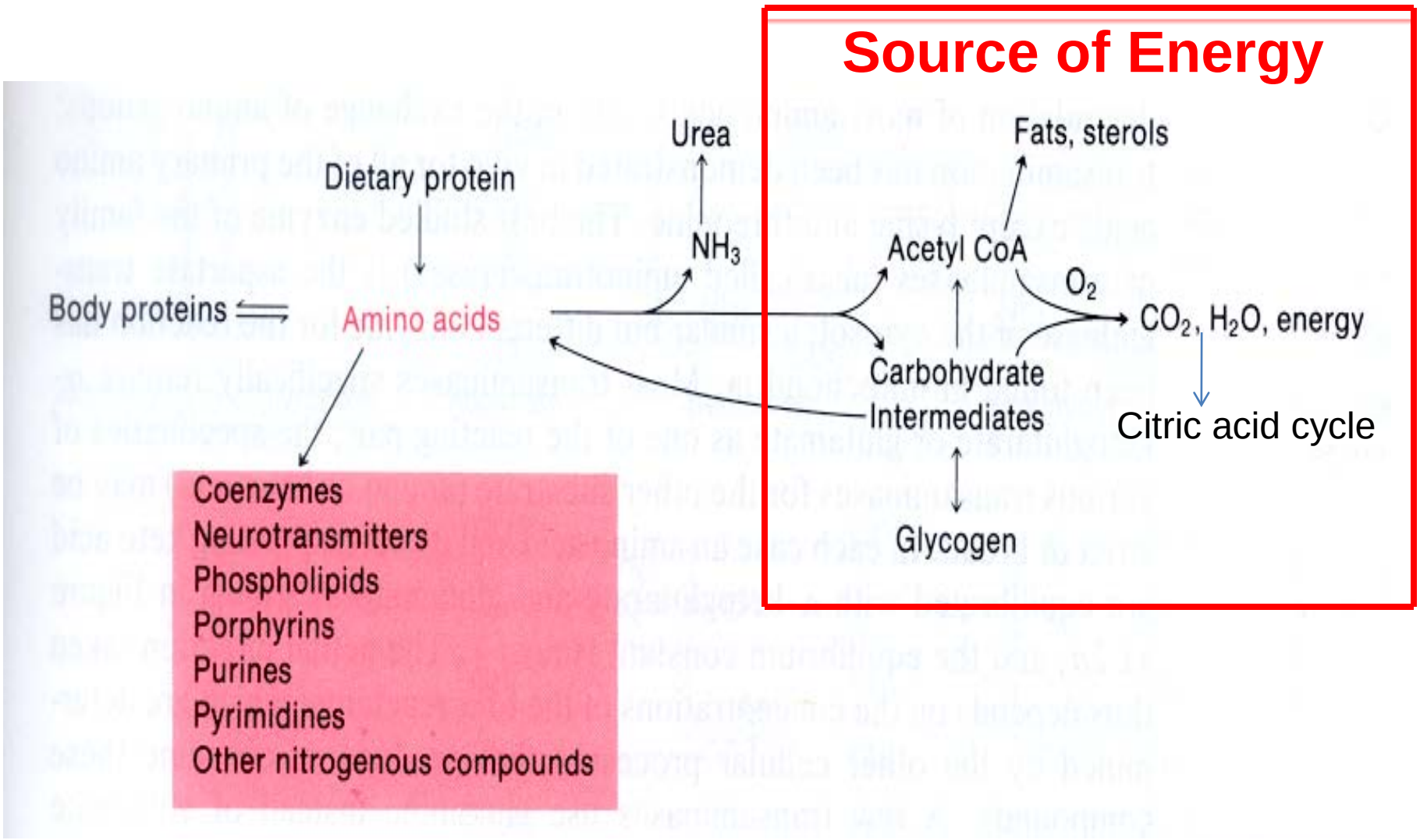
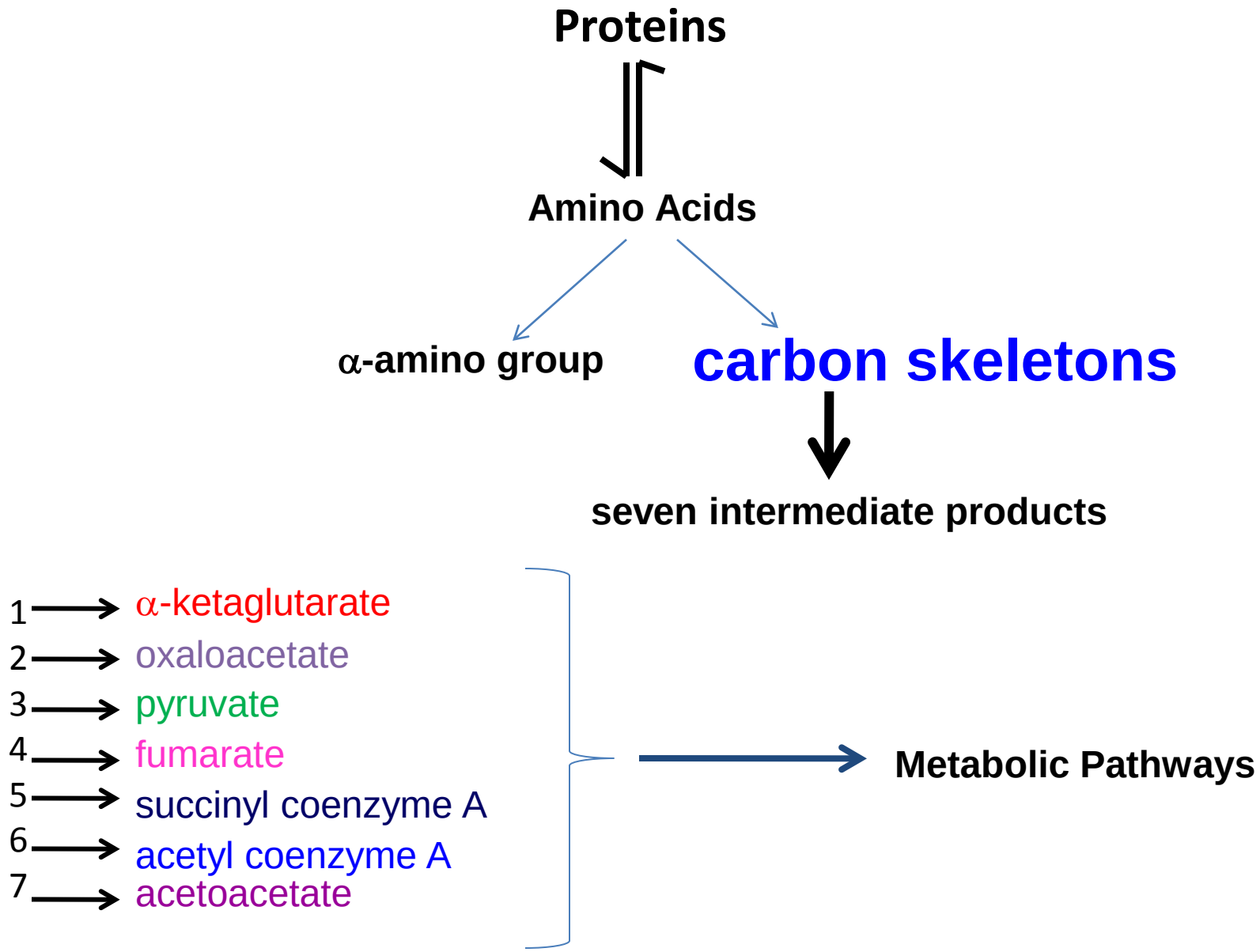
Amino Acid Metabolism

Dr. Shyamal Desai
October 1, 2010

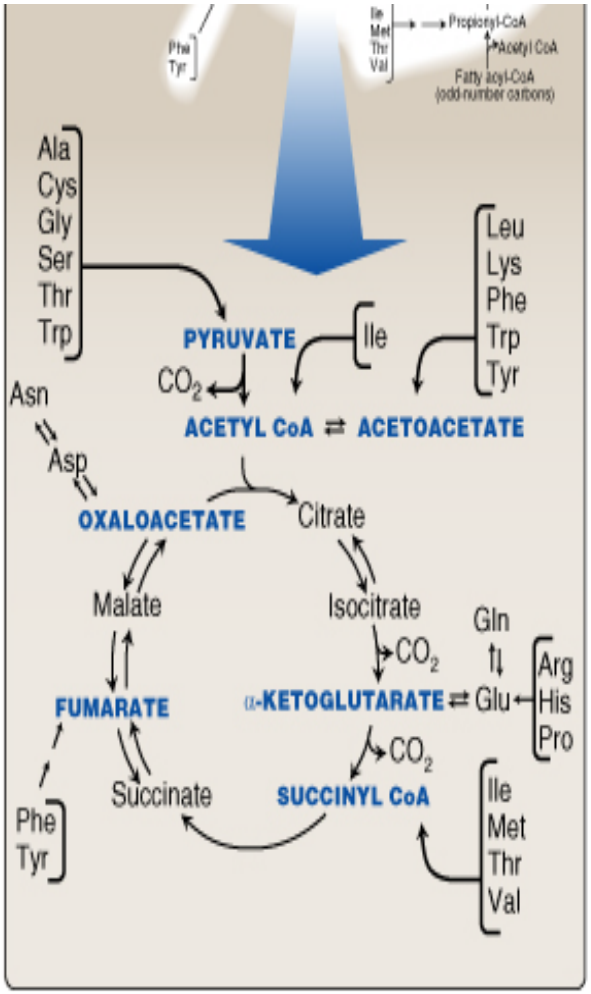
AMINO ACID METABOLISM AND CATABOLISM



Amino Acid metabolism/catabolism → **Metabolic pathway**



Classification of Amino Acid



	Glucogenic	Glucogenic and Ketogenic	Ketogenic
Nonessential	Alanine Arginine* Asparagine Aspartate Cysteine Glutamate Glutamine Glycine Histidine* Proline Serine	Tyrosine	
Essential	Methionine Threonine Valine	Isoleucine Phenyl-alanine Tryptophan	Leucine Lysine

Pyruvate and other TCA cycle intermediates

↓

Citric acid cycle (TCA)

↓

Gluconeogenesis

Acetoacetate (Ketone Bodies) or Acetyl CoA Acetoacetyl CoA } precurssors of acetoacetate

