Wilson's Disease Support Group - UK

BRITISH LIVER TRUST

AFFILIATED TO THE BRITISH LIVER TRUST

NEWSLETTER MARCH 2010

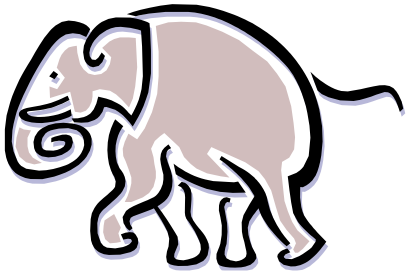
Welcome!

The Wilson's Disease Support Group - UK (WDSG-UK) is an all volunteer organisation which strives to promote the wellbeing of patients with Wilson's disease, their families and friends.

The organisation aims to provide informative articles about the nature of the disease, articles written by patients, families and friends about their experiences of the disease, recent progress in treatment and much more by way of an annual newsletter.

The organisation also aims to promote networking of Wilson's disease patients and their families by helping and encouraging them to correspond with one another.

The organisation also strives to promote a wider awareness of Wilson's disease within the medical profession.



WDSG - UK

The Support Group will be ten years old this year and I think we should all give ourselves a pat on the back for our part in it.

The year has been relatively quiet with no EuroWilson meetings or BLT conferences, but we have several new members and lots of contact with existing members. Caroline, Valerie and I have been working on a constitution which we are about to sign with Rupert Purchase, who has kindly agreed to join our committee as chair. The constitution will then be submitted to the Inland Revenue to be allotted a registration number which we can use for tax advantages. If anybody else is interested in joining our committee, please let me know.

New membership categories are being considered but meanwhile after ten years of charging a nominal sum of £5.00 per member, we are this year increasing subscriptions to **£7.50**. Printing costs and postage have both increased considerably since 2000 and so we consider this to be reasonable. Renewal forms are enclosed with the newsletter.

Thanks to everyone who sent donations with their memberships last year and in particular we would like to thank Univar, the manufacturers of trientine, for their continued sponsorship of the Group.

As well as 2010 being our tenth anniversary, it is also **Dr Walshe's 90th** birthday on **24 April**. Happy Birthday Dr Walshe.

Please make a note of our annual meeting, which will again be held at CRUFC in Cambridge (www.crufc.co.uk) on **Sunday 11 July**. Booking forms are enclosed and we hope lots of you will be able to join us to help make it a special and memorable day. Photographs from our 2009 meeting are now available to view on our website www.wilsonsdisease.org.uk.

I hope you'll enjoy reading the newsletter and wish you all a very Happy Easter with not too many eggs of the chocolate variety! Linda

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FUNDRAISING EVENTS - 2009/10

THE LOONY DOOK - David Reid

Stephanie

My wife, Stephanie, was diagnosed with Wilson's disease in 1966, aged seven. She has been taking penicillamine ever since and is keeping well. Last year she gained a degree in nursing after an intensive year of study.

I decided to raise funds for the Support Group and so took part in the famous *Loony Dook* . This is an annual tradition in Scotland taking place on New Year's Day, where the hardy few go for a swim in the chilly waters of the River Forth. This year there was a very good turnout of approximately 600 people. However, unfortunately, this does not make the water any warmer! It was still very cold.

After my initial swim I came out the water to the cry of "We didn't get a proper picture, can you go back in?" So I had to return in order for the photographs to be retaken.

I raised £160.00 from private sponsors by doing my swim and the company for which I work, Norbulk Shipping UK Ltd, made the amount up to £250.00 as a goodwill gesture.

The Loony Dook

Take 2

PUPILS' FUNDRAISING CONCERT - Liz Morell

Far left Liz - far right, her mum, Barbara

Liz, who is a WD patient, has again organised a summer concert with her mother, Barbara Fordham, in which their students either played or sang something that they have been working on during the year.

There were no admission charges, but Liz gave a short talk about Wilson's disease before the concert began and then had a collection at the end in which she raised £130 towards Group funds.

COFFEE MORNING - Sylvia Penny

Sylvia has also been busy and held a coffee morning with stalls and a raffle at Victoria Park Methodist Church Hall in Babbacombe last year, together with her granddaughter, Emma who has WD, Emma's mum Sylvia, Emma's sister, Daisy, and Emma's two children, Amy and Thomas. The event was a great success and raised a further £360 for the Support Group funds.

Emma was diagnosed with Wilson's disease in March 2007 and is making a very good recovery.

Thomas, Rev. Valerie Price, Emma & Amy

CHRISTMAS SALE - Belinda Diggles

Belinda had another big baking day before Christmas and sold the puddings and mince pies that she had made to her friends and colleagues. In so doing she raised £100 for the Group.

GROUP MEETING - CAMBRIDGE - 5 JULY 2009

Dr Walshe presents Joan with her prize of a signed drawing of *The Woolly Mammoth*

The Support Group meeting was held for the third consecutive year at Cambridge Rugby Club, which we now consider to be our favourite venue. The weather was magnificent and some sixty people turned up for the event. Light refreshments were served on arrival and patients, their families and friends were able to chat informally to one another and to members of the medical profession, who included Drs John Walshe and Godfrey Gillett, James Dooley from The Royal Free and Bill Griffiths from Addenbrooke's. Also in attendance were Kay Gibbs, whom many of you will remember fondly from Dr. Walshe's days in Cambridge, and Dr Rupert Purchase, who is an honorary member of the Group.

We were especially pleased to be joined by four new patients: Verity and her brother, Stuart, from Southampton, Rozmin from Leicester and James from Dublin. We believe that the meetings are particularly useful to new patients giving them the opportunity to meet other patients, possibly for the first time, and bringing them together with Wilson's disease specialists under the same roof. We are mindful of the sacrifice the doctors make in giving up their valuable time to join us and we thank them for this.

Ray Estall presenting a cheque for £500 from Univar to (l to r) Valerie, Linda and Caroline

Linda opened the meeting by welcoming us all, reporting the Group's activities in 2008-09, handing out the accounts for the year and then giving us the itinerary for the day. We continued to mix and chat while Belinda Diggles, in her inimitable way, persuaded us to buy lots of raffle tickets and in so doing raised the very respectable sum of £122 towards Group funds. We are grateful to everybody who donated prizes and bought tickets. Belinda's husband, Barry, again acted as photographer for the day with some of his photographs shown here. The complete album is available to view on the Group's website at www.wilsonsdisease.org.uk, should you wish to take a look.

