utilization of purines ( Hypoxanthine & guanine ) by salvage pathway, resulting in the accumulation & divertion of PRPP for purine nucleotides.

  Secondly, the defect in salvage pathway leads to decreased levels of IMP & GMP causing impairment in the tightly controlled feedback regulation of their production.

# Contd.

- From Base to Nucleotides

APRT

- A + PRPP----------→AMP + ppi

HGPRT

- H + PRPP----------→ IMP + ppi

**HGPRT**

- G + PRPP----------→GMP + ppi

## Glucose 6-phosphatase dificiency:

Intype I glycogen storage disease ( von-gierke's ), glucose-6-phosphate cannot be converted to glucose due to the deficiency of glucose-6-phosphatase.

This leads to the increased utilazation of glucose-6-phosphate by HMP shunt resulting in elevated levels of ribose-5-phosphate & PRPP &, ultimately, purine overproduction.

von gierke's disease is also associated with increased activity of glycolysis.

Due to this, lactic acid accumulates in the body which interferes with the uric acid excretion through renal tubules.

## ELEVATION OF GLUTATHIONE REDUCTASE :

varient of glutathione reductase generates more NADP+ which is utilized by HMP shunt .

This leads to increased ribose 5-phosphate and PRPP synthesis.

Glutathione reductase is **responsible for maintaining the supply of reduced glutathione** , glutathione plays key roles in the cellular control of oxygen species

## 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, polycythemias, lymphomas, etc).**

**Psoriasis and increased tissue breakdown (trauma, starvation etc).**

## Treatment of Gout:

The drug of choice for the treatment of primary gout is 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.

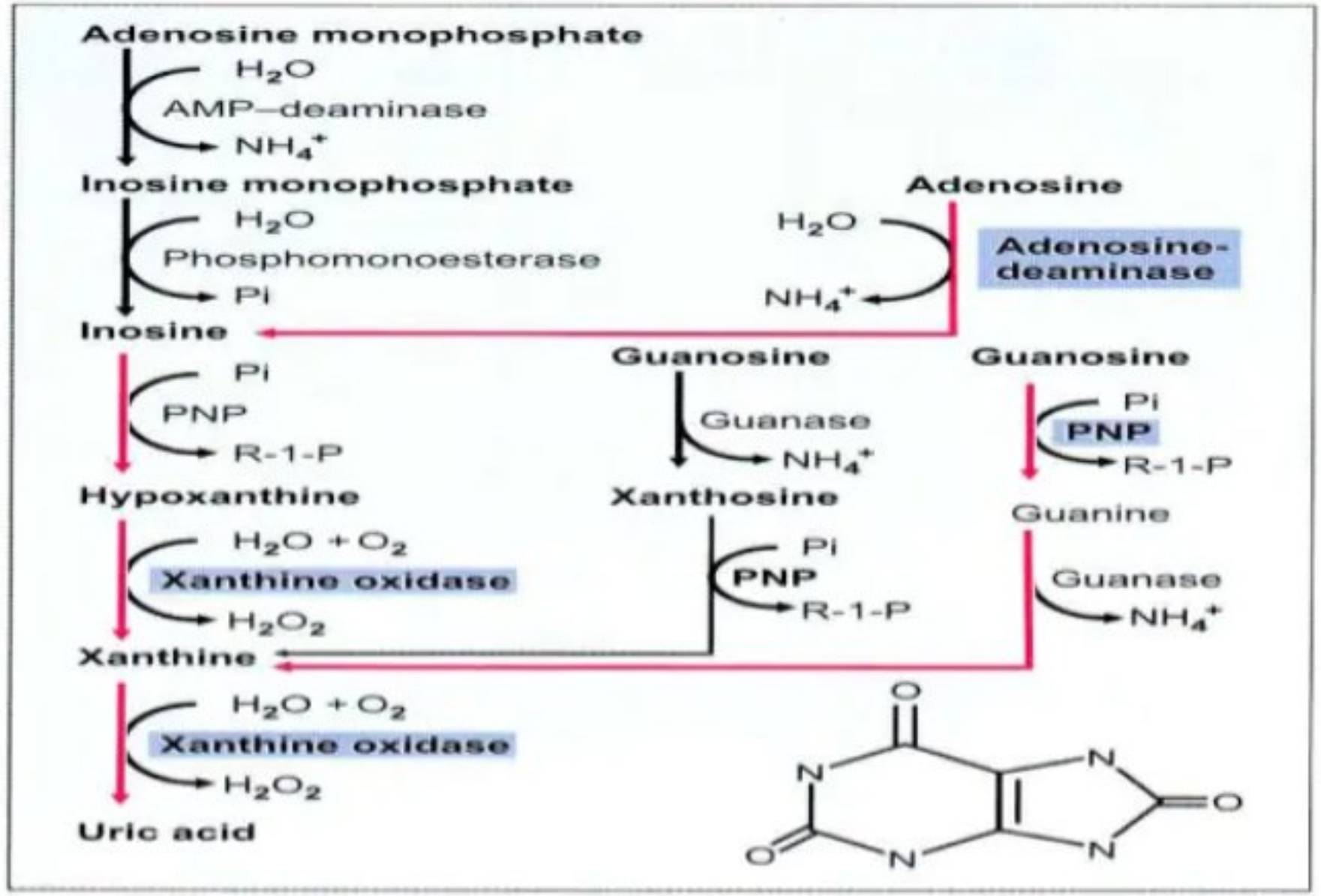



**Fig. 39.15.** Degradation of purine nucleotides. Main pathway is in red arrows. PNP = purine nucleoside phosphorylase; R-1-P = ribose-1-phosphate

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.

Besides the drug therapy, restriction in dietary intake of purines and alcohol is advised.

Consumption of plenty of water will also be useful.

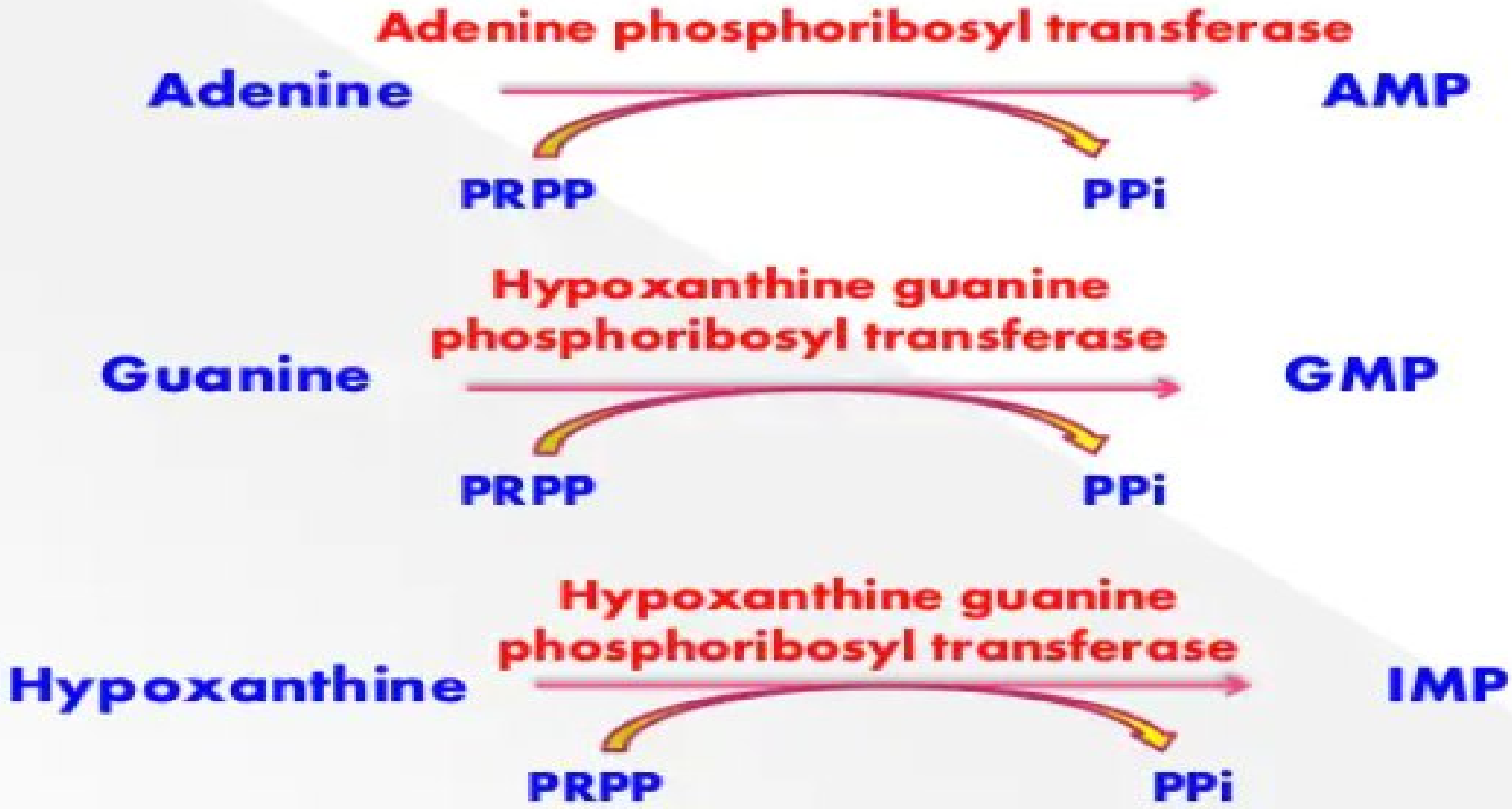
## Lesch-Nyhan syndrome

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 ontlhe X-chromosome.

It affects only the males and is characterized by excessive uric acid production (often gouty arthritis).

# Salvage pathway for purines



Neurological abnormalities such as mental retardation, aggressive behavior, learning disability etc.

The patients of this disorder have an irretible urge to bite their fingers and lips, often causing self-mutilation.

The overpodluction of uric acid in lesch-nyhan syndrome is explained .

HGPRT deficiency results in the accumulation of PRPP and decrease in GMP and IMP, ultimatelyleading to increased synthesis and degradation of purines.

The biochemical bases for the neurological symptoms observed in Lesch-Nyhan syndrome is not clearly understood.

This may be related to the dependence fo brian on the salvage pathway for de novo synthesis of purine nucleotides.

Uric acid is not toxic to the brain, since patients with severe hyperuricemia (not related to HGPRT deficiency) do not exhibit any neurological symptoms.

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. (Adenosine deaminase )