Succinyl coenzyme A

↓

Alternate energy source

Role of “one-carbon pool” in Amino Acid Metabolism/catabolism

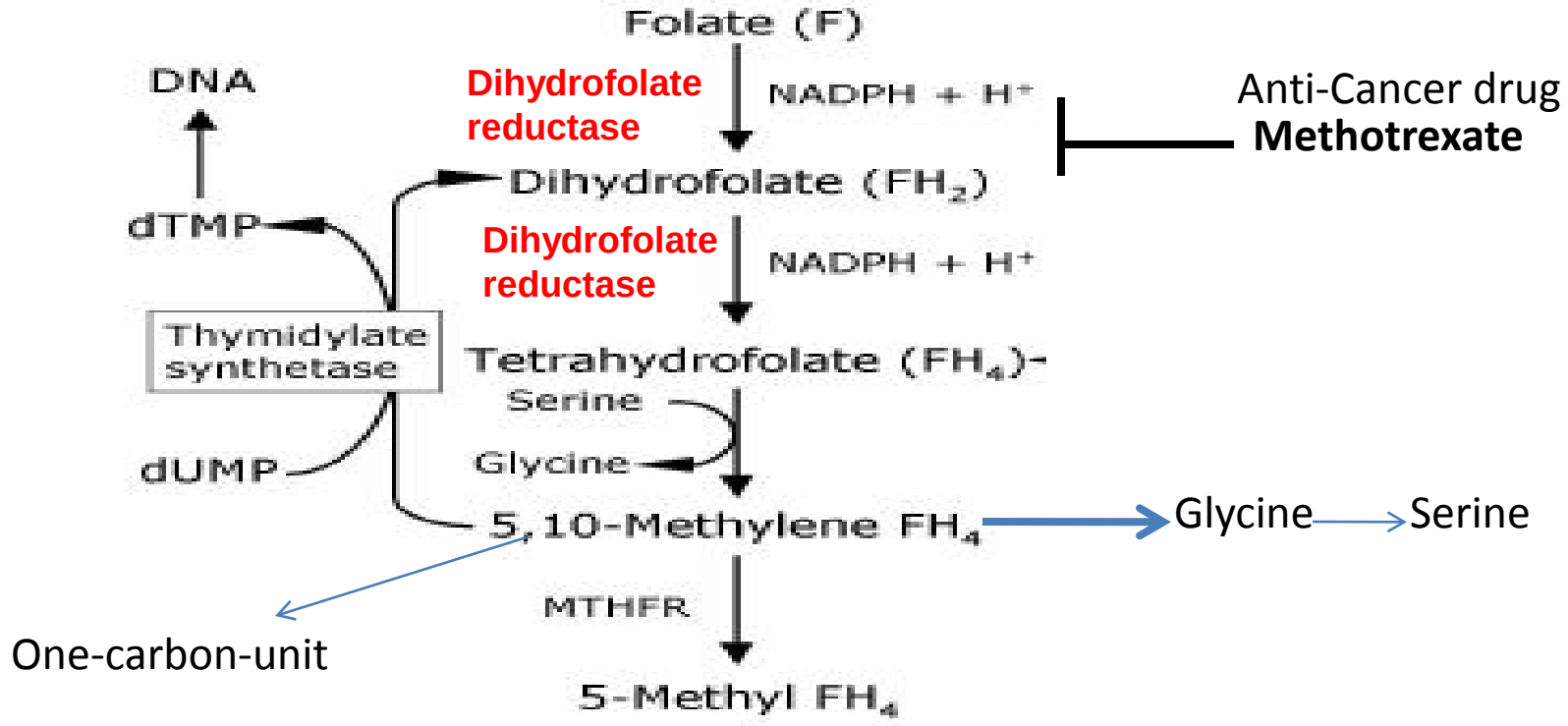
The “one-carbon pool” refers to single carbon units attached to the group of carrier compounds such as Tetrahydrofolate, S-adenosylmethione, Biotin etc.

These single carbon units can be transferred from carrier compounds to specific structures that are being synthesized or modified.

Tetrahydrofolate

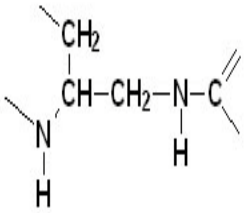
Tetrahydrofolate is an active form of Folic acid (vitamin B9 or folacin).

Folate → Dihydrofolate reductase → THF → Nucleotide and protein synthesis, Methylation of many biological compounds etc

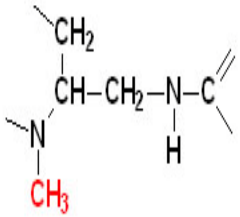


Tetrahydrofolate

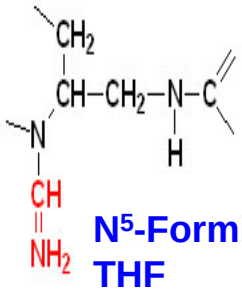
The One-Carbon Units include different groups linked to THF:



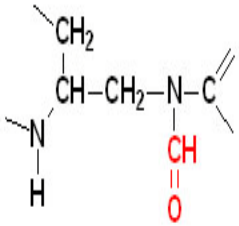
Tetrahydrofolate (THF)



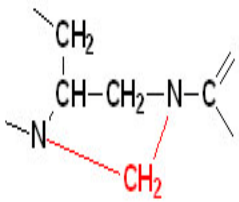
N^5-Methyl THF



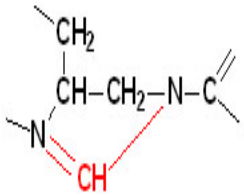
N^5-Formimino THF



N^{10}-Formyl THF



N^5, N^{10}-Methylene THF



N^5, N^{10}-Methenyl THF

THF acts as a carrier of reactive single carbon units, which are bonded to N-5 and N-10.

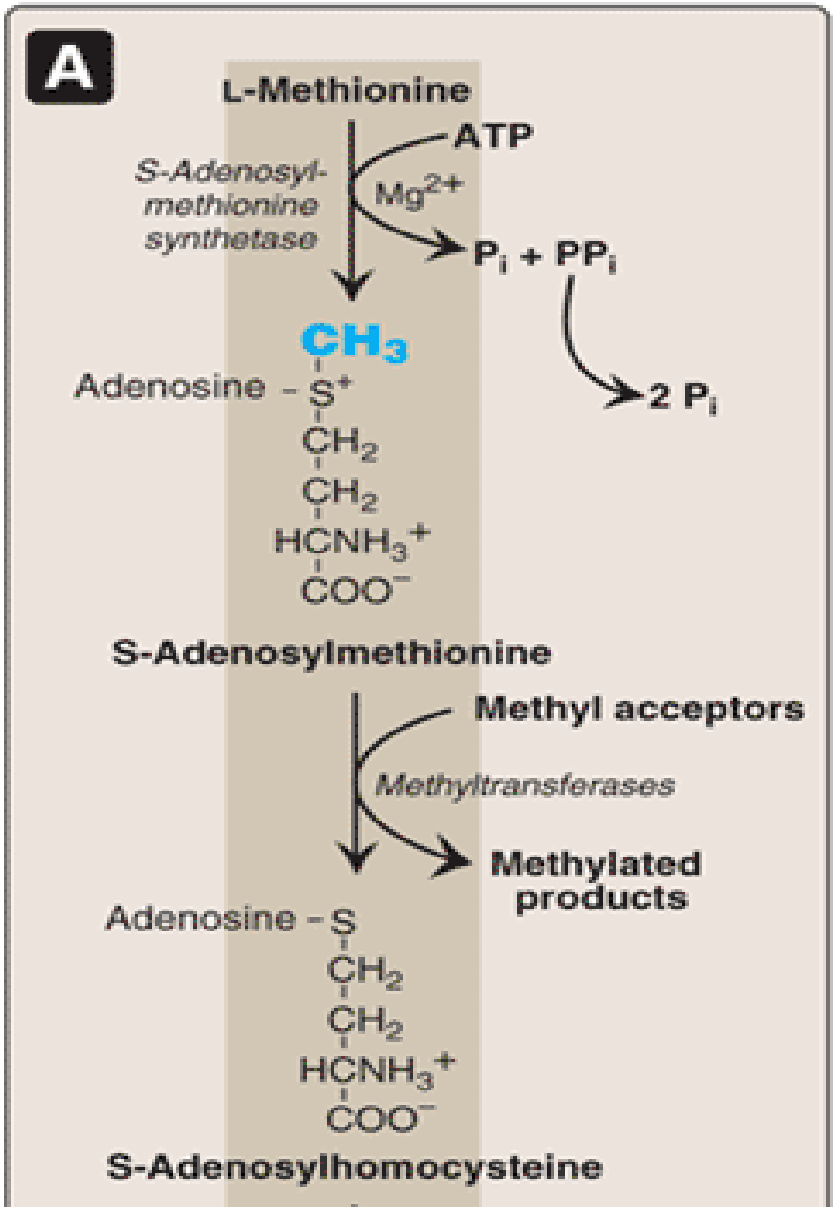
The oxidation level can be changed to methyl or methenyl by reduction or oxidation; methenylTHF can be hydrolyzed to formylTHF.

These derivatives can be used in synthetic reactions as donors of single C at the appropriate oxidation level.

S-adenosylmethionine SAM

Methionine adenosyltransferase (MAT), which catalyzes the biosynthesis of **S-adenosylmethionine (SAM)** , the principal methyl donor.

