

# Gauchers NEWS

JANUARY 2009

Gauchers ASSOCIATION



*Hajira enjoys the arts and crafts programme*



*Maddie, Hayley and Nadia enjoy a relaxing chat*



*Gaucher patients and their siblings enjoy the conference*



*Clinical Nurse Specialists Niamh and Lynne together with Elin after their session with the Type 3 girls*

Pictures from the European Neuronopathic Gaucher disease Family Conference.  
(See pages 11 – 23 for full Conference details)

Visit Gauchers News online at [www.gaucher.org.uk](http://www.gaucher.org.uk)

# Lysosomal Storage Disorder Centres

## Addenbrooke's Hospital

Hills Road, Cambridge CB2 2QQ  
Head of Clinic: Prof Timothy Cox  
Tel: 01223 336 864  
Fax: 01223 336 846  
National Helpline: 01223 216 295

## Birmingham Children's Hospital

Diana, Princess of Wales Children's Hospital  
Steelhouse Lane, Birmingham B4 6NH  
Head of Clinic: Dr Chris Hendricksz and  
Dr Anupam Chakrapani  
Tel: 0121 333 9999  
Fax: 0121 333 9998

## Great Ormond Street Hospital for Sick Children

Great Ormond Street  
London WC1N 3JH  
Head of Clinic: Dr Ashok Vellodi  
Tel: 020 7405 9200 ext 0075  
Fax: 020 7813 8258

## Hope Hospital

Department of Lysosomal Storage Disorders  
Hope Hospital  
Stott Lane, Salford  
Manchester M6 8HD  
Head of Clinic: Dr Steve Waldeck  
Tel: 0161 206 4365 / 1419 / 1080.  
Fax: 0161 206 4036

## National Hospital, London

Charles Dent Metabolic Unit, Box 92  
National Hospital for Neurology  
and Neurosurgery  
Queen Square, London WC1N 3BG  
Head of Clinic: Dr Phil Lee  
Tel: 020 7837 3611  
Fax: 020 7209 2146

## Royal Free Hospital

Pond Street, London NW3 2QG  
Head of Clinic: Dr Atul Mehta  
Tel: 020 7830 2814  
Fax: 020 7830 2313

## Royal Manchester Children's Hospital

Willink Biochemical Genetics Unit  
Hospital Road, Manchester M27 4HA  
Head of Clinic: Dr Ed Wraith  
Tel: 0161 922 2137 (9am - 5pm)  
Fax: 0161 922 2137  
Helpline: out of hours ring  
0161 794 4696  
and ask for the metabolic consultant.



# Chairman's Forward

Dear Friends,

Happy New Year to all members and friends. On behalf of the Executive Committee I send you personal good wishes for good health and happiness in 2009.

The year ahead is going to be full of challenges and the economic situation will undoubtedly raise issues for the Gaucher world. Patients with rare diseases know only too well that their treatment is costly but they are as entitled as any other citizen to receive treatments which have been approved by the appropriate regulatory authorities. We will remain vigilant to ensure that no patient's treatment is compromised in these difficult times.

As you will see from this Edition of Gauchers News there is much happening. The formation of the LSD group is an important step in ensuring that the interests of all patients with Lysosomal Storage disease remain fully represented and articulated. The National Treatment Centres are designated as "LSD Centres" and as such it is vital the various patient groups continue to work together in a concerted fashion both to offer constructive comments on the existing service and most importantly to ensure that this world class service continues in the future. The Health Technology Assessment process has undoubtedly already benefitted from the input of the LSD group both in the formation of the data to be collected and the way the whole process is to be managed.

This edition also has reports from the very successful European Neuronopathic family conference. As always this proved to be an important event in our calendar where families come together to share experiences of the challenges that they and their children face.

We are always pleased to report on new avenues of research and this issue details the exciting project being undertaken by Dr Nick Smith in Cambridge which is investigating a new approach to a much needed better understanding Neuronopathic Gaucher Disease. Future editions will report on his progress.

I draw your attention to the new fundraisers packs that have been put together to help with fundraising efforts. Do ask Tanya for to let you have our leaflets posters and stickers whenever you are organising an event.

Finally I am delighted that we have launched our new website which I am delighted to report has been generously funded by the National Commissioning Group of the NHS. Congratulations to everybody involved especially Tanya who has invested hundreds of hours of hard work to get it up and running. Do visit. It is very much a work in progress and suggestions and comments will be most welcome.

With Good wishes

Jeremy

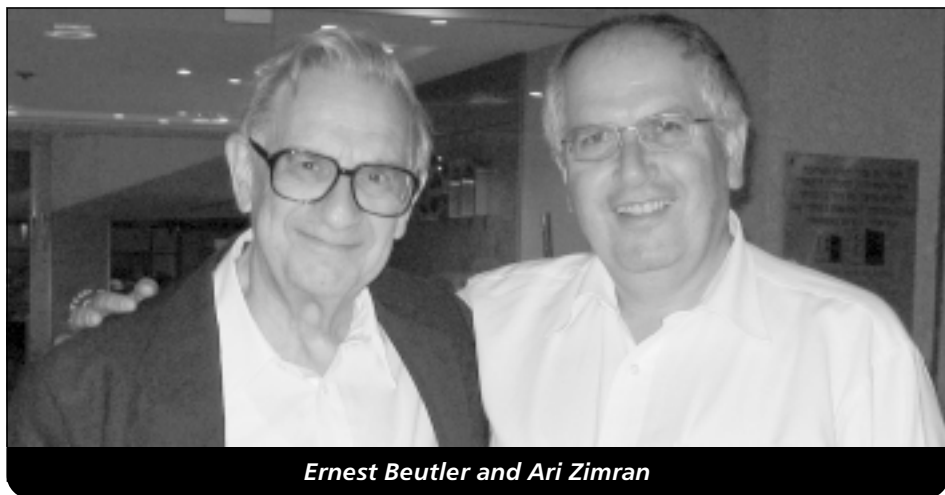
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# A Personal Tribute to Prof Ernest Beutler



*Ernest Beutler and Ari Zimran*

***Prof Ernest (Ernie) Beutler, among the world's most prominent hematologists and scientists, died at age 80 years on October 5<sup>th</sup> 2008. 'Ernie was a true genius, one who has made an impact on many and varied topics in medicine and genetics that have served as the foundations for scientific inquiry and will continue to remain important for decades to come' writes Prof Ari Zimran who described Ernest as his mentor;***

Among his most important discoveries are: chromosome X inactivation; novel therapies for forms of leukemia including 2CdA for hairy cell leukemia; diagnostics of red cell enzyme deficiencies; Gaucher disease; and iron metabolism. He had authored more than 800 papers, many book chapters, and has edited the famous "Williams' Hematology" textbook; Ernie also invented the first version of the "Reference Manager" program.

