



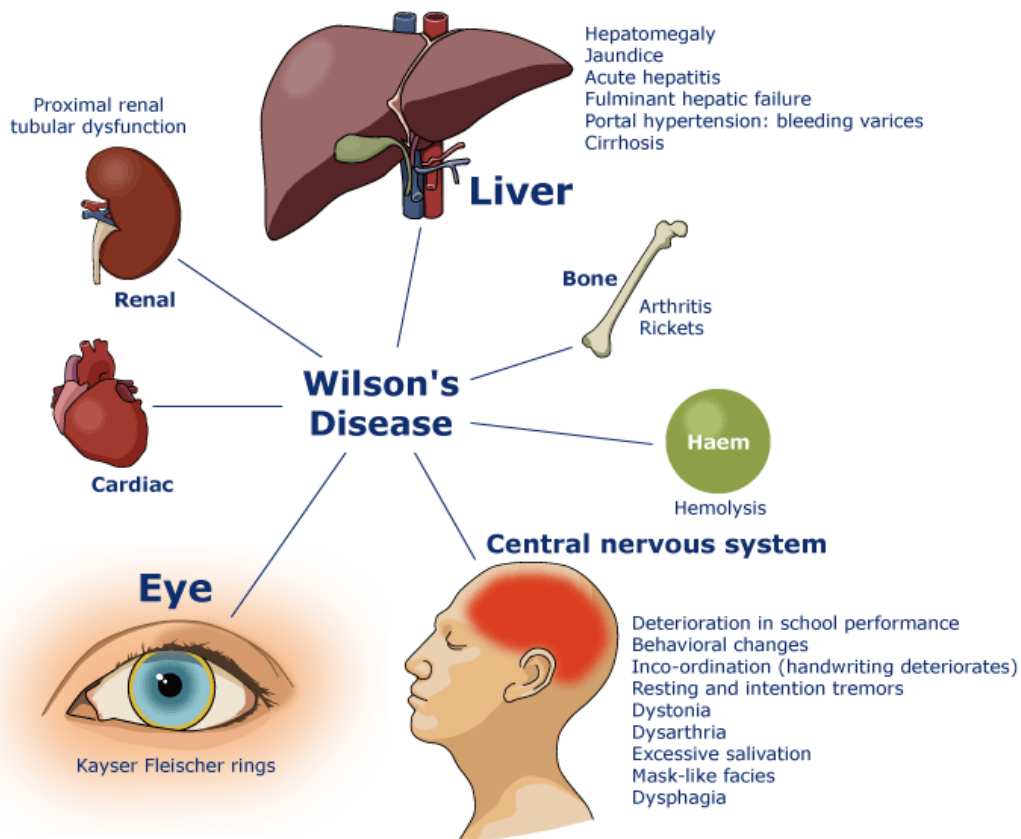
## **Wilson's disease for patients and families**



## What is Wilson's disease ?

Wilson's disease is an inherited condition in which copper is not excreted properly from the body. The excess copper can build up in the liver and/or brain causing liver damage and/or neurological problems. It can also collect in other parts of the body including the eyes and the kidneys.

Copper begins to accumulate immediately after birth but the symptoms usually appear in the 2nd to 3rd decade. The first signs are hepatic (liver) in about 40% of cases, neurological (brain) in about 35% of cases and psychiatric, renal (kidney), haematological (blood), or endocrine (glands) in the remainder.





## What are the signs and symptoms of Wilson's disease?

In some cases these can be very mild, everyday symptoms such as tiredness, loss of appetite, abdominal pain, vomiting, weight loss, nose bleeds and anaemia. These symptoms may come and go over a period of months or even years, or they may be more persistent. Some patients also experience kidney problems, i.e. tubular dysfunction, which generally causes no symptoms, and joint problems, which are very rare. In other cases the symptoms may be more acute, especially when the liver is involved.

Liver disease can be broadly subdivided into:

- acute liver disease due to copper overload. In this case the patient is likely to be severely ill and yellow. A liver transplantation may be necessary if treatment does not quickly result in improvement
- acute hepatitis: this is more or less the same as acute liver disease
- chronic liver disease: slow scarring of the liver due to copper overload, which will ultimately also result in severe damage to the liver.