Methylation targets are:
DNA
RNA
Proteins
Lipids
Hormones and neurotransmitters

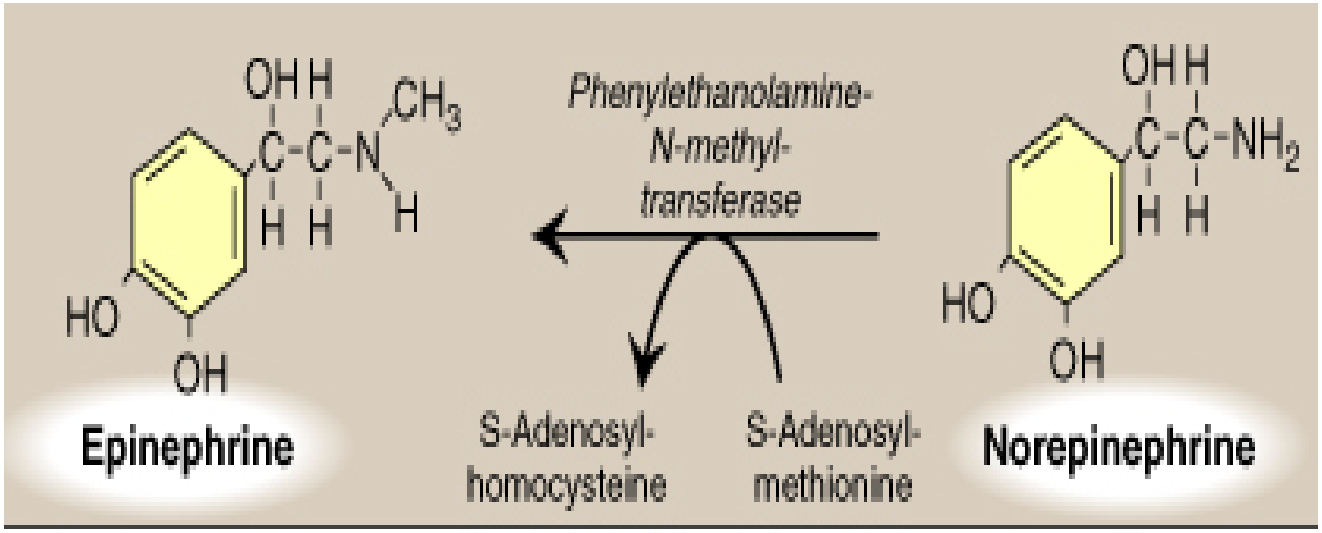


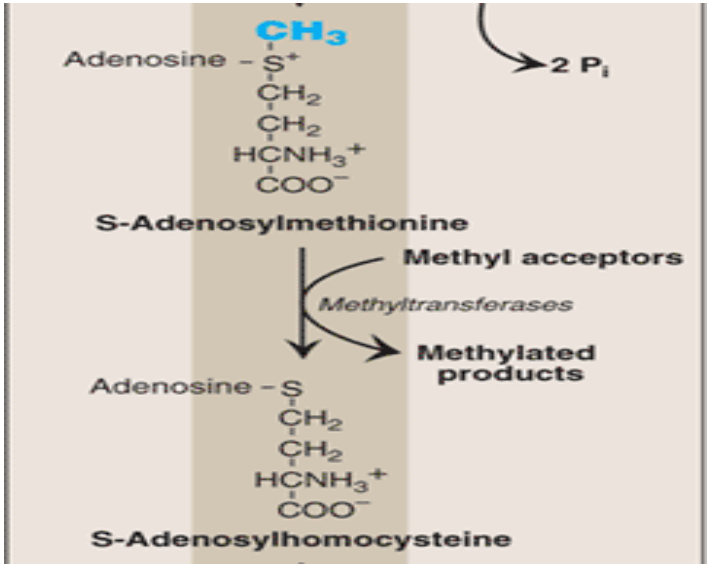
Synthesis of SAM

S-adenosylmethionine SAM

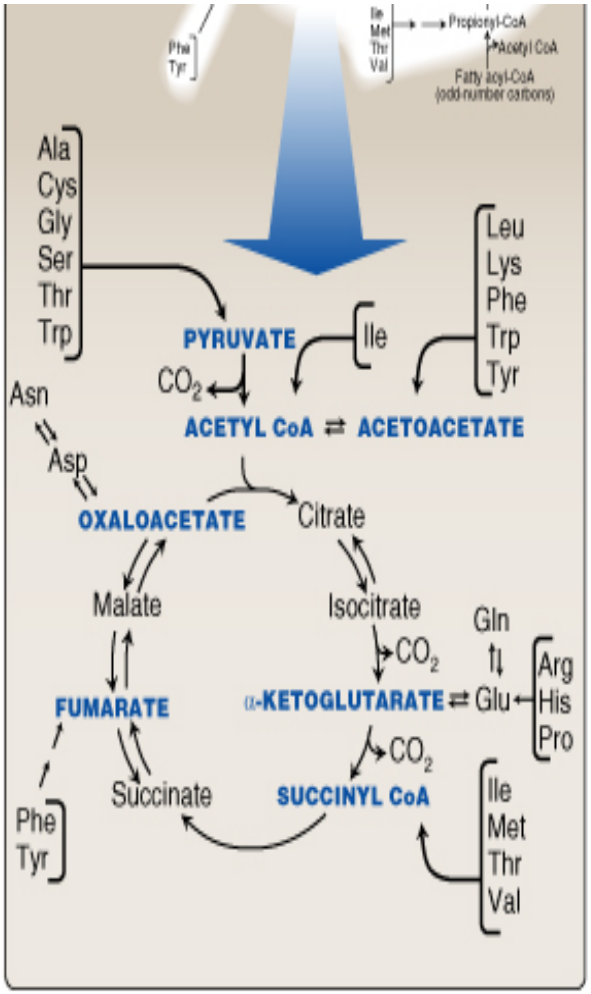
SAM serves as a precursor for numerous methyl transfer reactions

Conversion of Norepinephrine to Epinephrine requires SAM





Classification of Amino Acid



	Glucogenic	Glucogenic and Ketogenic	Ketogenic
Nonessential	Alanine Arginine* Asparagine Aspartate Cysteine Glutamate Glutamine Glycine Histidine* Proline Serine	Tyrosine	
Essential	Methionine Threonine Valine	Isoleucine Phenyl-alanine Tryptophan	Leucine Lysine

Pyruvate and other TCA cycle intermediates

↓

Citric acid cycle (TCA)

↓

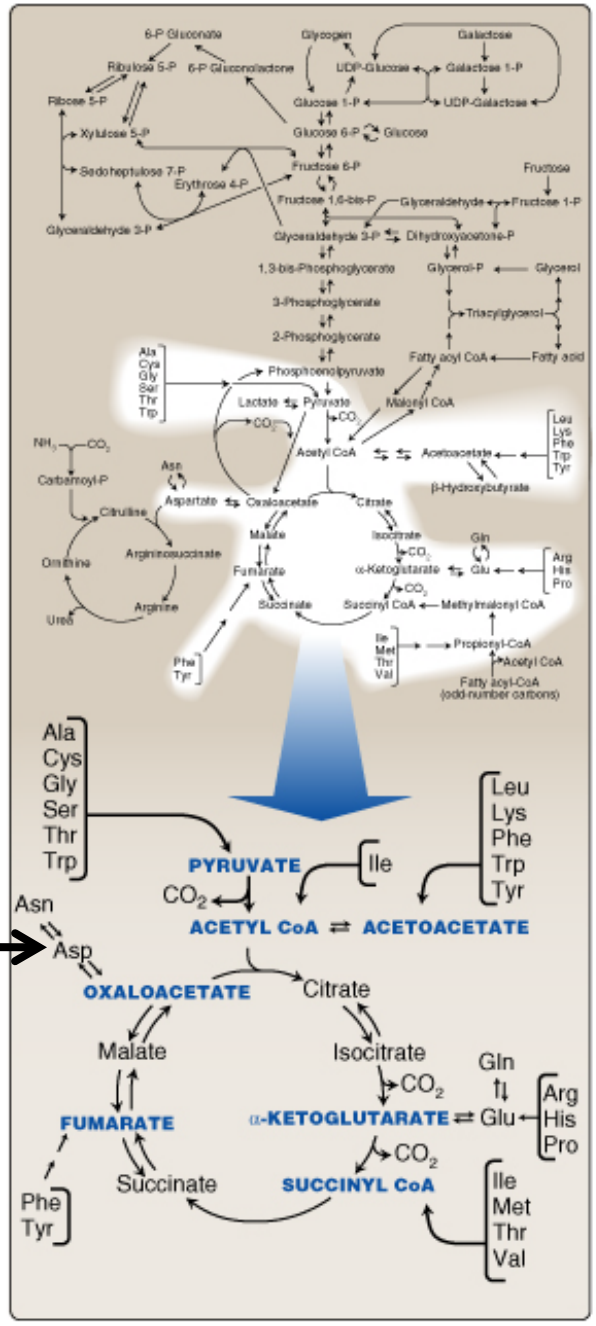
Gluconeogenesis

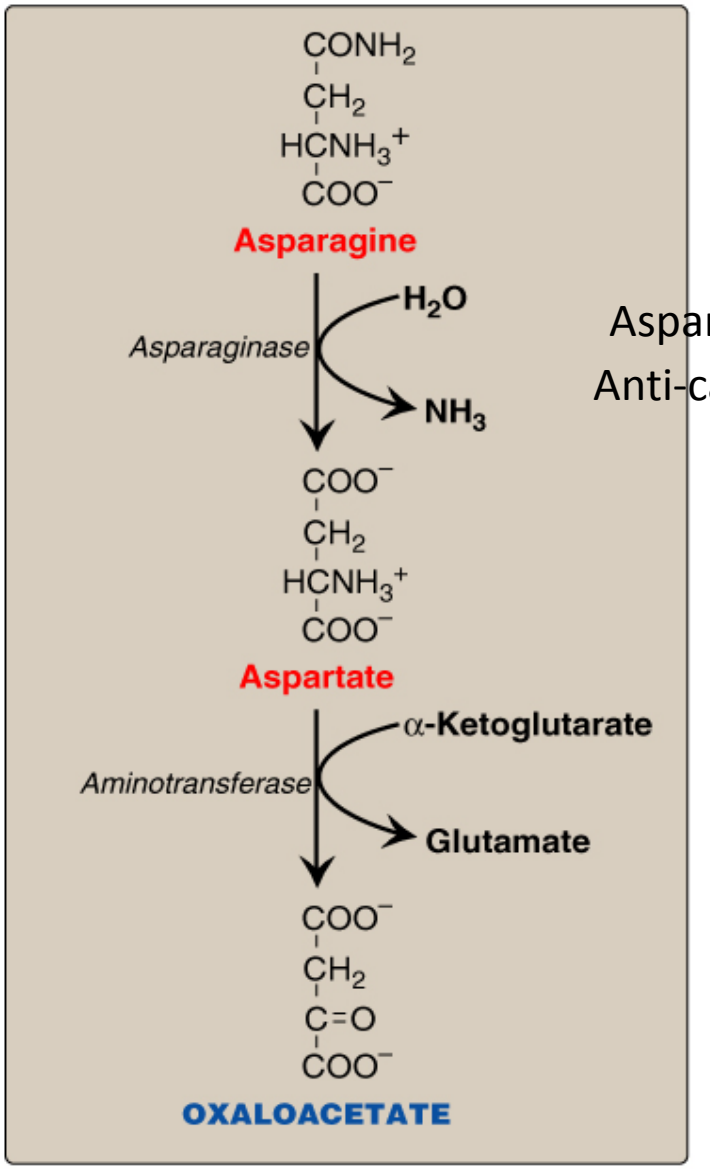
Acetoacetate or Acetyl CoA
Acetoacetyl CoA
Succinyl coenzyme A

