Alkaptonuria
a rare genetic disease
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www.alkaptonuria.info

The Alkaptonuria Society would like to thank the many people who
have provided the information and stories included in this brochure.
What is Alkaptonuria?

Alkaptonuria is a debilitating and rare genetic disease that affects the cartilage and bone, slowly destroying them. Adults with the disease often have to undergo major surgery, hip, shoulder and joint replacements, and suffer from heart disease, kidney illnesses, and many other problems.

Because Alkaptonuria is so rare, it is unknown to the general public and poorly understood by many doctors. It is what is known as an orphan disease – orphaned from society, orphaned from the medical profession, and orphaned from government. Sufferers are on their own: isolated from support networks, ignored by society, and overlooked by the medical establishment.

The Alkaptonuria Society was set up to tackle these problems. It aims to raise awareness about Alkaptonuria among patients, their families, the public, and the medical profession, and to fund research to help find a cure to this serious and rare disease.

‘One of the worst things about this disease is not knowing what is causing all the pain,’ wrote one sufferer. The Alkaptonuria Society exists to promote information, show sufferers that they are not alone, and give them the hope that one day a cure will be found.
Living with Alkaptonuria

Alkaptonuria is caused by a missing enzyme, which means that the body cannot break down a substance known as homogentisic acid. This then accumulates in the body at more than 2,000 times the normal rate, eventually leading to severely disabling health problems.

Some people with Alkaptonuria may not know that they have the disease until they start to suffer from symptoms such as chronic pain in their back or joints. Others may be diagnosed at an early age, but not fully understand the implications. Either way, Alkaptonuria is like a time bomb: a disease for which there is no cure, and which sooner or later will make it impossible for sufferers to lead a normal life.

Simon Laxon is just one person with Alkaptonuria who has had to live his life under a cloud of misinformation, uncertainty, anxiety and pain. See his story on the next page.

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Simon Laxon lives in England.

‘It has been a struggle to get help as Alkaptonuria is such a rare and little known genetic disorder’
Understanding Alkaptonuria

A rare genetic disease
Alkaptonuria was first identified and described in 1902. It is a rare disease: less than one in 250,000 people are affected. Many physicians will never see a patient with Alkaptonuria in their career.

Alkaptonuria is a genetic disease, meaning that it is passed on by the sufferer’s parents. For this to happen both parents must be a carrier of the gene that can cause Alkaptonuria. Because the gene does not always cause Alkaptonuria, people can be carriers without themselves suffering from the disease.

If both parents are carriers, the child has a one in four chance of having Alkaptonuria. This happens when the child receives the gene with the disease-causing change from both parents.

So even if both parents are carriers, there is still a 75 per cent chance that the child will not have Alkaptonuria. This would be the case if the child receives the gene that doesn’t have a disease-causing change from one or both parents.

This explains the low incidence of the disease: both parents must be carriers, and both parents must pass on the gene with the disease-causing change. It also explains why one child in a family may have Alkaptonuria but their siblings may not.

What Alkaptonuria does
People with Alkaptonuria do not have enough of an enzyme called homogentisic acid oxidase. The body uses this enzyme to break down a substance called homogentisic acid. Because normal amounts of this enzyme are missing, homogentisic acid is not used and builds up in the body. Some is eliminated in the urine, but the rest is deposited in body tissues, where it accumulates at 2,000 times the normal rate.

This accumulation of homogentisic acid causes ochronosis, a blue-black discoloration of connective tissue including bone, cartilage, and skin caused by deposits of ochre-colored pigment. And because homogentisic acid is toxic, this build-up in the body tissues eventually leads to multiple and chronic health problems for Alkaptonuria sufferers.

Diagnosis and symptoms
Babies born with Alkaptonuria do not suffer any immediate ill effects. However, because of the presence in their urine of homogentisic acid, which turns a dark colour after several hours’ exposure to air, parents may notice dark staining of the baby’s nappies or diapers. If proper tests are then carried out, this can lead to diagnosis of the disease.

Many sufferers, however, are not diagnosed with Alkaptonuria until symptoms appear later in life, after years of accumulation of homogentisic acid in their body tissues. The onset of clinical joint disease may differ from an age of six years to an age of 60 years. Generally, there is increasing joint pain and limited and painful use of the large weight-bearing joints: knees, hips, spine and shoulders.
The main symptoms and some of the health problems caused by Alkaptonuria and ochronosis are described below.

**Skeletal (bones and cartilage)**
The knees, shoulders, and hips are most affected. Deposits of pigment cause cartilage to become brittle and eventually to fragment (break apart). Arthropathy (diseased joints characterised by swelling and enlarged bones) is common.