The deficienc 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

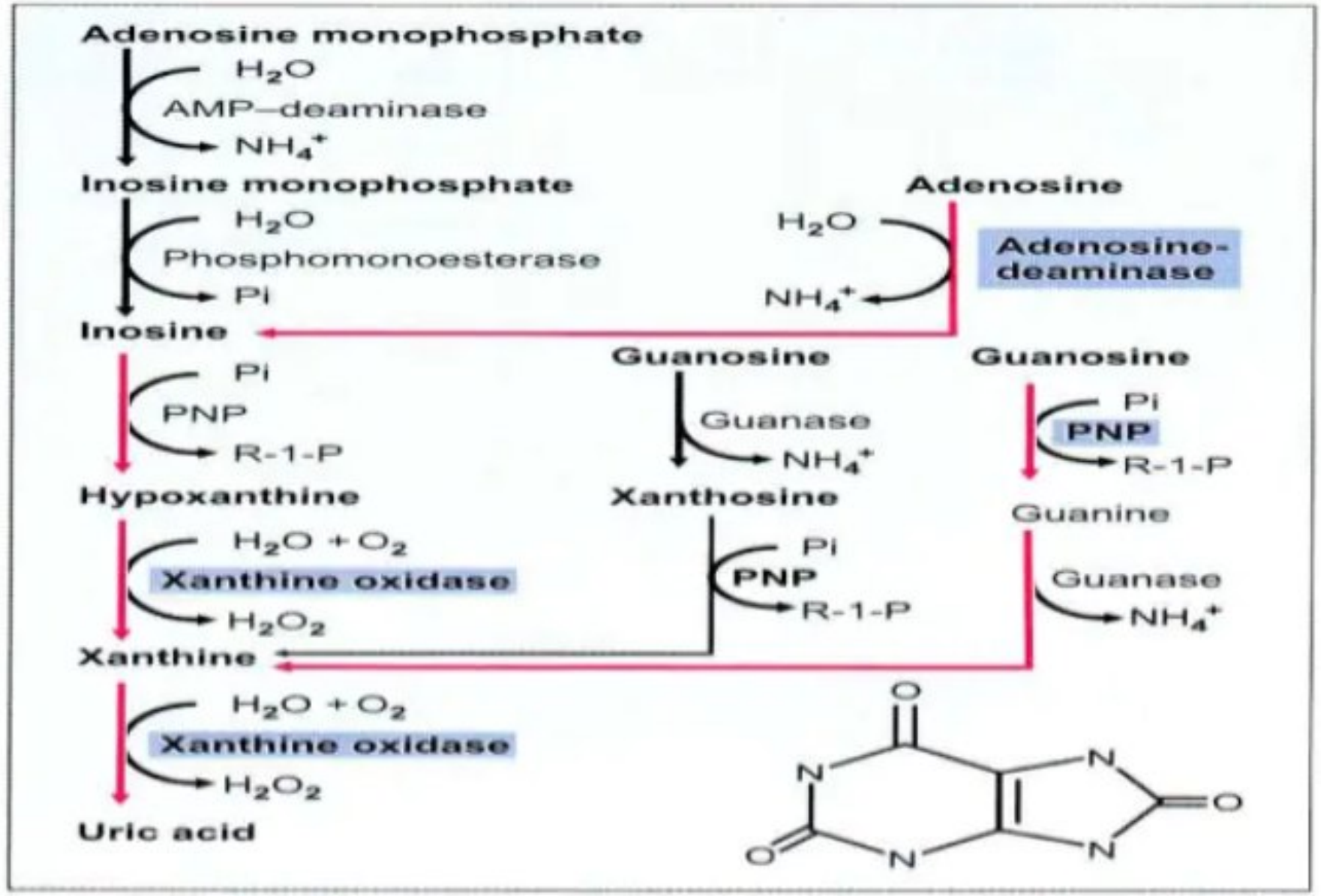
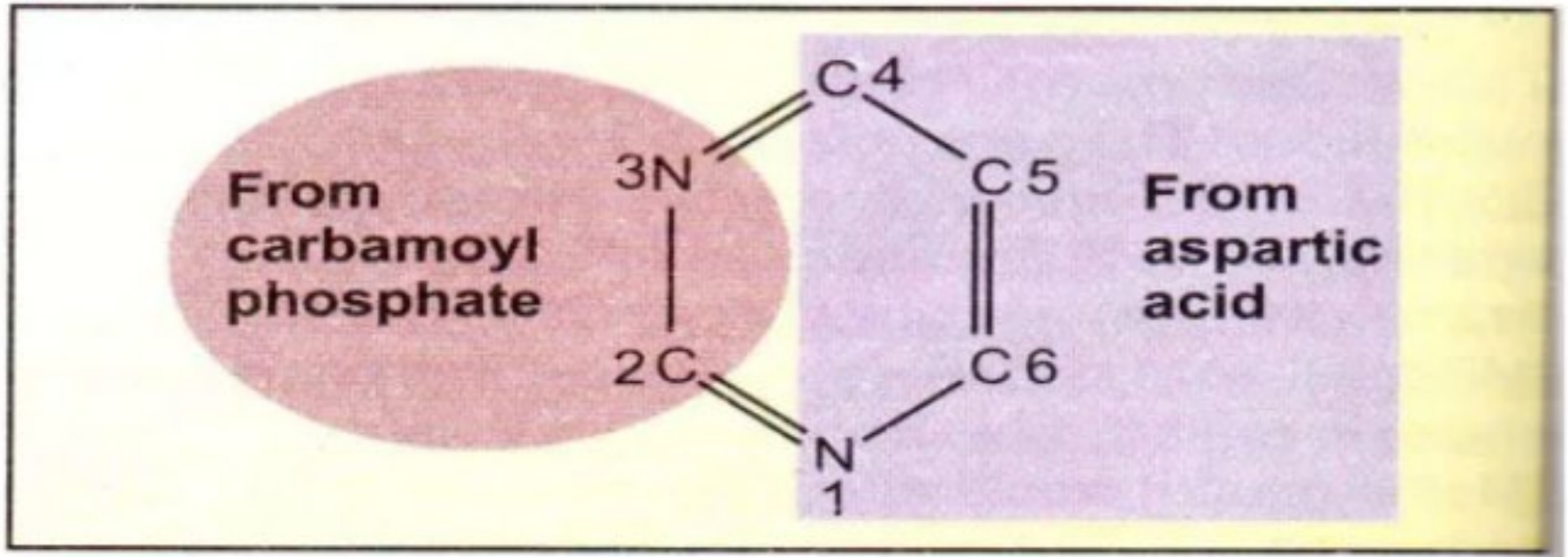



**Fig. 39.15.** Degradation of purine nucleotides. Main pathway is in red arrows. PNP = purine nucleoside phosphorylase; R-1-P = ribose-1-phosphate

# PYRIMIDINE METABOLISM

# Pyrimidine is a heterocyclic ring.



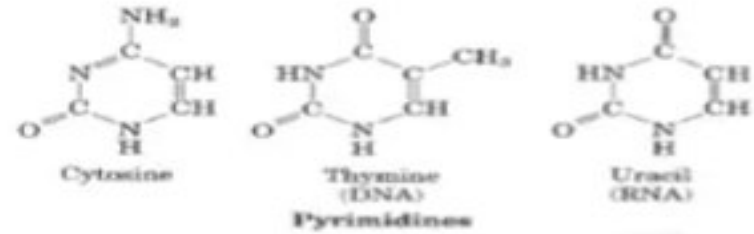

Sources of C and N atoms of pyrimidine ring

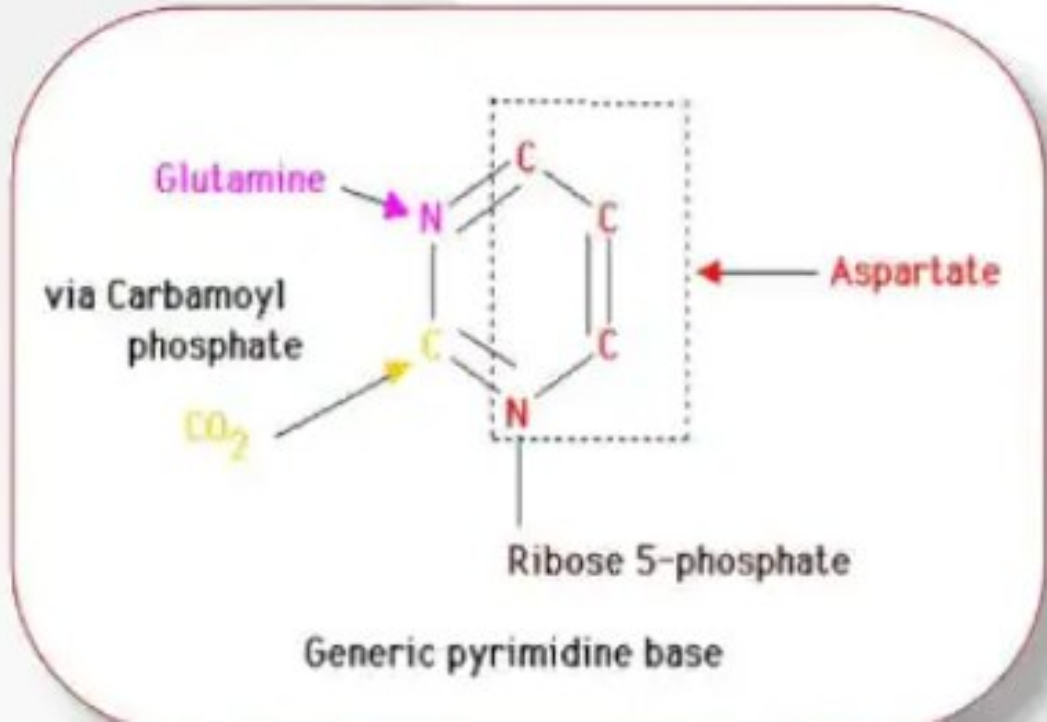
Pyrimidine is first synthesized .

Later, it is attached to ribose -5 phosphate

# Pyrimidine

- Cytosine
- Thymine
- Uracil



# BIOSYNTHESIS OF PYRIMIDINE RIBONUCLEOTIDES

The synthesis of pyrimidines is a much simpler process compared to that of purines.

aspartate, gutamine and $CO_2$ contribute to atoms in the formation of pyrimidine ring.

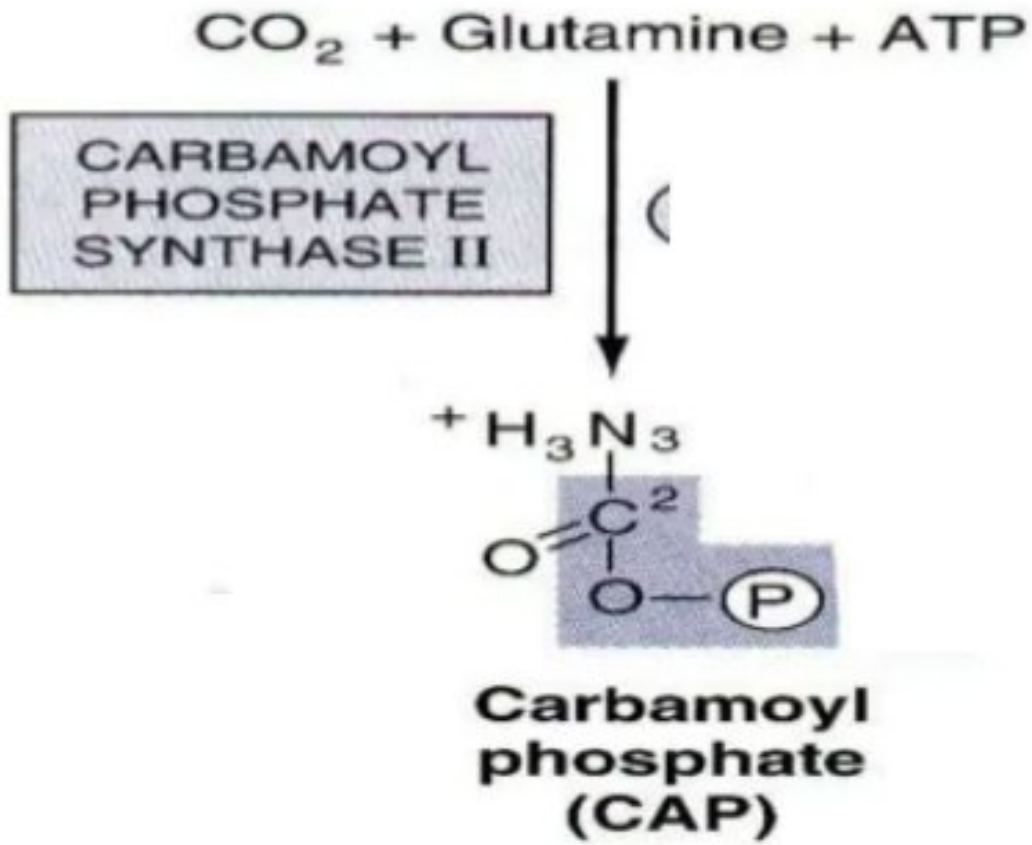
Pyrimidine ring is first synthesized and then attached to ribose 5-phosphate.

this is in contrast to purine nucleotide synthesis where in purine ring is built upon a pre-existing ribose5-phosphate.

## 1.Formation of carbomyl phosphate:

Carbomyl phosphate is formed from ATP, **GLUTAMINE** and CO2.

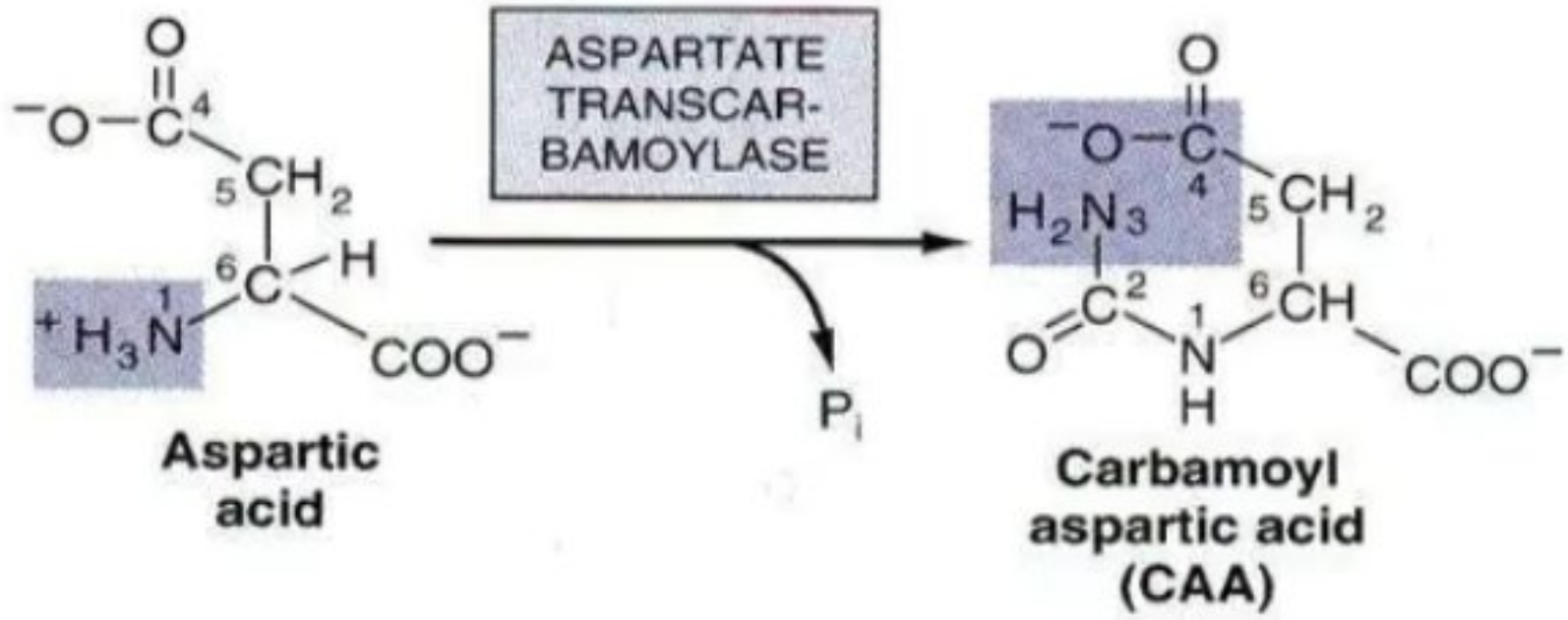
The reaction is catalysed by ***CPS –II***.