↓

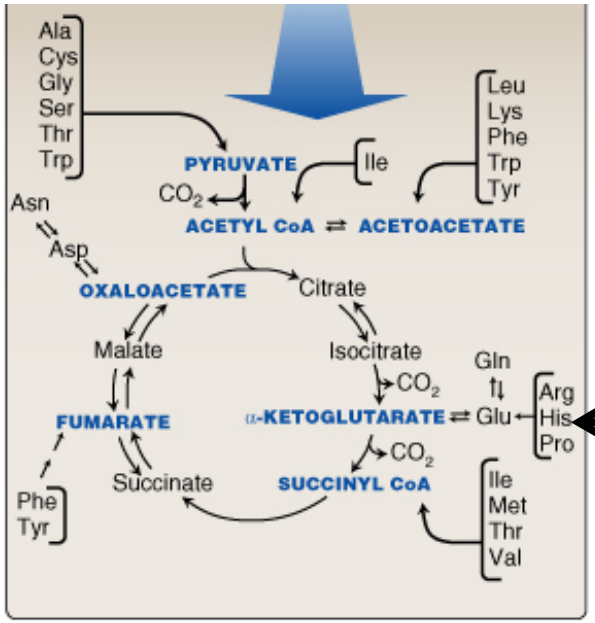
Alternate energy source

Asparagine and Aspartate enter metabolism as oxaloacetate





Asparginase
Anti-cancer drug



Gln, Pro, Arg, and His enter metabolism as α-ketoglutarate

Amino acids that forms α-ketoglutarate

Glutamine

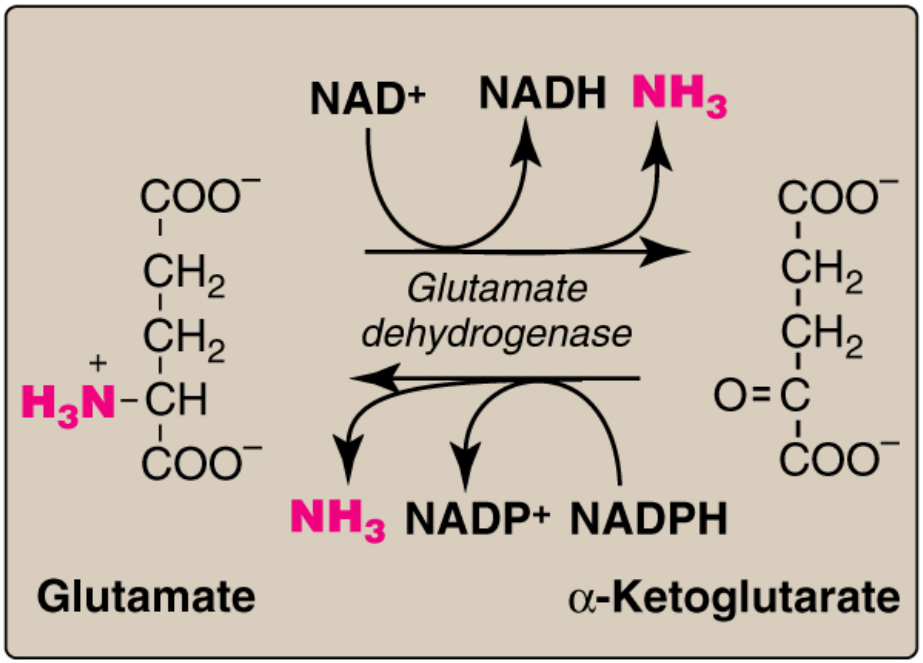
Glutamine

↓ Glutaminase

Glutamate + NH3

↓

Oxidative Deamination

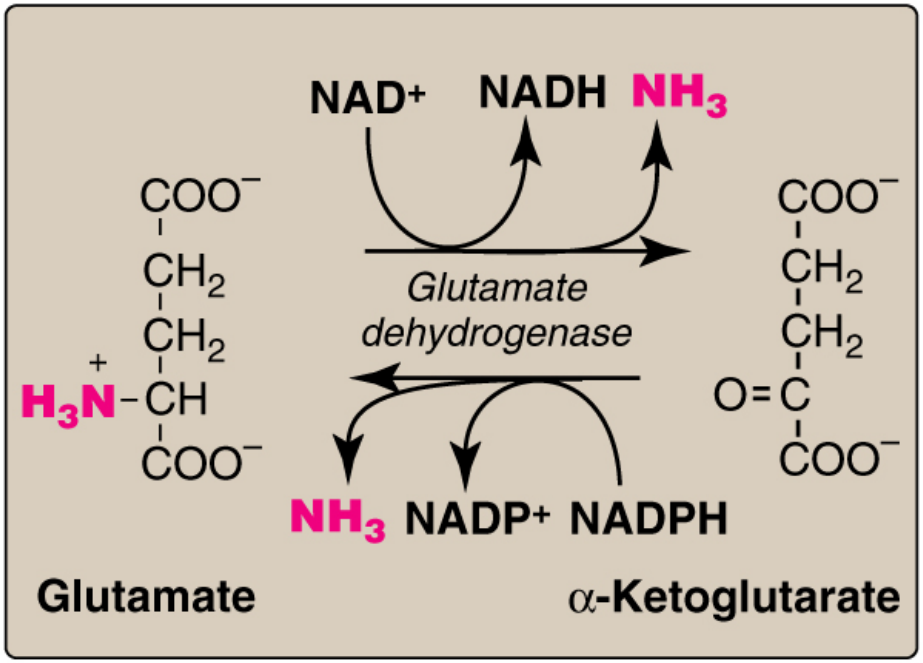


Amino acids that forms α-ketoglutarate

Proline

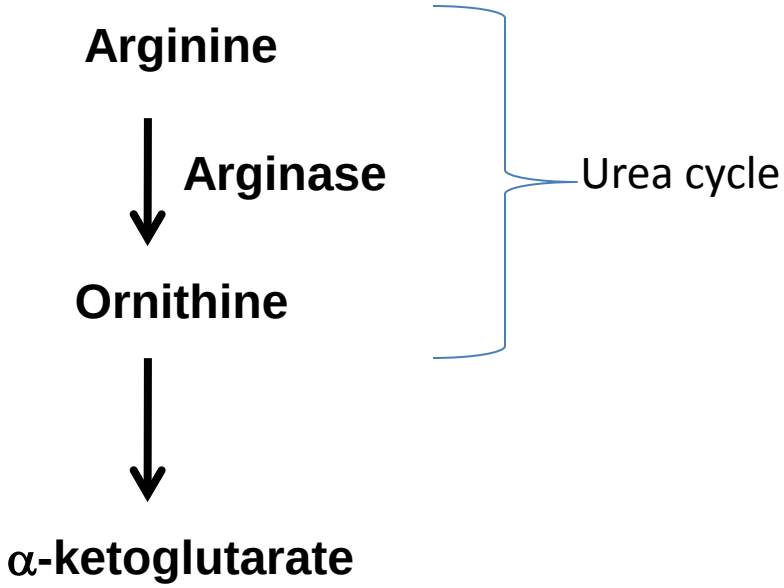
Proline —Oxidized→ **Glutamate**

Oxidative Deamination



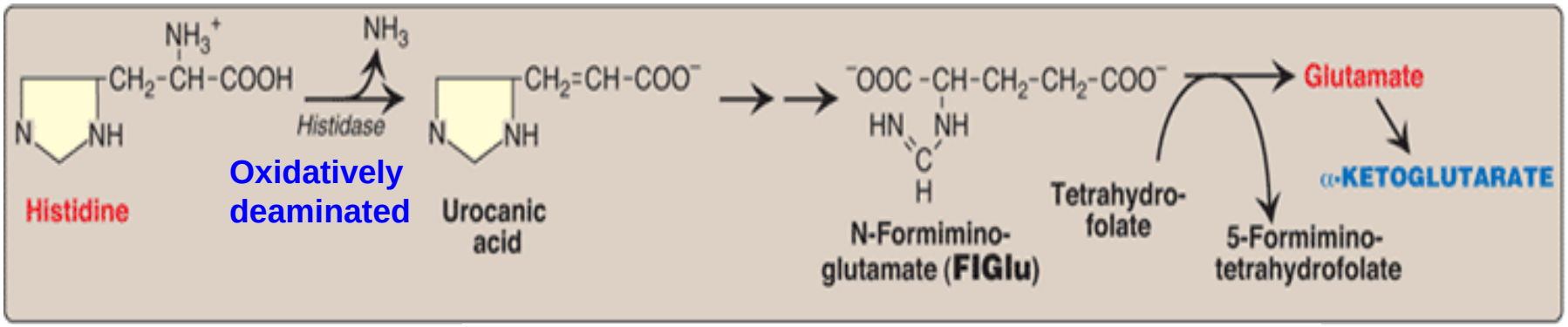
Amino acids that forms α-ketoglutarate

Arginine

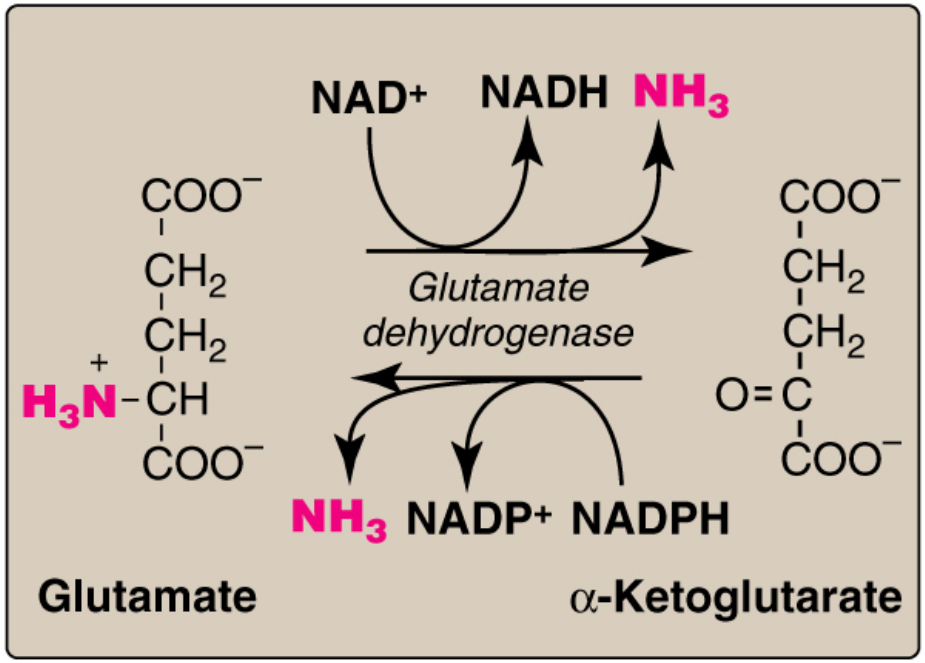


Amino acids that forms α-ketoglutarate

Histidine



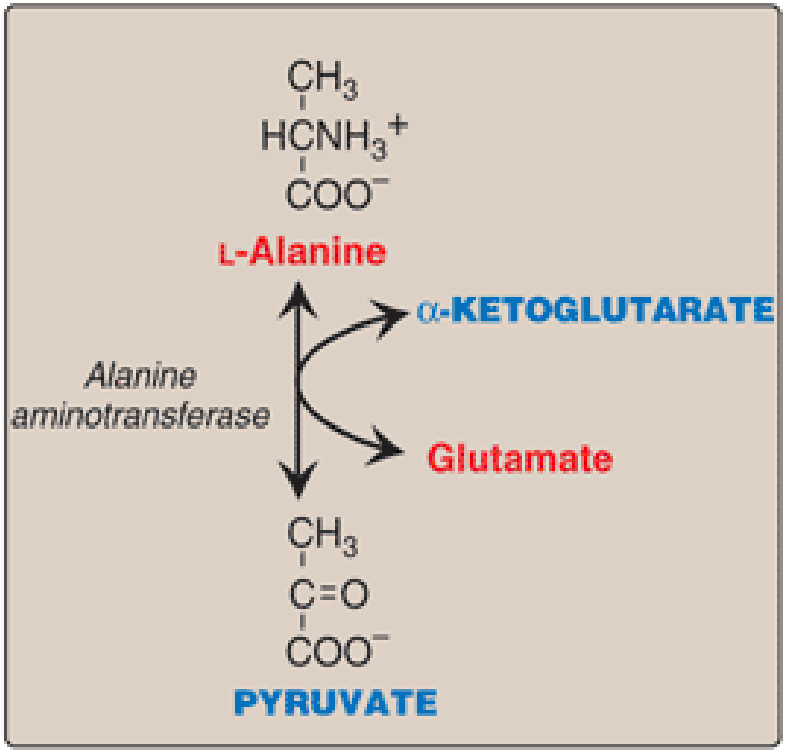
Oxidative Deamination



