Chapter 10

Metabolism of Amino Acid

Overview

- Nitrogen is contained in amino acids, nucleotides
- Biologically useful nitrogen compounds are generally scarce in nature.
- Most organisms maintain strict economy in their use of nitrogenous cpds (ammonia, amino acids, and nucleotides)
  - often salvaging and reusing them.
- The nitrogen cycle maintains a pool of biologically available nitrogen.

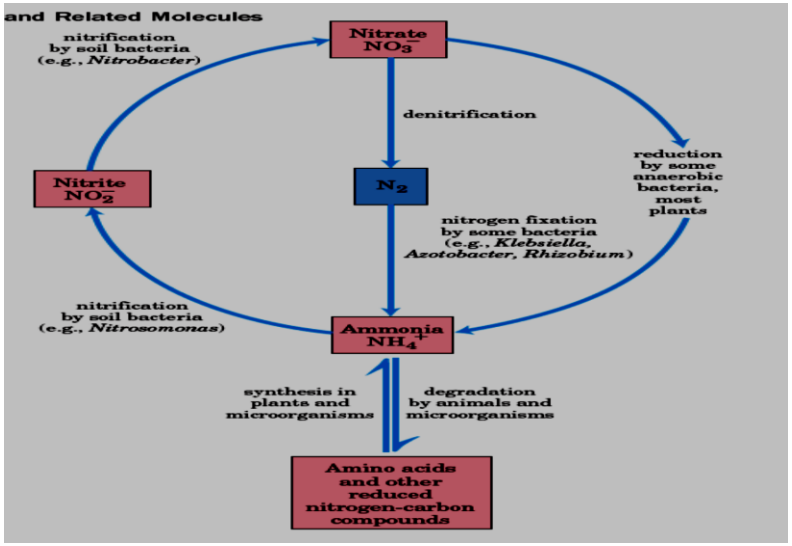
Nitrogen cycle

- Involve conversion of atmospheric nitrogen into forms useful to living organisms (NO_2^-, NO_3^-, NH_4^+) and then set it free back

- Soil bacteria play significant role in recycling N in biosphere

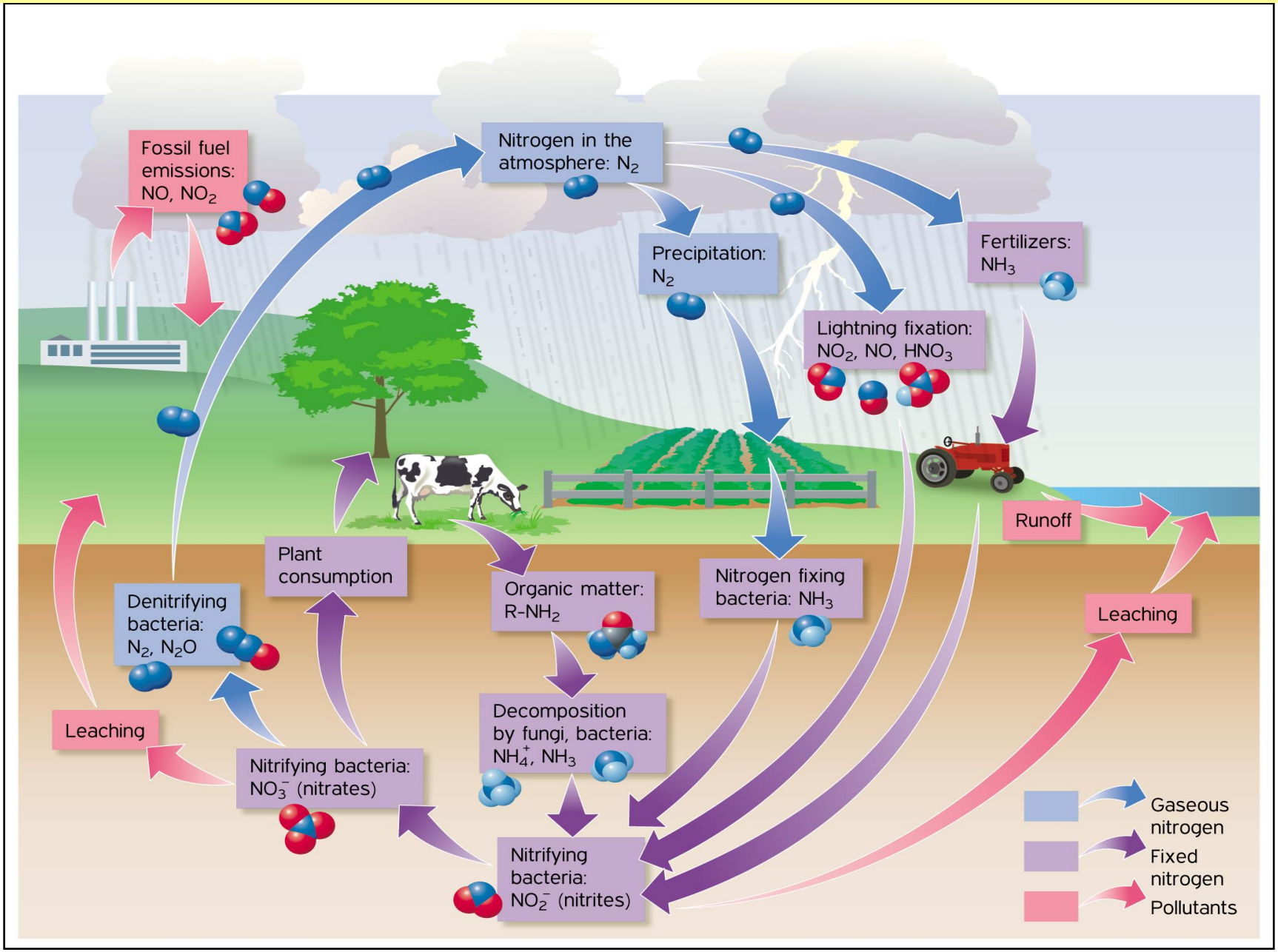
• Nitrogenase containing bacteria	$N_2 \rightarrow NH_3$
• Nitrite bacteria (*Nitrosomonas*)	$NH_3 \rightarrow NO_2^-$
• Nitrate bacteria (Nitrobacter)	$NO_2^- \rightarrow NO_3^-$
• Denitrifying bacteria	$NO_3^- \rightarrow N_2$

- The cycle involves nitrogen fixation (reduction), nitrification and denitrification



- Lightning also produce nitrates

Nitrogen cycle



Assimilation of ammonia in biological system

- Ammonia generated from N_2 is assimilated into low molecular weight metabolites such as glutamate or glutamine

- At pH 7 ammonium ion predominates (NH_4^+)

- At enzyme reactive centers unprotonated NH_3 is the nucleophilic reactive species

Catabolism of amino acid

Digestion & absorption of dietary proteins

- Mammalian body lack protein stores
  - Hence essential amino acids must come from diet.

- Proteins are broken down in to peptides and amino acids by
  - **Pepsin** in the stomach
  - Pancreatic proteases (**trypsin** & **chymotrpsin**) in the SI

- Intestinal wall produces peptidases which continue to split remnants into tripeptides, dipeptides, and some amino acids

- Resulting amino acids are absorbed by the intestinal mucosa and enter the capillaries for travel to the liver. (**Portal circulation**) → ≈99%

  - Absorption is through **active transport** (most) and **facilitated diffusion** (Leu,Ile)

- Proteins may be absorbed as such during **infancy** (e.g clostrum) and certain **diseases (e.g allergy)**

Digestion & absorption of dietary proteins

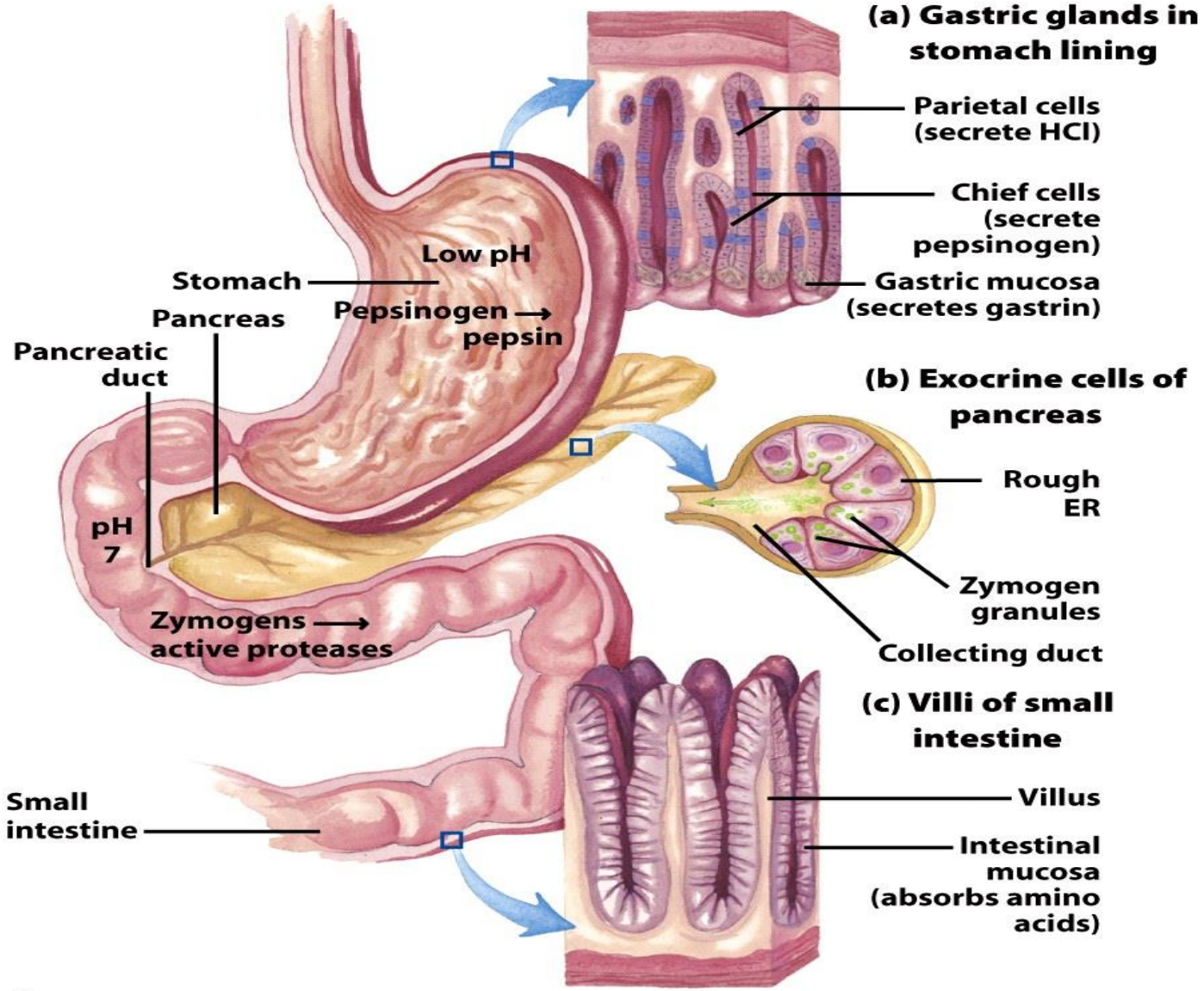


Figure 18-3
Lehninger Principles of Biochemistry, Fifth Edition

Fates of absorbed aminoacids

- Amino acids are used as
  - Building blocks for proteins (200mg /day)
  - Energy source (cover ~10% of our daily energy needs)
    – or more during starvation or following protein diet
  - Synthesis of some non-protein metabolites

- Liver catabolise (oxidize) all amino acids
  - **Nitrogen (amine)** in them is safely removed to avoid **ammonia toxicity**.
  - The remaining **c-skeleton** of amino acids can be harvested for **energy converting reactions**

Removal of amino groups from α-amino acids

Transamination (occur in liver cytosol)

- Major reactions involved in the removal of nitrogen from aa's

- Amino groups to transferred to
  - ✓ **α-ketoglutarate** to form **Glutamate** or
  - ✓ **Oxaloacetat**e to form **Aspartate**