## 2. Condensation :

Carbomyl phosphate condenses with aspartate to from carbomylaspartate, cataylsed by aspartate-transcarbomylase.

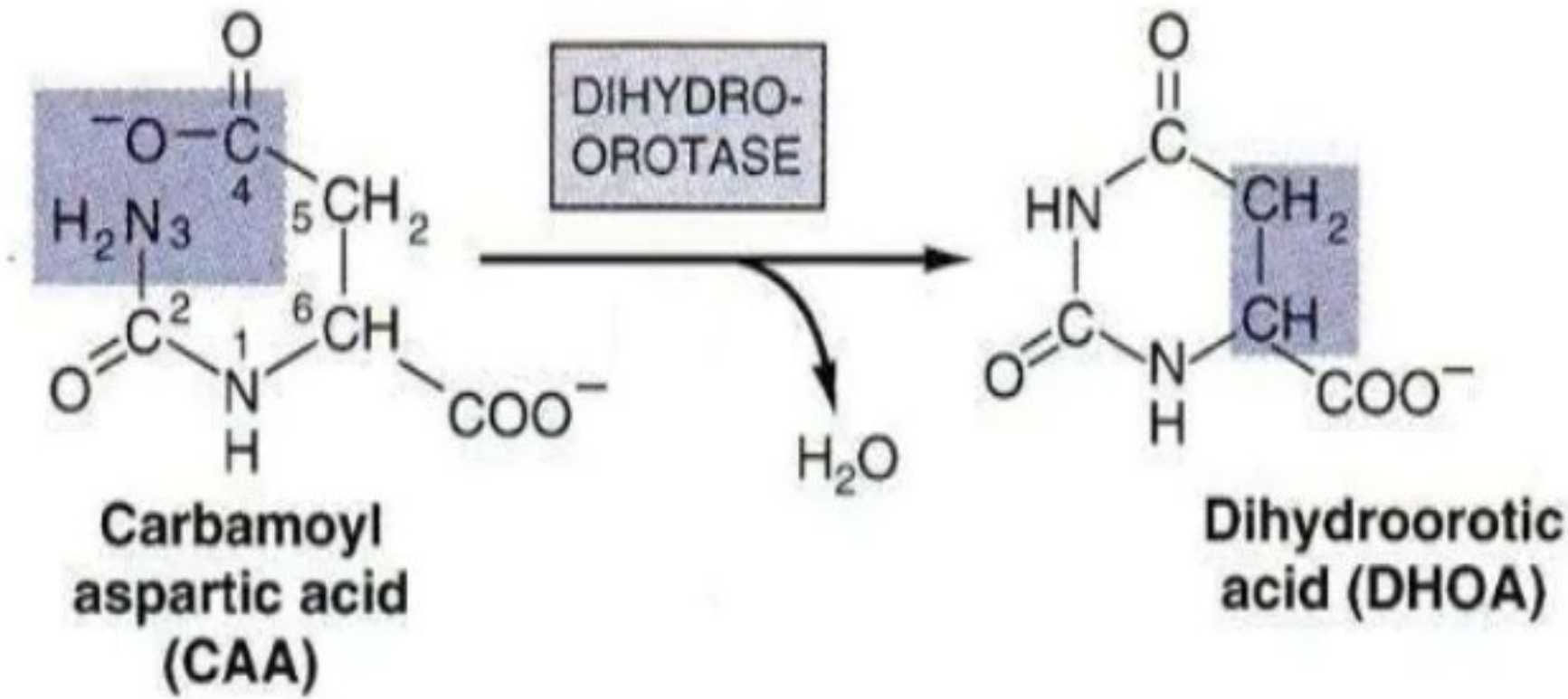
Carbomyl phosphate +



## 3. Ring closure:

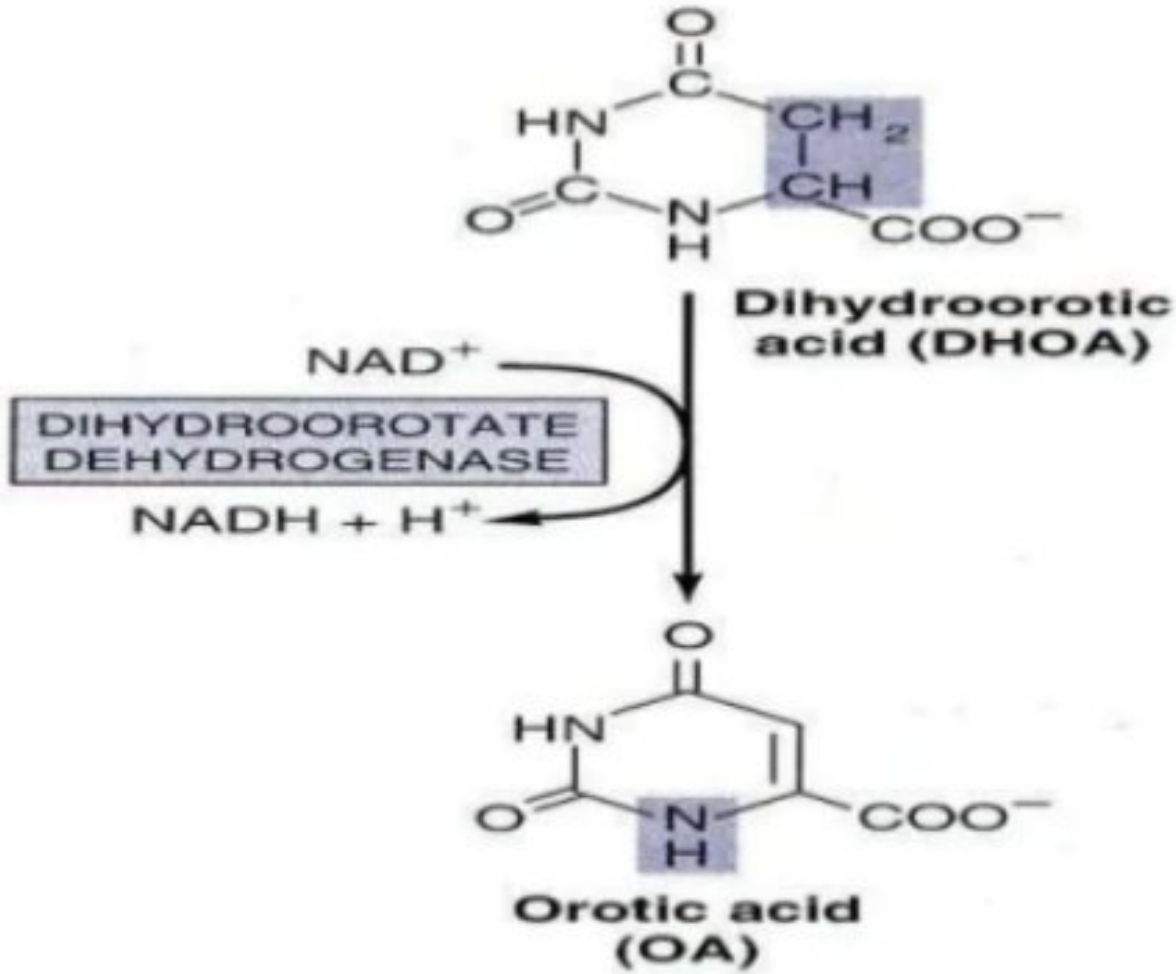
This occurs via loss of water. This reaction is

catalysed by **dihydroorotase,** forming dihydroorotic acid.

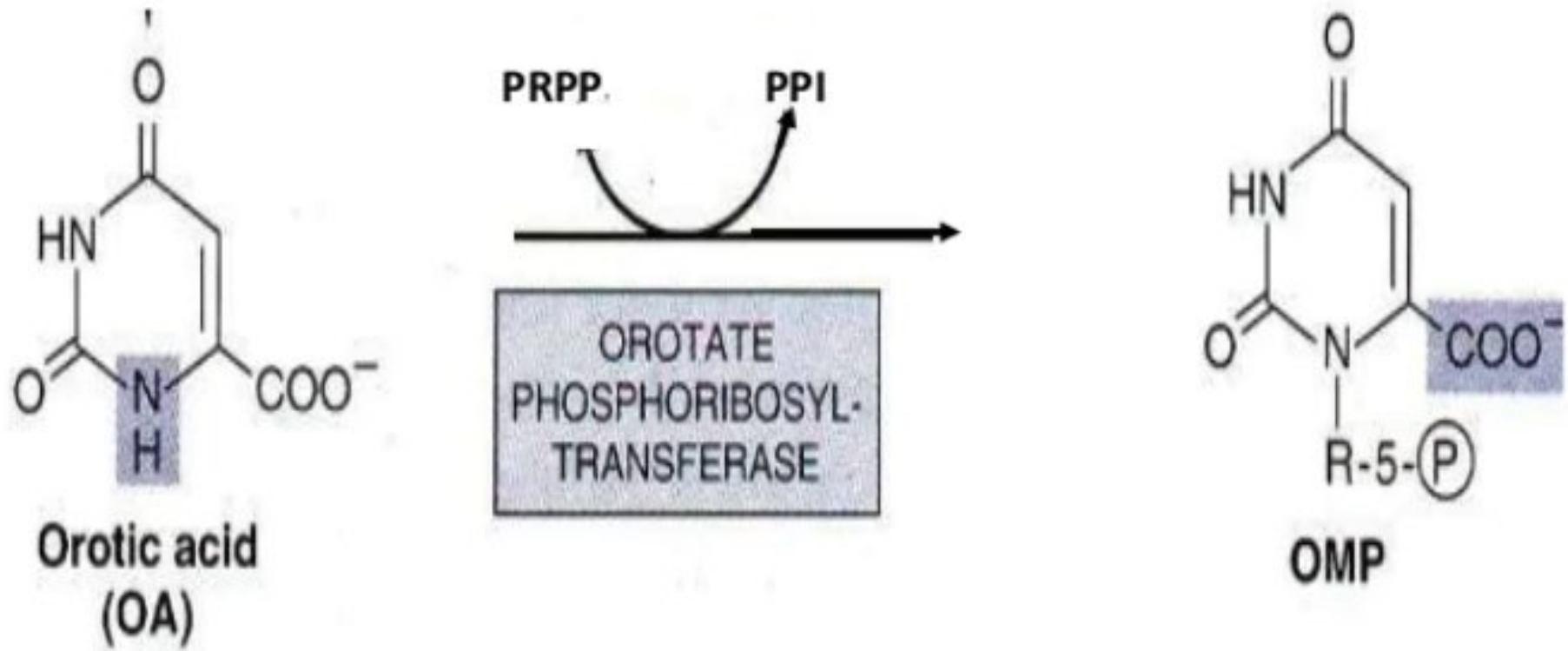


## 4. Dehydrogenation :

Removal of hydrogen atoms from C5 and C6 , by **dihydroorotate dehydrogenase.(mitochondrial).**