Patients suffer intense joint pain and decreased mobility. Many will have surgery to replace affected joints. Sometimes patients end up wheelchair-bound.

In general, people start complaining of back pain in their 20s and 30s, and knee pain in their 40s. However, the onset of symptoms depends on the individual and can vary greatly. Hip and shoulder pain often occurs later, but usually by the age of 50. Many people have at least one joint replaced by age 55.

**Cardiovascular (heart and blood vessels)**
Heart problems often start after age 50. These include calcification of the coronary arteries (the vessels that feed the heart). The aortic and mitral heart valves – which separate chambers of the heart – are most affected. The build-up of homogentisic acid can cause valves to calcify or harden, leading to narrowing of the valve causing problems with blood flow. Pigment deposits also can lead to the formation of atherosclerotic plaques (hard spots in arteries) containing cholesterol and fat.

**Genitourinary (genital and urinary systems and organs)**
In men, the prostate is most commonly affected. Pigment deposits can form stones in the prostate.

**Respiratory (organs and structures involved in breathing)**
Heavy pigment deposits are common in the cartilage of the larynx (voice box), the trachea (windpipe), and the bronchi (air passages to the lungs).

**Ocular (eyes)**
Vision is not usually affected, but pigmentation in the white part of the eye is evident in most patients by their early 40s.

**Cutaneous (skin)**
Again, the age at which this becomes noticeable varies according to the individual. Effects are most noticeable in areas where the body is exposed to the sun and where sweat glands are located. Skin takes on a blue-black speckled discoloration. Sweat can actually stain clothes brown.

Pigmentation of the skin is more visible in some patients than others. It is often first seen in the ear lobe. It can also be seen in the bridge of the nose, cheeks, hands, and skin overlying tendons.

**Other body systems**
The teeth, central nervous system (brain and spinal cord), and endocrine organs (which make hormones) also may be affected.
I was diagnosed with Alkaptonuria shortly after my birth because of dark urine in my nappies – it is known as the Black Nappy Disease in the UK and the Brown Diaper Disease in the USA. My mother informed me that the doctors at the time said it would not cause me any harm.

At the age of 34, early in 1966, I bent down on one knee. I screamed because I just could not move my legs. The pain was horrific from the lower spine and down my left leg. The doctor sent me to the Royal Bath Hospital for three months. They laid me on a bed with weights around my ankles for six weeks, which failed to make me any better. Then a brace was fitted around my shoulders and attached to a high beam, weights were attached to both ankles and I was hoisted off the floor. It was torture for another six weeks, and not very successful. I was then fitted with a plaster corset from my hips to shoulders and discharged.

In the mid-1970s I noticed my head and shoulders were beginning to lean over slightly to the left and also forward, so it looked like I was peering down at the gutter. I was referred to a spinal specialist who told me I needed an operation on my spine. He said if I did not have the operation I was likely to be paralysed from the waist down within six to nine months.

The operation went ahead the next day and was successful, but the surgeon confirmed that Alkaptonuria was attacking my lower spine. He said it was in a terrible mess and that nobody should operate on it again. On my discharge I was told I could either stand up or lay flat on my back, but should not sit down for three months. In those days we were terribly naive. I found out later that the operation was actually to fuse the lower vertebrae of my spine together.

Until 1985 I was able to lead a normal, active, socialising, dancing life. But from about 1985 the joint pain and pain throughout my body was beginning to take its toll. Since then I have had countless operations, including hip, knee and shoulder replacements. I lost six inches in height because of the homogentisic acid attacking the discs between the vertebrae in my spine. In the early 1990s I was diagnosed as having osteoporosis. The rheumatologist refused to offer me any treatment for the over-riding, terrible body pain I endured, because of the effect it may have on the Alkaptonuria.

Since 1985, as my disabilities got worse, many of the people I socialised with, who I thought were good friends or neighbours, have slowly dropped away. It is as if they did not really believe what was happening to me.

Treatment of Alkaptonuria

There is no cure for Alkaptonuria: no way of preventing people getting it, and no way of curing people who have it. At present the best outlook for Alkaptonuria sufferers is early detection followed by management and treatment of symptoms.

The key area is managing and treating the joint deterioration caused by build-up of homogentisic acid in the cartilage and bone. Close attention to control of joint pain is critically important. Inadequate pain control may lead to limited use of the affected joint, further reducing the range of motion in that joint. The use on a regular basis of a long-acting non-steroidal anti-inflammatory medication, in combination with a more potent short-acting medication for periods of increased pain, can be beneficial.

