www.wilsonsdisease.org.uk

Wilson's Disease Support Group – UK

NEWSLETTER

APRIL 2017

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.

It publishes an annual newsletter with informative articles written by medical professionals, and also articles written by patients, their families and friends about their experiences of the disease.

It promotes networking of Wilson's disease patients and their families by helping and encouraging contact with one another.

And the Group strives to promote a wider awareness of Wilson's disease within the medical profession.

AFFILIATED TO :

BRITISH LIVER TRUST

The Liver Patients' Transplant Consortium

GENETIC ALLIANCE UK

RARE DISEASE UK

Children's Liver Disease Foundation fighting childhood liver disease

Climb Children Living with Inherited Metabolic Diseases

Welcome to the latest edition of the WDSG-UK newsletter with the return by popular demand of the complementary *fun* Dingbats quiz. Last year's quiz raised over £300 for the Group, so if you don't wish to take part yourself then perhaps you could sell it on to somebody who does (see *p7)*. Since turning down sponsorship from Univar last year, we are now entirely dependent on membership, donations and fundraising to keep the Group going. We thank everybody who continues to support us in this way.

It has been another busy but enjoyable year for me managing the day to day affairs of the Group while meeting patients up and down the country whenever I can. It's also been all change within the committee this year with **Linda** having left and **Caroline** having returned. More recently, Anne Marie has stepped down and **Rupert** will be retiring at the next AGM. This creates two further vacancies, so if anybody is interested in taking their place please let me know. The committee was formed in 2010 when WDSG-UK was first granted charitable status and we would like to thank Rupert and Anne-Marie for their hard work and commitment ever since. Linda of course has been part of the Group since founding it with Caroline in 2000 and we hope that after her recent op, from which we wish her a speedy recovery, she will come back and join us. Meanwhile, **Jerry** has kindly agreed to take on the role of Chair for the next twelve months.

In last year's newsletter there was much mention of **Alicia's** planned television appearance in the *Medical Mysteries* series. In the event it was postponed for six months. For those of us who were patient enough to wait, although slightly critical of the short broadcasting time, we were nonetheless appreciative of the publicity she and her family gave to Wilson's disease which prompted several enquiries afterwards from members of the public. We would like to thank Alicia for her goodwill in taking part in the programme and we wish her a very happy **21st** birthday and many happy returns!

At the same time, we would like to thank the Oxford University students for giving us a talk at our meeting last year and we congratulate them on winning a Gold Award for their work (see *p17*). At this year's meeting we will be welcoming **Dr Emily Reed** from the University of Sheffield as a speaker. She has kindly written an article for this year's newsletter (see *pp 14-15*) as have **Dr. Alan Stevens** (*pp 10-11*) and patients **Shirley, Katy** and **Caroline**. On *p18* you will find a map of the UK showing where WD patients known to us live. I drew it up recently after receiving a request for this information from the NHS, and have decided to include it as an aid for this year's Dingbats entrants!

Finally, our AGM in Cambridge last July was very well attended and we were particularly pleased to welcome members of the Danish Support Group, together with so many children who were a delight! We hope that you will choose to join us at this year's AGM which will take place in Cambridge on **Sunday, 23 July 2017** (details and booking forms enclosed). Please remember to renew your subscriptions promptly (apologies for the price increase) and remember also to keep up to date with news through our Facebook site. I wish you all a very happy Spring and look forward to seeing you all soon.

Valerie

IN THIS ISSUE ...

Chairman's Report for 2016-17

Photograph: Rare Disease UK/Joshua Tucker

Your committee remains concerned about the price and availability of 300 mg **trientine dihydrochloride** capsules for Wilson's disease patients. We are also monitoring the supply of **D-penicillamine** tablets in the UK. Our **Facebook site** develops as a focal point for patients and their families worldwide to share information and advice on Wilson's disease. We continue to support **Rare Disease UK** and the implementation of the **UK Strategy for Rare Diseases**.

Trientine Dihydrochloride

The repercussions of the price increase for trientine dihydrochloride capsules announced in November 2015 continue to be felt by patients and health professionals. Your committee is involved in several initiatives resulting from this price increase:

1. Jerry and Valerie are collaborating with a number of clinicians and pharmacists in England on a review of the use of trientine.
2. We have responded to reports of patients' difficulties in obtaining trientine dihydrochloride by contacting Univar (the UK manufacturer of the drug) directly and asking Univar for help in individual cases. Assistance has been sought for Wilson's disease patients in the European Union, Australia and India.
3. We are supporting a Sussex-based Wilson's disease patient in his social media campaign to raise awareness about the price increase of trientine dihydrochloride capsules: <www.theargus.co.uk/news/14653201.Concern_as_cost_of_Liver_disorder_drug_increases_by_600_> Accessed 4th March 2017.

The price adjustment for trientine dihydrochloride appears to be part of a trend noted in recent newspaper reports for pharmaceutical companies to increase the price of off-patent drugs, which are cheap to manufacture and which are required by often a relatively small group of patients. For example, see *The Observer*, 29th January 2017, p 8; <www.theguardian.com/society/2017/jan/28/nhs-drug-firms-cancer-patients-at-risk-prices-inflated>

The concern for Wilson's disease patients is that the cost of D-penicillamine might follow this trend. Any unexpected increase in the price of D-penicillamine will be strongly contested by WDSG-UK.

WDSG-UK Meetings

The WDSG-UK management committee met twice during 2016-2017 – in June 2016 and in March 2017. We held the sixth WDSG-UK AGM as part of our annual meeting for members, family and friends in Cambridge on 24 July 2016, and a report of this meeting appears on ***pp4-5*** of this Newsletter.

Donations and Fundraising

We are particularly grateful to those of you who continue to make donations with your membership fees. At the same time we should like to thank our fundraisers (see ***pp6-7***) who between them this year have raised **£2,500**. In the absence now of sponsorship from *Univar*, the manufacturers of trientine, we are entirely reliant on your generosity to finance us.

WDSG-UK Facebook Site

Expertly managed by Valerie, our Fb site (currently, March 2017, with over 630 members worldwide) continues to provide a lively and informative forum for patients' concerns and queries about Wilson's disease.

Wilson's Disease Patient Register – UK

Our Patient Register currently has the names of over fifty patients on it. If you have not registered already, then please consider doing so (form available from Valerie or off our website: www.wilsonsdisease.org.uk). WDSG- has been approached by several organisations embarking on research into Wilson's disease (see ***p17***).

NHS Blood & Transplant (*NHSBT*), British Liver Trust, and Liver Patients' Transplant Consortium

On 13 July last Valerie, on behalf of WDSG, attended the annual meeting in London of representatives from the above Groups where organ donation and transplantation in the UK was discussed. It is encouraging to learn that organ donations are increasing, leading to a reduction in waiting time for patients needing transplants.

Genetic Alliance UK AGM

Three presentations from this September meeting, attended by Jerry, were of particular relevance for WDSG-UK:

1. An account by Dr Gina Radford Deputy Chief Medical Officer of the UK's 100,000 Genomes Project and

her role as 'Rare Disease Champion'. Dr Radford's remit should lead to a greater focus on rare disease issues within the NHS

2. A talk by Dr Jonathan Fielden, Director of Specialised Commissioning and Deputy National Director, who is responsible for a £15 billion budget, which includes spending on services for rare disease. In 2017, he will be negotiating with pharmaceutical companies on the cost and supply of drugs for the NHS.
3. The launch by Genetic Alliance UK of their report 'The Hidden Costs of Rare Diseases' The study outlined the costs associated with managing rare disease patients, and highlighted the need for a full-scale research project about managing and treating rare diseases.

Midlands Rare Disease Showcase

In October, Jerry attended this event organised by Birmingham Children's Hospital (BCH) to promote awareness of rare diseases. BCH treats 9,000 young patients with rare diseases a year, and 75% of all rare diseases are diagnosed in children. BCH's expertise covers the management of 500 rare diseases. A new paediatric rare disease centre at BCH will come into service in 2018. This new building is specifically designed to offer co-ordinated clinics, assessment and diagnostic services, and aims to ease the transition of children with rare diseases into adult services. BCH is keen to engage with patient organisations within the new centre, and WDSG-UK welcomes this approach.

NIHR *Think Research* Rare Disease Patient Support Groups' Day

Also in October, Jerry and Valerie represented WDSG-UK at an event organised by the National Institute of Health Research (NIHR) at the Barbican Centre, London. Medical research grant applications now require the endorsement of Patient Support Groups. The meeting included a discussion on the future of rare diseases, and four very helpful workshops on 'Ethics', 'Reading Study Protocols', 'Patient Information Leaflets', and 'Running a Successful Patient Group'.

Rare Disease Day 2017

This year's Rare Disease Day was recognised by a number of meetings in the UK, including a reception on the terrace of the House of Commons on February 28th attended by representatives from the many rare disease organisations, including WDSG-UK, who belong to Rare Disease UK. Nicola Blackwood MP, Parliamentary Under Secretary of State at the Department of Health, spoke movingly about her commitment to implementing the UK Strategy for Rare Diseases, and there were additional presentations from Fiona Marley, Head of Highly Specialised Commissioning, NHS England, who reported on the successes of the UK 100,000 Genomes Project, and Sarah Stevens, who works for the National Congenital Anomaly and Rare Disease Registration Service (NCARDRS), Public Health England.

WDSG-UK Annual Meeting and 7th AGM

The 2017 Wilson's Disease Support Group – UK meeting has been arranged for Sunday, **23 July 2017** at the clubhouse of the city of Cambridge's Rugby Union Football Club. During the course of this meeting the 7th WDSG-UK AGM will be convened. An agenda for the AGM is included with this Newsletter. As part of the AGM, the election of officers and members of the WDSG-UK Management Committee for the year 2017-2018 will take place. I will be standing down as Chair this year and like Anne-Marie Le Cheminant will be leaving the committee. We will therefore be recruiting WDSG-UK members who wish to join the committee. If you would like to become involved with committee work, please forward your name to Valerie. We also welcome and encourage our Facebook friends who are not WDSG-UK members to join the WDSG-UK and attend our annual meeting in Cambridge.