Before lunch we had a short talk from Rupert Purchase about new ideas in chelation therapy, which had been reviewed recently in scientific literature. Ray Estall, on behalf of Univar, then presented Linda, Caroline and me with a cheque for £500 towards Group funds and the newsletter in particular. Finally, Dr Walshe presented Joan Smith, as winner of our anecdote competition, with his signed drawing of 'the' woolly mammoth. The relevance of the woolly mammoth is that Dr Walshe used to ask newly diagnosed patients to draw the outline of a mammoth/elephant, so that he could assess our fine motor skills. The mammoth, you will have noticed, was adopted as the logo for the Group.

Question time with the doctors

Lunch was again very popular with a good selection of sandwiches and delicious puddings prepared for us by the Rugby Club's in-house caterers. After lunch Caroline chaired our popular question and answer session in which patients are able to put questions directly to the doctors for us all to hear. Finally, just before 1530, Belinda drew the raffle and Barry then ushered us outside for our traditional farewell group photograph.

Valerie

Going home time!

Kayser Fleischer Rings

All newly diagnosed patients with neurological Wilson's disease will have Kayser Fleischer (KF) rings and those with hepatic Wilson's disease probably will have. What exactly are they and who were Kayser and Fleischer? Not being a medical historian I really don't know who these two doctors were except that their names suggest that they were German physicians who first described the rings, Kayser in 1902 and Fleischer a year later. In both cases the rings were seen in patients with a nervous condition. Kayser described his patient as suffering from 'pseudosclerosis' and Fleischer's patient was said to be suffering from multiple sclerosis. Both patients had marked tremor. When Dr Wilson first described the disease which now bears his name he did not observe the rings and ten years later he still denied that they were related to 'his disease.'

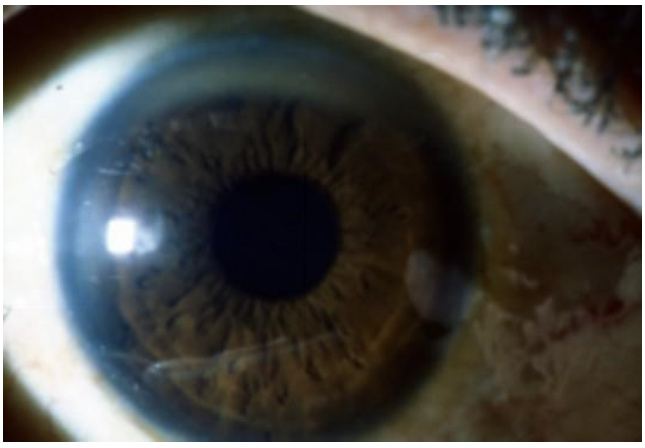
What are the rings and why are they so important? As far as the patient's clinical condition is concerned they really are of no symptomatic importance. What makes them so significant is their diagnostic value. Once seen in the eyes you have the diagnosis ready made and their disappearance under treatment is a valuable marker that you, the patient, are sticking to your treatment and to the physician that his treatment really is removing the excess copper from your body.

The rings are brown deposits of copper, probably as a copper-protein complex which gets deposited in the cornea, the clear 'window' at the front of the eye. They are in what is called Descemet's membrane, part of the cornea, though when viewed directly they appear as rings over the iris. The copper deposits are not necessarily complete rings but start as small crescents in the top of the cornea say from 10 to 2 o'clock and then as inferior crescents from 5 to 7 o'clock. These then spread laterally until they join up to form the complete ring and also centrally to become broader and denser. A dense complete ring goes with heavy copper overload. That the deposits appear first as top and bottom crescents is probably related to the flow of liquid in the anterior chamber of the eye. Once treatment is commenced the copper is removed and the rings shrink in reverse order so the last remnants are to be found in the top crescent. That is why, when in doubt, they should always be most carefully sought in this region. After the copper is removed from the cornea the area looks like beaten silver. The usual appearance is of a brown ring and this is quite obvious in patients with blue eyes. When the iris is brown the ring is much more difficult to see and needs some experience. Sometimes, in brown eyes, the ring appears grey and it is also said that sometimes the rings appear green, though I have never seen a green ring myself.

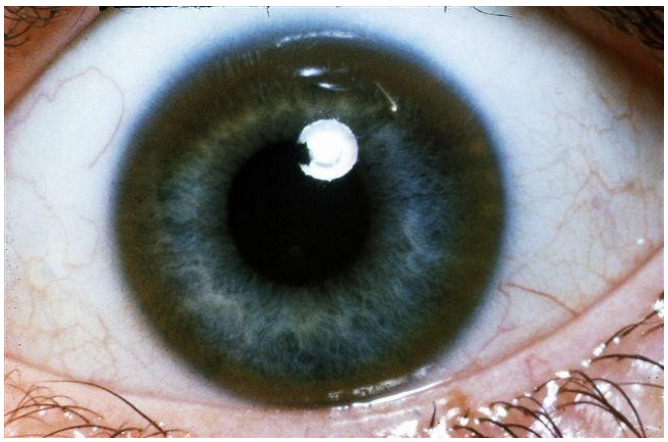
However, if the ring is viewed in infrared light, it does appear green. One other thing copper can do to the eye is to form a cataract in the lens, though this is rather rare. This has a typical frond-like appearance and is known as a 'sunflower cataract.' It does not affect the patient's vision and does disappear, quite quickly, with treatment.

Some patients can see their own rings. If you have blue eyes it just needs a bit of practice. If you have brown eyes you will probably not be so lucky! Below are two pictures, one of a brown ring on a blue iris, one of a ring seen, with an oblique ray of light, on a brown iris.

