Non-oxidative deamination:
In these reactions, deamination occurs without oxidation. The enzymes involved in this mechanism cause deamination of hydroxy- amino acids (serine, homoserine and threonine) and sulfur containing amino acid (cysteine):

1. Serine dehydratase (SDH):

\[
\begin{align*}
\text{HO-CH}_2\text{-CH-COOH} & \xrightarrow{\text{SDH, PLP}} \text{CH}_3\text{-CH-COOH} \quad \text{H}_2\text{O} \\
\text{Serine} & \quad \text{Imino acid} \\
\text{I} & \quad \text{II} \\
\text{NH}_2 & \quad \text{NH} \\
\end{align*}
\]

2. Cysteine desulphhydratase (CystDH):

\[
\begin{align*}
\text{HS-CH}_2\text{-CH-COOH} & \xrightarrow{\text{CystDH, PLP}} \text{CH}_3\text{-CH-COOH} \quad \text{H}_2\text{S} \\
\text{Cysteine} & \quad \text{Imino acid} \\
\text{I} & \quad \text{II} \\
\text{NH}_2 & \quad \text{NH} \\
\end{align*}
\]

METABOLISM OF AMMONIA
Although ammonia is involved in the formation of urea in the liver, the level of ammonia in the blood must be kept low because even slightly elevated concentrations (hyperammonemia) are toxic to the central nervous system. There must, therefore, be a metabolic mechanism by which nitrogen is moved from peripheral tissues to the liver for ultimate disposal as urea, at the same time maintaining low levels of circulating ammonia.

A. Sources of ammonia
Ammonia is produced from the metabolism of a variety of compounds. Amino acids are quantitatively the most important source of ammonia, because most western diets are high in protein and provide excess amino acids, which are deaminated to produce ammonia.

1. From amino acids: Many tissues, but particularly the liver, form ammonia from amino acids by the aminotransferase and glutamate dehydrogenase reactions previously described.
2. **From glutamine**: The kidneys form ammonia from glutamine by the action of renal glutaminase. Most of this ammonia is excreted into the urine as NH$_4^+$, which is an important mechanism for maintaining the body's acid-base balance. Ammonia is also obtained from the hydrolysis of glutamine by intestinal glutaminase. The mucosal cells obtain glutamine either from the blood or from digestion of dietary protein.

3. **From bacterial action in the intestine**: Ammonia is formed by the bacterial degradation of urea in the lumen of the intestine. Ammonia is absorbed from the intestine by way of the portal vein and is almost quantitatively removed by the liver by conversion to urea.

4. **From amines**: Amines obtained from the diet and monoamines that serve as hormones or neurotransmitters give rise to ammonia by the action of amine oxidase.

5. **From purines and pyrimidines**: In the catabolism of purines and pyrimidines, amino groups attached to the rings are released as ammonia.

**B. Transport and fate of ammonia in the circulation:**

Although ammonia is constantly produced in the tissues, it is present at very low levels in blood. This is due to both the rapid removal of ammonia from the blood by the liver and the fact that many tissues, particularly muscle, release amino acid nitrogen in the form of glutamine or alanine, rather than as free ammonia.

1. **Urea**: Formation of urea in the liver is quantitatively the most important disposal route for ammonia. Urea travels in the blood from the liver to the kidneys, where it passes into the glomerular filtrate.

2. **Glutamine**: This amide of glutamic acid provides a nontoxic storage and transport form of ammonia. The formation of glutamine occurs primarily in the muscle and liver but also is important in the nervous system, where it is the major mechanism for the removal of ammonia in the brain. Glutamine is found in plasma at concentrations higher than other amino acids, a finding consistent with its transport function. Circulating glutamine is removed by the kidneys and deaminated by glutaminase as described above. The metabolism of ammonia is summarized in the next figure.
C. Hyperammonemia

Elevated concentrations of ammonia in the blood cause the symptoms of ammonia intoxication, which include tremors, slurring of speech, and blurring of vision. At high concentrations ammonia can cause coma and death.