I am once again grateful to members of the WDSG-UK management committee for their support during the past year: Valerie Wheater, Jerry Tucker, Anne-Marie Le Cheminant and Mary Fortune. I particularly wish to acknowledge the hard work and commitment of Valerie to the worldwide Wilson's disease community during my tenure as Chair of WDSG-UK, 2010 to 2017.

Rupert Purchase,
March 2017

Wilson's Disease Support Group Meeting & 6th AGM

Cambridge Rugby Union Football Club, Sunday 24 July 2016

A warm July day saw the largest ever gathering of the Wilson's Disease Support Group – UK for our annual meeting at the Cambridge Rugby Union Football Club. Many new members of the Group were able to attend this year, including **George Fortune**, **Ellie Gurnett, Jean Turley**, **Parbinder Singh** and **Kam Kaur**, **Katy Quinlan**, **Marta Targowska** and the **Chicu** family. From Denmark, we were delighted to welcome **Marie-Louise Ottesen** and her mother **Lisbet**. Lisbet runs the WD Support Group in Denmark and was keen to make a connection with our Group.

It was also good to welcome back **Katie Hibbard**, **Alicia Goss, the Jeon family**, **Scott Walker**, **Emma Collcott, Anusha Joseph** (our photographer again for the day), **Keith Pereira,** and **David Lin**. David, whose story appeared in the 2016 newsletter, had flown in especially from Taiwan to surprise us all!

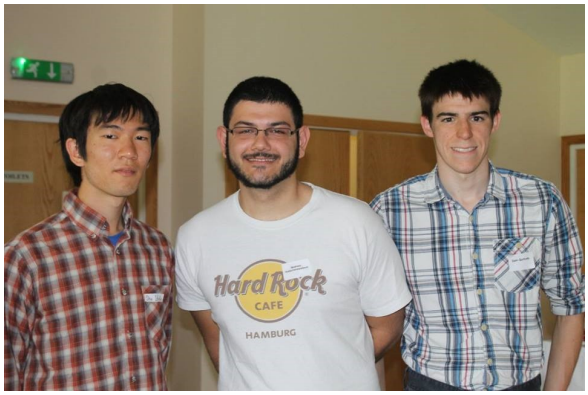
Another surprise guest was the singer-songwriter **Danny O'Donoghue** accompanied by his sister **Victoria**. The meeting was further enhanced by the presence of **Kay Gibbs**, the nonagenarians **Dr John Walshe** and **James Kinnier Wilson**, and the participation of clinicians **Dr Godfrey Gillett** and **Dr James Dooley**, whose presence and support we always appreciate.

In his introductory remarks, **Rupert Purchase**, Chair WDSG-UK, reported the sad news of the deaths of two of our members Jon Tarbin and Charlie Watsham, who regularly attended our meetings. On a more positive note, he presented **Katie Hibbard** with a prize for winning Valerie's ingenious *WDSG-UK* Dingbats competition, which was published and distributed with the 2016 Newsletter.

Jerry Tucker, Vice-Chair (WDSG-UK), summarised recent developments with the Wilson's Disease Patient Register – UK, and the involvement of the two rare disease centres in Birmingham with this project. The proceedings before lunch concluded with a presentation by three biochemistry students from Oxford University – **Andreas Hadjicharalambous**, **Sam Garforth** and **Shu Ishida** – on their novel idea for the treatment of Wilson's disease. In simplified terms, it is suggested that a genetically-modified gut bacterium, which can chelate copper, could colonise the gut microflora and thereby reduce the absorption of dietary copper, thus alleviating the organ-specific effects of copper in patients with Wilson's disease. The design of this bacterium and news of this Oxford initiative may be found at https://oxfordigem2016.wordpress.com/

Lunch was followed by the 6**th WDSG-UK AGM** and the election of the WDSG-UK management committee for 2016-2017, with **Caroline Simms** replacing **Linda Hart** as a committee member. Linda was presented with two garden-themed gifts in recognition of her many years' work on the committee and supporting patients. Rupert thanked members of WDSG for the imaginative ways in which they have raised funds over the past year, before **Danny** and **Alicia** hosted this year's raffle, which produced a further **£99** for the Group.

The steep rise in the cost to the NHS of the price of trientine



Shu, Andreas and Sam from Oxford University's iGEM team talking about a synthetic biology future

At front of picture, James Kinnier Wilson (l), Dr Walshe (r)

Exchanging glances...

Over lunch

dihydrochloride imposed by the UK supplier Univar (600% in two years) has caused much concern to patients and clinicians. This meeting was therefore an opportunity for us to share these concerns. Opening a 30-minute discussion on trientine, Rupert summarised the current situation and mentioned that in the USA Valeant Pharmaceuticals has increased the price of both trientine and penicillamine to over $20,000/100 capsules or tablets for each drug (November 2015 data). Options to challenge Univar are limited at present. There are initiatives by the UK government to examine the role of trientine in Wilson's disease, and WDSG-UK members are encouraged to sign an online petition to protest about Univar's price increase: https://you.38degrees.org.uk/petitions/stop-pharmaceutical-companies-hiking-vital-drug-prices-unfairly.

The meeting concluded with a question and answer session between the audience and the three consultant physicians present. Questions on gene therapy, and UK genetic services for testing for Wilson's disease were raised for discussion.

Finally, as is our tradition, a Group photograph was taken before we dispersed into the afternoon sunshine. We hope members felt it was a useful and helpful day.

Alicia and Danny drawing the Raffle

Jean with her son, John and husband, John

Danny and Emma

Scott with mum, Dawn

Patients' Group photograph with Dr Walshe far right…

Stuart and baby, Eleanor

Fundraising 2016-17

The Goss Family's Car Boot Sale

Alicia and her mum and dad, **Trixie** and **Patrick**, and her sister **Elise** and her boyfriend, set their alarm clocks to wake them up at some unearthly hour on the morning of Sunday, 17 July and set off with a car full of personal and household effects that they had decided to part company with. Arriving at 6 a.m. at Tripes Farm Car Boot Sale on the outskirts of Orpington with views over the surrounding Kent countryside, they were amazed to find that so many other people had arrived there ahead of them!

Alicia running the stall singlehandedly...

This was as much about raising awareness of Wilson's disease as it was about getting rid of unwanted household possessions. Alicia and Trixie took every opportunity to explain the condition to all who stopped at their stall, handing out fact sheets to reinforce the message. Alicia also took the opportunity to tell everybody who didn't stop at the stall but who were merely walking past!

They were delighted to have raised just over **£130.00** for the Group and we are grateful to them for all their hard work. They said, "It was a long, tiring day and there were a few mutterings of "never again" in the car on the way home not to mention later regrets when we found we had sold something that we wished we'd kept! However, the money collected made it all worthwhile and besides, Alicia is determined to raise awareness of Wilson's disease, wherever and whenever she can."

...while mum hands out fact sheets about WD and dad takes a well earned rest!

I understand from Patrick that Trixie now has an old sweet jar sitting on the shelf at home. She has labelled it *Wilson's disease* and anyone who pops round to see them is *nabbed* for their loose change. As Patrick amusingly says, "There's no such thing as free coffee in **our** house!"

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Sylvia's Summer Bring & Buy Sale

On 27 August last **Sylvia Penny** held her tenth consecutive Summer Bring and Buy Sale at the Victoria Park Methodist Chapel in her home town of Torquay. Her granddaughter, **Emma Coombes,** was diagnosed with Wilson's disease in 2007 at the age of 26 (see her story in the 2014 newsletter) and by holding these fundraising events for *WDSG*, Sylvia feels that she is making a contribution to the Group in appreciation of the help that it has given her over the years.

Emma crouched behind Ashton (sitting on the floor at the front next to her sister Daisy), with Sylvia behind Emma and Sheila on Sylvia's left.
Iris, who has died recently, stands between Sylvia and Sheila in the row behind.

I was particularly sorry not to be able to join them again this time and to catch up with all the family including Sylvia's daughter, **Sheila**, her granddaughters **Daisy** and Emma and Emma's children **Amy** and **Tom**. Together, they work hard to make the event such a success, spending the entire year collecting raffle prizes and goods for the stalls from friends, neighbours and local businesses. We thank them once again for raising a further **£400** for the Group.

On a sadder note, we would like to say how sorry we were to hear that their dear friend, **Iris Keay**, died on 23 January 2017 aged 94. Iris always helped at these events and more generally in the cause of raising funds for the Group and we were touched to hear from her solicitor recently that she has kindly made a small bequest to *WDSG-UK* in her Will.

Belinda's Baking Bonanza

Belinda Diggles who was diagnosed with Wilson's disease in 2001 raises funds all year round for *WDSG-UK* and also for local charities in the St Helens area, where she lives. This year has been no exception. Having reached her target of raising **£1,000** for us by the end of our last financial year (April '16), she found herself back in the kitchen this summer stewing apricots and berries and simmering onions and tomatoes in her quest to restock the jams and chutneys which she makes for her friends. The sale of these, together with a magnificent tea party she held at her home in July, her traditional Christmas puddings and mince pies and her assorted January marmalades, have raised a further **£850** for the Group.

Supercalorificisticexpialidocious!

One has to remember that on top of this Belinda also has a husband to pamper, a son and daughter-in-law living in the States whom they visit whenever they can, another son and daughter-in-law who recently got married, a part-time job that takes her out of the house three days a week and, most recently, a ten week old puppy called **Jess** who is proving to be more demanding than the rest of them put together! We are therefore particularly grateful that she still has time to think of us and we thank her and all her supporters for raising this **outstanding** sum between them.

Belinda at her son's wedding

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Lesley's Pottery Stall

Lesley Galloway, whose daughter **Emma** was diagnosed with Wilson's disease in 2005 has in the past few years turned her hand to potting, attending weekly classes at her local Arts Centre. Recently, she has learnt to use a wheel which took her a year to get to grips with, during which time very few of her creations survived. She says, "I find it hard but I do enjoy it and it is very therapeutic. The glazing is particularly difficult. I have yet to reach the standard of the potters in *The Great Pottery Throw Down*! It is so frustrating that there are many ways of getting it wrong and only a few ways of getting it right!"

