

UNDERSTANDING UREA CYCLE DISORDERS

What is a urea cycle disorder?

A urea cycle disorder is a genetic disease that affects how protein is broken down in the body. It is therefore classified as a **metabolic disorder**. There are six different urea cycle enzymes in the body, and therefore six different urea cycle disorders:

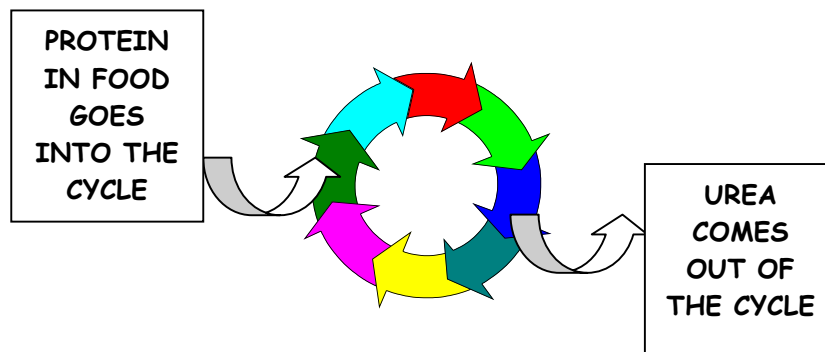
- CPS (carbamylphosphate) deficiency
- AL (argininosuccinic acid lyase) deficiency
- AS (argininosuccinic acid synthetase) deficiency
- Arginase deficiency
- OTC (ornithine transcarbamylase) deficiency
- NAGS (N-Acetylglutamate Synthetase) deficiency

The name of the disorder indicates the **enzyme** that is missing. Enzymes can best be described as keys that unlock doors in the body. When the enzyme is missing or not working properly, the waste products build up.

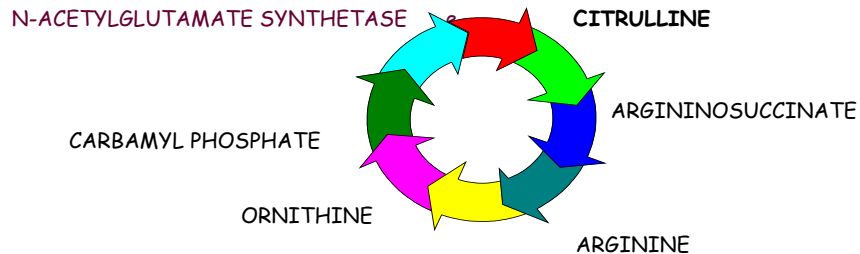


What is the Urea Cycle?

The urea cycle is a series of steps that uses all of the above enzymes to change excess protein into a safe waste product that can be eliminated in urine. This waste product is called **urea**.



How does the Urea Cycle work?



Everyone needs protein, found in meats, dairy products, fish, eggs, nuts and other foods. The body uses protein to build new tissue and to repair damaged tissue. When someone eats food that contains protein, the body uses what it needs by breaking it down into **amino acids** (the building blocks of protein) and changes the rest into ammonia. Amino acids are used by the body to build skin, muscle, blood and other tissues. **Ammonia** is a waste product that must be removed from the body. The urea cycle gets rid of the ammonia that results from the protein breakdown. The urea cycle changes the ammonia into urea, which the body can easily and safely eliminate in urine. The urea cycle also makes **arginine**, an amino acid that the body must have to make new proteins for tissue growth and repair. The urea cycle occurs in **liver cells**.

People with urea cycle disorders have a "block" in their urea cycle. They are missing an enzyme critical for protein breakdown.



This can be compared to construction on a highway. Ammonia waste is like traffic that usually travels along at a steady rate and gets eliminated out of the body. People with urea cycle disorders have a "road block".

The ammonia either cannot get around the block or gets around very slowly and builds up in the blood, depending on the amount of enzyme present. Some people with urea cycle conditions make no working enzyme while others may make a small amount. In other words, some people have a complete "road



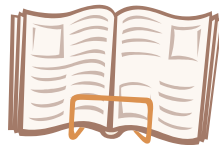
block" while others may be able to move the ammonia through on one lane or on the shoulder.