Some of the kinds of neurological problems can include:

- deterioration in school performance or handwriting
- mild tremors
- dystonia: this is a type of cramping or stiffening of the muscles. Often this begins with muscle cramps in the arms or legs, and as the disease progresses, it may result into pulling parts of the body more or less permanently into abnormal postures
- ataxia: loss of the ability to coordinate muscular movement
- muscular rigidity
- dysarthria: this is the medical term for speech abnormality. The dysarthria in Wilson's disease can take many forms, including slurring, low volume, a repetitive aspect in trying to pronounce certain words, and can progress to complete inability to speak (anarthria).

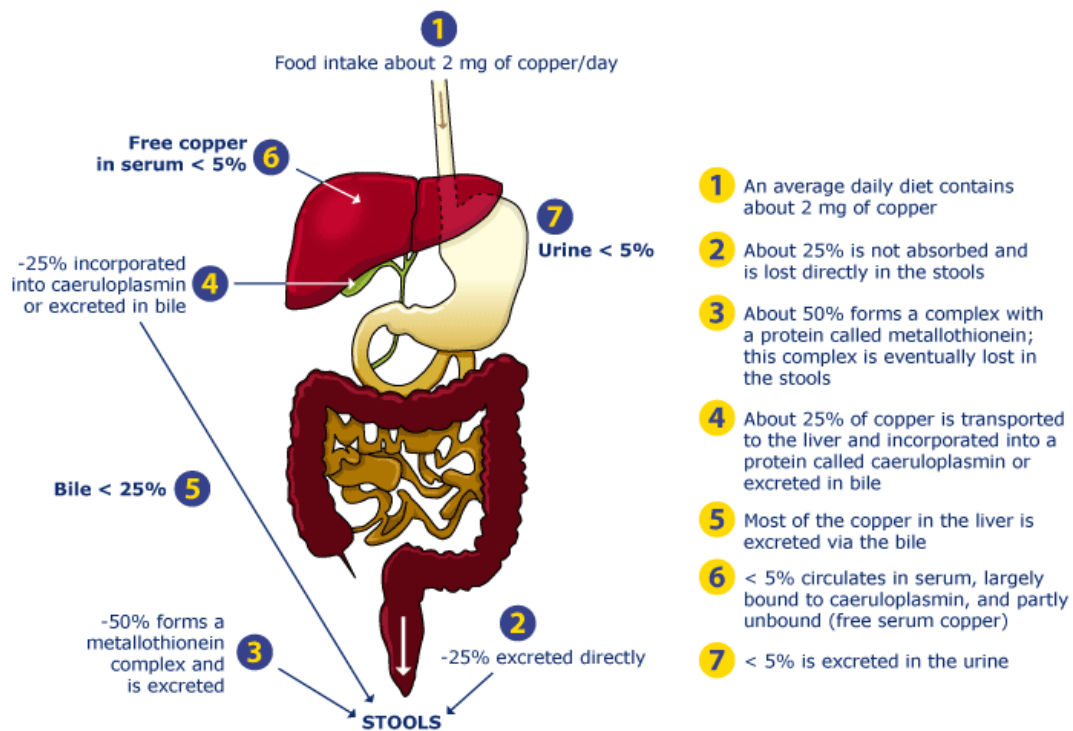
About one third of patients initially present with psychiatric abnormalities, including depression, personality and mood changes.