Lesley very kindly had a stall at our AGM last July and sold fifteen mugs that **had** survived. We thank her for this fundraising venture which raised **£90** for *WDSG*.

Lesley's WDSG glazed mugs

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In addition, we would like to thank the students of ***Fife College*** in Scotland who hosted a *Movie Night* on 5 May 2016 to raise funds for the Group in support of a fellow pupil of theirs who had recently been diagnosed with Wilson's disease. The event raised **£254.82.**

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We would like to thank the **Oxford University's *iGEM* team** who gave us a talk at our meeting last summer and then returned to Oxford and held a cake sale in the department to raise awareness of Wilson's disease. They raised **£237.59** for us. We send our congratulations to them for winning a Gold Medal for their WD project (see *p17*).

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We would like to congratulate **Lucy Neville** and **Dan Weaver** on their marriage in August last year, and to thank them and their guests for holding a collection at the wedding in memory of Lucy's mum who died of Wilson's disease in the 1980s. They raised **£112.00** for the Group.

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And finally, the ***Dingbats*** quiz that I produced last year and included in the 2016 newsletter raised over **£300.** Although free to members, copies were kindly sold to friends on my behalf by **Linda, Belinda, Kath** and **Jane**, and by me to the unsuspecting Cambridge public! In particular, I would like to thank ***Stratajet*** who generously sponsored the venture in the sum of £100. If anybody would like to sell copies of the 2017 *Dingbats* quiz or even just their own, then please let me know. Let's see if we can raise as much again this year. Every penny counts!

Shirley's Story

by Valerie

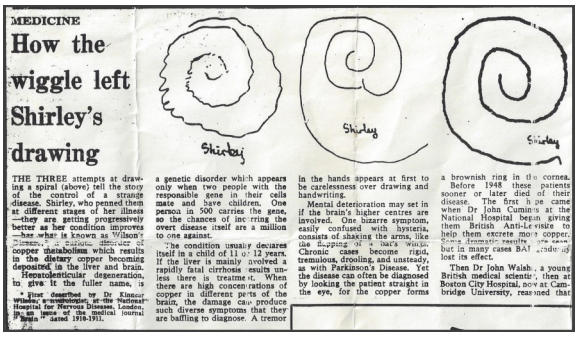
At the end of October last year I received an email out of the blue from a lady living in London. The email was headed *How the Wiggle left Shirley's Drawing* and it continued, "My name is Jennifer and I manage a small community hall called William Gibbs in Westminster, London. What is really fascinating is that the above caption is about my coffee morning attendee **Shirley** who lives here on the *Peabody* Estate. She was one of the first people that Dr Walshe saw in the 1950s when he first discovered penicillamine..."

Shirley - Feb 17

Now that was an email that I wasn't likely to ignore. Dr Walshe has on several occasions asked the Group if it had ever heard from a lady called Shirley who was one of the first patients that he ever treated. None of us ever had. Surely it was too big a coincidence that two ladies called Shirley had been treated by Dr Walshe in the 50s. There was only one way to find out - a trip to London!

With Christmas intervening it was quite a while before I could arrange a visit. I had had no direct contact with Shirley at all but Jennifer and I continued to email one another, she acting as the intermediary. She assured me that if I turned up at 2.00 o'clock on a particular afternoon, she would make sure that Shirley would be there to see me. On an uncharacteristically sunny St Valentine's Day afternoon, I presented myself in the courtyard of a grand Victorian building set in the shadows of the Houses of Parliament, to be greeted by Jennifer and later by Dr Walshe's seventy-seven year old former patient, Shirley Wylie. What a treat!

Jennifer had kindly opened the hall especially for us and we went inside for coffee. Shirley began by handing me a copy of a 1964 cutting from the *Sunday Times* headed *How the wiggle left Shirley's drawing.* This obviously was the explanation for Jennifer's subject heading in her emails. Above the article were pictures of three spirals, the symbol Caroline and Linda adopted for the welcome section on the front page of the newsletter. Historically, Dr Walshe used to ask all his patients to draw spirals when they were first diagnosed and to repeat them on subsequent visits to see if motor control had improved. Their presence in this newspaper cutting indicated that Dr Walshe was associated with the article.



MEDICINE

How the wiggle left Shirley's drawing

THE THREE attempts at drawing a spiral (above) tell the story of the control of a strange disease. Shirley, who penned them at different stages of her illness —they are getting progressively better as her condition improves —has what is known as Wilson's Disease, a hitherto obscure [illegible] copper metabolism which results in the dietary copper becoming deposited in the liver and brain.

Hepatolenticular degeneration, to give it the fuller name, is

* First described by Dr Kinnear Wilson, a neurologist, at the National Hospital for Nervous Diseases, London, in an issue of a medical journal dated 1910-1911.

a genetic disorder which appears only when two people with the responsible gene in their cells mate and have children. One person in 500 carries the gene, so the chances of incurring the overt disease itself are a million to one against.

The condition usually declares itself in a child of 11 or 12 years. If the liver is mainly involved a rapidly fatal cirrhosis results unless there is treatment. When there are high concentrations of copper in different parts of the brain, the damage can produce such diverse symptoms that they are baffling to diagnose. A tremor

in the hands appears at first to be carelessness over drawing and handwriting.

Mental deterioration may set in if the brain's higher centres are involved. One bizarre symptom, easily confused with hysteria, consists of shaking the arms, like the flapping of a bird's wings. Chronic cases become rigid, tremulous, drooling, and unsteady, as with Parkinson's Disease. Yet the disease can often be diagnosed by looking the patient straight in the eye, for the copper forms

a brownish ring in the cornea. Before 1948 these patients sooner or later died of their disease. The first hope came when Dr John Cumings at the National Hospital began giving them British Anti-Lewisite to help them excrete more copper. Some dramatic results [illegible] but in many cases BAL [illegible] lost its effect.

Then Dr John Walsh, a young British medical scientist, then at Boston City Hospital, now at Cambridge University, reasoned that

▲ ***The Sunday Times article 26.01.1964***

So what exactly was Shirley's story? She told me that she was born in Islington in July 1939 as the youngest of six children, all of them girls! There were twenty-two years between her oldest sister, Mary, and her although Mary had died as a child so she never actually knew her nor what she had died of. War broke out less than two months after Shirley's birth and although she remained with her parents in London throughout the War, narrowly escaping several bombs, she was lucky enough to have survived the period to now tell the tale!

Asked about her memory of childhood, Shirley remembers doing well at school and specifically being around third from the top of her year in her teens. She considers herself to have had a normal childhood and good health apart from a stay in hospital when she was about ten. She had developed pneumonia and had a collapsed lung. She made a speedy recovery and returned to school. The only other health problems she can recall in her adolescence were several very severe nosebleeds. In 1953 she vividly remembers attending a Street Party that was held to celebrate the coronation of Queen Elizabeth II, and it was around that time that people began commenting to her parents that they thought something was wrong with her. On one day in particular, she had been out food shopping as was her custom and she remembers having difficulty walking home, staggering along the street in an erratic fashion. Thereafter her memory of events is hazy and Dr Walshe takes up the story.

"Shirley was the first patient that I ever treated. I returned to the UK in August 1955, after a 12 month scholarship at the Boston Hospital in the States, with 50 grams of penicillamine, a drug which I had discovered while working over there as a possible chelating agent for patients with Wilson's disease. On my return I went back to work at University College Hospital (UCH), London, in search of patients on whom to trial my new medication. My father was a leading neurologist at the National Hospital for Nervous Diseases (now known as the National Hospital for Neurology and Neurosurgery (NHNN)) at Queen Square, London, the same hospital where Dr Samuel Kinnier Wilson, who first described Wilson's disease in 1912, had worked. I asked my father if he would enquire among his professional colleagues whether any of them had patients with Wilson's disease in their care. My father found three such patients, two that were based at NNHN and another that was in the care of Dr Ashby, a consultant neurologist at Whittington Hospital in North London. This last patient turned out to be sixteen year old Shirley.

I visited her in hospital and with the agreement of Dr Ashby, gave her a low dose of penicillamine. I had taken some myself previously and had suffered no ill effects. Shirley had been at *The Whittington* for some time and had received no effective treatment. She was bedridden, had to be fed and dressed, was shaking uncontrollably and her speech was practically incomprehensible. She tolerated the penicillamine I gave her very well and Dr Ashby agreed for her to be transferred into my care at UCH. There she remained for some time until she gradually started to improve. The chief biochemist at *Distillers* kindly agreed to make further quantities of penicillamine for me and I went on to use it successfully on many more patients. In 1957 I moved to Addenbrooke's Hospital in Cambridge and Shirley remained my patient until I retired in 2000.

On 7 January 1956, roughly six months after starting her on treatment, I was able to write up Shirley's case in *The Lancet: Wilson's disease new oral therapy (pp25-26)* based on her positive response to penicillamine. Thereafter penicillamine was accepted by other doctors in the treatment of Wilson's disease."

I asked Dr Walshe about the article Shirley had shown me from the newspaper. He said that he had been approached by the Medical Correspondent of *The Sunday Times* who had been reading through past issues of *The Lancet* and had read the story of Shirley. The medical correspondent had promised Dr Walshe fame and fortune once his article had been published. As it was Dr Walshe waited for the telephone to ring on the day of circulation, but he received only one call, from the daughter of Samuel Kinnier Wilson, who pointed out that her father's name had been spelt incorrectly in the article! So much for the fortune and fame that had been promised!