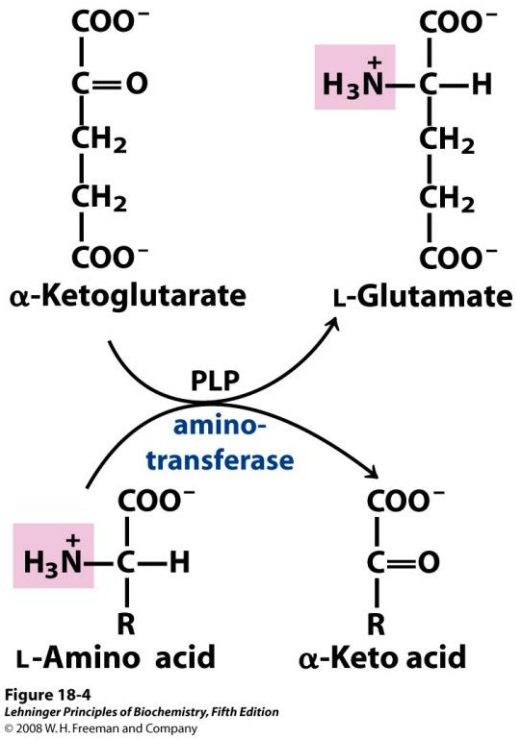


Figure 18-4
Lehninger Principles of Biochemistry, Fifth Edition

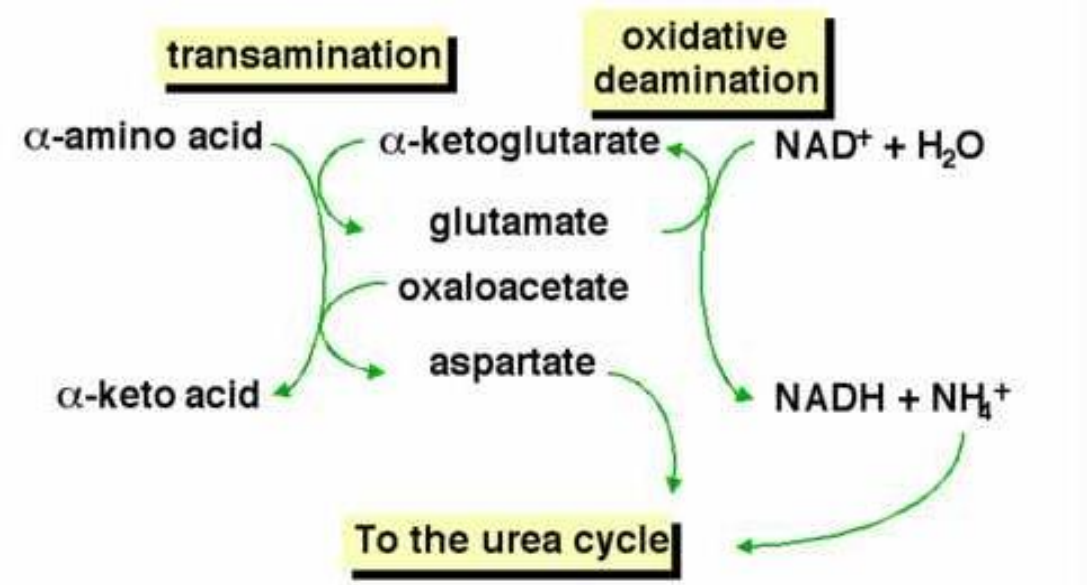
- **Transaminases** (aka aminotransferases) catalyze the reaction
  - ✓ Require **pyridoxal phosphate as a** cofactor

- Transaminases exist for all amino acids except <u>threonine</u> and <u>lysine</u>.

Removal of amino groups from α-amino acids

Oxidative deamination (in hepatocyte matrix)

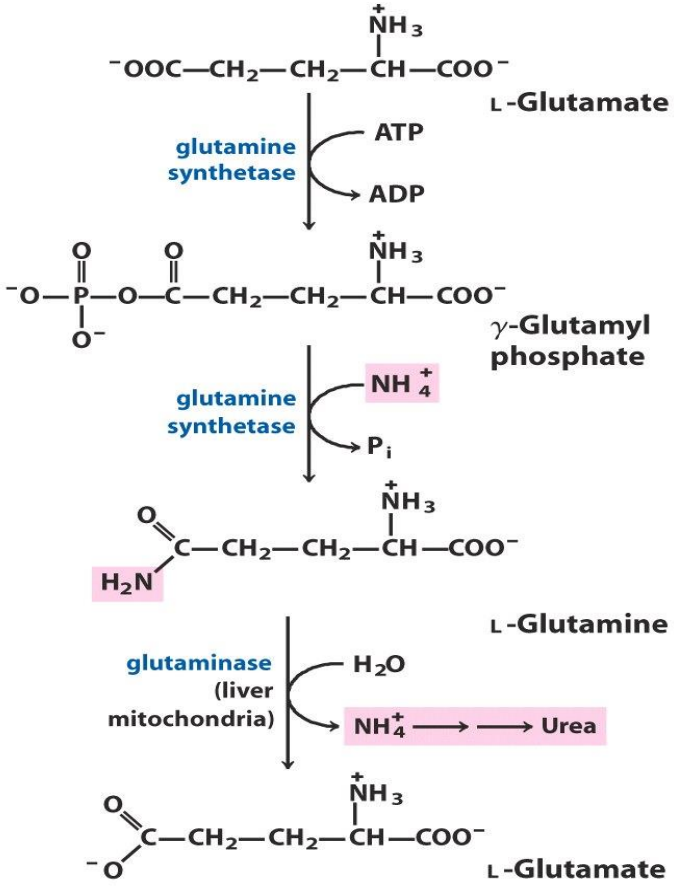
- Catalyzed by **glutamate dehydrogenase** it cause removal of amino groups from glutamate
  - ✓ To set free **α-KG**
- Amino group must be processed for excretion (urea cycle).



Other ways of transport of amino groups

Transport of amino groups as glutamine

- Other tissues may send their amino groups as glutamine through the bloodstream to the liver for processing

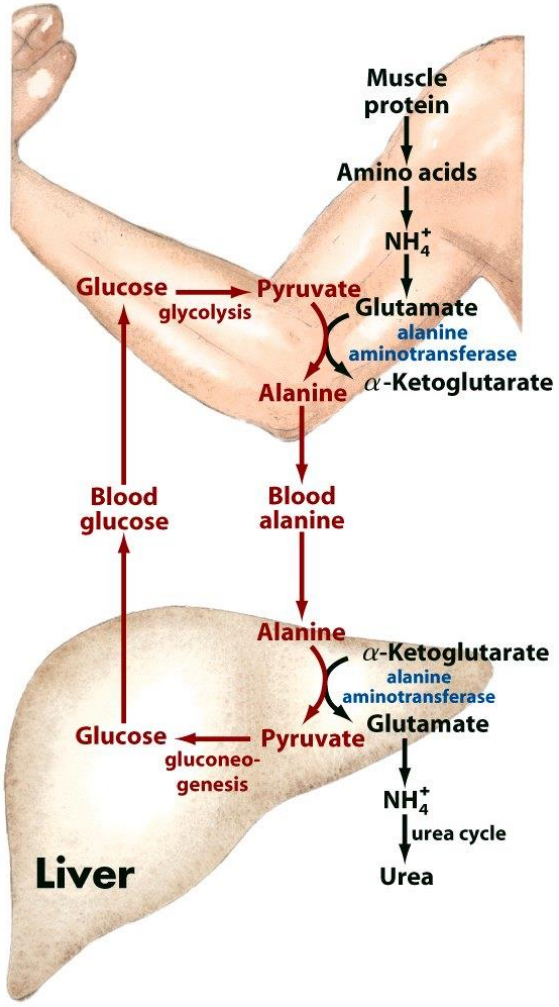


Other ways of transport of amino groups

Transport of amino groups as alanine

- In concert with the Cori cycle, skeletal muscle may send pyruvate through bloodstream as Ala (the glucose-alanine cycle).

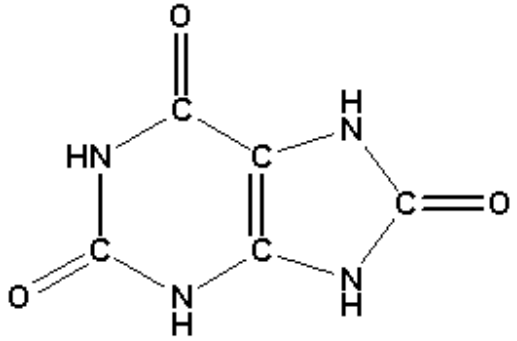
- Operates when muscle proteins are undergoing catabolism.



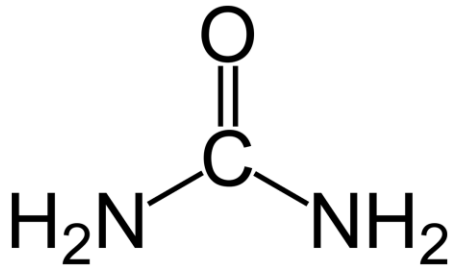
Fate of Ammonium ion (NH_4^+)

- Depends on type of organism

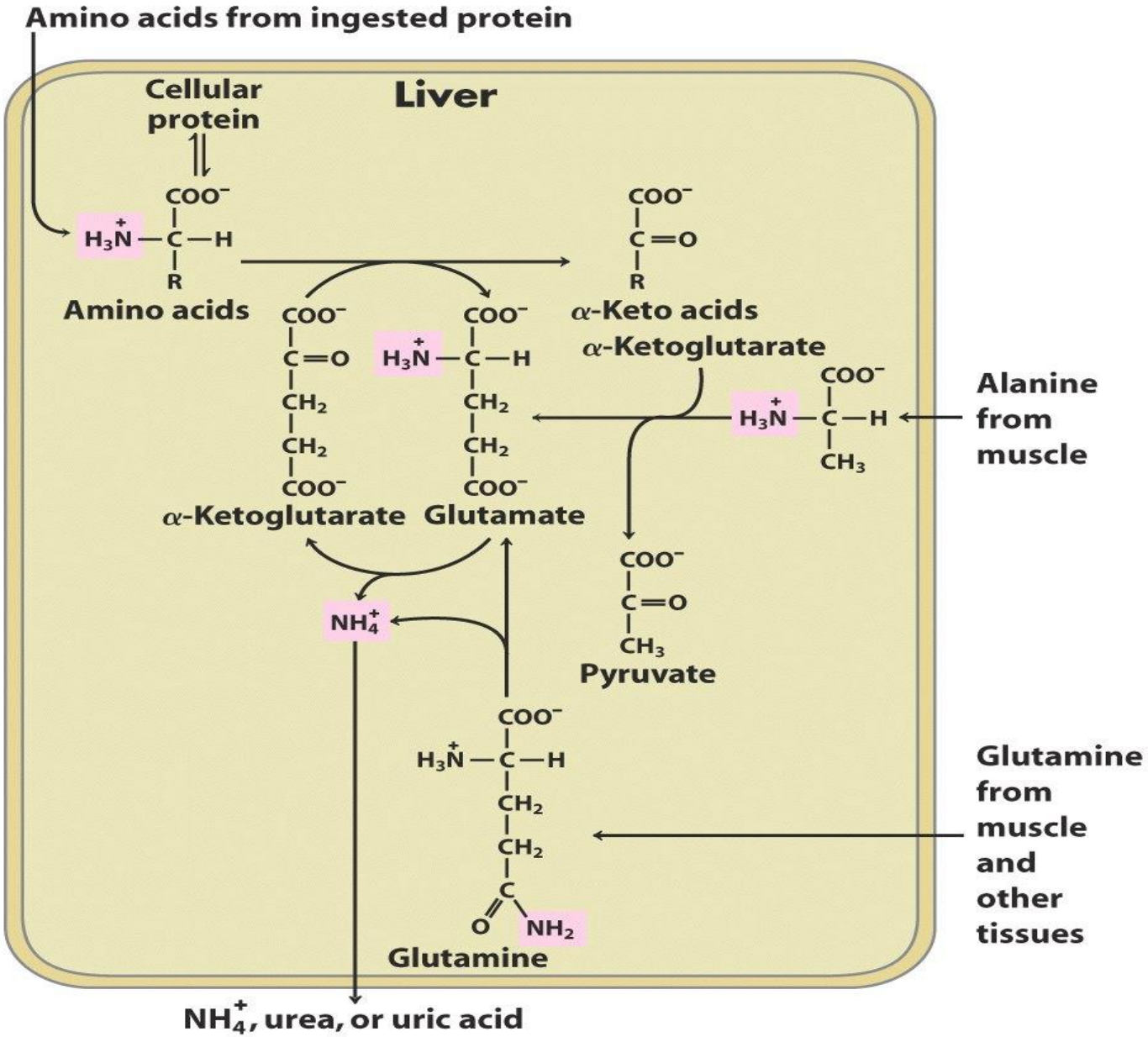
Organism	Form of excretion
Fishes	NH_3(ammonotelic)
Birds	Uric acid (uricotelic)
Humans	urea in H_2O(ureotelic)