## Metabolic pathway of copper?

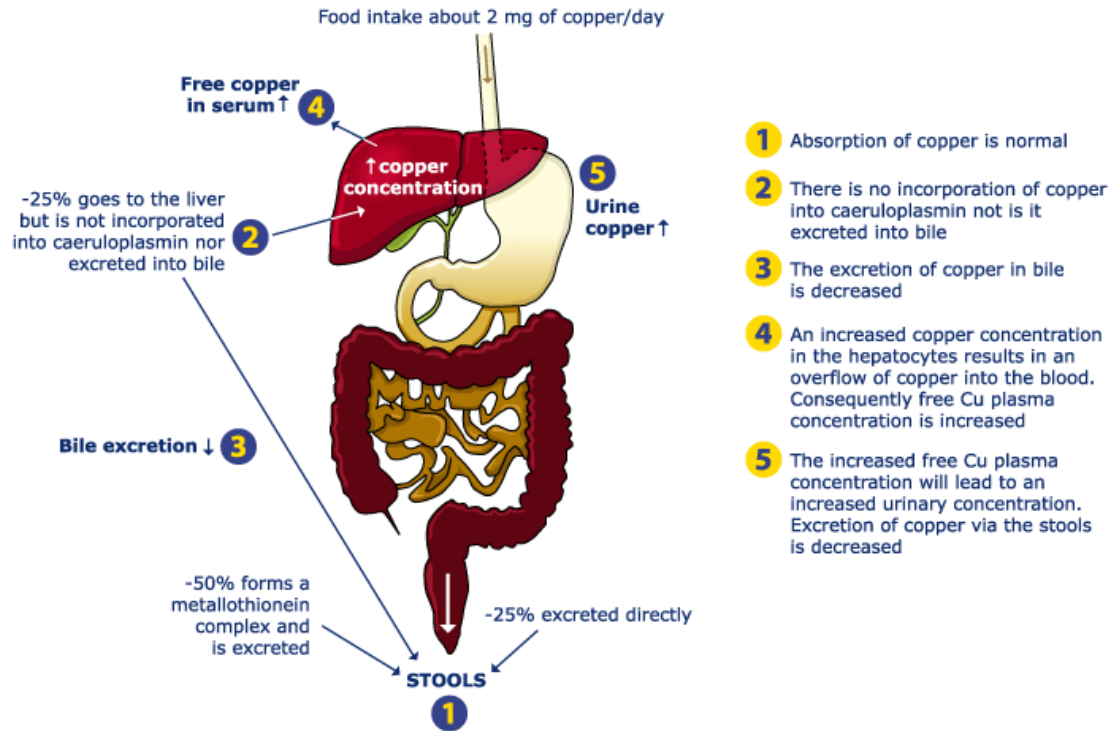
Copper is present in most foods and is necessary for normal growth and development. Diagrams I-IV show the way copper is metabolized in healthy subjects, and in people with Wilson's disease (without treatment and with treatment).