Dr J.M. Walshe - 2010



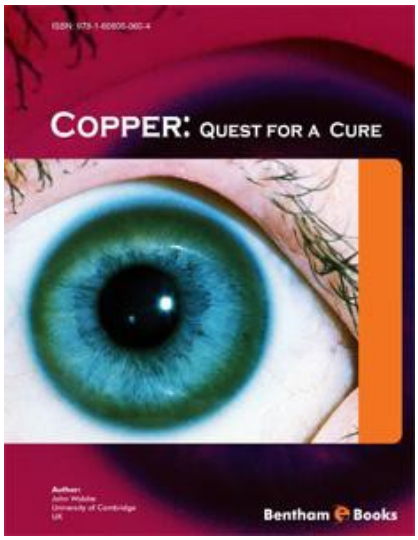
Kayser Fleischer ring on brown iris



Kayser Fleischer ring on blue iris

Copper: Quest for a Cure - J M Walshe

In 2009 Dr Walshe had an e-book *Copper: Quest for a Cure* published. It describes his medical career and researches into the treatment of Wilson's disease.



The e-book (a book available in an electronic format only) can be downloaded from the publisher's website: *Copper: Quest for a Cure*: eISBN: 978-1-60805-060-4; price US$ 85.00; http://www.bentham.org/ebooks/9781608050604/index.htm.

Also in 2009, Dr Walshe contributed an "occasional paper" to the leading journal of neurology, *Brain*, which focused on the discovery and development of the three drugs: D-penicillamine, trientine and ammonium tetrathiomolybdate (J M Walshe, *The Conquest of Wilson's disease*," *Brain*, 2009, **132**,2289-2295; doi: 10.1093/brain/awp149).

Rupert Purchase February 2010

Dr Walshe in Canham's Yard, Cambridge

Canham's yard, Cambridge

A dashing Dr Walshe

This photograph with Dr Walshe appears both in the e-book and the paper in *Brain* mentioned above. Captioned as *Myself outside my lab in Canham's yard, Cambridge*, it depicts a somewhat youthful Dr Walshe outside a somewhat state of the art research facility! But when was it taken and where is Canham's yard? The three cars in the foreground, including an Austin A30, suggest the late fifties or early sixties.

Have we any readers with memories of this laboratory who can give us more information? All answers on a postcard please!

Congratulations Dr Walshe on your ninetieth birthday
from all your grateful patients across the globe

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The patient story that appeared here in the original 2010 newsletter has been removed at the patient's request.

New Ideas in Chelation Therapy

Introduction

The cornerstone of the treatment of Wilson's disease is a reduction of copper levels *in vivo* using the orally-administered chelating agents **D-penicillamine** and **trientine dihydrochloride**. Patients with side-effects from receiving multiple blood transfusions for the amelioration of inherited anaemias are also successfully treated with chelating agents. Blood transfusion elevates these patients' iron concentrations, which, if not reduced by chelation, will damage vital organs. In recent years the deleterious role of metal ions in neurological diseases has come under the spotlight. In particular, some investigators believe that iron, copper and zinc have a role in the progression of Alzheimer's disease (AD) and that chelating agents could mitigate the disease.

The treatment of the blood disorder β-thalassemia and the world-wide research into Alzheimer's disease has produced some new ideas on the design of metal ligands for treating metal-related diseases. It is the aim of this article to briefly review a few of these developments in the hope that some impetus can be given to finding new ways of treating Wilson's disease, and in particular the neurological form of the disease. Of necessity, only a brief outline can be given here, and much of the information is codified in the structural formulae used by organic chemists. But the author would be pleased to provide more information, if requested, on the molecules which might be considered as candidates for testing in animal models of Wilson's disease.

Chelating agents introduced between 1940-1970 for treating metal intoxication

Some of the chelating agents which have been successfully used to treat metal intoxication are shown in **Figure 1**. **BAL** was originally developed to treat arsenic toxicity, but its potential for treating Wilson's disease was recognised by J. N. Cumings in 1948. The need to find an oral alternative to **BAL** for treating Wilson's disease led to the introduction of **D-penicillamine** and **trientine** by Dr John Walshe in 1956 and 1969, respectively. **DMSA** and **DMPS** are less toxic and more hydrophilic analogues of **BAL**, and are used to treat mercury intoxication. **EDTA** and its congener **DTPA** can be used to treat lead poisoning and are effective in removing radionuclides.

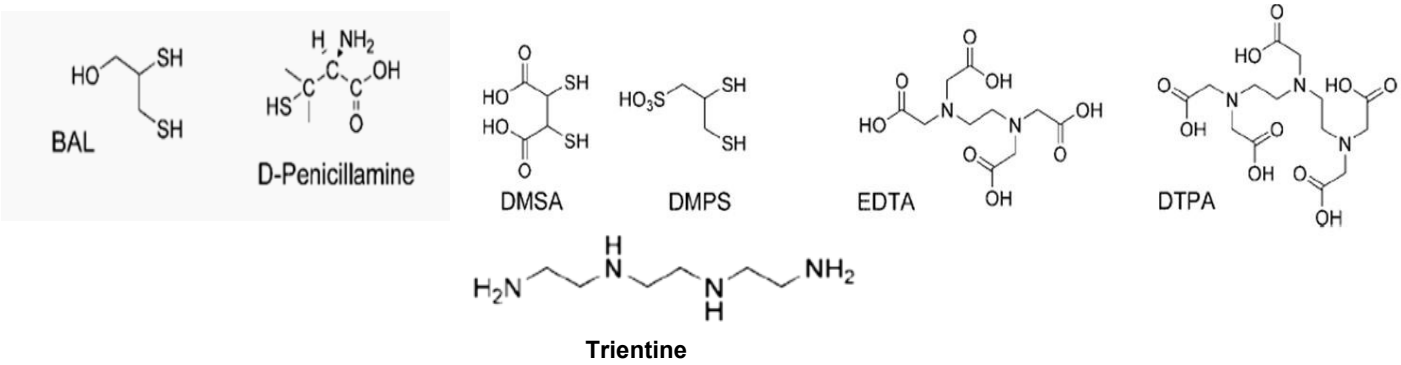

Figure 1: *Ligands developed from 1940-1970 to treat chronic and acute metal intoxication*

Chelating agents for treating transfusion-related iron overload disorders

Desferrioxamine (**DFO**) (**Figure 2**) is a hydroxamate-based hexadentate ligand, which has been used to treat iron overload since the 1970s. Disadvantages of using **DFO** (long subcutaneous infusion times; multiple reported side-effects) led to a search for new iron-chelating agents. Two of these are shown in **Figure 2**. **Deferiprone**, also known as **L1**, is a 3-hydroxy-4-pyridone derivative and has been used, with reservations, as an oral alternative to **DFO**. It effectively coordinates with Fe(III) *via* a deprotonated canonical di-oxo form derived from the parent molecule. A more accepted oral drug for iron overload disorders is **deferasirox** (**ICL670**) (**Figure 2**), first reported in 1999. This compound is a tridentate chelator, which selectively coordinates Fe(III) over Fe{II) and has little affinity for Zn(II) or Cu(II) ions.