Uric Acid



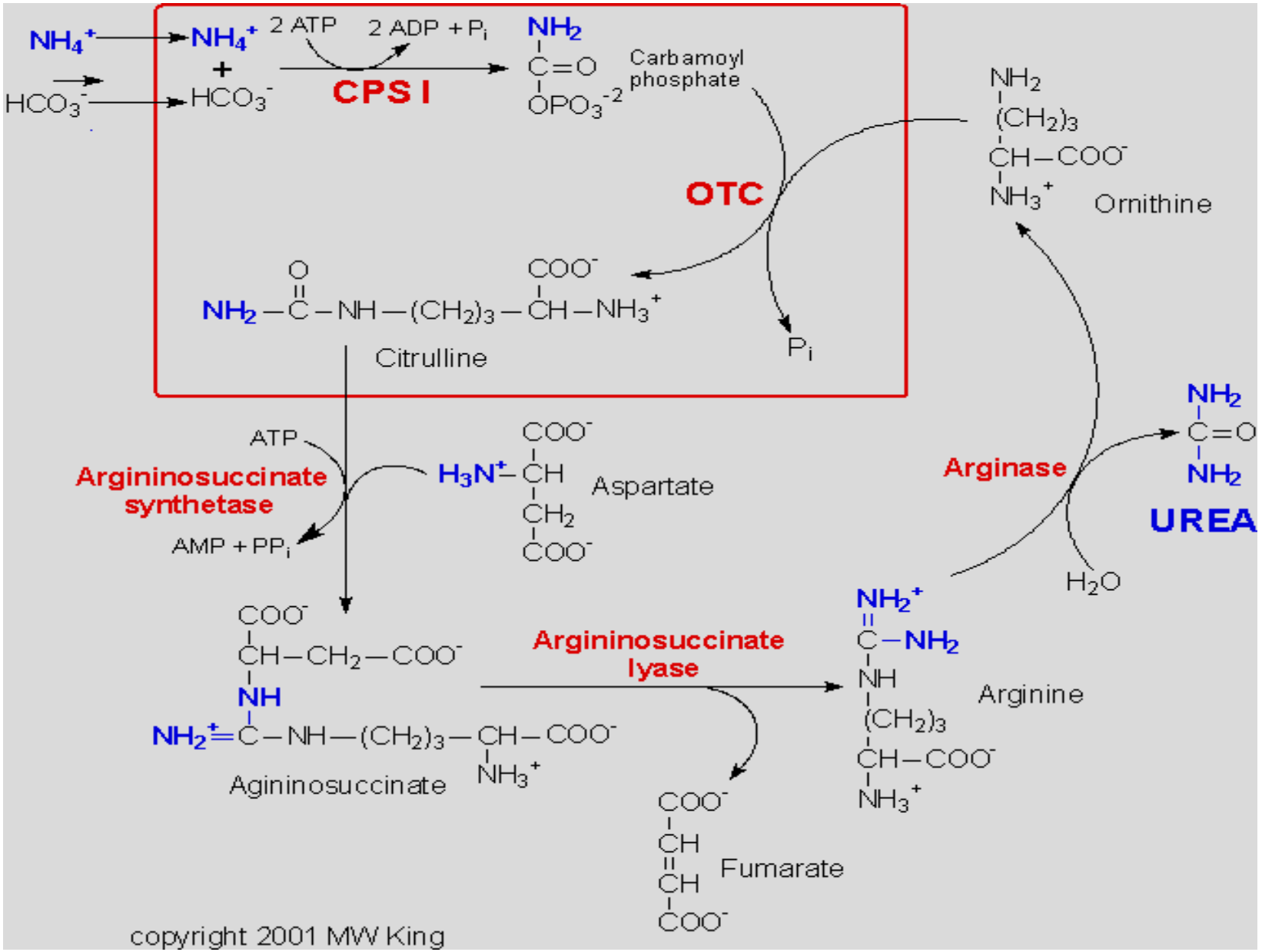
Summary of paths of amino groups



Urea cycle

- A cyclic pathway that synthesize urea from **aspartate** and **carbamoyl phosphate (**produced from NH_4^+ and CO_2)
  - The pathway dispose most (80%) of nitrogen as urea
- Urea is excreted to maintain **daily nitrogen balance**
- Occurs in the liver in:-
  - Two compartments: ***Mitichondrial matrix*** and ***cytosol.***
  - Two sites: partly in mitochondria and cytosol

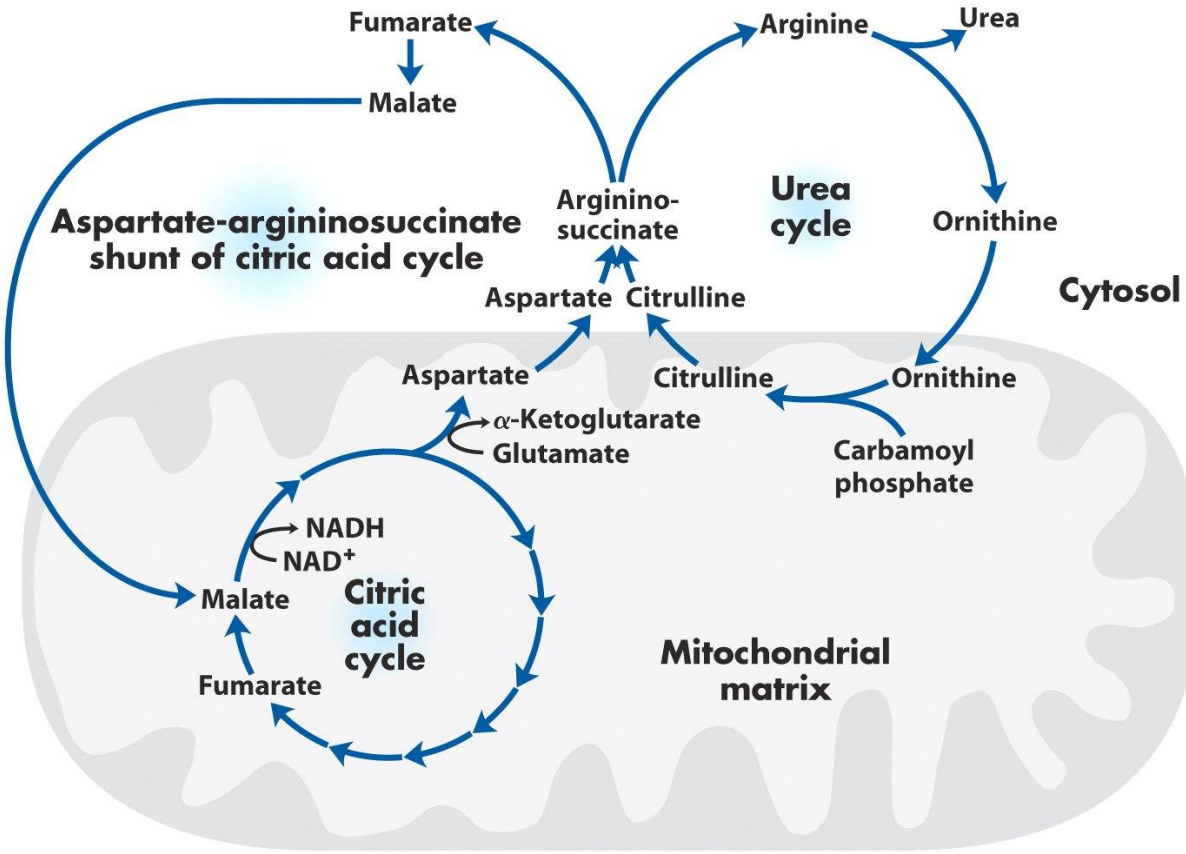
Urea cycle


NH4+
HCO3-
NH4+
HCO3-
2 ATP
2 ADP + Pi
CPS I
NH2
C=O
OPO3-2
Carbamoyl phosphate
OTC
NH2
(CH2)3
CH—COO-
NH3+
Ornithine
NH2—C—NH—(CH2)3—CH—NH3+
COO-
Citrulline
Pi
ATP
Argininosuccinate synthetase
AMP + PPi
H3N+—CH
CH2
COO-
Aspartate
Arginase
NH2
C=O
NH2
UREA
H2O
COO-
CH—CH2—COO-
NH
NH2+=C—NH—(CH2)3—CH—COO-
NH3+
Agininosuccinate
Argininosuccinate lyase
NH2+
C—NH2
NH
(CH2)3
CH—COO-
NH3+
Arginine
COO-
CH
CH
COO-
Fumarate
copyright 2001 MW King

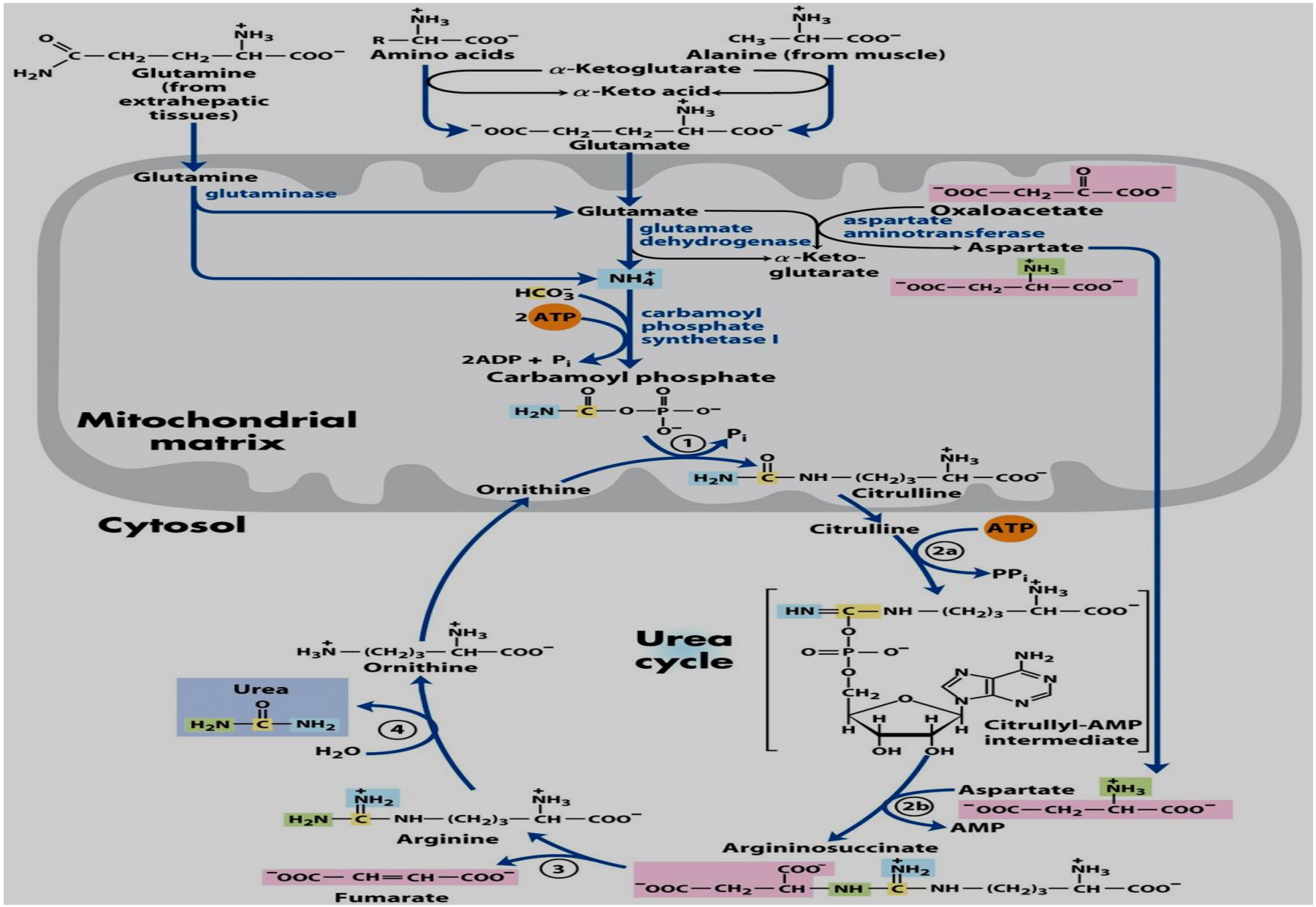
Urea cycle

Urea cycle is linked with Citric acid cycle

- Fumarate released here can taken up by citric acid cycle which intern gives free aspartate



Summary of nitrogen metabolism



Fates of carbon skeletons (α-Keto acids)

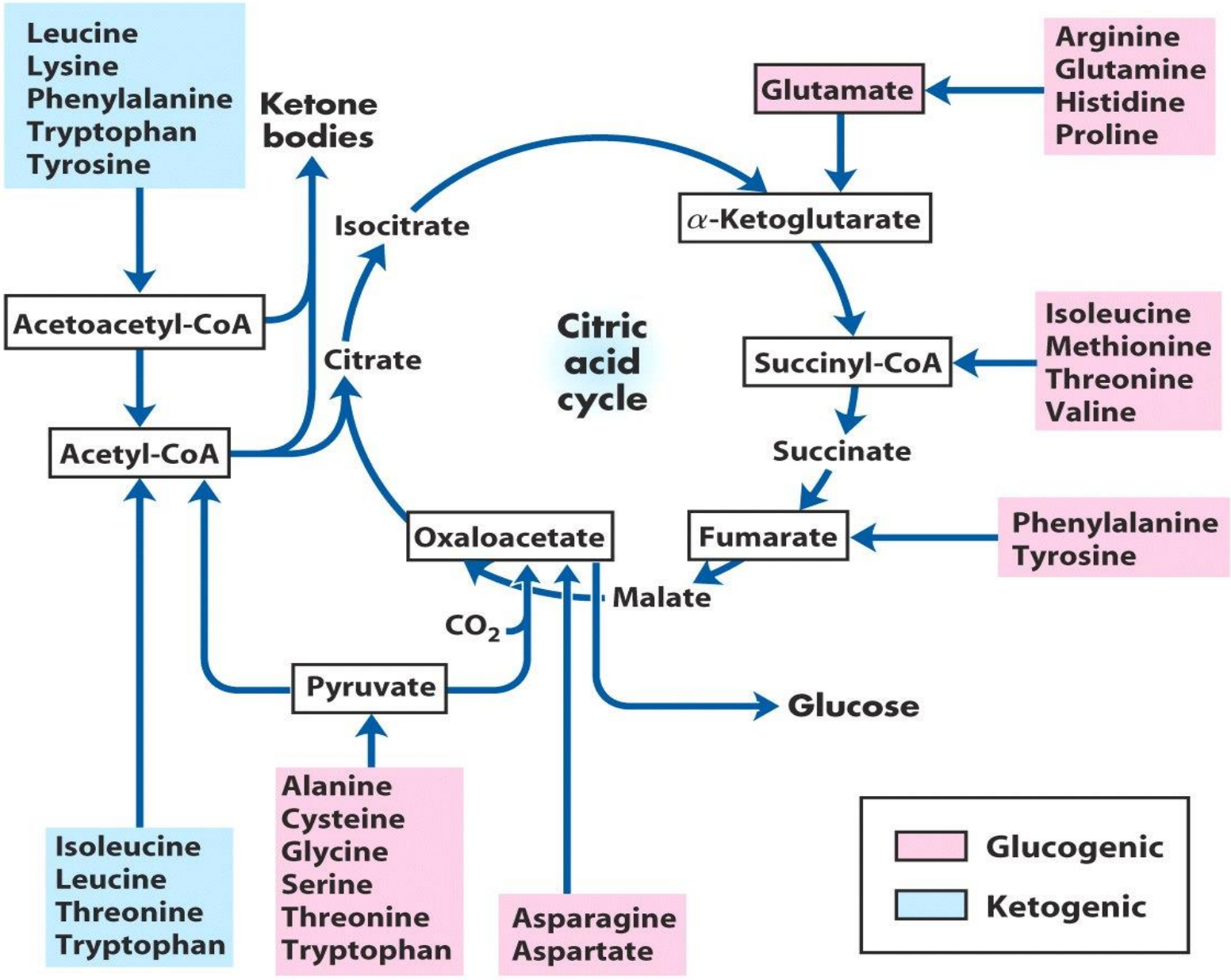
- Degradation(N-removal) of amino acids give α-keto acids which can be converted in to ***Pyruvate , TCA cycle intermediates , Acetyl CoA & Acetoacetyl CoA***
- Accordingly amino acids can be classified as **glucogenic** or **ketogenic**