**Diagram I: healthy subjects: intake and excretion is well balanced**

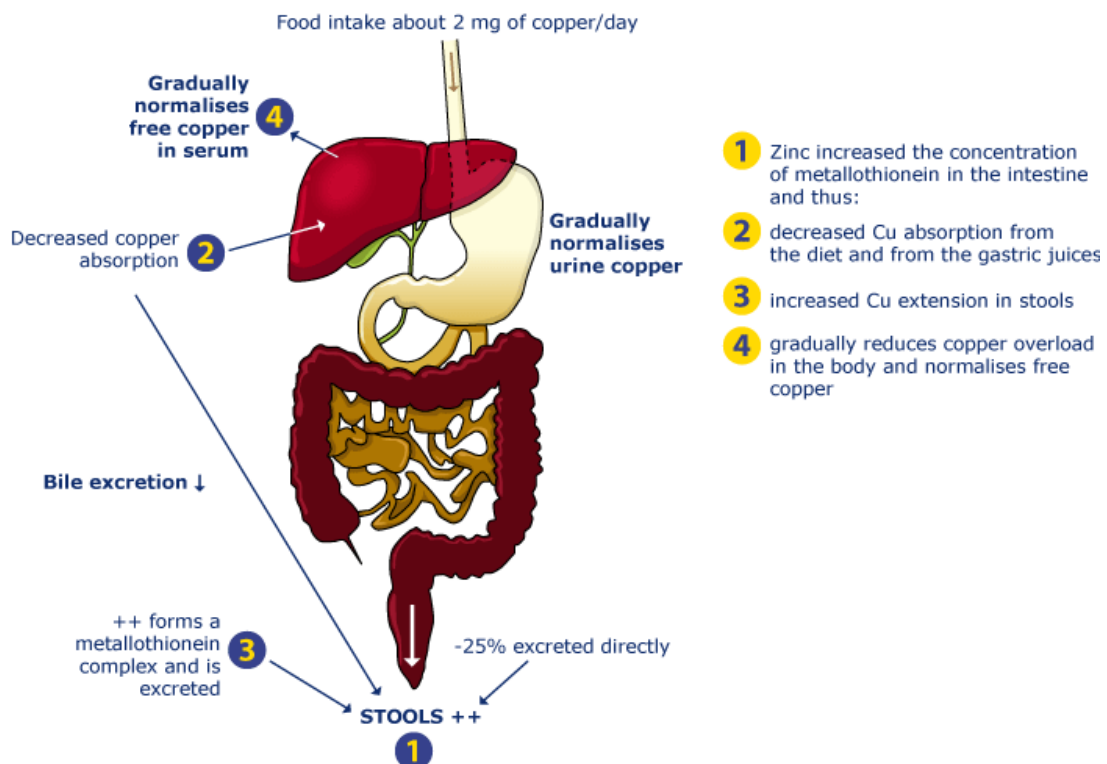




## Diagram II: Wilson's disease patients before treatment: reduced excretion and retention of copper

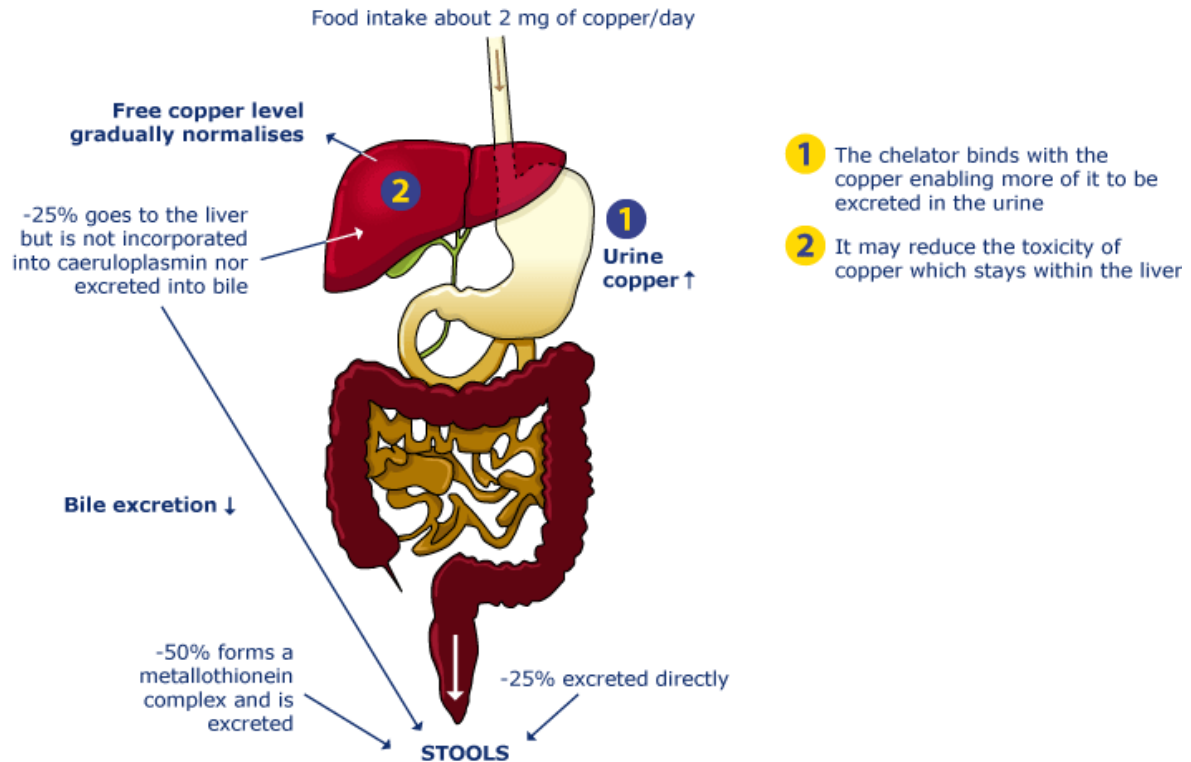


## Diagram III: Wilson's disease patients on zinc therapy: enhanced faecal excretion of copper





### Diagram IV: Wilson's disease patients on chelator therapy: enhanced urinary excretion of copper



### How have I or my child got this condition?

Wilson's disease is a genetic disorder. This means that it is not brought about by anything that may have occurred during pregnancy, neither is it an infectious or contagious disease. Genetic disorders are inherited and the pattern in which you or your child may have developed the condition will now be described.