Shirley and Harvey - 1962

Shirley's memory of events since she started to get better are a lot more clear. She was discharged from hospital at the end of 1955, continuing to improve by the day. She returned home to her parents and tried to make up for the time that she had spent in hospital. Seven years later, on 20 October 1962, she married her husband, Harvey, and they are still happily married today. The wedding took place at Caxton Hall in Westminster, a venue favoured by the rich and famous and near which they still live today. She had been a regular churchgoer but decided that a church service would take too long and would not be conducive to her wearing a new lilac coat and dress which she had recently bought! She and Harvey took the train to Southend afterwards where they spent a very happy honeymoon.

She was worried about starting a family, as in 1962 few treated Wilson's disease patients had done so already, but by 1971 at the age of thirty-two, she gave birth to her first child, a son, followed by two further healthy children at two yearly intervals. At that time, of the few children that had been born to Wilson's disease mothers, all had turned out to be boys. Dr Walshe had speculated that penicillamine might have been responsible for this. Unfortunately for him, in April 1975 Shirley produced her third child, a daughter, and any commercial interest in him having discovered a drug which determined male selection had been eradicated in one. My producing a daughter six months later didn't help!

Shirley has remained on penicillamine throughout her life, and will have been taking it for 62 years at the end of the summer, longer than any other patient in the world. She has had good health and has worked throughout her life. She has asked me through this article to pass on her personal thanks to Dr Walshe in the knowledge that, without him, she is unlikely to have been here today to tell her remarkable story.

Elastosis Perforans Serpiginosa

by Dr A. Stevens

Wilson's disease itself rarely gives rise to skin problems, although patients with liver involvement may develop spider naevi or, in severe liver disease, some degree of jaundice. Most of the skin problems associated with Wilson's disease arise as a complication of the treatment.

Penicillamine, a highly effective and often life-saving drug used in the treatment of Wilson's (and also used in treating rheumatoid arthritis) is well-known to produce a range of skin rashes as a side-effect. Here I will concentrate on one particular skin disease which is rare but dramatic (and quite a mouthful to pronounce), **elastosis perforans serpiginosa** (**EPS** for short).

EPS occurs in three main circumstances:-

- it can occur spontaneously, with no obvious cause or association with other disease ("idiopathic EPS");
- it can occur in association with other disorders such as Ehlers-Danlos syndrome, Marfan syndrome and Down's syndrome;
- it can occur as a complication of some drug treatments, including penicillamine.

Fig 1 is a picture of a patient with this disorder, located on the neck, a common site. It usually presents as a cluster of small raised, often reddish, nodules about 3 - 5 mm in diameter, arranged either in a line, circle or in a wavy snake-like line. Each nodule eventually develops at its peak a pit filled with brownish crusty material. As in Fig 1, the commonest site is the back of the neck, but it can also occur on the side and front of the neck and elsewhere on the face, and occasionally on the arms. Rarely it occurs on the legs or trunk. The most prominent lesion (***x***) represents a perforated lesion as shown in ***Fig 2c***. The earlier (unperforated) lesion marked (***y***) equates to ***Fig 2b***.

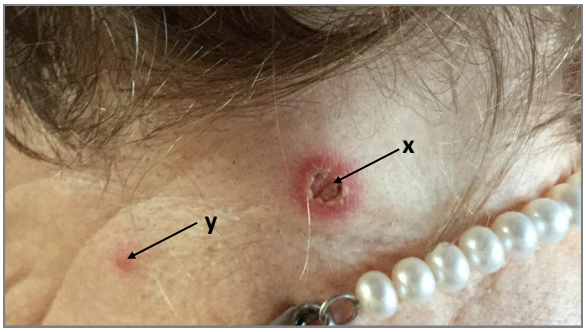


Fig 1

To understand what happens in this skin lesion, it is necessary to know the microscopic structure of the skin (see ***Fig 2a***). The skin has three layers:-

- the **epidermis,** which is the top surface in contact with the air. It is made up of layers of epithelial cells called keratinocytes;
- underneath the epidermis is the **dermis** which contains blood vessels and nerves, and is made up of **collagen** and **elastic** fibres produced by cells called fibroblasts. The dermis is the layer which gives the skin its texture. In youth the skin is taut and smooth, but with ageing it becomes progressively less taut and more wrinkly. This is entirely due to ageing changes in the dermis; and
- underneath the dermis is the **subcutis**, which is mainly composed of fatty tissue which acts as a shock absorber and a thermal insulator.

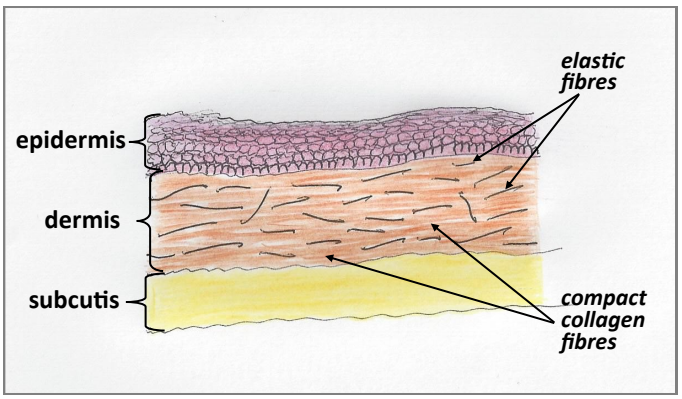


Fig 2a Normal skin with intact straight elastic fibres in dermis

In EPS, the major abnormality occurs in the dermis, and is associated with abnormalities in the **elastic fibres.** Elastic fibres are composed of two fibrous proteins called **elastin** and **fibrillin.** Elastic fibres can be likened to an elastic band in that it is stretchable, and maintains the smooth texture of the skin in youth. However, like an elastic band, as it gets old it can become less stretchable and brittle, and may fragment. This deterioration in the quality of the elastic fibre is what makes our skin less smooth and more wrinkly in old age (very little to do with

the collagen in the dermis which the beauty industry tries to make you believe, with its so-called collagen improving creams!) The main problem lies in the fibrillin component which holds the elastin fibres in stable position, and this fibrillin component is most vulnerable to the effects of ageing, and probably most sensitive to toxic effects. Before I go into the detail of how penicillamine may affect elastic fibre structure and function, let us look at what happens in the skin in elastosis perforans serpiginosa.

The early changes (lesion ***y*** in *Fig 1* opposite) are shown in ***Fig 2b***. The elastin fibres, instead of being long and straight, are fragmented and a bit knobbly, an appearance (under the microscope) fancifully likened to blackberries on a branch of a bramble bush. These abnormal fragmented elastic fibres accumulate in clumps in the upper dermis, producing a raised lump in the skin. Because the fibres are abnormal they produce inflammation around the clumps, and this makes the raised skin lumps red.

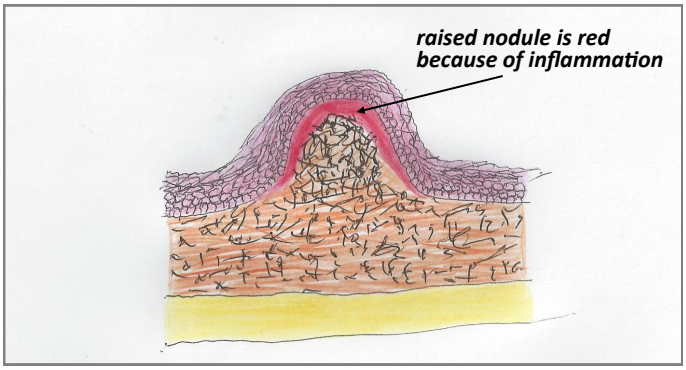


Fig.2b Early lesion of EPS with degenerate elastin forming raised nodule

In the fully developed lesion shown in ***Fig 2c***, the clump of abnormal and fragmented elastic fibres is being extruded on to the surface of the skin by perforating through the overlying epidermis. The brownish crusty material in the pit at the tip of each nodule is made up of this extruded degenerate elastin. Again there is inflammation in the raised skin lump, producing reddening. This stage can be seen in the clinical photograph *Fig 1*, as the main lesion identified as ***x***.

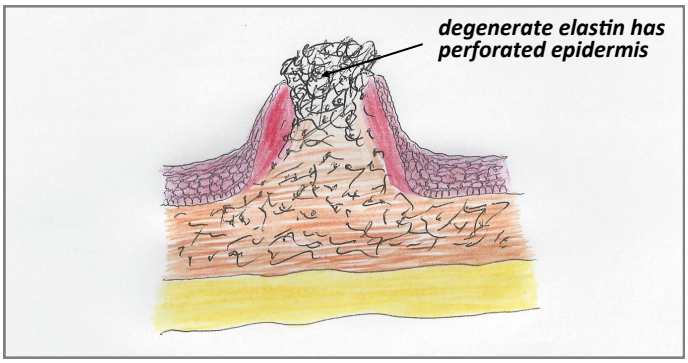


Fig. 2c Late lesion in EPS. Nodule of degenerate elastin has broken through epidermis and formed brown plug

EPS can occur as a complication of treatment by penicillamine for Wilson's disease, rheumatoid arthritis and a rare genetic disease called cystinuria; its incidence is thought to be related to the dose of penicillamine (more common if the dose is greater than 1 gram per day), although cases have been described in rheumatoid arthritis patients on lower doses. Only 1 in a 100 Wilson's patients on penicillamine will develop EPS.

EPS is but one of a group of skin diseases in which the underlying abnormality is damage to, and disruption of, the elastic fibres (*elastolysis*); other diseases in this group include **cutis laxa** (in which the skin is lax and forms folds) and **pseudoxanthoma elasticum** (in which yellowish lumps appear in the skin of the neck, armpits and other areas). Patients who develop EPS after penicillamine sometimes have associated cutis laxa, and skin changes which mimic pseudoxanthoma elasticum in clinical appearance but with slight differences in the appearances under the microscope.

It is interesting that genetic abnormalities have been discovered in idiopathic EPS, in cutis laxa, and in pseudoxanthoma elasticum, a point I will come to below.