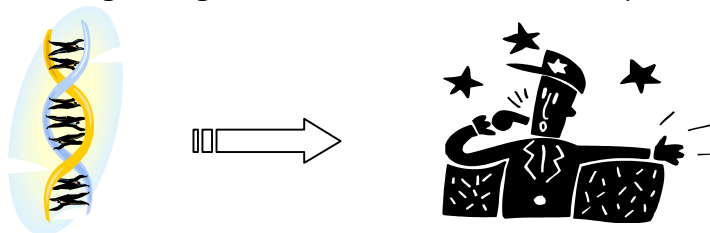
If ammonia builds up, it is like poison in the body. A person with too much ammonia in the blood may not have an appetite, feel confused, not think clearly, sleep more than usual, or vomit. If the extra ammonia is not removed quickly, the person may have seizures or may go into a coma.

How do people get urea cycle disorders?

Urea cycle disorders are genetic. This means that the person has the disorder from the time they are conceived. At conception, a baby receives two sets of genetic material, one from the mother and one from the father. This genetic material, called **DNA**, acts as a recipe for the baby's development.



DNA includes information about the baby's eye and hair colour, sex, and even whether the baby will be right or left-handed. DNA comes in units called **genes**. Each pair of genes gives directions to a certain part of the body.



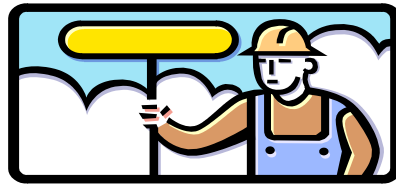
Genes also give instructions on how the body breaks down protein. If the gene gives the wrong instructions, protein will not be broken down properly in the body.

The first four urea cycle disorders on the list above are caused by getting **two copies** of the faulty gene, one from the mother and one from the father. If the child inherits only one copy of the gene, they are a **carrier**

for that gene but are not affected by the disease because they make enough enzyme to stay healthy.

There is a 1 in 4, or 25% chance, that if both parents are carriers of the gene, they will have a baby with a urea cycle disorder. These four urea cycle disorders affect boys and girls equally.

OTC deficiency, the most common urea cycle disorder, is a bit different. It is passed to the baby through the DNA of its mother. Both baby girls and baby boys can inherit this genetic material, but girls can be less vulnerable to the effects of the gene. Most boys and some girls with OTC deficiency have little or no working enzyme and have significant problems due to high ammonia levels. Some girls or women don't even know that they carry the gene for OTC until their bodies are under a lot of stress as in pregnancy, childbirth or menopause. Back to the construction comparison, being a carrier of the OTC deficiency gene is like traffic moving slowly around the roadblock. The enzyme to break down protein is being produced, but only in very small quantities. Traffic is inching along.



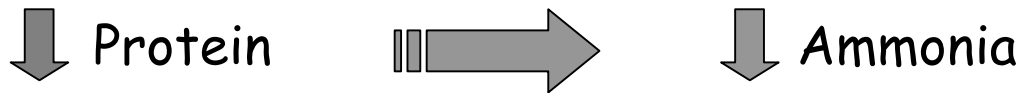
When the woman is pregnant, giving birth or going through menopause, the body is stressed and there can be a complete "road block". Ammonia levels rise and the woman may experience seizures, confusion or coma. These women and their female relatives may have a history of miscarriages and losing baby boys in infancy. This is due to the fact that the baby boys with OTC deficiency are fully affected by the urea cycle disorder and often do not survive.

How are Urea Cycle disorders treated?

DIET



Knowing how the urea cycle works will help you to understand the treatment better. The first part of treatment is **reducing protein in the diet**. If less protein is taken in, there is less ammonia for the urea cycle to remove.



Protein in the diet is lowered by avoiding protein-rich foods like meat and milk. Examples of low protein foods are fruits, vegetables and starches. These foods provide calories without loading the body with protein.