Every person carries more than 30000 genes, amongst which there is an estimated defect in approximately seven genes. If by accident you and your partner both carry the same genetic defect (in this case for Wilson's disease), with each pregnancy, there is a one in four chance that your baby will be born with Wilson's disease. If the gene is inherited from both mum and dad, like in Wilson's disease, it is described as being "autosomal recessive".

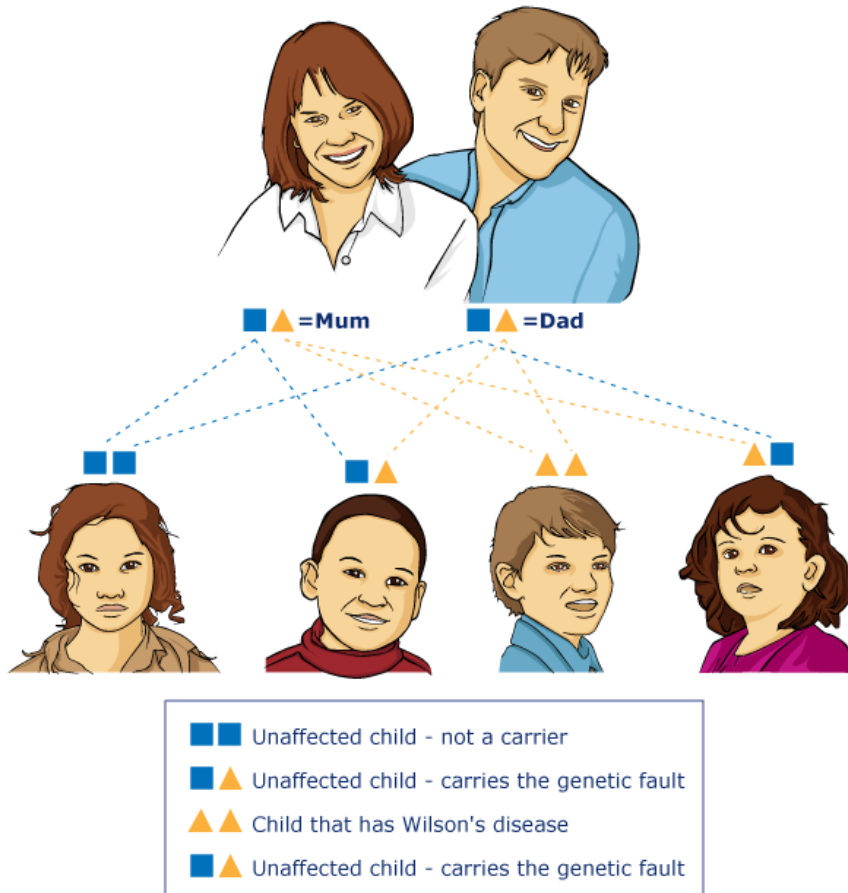
The risk of being affected is the same for both girls and boys. The frequency of Wilson's disease is very low: 1 out of 30000 to 50000 births.



## How does this occur?

Diagram V shows you how this happens.

Diagram V



In this diagram both mum and dad carry the same genetic defect (orange triangle). Each time that mum gets pregnant, there is a one in four chance that the child will inherit the genetic defect from both parents and will be born with Wilson's disease.

## Diagnostic tests for Wilson's disease

The diagnosis of Wilson's disease is made by relatively simple tests. These tests can diagnose the disease in both symptomatic patients and people who show no signs of the disease "pre-symptomatic"

The copper accumulation in the eye in Wilson's disease may cause a diagnostic golden-brown ring to form around the edge of the iris, called a Kayser-Fleischer ring. This ring is only visible using a special instrument (slit-lamp) and is rarely present before the age of 10 years.