Physical and occupational therapy are important to maintain muscle strength and flexibility. A programme involving swimming or pool physical therapy is ideal, since this puts less stress on the joints. Avoiding manual labour or high impact sports, which can stress the spine and large joints, may help delay the progression of arthritis. Joint replacement surgery is an option available for significant arthritis, and is generally performed with the goal of pain relief rather than increased mobility.

After age 40, patients should be monitored for possible heart complications related to Alkaptonuria. An echocardiogram can detect aortic or mitral valve calcification and a CT scan of the chest can detect coronary artery calcification.

Kidney and prostate stones can also occur in individuals with Alkaptonuria and may require surgery.

There is no clinically proven treatment available to prevent or reverse the pigmentary changes (ochronosis) seen in Alkaptonuria.

There is no cure for Alkaptonuria: no way of preventing people getting it, and no way of curing people who have it.

JEAN-LUC’S STORY

About five years ago, during a back operation, the surgeon noticed black spots and diagnosed ochronosis. Since then I have continued to suffer from pains in my back, hips, shoulders, knees and elbows. The pain is at its greatest when I get up in the morning or when I have been sitting for a while. That’s why I try to go swimming as often as possible or to ride my bike or just go for a walk to keep my body in movement ... because movement and keeping my mind busy is the best way to forget the pain and enjoy life despite my reduced mobility.

Jean-Luc Van Cauwenbergh lives in Belgium. He is 40.
Dietary treatments
There are anecdotal reports that a diet low in protein – especially in amino acids, phenylalanine and tyrosine – can help delay joint problems. However, there have been no formal clinical trials and there is no proof that such a diet is of any benefit. Maintaining a low-protein diet in order to restrict these amino acids is also extremely difficult to do.

Some Alkaptonuria sufferers take vitamin C as an anti-oxidant. However, this has not been shown to have any impact on the damage to cartilage caused by homogentisic acid. In guinea pigs induced to have Alkaptonuria by feeding them large amounts of tyrosine, the anti-oxidant vitamin C apparently prevents Alkaptonuria. However, vitamin C has no proven effect on the hereditary type of Alkaptonuria in humans.

Trials of a new drug
Some hope is offered by a new drug that is a potential treatment for Alkaptonuria. Nitisinone, or NTBC, is a herbicide which causes plants to bleach. It inhibits the enzyme which produces homogentisic acid. Short-term studies have shown that the amount of homogentisic acid in the urine of patients with Alkaptonuria is reduced by up to 95 per cent when taking NTBC.

The National Institutes of Health in the USA began a three-year clinical trial of NTBC in April 2005. The trial will examine the benefit of NTBC in retarding progression of joint disease in patients with Alkaptonuria.

NTBC is currently approved for use in tyrosinemia type I, a severe liver disease in infants and children, but not for Alkaptonuria. The possible side-effects are related to the elevated tyrosine levels that occur with the use of NTBC. This could lead to eye complications, such as sensitivity to light and crystal formation in the cornea. There have been no reports of permanent eye damage.

If the trial shows that the drug is safe for use and does help with joint problems in Alkaptonuria patients, it would probably still take some time to get NTBC approved for clinical use for patients with Alkaptonuria. Whether and when it becomes accessible to patients around the world depends on the drug approval processes of individual countries.

Some hope is offered by a new drug that is a potential treatment for Alkaptonuria

PAUL’S STORY
My problems started in my lower back in my early 20s. By the age of 25 I could not stand straight and walked bent over. I was told by one doctor that I had the back of a 70 year old man. My lower back has fused itself and is not as painful now.

I have seen many different doctors but got very little relief. They didn’t know anything about this disease. I was usually told to learn to live with it. I worked as an auto body repair man, which is a fairly physical occupation, and had many days that were very painful. I have taken almost all of the anti-inflammatory drugs that have been available in the last 35 years.

I was finally diagnosed with AKU in 1989 when I saw a new doctor. He told me that he had seen only one other case in his entire career.

Even though there was no real course of treatment it was good to know what was wrong. I think one of the worst things about this disease is not knowing what is causing all the pain.

Paul Whitehead is 60 years old and lives in Missouri.
The Alkaptonuria Society

The Alkaptonuria Society was set up by a group of concerned people in March 2003 to develop a website to provide information and support to Alkaptonuria sufferers. However, it soon realised that in order to make a real difference to people with Alkaptonuria, it had to become more proactive, supporting medical research and developments that could benefit Alkaptonuria sufferers.

In June 2003 the society became a limited (non profit making) company registered in the UK. The incorporation of the society has put us in the position of being able to apply for funding from public agencies such as the UK Lottery Board.