'Ernie's involvement in Gaucher disease include the cloning of the glucocerebrosidase gene (in fact, Cerezyme® is made from the original cDNA clone provided by him to Genzyme) and identification of dozens

of clinically important mutations (e.g. 84GG and IVS2+1). His concept of low-dose therapy, which has withstood the test of time as clinically safe and efficacious, has also resulted in savings of hundreds of millions of dollars to health care systems worldwide.

'His many responsibilities notwithstanding, nothing excited Ernie more than discussing experiments with his technicians, students, and colleagues; and when it came to medical discussions, whether in basic sciences or clinical cases, he was always original and creative and never felt constrained to present anything but the evidence-based truth, regardless of its

"popularity". Ernie was equally free of conflicts of interest because of his strictly moral code of behavior in the scientific arena. He was not a man for small talk, although he always appreciated a good joke. Ernie was a "slave-driver": he used to express his disappointment when the lab equipment was not used continuously during the weekends.

'I was very fortunate and privileged to have had Ernie Beutler as my mentor: he was also the one who directed me to Gaucher disease as an appropriate "niche" disease for an Israeli. Ernie was always available to me in the ensuing decades, both at various medical meetings as well as by correspondence: talking with him and discussing a range of medical and scientific questions, always made me appreciate his brilliance and extraordinary intellectual power.

'Several years ago on the occasion of reviewing his many past achievements and discoveries, Ernie was asked how he would like to be remembered: he answered with one word, "warmly". Ernie will always have a very warm spot in my heart and in that of so many, many colleagues and students whom he has touched during his many years as a recognized leader. While we no longer will be able to enjoy an on-going dialogue, I have no doubt that we will all continue to be inspired by his grand but modest personality and by the depth of his moral commitment to scientific inquiry for the betterment of patients'.

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## UK Gaucher Patient Dan Brown to join Patient Advisory Board

***Amicus Therapeutics, the U.S. pharmaceutical company, have recently set up a Patient Advisory Board made up of a number of Type 1 Gaucher patients from around the United States writes Tanya Collin-Histed, Executive Director of the UK Gauchers Association;***

'Their intention is to meet on an annual or bi-annual basis to discuss the issues facing Gaucher patients and how Amicus, as a key player in the medical arena for Gaucher treatment and research, can assist in promoting these issues and addressing them

directly where possible. Amicus were keen to also have the viewpoint of patients outside of the United States and so contacted the UK Gauchers Association and invited nominations for the only non-US member of the Patient Advisory Board.

'Daniel Brown, a 31 year old Type 1 patient from London was nominated to apply and following an informal application and interview process Daniel was accepted on to the Board. Daniel said, "I am really looking forward to travelling to New Jersey for the first meeting at the end of January 2009. It will be very interesting to hear the perspectives of patients from another country and understand the different challenges they face".

# Dependence of reversibility and progression of mouse neuronopathic Gaucher disease on acid $\beta$ -glucosidase residual activity levels

*Dr Ashok Vellodi, Paediatric Consultant at Great Ormond Street Hospital, London reports on work being carried into neuronopathic Gaucher disease by Prof Greg Grabowski's group from Cincinnati, USA, Dr Vellodi writes:*

In the March 2008 issue of *Molecular Genetics and Metabolism*, Prof Greg Grabowski's group from Cincinnati, working with a group at the Swiss Institute for Experimental Cancer Research in Lausanne, Switzerland, have reported important observations in mouse models of NGD previously created by Prof Grabowski's team. The objective was to see whether the development of neurological involvement is related to the residual activity of glucocerebrosidase, and if so, whether the changes can be reversed by increasing the enzyme level again. They did this by treating the mice with conduritol B epoxide (CBE). This substance has been shown to inhibit

glucocerebrosidase throughout the body, including the brain. Different mouse models were treated with CBE for varying periods. There were two important findings. Firstly, mice with lower enzyme activity tended to develop more severe neurological symptoms, the neurological symptoms continued to progress even after CBE was stopped. In the others, the neurological symptoms persisted but did not progress.

These findings have important implications for treatment, such as direct CNS gene therapy and chaperone treatment. Such approaches are unlikely to result in permanent satisfactory enzyme levels

in the brain. Unfortunately, what is not clear is how long this effect lasts. After a while, as their effect wears off, the enzyme level may start to drop. Clearly, if this happens, and the level drops below a critical level, further neurological deterioration could occur. Also, this effect might be more pronounced if the mutation was more severe, and associated with a lower residual enzyme activity.

More work needs to be done in this area in order to determine how long enzyme activity can be sustained in the brain from single doses; this will help us to calculate how often such treatments may need to be repeated, which is one of the most important challenges in this area of clinical research. Now that we have good mouse models, this should be possible.

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## UK LSD Collaborative Group Established

*Patient Organisations representing patients with Lysosomal Storage Disorders have joined together to form a new action group to work and lobby on behalf of LSD patients and their families in the UK. The group is made up representatives from the Gauchers Association, The Society for Mucopolysaccharide Diseases (the MPS Society), Battens Disease Family Association, Niemann-Pick Group (UK) and the Pompe Association, reports Tanya Collin-Histed, Executive Director of the UK Gauchers Association;*

The group first met in January 2007 and agreed to operate as a forum to discuss issues common to all groups including working with the Pharmaceutical Industry, the development of homecare services for patients, newborn screening, the development of metabolic networks in the UK, the need for research into

the brain and representation on the Health Technology Assessment longitudinal study into enzyme replacement therapy for LSDs.

The group meets three times each year and are developing their own 'Terms of Reference' and a work programme for the next 12 months. Future activities for the group will

include; assisting in the development of a patient group for Metachromatic Leukodystrophy (MLD), providing information at the 2009 Party Political conferences about the patient bodies and the need for a continuation for the specialised service status for LSD's, and ongoing representation on the HTA study into ERT for LSDs.

We are keen to open membership of the group to other LSDs conditions. If you would like more information contact; Tanya Collin-Histed on: 00 44 1453 549231 or e-mail: ga@gaucher.org.uk

# Neuronopathic Gaucher disease: does LIMP-2 play a role?

*Dr Nicholas Smith is an Australian physician specialising in paediatric neurology. Dr Smith has recently joined the University of Cambridge Lysosomal Storage Disease Research Group led by Prof. Timothy Cox where he plans to study the neuropathology of a variety of lysosomal storage disorders including Gaucher Disease. Dr Smith hopes that a greater understanding of the neurological pathogenesis in these conditions will contribute to the development of improved therapeutic interventions for patients with neurological disease. As part of his work at Addenbrooke's Dr Smith plans to undertake a collaborative study into the role LIMP – 2, he explains the theory behind the study:*

'With a population frequency variously estimated at 1/200,000 – 1/40,000 Gaucher disease represents one of the most common inborn errors of lysosomal function. In the UK this equates to around 200 – 300 individuals, 5-10% of whom manifest neurological involvement; the so called neuronopathic variant.