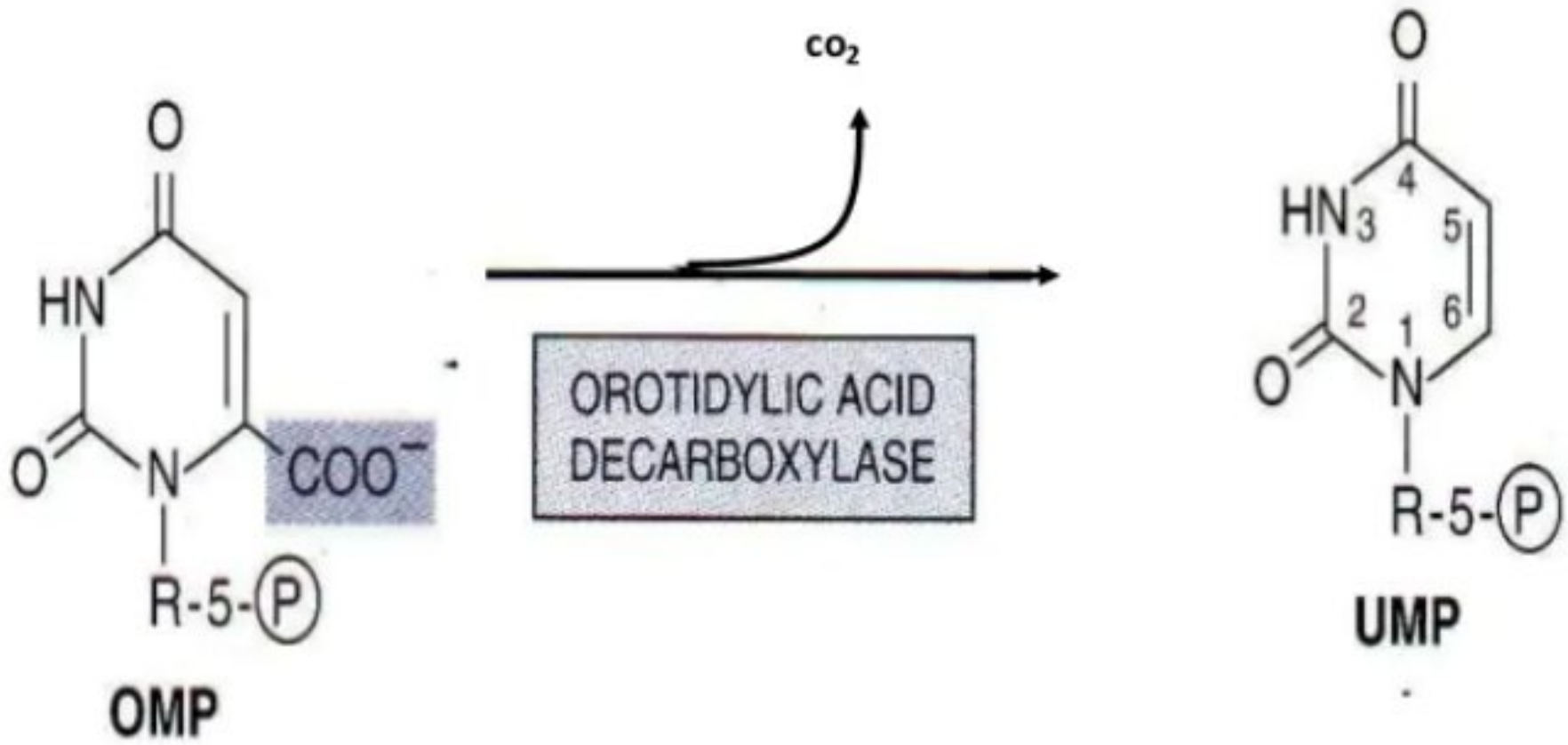
**5.Transfer of ribose phosphate** : This is transferred from PRPP, forming OMP(orotidylate), catalysed **by orotate – phosphoribosyl transferase.**



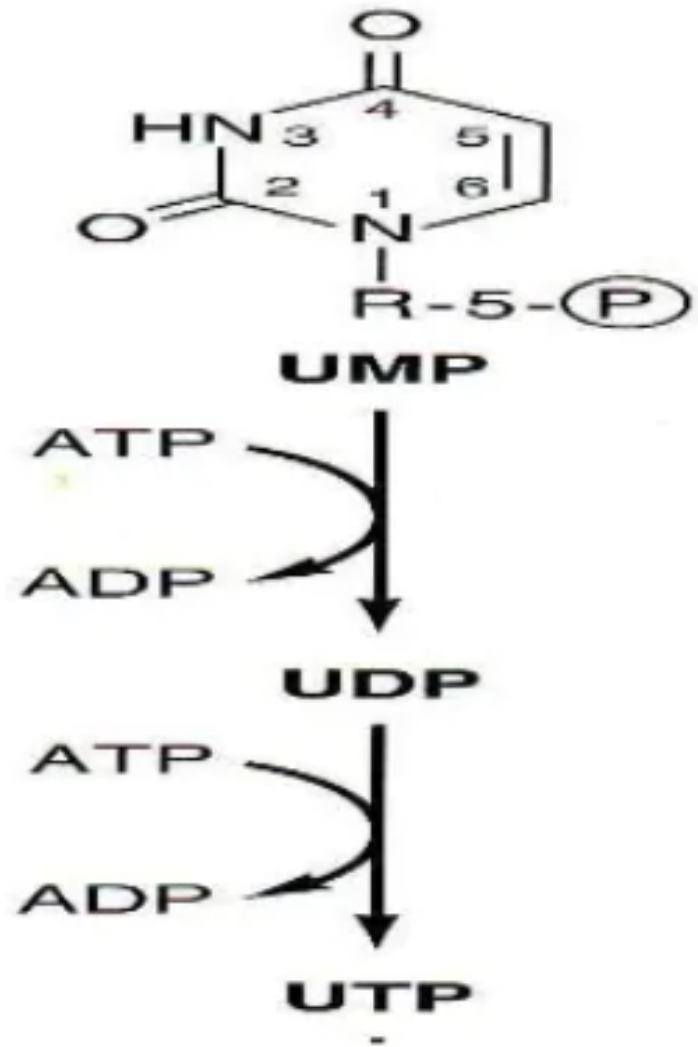
## 6.Decarboxylation:

OMP is decarboxylated forming UMP.

