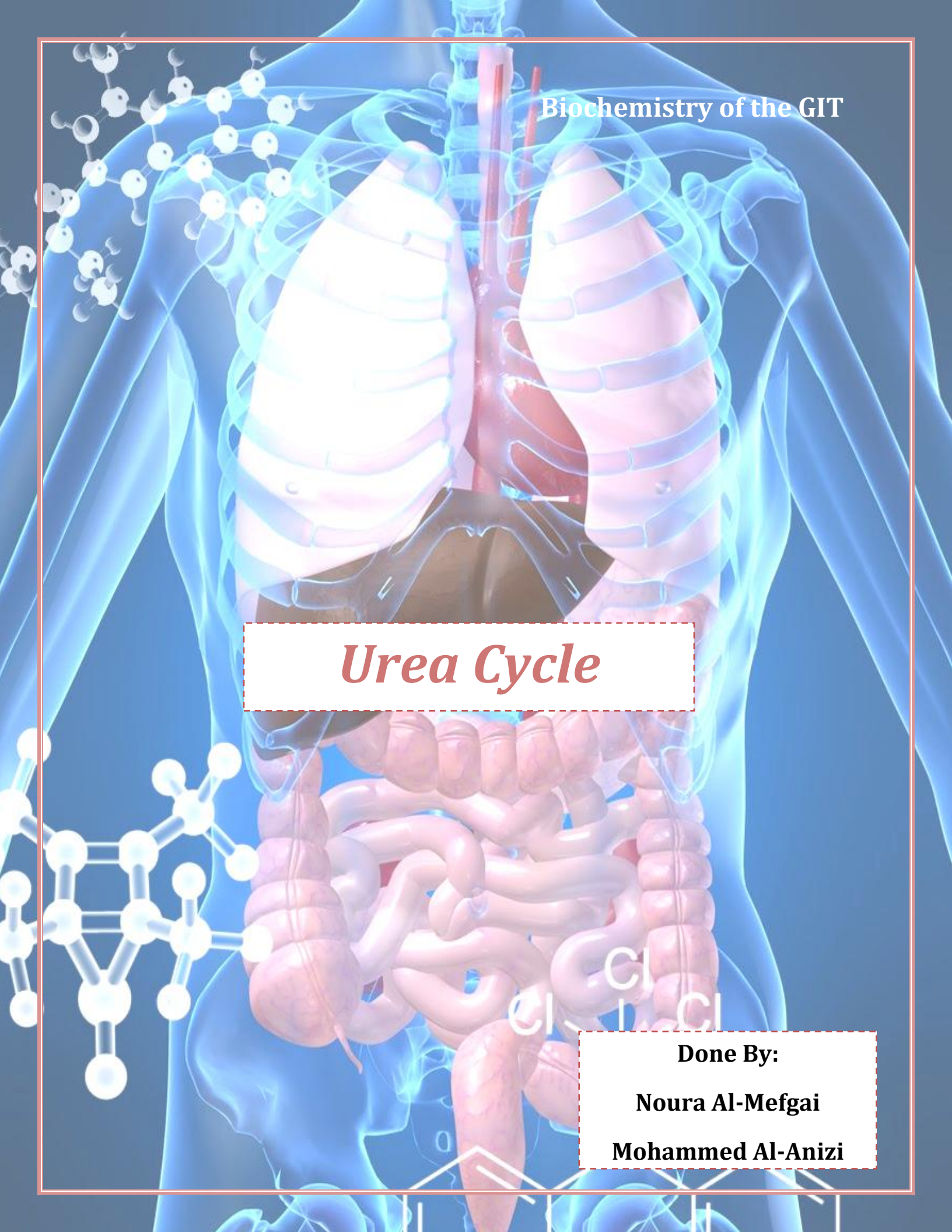

Biochemistry of the GIT

Urea Cycle

Done By:

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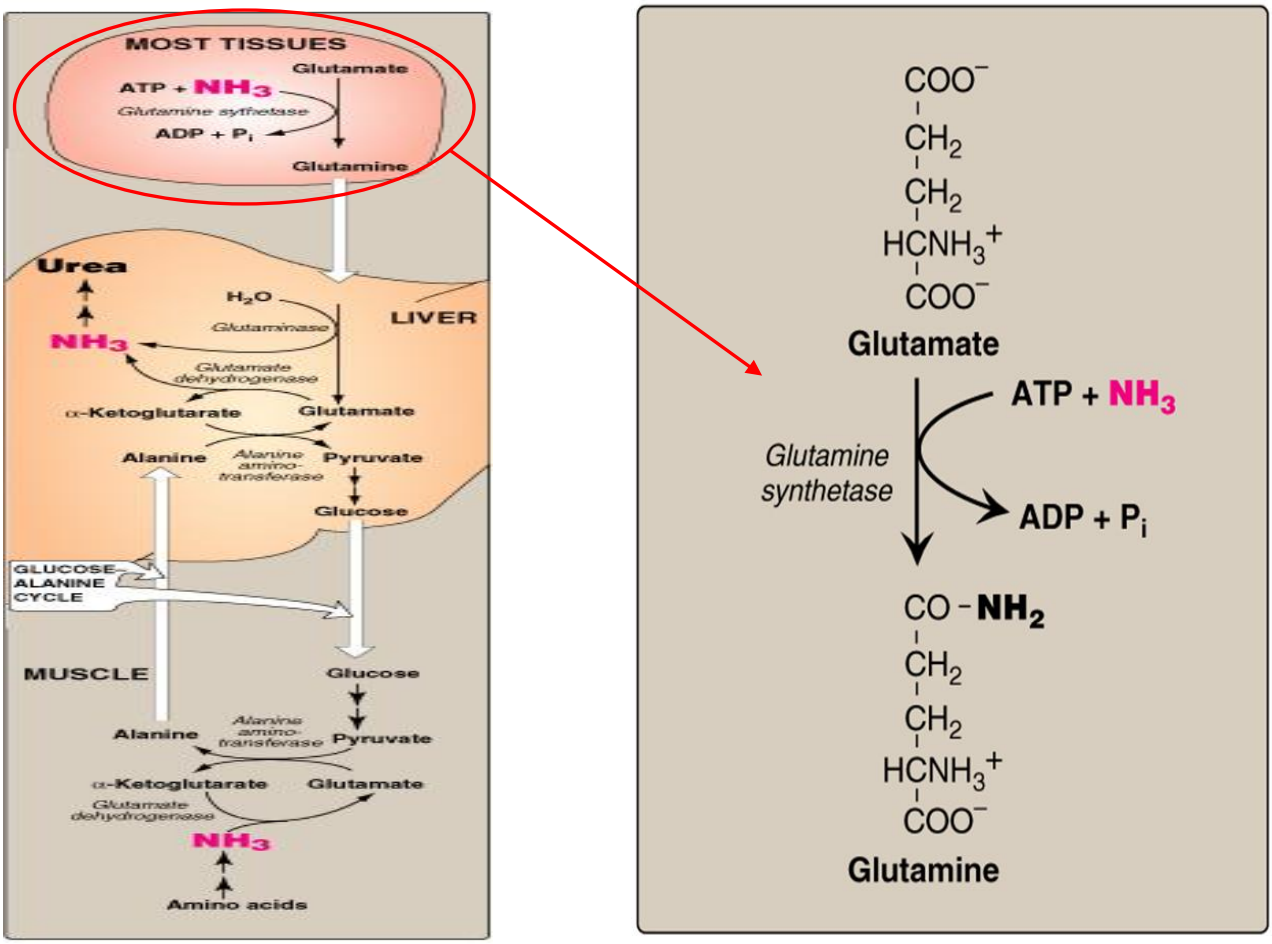
- Unlike glucose and fatty acids, amino acids are not stored by the body.
- Amino acids in excess of biosynthetic needs are degraded.
- Degradation of amino acids involves:
  - Removal of α-amino group → Ammonia (NH_3)
  - Remaining carbon skeleton → Energy metabolism