'Together with the management of bone disease, effective therapy for neurological manifestations of Gaucher disease continues to represent an unmet clinical need for patients.

'Neuronopathic disease has traditionally been categorised as one of two subclasses; type 2 (acute neuronopathic) and type 3 (chronic neuronopathic) disease. Type 2 disease is characterised by relentlessly progressive neurodegeneration beginning in infancy, whilst type 3 disease is more variable with onset ranging from infancy to adulthood with a generally slower, at times almost indolent, rate of progression. However, a further subset of patients increasingly recognised and previously thought to be free of central nervous system (brain and spinal cord) involvement are those with late onset neurological features. These patients develop abnormalities of movement resembling Parkinson's disease. This has led to the now widely accepted view that neuronopathic Gaucher disease most likely represents a continuous spectrum of central nervous system involvement. Nevertheless, the traditional classifications are still widely used and remain helpful to patients, families and clinicians when attempting to predict how a particular person with Gaucher disease may fare.

'Why then do some Gaucher patients develop nervous system involvement whilst others do not? Despite a global effort to address this question the answers remain frustratingly elusive. Over 95% of all cases arise from genetic variation in the gene encoding the critical enzyme (glucocerebrosidase) that is deficient in Gaucher disease. In a further small group of patients disease results from an abnormality of an associated protein SAP-C (the sphingolipid activator protein C) that is required to assist the critical enzyme in its function. However, numerous studies throughout the international Gaucher population, have failed to identify all but broad correlations between specific genetic variations and the clinical presentation of disease. In fact, individuals with identical genetic changes can have neuronopathic or non-neuronopathic forms of disease. Various suggestions to explain this phenomenon include the possibility of associated factors, often termed epigenetic factors, which influence a particular gene's function, individual differences in the number of repeat sequences in a person's genetic code (termed copy number variation) and the presence of secondary 'modifier' gene changes which predispose an individual with the Gaucher disease mutation to manifest a particular clinical pattern.

## **Limp – 2 Gene**

'Recent, exciting work by **Professor Paul Saftig** and his team from Christian-Albrechts University Kiel, in collaboration with **Dr. Tim Edmunds**, a top scientist in the Genzyme corporation, has identified a protein, the Lysosomal Integral Membrane Protein type 2 (LIMP-2) which plays an important functional role in ensuring



*Dr Nicholas Smith*

that the enzyme which is deficient or dysfunctional in Gaucher disease is transported from its site of production to its site of action, the lysosome. Studies in mice that are genetically engineered to be deficient in LIMP-2 results in animals with prominent neurological abnormalities; including poor balance, deafness, disease of the peripheral nerves and an accumulation of an abnormal, as yet unidentified, storage material in their brains. People without Gaucher disease, who have been found to have abnormalities in both copies of the LIMP-2 gene are extremely rare. These individuals manifest a severe, adult onset disorder called Action Myoclonus Renal Failure Syndrome (AMRF); which surprisingly displays some features in common with neuronopathic Gaucher disease. A few cases of Gaucher disease have also been reported to occur secondary to abnormalities of the LIMP-2 gene. One such case was highlighted at the recent European Working Group on Gaucher Disease (EWGGD) meeting in Budapest earlier this year. It therefore seems possible that variation in the genetic sequence of the LIMP-2 gene may be an important determinant of neurological manifestations in Gaucher disease.

'Confirmation of such a relationship would provide a valuable tool helping to predict the course of disease in individual patients. Additionally it would help identify those in whom experimental therapies targeted to the brain may be of benefit.

*(continued on page 6)*

(continued from page 5)

### Planned Study

A study aimed to address the possibility of this association in UK Gaucher patients is planned as a collaborative effort amongst the national Gaucher treatment centres with the support of the UK Gaucher

Association. Voluntary participation in the study would involve the granting of permission to review patient medical files and obtain a blood sample for DNA analysis (in most cases this sample will have already been taken and stored at the time of diagnosis). Strict patient confidentiality will be employed and

no identifiable information will be included in the study. Further details can be obtained from the co-ordinating centre, The Lysosomal Diseases Research Group, University of Cambridge, Addenbrooke's Hospital [Please contact Dr. Nicholas Smith; Ph: 01223 336868 or email: njcs3@medschl.cam.ac.uk]

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## All Wales LSD Service

***On 4 November the All Wales Inherited Metabolic and Lysosomal Disease Service was launched at the University of Wales Hospital, Cardiff. Tanya Collin-Histed, Executive Director of the UK Gauchers Association attended on behalf of the Gauchers Association and reports on this new service for Welsh patients;***

The launch of the new commissioned clinical service for the diagnosis, assessment and treatment of adult and paediatric patients with inherited metabolic and lysosomal storage disorders in Wales was attended by clinicians, nurses, representatives from the Pharmaceutical Industry, representatives from patient organisations, laboratory staff and healthcare commissioners. **Dr Graham Shortland** opened the meeting by outlining the services and facilities on offer at the University of Wales Hospital and gave examples of the experience at the hospital in treating patients with lysosomal storage disorders. This was followed by **Dr Jeffery Carroll**, Medical Director for Health Commission Wales gave an overview of the financial commitment that the Welsh Assembly has made to the development of this new service.

**Christine Lavery**, Chief Executive

of the MPS Society who spoke on behalf of LSD patients gave a clear presentation on what patients and their families expect to see from such a specialist service.

**Dr Chris Hendrikz**, Consultant Metabolic Physician at Birmingham Children's Hospital gave a comprehensive description on infantile and adult Pompe disease and **Dr Atul Mehta**, Clinical Director of the LSD Unit at the Royal Free Hospital, London spoke about Fabry disease.

The new service will comprise of a Lead Clinician (Dr Graham Shortland), Consultant Biochemist (Dr Mike Badminton), Nurse Specialist (Andrew Dobson), Specialist Pharmacist (Zoe Taylor), Dieticians (Angharad Banner and Kath Singleton), Physiotherapist (Ann Baldwin), Clinical Psychologist (Bethan Phillips) and support services.

Currently all Welsh Lysosomal

Storage Disorder (LSD) patients are seen at one of the seven LSD centres of excellence in the England. With the launch of this new service all Welsh patients will be offered the opportunity to transfer their care to the new service. Patients who wish to continue being seen at one of the centres in England will be able to continue to do this on a shared care basis, and where Dr Shortland and his team will be integral in their clinical management and treatment decisions.