**UMP** is the **first true pyrimidine ribonucleotide**.

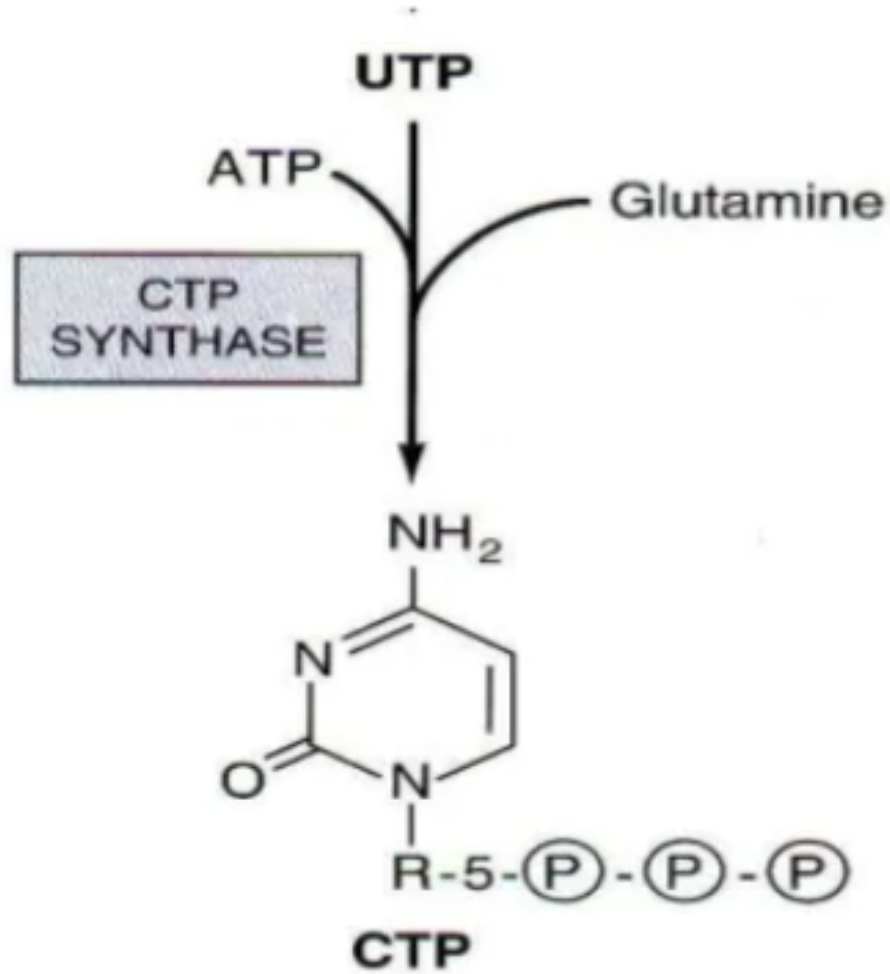


7. Phosphorylation of **UMP forms UDP and UTP** , with help of ATP.

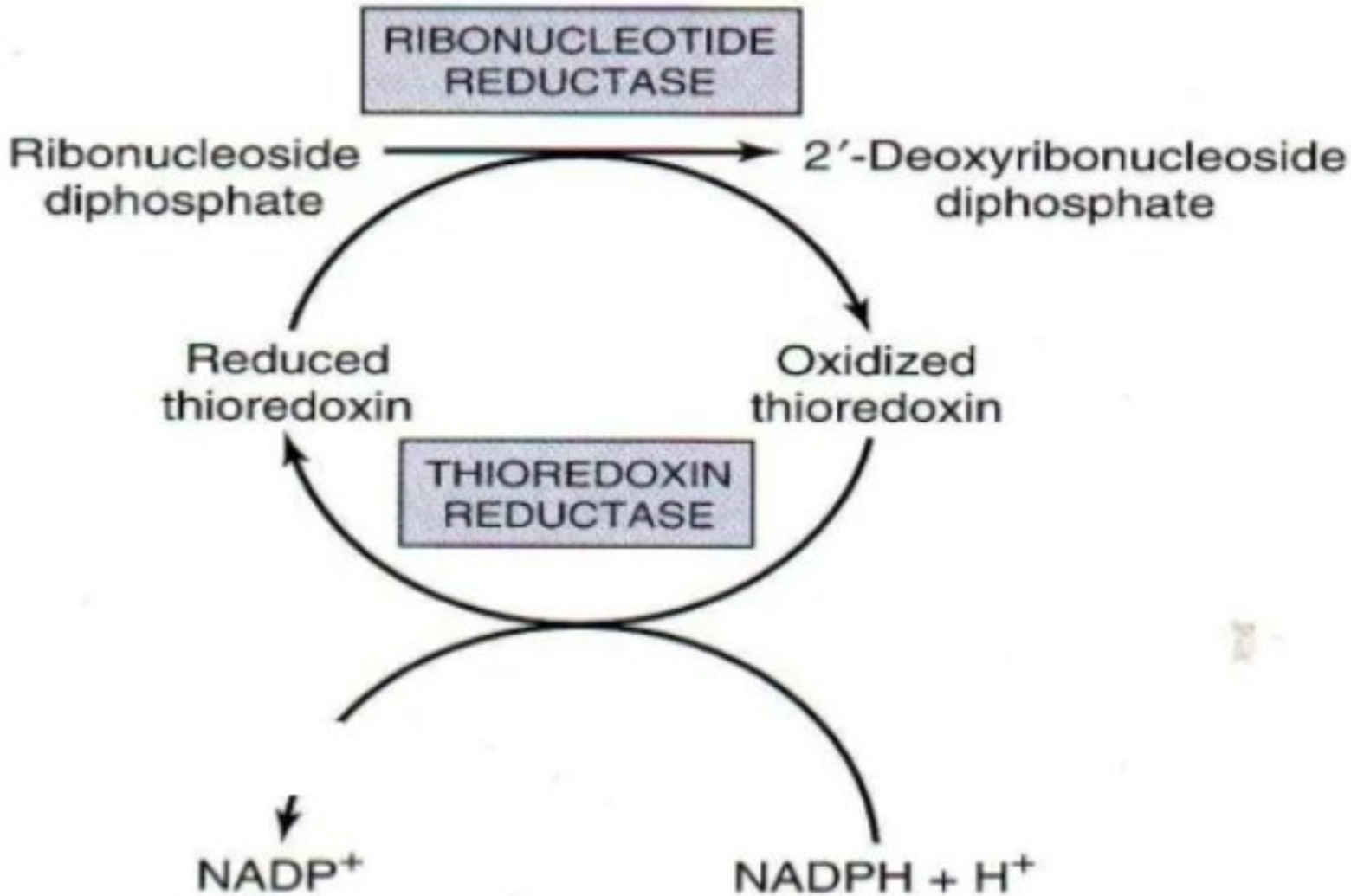


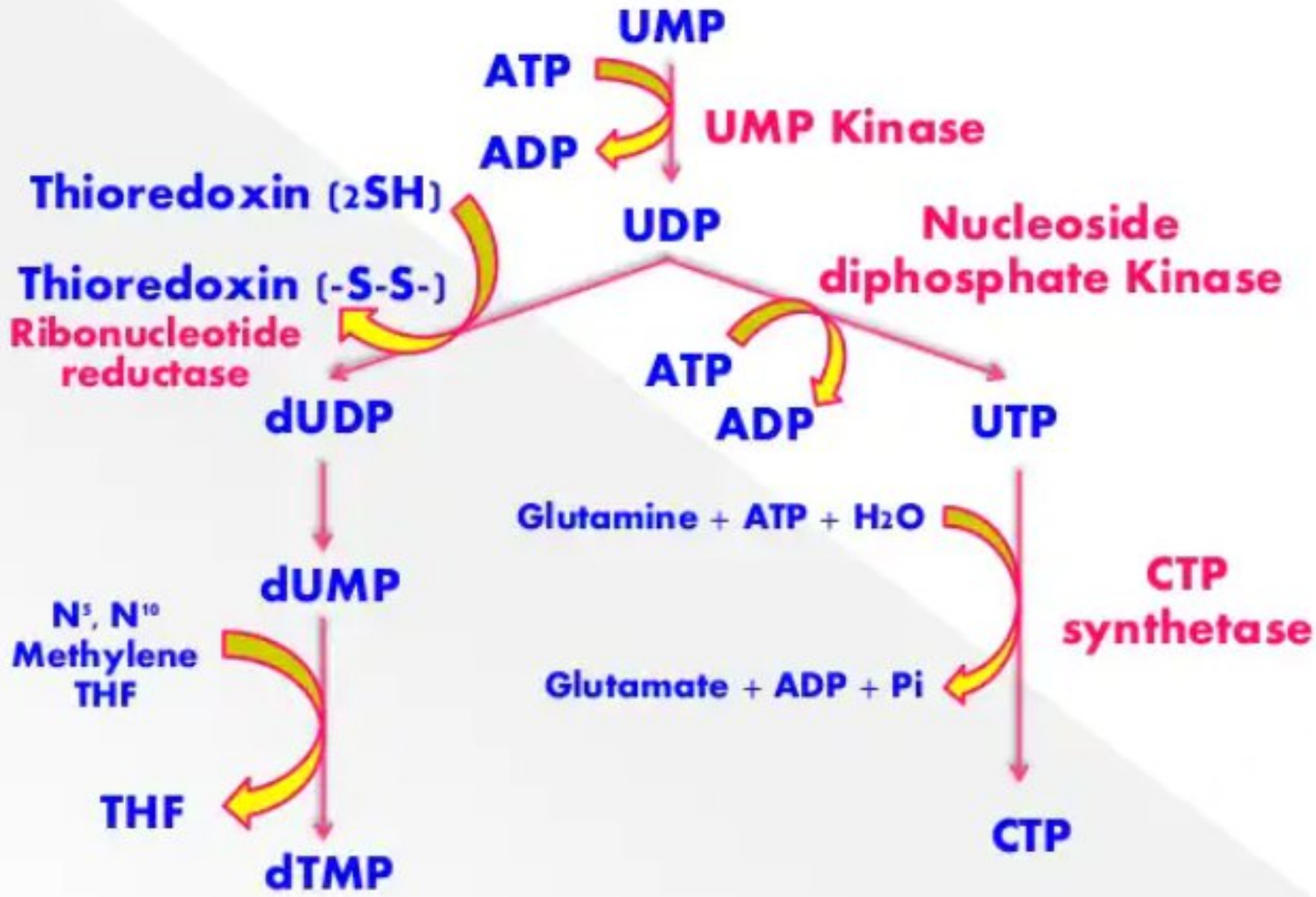
## 8.Formation of CTP :

UTP is aminated by **glutamine** and ATP, catalysed by **CTP synthase**.



## 9.Reduction of ribonucleoside diphosphates to their corresponding dNDP's .

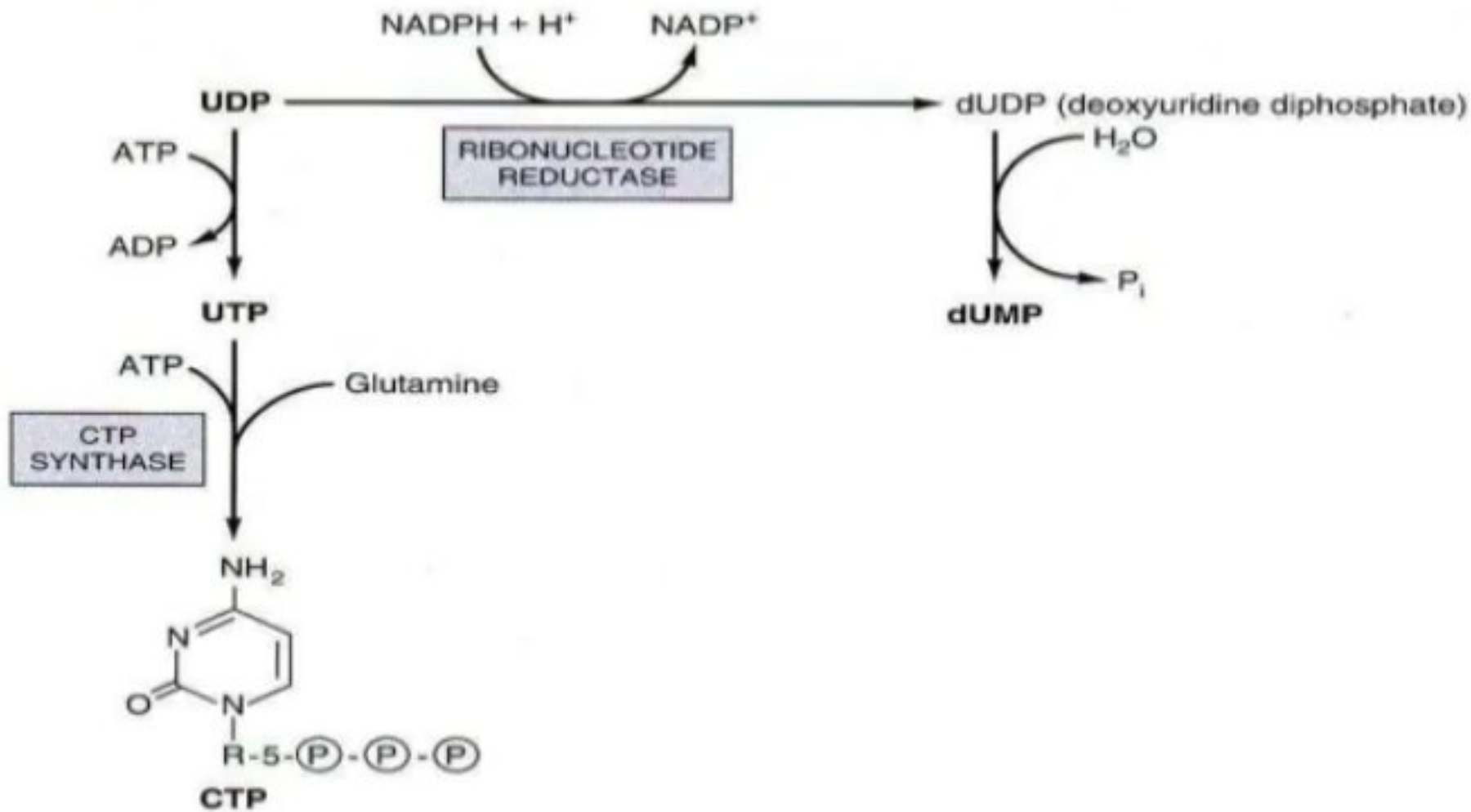



UMP
ATP
ADP
UMP Kinase
Thioredoxin (2SH)
Thioredoxin (-S-S-)
Ribonucleotide reductase
UDP
Nucleoside diphosphate Kinase
ATP
ADP
dUDP
UTP
Glutamine + ATP + H2O
CTP synthetase
Glutamate + ADP + Pi
dUMP
N5, N10 Methylene THF
THF
dTMP
CTP