Listed below are the standard laboratory tests used to diagnose Wilson's disease:

- Urine copper is high; this should be measured in a 24 hour urine collection.
- "Caeruloplasmin", a copper-containing protein in blood plasma is usually low.
- The copper concentration measured in a liver biopsy specimen will be high.
- The cerebral imaging (MRI) may be abnormal.
- In cases which are difficult to diagnose, copper isotope studies (more complex copper tests) may be performed.

| Parameter              | Normal                              | Wilson's   |
|------------------------|-------------------------------------|--|
| Plasma caeruloplasmin  | >200 mg/l                           | <200 mg/l  |
| Urine Cu               | <0.6 $\mu\text{mol}/24\text{ h}$    | >1.6 $\mu\text{mol}/24\text{ h}$   |
| Hepatic copper         | < 250 $\mu\text{g}/\text{g}$ dry wt | > 250 $\mu\text{g}/\text{g}$ dry wt  |
| Kayser-Fleischer rings | Absent                              | Present in neurological cases,<br><b>but may be absent in younger children</b> |
| Cerebral imaging (MRI) | Normal                              | May be abnormal  |

## What is the treatment?

With proper drug therapy, disease progression can generally be halted, and usually symptoms can even be improved. The treatment goal is to first remove the copper which has accumulated in the body, and then prevent its re-accumulation. Therapy must be life-long.

Treatment should be adapted to the clinical stage of the disease (pre-symptomatic stage, hepatic presentation, neurological presentation, maintenance therapy, and pregnancy). Patients should consult with their physician to see which drug is most appropriate.

## Treatment compliance

The expression "good compliance" describes the fact that the medical prescription is respected, whether it is a medical treatment, taken in correct doses and regularly, or other prescriptions such as a diet, or respecting an appointment with the doctor. "Poor compliance" describes medical prescriptions that are not respected and medical treatment that is not taken regularly.

Treatment for Wilson's disease is a life-long therapy. The effectiveness and side effects of treatment will be monitored at regular hospital follow-up visits which include blood and urine tests. If taken correctly and continuously (good compliance) treatment is very effective. If doses are missed regularly or treatment stopped for a period of time (poor compliance), the liver and/or brain may be permanently damaged before any problems are noticed.