Calories are a very important part of the diet. The body can use them for fuel without breaking down its own reserves. If the body does not have adequate fuel in the form of calories, it will actually begin to break down muscle to provide energy. Muscle is protein and will increase ammonia levels in the same way as eating protein will.

The metabolic dietitian works with people with urea cycle disorders to make adjustments to diet. This ensures that adequate calories and nutrients are being provided. People with OTC are often asked to keep a record of what they eat on a daily basis for the dietitian to review. If people with OTC deficiency are not able to safely eat enough protein to meet their bodies' needs, a special medical formula can be prescribed.



MEDICATIONS

Some people with urea cycle disorders need to take medication to help rid their bodies of excess ammonia. **Sodium benzoate** and **sodium phenylbutyrate** are oral medications that bind to ammonia and carry it out of the body in the urine.



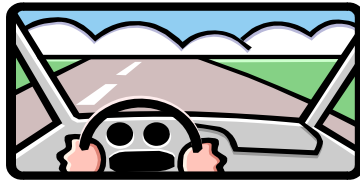
AMINO ACIDS

The third part of treatment is supplementing the diet with the amino acid **arginine** or **citrulline**, depending on the type of urea cycle disorder. Before

treatment, people with urea cycle disorders cannot make arginine. It must be added to their diets so their bodies can have what is needed to make proteins that are important for growth and tissue repair. People with CPS or OTC deficiency are usually given the amino acid citrulline instead of arginine, since they are able to make arginine from citrulline and remove more ammonia from their blood at the same time. People with AS, AL or arginine deficiency take arginine because the blocks in these conditions prevent them from using citrulline to make arginine.



Back to the construction comparison, the diet low in protein keeps the ammonia levels in the blood down. Ammonia, like traffic, flows along nicely and is eliminated from the body. The driver is not confused or disorientated by high levels of ammonia.



The medications and arginine or citrulline supplementation provide a detour around the roadblock. They form an alternative way for the body to get rid of ammonia.



There are therefore four basic parts to treatment of urea cycle disorders:

- reducing protein in the diet
- maintaining adequate calories
- using medication to remove excess ammonia from the blood
- adding arginine or citrulline to help the body make protein

The balancing act

The challenge in treating urea cycle disorders is to provide enough protein to meet body requirements without overloading the person with protein waste. Visits to the metabolic clinic are needed to consult with the team and make

adjustments to food and medication. Regular blood work is necessary to monitor changes in blood levels of ammonia and other nutritional indicators.

The delicate balance can be upset by strenuous exercise and illness. Both can cause the ammonia levels to rise. Extra calories are needed at these times to provide the stressed body with fuel.

What is a "normal" ammonia level?

A normal ammonia level is between 9 and 33 $\mu\text{mol/L}$. This is measured by a blood test.



How can friends and family help?

Learn to recognize the signs of trouble. If you know the person well, you will be the first to notice changes in behavior that suggest the ammonia levels are too high. For example, the person may become irritable, less active and sleep more than usual. Encourage the person to call the clinic. A **plasma ammonia** level needs to be drawn.

Very high levels of ammonia in the blood occur rarely, but may cause other problems like:

- confusion
- vomiting
- increased sweating
- laboured breathing
- loss of consciousness
- seizures

If your friend or family member show any of the signs or symptoms of high ammonia levels or **hyperammonemia**, take them to the emergency room immediately. The person with the urea cycle disorder has a yellow wallet card with emergency room instructions and phone numbers.

Other treatments

1. Gene therapy for urea cycle disorders is currently under investigation. Since genes are proteins, they cannot be swallowed in a pill form because the acids in the stomach will destroy them. The missing gene is therefore injected into the body disguised in a virus. It enters the bloodstream and produces enzyme in the liver for a short period of time.
2. Because urea is mostly made in the liver, it is possible to treat urea cycle disorders by doing a liver transplant. There are numerous risks to liver transplants and this decision must be made with careful consideration of the pros and cons.

Helpful resources

National Urea Cycle Disorders Foundation
4841 Hill Street
La Canada, CA 91011
1-800-38NUCDF
www.nucdf.org/