It is known that the formation and maintenance of elastic fibres is partly dependent on the activity of an enzyme called lysyl oxidase, and that the functioning of this enzyme is dependent on the presence of copper ions. It is proposed that high doses of penicillamine clears the skin of copper, and that this leads to malfunctioning of lysyl oxidase and hence damage to elastic fibres. It is unlikely that this is the sole reason for EPS developing since, if it were so, every patient on high-dose penicillamine would develop it, instead of only 1 in a 100. Furthermore, patients on other copper-chelating drugs, such as trientene, would probably also develop it, although trientine may be less efficient at chelating copper from the skin than penicillamine. Taking into account the known genetic basis of idiopathic EPS and the other skin lesions based on abnormal elastic fibres, it may be that there is a genetic predisposition, whereby only certain patients develop EPS when treated with penicillamine.

Caroline's Story

by Caroline Simms

For those of you who are new to the Group, I am **Caroline**. In 2000 I set up the Wilson's Disease Support Group - UK with Linda Hart in Nottingham, where we both lived. We ran the Group together until my liver transplant in 2004, when Valerie stepped in to help. It took me a long time to recover from the transplant, as the steroids they put me on knocked me for six. I moved down to Cambridge at the end of 2015 to start a new job there and now live in Bury St Edmunds which is thirty miles away. I was re-elected on to the committee last July.

Caroline today in her home town of Bury St Edmunds

I wanted to write about my diagnosis of Wilson's disease. My symptoms started when I was 11 after I transferred from Junior school where I had been well and happy, to Redhill Comprehensive a large school in Arnold outside Nottingham. I was one of the youngest in my class. In the first year I started to get symptoms. I was the shaky freak who everyone in my class thought it would be fun to tease. Perhaps fun for them but certainly not for me. Aged 11, I was playing the violin and swimming for Arnold Swimming Club, but two years later all this had stopped. I was bullied because I was ill and different from the others. If you stand out from the pack you are fair game for the bullies.

At the age of 12, I started to have problems with painful knee joints, probably due to the onset of copper toxicity. Life at this point was difficult. My schoolwork deteriorated, I choked on food and liquids constantly and dribbled a lot. Still I persevered. I was always academic but had started to become withdrawn. I felt there was something seriously wrong with my health but after repeated trips to my GP it just felt like no one was listening and that I was making these symptoms up. I was repeatedly diagnosed with stress and anxiety and not investigated further. At the time little did we know that Wilson's disease, a potentially fatal yet treatable condition, was the cause and that my late diagnosis would mean a future liver transplant.

I don't blame anyone, not even the GP who couldn't even be bothered to refer me to the hospital for further neurological tests. He eventually did, but too much damage had been done to my liver. I suppose I am a bit angry but have since met patients whose siblings died from the disease, having been undiagnosed or diagnosed too late. So I am lucky in that respect. Anyway I gave up playing the violin aged 14, failing Grade V, and could no longer swim as I could not coordinate my breathing due to the neurological effects of the disease. I would just swallow water and choke.

In my third year we were studying Romeo and Juliet in the English class. All the class volunteered me to read the part of Juliet. I suppose they thought this would be a laugh knowing that I slurred my speech. The teacher was no better as when I said I didn't want to read the part, he insisted that I did. Anyway, the class were in hysterics. I did my best until I told myself this was totally unacceptable. I stopped reading, stood up, threw the book at the teacher, told the class I would read no more and that they were indeed a cruel bunch of idiots, left the classroom, walked home and refused to go back to school. I had finally had enough. We were given the Lord of the Flies to read over summer, but I dreaded going back. Never have I been so humiliated in all my life. I decided that it was show time: I needed to find out what was wrong with me and fight back.

Struggling to play the violin shortly before her diagnosis in 1987

I got diagnosed in September 1987 after one week in Queen's Medical Centre, Nottingham. Dr Jefferson, consultant neurologist, was the main man who recognised what might be wrong as he had had another Wilson's patient the year before. I will always be grateful to him for diagnosing me so quickly. I remember feeling a great sense of relief to know I had not been making things up and that WD was a treatable condition. I spent a further week in hospital while they started me on D-penicillamine, but it didn't suit me as it severely affected my white blood count. Trientine was the next drug of choice which suited me better, so they put me on that and my symptoms seemed to stabilize and over four to five months gradually improve. However, they never completely went away. I stopped drooling and choking on food and drink but the shaking never completely disappeared and my speech was often slurred. I was never able to return to the violin and nor was I able to resume swimming competitively, but I did get back to some sort of normality, whatever normal is!

I think in the end I missed four weeks of school. My form teacher explained to my classmates that I had been diagnosed with a serious condition and that anyone seen teasing me would be dealt with by the headmaster. This threat seemed to stop most of the teasing and bullying. Yes I did my GCSEs eighteen months later and got four As, four Bs and a C and then left school to do my A' levels at Sixth Form College which was a lot better with new friends, etc. I refused to do general studies as this, in my opinion was a waste of my time and I felt it better to concentrate on my A' level Physics, Chemistry and Biology, for which I got 2 Bs and a C. I was proud of my achievements. During my time at 6th Form, I spent two years working as a Saturday girl in my grandparents' haberdashery shop in Arnold, to fund my nights out watching bands at *Rock City* in Nottingham City Centre!

I then got a place at the University of Leicester for three years fulfilling my dream of studying Chemistry at degree level. In my first year I very nearly died of an oesophageal variceal bleed. Surviving by the skin of my teeth, my studies continued but I discovered my liver was so badly damaged that I would need a liver transplant at some point. I had many endoscopies during that time and my varices were banded which kept me alive. Following graduation, I moved to Brighton to embark on a PhD in Bio-organic chemistry. This was hard graft but I learnt a lot about self-motivation with respect to research, the strive for greater knowledge spurring me on. I met some very interesting people on the south coast and it was refreshing to live by the sea, especially because the nearest coastline to Nottingham is 80 miles away at Skegness.

Graduating on her 21st birthday in July 1994

After Brighton I began working for a company manufacturing Agrochemicals in Huddersfield. Huddersfield, in case you've never been, is a lovely town in West Yorkshire surrounded by beautiful countryside. I lived at Dalton Grange, which was owned by the company and was used as a conference hall. It used to be the place where all the company bigwigs lunched and smoked cigars and drank brandy, back in the day. I was there for eighteen months until the contract ended. I then moved to a Pharmaceutical Company in Loughborough where I had a permanent contract working as a Chemical Information Scientist. That was a great job, but some of the people I worked with were extremely unpleasant and I started to get bullied again. I had rent and bills to pay and felt unable to stand up to the manager. I became very unhappy there despite the fact that the job was interesting and I was good at it. In the end I left.

So at the beginning of 2004, thirteen years ago when I was 30, my liver consultant at the *Queen Elizabeth Hospital*, Birmingham put me on the Transplant List and within six weeks I had been given a transplant (see my story *pp 5-6* : Vol 8, Feb 2008 newsletter). I lost my job afterwards due to severe depression, but I am much better now. It just goes to show hard times can make you stronger. My health remains stable and most recently I have moved to the Cambridge area to take up full-time employment again, which is going very well. I have had to leave behind my partner of nine years, Eamon, but we see one another whenever we can. I have made a few new friends here and life is good once more.

I wanted to write about how WD has impacted my life and how against all the odds I have still managed to achieve goals and get on with things the best I can. I am ever thankful for having such supportive parents and wonder how this illness has affected their lives. Not having had children myself, I can only imagine what it must be like to have a sick child. So my advice to you is to do what pleases you, do what works for you, be kind to yourself and others, and always remember *Your best is good enough.*

Animal Models of Wilson Disease

Why do we need animal models for Wilson disease?

Animal models are used by scientists to understand more about human diseases and to find new ways to test for them or treat them. Sometimes we need animal models instead of other models (such as cell samples taken from people) because we need to see how the disease progresses over time and spreads from one organ of the body to others. It is also often impossible to study how different types of cells contribute to the disease even if we just look at one organ, such as the brain. Most importantly, animal models are still very important to test new drug treatments.

Animal models and Wilson disease?

You might know that Wilson disease is caused by a defect in the *gene* ATP7B. The ATP7B *gene* is responsible for making ATP7B *protein*. Normal ATP7B *protein* mostly works in the liver, where it has two main roles. One is to package the copper that we absorb from our food into another protein, ceruloplasmin, which then circulates around the body in your blood. The other role is to remove copper from the body by adding it to bile in your liver. Bile then leaves the body through your gut as waste.

In Wilson disease, faulty ATP7B means that copper isn't added to ceruloplasmin, causing low levels of this protein in your blood (this is one of the tests we use to diagnose Wilson disease). It also means that copper isn't removed in bile. Because both these ways of removing copper from the liver are lost, copper builds up in the liver at toxic levels. Very often, the copper levels are also increased in other organs such as the brain.

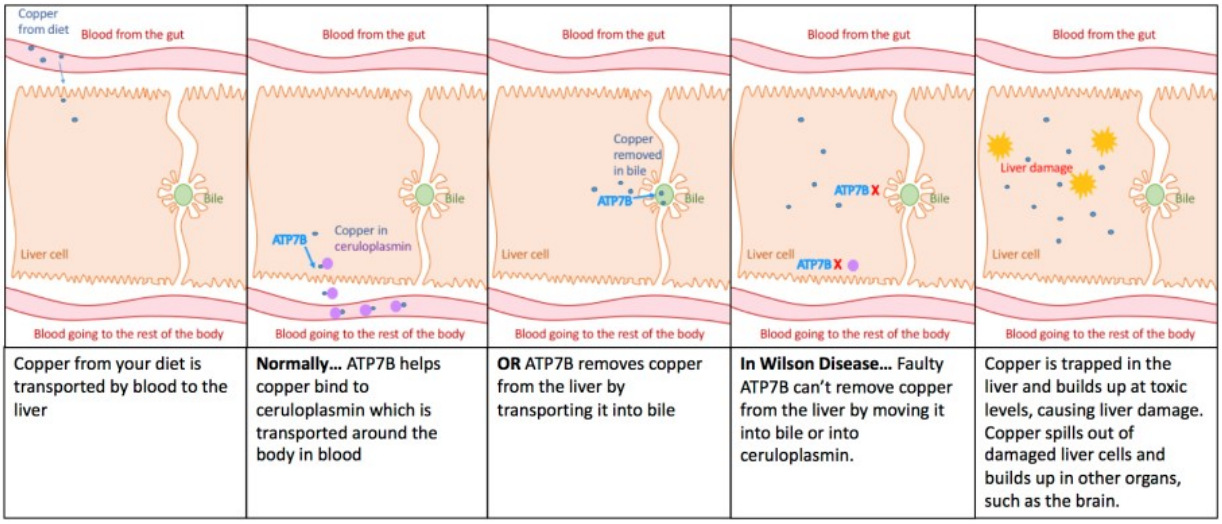


Diagram to show how ATP7B works in the liver

There are several different rodent (rat or mice) animal models of Wilson's disease, called the Long-Evans Cinnamon rat, the toxic milk mouse and the Atp7b knockout mouse. They all have copies of the *Atp7b* gene that don't work meaning that they also get toxic build-up of copper in their liver and other organs.