**Mechanism of ammonia toxicity:**

The toxicity of high levels of ammonia is thought to result, in part, from a shift in the equilibrium of the glutamate dehydrogenase reaction toward the direction of glutamate formation:

\[
\alpha\text{-ketoglutarate} + \text{NADPH} + \text{H}^+ + \text{NH}_3 \rightleftharpoons \text{glutamate} + \text{NADP}^+ 
\]

This depletes \( \alpha\text{-ketoglutarate} \), an essential intermediate in the citric acid cycle, resulting in a decrease in cellular oxidation and ATP production. The brain is particularly vulnerable to hyperammonemia, presumably because it depends on the citric acid cycle to maintain its high rate of energy production.
UREA CYCLE

Urea is the major disposal form of amino groups derived from amino acids, and accounts for about 90% of the nitrogen-containing components of urine.

One nitrogen of the urea molecule is supplied by free NH₃ and the other nitrogen by aspartate. Glutamate is the immediate precursor of both ammonia (through oxidative deamination by glutamate dehydrogenase) and aspartate nitrogen (through transamination of oxaloacetate by aspartate aminotransferase). The carbon and oxygen of urea are derived from CO₂. Urea is produced by the liver and then is transported in the blood to the kidneys for excretion in the urine.

b- Reactions of the cycle

The first two reactions leading to the synthesis of urea occur in the mitochondria, whereas the remaining cycle enzymes are located in the cytosol. Note: Glutamate dehydrogenase also occurs in the mitochondria, providing ammonia for incorporation into carbamoyl phosphate.]
1. **Formation of carbamoyl phosphate**: Formation of carbamoyl phosphate by **carbamoyl phosphate synthase I** is driven by cleavage of two molecules of ATP. Ammonia incorporated into carbamoyl phosphate is provided primarily by the oxidative deamination of glutamate. Ultimately, the nitrogen atom derived from this ammonia becomes one of the nitrogens of the urea molecule. Carbamoyl phosphate synthase I requires N-acetylglutamate for activity. [Note: A second enzyme, **carbamoyl phosphate synthetase II**, participates in the biosynthesis of pyrimidines. It does not require N-acetylglutamate, and occurs in the cytosol.]

2. **Formation of citrulline**: Ornithine and citrulline are basic amino acids that participate in the urea cycle but are not incorporated into cellular proteins because there are no codons for these amino acids. Ornithine is regenerated with each turn of the urea cycle, much in the same way that oxaloacetate is regenerated by the reactions of the citric acid cycle. The release of the high-energy phosphate of carbamoyl phosphate as Pi drives the reaction in the forward direction. The reaction product, **citrulline**, is transported to the **cytosol**.

3. **Synthesis of argininosuccinate**: Citrulline condenses with aspartate to form argininosuccinate. The α-amino group of aspartate provides the second nitrogen that is ultimately incorporated into urea. The formation of argininosuccinate is driven by the cleavage of **ATP** to AMP and P Pi. This is the third and final molecule of ATP consumed in the formation of urea.

4. **Cleavage of argininosuccinate**: Argininosuccinate is cleaved to yield **arginine** and **fumarate**. The arginine formed by this reaction serves as the immediate precursor of urea. **Fumarate** produced in the urea cycle provides a link with several metabolic pathways:
   a- Fumarate is hydrated to malate, which is transported into the mitochondria and reenters the TCA cycle.
   b- Alternatively, cytosolic malate can be oxidized to oxaloacetate, which can be converted to aspartate or glucose.

5. **Cleavage of arginine to ornithine and urea**: **Arginase** cleaves arginine to ornithine and urea. Arginase occurs almost exclusively in the liver. Thus, whereas other tissues can synthesize arginine, only the liver can cleave arginine and thereby synthesize urea.