The All Wales service will adopted the current National Commissioning Group (NCG) guidelines used at the seven LSD centres in England when assessing patients for treatment.

Jeremy Manuel Chairman of the Gauchers Association said of the launch of the new service "We are delighted that this new service which will facilitate the access to treatment for Welsh patients will follow the NCG guidelines which have been developed after much hard work from the experts at the seven English centres".

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## 1<sup>st</sup> EGA Board meeting held in Holland

***The first official meeting of the newly elected EGA board took place on Sunday 14<sup>th</sup> December in Houten, Holland during the 25<sup>th</sup> Anniversary meeting of the Dutch Gaucher Organisation.***

A full report of the meeting and the 25<sup>th</sup> Dutch Anniversary celebrations at which Ria Guijt received a knighthood from the Queen of the Netherlands will be published in the next edition of the Gauchers News.

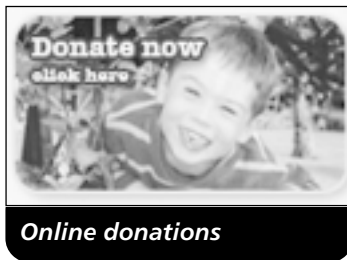
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Congratulations to **Dr Gregory Pastores** and **Dr Derralyn Hughes** on the birth of their daughter **Paloma**

Congratulations to **Dan** and **Kate Brown** on the birth of their daughter **Betsey Honey**

# New Gauchers Association Website Launched

*The Gauchers Association is pleased to announce the launch of its new website at: [www.gaucher.org.uk](http://www.gaucher.org.uk). The new website incorporates all of the old sites information but with many new features including;*



**News alerts** – sign up for news alerts through RSS and when we update the site with news you will automatically get an e-mail alert.

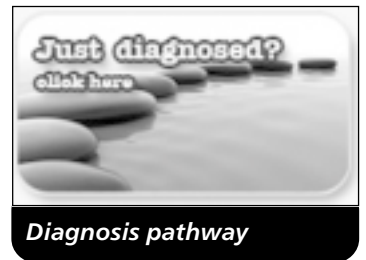
**Online newsletters** – view our current and past newsletters in either PDF format or online. Sign up for our new electronic of the newsletter which will be sent to you by e-mail as soon as it is published.

**Join online** – become a member of the Gauchers Association by downloading our membership form and e-mailing it back to us.



**Links** – provides information on Gaucher Association around the world; links to recent published papers on Gaucher disease, links to other organisation that visitors may find useful.

**Research updates** – see updates on research projects funded by the Association and external research projects being undertaken into Gaucher disease.



**Donate online** – support the Association by making an online donation, pay your annual membership, set up a fundraising page.

**Fundraising stories** – read members stories on how they raised money for the Association, request one of our new fundraising packs, learn about Gift Aid.

**Just diagnosed pathway** – follow our pathway of information if you have just been diagnosed or know someone with Gaucher disease and would like more information.

The website is an ongoing project and will be updated and added to on a almost daily basis, please have a look at the new site and feedback your comments to Tanya Collin-Histed either through the site at 'Contact Us' or e-mail: [ga@gaucher.org.uk](mailto:ga@gaucher.org.uk)

The Gauchers Association would like to thank the National Commissioning Group (NCG) of the NHS for the educational grant given to support the development of its new website.

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## Fund Raising raises £12,385 for Association

*The Association is always touched by the way its members, friends and families support patients through organising events, making donations and request donations instead of presents on birthdays and weddings and is grateful for all support, writes Treasurer Don Tendell.*

### In Memory

Friends and family of the late Tom Downes held a Darts tribute night in October and raised £1250 for the Association. Everyone enjoyed the evening and they have decided to make it an annual event. Tom's daughter **Angela** has also created a 'Justgiving' Page for all those who were unable to attend the darts night but would like to make a donation, to date an additional £263.00 has been raised.

Thanks go to the guests of **David and Val Hewitt** who we're married in June last year. Donations from friends and family raised £1030 for the Association.

**Tina, Paul, Heather and Mark Alvey** generous donated £6,842 to the Neuronopathic fund in memory of their son Jonathan who passed away in 2001. The money had been raised through an appeal to fund Jonathan's enzyme replacement therapy.

### Donations raise £3162

Generous donations have been received from; the family of the late Clive Harries, William Brake Charitable Trust, Chanctonbury Lodge from their Ladies festival, Gableholt Ltd, Deacon Search Ltd, Quilters Infant School, Ian and Pat Rothwell and from Raymond Cummins in memory of his father John Cummins who recently passed away.

Thanks go to **Alex and Clara** of South Harting who had a cake sale and raised £12 for the Association.

# New Charity Fundraising Pack Available



Gaucher fundraising pack

The Gauchers Association are pleased to announce the launch of their new fundraising pack. The pack is available free of charge to all members and friends who wish to raise funds for the Association. Each pack includes; balloons, stickers, posters (A4 and A3), leaflets, and sponsorship forms. A T-shirt is available on request (see picture opposite).

To request a pack simply call Tanya Collin-Histed on: 00 44 1453 549231, go online at: [www.gaucher.org.uk](http://www.gaucher.org.uk) or e-mail [ga@gaucher.org.uk](mailto:ga@gaucher.org.uk)

## One marathon too far for Elin

*The goal was to run/walk/shuffle six marathons in six days in the Sahara! Training for the event had gone well with a few days hiking in the Swiss Alps, completing the Three Peaks Challenge (including Crib Coch) in 24 hours and achieving a personal best at the Loch Ness marathon. I was still nervous and apprehensive as I boarded my flight to Cairo on the 24th of October however, and my pre race anxiety was not helped by British Airways deciding to leave my bag (containing all of my equipment!) at Terminal 5 for a further 48 hours!*

Luckily however it arrived just in time, and I joined the other 160 competitors for an eight hour bus drive to the heart of the Western Sahara. We all settled to sleep for our first night in the desert, in tents of 10!

The first day went very well. There were water stops every 10km or so. The sand wasn't too soft and the rock formations in the desert provided stunning views. I was delighted to finish that day 7th female overall.

The second day wasn't so great, the sand seemed much softer and the heat harder to manage. By this point I had 10 blisters, my gaiters had fallen apart and I was carrying a lot of sand in my trainers! But I completed it, just! And then it started to go wrong. When I started to feel unwell and then was sick at the 12 mile mark of the third day I knew I was in trouble. The race started daily at 8am, but even by 10am the heat was 38-39 degrees. The highest recorded temperature during the race was 45 degrees. The biggest problem in that sort of heat is the amount of salt you lose through sweating. It's a difficult balance to replace the electrolytes as it is, let alone when you start being sick. I always thought that since I run so slowly that I would never run the risk of "hitting the wall" as often discussed in the running world. But I was proved certainly proved wrong.