Glcogenic amino acids	**Ketogenic amino acids**
❖ Are degraded to give pyruvate or TCA intermediate ➢ finally used for glucose synthesis ❖ Include alanine, glycine, valine , isoleucine, serine, threonine, cysteine, methionine, arginine , histidine aspartate, asparagines, glutamine, tryptophan ,phenylalanine, tyrosine proline	❖ Are degraded to give acetyl-CoA. or acetoacetyl-CoA ➢ finally used for synthesis of ketone bodies ❖ Include tryptophan, lysine, leucine, phenylalanine, tyrosine and isoleucine

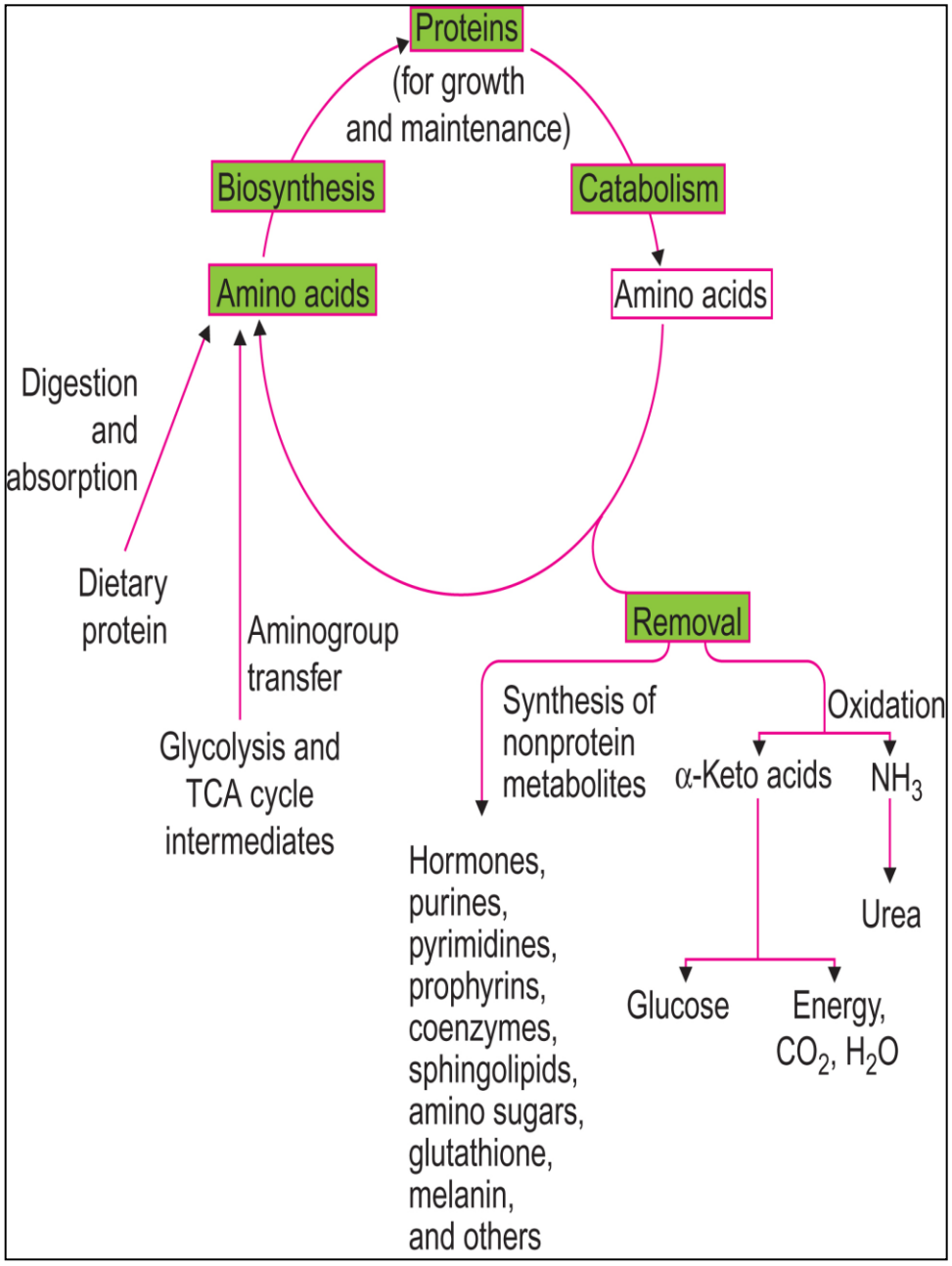
Note

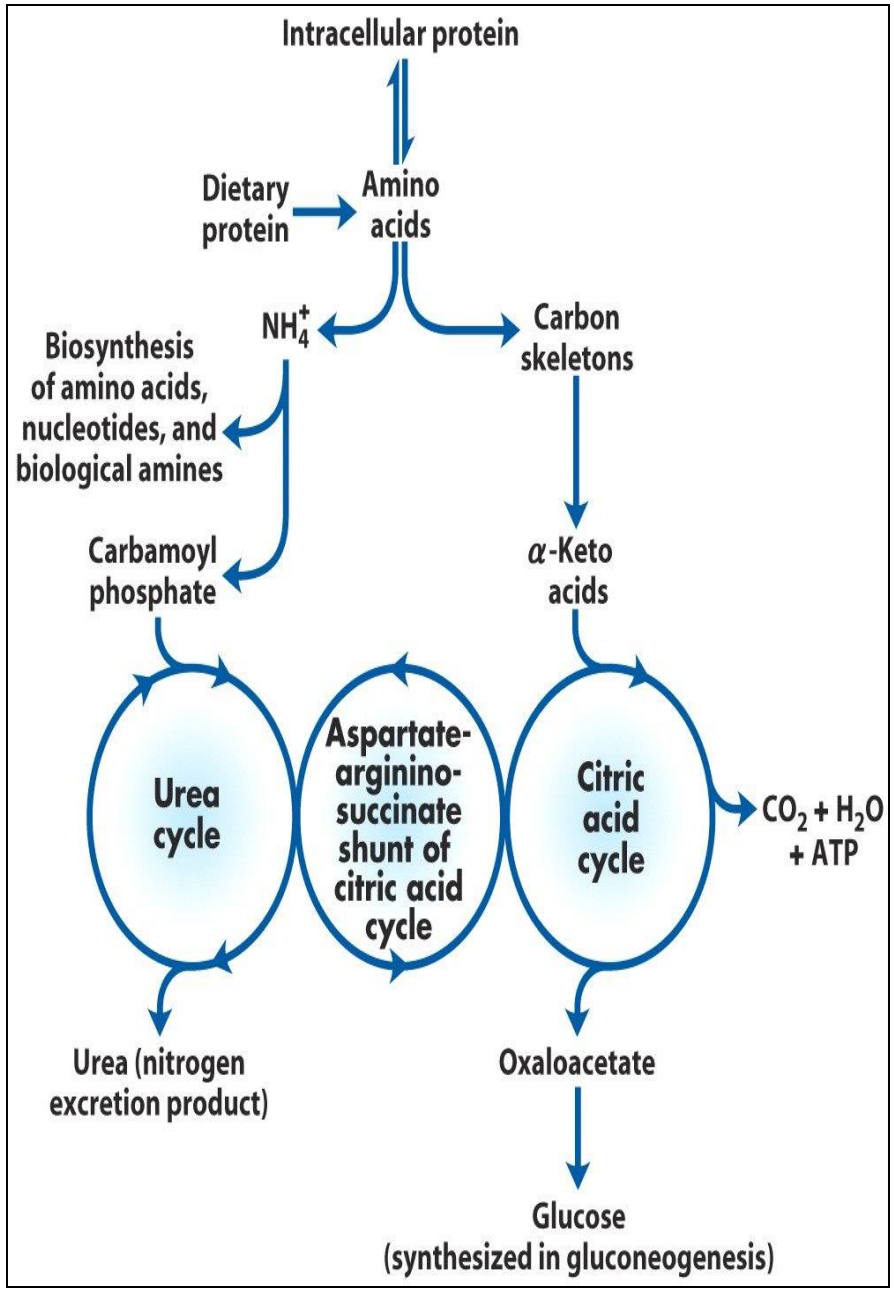
- Normal amino acid degradation accounts for ~10-15% of the metabolic fuel for animals (increased when high protein diets are consumed or during starvation)

Fates of carbon skeletons (α-Keto acids)



Divergent pathways of NH_3 groups and carbon keletons





Biosynthesis of amino acid

Introduction

- A normal healthy adult needs about 400 g protein daily to maintain nitrogen balance.

- In contrast, young children & pregnant women have a +Ve N-balance
  - because they accumulate nitrogen in new protein

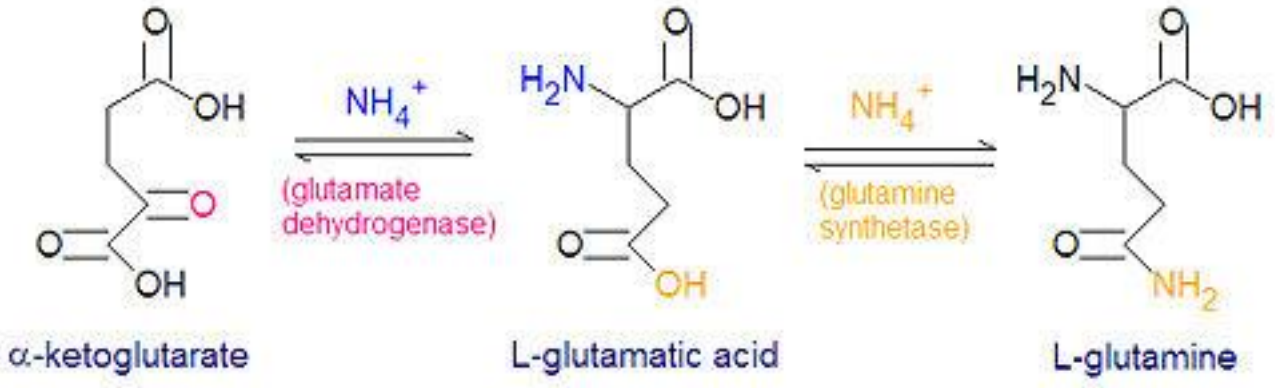
- A –Ve N-balance is a sign of disease or starvation due to:-
  - Elevated rates of protein breakdown (loss of muscle tissue) or
  - Insufficient amino acids in diets

- Bothe cases require synthesis of more proteins

- Humans can only synthesize about half of the twenty amino acids. (the less complex ones)
  - But **plants** and **bacteria** can do all

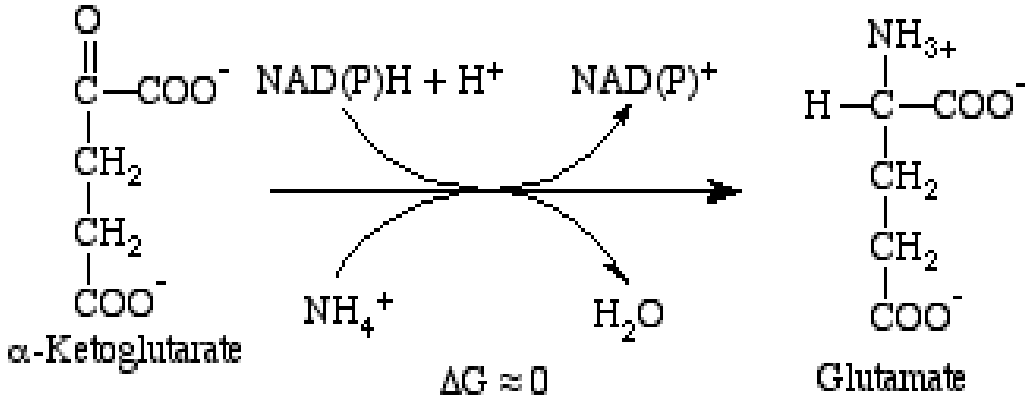
Assimilation of NH_3 into amino acids

- First nitrogen is incorporated into either glutamate or glutamine'
  - **Glutamate** is the source of amino groups for synthesis of most amino acids
  - **Glutamine** is the source of amino groups for synthesis of most other nitrogen-containing molecules (e.g., nucleotides)