The society has been very fortunate to have as board members individuals who can really assist us in our new plans. They bring to the charity a wealth of experience in medicine, community politics and voluntary service.

www.alkaptonuria.info
The Alkaptonuria Society website provides an information and support network for people with Alkaptonuria, their families and friends, and others concerned about or interested in the disease, including the medical profession. The website aims to find and make available information about the latest news, research and treatments for Alkaptonuria and its symptoms.

It also acts as a networking resource for people with Alkaptonuria, giving people the opportunity to tell their stories and get in contact with other sufferers. It is seeking to collate a database of Alkaptonuria sufferers worldwide and is a multinational resource available in several languages including English, French, Italian, German and Russian.

www.jrin.info
The Joint Replacement Information Network website is designed to provide support to those who are about to have, or who have recently had, an artificial joint replacement. The site provides general information on joint replacement, and more detailed information on knee and hip replacement. The Joint Replacement Information Network is a project of the Alkaptonuria Society.

Research
The Alkaptonuria Society is working in partnership to develop research with the Division of Clinical Chemistry, School of Clinical Sciences, Faculty of Medicine, at the Royal Liverpool University Hospital. The first part of the research will be clinical: a study of patients with Alkaptonuria to find out how the disease affects them. The second part will be fundamental research to find out just how Alkaptonuria damages body tissues.

We are looking for funds to support this research, and any donation will be very much appreciated. Please see page 12 for more on how you can help.
Somewhere in my late 20s I started having lower back pain. I went through all kinds of tests from ages 32 till 36, but the pain kept getting worse. During my late 30s I couldn’t deal with it any more, but I couldn’t get anyone to listen.

My biggest problem has been getting doctors to understand that my condition is due to Alkaptonuria. Most have never heard of it, or don’t want to put the effort into learning about it. Over the years this has caused many problems. Thankfully, now I’ve got a doctor who takes it seriously and is willing to learn.

I’ve noticed a big change in the last year or so. I try to stay active, walking, skiing in winter. I keep my weight down to lessen the weight my bones have to carry. But my mobility is decreasing faster, and pain in my shoulders and hips wakes me at night. I have problems with my elbows and knees; I have no feeling in my fingers most of the time. I seem to be clumsy. I cannot feel my arms in relation to my hands and body — that sounds strange but it’s how it feels. Like my shoulders are disconnected.

I have to take each day as it comes and deal with a bad day the best way I can — by doing as little as possible. On bad days, my knees feel hot. My hands are red and warm. I feel even more pain — I just feel ‘yucky’.

The funny thing is I look normal and try to have a positive outlook on life. I have a beautiful granddaughter, and every day I can walk on my own two feet is a holiday to me.

Kimberley Horning is 42. A former nurse, she retired due to poor health. She lives in Michigan.

When I was two years old, I was admitted to a hospital because my mother was concerned about reddish-brown discoloration of my urine. My doctors diagnosed me as having Alkaptonuria and dismissed me from the hospital with recommendations to take vitamin C.

I began to experience symptoms associated with Alkaptonuria beginning in my late teens. Initially, I only noticed bluish pigment in the cartilage of my ears. In my early 30s, I started treatments with a chiropractor for back pain and stiffness. By the time I was 50, I was suffering with kidney and prostate stones and ochronosis in my back, neck, shoulders, hips, and knees.

I have also experienced dizziness, the origin of which could not be determined by a neurologist. I assume it is related to Alkaptonuria. I worked for 36 years as a software engineer. Recently I have been unable to work because of this dizziness and the joint problems associated with ochronosis which have severely limited my range of motion and ability to walk.

Before I found out about other sufferers, I felt isolated. I was uncomfortable talking to doctors about AKU because it seemed that they were not associating some of my problems with it. Now I know that other people with AKU are experiencing similar problems and this disease is not a benign condition like some doctors may think.

Bill Fowler, 60, lives in South Dakota.
‘Before I found out about other sufferers, I felt isolated’

NICK’S STORY

I found out about Alkaptonuria when my first child was six months old. A few days after his birth, we started noticing that his nappies were turning dark red. We contacted an emergency doctor, because we thought it was blood, but tests showed that it wasn’t. The doctor’s initial reaction was that my wife was eating too much red cabbage and that this was going through the breastmilk into the baby boy and into his urine. Sounded ridiculous to us!

Our family doctor was much wiser and sent off for some urine tests. These took a few months and came back positive for Alkaptonuria. We’d never heard of the disease and our first reaction was to search the Internet for information. What came back alarmed us: joint and cartilage damage, heart illnesses, and much more.