6. **Fate of urea**: Urea diffuses from the liver and is transported in the blood to the kidneys, where it is filtered and excreted in the urine. A portion of the urea synthesized in the liver diffuses from the blood into the intestine and is cleaved to CO₂ and NH₃ by bacterial urease. This ammonia is partly lost in the feces and is partly reabsorbed into the blood. In patients with kidney failure, plasma urea levels are elevated, promoting a greater transfer of urea from blood into the gut. The intestinal action of urease on this urea becomes a clinically important source of ammonia, contributing to the hyperammonemia often seen in these patients. Oral administration of **neomycin** reduces the number of intestinal bacteria responsible for this NH₃ production.

**Overall reaction of urea cycle**

\[
\text{Aspartate} + \text{NH}_3 + \text{CO}_2 + 3\text{ATP} \rightarrow \text{Urea} + \text{fumarate} + 2\text{ADP} + \text{AMP} + 2\text{Pi} + \text{PPi} + 3\text{H}_2\text{O}
\]

Four high-energy phosphates are consumed in the synthesis of each molecule of urea: two ATP are needed to restore two ADP to two ATP, plus two to restore AMP to ATP. One nitrogen of the urea molecule is supplied by free NH₃, and the other nitrogen by aspartate. Glutamate is
the immediate precursor of both ammonia (through oxidative deamination by glutamate dehydrogenase) and aspartate nitrogen (through transamination of oxaloacetate by aspartate aminotransferase).

**Regulation of the urea cycle**

N-Acetylglutamate is an essential activator for carbamoyl phosphate synthetase I, the rate-limiting step in the urea cycle. N-Acetylglutamate is synthesized from acetyl CoA and glutamate. The intrahepatic concentration of this compound increases after ingestion of a protein-rich meal, leading to an increased rate of urea synthesis.
I- Metabolism of glycine

Glycine is a nonessential amino acid. Although it the simplest amino acid, it is involved in many important metabolic pathways.

A) Biosynthesis of glycine:

1- From serine:

\[
\text{H}_2\text{N-CH-COOH} + \text{H}_4\text{Folate} \xrightarrow{\text{Serine Hydroxymethylase}} \text{H}_2\text{N-CH-COOH} + 5,10\text{-methylene H}_4\text{Folate} \]

2- From choline:

\[
\text{H}_3\text{C} - \text{N}^+\text{CH}_2\text{CH}_2\text{OH} \xrightarrow{\text{Choline oxidase}} \text{H}_3\text{C} - \text{N}^+\text{CH}_2\text{CHO} \xrightarrow{\text{Dehydrogenase}} \text{H}_3\text{C} - \text{N}^+\text{CH}_2\text{COOH} \]

\[
\text{H}_2\text{N-CH-COOH} \xrightarrow{\text{Oxidase}} \text{H}_3\text{C} - \text{N}^+\text{CH}_2\text{COOH} \xrightarrow{\text{Oxidase}} \text{H}_3\text{C} - \text{N}^+\text{CH}_2\text{COOH} \]

3- From glyoxylic acid (transamination):

\[
\text{H}_2\text{C} = \text{O} + \text{GLUTAMATE} \xrightarrow{\text{Transaminase}} \text{H}_2\text{C} - \text{NH}_2 + \alpha\text{-KETOGLUTARATE} \]

\[
\text{GLYOXYLIC ACID} \xrightarrow{\text{PLP}} \text{GLYCINE} \]
B) Catabolism of glycine:
It occurs mainly in liver and kidney:

Glycine \( \rightarrow \) Glyoxylic acid \( \rightarrow \) Oxalate \( \rightarrow \) Formate

Metabolic functions of glycine:

- Glycosylic acid
- Choline
- Serine
- Pyruvate
- Glucose
- Glutathione
- Protein synthesis
- Hb
- Creatine
- Glycocholate (Bile acid)
- Purines