The Long-Evans Cinnamon (LEC) Rat

The LEC rat was discovered when scientists noted that a strain of rats with cinnamon-coloured coats developed liver disease at 3-4 months of age as a result of high levels of copper[1,2].

It was experiments in LEC rats that helped explain how ATP7B works and why the loss of ATP7B causes high copper[3,4]. LEC rats also gave us more information about how copper causes liver disease. The microscopic appearances of LEC rat livers are similar to human disease, with inflammatory, fatty and fibrous changes[1,5-8]. In LEC rat livers, it could be seen that copper causes oxidative stress (a process where charged oxygen particles damage parts of cells and cause inflammation) and damage to mitochondria (the cell batteries)[9-16].

New treatments targeting oxidative stress have been tested and found to be effective in treating liver disease in LEC rats. These include D-mannitol, N-acetylcysteine (NAC), D-galactosaminehydrochloride, proline solution, ascorbic acid, alpha-lipoic acid and thioredoxin[17-20]. A new chelation treatment (meaning it acts in a similar way to penicillamine or trientine), N-benzyl-D-glucamine dithiocarbamate (BGD) is also effective in treating liver disease in LEC rats[21].

Unfortunately, despite high copper levels in the brain, LEC rats do not develop symptoms of brain disease nor the brain changes seen in human disease[6,22,23]. This means we cannot use the LEC rat to study how the brain is affected by Wilson disease.

The toxic milk mouse

The toxic milk mouse has its name because the infant mice die early due to their mother's milk being too low in copper[24,25]. This can be prevented by feeding the pups from a healthy mother[26]. If normal milk is fed to these toxic milk mice, then they get a build-up of copper in the liver and develop liver disease[24,26,27] similar to the liver disease we see in patients with Wilson disease.

These mice also have high copper levels in their brain. They also have behavioural changes and changes in the way that they walk, which could be similar to a brain disorder caused by Wilson's disease. However, scientists think it is more likely these are symptoms of more general bad health. They also show some signs of having inflammation in their brains but, unlike in people who have a brain disorder because of Wilson's disease, there is no sign of brain cell loss[28].

The Atp7b knockout mouse

The Atp7b knockout mouse is the only model of Wilson disease which was made intentionally by scientists [29]. Scientists have used this model to look very closely at liver disease in Wilson disease and by doing so, have divided it into 3 different stages. In stage 1 (early) disease, copper starts to build-up in the liver. Changes to the cell batteries (the mitochondria) and to the nucleus (the command centre of the cell) can be seen already but the rats are still healthy otherwise. In stage 2 disease, there is inflammation and cell death in the liver. By stage 3, the liver either starts to repair itself or fibrous changes and cancer can develop[30,31].

Experiments in Atp7b knockout mice also revealed that the way the liver handles fat and cholesterol is changed in Wilson disease[31,32]. This is also seen in the brains of Atp7b knockout mice, which might help to explain how Wilson's disease causes brain damage[33]. Atp7b knockout mice also have oxidative stress and damage to mitochondria in their brains but, like the other models, they don't get loss of brain cells[33].

Scientists have treated Atp7b knockout mice using "gene therapy". To do this, healthy *Atp7b* DNA was introduced into Atp7b knockout mice using a virus. This successfully improved liver function in the treated mice[34].

Atp7b knockout mice have also been used to develop new ways to diagnose Wilson's disease using PET scanning. Scientists gave the mice radioactive copper before scanning. The radioactive copper caused the livers of the Atp7b knockout mice to light up on the PET scan more than the livers of healthy mice[35].

What are the next steps?

Obviously, there is still a lot that we do not yet understand about Wilson disease and we are yet to find a cure for this disease! The three animal models of Wilson disease described in this article have given us lots of new information about Wilson disease and these could lead to new tests and treatments being developed in the future. Unfortunately, none of the currently available animal models for Wilson disease gets a brain disorder in the same way patients with Wilson disease often do. As it is often the brain disorder that is hardest to treat in Wilson's disease, we badly need to develop new models for Wilson disease. It would be particularly important for this new model to be suitable for drug screens so that we can find a cure.

Dr Emily Reed and **Professor Oliver Bandmann**,
Sheffield Institute for Translational Neuroscience (SITraN)
University of Sheffield

The superscript numbers in the above article refer to the scientific references which are given in full on our website www.wilsonsdisease.org.uk - *Info section - WDSG articles*

Katy's Story

by Katy Quinlan

My name is **Katy** and I have been living in the UK for sixteen years. Some of you may remember me from the WDSG-UK AGM in Cambridge last July. I was diagnosed with Wilson disease in 2001 when I was twenty-four. At the time, I was studying Agribusiness in Brittany, France and I was doing my final placement in the UK near Banbury. It was a six month placement and I was enthusiastic and happy. I settled down fine but after a couple of months of working, I was feeling quite tired. However, working hard, exploring a lot and having late nights could easily have explained my lethargy, so I dismissed my concerns and carried on with life.

Katy, with her husband and son

When I was feeling no better a couple of weeks later, I went to see the local GP who ordered some blood tests. The results were inconclusive so he ordered further tests and referred me to an hospital in Oxford. In the meantime, my mum came over from France to visit. It was June and she had not seen me for a couple of months. She was very concerned. To her it was more obvious that something was wrong with me. I was still extremely tired, my skin had a yellowish shade to it and I was starting to get swollen ankles.

My hospital appointment in the UK was not until August, so to stop her worrying I decided to go back to France to be investigated there. It could not be anything serious, could it? It was early July and the summer holiday period had just started in France, when everything slows down. The first hospital I attended was the *American Hospital of Paris,* where they ran further tests to explain my abnormal liver function results and at the same time investigated me for auto-immune disease.

But it was at the second hospital I went to *Centre Hospitalier Sud Francilien* that I was finally diagnosed. By now it was the end of July 2001. I was given penicillamine and sent to a third hospital in Paris *Hopital Lariboisière*, where they specialise in Wilson's disease and perform liver transplants. I was put on the transplant list in case the medication did not work and it was then that I realised how serious my condition was. I underwent a long series of further tests during which they found Kayser-Fleischer rings in my eyes. At its worst, in August 2001, my serum bilirubin level which indicates liver disease was **113** (normal range 3-20 **µmol**/L) and my INR value which indicates how well the blood coagulates was **3.6** (normal range 0.8 - 1.2).

In Italy just after diagnosis

I was very "fat" as I was experiencing water retention as a side effect. I was still feeling very tired all the time and my medication was making me sick. The hospital put me on a low salt diet which meant I wasn't able to eat normal foods like cheese and baguettes, which being French naturally made me very depressed! I was allowed to go on a trip to Italy later in the month during which time my British boyfriend proposed to me. I remember thinking all the time that I was pregnant because my tummy was so big and it didn't help that other people kept asking about the "bambino" which made me feel sad.

Luckily, my medication started to work by September and the fluid was drained out of my abdomen which made me feel a lot better. It meant we could organise an engagement party which we held at my parents' house in France in October that year. Happily, my fiancé became my husband and in June this year we will have been married for thirteen years.

I now have a stable but challenging job working in the chocolate industry in York. I have a son who is only a Wilson's carrier as far as tests can tell and I lead a normal life. I am seen twice a year at Queen Elizabeth Hospital, Birmingham and am now taking trientine and zinc. I consider myself very lucky as I avoided a liver transplant and am now asymptomatic sixteen years later. I realise the early diagnosis was critical for me as my health had deteriorated so quickly in such a short time. The most important thing for me now is to take the medication: **It cannot** be forgotten and **it is** for life!

WD Research Notes

In this and subsequent Newsletters, we hope to keep you informed of research projects related to Wilson's disease. We strongly support continuing research, and for this reason we initiated our Wilson's Disease Patient Register - UK so that patients could make a contribution to research. The Oxford University iGEM group of students who spoke at our meeting last July were invited to participate in the international iGem jamboree in Boston in the USA. Julia Davis, one of the Group, sent the following report for inclusion in our newsletter.

iGEM

"During the summer of 2016 a group of undergraduates from Oxford University took part in iGEM, a synthetic biology project in which students from around the world use new biological techniques to solve real world problems. We decided to focus on Wilson's disease as it was an area that had not been studied by this sort of project before and because we wanted to bring awareness of this rare but important disease to a wider audience.

We were fortunate enough to be invited to your AGM last July to meet patients in person and were very grateful to those of you who filled out our survey on the WDSG Facebook page. This was invaluable in finding what sort of solution would work best for people who know the realities of having Wilson's disease so we could select our delivery mechanism.

After several months of lab work to try to make a functioning proof on concept, we presented our project at the iGEM Giant Jamboree in Boston in October, alongside over 300 teams from around the world. This sparked a lot of interest in Wilson's disease in many aspiring young scientists who may not otherwise have come across it. Our project was awarded the gold medal and we were nominated in the top five for four special awards: Best Therapeutic Project, Best Wiki, Best Presentation and Best Public Education and Engagement. We would not have been nominated for the latter but for the enthusiastic responses and help we received from your members so thank you once again for your support.