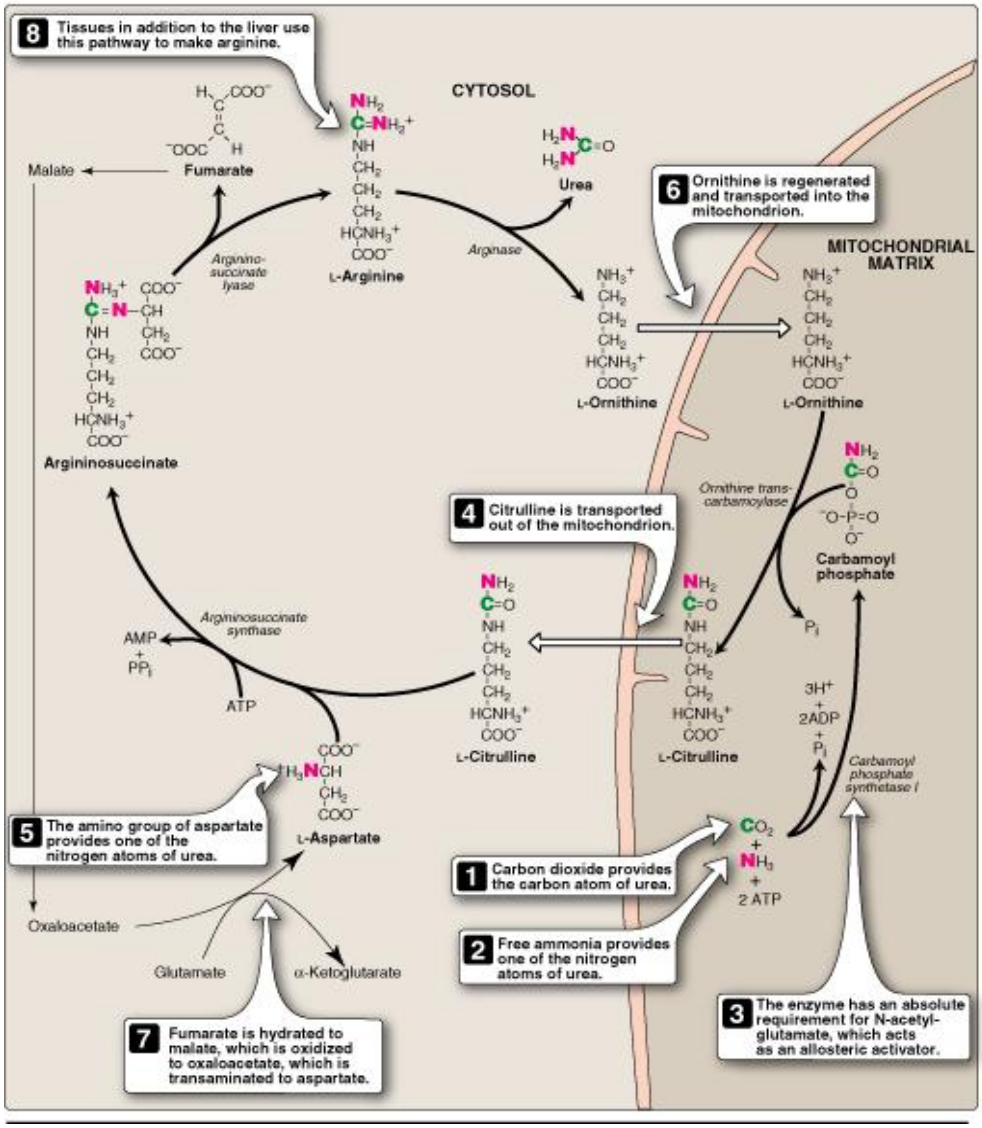
Biosynthetic: *Process of protein synthesis*