The course was very flat on the third day, with no rocks at all to even give a bit of shade, and nothing to see for miles around. I started feeling dizzy. The race doctor stopped with me when I was down, and sitting in the shade shivering, with spasms in belly, I decided that I just couldn't go on. I had nothing left to give. It was the worst and best decision I ever made, but as I sat in the truck to head back to camp it felt awful. The race medics gave me some medication, and the spasms stopped.

Although I was clearly out of the race rankings, I didn't want to give up completely, as it would be like falling at the first hurdle. So I decided to battle it again on the 4th day.

I woke up feeling optimistic after a good sleep. I was feeling strong at check point one. Half way to check point two however I started to feel unwell again and shortly after I was sick. I took some anti emetics and antacids, and kept on my way, but was flagging fast. But the sickness continued. And then I was the last one in the race and the camels who sweep the course were hot on my heels. When I stopped to sit in the shade of the only rock for about a 25 mile radius, the guides said that the camels couldn't stay out for much longer without water. Oh the shame!

When I finally made it to check

point three all the other competitors were moving on and the volunteers were packing up. As a result there were five medics at that check point when I made the decision to hobble it to the 4x4 and call it a day, my head hanging very low having failed again. The rest is a bit vague, but I remember turning round to DJ, one of the medics to say I didn't feel so well.... and then I woke up - my shirt cut open, intravenous fluids running, an ice pack behind my neck and in my groin, and somebody pouring water all over me.

Later after another bag of fluids, and a ride in a 4x4 over sand dunes lying flat on my back and I was on the way to recovery. I spent the following day with the race doctor, giving out sweets, drugs, dressing blisters and generally cheering on the runners through their 60 mile day! An incredibly long distant on foot in any context, but even more out there in that heat, that terrain and carrying a back pack. It was inspiring to see.

On the last day I joined the runners for the last 5miles up to the pyramids. It was an amazing atmosphere with pizza and cold drinks waiting for us all.

I'm very frustrated and disappointed that I didn't complete the challenge. But I learnt loads, and determined to bounce back to do other challenges. In the words of Arnold ... "I'll be back".

As always, I was overwhelmed about the level of support I received, the daily messages of encouragement and very generous fundraising. I'm astounded that I managed to raise £500 and want to express my very sincere gratitude to everyone that sponsored be so generously.

# Dan Brown runs the New York Marathon and raises over £4,000 for the Gauchers

*'In April 2006 I ran the Flora London Marathon' writes Dan, it was a fantastic experience and one I will remember for the rest of my life but afterwards I vowed.....never again. But how soon one forgets. About 18 months later the stresses and strains of completing the 26.2 mile course must have been erased from my memory because somebody mentioned running the New York marathon and I thought to myself, "That sounds like a good idea".*

So I committed to running in New York on 2<sup>nd</sup> November 2008. I managed to secure a place and booked the flights. There was no turning back. The four month training programme began in July 08 and before I knew it I was running my final long-distance training run (20 miles and no medal at the end of it!) and there were only three weeks to go.

I flew out to New York on October 30<sup>th</sup> – four days before the run. Sadly I was flying on my own as my heavily pregnant wife was advised not to fly and so I had to wave goodbye to Mrs B and my little boy, Milo, for 5 days. One of my best friends lives in Manhattan and had invited me to stay with him so on arrival I headed straight for his apartment for a little rest. However, anyone who has been to New York will know how true the Frank Sinatra classic is when it describes NYC as the city that never sleeps! Sadly, neither did I due to the non-stop noise of the hustle and bustle all through the night so the next day I checked in to a hotel for a bit of TLC before setting off a shopping trip to try and warm up the joints and tick off as many items as possible on Mrs B's shopping list!

After a couple of days of shopping, site seeing, shopping, eating lots of pasta (the technical term is carbohydrate!), shopping and a bit of rest, the big day arrived. The marathon



*Running for the UK Gauchers Association*

starts on Staten Island, south of Manhattan, at around 10 a.m. With 35,000 people to transport to Staten Island the organisers decided to run official buses from Manhattan to the island starting at 4am!!! Every runner was allocated a bus time which couldn't be changed and...yes you've guessed it...I was on the 4am bus! Fortunately my body hadn't quite acclimatised to the 5 hour time difference so it wasn't as bad as it might have been getting up just after 3am to run 26 miles but nevertheless it was going to be a long day.

We arrived on Staten Island just before 5am and made our way to the holding areas. Being set on the coast of the Atlantic there is a ferocious wind that swirls around at that time of the day which made temperatures feel freezing despite the otherwise clear sky and the promise of sunshine all day. Thankfully I had been pre-warned and was wearing four layers of clothing but still sat shivering along with the thousands of others I was with as we huddled into the small tents that had been erected to house all the runners for the morning.

After munching through a few bagels and topping up on energy drinks the hours soon passed and we were called in our groups to make our way to the start line which was on one end of the Verazano bridge connecting Staten Island to Brooklyn. It's actually a very steep and long bridge so the longest climb of the whole run was actually the first  $\frac{3}{4}$  mile or so. I was certainly relieved to reach the mid-point of the bridge and start going downhill although couldn't believe that I hadn't even run 1 mile yet.

I soon got into my stride once the first 2 or 3 miles had passed and the route took us into Brooklyn. This part of the course is relatively flat and takes up the first 12 miles or so. It was interesting running through the various areas within Brooklyn and



*Dan after crossing the finishing line in Central Park*

seeing the Mexican area, then the Italian, then the Jewish quarter etc. The crowds were great and lined the streets all along the way.

Once Brooklyn was behind us, a few hours had passed and we were almost at the half way point and I was making good time running roughly 10 minute miles which would have given me a finishing time of around 4 hours 20 minutes. But the legs were starting to hurt! The next 3-4 miles took us through Queens but I wasn't paying much attention to the scenery around me as the fatigue was starting to kick in and I was trying to delve deep into my mental resources to ignore it! Unfortunately the next significant landmark marked the starting point of what would prove to be my toughest few miles.

The Queensboro bridge connecting Queens to Manhattan appeared at mile 15. Being another steep bridge this was not a welcome sight as the legs were tiring and mental resources were depleting. I slowed down the pace, leant into the incline and pumped my arms. Reaching the peak of the bridge I felt a huge sense of relief but as I started to come down the other side felt the first twinges of cramp in my upper legs. Trying not to think about it I ploughed on and got a welcome boost when my friend Stuart managed to find me amongst the crowds on First Avenue at mile 16. A quick hug and a chat and I was on my way again but I as neared the mile 17 marker the cramp kicked in.