Amino Acid that forms pyruvate

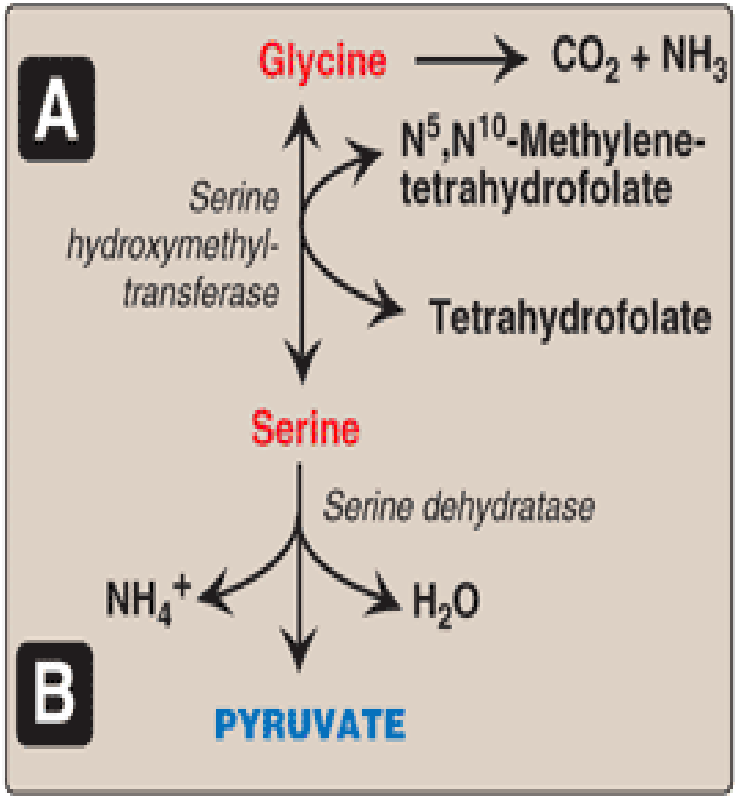
Alanine

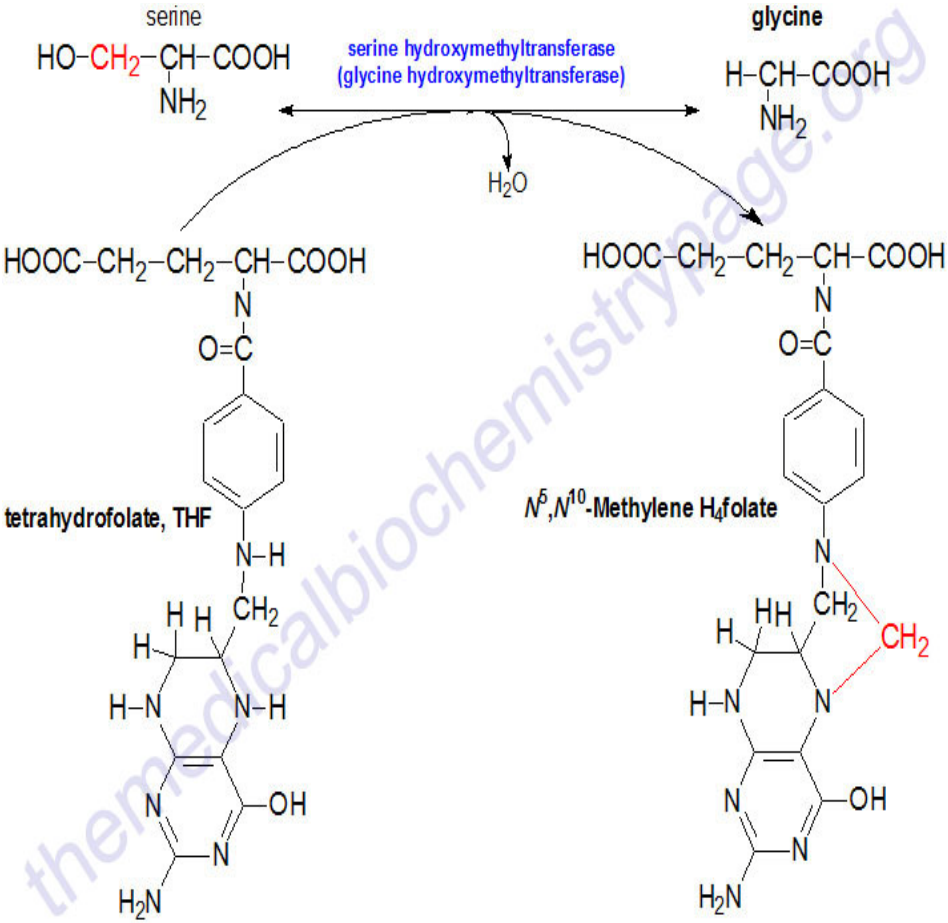
Transamination of alanine to form pyruvate



Amino Acid that forms pyruvate

Glycine

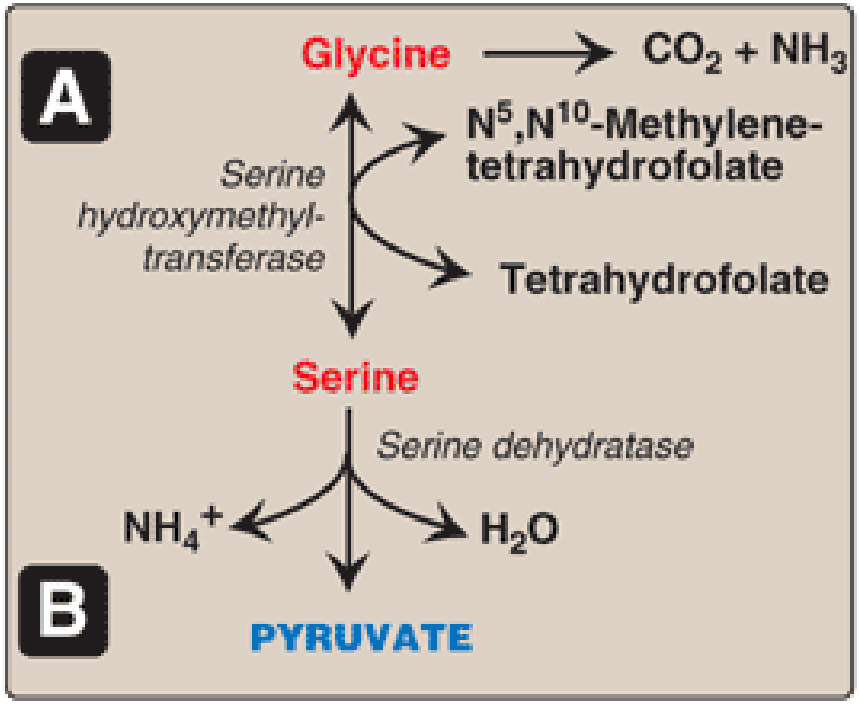




This reaction provides the largest part of the one-carbon units available to the cell.

Amino Acid that forms pyruvate

Serine



This reaction provides the largest part of the one-carbon units available to the cell.

Amino Acid that forms pyruvate

Cystine

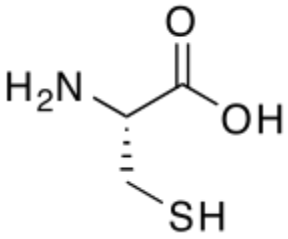
↓ **Reduced using $NADH + H^+$ as a reductant**

Cysteine

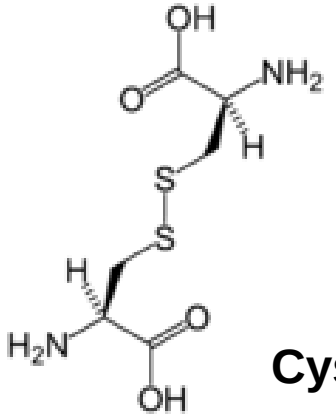
↓ **desulfuration**

pyruvate

Cystine is a dimeric amino acid formed by the oxidation of two Cysteine residues which covalently link to make a disulphide bond.