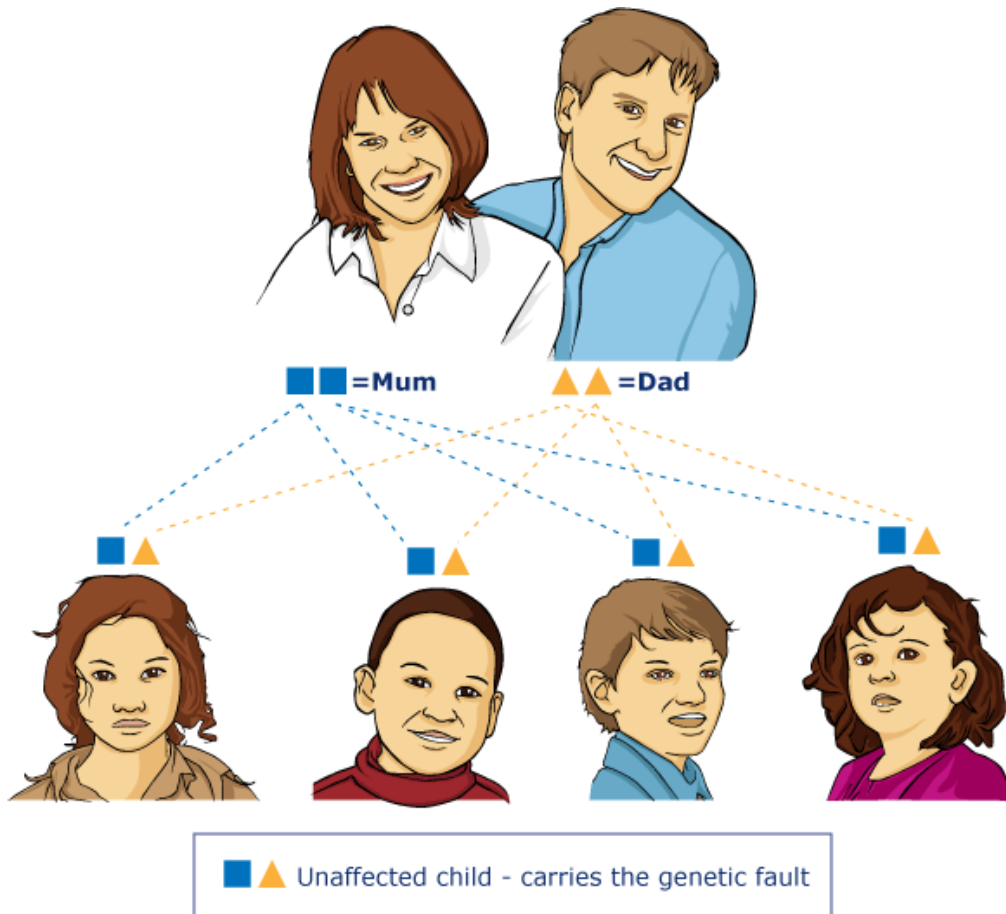




## Pregnancy

Treatment must be continued throughout pregnancy, because of the risk of fulminant liver failure if it is stopped. Many successful pregnancies have occurred in women treated with anti-copper drugs. Infants of Wilson's disease mothers present no particular problems. Assuming that there is no parental consanguinity, the risk that the baby has Wilson's disease is approximately 1:200; though all will be obligate heterozygotes (i.e. will carry the genetic fault see diagrams VI-VII). Breast feeding is not contraindicated.

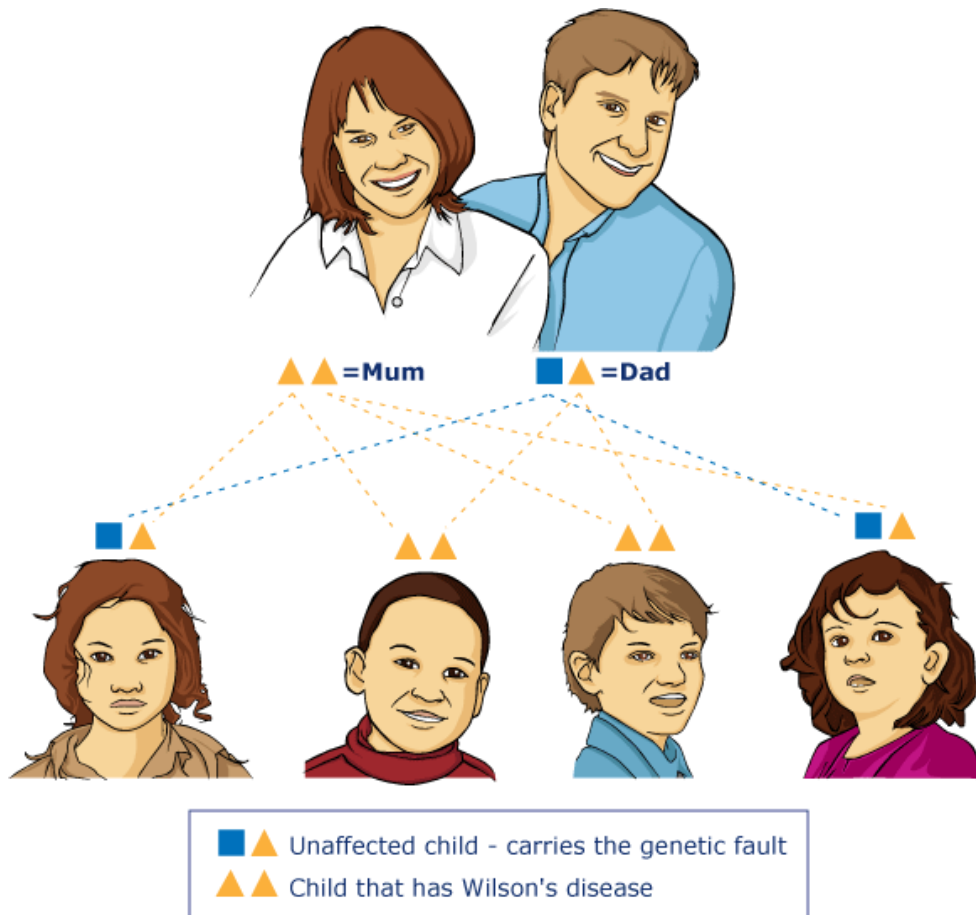
Diagram VI



In this example dad has Wilson's disease (2 orange triangles). Each baby will be an obligate heterozygote. That is to say the child will be unaffected but carry the genetic fault (one orange triangle and one blue square).

This is just an example; it would also have been the same outcome if mum had Wilson's disease and dad did not.