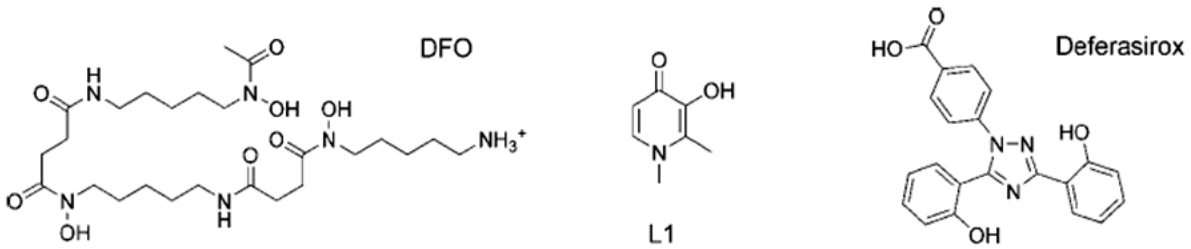

Figure 2: *Multidentate ligands used for the treatment of transfusion-related iron-overload conditions: DFO; deferiprone (L1); deferasirox*

The design of chelating agents for treating Alzheimer's disease

A characteristic pathology of Alzheimer's disease (AD) is the presence of extracellular fibrillized plaques, which are formed from β-amyloid (Aβ) peptides. Metal ions, especially zinc, copper and iron ions, are implicated in Aβ amyloidogenesis. Age-related increases in brain metal ion concentrations are associated with Aβ plaque deposition. In addition, the Aβ peptide can reduce Cu(II) and Fe(III) ions leading to Fenton and Haber-Weiss chemistry, the formation of hydroxyl radicals, and oxidative damage in brain tissue. Metal ions are therefore a therapeutic target for treating AD, and the disease might be amenable to chelating agents, which can either remove or redistribute localised concentrations of metal ions. Early promising results were shown both *in vitro* and in clinical trials with AD patients with the iron-chelator **DFO** (**Figure 2**). Chelating agents for treating AD need to cross the blood brain barrier (BBB), and should target specific sites rather than disrupt net metal homeostasis. These goals have resulted in several new strategies for designing ligands. One example, from the laboratory of Professor Chris Orvig at the University of British Columbia, Vancouver, Canada, is shown in **Figure 3**.

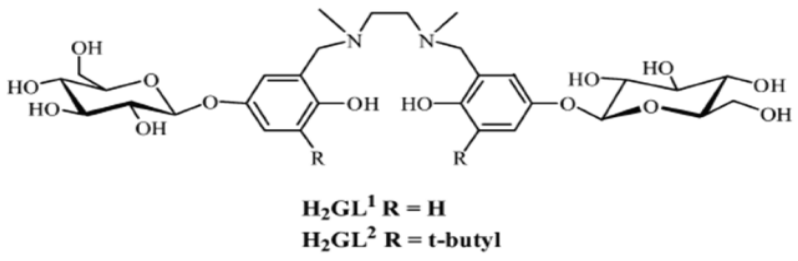

Figure 3: *Two multifunctional carbohydrate-containing ligands designed for brain-directed metal chelation and redistribution*

The two compounds shown in **Figure 3** contain a modified ethylenediamine metal chelating group, which is substituted on each nitrogen atom with a glucose-substituted phenolic moiety. The phenolic part of these compounds has antioxidant capability (for counteracting cellular oxidative stress), and the glucose residues are designed to aid water solubility and improve targeting, possibly by facilitating passage across the BBB. Both **H2GL1** and **H2GL2** were found to reduce Zn2+- and Cu2+-induced Aβ aggregation *in vitro*, and have potential as multifunctional agents in AD therapeutics.

Some other rationally-designed ligands, which have been tested in models of AD, are illustrated in **Figure 4**. **Feralex** is a glucose-bearing variant of **deferiprone**. In AD brain issue experiments, **Feralex** was comparable with **DFO** in removing Fe(III) ions from neurofibrillary tangles. This ligand is also likely to be effective for chelating Cu(II) ions. **DP-109**, which may be regarded as a highly substituted analogue of **EDTA,** is a hexadentate ligand with long-chain ester substituents to enhance lipophilicity. **DP-109** was designed for oral administration, greater brain penetration, increase residence time in the brain, and selective chelation of Zn(II), Cu(II), and Fe(III) ions within membrane compartments. In a mouse animal model of AD, **DP-109** reduced the amount of aggregated insoluble Aβ peptide while increasing the level of soluble Aβ forms. The ligand **XH1** contains two modified benzothiazole substituents, which are designed to covalently link with Aβ peptides, and a **DTPA**-metal chelating core. *In silico* **XH1** binds to the Aβ1-40 peptide and reduces zinc-induced Aβ1-40 aggregation in solution. *In vivo*, in a mouse model, **XH1** attenuated amyloid pathology in the brain.