Cysteine

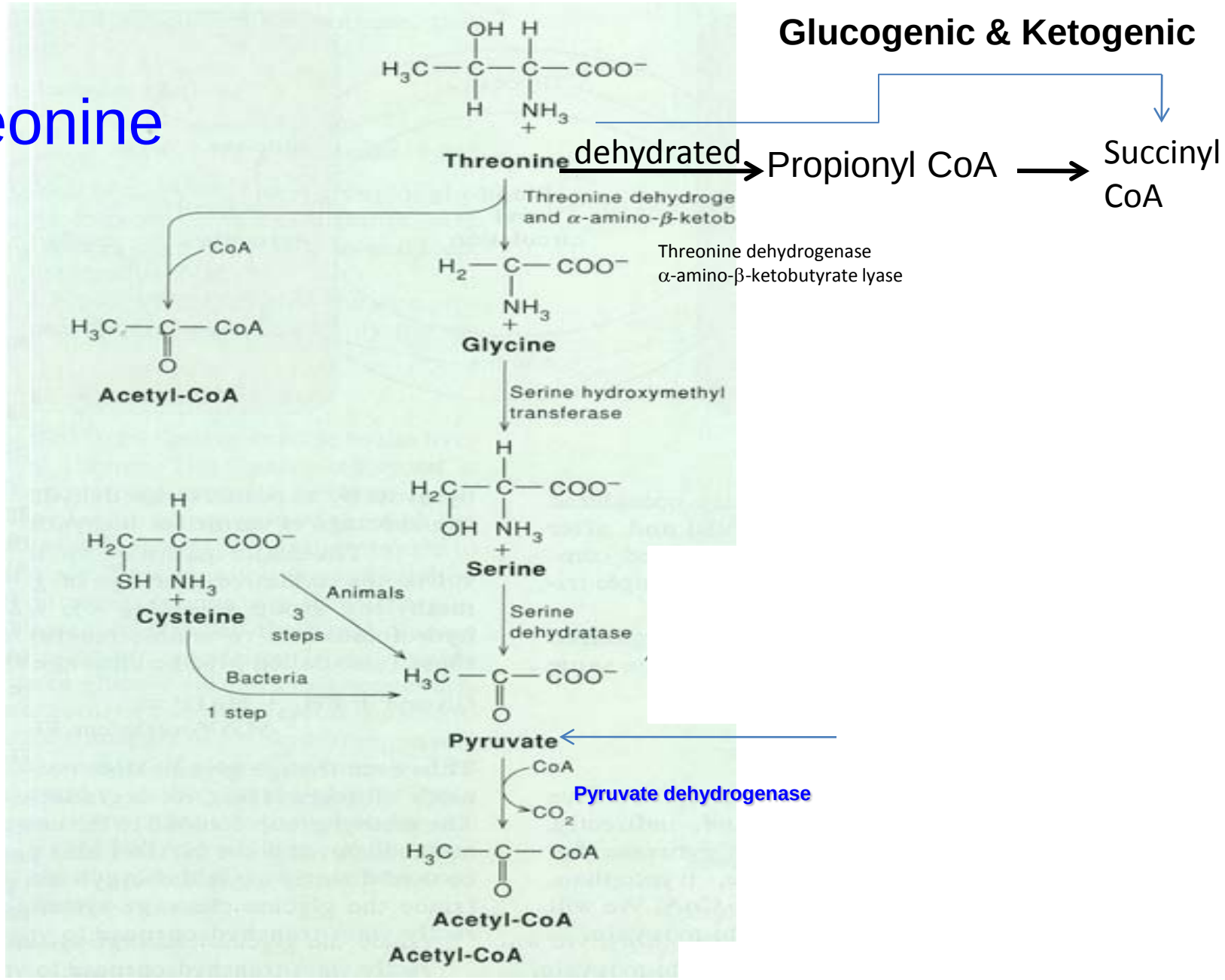


Cystine

Amino Acid that forms pyruvate

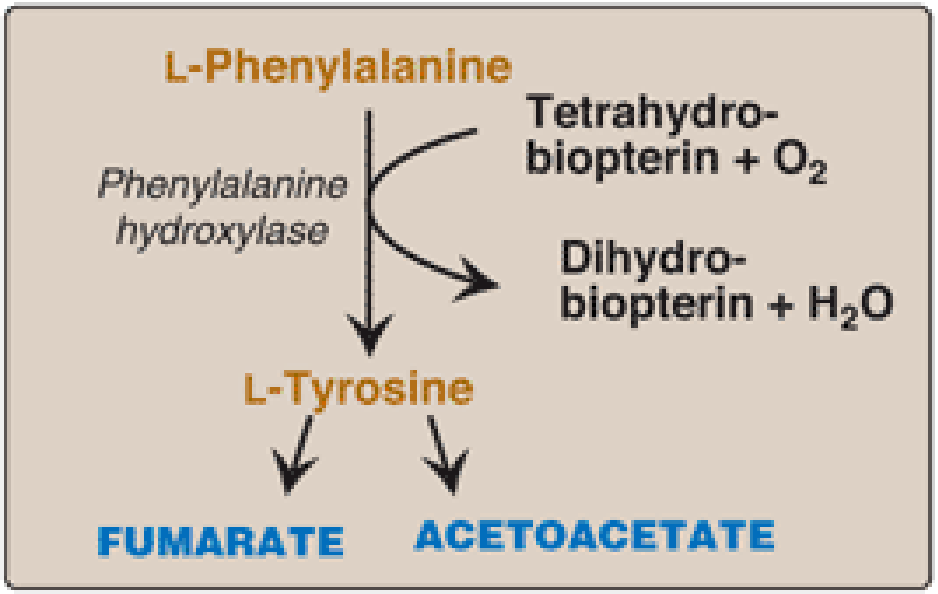
Threonine

Glucogenic & Ketogenic



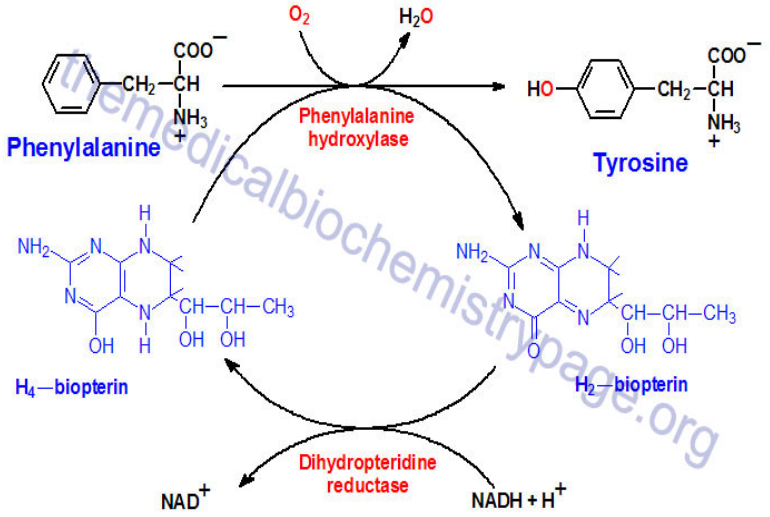
Amino acids that form fumarate

Phenylalanine and Tyrosine



Glucogenic

Ketogenic



Essential	Nonessential
Arginine[a]	Alanine
Histidine	Aspartate
Isoleucine	Cysteine
Leucine	Glutamate
Lysine	Glycine
Methionine[b]	Proline
Phenylalanine	Serine
Threonine	Tyrosine
Tryptophan	
Valine	

[a] Arginine is synthesized by mammalian tissues, but the rate is not sufficient to meet the need during growth.
[b] Methionine is required in large amounts to produce cysteine if the latter is not supplied adequately by the diet.
[c] Phenylalanine is needed in larger amounts to form tyrosine if the latter is not supplied adequately by the diet.

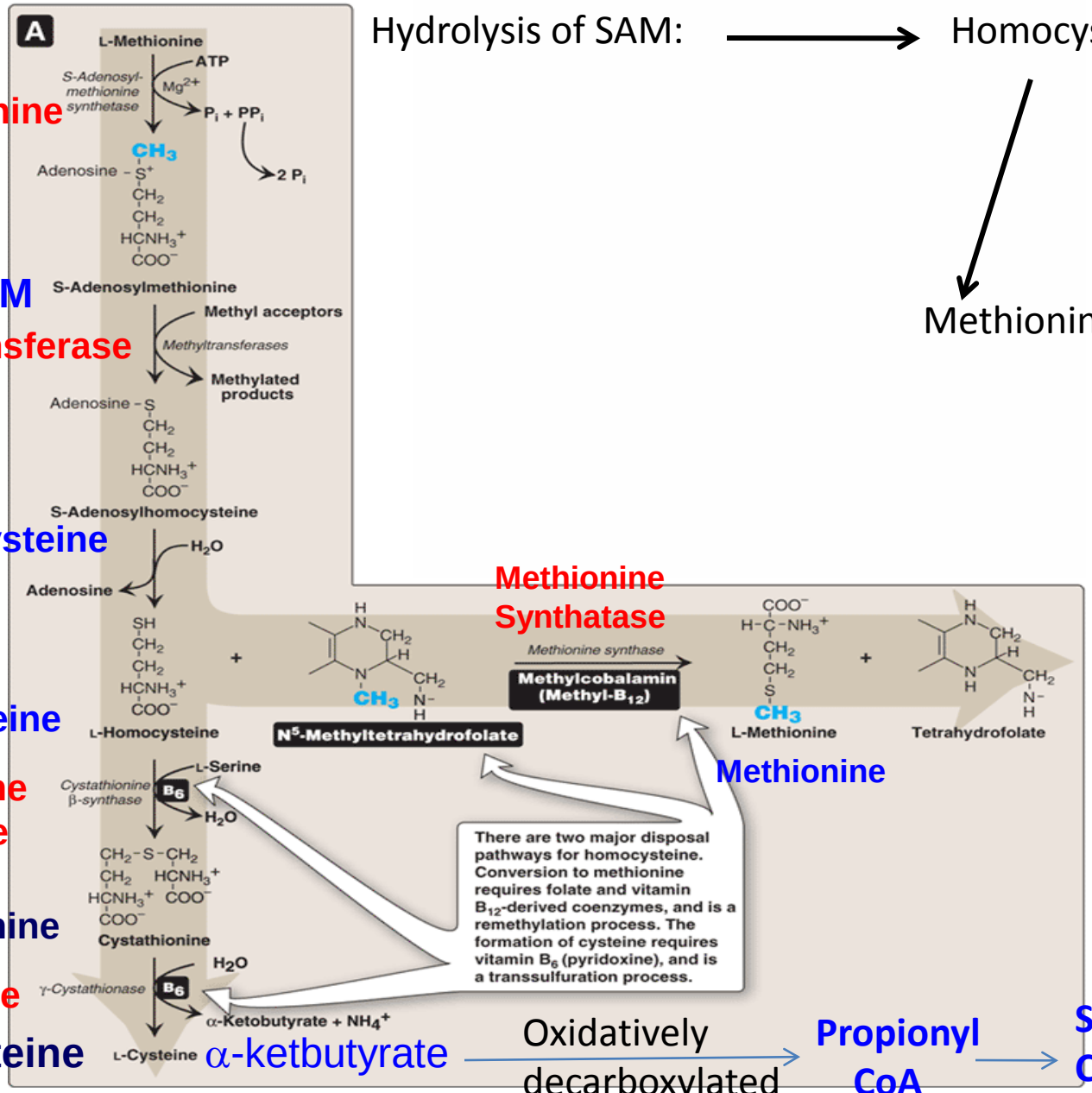
Amino acids that form succinyl CoA

Methionine

Methionine is special because:

* Converted to S-adenosylmethionine (SAM), the major methyl-group donor in one-carbon metabolism
* Source of homocysteine ----a metabolite associated with atherosclerotic vascular disease