## 10.Formation of TMP from UDP:

**dUMP is substrate for TMP synthesis.**

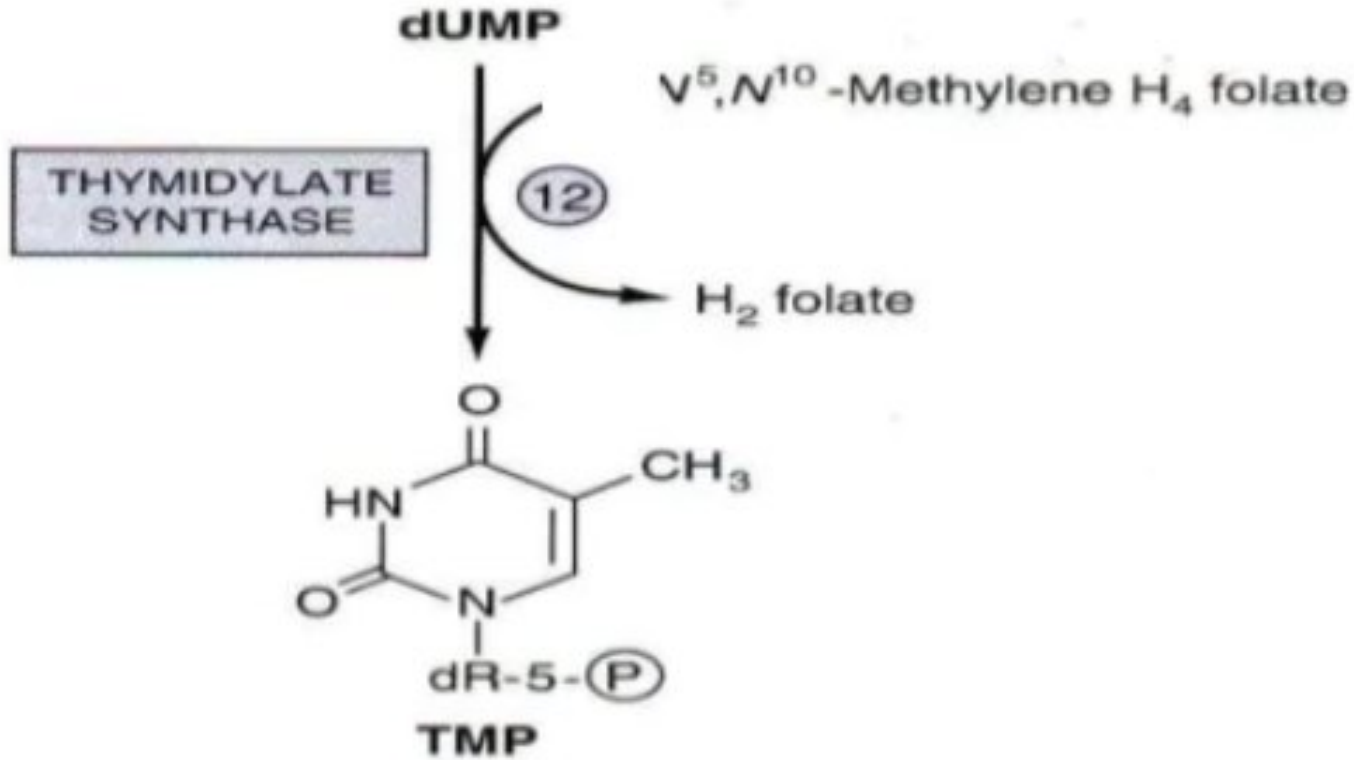
**dUDP is dephosphorylated to d UMP.**

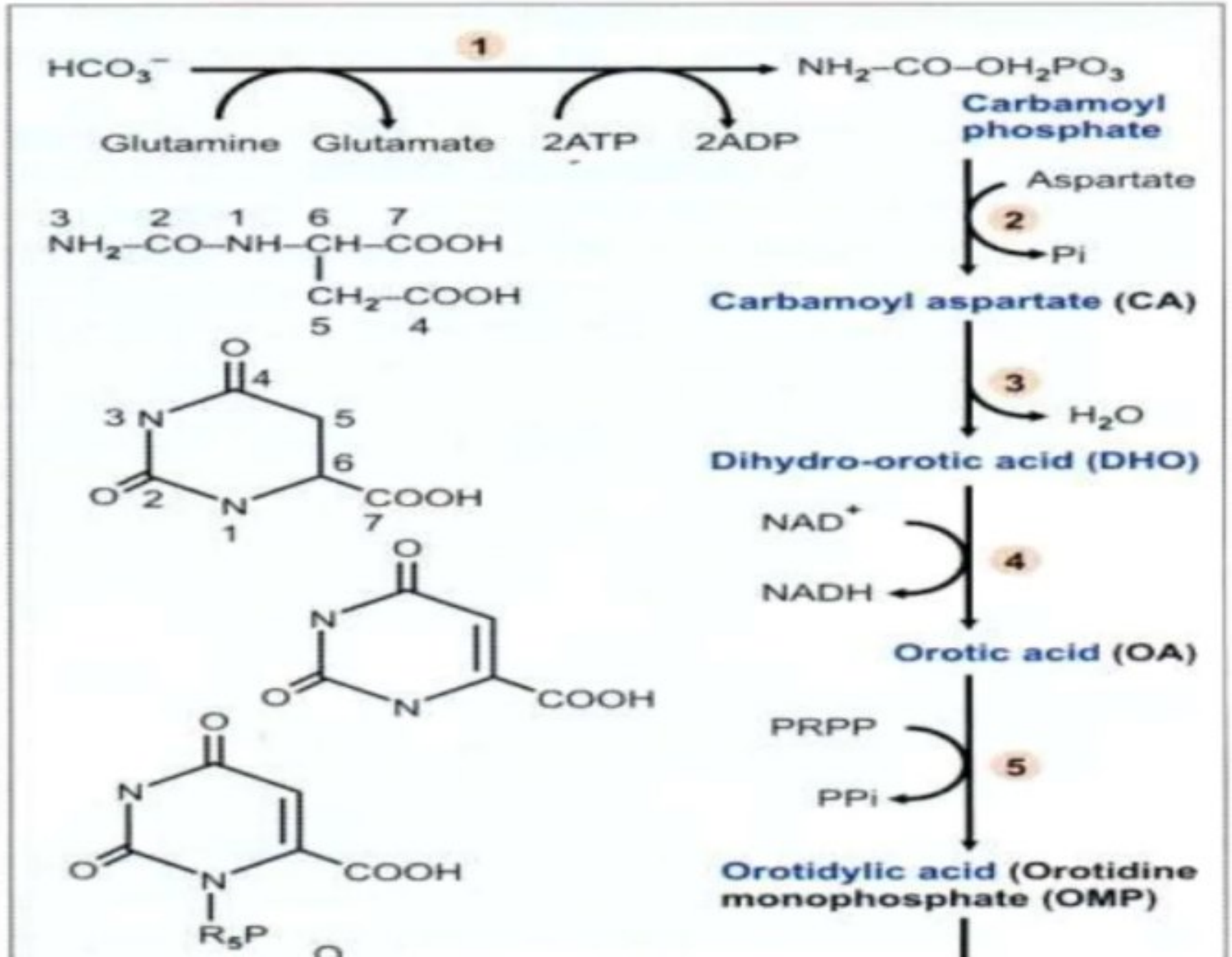


## 11. Methylation of dUMP:

This occurs at C5 by **N5,N10methyleneTHF, forming TMP.**

**This reaction is catalysed *by Thymidylate synthase*.**




$HCO_3^-$
1
$NH_2–CO–OH_2PO_3$
Carbamoyl phosphate
Glutamine
Glutamate
2ATP
2ADP
Aspartate
2
Pi
Carbamoyl aspartate (CA)
3
$H_2O$
Dihydro-orotic acid (DHO)
$NAD^+$
4
NADH
Orotic acid (OA)
PRPP
5
PPi
Orotidylic acid (Orotidine monophosphate (OMP)
COOH
$R_5P$

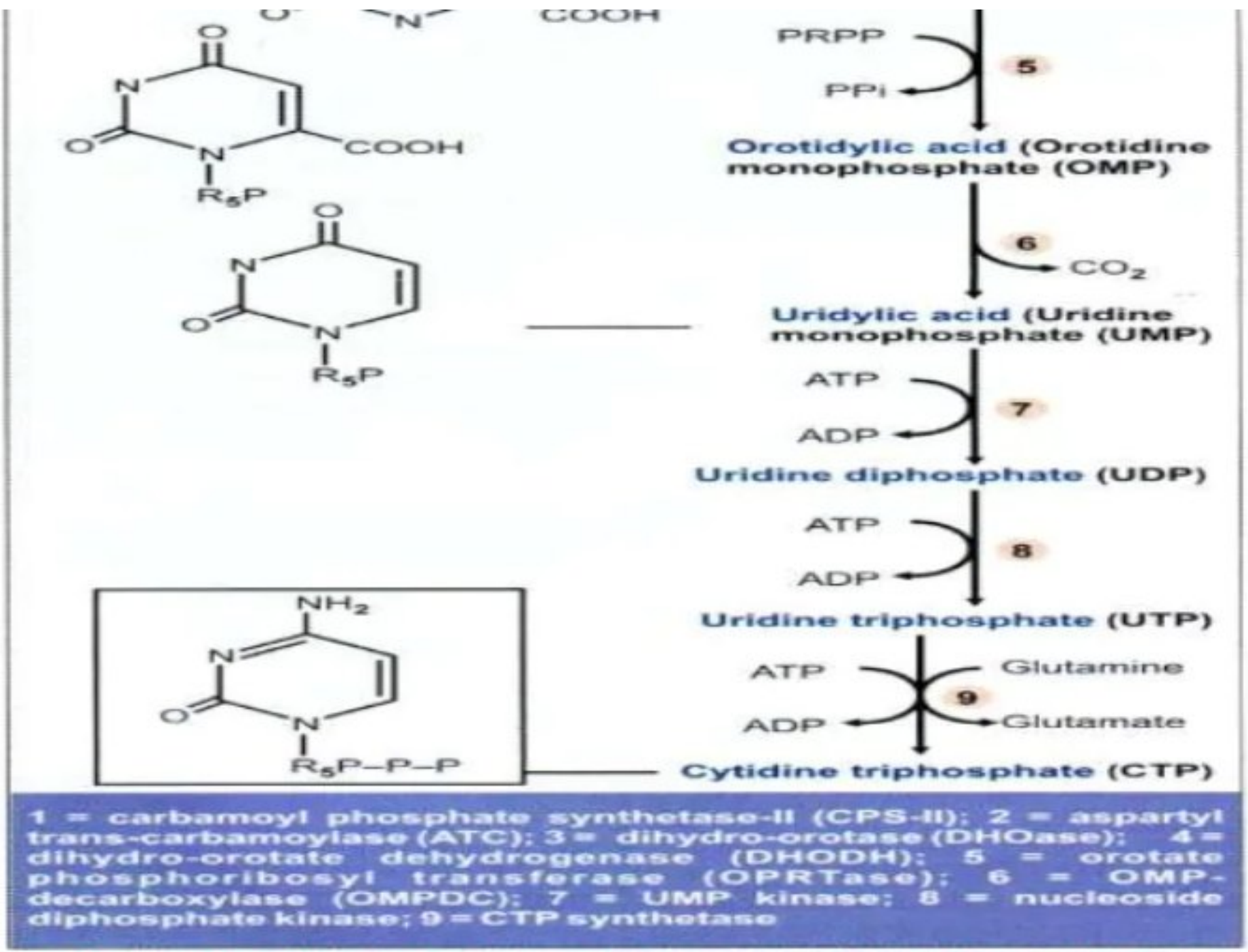


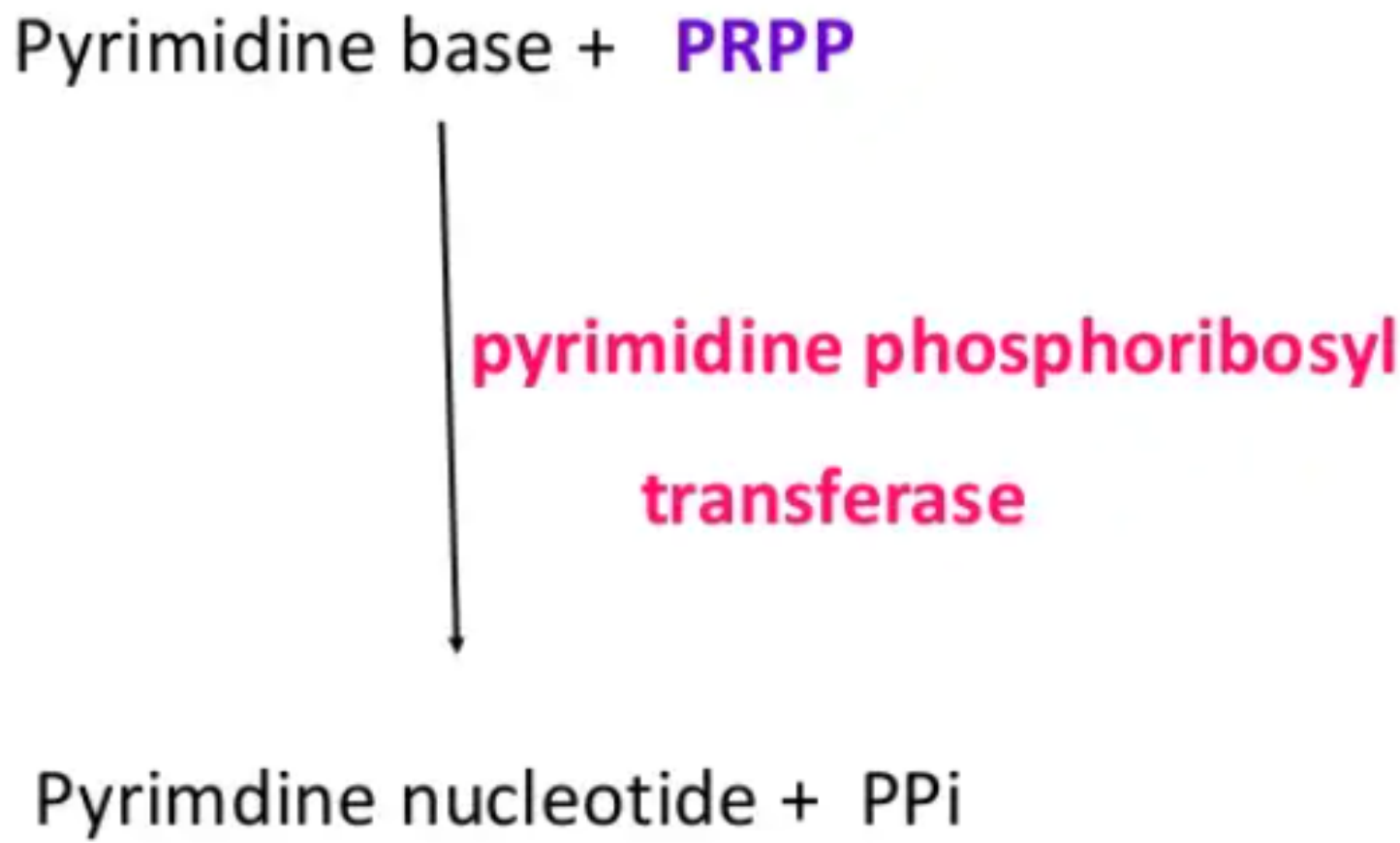

**Fig. 39.18.** Synthesis of pyrimidine nucleotides

## Salvage pathway

The pyrimidines (like purines) can also serve as precursors in the salvage pathway to be converted to the respective nucleotides.

This reaction is catalysed by pyrimidine phospshoribosyl transferase which utilizes PRPP as the source of ribose 5-phosphate.

# SALVAGE PATHWAY OF PYRIMIDINE SYNTHESIS



## Regulation of pyrimidine synthesis:

- CPSII,aspartate transcarbomylase and dihydrooratase are present as ***multienzymecomplex.***
- Orotate phosphoribosyl transferase and OMP – decarboxylase are present as ***single functional*** enzyme. Due to clustering of these enzymes , the synthesis is well coordinated.
- Dihydroorotate dehydrogenase is **mitochondrial** enzyme.

## 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 highlyl soluble products

**β-alanine and β-aminoisobutyrate.**

These are the amino acid which undergo transamination and other reactions to finally produce

acetyl CoA and succinyl CoA

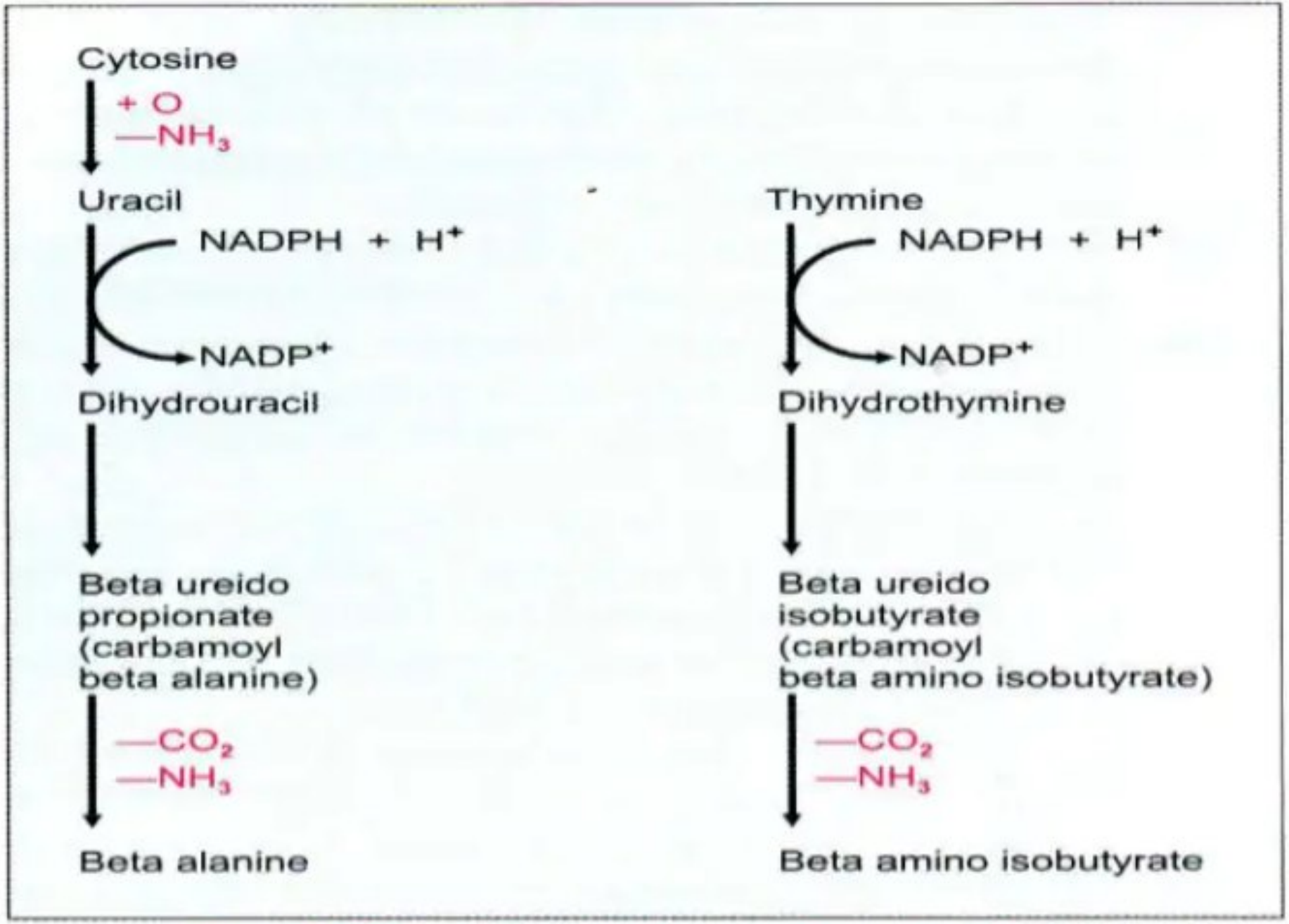



**Fig. 39.21.** Catabolism of pyrimidines

## Disorders of pyrimidine metabolism:

### 1.OROTIC ACIDURIA:

Orotic aciduria type I – deficiency of

Orotatephosphoribosyl transferase and OMP –

decarboxylase.