We never intended to take this further because we had a very limited timeframe to work in but it has definitely taught us a lot about the realities of lab work! Further details of what we did are available on our wiki page http://2016.igem.org/Team:Oxford, including the analysis of the surveys you kindly filled in for us. We hope the Wilson's Disease Support Group continues to go from strength to strength!"

And here are brief notes on other research projects we have been notified of this year.

National Hospital for Neurology, Queens Square, London

Prof. Tom Warner of the National Hospital for Neurology, Queens Square, London, is planning a research project into Wilson's disease.

In summary, he and his team will be looking at the genetic abnormalities in WD patients to determine why there is such a variation in the features of neurological disease, and variations in severity, progress and response to treatment. If these variations can be ascribed to genetic differences, it will lead to better understanding of optimal therapy in each case. Ultimately it is anticipated that specific gene therapy will be developed for the disease.

The study will also try to identify markers in blood and cerebro-spinal fluid that indicate how the neurological damage occurs and could be used to measure the effect of potential treatments in the future.

University of Sheffield, Dept of Neuroscience.

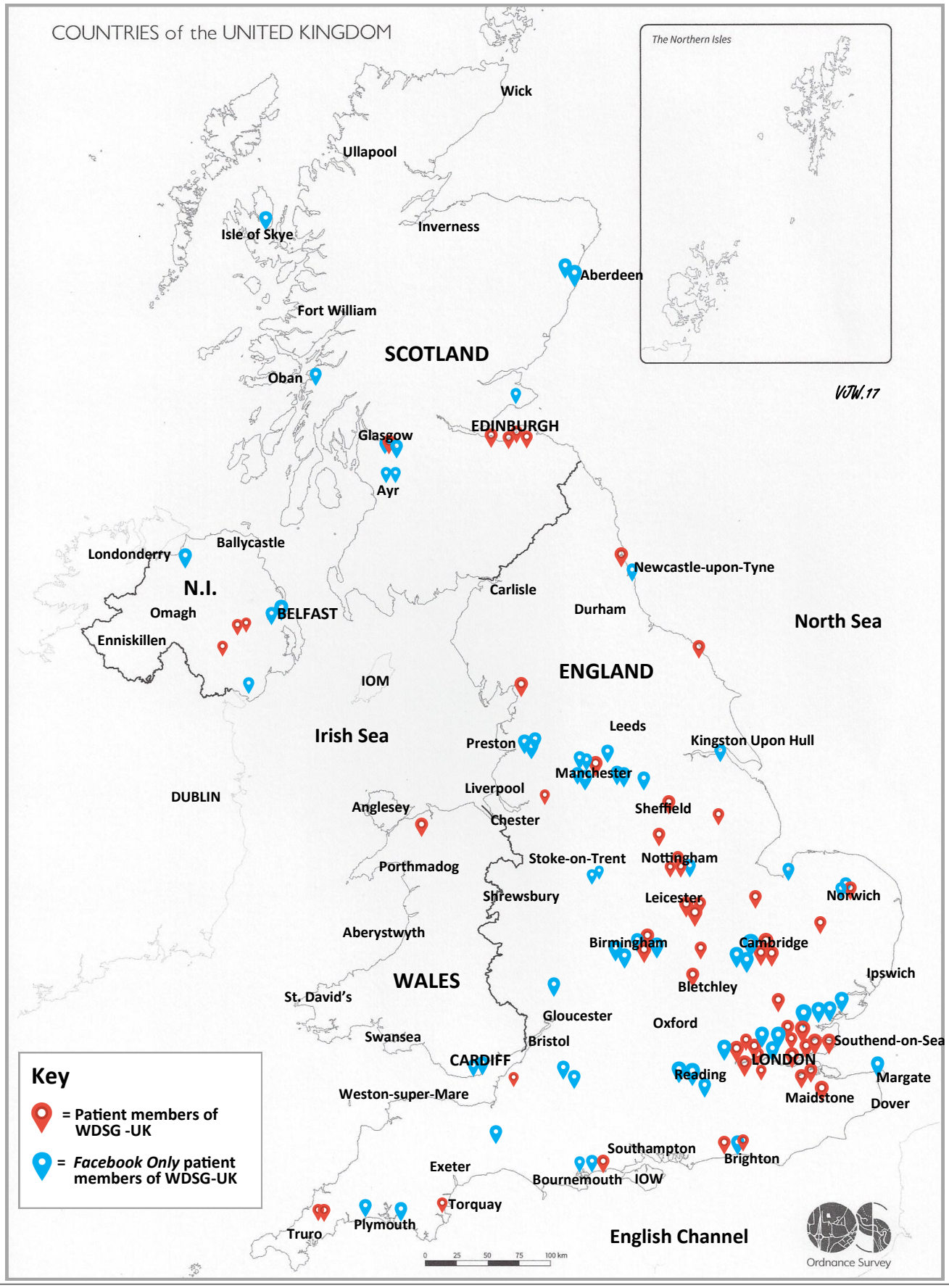
Prof. Oliver Bandmann and his team are investigating mitochondrial biomarkers in Parkinson's disease and other neurodegenerative diseases, including Wilson's disease. If abnormalities are found in mitochondria, there is the possibility of using so-called "mitochondrial rescue" drugs as treatment. Cells obtained from patients by skin biopsy will be investigated for their mitochondrial function, and will also be processed to convert them into neurones (brain cells) on which further studies can be performed.

Royal Surrey County Hospital and University of Surrey, Guildford, Surrey.

This centre is participating in an international multi-site study into the efficacy and safety of bis-choline tetrathiomolybdate as a treatment for Wilson's disease, in 2017. Furthermore, they hope to participate in international trials of a new trientene salt (TETA-4HCL), and to undertake an epidemiological study of Wilson's disease in south-east England later in the year. For further information, please contact Prof. Aftab Ala aftabala@nhs.net or a.ala@surrey.ac.uk ".

Distribution of WDSG-UK's WD Patients in the UK

The map below gives you some idea of where the 120+ Wilson's patients known to us, who are either members of WDSG-UK and/or belong to our Facebook Group, live. If I have missed anybody out, please let me know!



Members' News 2016-17

Our President **Dr John Walshe** is still "ticking over quietly," I am delighted to say, even though he now claims to be past his *best before date*! At ninety-seven next month, I asked him what he puts his longevity down to? "Well choosing the right parents is always a help" he tells me, "but it's more a case of medicated survival." "Medicated survival?" "Yes," he says, "I have a pacemaker, two coronary artery stents and I take eleven tablets a day!"

At Home - March '17

Despite, or possibly because of this, he continues to follow the Group's activities with interest and is always willing to offer medical advice, when requested. Having devoted his professional life to the treatment and management of over three hundred Wilson's disease patients worldwide, he has a wealth of experience from which to draw.

As I live nearby I try to visit him when I can. We haven't had as many outings this year as last, but we did manage *a tootle* in the Autumn around the pretty Suffolk villages of Clare, Cavendish and Long Melford ending up at the Guildhall in Lavenham. The Guildhall is now owned by the National Trust, but it was built in 1530 as a religious meeting place for wealthy wool merchants, and has since served as a prison, workhouse, pub, chapel and social club for US troops. For us it worked very well as a luncheon venue! It is said to be one of the finest timber-framed buildings in England. Disappointed that the timbers weren't black, Dr Walshe was assured by the curator that the limewash that had been applied to them recently was an excellent preservative and more befitting of a building that was 500 years old. Black painted timbers we were told only became fashionable in Victorian times!

Outside the Guildhall in Lavenham

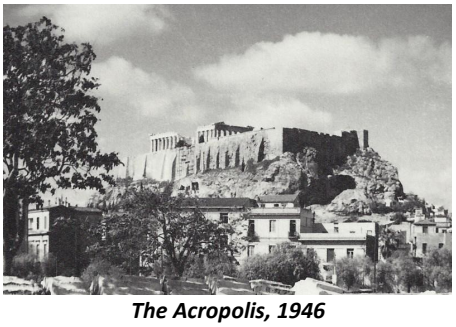
More recently, we stayed closer to home visiting another National Trust property called Houghton Mill, which is a fully working 18th century water mill on the other side of the River Great Ouse, and only a stone's throw away from where Dr Walshe lives. Unfortunately, it necessitates a 10 mile drive to reach it and we arrived to find that on this occasion it wasn't working at all, and wouldn't be working again until the beginning of next season! Even more upsetting was the fact that the adjoining café which was the focus of our visit wasn't open either! Undeterred we found ourselves an alternative tearoom nearby where we passed a very pleasant half hour drinking tea with the natives!

At Houghton Mill

One of the pleasures of being with Dr Walshe is listening to his many stories and amusing reminiscences. When I saw him last I heard all about his time doing National Service in 1946-8. He was very agreeably posted to Greece in the first instance as a Medical Officer in the Light Field Ambulance Unit. Acting as an anaesthetist in temperatures of over 90^{o} F and not knowing why the *open ether* he used didn't put everybody to sleep, he remembers taking the air in Athens and wandering around the Acropolis without another tourist in sight. He also remembers that he was under the command of Major Pearce, known to everyone as Pi**y Pearce as he liked a drink or two! One of the maxims Major Pearce taught him which he has never forgotten was "Never volunteer for anything but at the same time never refuse a good offer."

Army headquarters, Patras, 1946

Let's hope that Dr Walshe considers our offer of hospitality at the Cambridge meeting on 23 July something he cannot refuse and if so, I'm sure we will all look forward to seeing him again then.



The Acropolis, 1946

Jane Ridley joined the Support Group when it was formed in 2000 and she and her husband, Peter, attend our annual meeting every year. They live outside Peterborough and Jane was diagnosed with Wilson's disease nearly forty years ago. Having been on holiday to Mexico last summer, I asked her if she would like to write something about the trip for this year's newsletter and she kindly agreed.