- Ammonia is produced by all tissues and the main disposal is via formation of urea in liver
- Urea is from the catabolism of proteins and it has no relationship to uric acid
- Blood level of NH3 must be kept very low, otherwise, hyperammonemia and CNS toxicity will occur (NH3 is toxic to CNS)
- To solve this problem, NH3 is transported from peripheral tissues to liver via formation of:
  - Glutamine (most tissues)
  - Alanine (muscle)



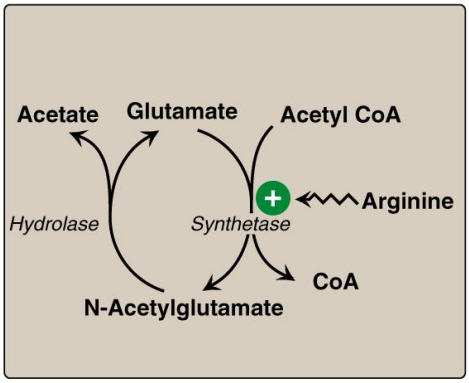
❖ Urea Cycle:

- Urea is the major form for disposal of NH3
- Urea cycle occurs in the liver
- One nitrogen of urea is from NH3 and the other nitrogen from aspartate
- Urea is transported in the blood to the kidneys for excretion in urine
- Five enzymes of urea cycle, if one of these enzymes are absent Hyperammonemia will occur:
  - **Carbamoyl phosphate synthetase I**
  - **Ornithine transcarbamoylase (OCT)**
  - **Argininosuccinate synthase**
  - **Argininosuccinate lyase**
  - **Arginase**



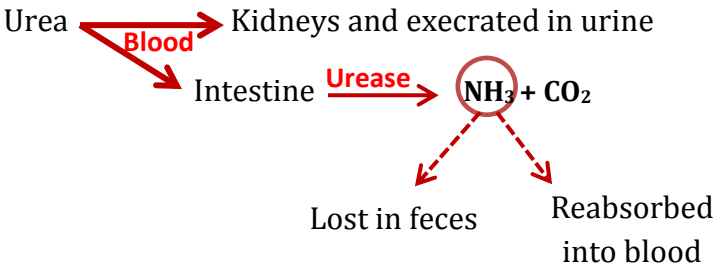
Ammonia provides one nitrogen atom of urea and carbon dioxide with **Carbamoyl phosphate synthetase I** → this will produce ***carbamoyl phosphate*** → ***carbamoyl phosphate*** with ***ornithine*** → will produce ***Citruline*** by **Ornithine transcarbamoylase (OCT)** in the mitocondria → ***Citruline*** goes out of the mitocondria with ***Aspartate*** (which gives one nitrogen atom of urea) by **Argininosuccinate synthase** → ***Argininosuccinate*** is produced → ***Argininosuccinate*** convert to ***Arginine*** by **Argininosuccinate lyase** → ***Arginine*** convert to **Urea** by **Arginase** .

❖ Regulation :



- Rate-limiting enzyme: Carbamoyl phosphate synthetase I
- N-Acetylglutamate: Activator of the enzyme
- **N-Acetylglutamate** → break down by **hydrolase** into →Acetate + Glutamate
- **Glutamate + Acetyl coA = CoA + N-Acetylglutamate by synthetase**
- **The presence of arginine stimulates the last reaction**
- N-Acetylglutamate is co-factor of **Carbamoyl phosphate synthetase I**

❖ Fate of Urea :



- The action of intestinal urease to form NH3 is clinically significant in renal failure:

Renal failure → ↑ Blood urea → ↑ Urea to intestine —Urease→ ↑ NH_3 blood level

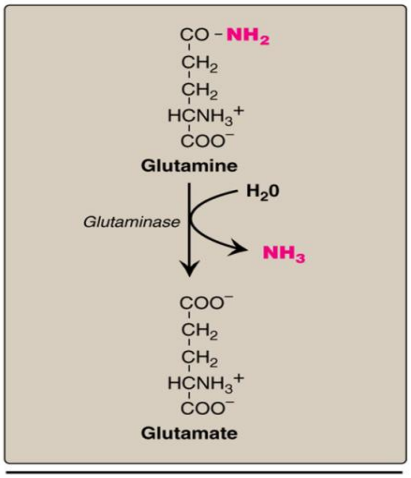
This condition is called (Acquired hyperammonemia)

❖ Sources of Ammonia :

1. Amino acids
2. Glutamine (By renal glutaminase, NH3 excreted in urine as NH4)
3. Bacterial urease in intestine
4. Amines e.g., catecholamines
5. Purines & pyrimidines

*The sources are arranged depending on the majority, so Amino acid is the **major source** of Ammonia.*

❖ Production of Ammonia by Glutaminase :

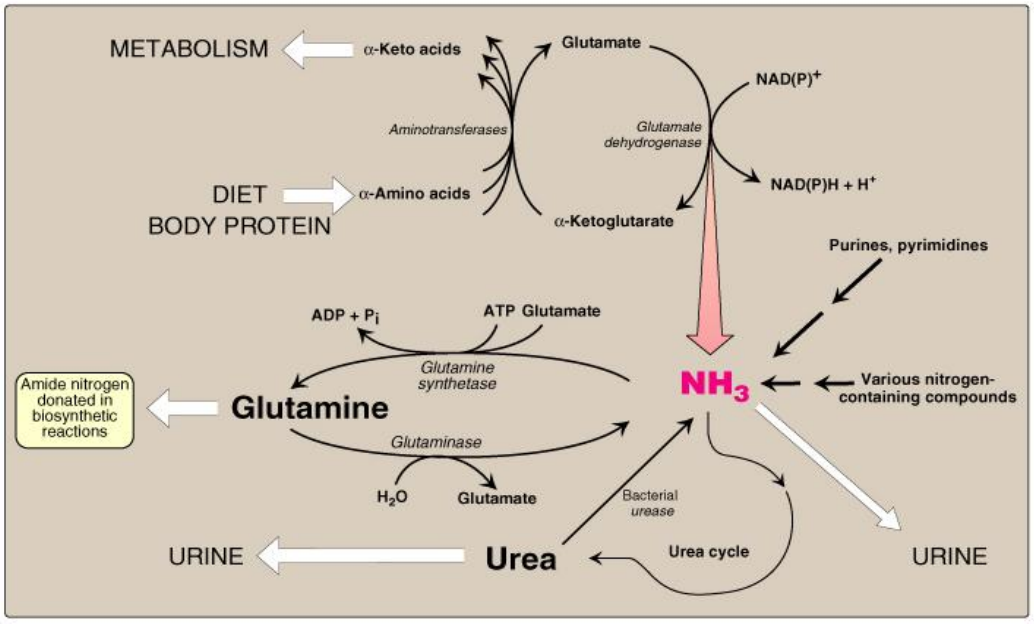


This process is reversible

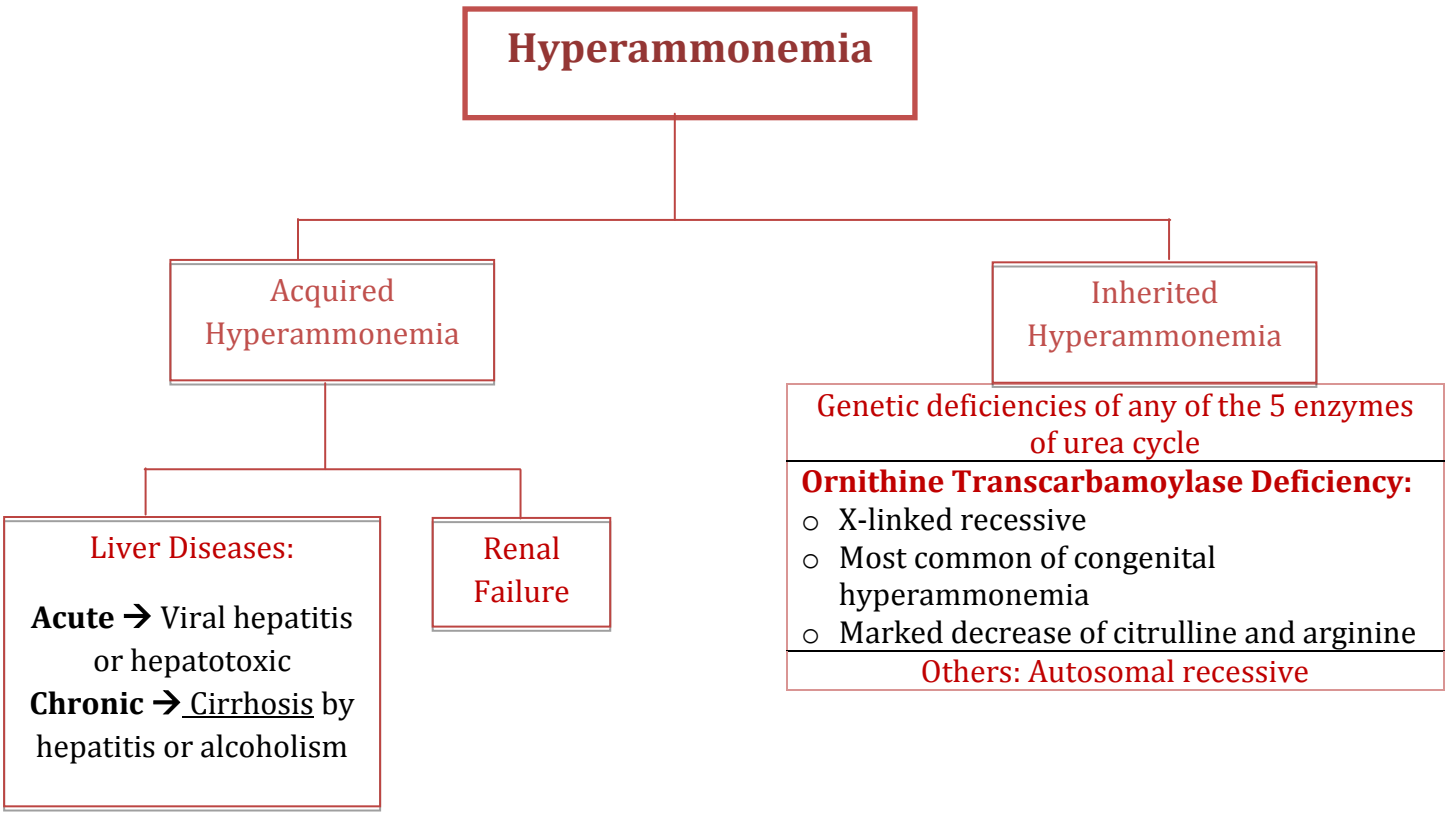
❖ Fates of Ammonia :

- Urea formation by the liver
- Glutamine synthesis in brain (Major mechanism for removal of NH3 in the brain)
- Glutamine is very active in the brain; because like any other tissues in our body, brain tissue can produce ammonia and cause a lot of damages so the mechanism of the removal of the ammonia in the brain will be very fast.

Summary of sources and Fates of Ammonia :



Normal blood level of ammonia: 5 – 50 µmol/L



❖ Clinical Presentation of Hyperammonemia :

- Lethargy and somnolence
- Tremors
- Vomiting and cerebral edema
- Convulsions
- Coma and death