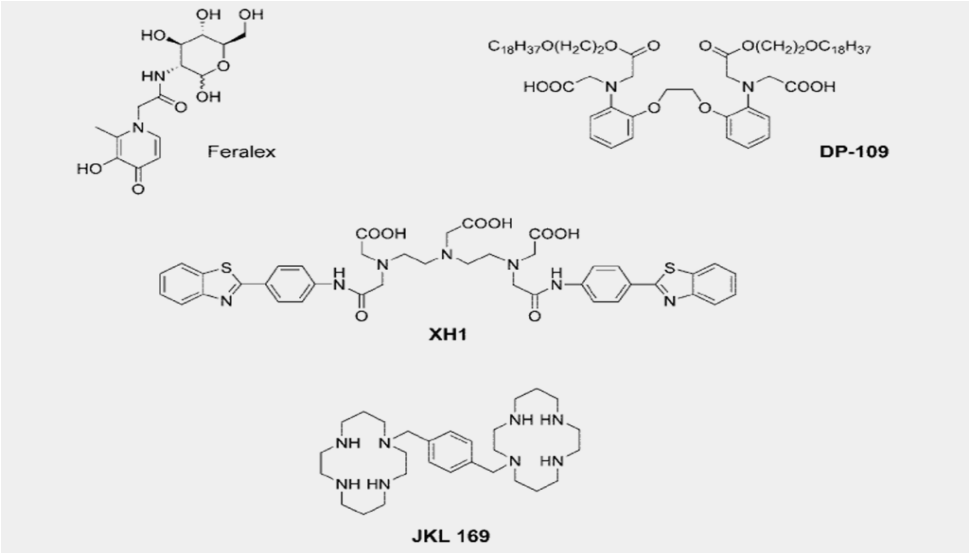

Figure 4: *Compounds developed for therapeutic metal ion manipulation: Feralex, a glucose-bearing deferiprone derivative; prodrug compound DP-109; a putative Aβ-associating chelator XH1; bicyclam JKL 169*

The copper chelator **JKL 169** contains two tetradentate cyclam rings (cyclic variants of **trientine**) linked through a *para*-phenylene group. In rats, **JKL 169** decreased copper concentrations of cerebrospinal fluid, slightly reduced serum copper, and significantly increased copper levels in the brain cortex. **JKL 169** therefore alters the distribution of copper *in vivo*, and is considered to be a viable AD therapeutic.

Conclusion

Research into a treatment for AD has stimulated new ways of targeting metals in the brain. Some of the ideas reported in this article should be applicable for treating Wilson's disease. The molecules shown here, although seemingly complex, are accessible using the armoury of modern synthetic chemistry. A first step would be to test some of these compounds in an animal model of WD, for example in the Long-Evans Cinnamon rat.

Reference

Professor Orvig's research group has contributed much to the literature of medicinal inorganic chemistry in recent years. This article is based mainly on one of Professor Orvigs's reviews: Scott, L. E.; Orvig, C., 'Medicinal Inorganic Chemistry Approaches to Passivation and Removal of Aberrant Metal Ions in Disease', *Chemical Reviews*, 2009, **109**(10), 4885-4910; doi: 10.1021/cr9000176

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February 2010

My Son, Alessandro

by Susheela Vigano

"So this is our story: At the age of 12 my son Alessandro was diagnosed Wilson's disease.

A routine blood test revealed high liver counts. The doctors started investigating: liver scan, which showed an enlarged liver more blood tests...more tests in hospital...nothing. All this took place at the Meyer Hospital for children in Florence. At this point they took in consideration a metabolic disease and decided for a liver biopsy and DNA, after which he was diagnosed with Wilson's disease.

At the beginning I did not quite understand what it was all about and what the right cure was, so I sat in front of the computer and browsed the internet (doctors can be efficient but lack in conversation and details). Mainly, I wanted to check the cure. I decided to write to Doctor Schilinsky and asked him about the cure for Wilson's disease. I did not know if he was going to answer, to tell you the truth, but he did. The next day I got an e-mail! I was so relieved as he reassured me that yes zinc was the right cure even if in Europe they tend to prescribe penicillamine, which is true as I found out later. So it was no surprise to me when Alessandro was given penicillamine! The result was that he was immediately sick. It was then decided to try him on trientine and zinc, starting with low dosage just to see if he tolerated the drugs, and that worked.

Eventually he was taken off trientine and given only zinc. As he was taking a low dosage the zinc was prepared in the pharmacy of S.Maria Nuova Hospital by Dott.Cappuccini and Dottssa.Ruffini (so terribly helpful in moments of doubt). At this point the liver counts improved, so we were relieved. In 2006 the liver counts started to rise again so the doctor decided to try the commercial zinc (Galzin). Shortly after taking Galzin Alessandro started complaining of burning sensation and was uncomfortable feeling nauseous at times, so he was put back to the zinc prepared by the pharmacy. Still the liver counts were not very good, not terrible but not good. The fact that Alessandro was a teenager and that he might not take the medicine correctly was a current topic! I was slightly puzzled about this because we were both pretty careful about taking zinc at the right time.

In 2008 the Doctors decided to give him again Galzin now called Wizin. I was not very happy about the choice but went along with the decision. They decided for a three week trial. The result was the same as before even worse as he had to persist in taking the drug. Doctors prescribed him a medicine, before taking the zinc, that would protect the lining of the stomach, nothing the burning continued. Alessandro even told the doctors that were trying to convince him that maybe it wasn't that bad, "How would you feel if you had a pain like a knife in your stomach at school trying to follow the lessons!!?" He managed to pull through the three weeks. The liver counts were just the same, if not a little worse!! Here they're are a bit sceptical about trientine ,they're not so sure about the side effects, but at this point their was no other choice. For us it was a relief. Alessandro started trientine last year and now the liver counts are normal!!!

At this point I have to thank Linda for her help and support. Linda is a trientine patient! So she told me not to worry and that she was perfectly fine - just check the iron during blood tests!! I even told Alessandro's doctor about this and that I had joined a Wilson's Disease Association in England (nothing like that exists here; I once asked if I could meet other Wilson's patients, but not possible for privacy reasons!!) The doctor I must admit was interested and took some information. As for Alessandro he is happy with trientine and says he feels better! So as a mother what can I say? I am relieved but still keep a keen eye to see if something new turns up."

Life is a great big canvas, and you should throw all the paint on it you can.
Danny Kaye

Ciao!

by Alessandro Vigano

I chose this photograph because it is a happy day! My mother, Susheela, and I

I am Alessandro and I'm 20 years old! I live in Florence, and, like you all, I have Wilson's disease. Hurray!

My story is one of the lucky ones. After a simple blood test during a check up, doctors found high liver counts, and from then I went through a series of examinations aimed at determining what I had. I never actually suffered from any of the effects that this disease has.

After a liver biopsy (which was a terrible experience, because for some reason the anaesthetic did not work), the doctors determined that I had Wilson's disease, as I had high levels of copper in the liver tissue.