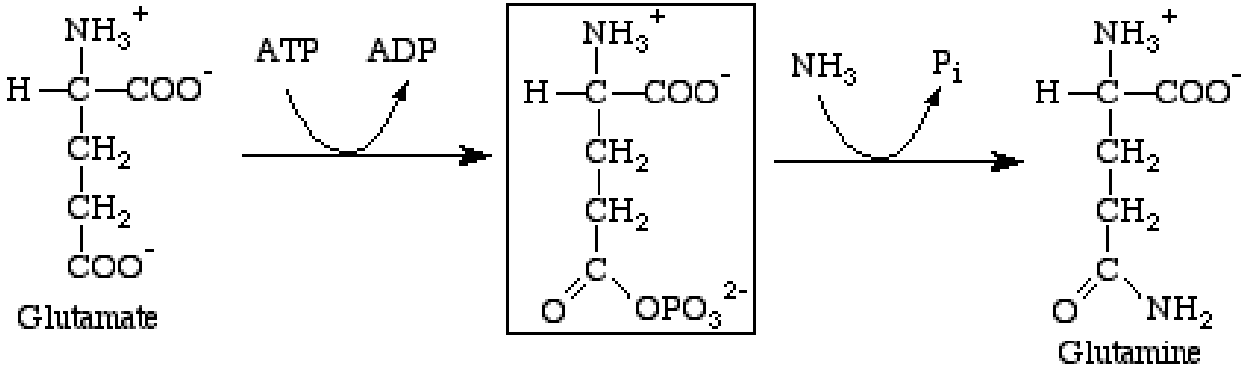


Assimilation of NH_3 into amino acids

- Formation of Glu: reductive amination of α-KG via glutamate dehydrogenase

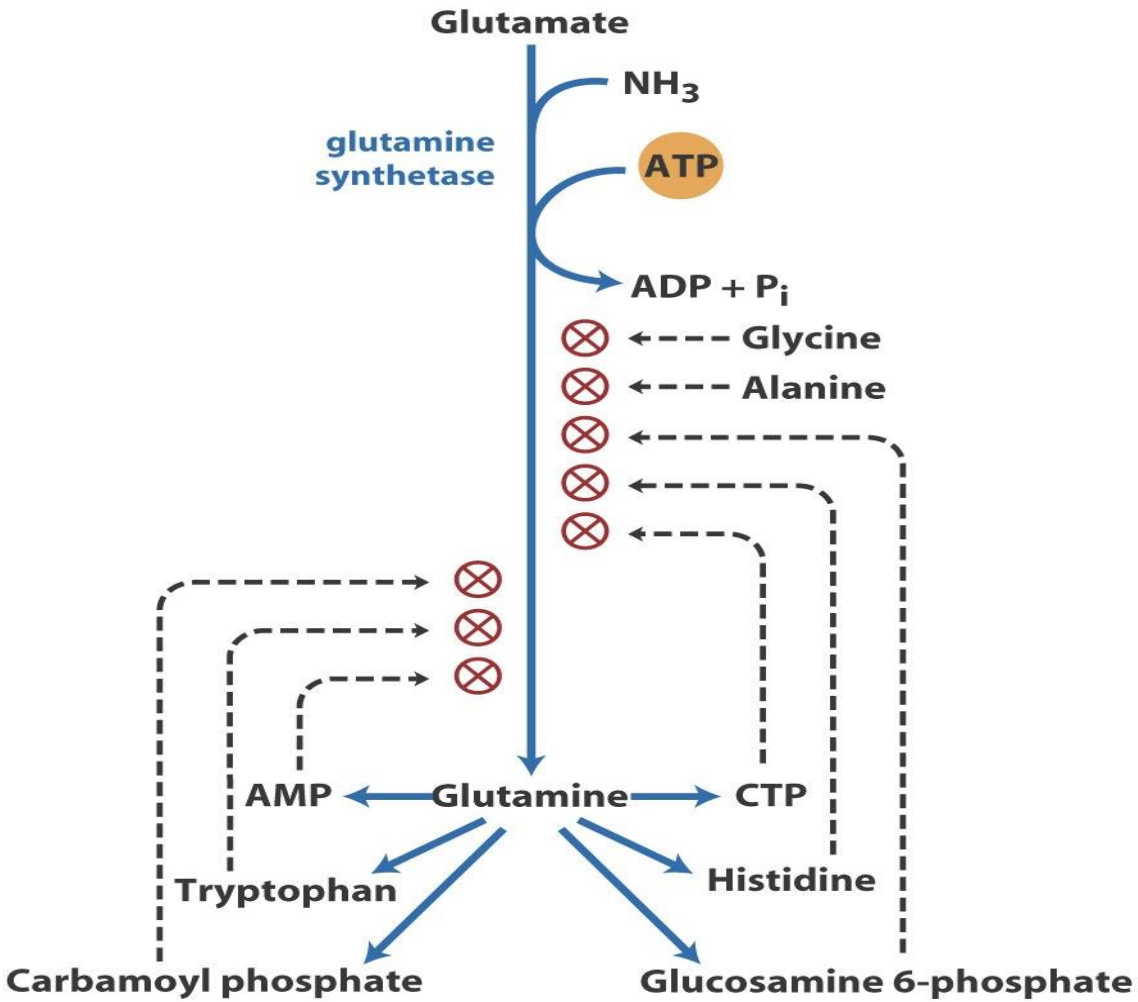


- Formation of Gln: glutamine synthetase reaction



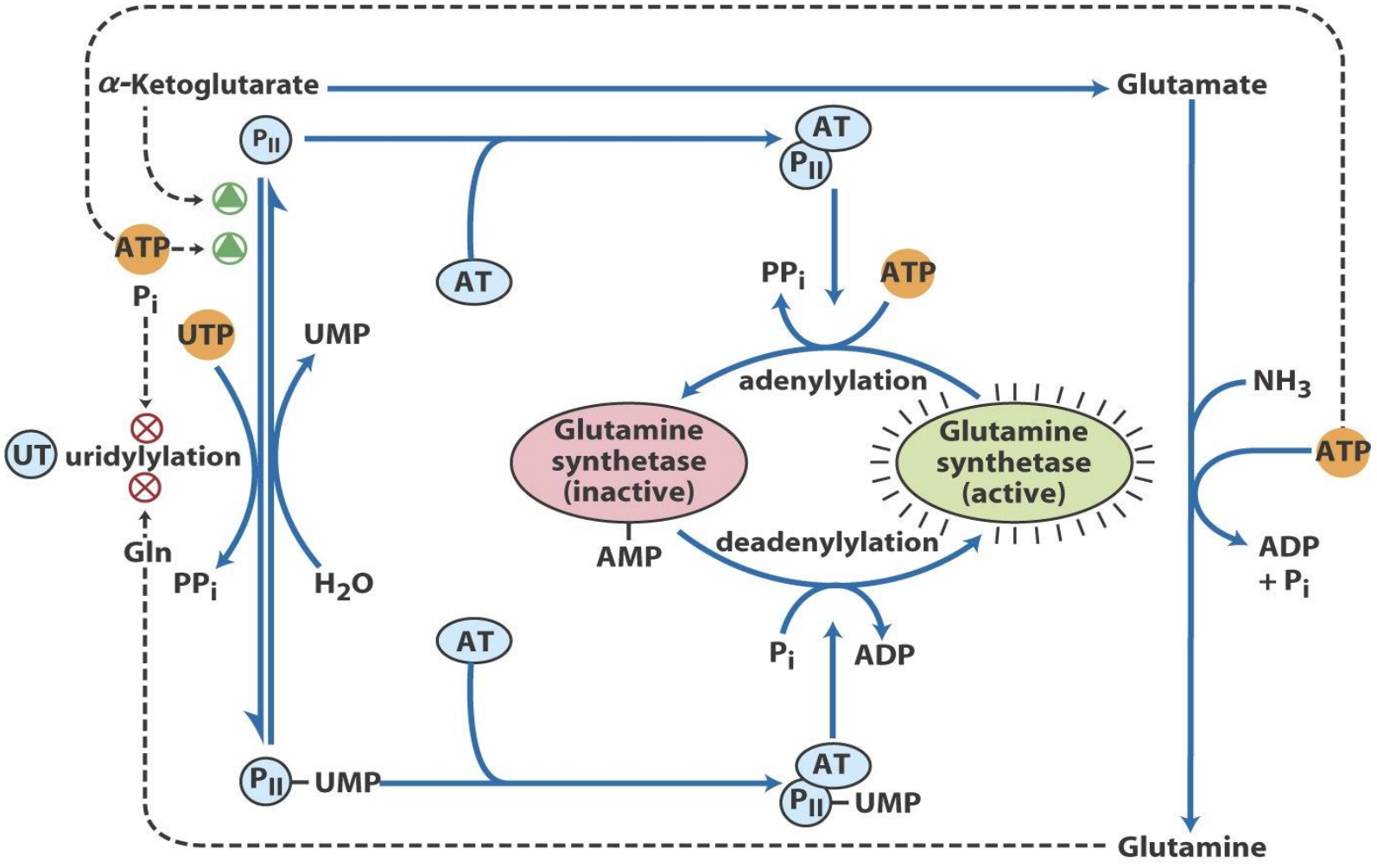
Assimilation of NH_3 into amino acids

- **Glutamine synthetase** is allosterically controlled



Assimilation of NH_3 into amino acids

- **Glutamine synthetase** is controlled by covalent modification (adenylylation)



Incorporation of C-skeleton into amino acids

- Carbon skeletons of amino acids are made from intermediates of glycolysis, TCA, or PPP

Amino Acid Biosynthetic Families, Grouped by Metabolic Precursor

α-Ketoglutarate
Glutamate
Glutamine
Proline
Arginine

3-Phosphoglycerate
Serine
Glycine
Cysteine

Oxaloacetate
Aspartate
Asparagine
Methionine*
Threonine*
Lysine*

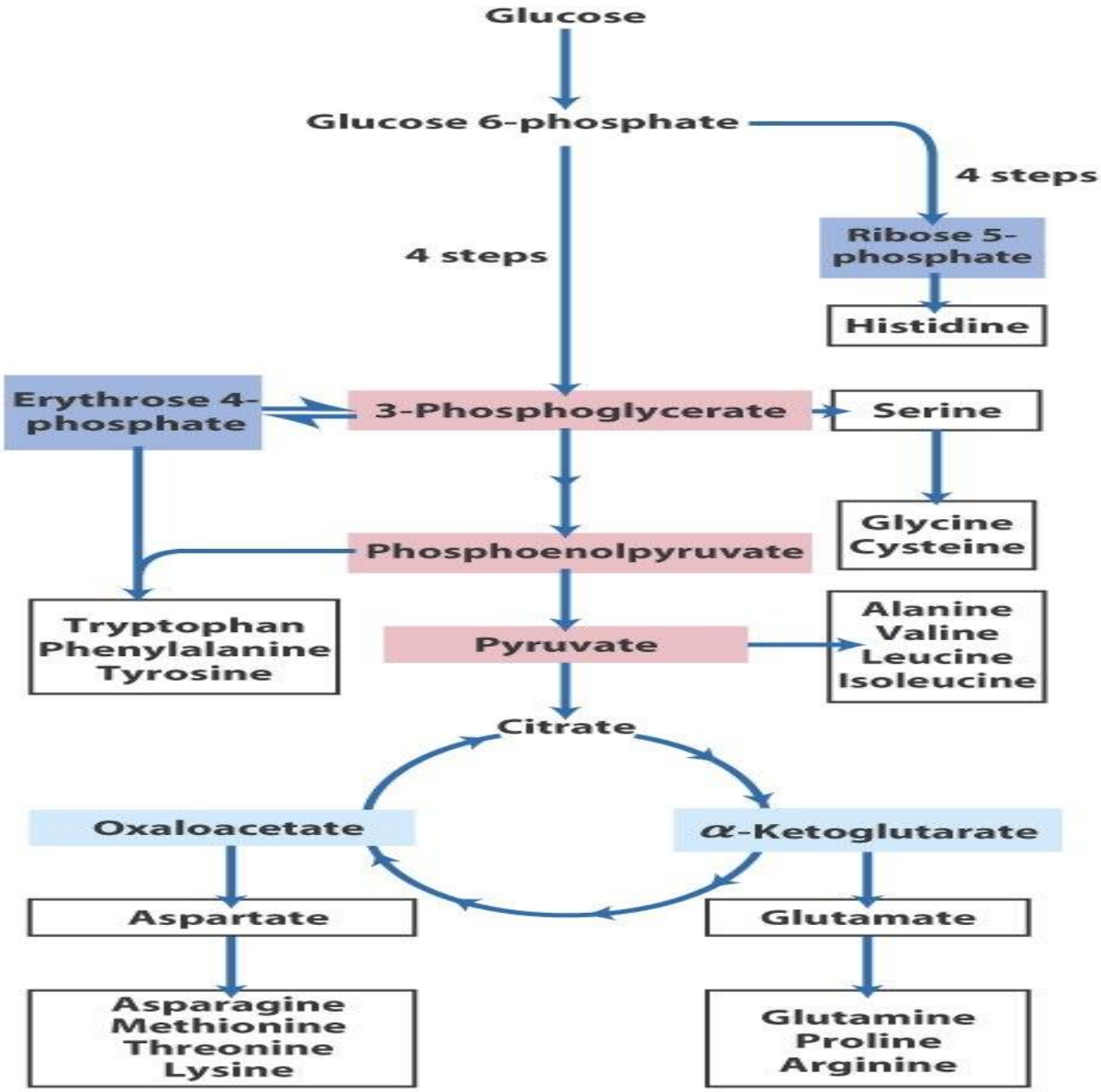
Pyruvate
Alanine
Valine*
Leucine*
Isoleucine*