Amino Acid that forms Succinyl CoA



Hydrolysis of SAM: → Homocysteine

Homocysteine → Methionine, cysteine

S-Adenosylmethionine synthatase

SAM

Methyltransferase

S-adenosylhomocysteine

L-Homocysteine

Cystathione β-synthase

Cystathionine

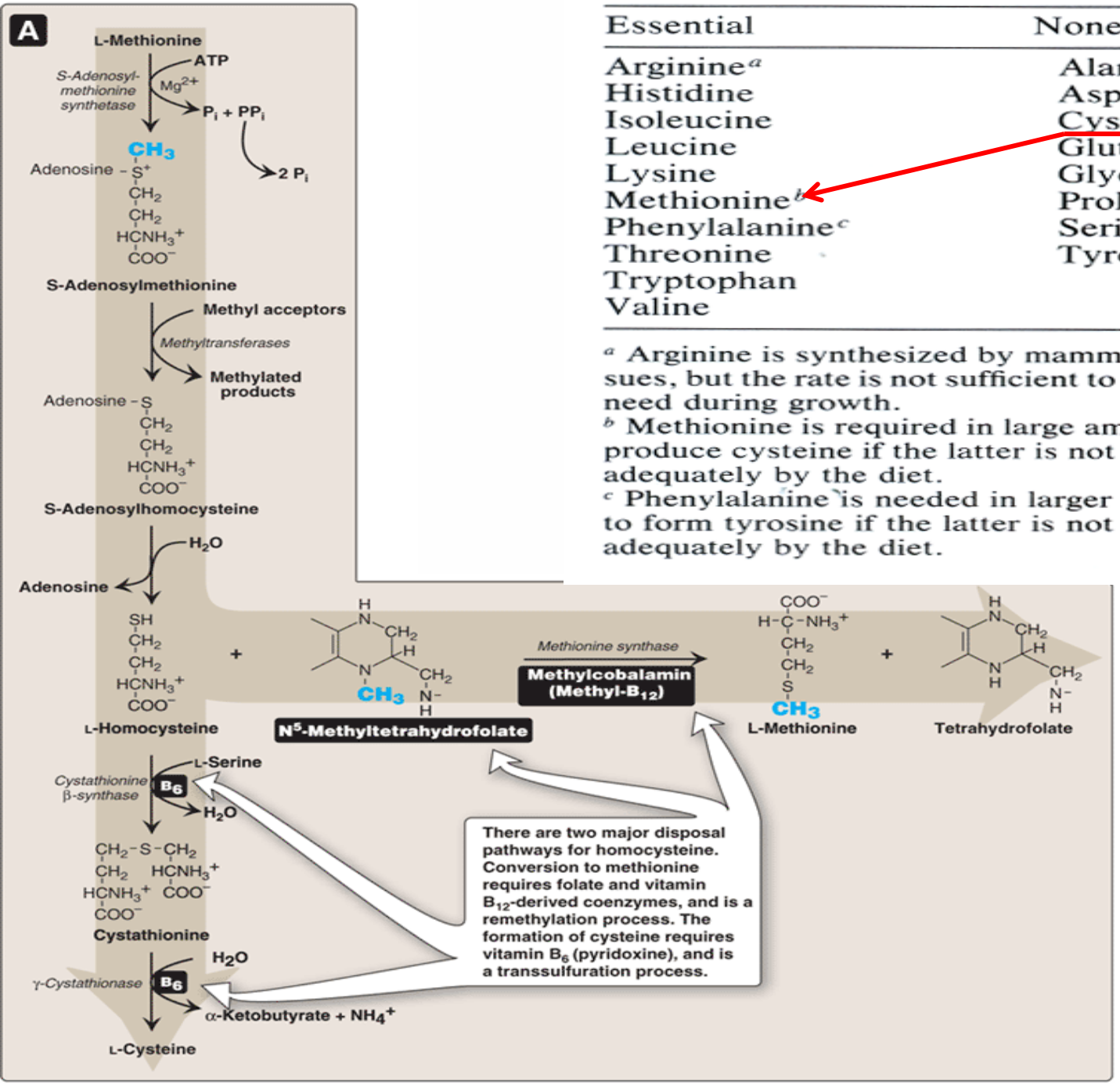
γ-cystathionase

L-Cysteine

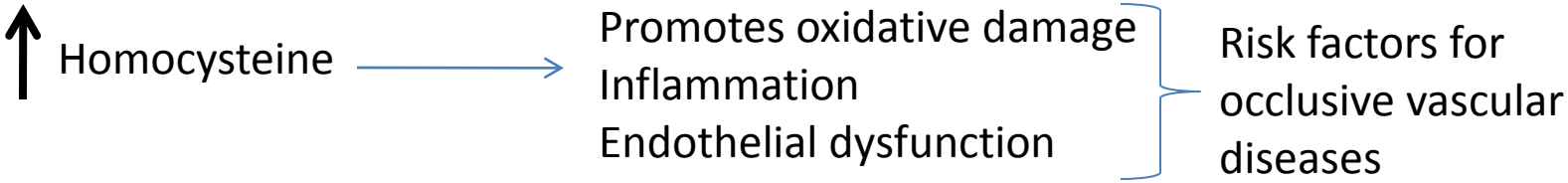
α-ketbutyrate → Oxidatively decarboxylated → Propionyl CoA → Succinyl CoA

Essential	Nonessential
Arginine[a]	Alanine
Histidine	Aspartate
Isoleucine	Cysteine
Leucine	Glutamate
Lysine	Glycine
Methionine[b]	Proline
Phenylalanine[c]	Serine
Threonine	Tyrosine
Tryptophan	
Valine	

[a] Arginine is synthesized by mammalian tissues, but the rate is not sufficient to meet the need during growth.
[b] Methionine is required in large amounts to produce cysteine if the latter is not supplied adequately by the diet.
[c] Phenylalanine is needed in larger amounts to form tyrosine if the latter is not supplied adequately by the diet.



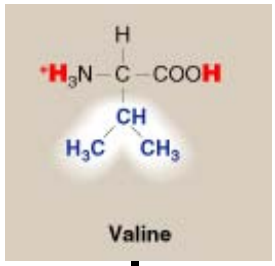
Homocysteine and vascular diseases

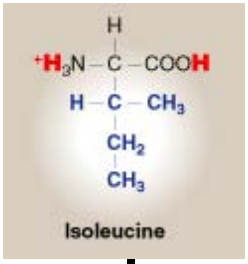


Plasma levels of homocystein is inversely related to folate, Vitamin B12 , and B6.

Homocysteine levels are also increased in Homocystinurea; disease caused due to the defective cystathione β-synthatase is defective

Catabolism of the branched-Chain amino acids





Essential aa

TRANSAMINATION
(Branched-chain α-amino acid transferase

α-Ketoisocaproic acid | α-Ketoisovaleric acid | α-Keto-β-methylvaleric acid

Maple Syrup Urine disease

OXIDATIVE DECARBOXYLATION
Branched-chain α-keto acid dehydrogenase complex (TPP, NAD, CoA Lipolic acid, FAD)