First I took Galzin, which always irritated my stomach and made me feel nauseous, and more recently I have been given trientine which I'm comfortable with.

At the moment I'm a very healthy young man. I'm getting good medical treatment and the doctors are good, although they probably need to be more organised (mainly for analyses responses) and to be a little more "human" but no major complaints. I'm very happy that this group exists, and it's very useful too! I found answers to some of my questions, that doctors at times did not give or maybe thought that for us patients it was not important. I think that for us every little detail is important! I wish you all the best and a big ciao from Italy!!!

Klem's Story"

by Robert Haycock

Hello readers: I hope you like my short article about my son, Klem, who was diagnosed with Wilson's disease in 2002.

In his early twenties Klem suffered a freak accident, falling off a mountain bike and breaking both his arms. His G.P. in Bangor, Gwynedd, realized that there was a bigger problem and arranged for him to be seen by a specialist quickly.

Because of his shaking hands and wobbly head the specialist investigated him further and was able to make the diagnosis of Wilson's disease. That was eight years ago now and he has been treated with penicillamine ever since.

The first few months after diagnosis were a very anxious and busy time for his partner, Emma. When I asked Klem what he remembers of that awful period, he says it is of his son, Josh, realizing that he (Klem) could no longer draw and saying "bechod," which in English means, "Oh! That's a shame."

When his medication relieved his worst symptoms, he returned to work. He was training to become a hospital chef and took great pride in keeping the kitchens hygienic for staff, patients and visitors alike. However, Klem's ambition had always been to become a fireman and after three attempts this ambition was realized in October last year.

I contacted Linda Hart several years ago through the WDSG-UK website. I am so glad that the Support Group exists and that other families with Wilson's disease can benefit from your fabulous work. I am so proud of Klem, his strength of character and recovery. I hope others can share my happiness and will have similar good fortune.

Are You Related to Me?

by Valerie (née GILBERT)

You may have noticed that I am listed on the back of the newsletter as having an 'interest in genealogy.' When I was first diagnosed with Wilson's disease in the late 1960s Dr Walshe wondered whether WD patients might have a common ancestor. He cited some obscure illness, found in patients in South Africa, which apparently had been traced back to a single Dutch immigrant. This information had stuck in my mind and in the early 1990s I set off on a personal journey to see if my parents, as WD carriers, were unknowingly related.

The BBC programme, *Who Do You Think You Are*, has popularised family tree research and nowadays, with the internet, it has become a whole lot easier. For me, it meant spending many hours visiting record offices around the country, searching through parish records and censuses, wandering around graveyards, writing letters to distant relatives and even sometimes knocking on strangers' doors! But the rewards were great. I was lucky enough that my ancestors all lived in the one country. I had no sooner started my research than I discovered my late father had had a brother, Jack, of whom he had never spoken, who had been brought up by their grandparents a hundred and twenty miles away in Gloucester. Would he, in his eighties, still be alive? It took me over two years to find him, but in 1996 we met at his home in Hampshire and I was introduced to my three 'new' cousins and aunt. In time I was able to mention WD to them, which of course none of them knew anything about.

Before that, during my search for my uncle, I had traced two hundred and fifty present day GILBERT descendants through a Will of a maiden great great aunt. I organized a family get-together for them in Dorset (where the family had originally lived) and eighty people turned up, only one of whom had ever even heard of Jack. However, they brought old family photographs and a bible, letters and mementos and most importantly stories from the past. It was fascinating. It turned out that when a manor had been built next to the village of Moor Crichel in Dorset (where in 1851 GILBERT was the most common surname) the entire hamlet had been submerged in a lake, as it was deemed to be a blot on the landscape! No wonder I had never been able to find it.

Over the years I have collected dozens of birth, marriage and death certificates from the 19C, which gave me an interesting insight into my ancestors' lives. They show that they were mainly northerners living in Lancashire, Cheshire and Yorkshire with the one branch coming from Dorset. Their occupations included farmers, thatchers, carters and agricultural labourers, cloggers, cotton, silk and wool workers. I was intrigued by the causes of death given on the death certificates, reflecting the lack of medical knowledge (and post mortems) at that time. Had any of my direct ancestors ever died of WD? I had a maternal great great grandfather who had died of a nose bleed aged thirty (incidentally, he had a daughter whose mantra was, "I were born fo't'be wide awake and see things," which I assume *were Lancashire for* "I'm a nosey parker"), but apart from him no-one had died especially young. Other causes of death were phthisis (TB), dropsy, chronic bronchitis, rheumatism, smallpox, apoplexy, paralysis, malnutrition, vital exhaustion, senility, decay, derangement and softening of the brain!

I have listed below the surnames of my ancestors from as early as the 17C through to the 19C. Note the HART and SIMMS, though Linda and Caroline believe it is nothing more than a co-incidence. Do any of the names mean anything to any of you? I have abbreviated the counties accordingly.

Surname	County	Date	Surname	County	Date
ASHTON	LAN	19C	**KERSHAW**	YOR	19C
BARTON	"	19C	**KIMBER**	DOR	18C
BIRCHALL	"	16-20C	**MORT**	LAN	18-19C
BROOK	YOR	18-19C	**NOBLE**	DOR	"
CROWTHER	DOR	18C	**PARR**	LAN	"
DAVENPORT	CHES	18-19C	**PARTINGTON**	LAN	17-18C
DOVE	LAN	"	**PENNY**	DOR	"
GASKELL	"	18C	**PYE**	LAN	18C
GILBERT	DOR/LAN	17-20C	**RAINFORD**	"	17C
GREENWOOD	YOR	18-19C	**ROBERTSHAW**	YOR	19C
HART	CHES/LAN	"	**SIMMS**	DOR	18C
HAZLEWOOD	CHES	"	**SMITHE/S**	LAN	18C
HIRST	YOR	"	**STOCKLEY**	"	18-19C
HOLCROFT	LAN	"	**TAYLOR**	"	"
HOWARTH	"	"	**WALTON**	CHES/LAN	"
HYDE	"	"	**WHITEHEAD**	YOR	19C
ISAACS	DOR	"	**WOODWARD**	LAN	18C
KEELING	LAN	19C			

If anybody feels inspired to do their own family history and would like some encouragement to get them started, I would be only too happy to offer mine. If you have the misfortune of finding that you are related to me, may I offer you my sympathy.