Phosphoenolpyruvate and erythrose 4-phosphate
Tryptophan*
Phenylalanine*
Tyrosine†

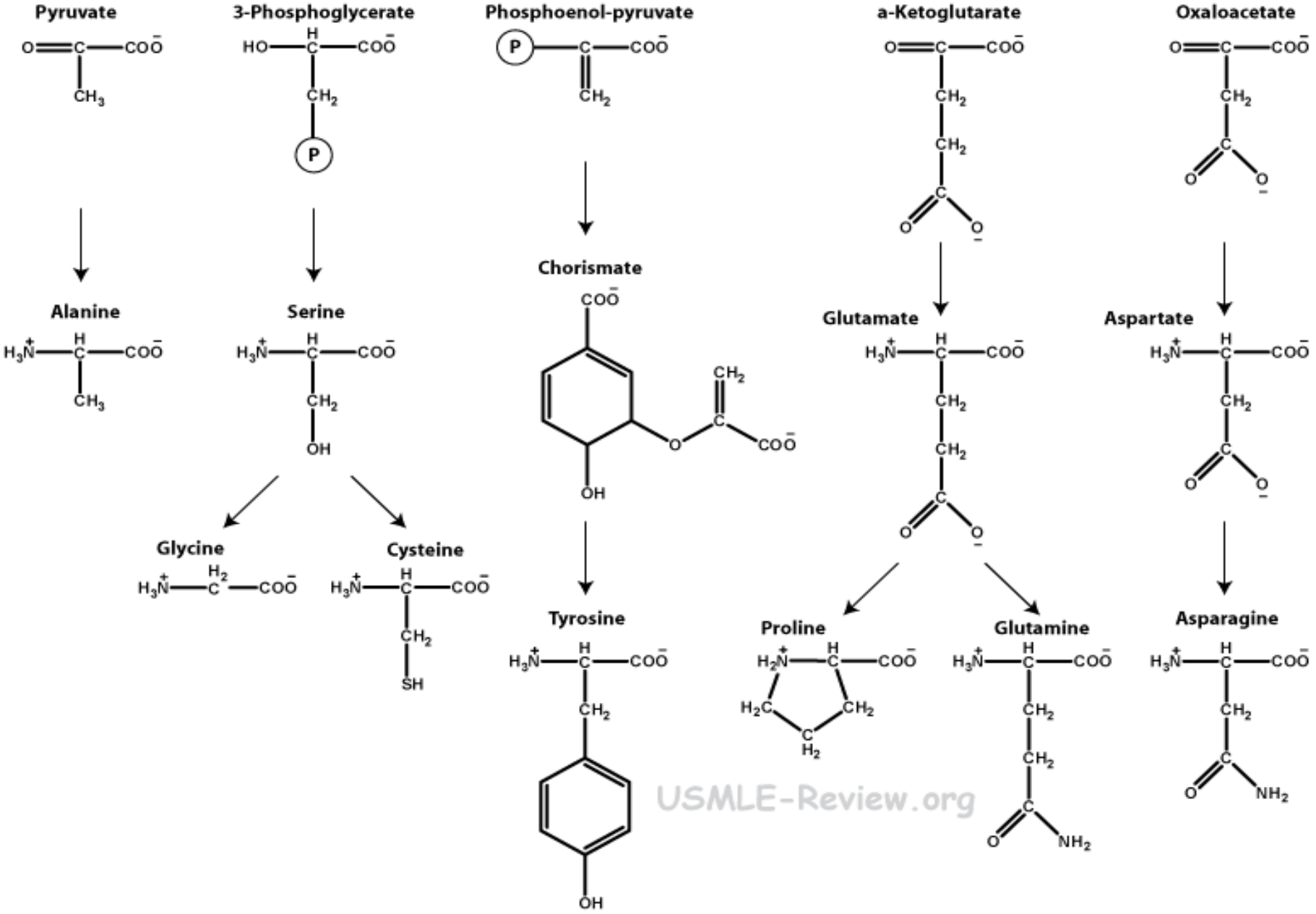
Ribose 5-phosphate
Histidine*

*Essential amino acids.
†Derived from phenylalanine in mammals.

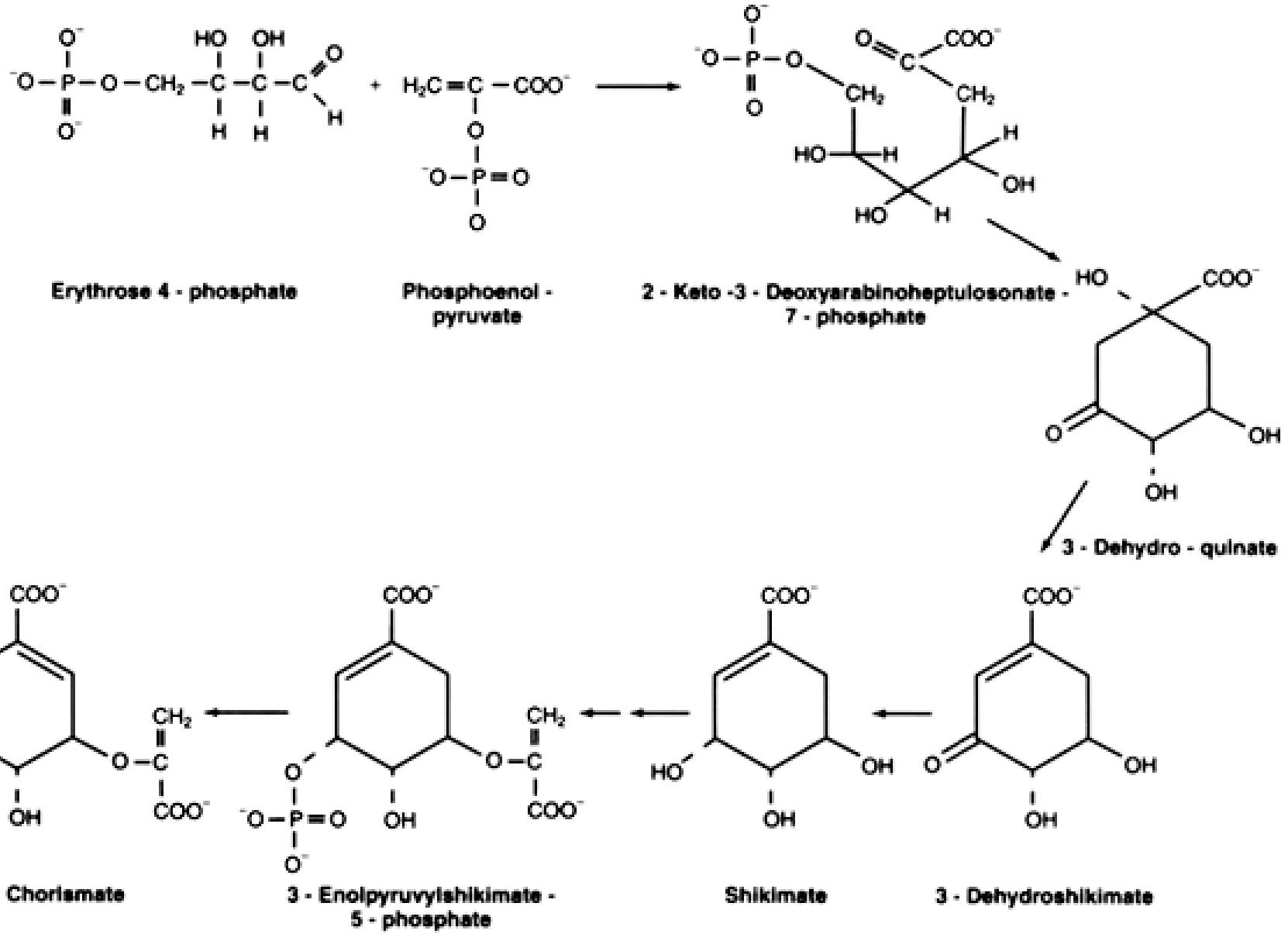
Incorporation of C-skeleton into amino acids