Orotic aciduria type II :

Rare, deficeincy of ONLY OMP decarboxylase.

Both types are inherited as **autosomal recessive** disorders.

# OROTACIDURIA

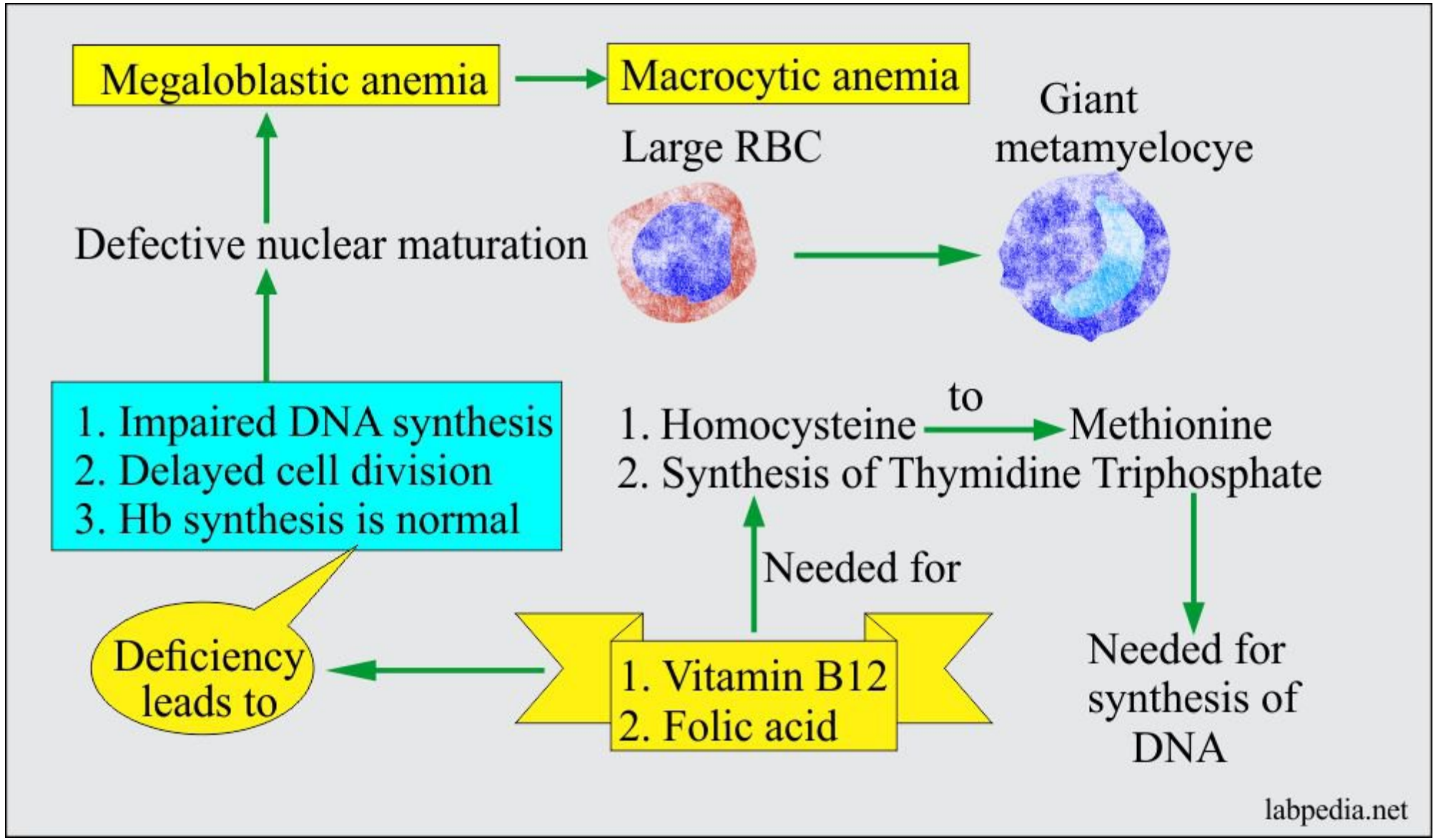
inherited disorder of pyrimidine synthesis caused by a deficiency of the enzyme of *orotate-phosphoribosyltransferase* and *decarboxylase*.

Symptoms:

–excess of orotic acid and its excretion with urine (1.0-1.5 g)

-mental and physical retardation

-megaloblastic anemia


Megaloblastic anemia
Macrocytic anemia
Large RBC
Giant metamyelocye
Defective nuclear maturation
1. Impaired DNA synthesis
2. Delayed cell division
3. Hb synthesis is normal
1. Homocysteine
to
Methionine
2. Synthesis of Thymidine Triphosphate
Needed for
Deficiency leads to
1. Vitamin B12
2. Folic acid
Needed for synthesis of DNA
labpedia.net

## 2. Drugs may precipitate orotic aciduria:

a)**ALLOPURINOL** , a purine analog is a substrate for Orotate phosphoribosyl transferase.

↓

It competes for phosphoribosylation with natural substrate, orotic aicd.

↓

The resulting nucleotide product inhibits

OMP DECARBOXYLASE

↓

leading to Orotic aciduria and orotiduniria

**Features :**

- Due to lack of feedback inhibition orotic acid production is excessive.(UMP inhibits OMP decarboxylase)
- Rapidly growing cells are affected – anemia
- Retarded growth
- Crystals excreted in urine causing **urinary obstruction.**
- Both types respond to uridine , as it is converted to UTP . This acts as feed back inhibitor.

**Reye's syndrome:**

This is considered as a secondary orotic aciduria.

It is believed that a defect in ornithine trascarbamoylase (or urea cycle ) causes the accumulation of carbamoyl phosphate.

This is then diverted for the increased synthesis and excretion of orotic acid.

**Reye's syndrome, a child's blood sugar level typically drops while the levels of ammonia in blood rise.**
**At the same time, the liver may swell and develop fatty deposits. Swelling may also occur in the brain, which can cause seizures, convulsions or loss of consciousness**

# Thank You

# What is Carnitine?

Carnitine - **substance** found in almost every cell in the body, it is biosynthesized from - **amino acids lysine** and **methionine.**

There are three different forms of carnitine:

L-carnitine

acetyl-L-carnitine

propionyl-L-carnitine

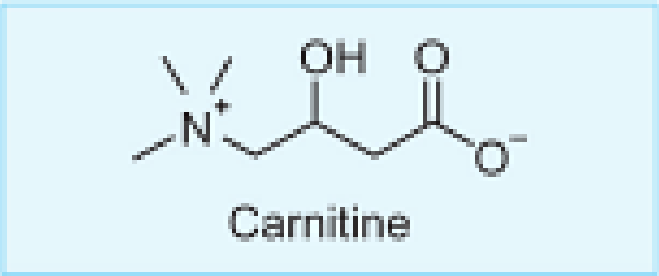



**Fig. 1:** Structure of carnitine

# Role of Carnitine?

Carnitine -helps the body **turn fat into energy** . Our body **makes** it in the liver and kidneys and **stores** it in the skeletal muscles, heart, brain, and sperm.

The compound plays role in **energy production** , as it is **responsible for transporting fatty acids to the mitochondria.** carnitine transports long-chain fatty acids into mitochondria where they are oxidized to produce energy.

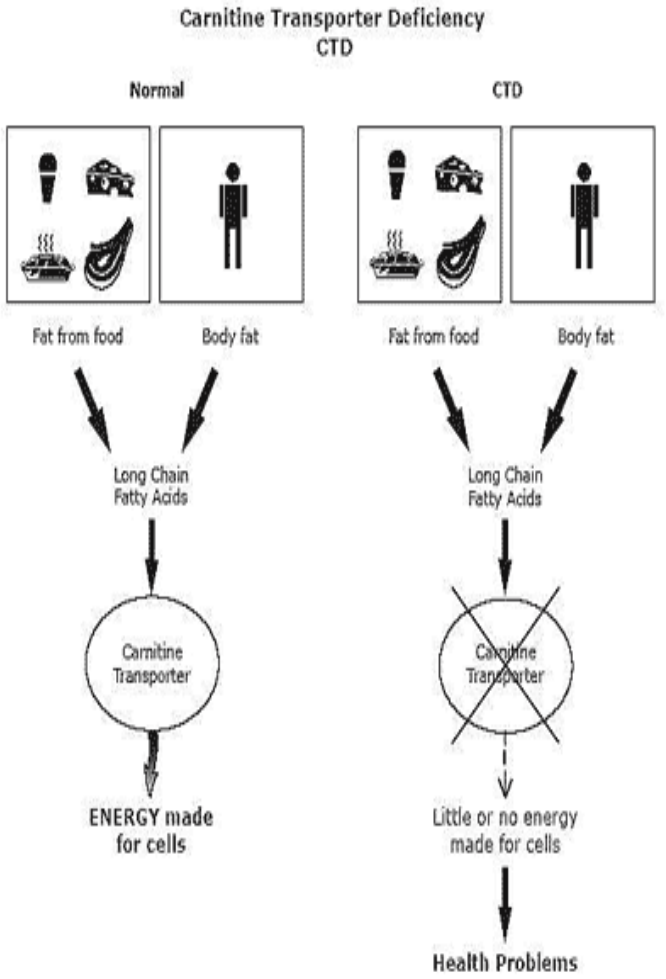
Carnitine-transports waste and

# Carnitine Deficiency

Carnitine deficiency is one of a group of **metabolic muscle diseases** that interferes with the **processing of food** (in this case, fats) for **energy production.**

Inborn error of fatty acid transport caused by a **defect** in the **transporter** responsible **for moving carnitine across** the **plasma membrane**

When **carnitine cannot** be **transported** into tissues,



# Who is at risk for carnitine deficiency?

The primary condition is passed down from parents to children.

A child needs to get an **abnormal copy** of the **gene** from **both parents**.

You may have a risk for the secondary condition if you have **liver or kidney disease**, or certain other health conditions

# What causes carnitine deficiency?

Response to a **genetic mutation** (gene defect) in the **protein** responsible for **bringing carnitine** into the **cell (primary carnitine deficiency)**

May occur **secondary** to other **metabolic** diseases **(secondary carnitine deficiency)**

**Primary carnitine deficiency**

This is a **rare condition** caused by an **abnormal gene**.

The g**ene causes a problem** with a **protein** that **carries carnitine inside cells** from the blood.

The condition only **leads** to **low carnitine** levels in **muscle**.

In this condition the **body can't use certain fats** for energy, particularly when the person goes without food (**fasting**).

If the **liver** and **heart** are also affected, it may be called **systemic carnitine deficiency** .

**Secondary carnitine deficiency**

This is a **more common** condition.

There **isn't** a problem **getting carnitine** into **cells**.

The problem is that there **isn't enough carnitine** in the **blood**. It can result from a number of health problems.

## Primary Carnitine Deficiency

A person with primary carnitine deficiency has **very low levels** of carnitine in the blood **due to a faulty carnitine transporter** which **prevents carnitine** from getting into the **cells** where it is needed.

The primary form of the disorder can be classified as either "**systemic carnitine deficiency** ", which affects many organ systems including the heart and the brain, or "muscle carnitine deficiency", which is restricted to **voluntary muscles**.

## Secondary Carnitine Deficiency

The secondary form of carntine deficiency can arise secondary to **metalobic disorders** in the **mitochondria**.