Timbuktu...and back in a week!

by Linda

Devil's Bridge

Last September Valerie and I holidayed just over the Welsh border in Clyro, a small village close to Hay-on-Wye, which is twinned with Timbuktu. We went for broke - a whole week arriving on the Saturday! The views of the Black Mountains from our cottage were outstanding and we made the most of our time there, having alternate days of 'action' and 'chilling.'

The evening of our arrival we limbered up by strolling into Hay across the fields, arriving just before dusk and enjoying a fish 'n' chip supper. We returned by road and as we crossed the bridge over the River Wye, we noticed that there were canoes for hire. We wondered whether hiring one for the day and exploring the river might, from past experience, be easier than navigating dry land but the idea was swiftly abandoned.

On Sunday we drove to the Elan Valley reservoirs and the spectacular Penygarreg dam (just one of a series in the area), which holds back the water of the River Elan which is piped all the way to Birmingham. Beneath the water are the remains of the poet Shelley's house and others, which can be seen when the reservoir is low. We continued to Aberystwyth, stopping off at Devil's Bridge on the way, where two rivers meet and where there are many beautiful waterfalls.

Only another twenty miles to go!

Not only were there canoes to hire in Hay, but also bicycles and we decided on Tuesday that we would have a gentle ride in the surrounding countryside. We were presented with two super deluxe mountain bikes, two bottles of water, a puncture repair kit and an *idiots' guide*. We chose what we thought was a 'short flat' circular route with plenty of hostelries along the way. In fact it turned out to be 22 miles long and only one hostelry was open, but we completed it and survived!

It was a lovely day and one of my best memories was sitting in the afternoon by the river in glorious sunshine as tractors pulling huge trailers piled high with potatoes or hay trundled over the old bridge. When we returned our bikes in the early evening, I suspect the man in the shop was mightily pleased to see us, having probably thought that he would never see either his bikes or us again.

Hart's *Haywain*

After our previous day's exertion we had an easy day on Wednesday, taking a trip on the Brecon Beacons' steam railway. The scenery was fantastic and my camera worked overtime! Afterwards we visited Crickhowell, a lovely little town with pastel painted cottages and more colourful window boxes and tubs than I have ever seen before.

Thursday, the day for scaling the lofty heights of Sugar Loaf Mountain, dawned. We set off bright and early for Llanbedr, where our walk began. It was a perfect clear warm day and the walk started gently through lush fields and along river banks. However, the landscape soon changed and the greenery disappeared. It wasn't until we struggled to the top of what we originally thought was the peak that Sugan Loaf actually appeared, far higher and steeper still and my heart sank into my walking boots! I felt more than a little daunted and I was all for giving up. Spurred on by *mummy longlegs*, I continued, whingeing all the way. We arrived at the summit. The wind was biting, but our sense of achievement was terrific.

At the Trig Point on Sugar Loaf, 596 metres

That evening, glowing, we went on to triumph at the village pub quiz, having invited ourselves to join a team of three local people, who we later found out won every month. The local pub is called The *Baskerville Arms* and having been warned about the huge hound with glowing eyes prowling the streets after midnight, we hotfooted it home with our share of the winnings, a bottle of wine.

All too soon it was Friday, our final full day and also Valerie's birthday. She had decided to spend a lazy day pottering around Hay, whilst I went off to the Brecon Beacons. I had spent some time there earlier in the week and was drawn back like a magnet. I loved its beauty and remoteness, very good for the spirit. That evening we returned to the pub for Val's celebratory birthday dinner at which we drank our previous evening's winnings.

Quiz Night at The *Baskerville Arms*

Saturday, and time to pack up and head home. The thought of Nottingham's hustle and bustle meant that I took the whole day to get there, stopping off at the food fayre in Ludlow and several other places on the way. All in all, definitely a holiday to remember!

Last of the Dinosaurs ?

The last year was an exceptionally sad one for patients with Wilson's disease for the reason that no less than three of the GREATS in the story of this disease died. Whilst the story really began in 1912 when Dr Wilson published the original article describing the disease, there were no real advances until 1948 when Professor John Cumings, the professor of chemical pathology at the National Hospital for Nervous Diseases in London, showed that the cause of Wilson's disease was an abnormal accumulation of copper in the brain and the liver. He went on to suggest that the progress of the illness might be arrested if the excess copper could be removed by injections of the metal binding drug, BAL (dimercaprol). This had been originally pioneered by Professor Peters in Oxford at the beginning of the war as an antidote to the war gas Lewisite.

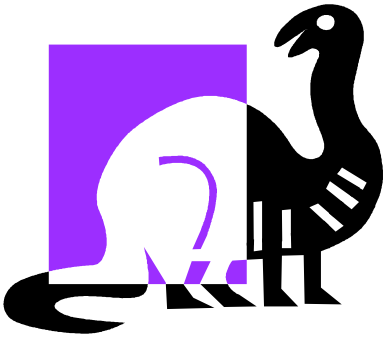
The time had now come for a whole new approach to understanding and treating Wilson's disease. By the early 1950s Cumings in London and Denny Brown and Porter working independently in Boston were able to report that repeated injections of BAL, painful though they may be, did result in real improvement in their patients. But at that time the disease was thought to be exceptionally rare and was seldom recognised which made finding patients to treat a real problem. About the same time Drs Scheinberg and Gitlin and Drs Bearn and Kunkel, both groups working at different centres in New York, reported that in patients with Wilson's disease there was a marked deficiency of the copper carrying protein caeruloplasmin and this was for some years believed to be the cause of the disease. Then in 1956 I was able to describe how a breakdown product of penicillin, penicillamine, was much more effective than BAL in removing copper from the body and had the great advantage that it could be given by mouth avoiding daily painful injections.