Isovaleryl CoA | Isobutyryl CoA | a-Methyl butyryl CoA

FAD-linked DEHYDROGENATION

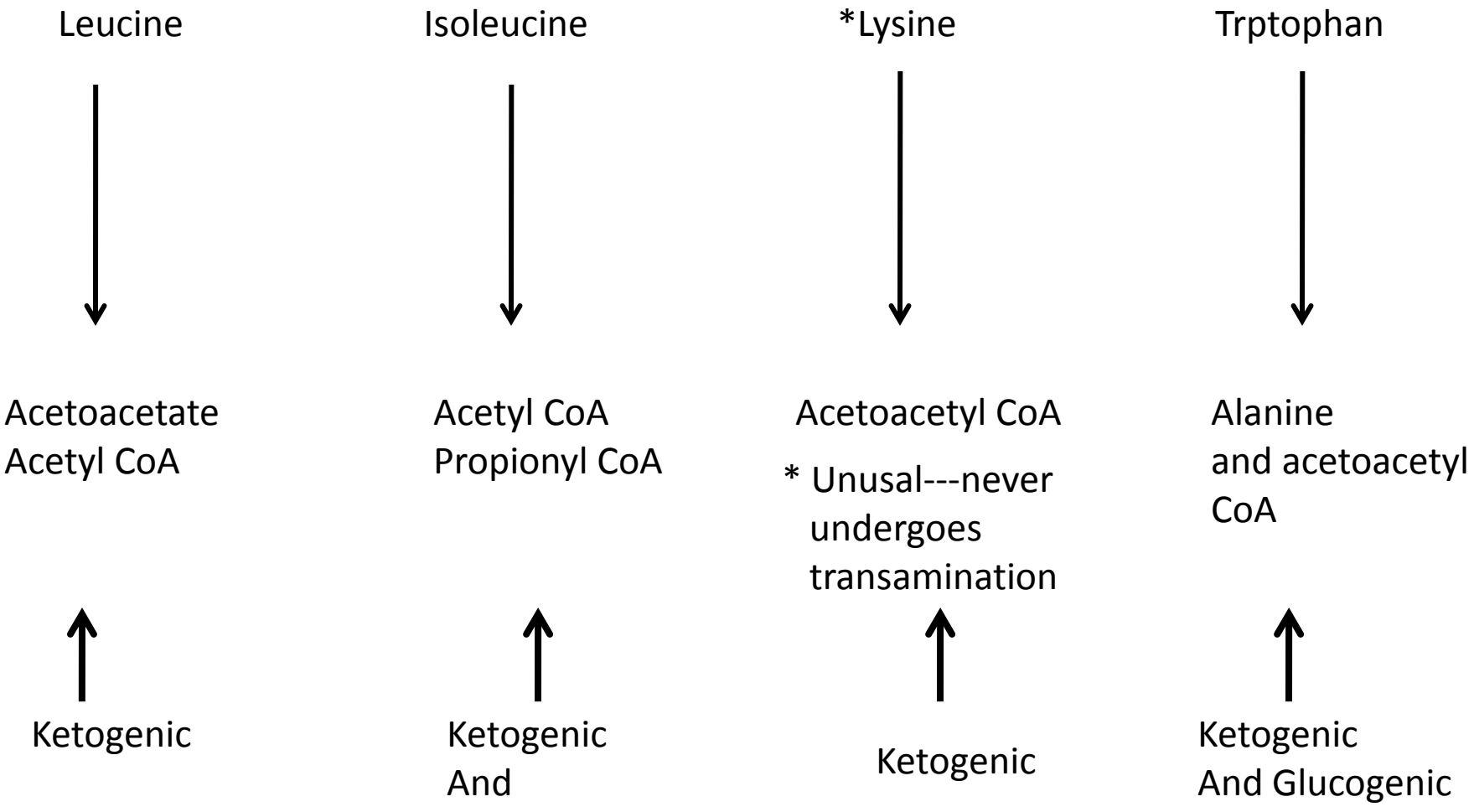
Acetoacetate + Acetyl CoA

Propionyl CoA

Acetyl CoA

Succinyl CoA

Amino acids that form acetyl CoA and acetoacetyl CoA

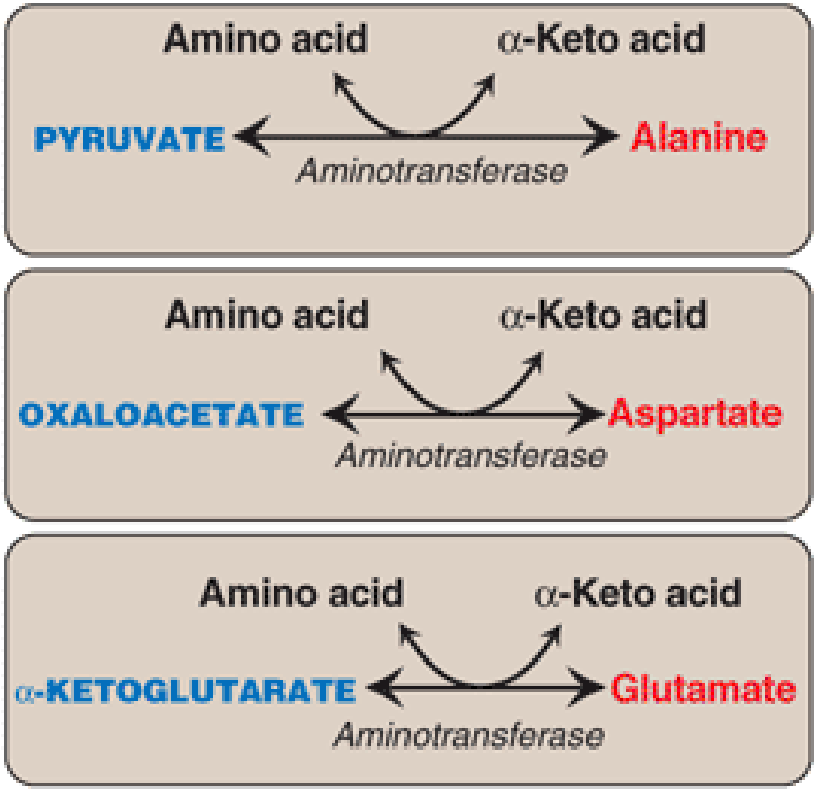


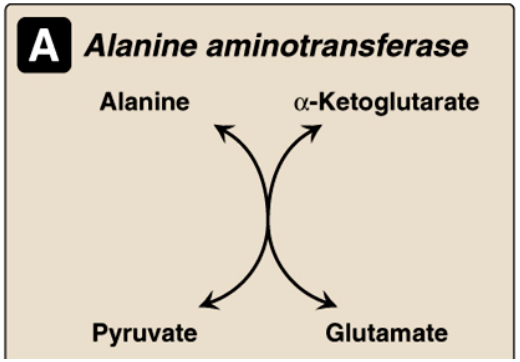
Biosynthesis of non-essential amino acids

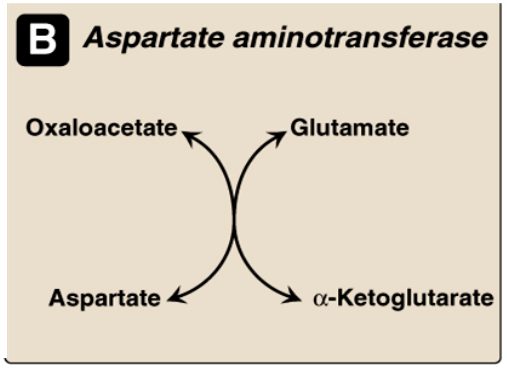
Biosynthesis of non-essential amino acids

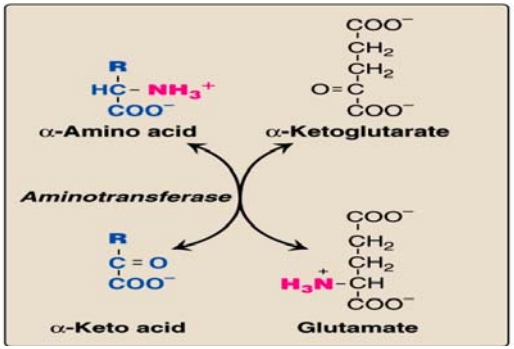
Synthesis from α-keto acids: Alanine, Aspartate, Glutamate

Alanine, aspartate, and glutamate are synthesized by transfer of an amino group to the α-keto acids pyruvate, oxaloacetate, and α-ketoglutarate, respectively.





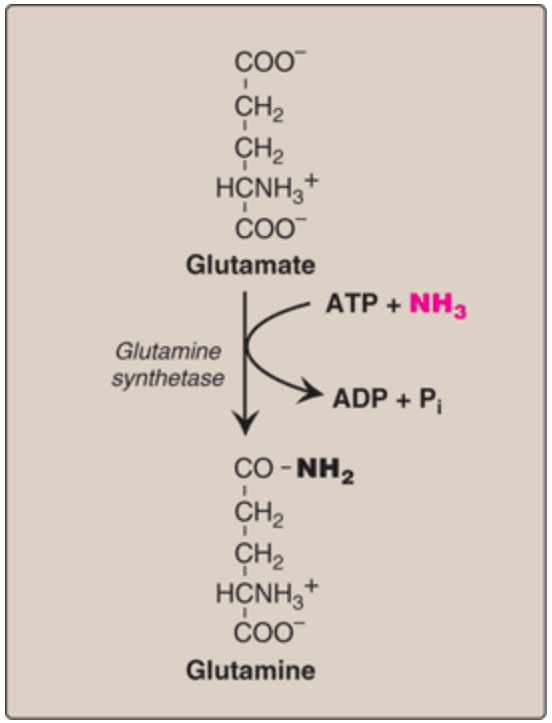




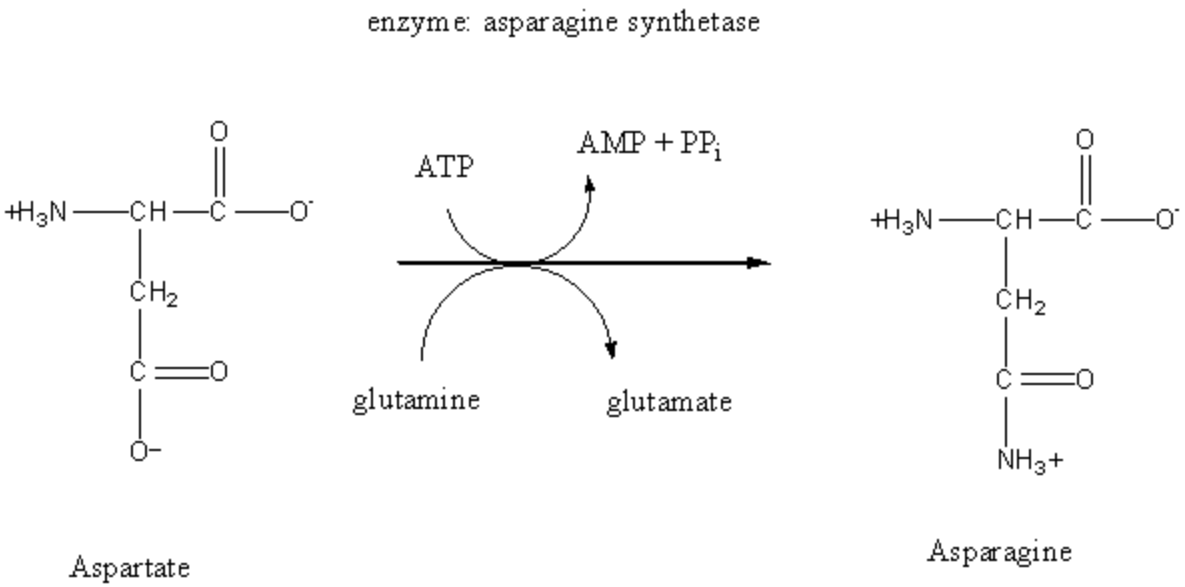
Biosynthesis of Glutamine and Aspargine

Synthesis by amidation: Glutamine, Aspargine

Glutamine



Aspargine



Biosynthesis of Proline, Serine and Cysteine

Proline

Cyclization and reduction

Glutamate ⟶ ⟶ ⟶ ⟶ **Proline**

Serine

3-phosphoglycerate

↓ **Oxidized**

3-phosphopyruvate

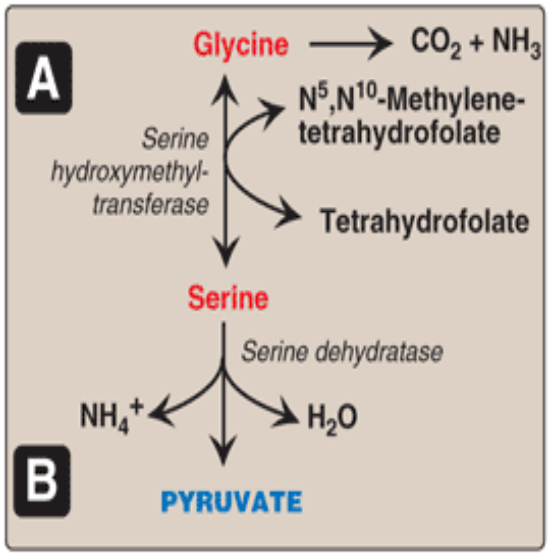
↓ **transaminated**

3-phosphoserine

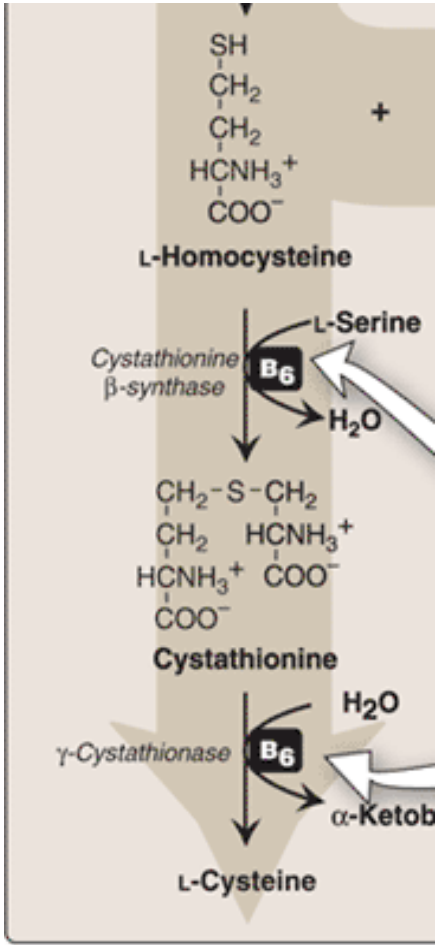
↓ **Hydrolysis of phosphate**

Serine

Serine and Glycine



Cysteine



Biosynthesis of Tyrosine

Tyrosine