**Blockage of metabolic** pathways in the mitochondria leads to **a build-up of acyl compounds**.

These compounds then **bind to carnitine** and the bound complex is then **excreted by the kidney** , causing **carnitine levels to drop.**

Some of these mitochondrial disorders include**, mitochondrial ATPase deficiency** , and **fatty acyl-CoA dehydrogenase** deficiencies.

**In both primary and secondary carnintine deficiencies, increased dietary intake and supplements of carnitine can be beneficial** .

**Simple explanation of carnitine transporter**

*The main function of **carnitine** is in the **uptake of fatty acids** into **the mitochondrial matrix** for **beta-oxidation** .

*Fatty acyl CoA **cannot cross** the **mitochondrial membrane**.

*At the **outer face of the outer mitochondrial** membrane the **fatty acyl group is transferred onto carnitine** , catalysed by carnitine acyltransferase 1 (**CAT 1**).

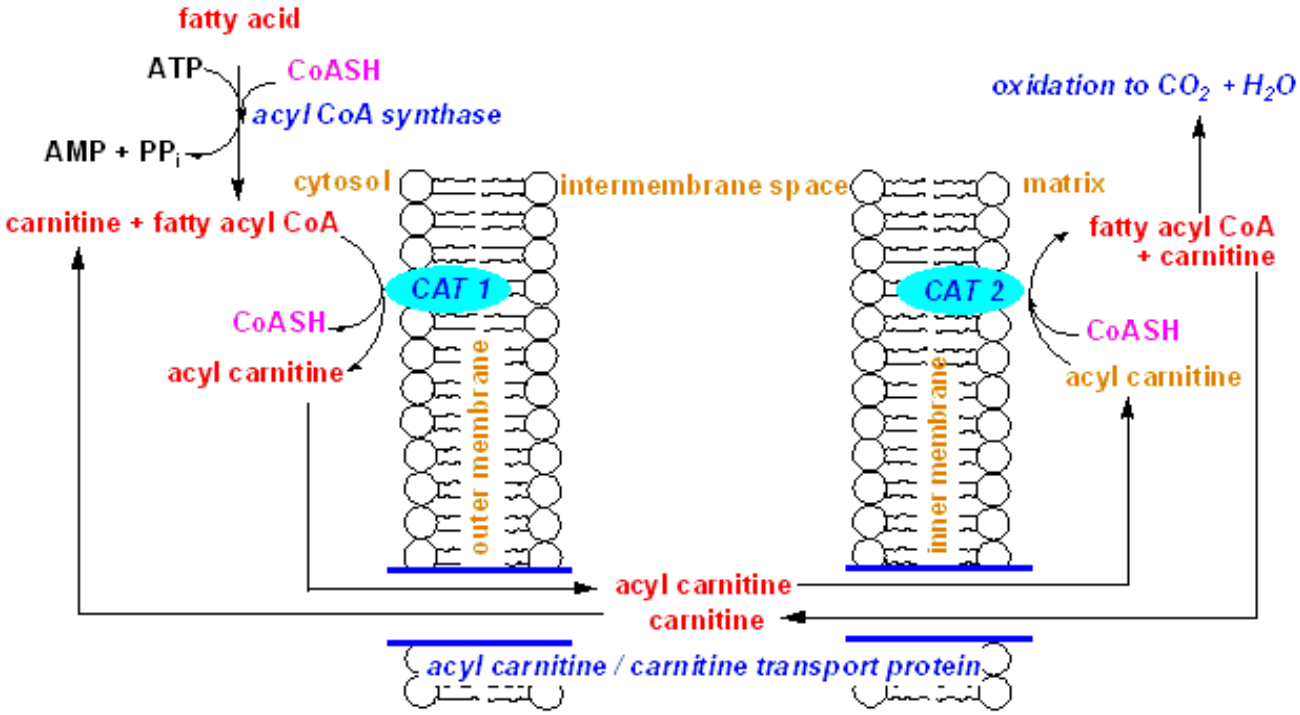
* **Acyl carnitine** is **transported across the membranes** in exchange for free carnitine and at the inner face of the inner mitochondrial membrane the acyl group is transferred onto CoA, catalysed by **carnitine acyltransferase 2** .

Fatty acid are **activated** on the **outer mitochondrian membrane**, whereas they are oxidized in the mitochodrial matrix

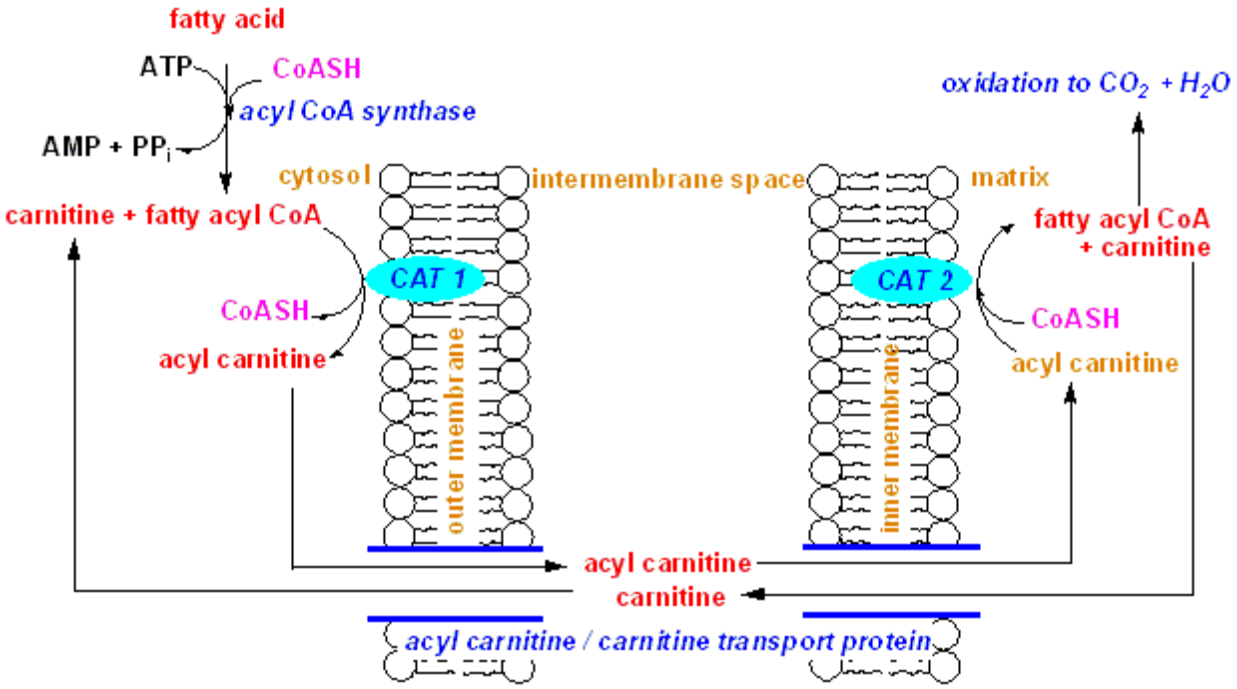
A special transport mechanism is needed to carry the long chain acyl CoA molecules across the inner mitochondrial membrane.

Activited **long chain fatty acid** are transported across the membrane by **conjugating** them to **carnitine**

**The acyl group** is the **hydroxyl grou**



- √ This reaction is catalyzed by **carnitine acyl transferase I** which is bound to **the outer mitochodrial membrane** .
- √ **Acyl carnitine** is then shuttled across the **inner mitochodrial** membrane.
- √ The acyl group is transferred back to CoA on the matrix side of the membrane. The reaction, which is catayzed by **carnitine acyl is transferase II** is simply the reverse of the reaction that takes place in the cytosol
- √ Finally, the **translocase returns carnitine** to the **cytosolic side** in exchange for an **incoming actyl carnitine**



# Basic Concept

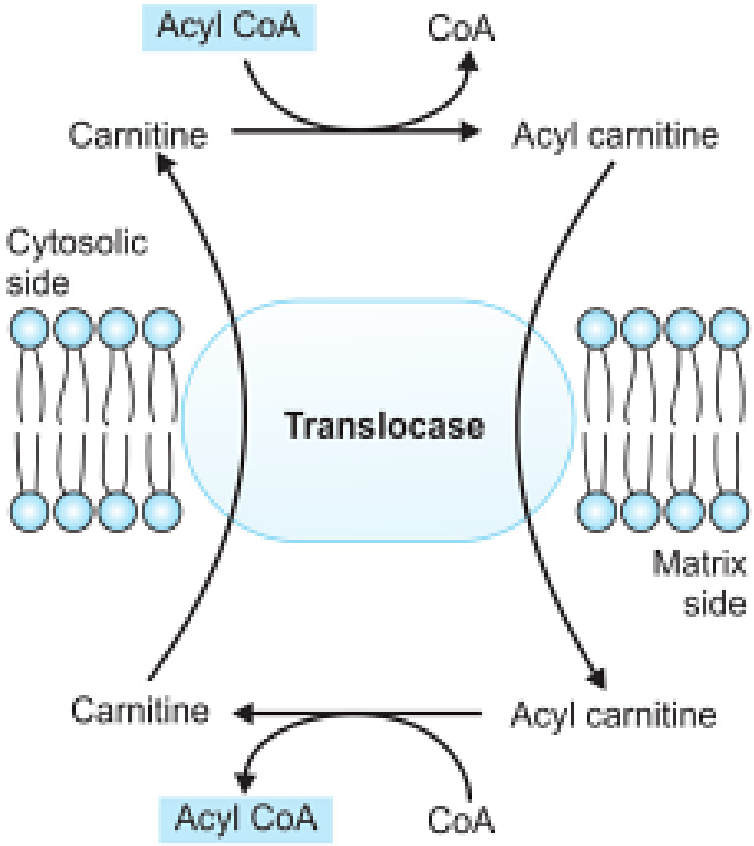



Fig. 2: Role of carnitine in transporting the activated fatty acids into the mitochondria

# Conclusion

Carnitine, absorbed from **dietary intake** or **synthesized** in **liver** and **kidney**, reaches the blood stream and the extracellular fluid.

Its **transport within cells of various tissues** is limited by their respective uptake capacities.

Plasma **concentration of free carnitine** is in **dynamic balance** with **acylcarnitine.**

# Excretion

Carnitine is highly conserved by the human kidney, which reabsorbs more than 90% of filtered carnitine.

Kidney plays a dominant role in the regulation of plasma carnitine concentration.

Renal excretion of carnitine adapts to the level of carnitine intake.

# Excretion

A small amount of carnitine is normally found in the urine, even in subjects with low plasma carnitine concentrations.

Some of this may come from the renal secretion of carnitine either in free form or as short-chain acylcarnitine esters.

# Renal function

- **Patients with renal disease managed with chronic hemodialysis can be depleted of carnitine owing to the loss of carnitine in the dialysate, which greatly exceeds the amount normally lost in the urine.**
- **Tissue depletion of carnitine has been related to the complications attendant to hemodialysis: hyperlipidemia, cardiomyopathy, skeletal muscle asthenia and cramps.**

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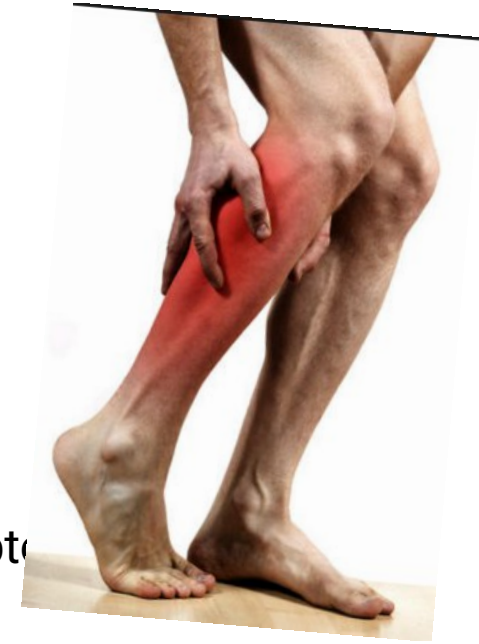
# What are the symptoms of carnitine deficiency?



If confined to muscles, this disease causes:

Weakness in the hips, shoulders, and upper arms and legs.
The neck and jaw muscles also may be weak.
Heart muscle weakness may occur.

In more severe cases, where other tissues are affected, sympt
low blood sugar
fatigue
vomiting
abdominal pain
growth retardation
low weight
enlarged liver
brain function abnormalities.

What causes carnitine deficiency?
The primary condition is caused by an **abnormal gene**.

A **variety of health conditions** can cause the secondary condition. These **decrease the amount of carnitine** in the body.

They may do this by **increasing** the amount **sent** out **in urine**.

Or, they may cause the body to **absorb less from food**. The health problems that can cause this include:

- ✓ Liver disease
- ✓ Kidney disease, especially with dialysis
- ✓ Digestive disease that causes poor absorption
- ✓ Malnutrition
- ✓ Mitochondrial disease
- ✓ Certain metabolic disorders
- ✓ Certain medicines, such as valproate

# THANK YOU