Amino Acid Biosynthesis Pathways

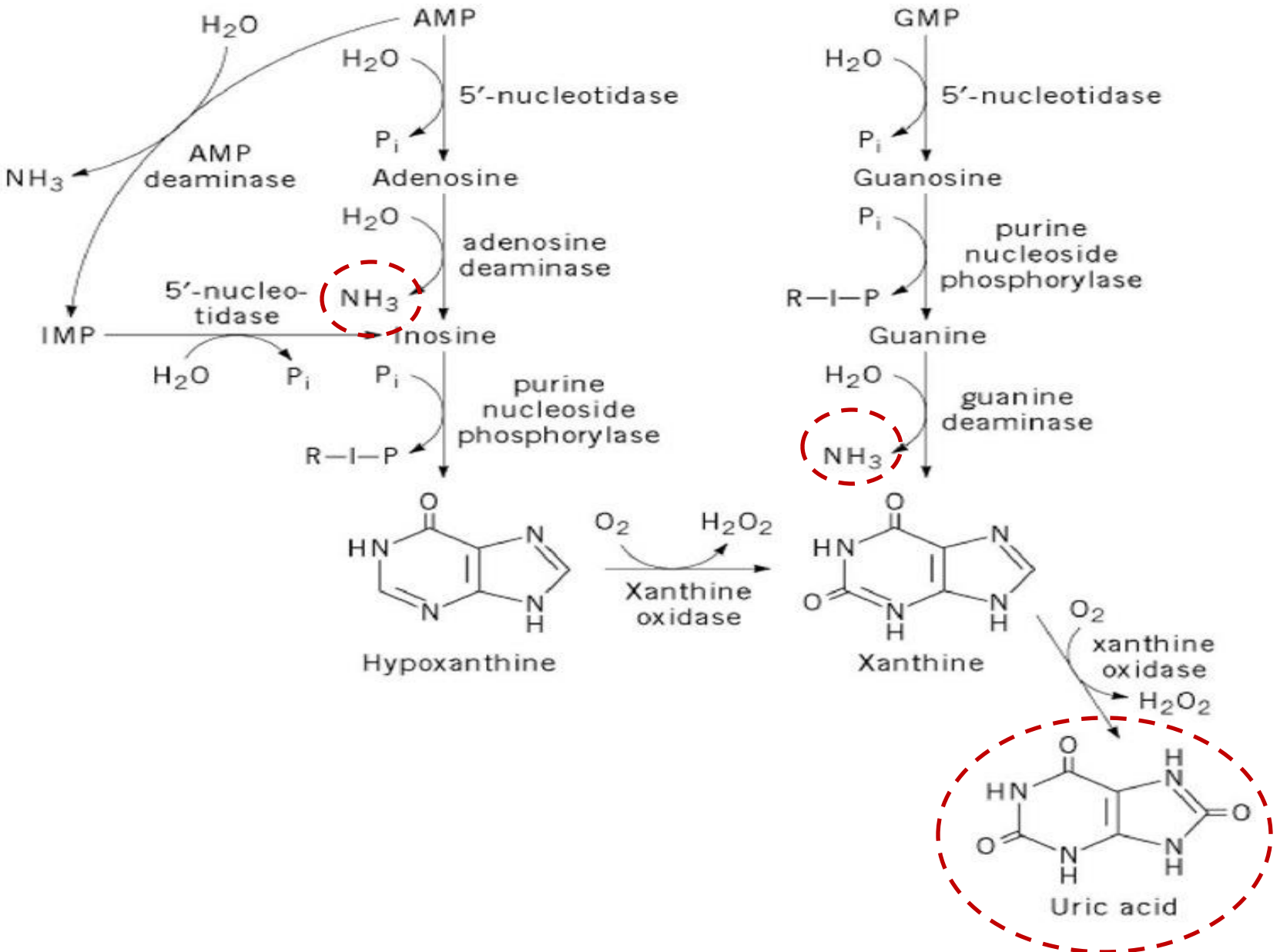


Amino Acid Biosynthesis Pathways



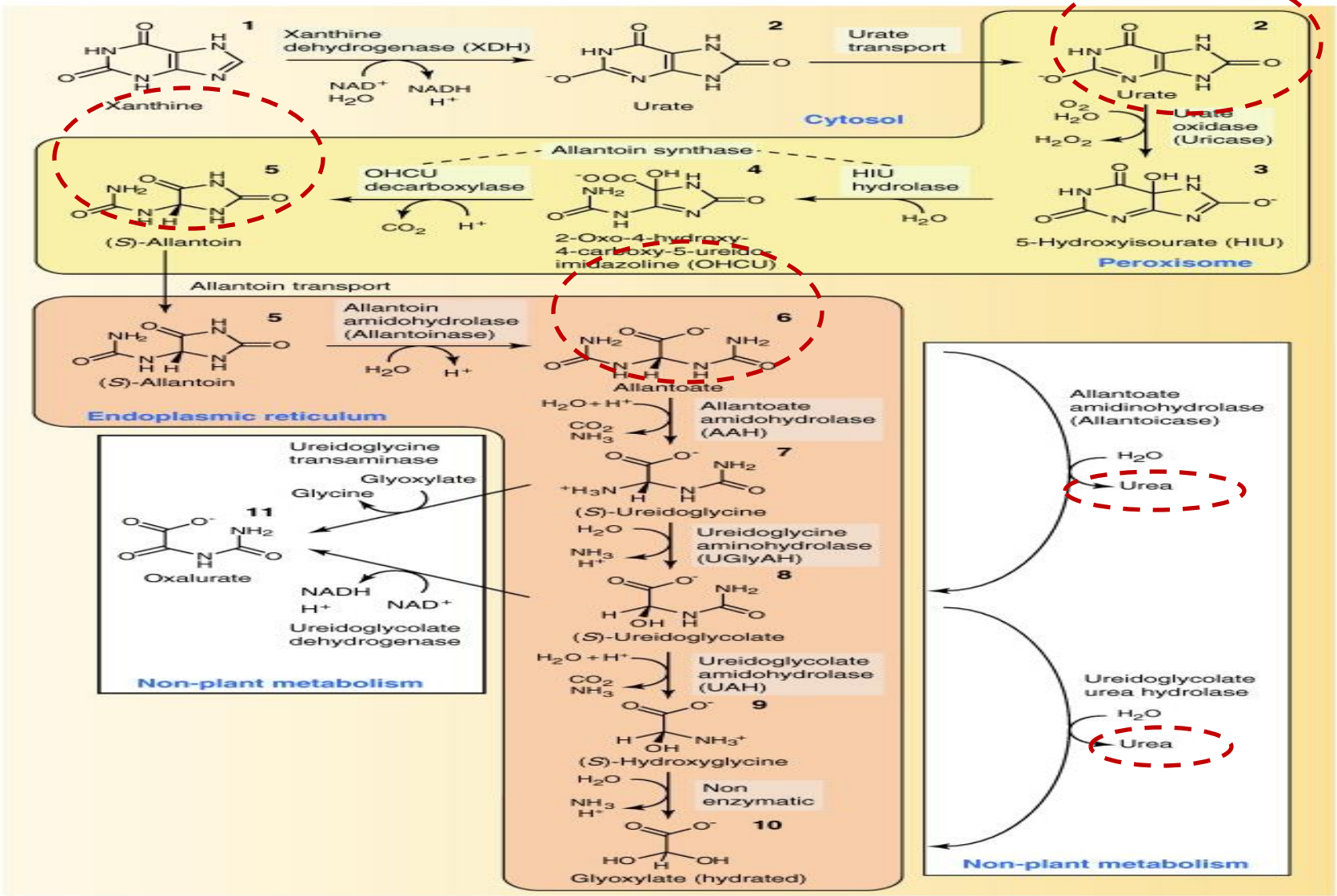
Catabolism of Nucleotides

Purine Nucleotide Catabolism

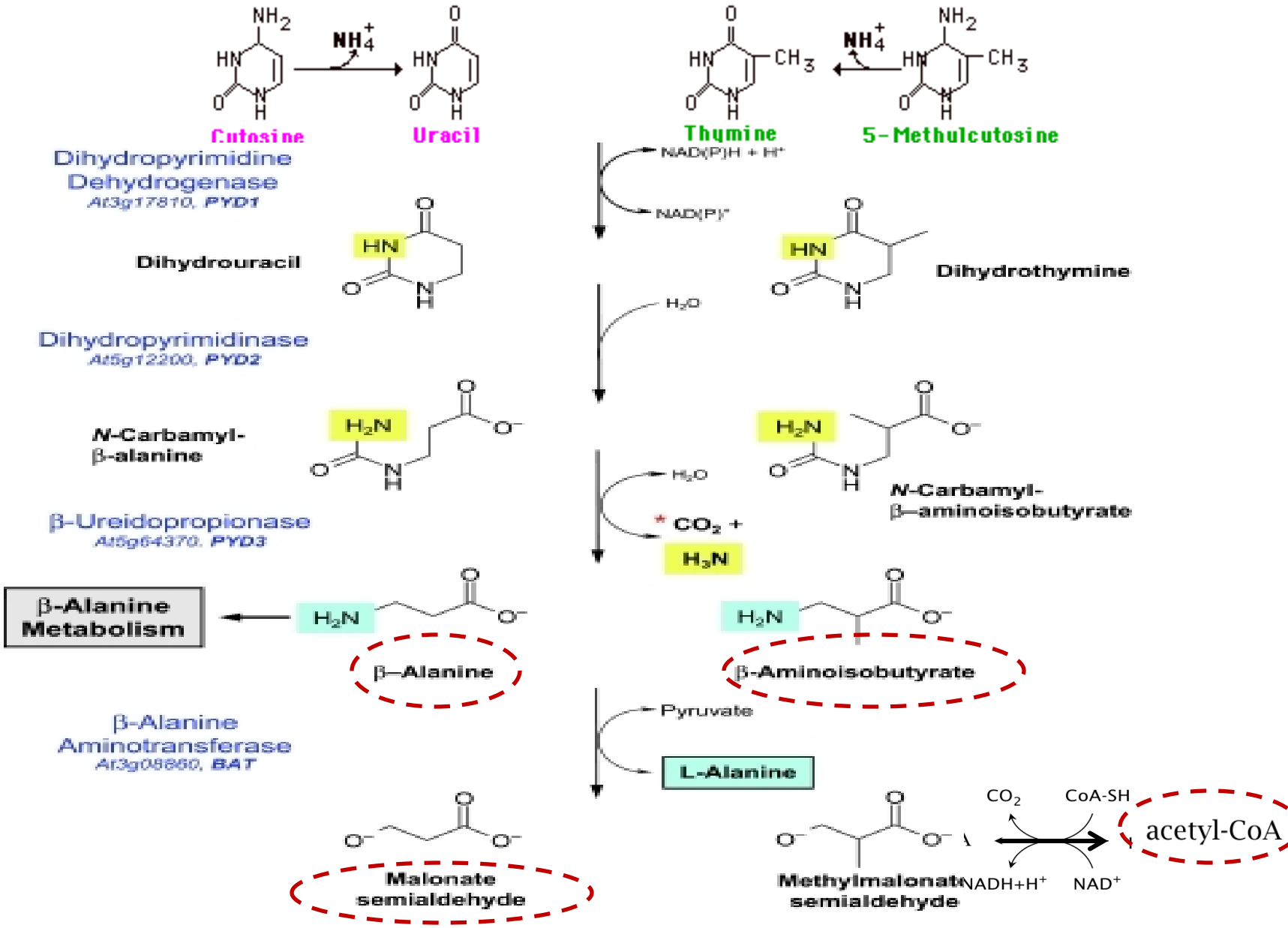


Purine Nucleotide Catabolism

- Excreted in different forms

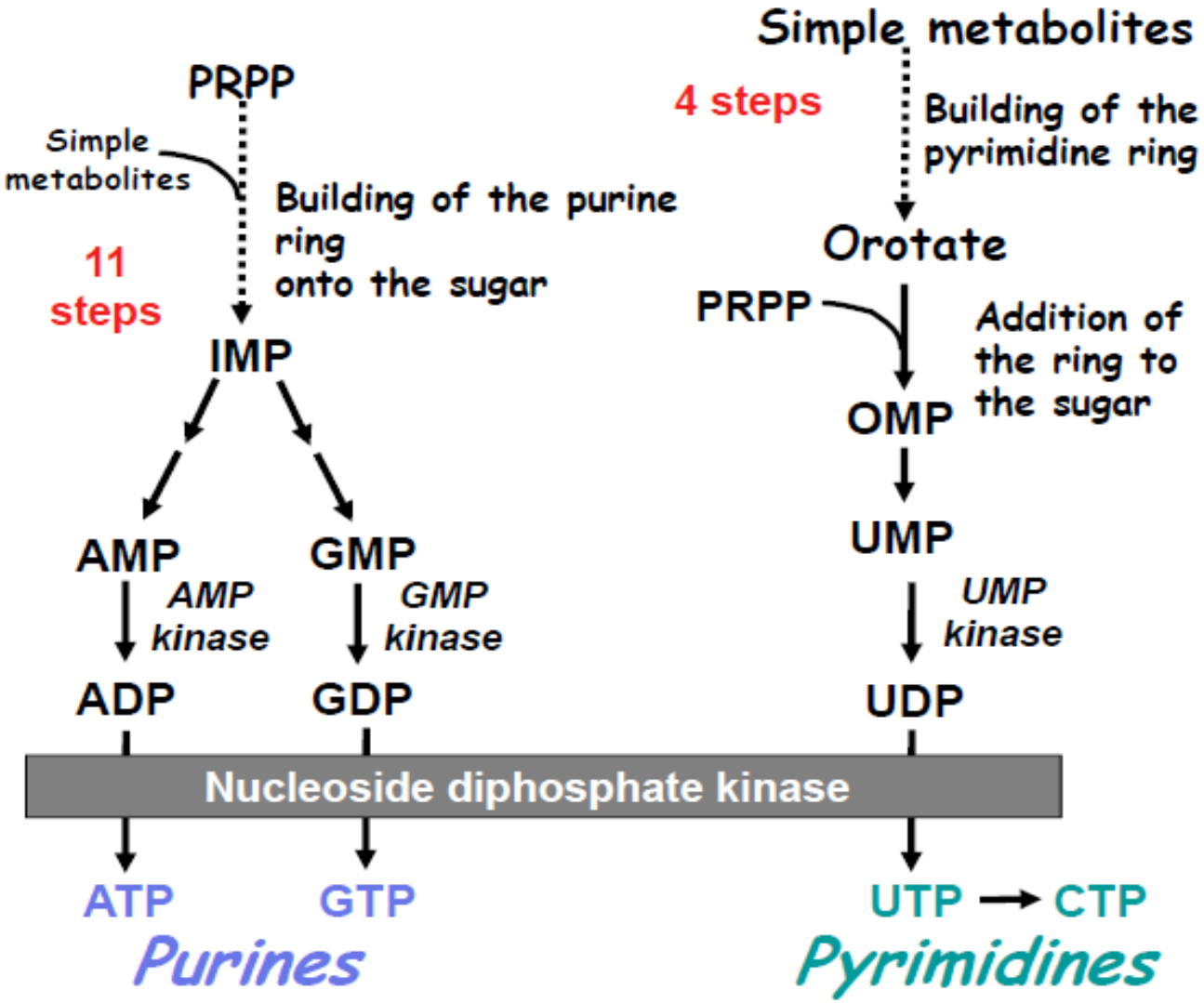


Pyrimidine Nucleotide Catabolism



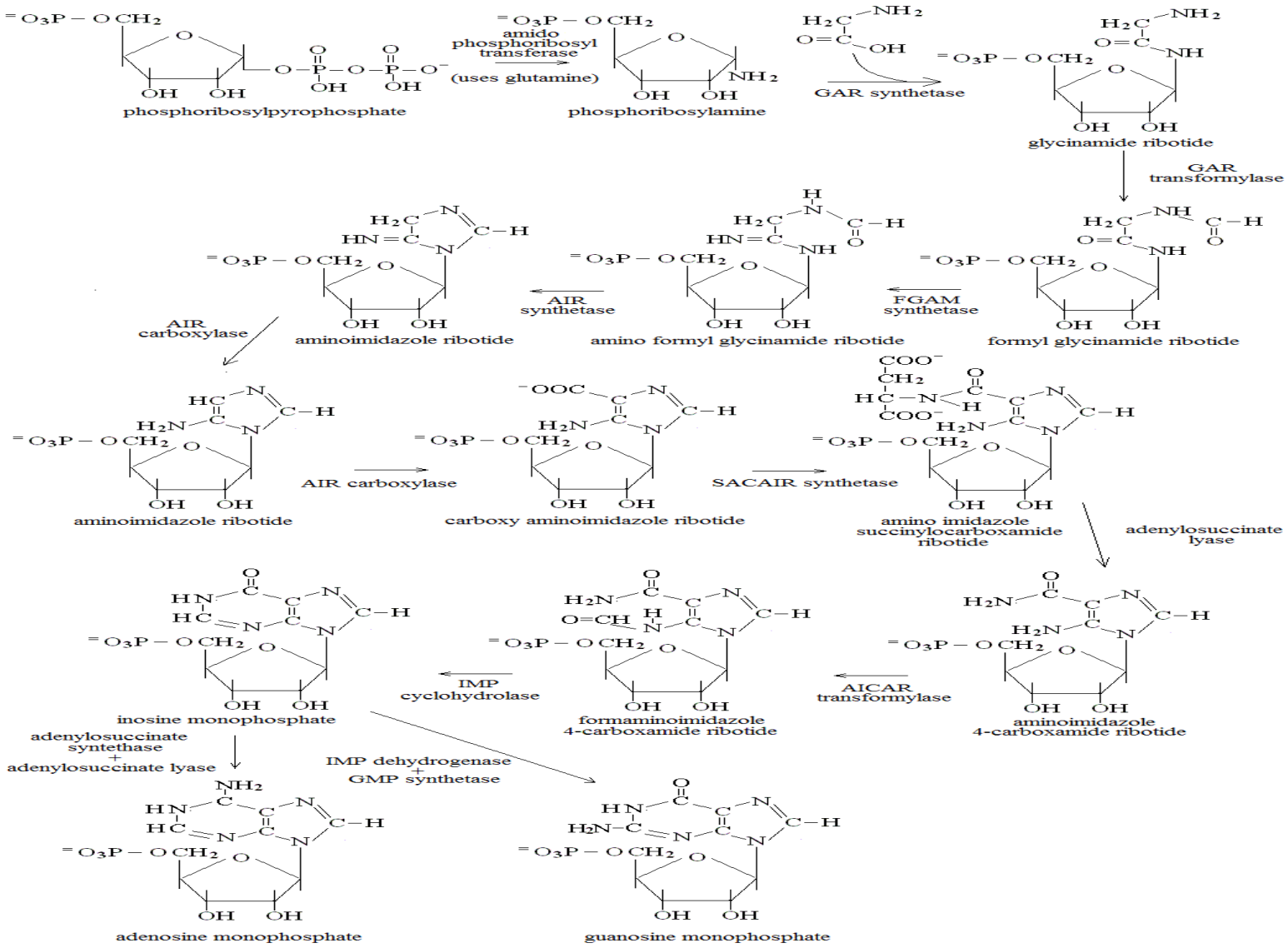
Biosynthesis of Nucleic acids

De novo synthesis of purins and pyrimidines



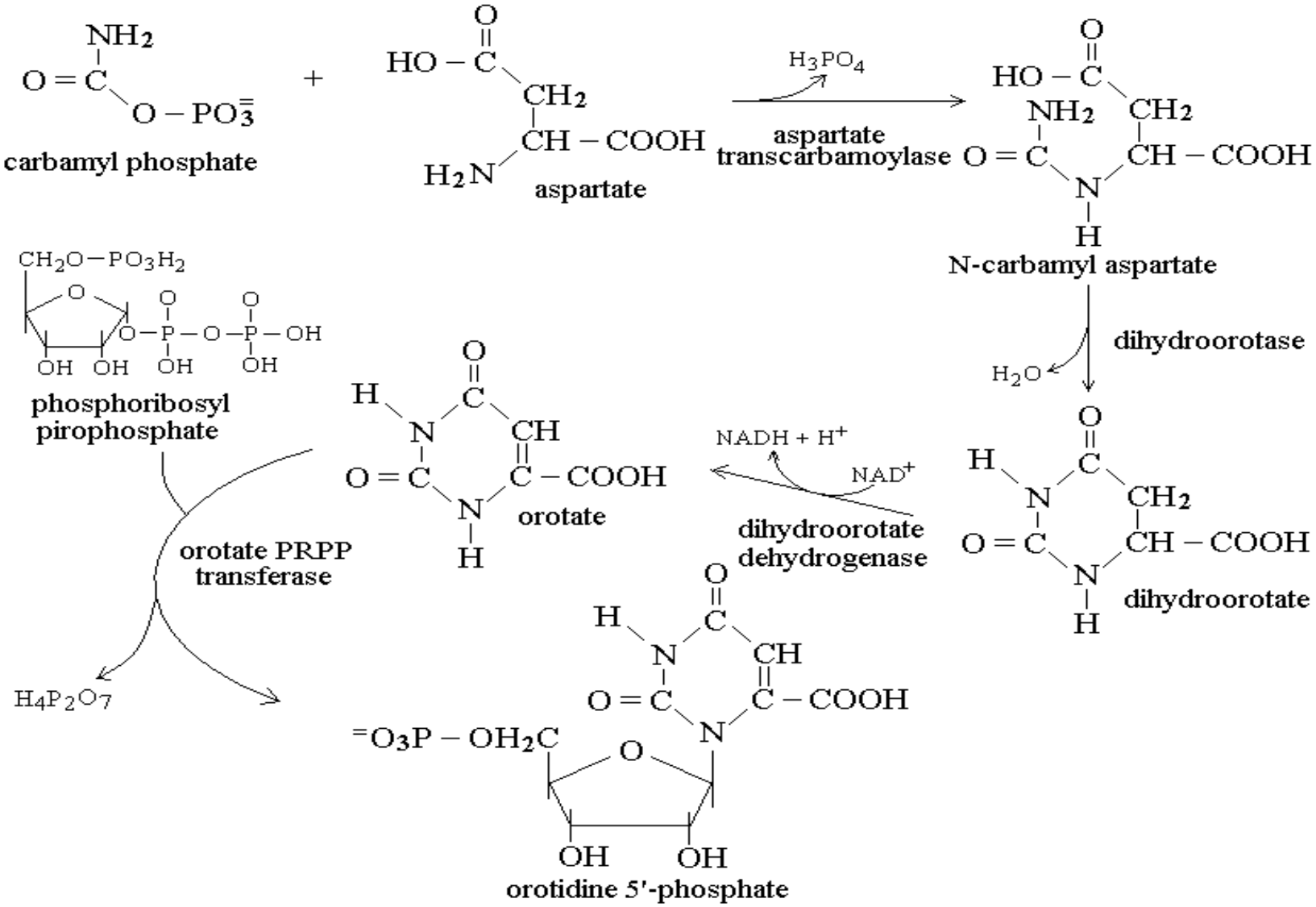
De novo synthesis of purines and pyrimidines

❑ Biosynthesis of purines