Trying to run with cramp in both

*(continued on opposite page)*

(continued from opposite page)

legs is almost impossible so I knew I had to slow right down to walking pace and try to relax. Throughout the run there are drinking stations and medical tents at each mile marker so I decided to stop at one of the medical tents for a quick massage on my legs. I was also given some form of pain killer and whilst it took a while to take effect this was to prove very helpful! The next 3-4 miles were really tough. I could only run for 3 or 4 minutes at a time until the cramp kicked in again and I would then have to walk until it had gone. Unfortunately this meant that the stretch from mile 17 to around mile 21 took me twice as long as it otherwise would have done and my aim of a sub 4.5 hour time was looking unlikely.

At mile 20 we entered the Bronx, an area notorious for crime and poverty, but the atmosphere was fantastic as the crowds grew and the music blared out. This really gave me a lift and I started to feel better both

physically and mentally. By the time we left the Bronx and were heading through Harlem and back towards Manhattan for the last 3-4 miles the pain killer started to kick in and I got a second wind. Picking up the pace again I could see a light at the end of the tunnel and knew that I was going to finish (a marathon runner's biggest pre-race concern!).

The last 3 miles took us south through Manhattan and in to Central Park for the finish. The crowds were fantastic, shouting my name out to keep me going (it was printed on my t-shirt in case you are wondering!) and I had a big smile on my face as I tried to take it all in. Amazingly there is another steep incline between miles 23 and 25 but I hardly felt it as the adrenaline spurred me on. Finally, I saw that magical sign – "1 mile to go!". Another 800 metres passed in a flash and turning a corner the finish line was in sight. Arms up, big smile and crossed the finish line. The feelings of satisfaction, relief and exhilaration all come at once. A few

more steps and I had the medal around my neck and the pain and stress of the run and the previous 4 months of intense training were forgotten in an instant.

My finishing time was 5 hours 1 minute and 58 seconds. Slower than I had hoped but I finished which was my principal goal! Sadly I just missed the cut off time for the results printed in the New York Times but this was a minor blotch on an otherwise fantastic experience.

However, the best part of all is that through the support of friends, family and colleagues I have managed to raise over £4,000 for the UK Gauchers Association. As a relatively recently diagnosed Type 1 patient who is now living a normal life due to effective ERT, I am acutely aware of the years of medical research and effort that have gone before me and to be able to give a little something back is hugely satisfying.

Having said that, I can safely say – never, ever again – and this time I mean it!

## UK Gaucher Chairman Addresses Israeli Patients Meeting

*Jeremy Manuel OBE Chairman of the UK Gauchers Association and the European Gaucher Alliance addressed the annual meeting of the Israeli Gauchers Association in Tel Aviv on 20 November 2008.*

The meeting held at the Dan Panorama Hotel in Tel Aviv attracted more than 200 patients and their families from throughout Israel. The meeting was also attended by the country's leading doctors and scientists and representatives from the pharmaceutical companies who have an interest in treating Gaucher patients.

Jeremy Manuel spoke of long association between the UK and the Israeli Patient Groups and the collaboration that existed in the early days of enzyme replacement therapy in accessing treatment for patients. He spoke of the significant contribution made to the understanding of Gaucher Disease by Professor Mia Horowitz of the Tel Aviv University and Professor Tony Futerman of the Weizmann Institute and the international role played by Professor Ari Zimran of the Shaare Zedek Medical Centre at Jerusalem in

the management and treatment of Gaucher patients.

Jeremy Manuel stated that he was particularly pleased that both of the books written on Gaucher Disease which were edited by Professor Zimran (the second with Professor Futerman) had been launched in the UK. His talk entitled "the Road Travelled Together" looked back at years of collaboration and forward to the future challenges facing Gaucher patients which the national groups and the European Gaucher Alliance seek to address. A particular concern is to encourage research in to unmet medical need and to achieve treatment for patients in parts of the world where this is not currently available.

The meeting also covered topics including the difficulties of Israeli patients achieving medical and travel insurance, the possibilities of pain relief through alternative therapy and



*Yossi Cohen and Dorit Levy of the Israeli patient Association, Jeremy Manuel and Prof Ari Zimran*

the information provided through the online patient forum.

The Israeli Patient Association Chairman Dorit Levy spoke about how far the Gaucher patient has come since the formation of the two Patient Associations in 1991.

Incoming Chairman Yossi Cohen who is himself a member of the Executive Board of the European Gaucher Alliance presented a medal to Ms Levy and pledged to continue her great work.

# Neuronopathic Gaucher Disease

## FAMILY CONFERENCE SUPPLEMENT

NOVEMBER 28<sup>TH</sup> - 30<sup>TH</sup> 2008



Brian and Tasha Andrews and their daughter Kaylee travelled from South Africa to the UK to attend the European Neuronopathic Gaucher disease Family Conference.

Hilton Hotel, Northampton, UK

# Introduction

***On the week end of 28<sup>th</sup> to 30<sup>th</sup> November the fourth European Family Neuronopathic Gaucher Disease conference took place at the Hilton hotel, Northampton. 115 people being parents, carers, patients, siblings, speakers, doctors, nurses and representatives from pharmaceutical homecare companies attended the three day conference. Tanya Collin-Histed, Executive Director of the UK Gauchers Association and mother of Maddie, 14 who has Type 3 Gaucher disease opened the conference on the Saturday morning, in addressing the audience she said;***

“Welcome to the fourth nGD Family conference, for some of you this will be your first meeting and we are delighted that you have been able to come. I would also like to welcome back many families who have attended all of these meetings over the past nine years.

We face many challenges, as a group of Gaucher parents and patients and as individuals living our lives coping with the day to day issues that the disease brings. Today we will hear about planned studies designed to understand further why some patients with GD have neurological involvement and some do not. We will also hear of a clinical study looking at behavioural issues; potential new approaches to treating GD; improved clinical management of patient with Central Auditory Processing Disorder; alternative approaches to improving quality of life and an update on what is going on in the research field of nGD.

Tomorrow we have a closed session. This will enable families and

older patients the opportunity to talk about the transition from childhood to adulthood. There are many nGD patients who in a few years will take more responsibility for their own disease as they become young adults. They will face issues such as further education, employment and independent living. I am delighted to welcome Sarah Long who will join tomorrow's session and share with us her experience of these challenging issues. Sarah will be accompanied by Rodney Bradbury who has Type 3 GD. Rodney who is in his 40's will tell us his experiences of growing up with a chronic condition. This session will be facilitated by Dr Vellodi.