Diagram VII



In this example mum has Wilson's disease (2 orange triangles) and dad is an unaffected carrier of the genetic fault. In this example there is a 50% probability that the baby will inherit Wilson's disease.

### Is carrier detection available?

If you have Wilson's disease, it is very difficult at present to reliably determine whether your partner is a carrier (diagram VII), for which the risk is low, approximately 1:100, or not (diagram VI). However, as this distinction generally cannot be made, it may be advisable to screen your child for Wilson's disease, although the chance that this has actually happened is low, i.e. around 1:200 (50% of 1:100). As the copper build-up is slow, reliable biochemical screening can only be done, when your child is a few years of age. Repeating this examination might also be necessary, sometimes more than once, as it may be difficult to make a final distinction between carriers (i.e. non-affected) and patients.



## Glossary of terms used

|                                |   |
|--------------------------------|---|
| <b>Anaemia</b>                 | A deficiency of red blood cells   |
| <b>Bile</b>                    | A fluid that is secreted by the liver, stored in the gallbladder, and discharged into the duodenum and aids in the emulsification, digestion, and absorption of fats  |
| <b>Biochemical</b>             | The study of the chemical substances and vital processes occurring in living organisms  |
| <b>Caeruloplasmin</b>          | A copper containing blood protein synthesized by the liver and released into the blood. The normal caeruloplasmin level is 20-35 mg/100 ml of blood. Wilson's disease patients often exhibit low levels of serum caeruloplasmin.                |
| <b>Cerebral imaging or MRI</b> | This is a noninvasive technique of magnetique resonance imagingto detect cerebral abnormalities   |
| <b>Cirrhosis</b>               | A chronic disease of the liver characterized by the replacement of normal tissue with fibrous tissue and the loss of functional liver cells   |
| <b>Consanguinity</b>           | Relationship by blood or by a common ancestor   |
| <b>Copper</b>                  | Copper is a metallic element which is a necessary nutrient for normal growth and development. An average diet provides about 2mg of copper per day. The body only requires some of this copper and the excess must be eliminated from the body. |
| <b>Chelator</b>                | Chelators are effective anti-copper drugs. They reduce the body's level of copper by increasing the amount of copper excreted in the urine. Trientine and penicillamine are chelators   |
| <b>DNA</b>                     | A nucleic acid consisting of large molecules shaped like a double helix; associated with the transmission of genetic information  |
| <b>Genes</b>                   | These are sections of DNA that are carried on the chromosomes and determine specific human characteristics, such as height or hair colour   |
| <b>Hepatomegaly</b>            | Abnormal enlargement of the liver   |
| <b>Fulminant</b>               | Occurring suddenly, rapidly, and with great severity or intensity   |

**Jaundice**

This is a yellow colour of the whites of the eyes due to a yellow pigment called bilirubin. Normally the liver clears bilirubin away from the bloodstream. If the liver is not working perfectly, the yellow bilirubin may stay in the blood.

**Kayser-Fleischer rings**

Copper accumulation in the eye may cause a golden-brown ring to form around the edge of the iris. This ring is only visible using a special instrument (slit-lamp) and is rarely present before the age of 10 years.

**Liver Biopsy**

Liver biopsy is a medical procedure performed in order to obtain a small sample of the liver. This is accomplished with a special needle, and does not leave a scar.

**Maintenance therapy**

Lifelong therapy with anti-copper drugs to prevent the reaccumulation of copper and copper toxicity. This phase of therapy occurs in patients who present with symptoms after copper toxicity has been brought under control by initial therapy. In presymptomatic patients, maintenance therapy begins when therapy is started. During maintenance therapy, monitoring for the long-term compliance with anticopper medications is necessary.

**Metallothionein**

A metal binding protein found in most tissues. When it binds to copper, metallothionein renders the copper non-toxic.

**Pre-symptomatic**

The disease has been diagnosed, but no symptoms have manifested

**Zinc**

An effective anti-copper treatment. Zinc acts by stimulating the production of metallothionein in intestinal cells. This metallothionein binds to the copper from foods and from gastrointestinal track secretions and therefore prevents its absorption into the body.

If you have any queries regarding your treatment or any other aspect of Wilson's disease please contact your doctor.



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[www.eurowilson.org](http://www.eurowilson.org)