Note: study the slides with this sheet **Transport of Ammonia to the liver**Let's start with the fact that Ammonia is very toxic to the human body  
  
In the metabolic pathway of Amino Acids, we deal with amino group by itself then we deal with its Carbon skeleton .   
  
How can we remove the amino group from an Amino Acid ?  
Answer: by two ways.   
A. Transamination :   
For each Amino Acid there's a specific transaminase which removes the amino group from the Amino Acid and gives it to the corresponding Keto Acid for this Amino Acid. Transaminases are only for non-essential Amino Acids, Since essential Amino Acids should be obtained from diets.

Transaminases belong to a class of enzymes called transferases.

Transaminases remove the amino group and move it to a Keto-Acid .

The most common used Keto Acid is α keto gluterate.   
α keto gluterate when it receives the amino group it becomes glutamate.   
So, Transaminases gather to give Glutamate.   
B. Oxidative deamination :  
To remove the Amino group from the Amino Acid and export it as free Ammonia (NH3 ) or Ammonium Ion ( NH4+).

Which Amino Acids release ammonia or ammonium when their amino group is removed?

Actually, all the Amino Acid do ! However, the only Amino Acid which can go rapid reaction in that way is Glutamate.  
  
So, all Amino Acids have their own transaminases, which removes the amino group and places it on an α keto gluterate which in turn becomes glutamate. Amino group is then taken from the glutamate. Now glutamate goes back to being an α keto gluterate. Then α keto gluterate goes back to become a transaminase to get another amino group and so on.

The reactions of the transaminases are reversible and the equilibrium constant is around (1) which means that they can go both ways depending on the concentration.

Glutamate dehydrogenase which removes the amino group from the glutamate behaves the same way, it's reversible, it can give glutamate and it can give α keto gluterate. Also the equilibrium constant for it is around (1).

We use in the forward reaction NAD+ ; we are performing an oxidative deamination ( Oxidation reaction will extract electrons ) .

Electrons will be carried on NAD+ to give NADH.

The reverse reaction doesn't use NAD+, instead it uses NADPH. We will take the electrons because it's a reduction reaction (reductive amination).

so, we have removed the amino group from glutamate! what's gonna happen next ?!

Free Ammonia or Ammonium can't be transported directly through blood, they're very toxic.

Actually, the ammonia becomes Urea. but wait Urea is made in the liver !!  
so how to send it there?!

Fact: Amino Acids are metabolized by all body cells.

Now : how to transport the ammonia through blood to the liver?

There's 2 ways :

A. we'll convert the Glutamate to Glutamine by replacing the O- with NH3 in glutamate by an enzyme called glutamine synthetase which is found in most tissues. Glutamine is an Amino Acid, and it can be transported through blood easily and safely to the liver.

In the liver we have an enzyme called glutaminase ( also found in intestines and kidneys ). Glutaminase breaks off the amino group from the glutamine and converts it back to glutamate.

In this way, we were able to transport ammonia safely to the liver.

B. The other way to transfer Ammonia through blood is through the Glucose-Alanine Cycle.   
The corresponding Keto-Acid of Alanine is Pyruvate (so Pyruvate + Amino group = Alanine ) . This cycle happens in the muscles as pyruvate comes from Glucose through glycolysis . There's a transamination reaction for Pyruvate by an enzyme called Alanine transaminase, As the name implies it converts Pyruvate to Alanine . Now it can be safe to transport Ammonia to the liver through Alanine . Another tranamination reaction happens in the liver that converts the Alanine to Pyruvate.

Pyruvate can through gluconeogenesis in the liver to give glucose . Then glucose can go back to the muscles to give later pyruvate.

Now Ammonia is in the Liver. How is it processed in the liver ??

Urea Cycle occurs exclusively in the liver. The safest way to deal with Nitrogen compounds is to convert it to urea.

Urea is relatively non-toxic, and hence could be dealt with and excreted.

Urea Cycle:

Cycle means (a metabolic pathway where the first material that you started with gets regenerated at the end of the loop through a series of reactions), urea cycle is needed to convert toxic compounds to non-toxic compounds. It takes place in the liver. WHY? Certain needed enzymes are only present there.