So imagine our concern when our second child, also a boy, was born with Alkaptonuria. We are understandably very worried.

Fortunately, the worst damage won’t start happening for some years. At the moment, both boys are happy and play around like normal little boys. But my heart sinks when I think of the homogentisic acid building up all the time in their bodies at 2,000 times the normal rate because they’re missing an enzyme.

That’s why the work of the Alkaptonuria Society is so important. It’s working to increase awareness and understanding of the disease and find money for research.

Nick Sireau, Chair of the Board of Trustees of the Alkaptonuria Society.

‘My heart sinks when I think of the homogentisic acid building up all the time in their bodies’

Please help people with Alkaptonuria

Please see overleaf for ways that you can help the Alkaptonuria Society
How you can help

We urgently need donations to help us fund research into Alkaptonuria and support people with the illness. You can give in so many ways:

- **Donate online** by credit card on [www.justgiving.com/alkaptonuria](http://www.justgiving.com/alkaptonuria)

- **Give every month** by direct debit: just contact the Alkaptonuria Society at the address below or email nick.sireau@alkaptonuria.info

- **Write a cheque** and send it to the Alkaptonuria Society.

- **Give shares**: giving shares is simple and one of the most tax-efficient ways of making a donation to the Alkaptonuria Society. Not only can you claim full income tax relief on the value of the shares but, in addition, no capital gains tax will apply. We can then sell the shares and use the money to fund research and support people with the disease.

- **Events**: carry out a sponsored event, such as a walk, a run, or a party. Just contact us and we’ll help you organise the fundraising.

- **Adventure**: we can also organise for you more adventurous fundraising events, such as trekking in Peru, bike rides from London to Paris, parachute jumps, white water rafting, and cycling in Vietnam.

- **Legacies**: leaving a gift in your will can be a wonderful way to support our work in the long term. Do speak to your solicitor about this.

- **Payroll giving**: a regular donation through your payroll, topped up by the tax office, can help the Alkaptonuria Society fund more research and help people with the disease. Payroll giving is one of the most tax-effective ways of donating to us. You can start, stop or change the amount of your donation at any time.

- **Foreign money**: do you have any foreign notes or coins lying around your house that you don’t need? It doesn’t matter which countries the money is from – we can convert any currency. Please send any spare foreign notes or coins to us at the address below.

- **Wedding gifts**: why not celebrate your wedding by asking your guests to donate to the Alkaptonuria Society, in lieu of wedding presents?

For donations, please give online at [www.justgiving.com/alkaptonuria](http://www.justgiving.com/alkaptonuria) or send a cheque to:
The Alkaptonuria Society
12 High Beeches
Childwall
Liverpool L16 3GA
Become a volunteer

Do you have skills in

- marketing
- fundraising
- accountancy
- computers
- website design
- editing
- writing
- media relations
- medical research
- administration
- management
- events organising
- networking

Or anything else you think might be useful to our cause?

Do you have time to spare?

If so, please let us know!

We need volunteers everywhere and anywhere to publicise our work, raise money, help us run our website, do our accounts, speak to journalists, organise events, do our admin, help us define our strategy, etc, etc. With today's computer technology and the Internet, you can help us from anywhere in the world: all you need in order to donate your time and skills is email and Internet access.

If you'd like to volunteer for the Alkaptonuria Society from whichever country you live in, please get in touch (email nick.sireau@alkaptonuria.info). We need all the support we can get!
Alkaptonuria is a rare and serious genetic disease, largely unknown to the general public. Sufferers are on their own: isolated from support networks, ignored by society, and overlooked by the medical establishment.

The Alkaptonuria Society was set up to tackle these problems. It aims to raise awareness, provide information, and fund research – to show people with Alkaptonuria that they are not alone, provide support in dealing with the disease, and give them some hope for the future.

JOHN’S STORY

The pain began in my hip, knees and back in my mid-20s. I saw a rheumatologist who knew about Alkaptonuria and he gave me injections against inflammation. He put me on crutches and knee braces for about 12 years.

I was on disability allowance at age 38. I had both hips and knees replaced and surgery on my elbows. You could hear the bone scraping on bone when I walked.

Today, aged 61, all my cartilage has worn out. My right hand fingers are stiff and cold. My right eye is blind and I’m nearly deaf, which affects my balance. I have had three heart bypasses, a kidney transplant and my gallbladder removed. Last year I fell and broke my neck. My vertebrae have fused together. I have congestive heart failure and diabetes type two. I use an electric three-wheeler to move.

John Harris lived in the USA. He died aged 63 in 2005.

www.alkaptonuria.info