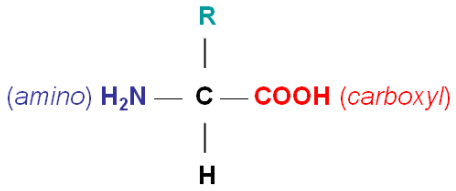
Unit V – Problem 2 – Biochemistry: The Urea Cycle and Ammonia Toxicity

- **Nitrogenous groups:**

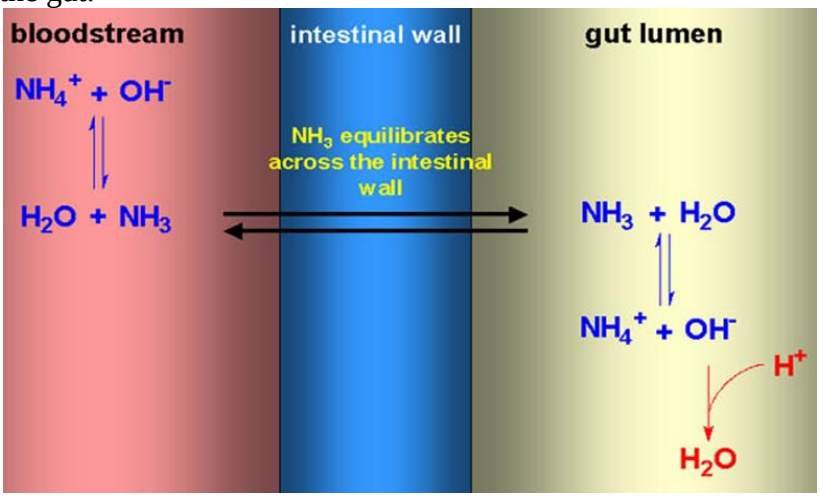
NH	Imino group
NH_2	Amino group
NH_3	Ammonia or azane
NH_4	Ammonium

- **Ammonia (NH_3):**
  - **Characteristics**: highly water-soluble; colorless; irritant gas with a unique pungent odor (رائحة حارقة ولاذعة).
  - **Ammonia reacts with tissue water to produce ammonium hydroxide:**
    - ✓ $NH_3 + H_2O \leftrightarrow NH_4OH \leftrightarrow NH_4^+ + OH^-$
  - **Sources of blood ammonia (notice that normal level = 10-50µmol/L):**
    - ✓ Protein catabolism (breakdown) in the liver.
    - ✓ Skeletal muscles during exercise.
    - ✓ Intestinal bacteria.
  - **Importance of ammonia:**
    - ✓ Intermediary role in metabolism of amino acids and proteins.
    - ✓ Maintenance of acid-base balance:
      - ❖ *Formation increases in metabolic acidosis.*
      - ❖ *Formation decreases in metabolic alkalosis.*
- **Disposal of Amino nitrogen:**
  - **Urea**: it is the major disposal form of amino acids amino groups.
  - **Urea cycle**: a series of reactions distributed between mitochondrial matrix and cytosol consuming 3 ATP equivalents to 4 high-energy nucleotide phosphates. Notice that urea is the only new compound generated by the cycle; all other intermediates and reactants are recycled.
  - **Structure of amino acid:**



  - **Aminotransferase reaction:**
    - ✓ Glutamate + α-ketoacid ↔ α-ketoglutarate + α-amino acid
  - **Glutamate (via glutamate dehydrogenase) can be converted to**: α-ketoglutarate + NH_4^+
  - **Transport of ammonia:**
    - ✓ Glutamate is converted (via glutamine synthase and the use of ATP & NH_4^+) to glutamine.
    - ✓ Notice that glutamine can be converted back to glutamate (via glutaminase) in liver and kidneys.
  - **Urea cycle (details):**
    - ✓ NH_4 is transported into mitochondria and then converted (via carbamoyl phosphate synthase-I and 2 ATPs) to carbamoyl phosphate.
    - ✓ Carbamoyl phosphate is converted (via ornithine transcarbamylase and ornithine) to citrulline.
    - ✓ Citrulline is transported out of the mitochondria to the cytosol where it will be converted (via argininosuccinate synthetase and aspartate) to argininosuccinate.
    - ✓ Argininosuccinate is converted (via argininosuccinate layase) to arginine with formation fumarate.
    - ✓ Arginine is degraded via arginase to produce urea and ornithine (which is recycled).

- **Ammonia toxicity:**
  - ✓ It involves glutamate dehydrogenase and glutamine synthase which decrease α-ketoglutarate and increase the extracellular glutamate.
  - ✓ Depletion of α-ketoglutarate decreases the generation of ATP in the brain.
  - ✓ Glutamate is both an excitatory neurotransmitter and a precursor to the inhibitory neurotransmitter GABA.
  - ✓ <u>Clinical manifestations:</u>
    - ❖ Cerebral edema.
    - ❖ Anorexia and vomiting.
    - ❖ Irritability, lethargy and somnolence.
    - ❖ Slurred speech and blurred vision.
    - ❖ Flapping tremor.
    - ❖ Disorientation and coma.
    - ❖ Death.
  - ✓ <u>Clinical correlates: conditions in which ammonia level offers valuable information</u>
    - ❖ Hepatic failure.
    - ❖ Reye's syndrome: viral infection in a children + aspirin → results in fulminant hepatitis!
    - ❖ Inherited disorders of urea cycle enzymes except argininosuccinate.
    - ❖ Portal-systemic shunt.
  - ✓ <u>How to manage ammonia toxicity?</u>
    - ❖ *High levels in infants*: exchange blood transfusion.
    - ❖ *For less critical cases, the treatment of choice is: synthetic disaccharide lactulose (orally or rectally).*
      - ➢ Principle of treatment with lactulose: NH_3 crosses intestinal wall but NH_4 does not! Fermentation of lactulose to lactate leads to fall in pH, resulting in a shift of the equilibrium further towards NH_4 which cannot cross the intestinal wall. As a result, NH_4 is trapped in gut lumen with net flux of NH_3 from blood to the gut.



    - ❖ *Limiting the amount of protein in diet.*
    - ❖ *Promoting waste nitrogen excretion:*
      - ➢ Sodium benzoate: conjugates with glycine to form hippuric acid which bypasses urea cycle and gets excreted in urine.
      - ➢ Sodium Phenylacetate: conjugates with glutamine to form phenylacetylglutamine which bypasses urea cycle and gets excreted in urine.