When we started these meetings it was about being together, having time to talk, listen, comfort, learn, challenge and be ourselves. I believe the informal, relaxed and friendly atmosphere that we had all those years ago remains and for me this is our success. We are a very small group and we have become a family, we

welcome new friends and are pleased to see old ones.

An integral part of this meeting has always been the children, having a children's programme has always been an important part of this event to enabled parents to attend the meeting but also brings our children together. With such a small number of nGD patients worldwide these friendships are important. These relationship have led to the development of the 'Aunty Days' and we are planning three one day workshops in 2009. These will allow these young people to continue meeting up, to have fun and also to have the time to discuss issues that affect them. I would like to take this opportunity to thank Elin, Niamh and Lynne from GOSH for their hard work on this project.”

***Editors Note; The following pages contain write ups of the presentations given at the conference. We present these in the format they were given to allow readers to experience the presentations. The Gauchers Association would like to thank Dr Ashok Vellodi from Great Ormond Street Hospital who very kindly wrote up all of the speakers presentations for Gauchers News.***

## Update on Type III Gaucher disease

***Dr Ashok Vellodi, Consultant Paediatrician, Metabolic Unit, Great Ormond Street Hospital for Children NHS Trust opened the formal proceedings and said;***

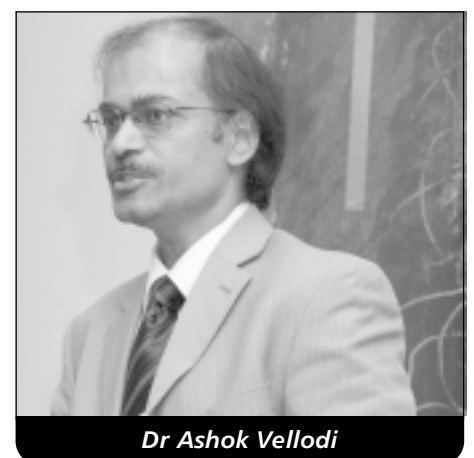
“I would like to discuss 3 topics

- Demography
- Neurogenesis
- Direct enzyme treatment

### ***Demography***

The following data is taken from the Neurological Subregistry of the ICGGR. A total of 122 patients have been enrolled ( as of March 2007). Nearly a third were from Egypt, with significant contributions from the UK (13%), Sweden (11%) and Poland (14%). The largest ethnic group was Caucasian

(45%) followed by Arab (35%). The mean age at diagnosis of Gaucher disease was 3.2 years, and 54% developed neurological signs and/or symptoms before the age of 2. The commonest genotype was L444P/L444P. Evidence of severe visceral disease was present in the majority of patients. For example, severe splenomegaly was seen in 94%. Growth retardation was seen in 56%. The commonest neurological signs at presentation were horizontal gaze palsy (69%) and head thrusting (64%). Seizures had been seen in 14%, and 13% were on medication for this. Developmental delay was seen in 42%. A small but significant number (13%) had extrapyramidal signs such as Parkinson's. The EEG was abnormal in



***Dr Ashok Vellodi***

64%, and of these, epileptic activity was seen in 69%. The audiogram (hearing test) was abnormal in 36% and of these, *sensorineural* hearing loss was seen in 44%.

## Neurogenesis

For many years, it was thought that new nerve cells could not be formed in the adult brain. It is now known that in fact this does happen. The process of formation of new nerve cells is known as *neurogenesis*. Primitive nerve cells, known as *neural stem cells* (NSC) or *neural progenitor cells* (NPC) are found in certain areas in the adult brain, from here they migrate to other areas. They are capable of differentiating into all known types of nerve cells. Their presence can be demonstrated using a special type of scan known as *spectroscopy*.

The process of neurogenesis is a complex one and is controlled by several factors. Scientists now have a good idea about the nature of these.

The fact that the adult brain is capable of making new cells suggests that it is capable of self-repair. Indeed, some evidence of this is seen after acute events such as stroke. Of course, the process is not perfect, otherwise recovery from stroke would always be complete! But scientists have identified the factors that control this process and are trying to develop ways of boosting them. Interestingly, there is evidence that some neurogenesis takes place from antidepressants such as Prozac and physical activity.

There is potential for treatment using NPC's. They can be genetically engineered to produce enzyme. Importantly, they can then be put back into the brain with few side-effects. Not only that, they are under the control of the same factors that control normal neurogenesis. This is very important.

## Treatment

It has become established that the treatments currently available for the systemic treatment of Gaucher disease (ie enzyme and miglustat) have little if any effect on the brain. There is clearly need for more effective treatment of the brain. It has been shown that if enzyme can be somehow delivered to the brain, it is taken up by neurons. Therefore there has been a lot of interest in delivering treatment directly to the brain, particularly *direct gene therapy* and *direct enzyme therapy*.

*Direct gene therapy*. Essentially, this comprises 4 steps:-

- The gene is attached to a *viral vector* that is capable of penetrating nerve cells. Not all

viruses can do this; it is important to choose the right one.

- The gene-vector complex is injected into brain
- The virus enters the cell, carrying the gene with it
- The enzyme defect in the cell is corrected

Examples of diseases in which this has been achieved in animal models are the neuronal ceroid lipofuscinosis (NCL) of which Batten's is an example, and some of the mucopolysaccharidoses (I, III and VI). It has been shown that the enzyme defect can be corrected and storage cleared. However, it is not as simple as this, and the results vary. There are several reasons for this; two important ones are *enzyme secretion-uptake* and *axonal transport*.

### Enzyme secretion-uptake.

Lysosomal enzymes are formed in the cell and are mostly transported to the lysosome. However, a proportion are secreted by the cell, and are then available for uptake by neighbouring cells. This process is best illustrated after bone marrow transplantation (BMT) where the donor cells have normal levels of enzyme and recipient cells are deficient. Enzyme is secreted by donor cells and taken up by recipient cells, correcting the enzyme defect. Exactly the same thing happens after injection of the virus-gene complex into the brain. The complex enters some of the cells, correcting the defect, and these cells in turn secrete enzyme which is taken up by neighbouring cells. However, the efficiency of this process varies from species to species and from disease to disease. For example, it is more efficient in mannosidosis than in GM1-gangliosidosis. As yet, it is unclear how efficient it will be in Gaucher disease.