II- Metabolism of serine:
Serine is a non essential amino acid.
1- Biosynthesis from glycine:
Glycine + active formate (5,10 methylene H\(_4\) Folate) \( \xrightarrow{\text{Hydroxymethylase}} \) Serine

2- Biosynthesis from intermediates of glycolysis:
Metabolic functions of serine:

\[
\begin{align*}
\text{Glycine} & \quad \text{Glucose} & \quad \text{Pyruvate} & \quad \text{Glucose} \\
\text{Choline} & \quad \text{Ethanolamine} & \quad \text{SERINE} & \quad \text{Proteins} \\
\text{Lecithin} & \quad \text{Cephalins} & \quad \text{Phosphatidyl} & \quad \text{Sphingosine}
\end{align*}
\]

Formation of ethanolamine:

\[
\begin{align*}
\text{CH}_2\text{OH} & \quad \text{CO}_2 & \quad \text{CH}_2\text{OH} & \quad \text{Transmethylation} \\
\text{CHNH}_2 & \quad \text{CH}_2\text{NH}_2 & \quad \text{SAM} \\
\text{COOH} & \quad \text{CH}_3 & \quad \text{CH}_2\text{N} = \text{CH}_3 & \quad \text{Choline}
\end{align*}
\]

III. Metabolism of sulfur containing amino acids:

1. Methionine:
   Methionine is an essential amino acid.
   a) Formation of S-adenosyl methionine (SAM) the active methyl donor:
**Transmethylation reactions:**

SAM is the donor of methyl group (one carbon) in many reactions e.g.:

a- Ethanolamine → Choline.

b- Norepinephrine → Epinephrine.

c- Guanidoacetic acid → Creatine.

d- Serotonin → Melatonin.

**b- Conversion of methionine to propionyl CoA and cysteine biosynthesis:**

[Diagram showing the conversion process]

2- **Cysteine:**

It is a nonessential glycogenic amino acid.

1- **Biosynthesis from cystine by reductase reaction:**

[Diagram showing the biosynthesis process]
1- Catabolism of cysteine via direct oxidation (cysteine sulfinate) and by the transamination (3-mercaptopyruvate) pathways:

\[
\text{Cysteine} \xrightarrow{\text{O}} \text{Cysteine sulfinate} \xrightarrow{\text{Transaminase}} \text{Sulfinylpyruvate} \xrightarrow{\text{Desulfinase}} \text{Pyruvate}
\]

3- Glutathione (GSH) biosynthesis

\[
\text{Glutamate} + \text{Cysteine} + \text{Glycine} \xrightarrow{GSH\;\text{synthetase}} \gamma\text{-glutamyl-cysteinyl-glycine (Glutathione)}
\]
One-carbon group transfer:

One carbon fragments are formed during the course of metabolic reactions from several amino acids. These include serine, glycine, histidine, and tryptophan. Also the methyl groups of choline, betaine, and methionine can be oxidized to HCHO and formate for use. One carbon group is formed in metabolism at all levels of oxidation from:

a) Methyl (-CH$_3$).  $\rightarrow$  

b) Methylene (-CH$_2$).  $\rightarrow$  

c) Methenyl (=CH-).  $\rightarrow$  

d) Formyl (O=CH-).  $\rightarrow$  CO$_2$.

Tetrahydrofolic acid ($\text{H}_4\text{folate}$) is a coenzyme carrier for the first 4 groups while biotin for CO$_2$. 
Methionine (SAM) is involved in the of spermine and spermidine biosynthesis:

Spermine and spermidine are polyamines function in diverse physiologic process, that share as a common thread a close relationship to cell proliferation and growth.

**Functions:**
1- They are implicated in cell proliferation and growth.
2- Stabilization of intact cells, subcellular organelles and membrane.
3- Being have multiple charges, they associate readily with polyanions as DNA, RNA and have been involved in stimulation of their synthesis and stabilization.
4- They act as inhibitor of protein kinases.

**Biosynthesis of spermine and spermidine:**