"On 28th June last, Peter and I arrived at Gatwick Airport at 9.00 o'clock in the morning and checked in straight away at the Virgin Atlantic desk. We had spent the previous night at the nearby Ibis Hotel so that we didn't have to get up in the early hours and risk being held up in traffic.

The plane took off at midday for what was to be a ten hour flight. Fortunately, the time passed very quickly with on flight meals, snacks and a welcoming drink and I also watched the film *The Lady in the Van* which I had not got round to seeing before. It was very entertaining. We could see ships in the Atlantic as we flew over and we also had an awesome view of Miami as we travelled across Florida.

We landed at Cancun Airport in the east of Mexico at around 1700 local time, being five hours behind the time back home. We were the last drop off point for the coach, but it wasn't long before we arrived at our hotel in the Barcelo Maya Beach Resort where we had booked a week's holiday.

Our room was lovely. It was on the ground floor and had a terrace, air conditioning (which we appreciated), king size bed, mini bar and flat screen TV (not that we watched it at all). As we had booked an *all inclusive* package we ate buffets in the hotel restaurant most evenings and at the beach restaurant most lunchtimes. There was nightly entertainment, but it started too late for a couple of oldies like us!

Trips were organised daily, but most were water based like swimming or snorkelling, and as I can't swim we decided to stay behind at the resort instead. There were five swimming pools on site, plenty of sun loungers and hammocks and even an 18 hole crazy golf course, which I particularly enjoyed although you did have to avoid the small lizards that ran across the paths while you were playing. Also, there was a dolphin pool on site with six dolphins and a free daily show, which was fun. For a fee you could go in the pool with the dolphins, but I wasn't brave enough to go in on my own.

The resort was large and an open topped London bus travelled around it until the early afternoon picking us up when our feet started to ache. However, we tried to walk as much as we could, lapping up the sun and enjoying a paddle in the Caribbean when we could. We saw shoals of fish swimming in the shallow waters and iguanas lazing on the beach in the afternoon heat, which was amazing.

While we were away Peter and I celebrated our twenty-eighth wedding anniversary by going out to a restaurant for a waiter service meal. It was certainly a wonderful and memorable holiday. We were sorry to come home, but not long afterwards our daughter, Tanya, gave birth to our very first grandchild, an 8lb 10oz bouncing baby boy named Oliver Daniel, whom we love very much. If you want to see more of the resort we stayed at, have a look on *YouTube!"*

Looking across to the Hotel Restaurant

Not a Tourist in Sight here either!

Topping up our Vitamin D levels

Ashok Pandit is a Wilson's disease patient from Kathmandu in Nepal, who has become familiar to us all through his articles in the newsletter and posts on Facebook. He was the youngest of three children and in 1993, when he was only three, his sister who was nine and brother who was seven both died within a month of one another and nobody knew why. Four years later, Ashok also became ill. He was admitted to hospital and as luck would have it a visiting American doctor saw him and suggested a diagnosis of Wilson's disease. He has been treated with penicillamine ever since, although from time to time obtaining his tablets has been challenging to say the least. Yet another misfortune befell the family, when in 2015 their house was badly damaged in the country's devastating earthquake and its aftershocks. This year they are finally hoping to build a new house. Ashok writes,

Ashok and his mum

Structural damage to our house in earthquakes

"After the devastating quake hit Nepal on 25 April 2015 and its two fatal aftershocks, it left many houses, public buildings, monuments and eco-systems destroyed. Thousands of people were killed or injured and many more were rendered homeless. Our family was lucky because although our house was badly damaged and needs to be rebuilt, we survived and have been able to continue living in part of it. It hasn't been easy living in the same room with mom. There is no privacy of life. To begin with it was fascinating and we were all pleased to be alive, but it has become tougher day by day. I miss my room and my life before the quake, and I am not settled enough in my career to afford to rent a flat.

The house as it is now...

The Government is slowly helping people who are victimised by the quake. It has set up a relief fund for people who have lost their family members and also it is giving families who lost their homes in worst affected areas (including where we live in Kathmandu) $3,000 in instalments towards rebuilding their homes. We have so far been given $750. It is also offering $25,000 loan at minimum interest rate of 2% and is providing relief to victims for getting construction map of new homes, up to 1000^2 feet, approved. We have sold our plot of land for building our new house, which we expect to cost $25,000.

Plans of the proposed new house

Building a new house has always been a really big dream for me actually and now through bad circumstances the dream has become reality. I have applied for getting site map of our new house approved in the municipality and I hope it will get approved within a month's time. I am very excited to be going back to my old life. I just need to have patience. But the way I am living now has taught me that life without any personal space is not much happening!

I would like to take opportunity of thanking various people in particular for their help. First of all, I would like to thank **Linda Hart** for contacting me and adding me to the group in 2012. Life has become easier finding out more about the disease, knowing that there are other people like me and being inspired by their stories. Then I would like to thank **Valerie** for giving me the chance to express my feelings in the articles I have written for the newsletter since. Most recently, I would like to thank the Pharmaceutical Wholesalers, ***Prime Pharmacare Ltd*** of Stanmore, Middlesex, for their help and generosity in supplying me with penicillamine last December when I was unable to get hold of it from my usual supplier in India.

Finally, I would like to give gratitude to every member who loves and supports me whenever I am in need and to send them best wishes for their life. We all have a common thing that binds us together and through that we can support each other."

Members' Photo Gallery

Katie and Jacob at Wimpole Hall Farm - May 16

The Ottesen Family from Denmark - Jul 16

David Lin at Easton Walled Gardens, Lincs - Aug 16.

Anusha with Marie-Louise - Jul 16

Sam outside his new living quarters - Aug 16

Maria and Dumitru - Jul 16

Linda - Mar 17

Katy, Eric and Maria over lunch - Jul 16

Olivia - Jul 16

Attendees of the Annual Gathering - Cambridge - July 16

WDSG-UK 2017 EVENTS

Date	Time	Event
Wednesday May 17	**1200 noon**	**ROWIKEM (est. 1987), K.E.M Hospital Research Centre, TDH Building, 3rd Floor Auditorium, PUNE, Maharashtra State, India.** All welcome.
Saturday May 13	***0900 - 1830***	***Morbus Wilson e.V.*** *Annual Symposium - Dresden, Germany*
Sunday July 23	**1100 - 1530**	**WDSG-UK Meeting and 7th AGM** – Cambridge Rugby Union Football Club Grantchester Road **Cambridge** CB3 9ED.
Saturday August 26	***1000 - 1200***	*Sylvia Penny warmly invites you to* ***a Coffee Morning, Bring and Buy and Raffle*** *in aid of* ***WDSG-UK*** *at Victoria Park Methodist Church, St Marychurch Road, Claymore,* ***Torquay.***

WILSON'S DISEASE MULTIDISCIPLINARY CLINICS

The Birmingham WD Clinic

Prof Gideon Hirschfield (Consultant Hepatologist) and **Dr David Nicholl** (Consultant Neurologist) hold a one-stop Wilson's disease clinic at **University Hospital Birmingham** on a Friday morning four times a year. This clinic offers patients the opportunity to have their management reviewed by a hepatologist and a neurologist at the same time and is intended to supplement otherwise established care. Referrals must come from the clinician looking after the patient and should be addressed to Prof Hirschfield at *Queen Elizabeth Hospital, Mindelsohn Way, Edgbaston, Birmingham, B15 2WB.*

The Sheffield WD Clinic

The Sheffield clinic is jointly run by **Prof Oliver Bandmann** (Consultant Neurologist), **Dr Mohammed Karajeh** (Consultant Hepatologist) and **Dr Godfrey Gillett** (Consultant in Clinical Biochemistry, Inherited Metabolic Disease, and adviser to WDSG-UK). Clinics take place every six months at the **Royal Hallamshire Hospital, Sheffield** on a Tuesday morning. Patients may be seen in interim clinics by arrangement. Referrals should be addressed to Prof Oliver Bandmann at *Department of Neurology, Royal Hallamshire Hospital, Glossop Road, Sheffield, South Yorkshire S10 2JF*. Either GPs or hospital specialists may refer to this Sheffield WD clinic.

Royal Surrey County Hospital NHS Foundation Trust, Guildford, Surrey

The centre is running a regular multidisciplinary clinic to assess and manage patients with Wilsons disease. The clinical team includes expertise in liver, movement disorder, chemical pathology and eye with access to clinical trials. If you would like further information please contact **Professor Aftab Ala** (aftabala@nhs.net) or (a.ala@surrey.ac.uk).

Children's Clinic at King's College Hospital, London

There is a Wilson's disease clinic for children and young people at King's College Hospital which is run by **Prof Anil Dhawan** (Paediatric Liver), **Dr Tammy Hedderly** (Paediatric Neurologist) and a psychologist. The clinic is directed at patients who are complex with both liver and neurological involvement and referrals should be made via the Paediatric Liver Centre at King's or enquiries sent to **Kathleen Meader, (**kathleenmeader@nhs.net), PA to Prof Dhawan.

Discontinuation of Manufacture of Penicillamine by Alliance Pharmaceuticals Ltd.

Alliance Pharmaceuticals has written to notify us that they have discontinued manufacturing Distamine 125 mg and 250 mg film-coated penicillamine tablets in the UK due to sourcing difficulties. They send their apologies for any inconvenience this may cause to patients and assure us that penicillamine will still be available from other manufacturers.

Wilson's

Wilson's Disease Support Group – UK

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Dr John Walshe Honorary President, World Authority on Wilson's disease
Dr Godfrey Gillett Group Adviser, Honorary Member
Dr James Dooley Group Adviser, Honorary Member
Linda Hart: Group Co-Founder, Adviser

Tell others about WDSG-UK

Please encourage anybody else that you know with Wilson's disease to join **WDSG-UK**

Inform your family, friends, consultant physicians, general practitioners and local MPs about the work of **WDSG-UK.**

The more people who know about **WDSG-UK**, the more we can promote a better awareness of Wilson's disease within the community and the better the chance of an early diagnosis.

If more copies of this newsletter or patients & families' correspondence lists are required, please contact Valerie:

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