Unlike humans, fish are able to deal with ammonia. This is because fish live in water which has a high surface area and hence ammonia is diluted and is no longer extremely toxic.

Do we need energy for Urea Cycle?   
Yes, energy is needed for the FIRST step that combines before getting into the cell.

First reaction of the cycle; free Ammonia or Ammonium Ion which was derived from Oxidative deamination Glutamate combines with ( CO2) from the tissues or Bi-Carbonate buffer to give Carbamoyl phosphate, for this reaction to take place, 2 molecules Of ATP will be degraded to 2 molecules of ADP, we have used two high energy molecules to drive the reaction because we want to combine materials together.

One of the phosphates will be ligated to the compound which is carbamoyl phosphate. The other phosphate is free.   
So why did we use 2 ATPs?

Answer : To get more Energy .

This reaction is catalyzed by an enzyme called Carbamoyl phosphate synthetase I (Found in the Mitochondria). And this is the rate limiting step for the urea cycle ( rate limiting step : Slowest step in any pathway).

Now we have Carbamoyl Phosphate (CO2 + NH3) which is united in the 2nd step an amino acid called Ornithine to give Citrulline .  
Citrulline is another basic amino acid like Ornithine .  
Ornithine is not involved in making proteins.

The enzyme of the reaction here is called Ornithine Carbamoyl Transferase .

Step#1 + Step#2 occurs in the Mitochondria

Now, Citrulline exits the Mitochondria and unites with Aspartate to give a compound named Arginosuccinate, the enzyme of the reaction here is Arginosuccinate synthase .

Arginosuccinate will get broken down and will degrade to give Fumarate out the cycle and arginine inside the cycle.

Arginine is the source of urea through Arginase enzyme( Arginase is found exclusively in the liver ), Actually it's the reason that urea cycle takes place only in the liver.

Arginine structure is Ornithine + Urea.

N- acetylglutamate works as a positive allosteric activator for the Carbamoyl Phosphate synthetase I .

N-acetylglutamate synthetase make the N-acetylglutamate. ( Arginine ) works as a positive regulator for N-acetylglutamate synthetase, and makes the reaction goes faster. This is related to the fed state.

Urea has a carbonyl group and two Amino groups .

The immediate source of both Amino groups is Glutamate(from oxidative deamination).

The source of the carbon in Carbonyl is CO2 from body tissues.

Now when Aspartate combines with citrulline, 1 ATP Molecule is consumed and degraded into AMP + Pyrophosphate (P2O74− ).

Pyrophosphate is further degraded to give more energy.

How many high energy bonds were used in the cycle ?   
Answer: 4 Bonds.

How many ATPs ?   
Answer : 3 ATPs

Urea Moves from liver through blood to the kidneys, but because it is moving through the blood, a small portion of urea will reach the intestines and some amount of it will be infiltrated by the vascular system of the intestines.  
There's an enzyme in the intestines called bacterial urease which can break down urea back to Ammonia.

This enzyme is only active in bacteria not humans.

The small amount of urea leakage to the intestines isn't a problem to a healthy body. But it can be a serious problem to people with kidney failure/problems. Those people are given antibiotics to reduce the amounts of ammonia produced by the bacteria there.

Remember: rate limiting step is Carbamoyl Phosphate synthetase I.   
we control this step by N- acetylglutamate which is synthesized by N-acetylglutamate synthetase and Arginine works as an activator for this enzyme.

Hyperammonemia is very toxic especially to the CNS (Central Nervous System).

Hyperammonemia is expected in people having kidney failure because we have bacteria urease in the intestines.

Hyperammonemia can be fixed by dialysis (immediate treatment).

Long term treatment is to decrease the content of protein in the diet.

Problems occurring in the urea cycle are either acquired or heredities.

Acquired- Anything affecting the liver usually affects the urea cycle

Examples: Hepatitis (acute (A) or chronic B or C), cirrhosis, alcoholism which may lead to fatty liver and cirrhosis.

Heredity- problem lies within the enzymes that catalyze the cycle.