Over the period of the next ten years Dr Scheinberg teamed up with Dr. Irmin Sternlieb, a gastroenterologist, to set up a centre for the study and treatment of patients with Wilson's disease at the Albert Einstein College of Medicine in the Bronx whilst Dr. Bearn did the same at the Rockefeller University in Manhattan and I started up a similar service in Cambridge. Another centre was at Salt Lake City and was run by Dr. Cartwright, who was an expert in copper metabolism and was thus drawn into the Wilson's disease story. By the late 1960s patients began to report toxic reactions to penicillamine so, with the help of Hal Dixon, whose obituary is opposite, I developed Trientine as an alternative copper removing drug. It took some fifteen years of struggling with Government bureaucracy to get this accepted and licensed in the British Pharmacopoeia. Also during the 1960s Dr Schouwink in Holland showed that zinc salts could be used in treatment as they blocked the absorption of copper from the gut. Then during the 1970s Dr Starzl in the USA did the first liver transplant for a patient with advanced hepatic Wilson's disease. The final advance in treatment came in the 1980s when I first showed that tetrathiomolybdate could be used in treatment. As it had a dual action, it blocked the absorption of copper from the gut more completely than did zinc and also it tied up copper already present in the body in a harmless form. Unfortunately, in this country, this drug is still not officially recognised and is hard to come by.

The sad part of my story is that during the past year first Sternlieb, then Scheinberg and finally Bearn have all died. Patients with Wilson's disease owe them all a great debt of gratitude. I knew all three well and for me it has been a great personal as well as professional loss. Herb Scheinberg got in touch with me as soon as I described the use of penicillamine and we met and became firm friends, both visiting each other's homes on a number of occasions. I found Herb an invaluable source of knowledge; he probably saw more patients with WD than any other physician and I was always pleased to take the opportunity to seek his advice in difficult cases. We also swapped a small number of patients who crossed the Atlantic. His colleague, Sternlieb, I knew less well but he was also a great source of information, particularly on the nature and understanding of the liver side of WD. He had an enormous fund of knowledge of the literature of WD and was also a very talented linguist. Dr Bearn originally started life in this country and went as a postgraduate scholar to the US, where he became interested in WD. He was a great help to me when I was starting up in this field by allowing me to work in his clinic in New York and try out some of my ideas on his patients at a time when I had none of my own. Later he drifted away from WD and became a leading expert in medical genetics moving from New York to Philadelphia. He kept open his links with this country, having a small house in Cambridge to which he made frequent visits. Dr Scheinberg's work was recognised by obituary notices in the *New York Times* and in this country by an article in the medical journal, *The Lancet*. Dr Bearn also was recognised by the *New York Times* and I rather think *The Guardian*.

Thus of all those involved in the early discoveries in the WD story, I remain as the last survivor, truly ***The Last of the Dinosaurs***.

Dr J.M. Walshe.



Dr H. B. F. (Hal) Dixon (1928-2008)

The Wilson's Disease Support Group-UK (WDSG-UK) will have special memories of Hal Dixon, who died in Cambridge on 30th July 2008. Hal was a Fellow of King's College, Cambridge, and through this connection he was able to arrange for several of our annual meetings to be held in King's College. These meetings concluded with Hal taking us for a 'private' view of the world-famous chapel of King's College followed by a visit to the Fellows' Garden. Hal's Fellowship at King's College spanned fifty-five years and the commentary and insights that Hal was able to provide us with for these privileged tours around King's reflected his commitment and service to the college.

'Insight' is an apt word to describe Hal Dixon, and it was displayed most notably for the benefit of Wilson's disease patients when John Walshe told him in the mid-1960s about the problem of a patient who had become intolerant of D-penicillamine. Hal's doctorate and later scientific work were in biochemistry, in protein chemistry, but he had a very deep understanding of organic chemistry. Hal suggested that the well-known chelating agent triethylenetetramine (trien) (a bottle of which happened to be sitting on his laboratory bench) was a likely candidate for treating Wilson's disease. It had been known from the early 1950s that trien, a quadridentate ligand, forms very stable complexes with cupric ions and with other metals. But Hal also realised that the similarity of the chemical structure of trien to some naturally occurring polyamines meant that it would probably not be toxic to humans if used as a drug.

A few other chelating agents (not related to trien) were also tested in animals around this time, but trien was the most promising agent of those selected for testing. The bottle of triethylenetetramine on Hal's shelf was a 'technical grade' product and was also a liquid. In order to be suitable for patients, trien had to be very pure and in a solid form. Trien is a strong base and can combine with acids to form salts. Salts are invariably crystalline in nature, and can be purified by recrystallisation from suitable solvents. Hal's next insight, based on his knowledge of protein chemistry, was to suggest that the dihydrochloride of trien was the most suitable salt to purify and to use as a drug. John Walshe, Hal Dixon, and Kay Gibbs in Cambridge University put these ideas to practical use, and by the 1970s triethylenetetramine dihydrochloride (now referred to more often by its 'official' INN name, trientine, rather than trien) was recognised as a drug of second choice for treating Wilson's disease.

I came to know Hal firstly through his *Lancet* papers on trientine, and later personally in Cambridge and at the WDSG-UK meetings. At one of these meetings (in Nottingham) I mentioned the problem of the bioavailability of trientine and in particular how to chelate intracellular copper. Hal offered a solution to this problem immediately, based on a paper tucked away in his mind. This solution was both ingenious and synthetically relevant. I think he made some progress experimentally, and I often suggested to him that he should publish at least the idea, if not the practical results.

Hal was always ready to share his scientific knowledge with others, and this willingness to communicate enabled him to carry on with useful scientific work all his life. He was a very courteous man with beautiful manners and a deep interest in his fellow man. It was a privilege to have known him.

Rupert Purchase, DPhil, CChem, FRSC
Honorary Member of the Wilson's Disease Support Group UK. February 2010

Our deepest sympathy goes to Jemima Martin on the sad and tragic loss of her husband Gavin who died in August 2009.

We are grateful to her for holding a collection for WDSG at his funeral in lieu of flowers, which raised a very generous £275.00.

Wilsons Disease Support Group UK

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WDSG-UK

Tell others about the WDSG-UK

Please tell others whom you may know who have WD, who might benefit from the support group and what we are doing.

Inform your family, friends, consultant physicians, GP surgery, local MPs about WDSG-UK

The more people who know about us, the more we can promote a better awareness of Wilson's disease within the community and the better the chance of early diagnosis of WD for future WD patients.

If more copies of this newsletter or patients & families' correspondence list are required, please contact:
Linda Hart

We're on the web
www.wilsonsdisease.org.uk