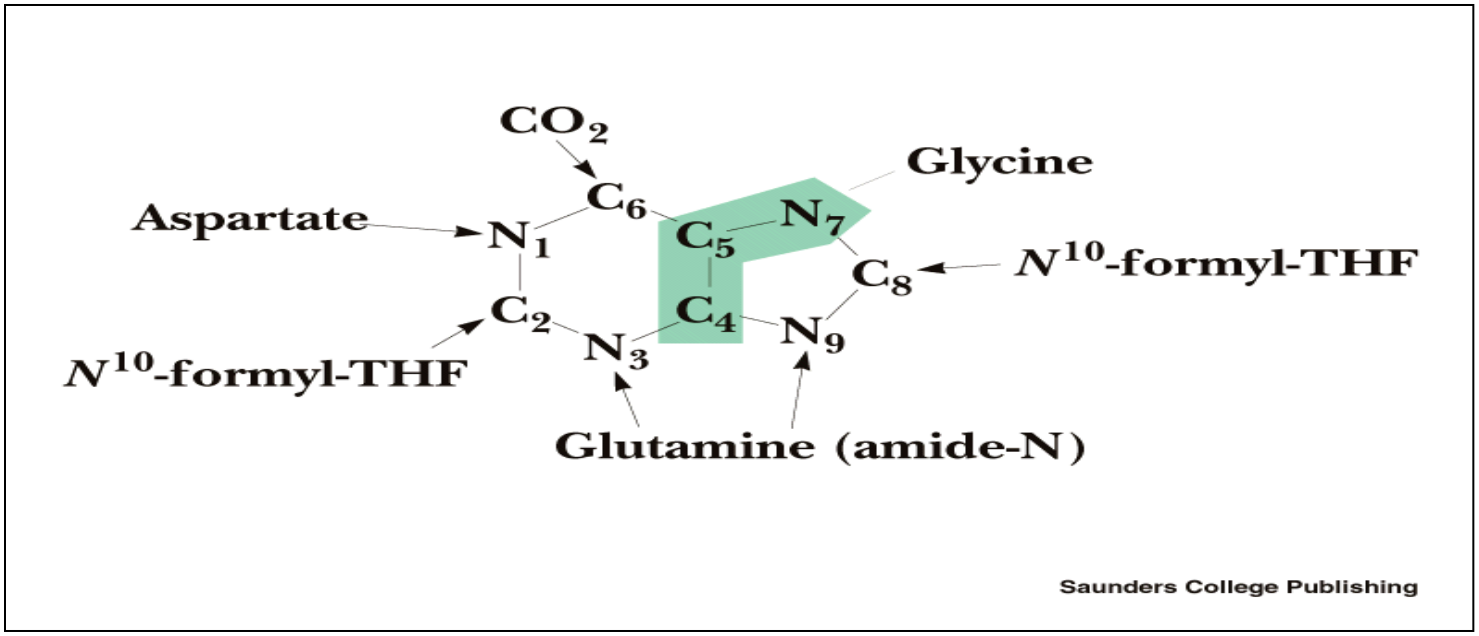
De novo synthesis of purines and pyrimidines

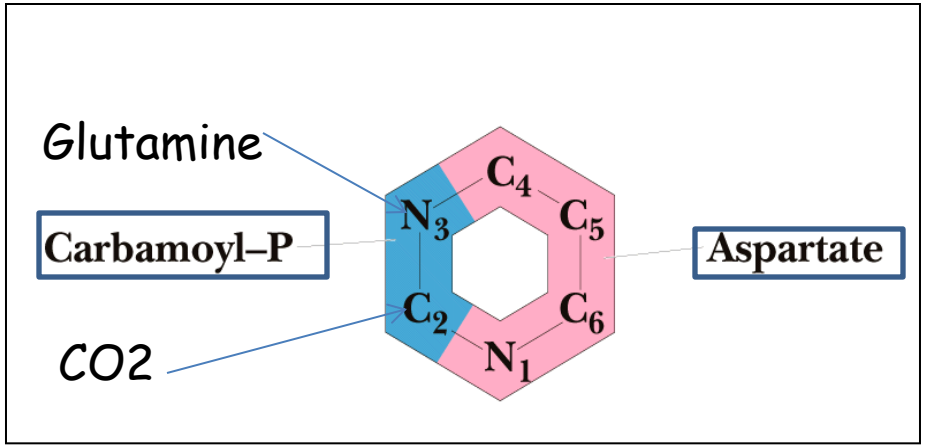
❑ Biosynthesis of pyrimidines



De novo synthesis of purines and pyrimidines

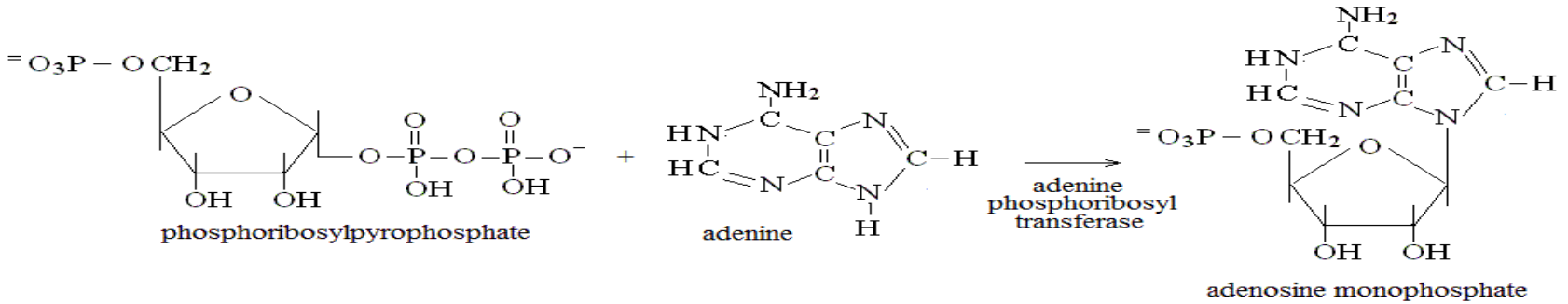
- Summary

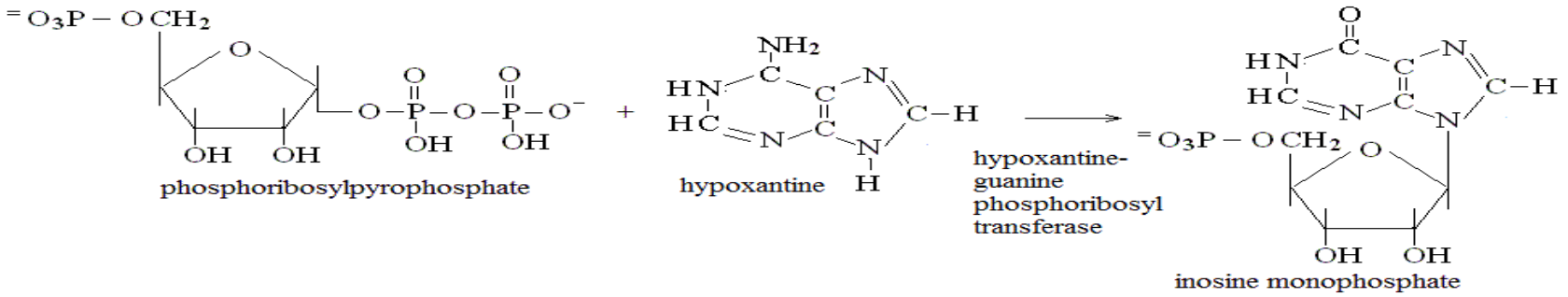


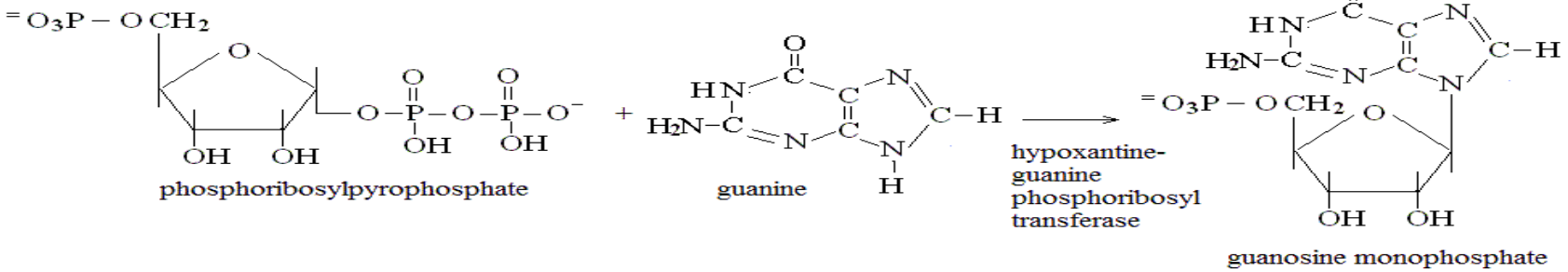


Salvage pathways

- Salvage pathways are used to dispatch most Purines (90%)







Biosynthesis of deoxyribonucleotide(dNTP)

- **Deoxyribonucleotide(**dNTP) are synthesized by replacement of 2'-OH of **ribonucleotide(**NTP)

  - with the involvement of enzymes Ribonucleotide reductase and Thioredoxin reductase