### Axonal transport.

Axons are the long processes of nerve cells. It has been known for many years that once a virus enters a nerve cell, it moves along the axon. This has been particularly well studied in the giant axon of the Atlantic squid, which is several thousand times wider than a human axon, and therefore easier to study. This process is known as *axonal transport*, and it is slowed down in storage diseases. It is more severely affected in some diseases than others. For example, it is slower

in NCL than in MPS I. This means that for some diseases, the virus carrying the gene may not travel as efficiently through nerves as in others. Again, we don't know what it will be like in nGD. There are some important challenges with direct gene therapy. The first is technical, the solution containing the virus-gene complex cannot be injected too quickly, and the volume must not be too large, otherwise the pressure in the brain will increase. Delivery has to be to the right areas, which means the tip of the needle has to be positioned very precisely. The second is immunological. A severe encephalitis (brain inflammation) has been observed following this procedure. It is not seen in mice but is seen in dogs, so there is a possibility that it may be seen in patients. It can be completely prevented by giving drugs that suppress the immune response prior to the procedure.

There are also logistic challenges.

- The viral vector referred to above has to be purified to a level sufficient for human use ie it has to be of *clinical grade*.
- The appropriate neurosurgical expertise needs to be available
- Sufficient funding needs to be available; the vector in particular can be very expensive.

Direct gene therapy to the brain is currently undergoing clinical trials in two neurogenetic diseases; Canavan's disease, which is not a lysosomal storage disorder, and Batten's disease, which is. As yet no results have been published. Clinical trials are also planned in two of the mucopolysaccharidoses; MPS IIIA and MPS IIIB. In both conditions, animal studies have already been performed in mice and dogs.

### Direct enzyme therapy

There are three possible routes by which enzyme can be given directly

- *Intrathecal* - Via a lumbar puncture
- *Intraventricular* - Via a reservoir place in the ventricles
- *Direct intracerebral* - Via a small catheter directly into brain tissue

Of these, the most experience has been with intrathecal therapy. In fact, this route is used to administer a drug called Baclofen to children with some forms of cerebral palsy. The tip of the catheter is placed in the intrathecal

space, and is connected to a reservoir place under the skin of the abdominal wall. This approach has been used in treating dogs with MPS I with the enzyme that is deficient in this disease. Considerable clearing of storage in the brain has been reported.

Direct infusion into the brain has been performed in a single child with type II Gaucher disease. However, this approach presents significant challenges.

Finally, a few words about designing clinical trials in type III GD. There are several important challenges. Firstly, the disease tends to be quite slowly progressive in most

patients, and so it could take a long time to detect a clinical effect, and even longer to be sure there was no effects. The second is that there are really no useful clinical endpoints, and so measuring response objectively can be very difficult. Thirdly, there is no good large animal model. In fact, until recently, there wasn't even a suitable mouse model. The only ones that were available died very soon after birth as they lost massive amounts of water from the skin. Fortunately, recently a much better mouse model has been created by Prof Stephan Karlson in Sweden, and hopefully it will prove useful both in our understanding of

the disease, as well as in trying out new therapies.

In conclusion, therefore

- Until the BBB can be dealt with more effectively, direct approaches are more likely to work
- CNS gene therapy is being developed, but the lack of large animal model is a disadvantage
- Therefore we have to make the leap from "mouse to man" in NGD
- We need much better tools than are currently available."

## Audiology in nGD patients

**Dr Tony Sirimanna, Consultant Audiological Physician, Great Ormond Street Hospital for Children NHS Trust gave a fascinating overview on audiology problems experienced by nGD patients, he said;**

"Our understanding of audiology in GD is still at an early stage. We are only just beginning to understand some of the issues that they present with.

It is important, firstly, to understand the process of hearing. It is one of the most sophisticated senses we have, together with vision. If one of these is affected, the other tries to compensate. In patients with nGD, both are affected, and this can be very disabling.

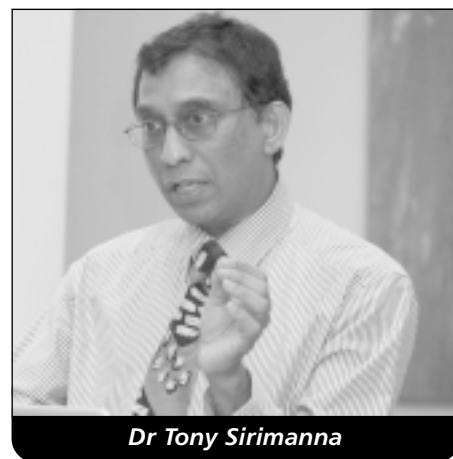
Sound travels through the ear canal and middle ear to reach the inner ear. In the middle ear, sound energy is transformed into mechanical energy, and in the inner ear, this is further transformed into electrical energy. These electrical signals pass through the neural connections to the brain, where they are interpreted and given meaning.

The inner ear contains the organ of hearing. This contains a series of hair cells. There are two groups of hair cells, inner hair cells and outer hair cells. The neural connections are formed with the inner hair cells; there is one row of these, and they transform the mechanical energy into electrical energy. There are three rows of outer hair cells. Their function is to act as a sort of graphic equalizer. They amplify sounds that you want to hear and dampen down background noise, the sort of sounds that you don't want to hear. The outer hair cells are under the control of the brainstem, which

itself is under the control of the cortex. This mechanism is the first step when we are filtering out background noise. It can be measured by means of Otoacoustic Emissions. These are small sounds that the outer hair cells generate when you hear a sound. They are generated by small muscle fibres in the outer hair cells. During this process, if a loud sound is heard, it is directed to the other ear which can then suppress it. This process can be tested using *contralateral suppression of otoacoustic emissions*, a test where OAEs suppression resulting from a loud sound presented to the other ear is measured.

When people talk about a hearing test, most of us picture the standard test in which you wear a set of headphones and listen to sounds of different frequencies in a sound proof room, to which you respond by pressing a button. This is known as pure tone audiometry (PTA). But it does not give you the whole picture. Most patients with type III GD have normal hearing when tested by PTA. Of course, some of them may have, for example, glue ear, which is what happens when one picks up a cold and fluid collects in the middle ear. This is seen in normal children, and results in *conductive hearing loss*. Nearly 50-60% of children will have had this by the age of 6-7 years. So of course a percentage of children with type III GD will also develop it. The outer hair cells (see above) are also normal in these children usually. However, because the brainstem is affected in type III GD, the *contralateral suppression of otoacoustic emissions* is not present.

The *stapedial reflex* is also



impaired. The stapedius is a small muscle in the middle ear that contracts when you hear a loud sound. It is thought that the stapedial reflex acts as a protective mechanism against loud sounds. The contraction of this muscle can be recorded using a special test. Since the reflex is controlled by the brainstem, it is impaired or absent in nGD children.

Brainstem auditory responses – this is a test in which the electrical signal generated by the inner ear can be recorded as it passes through the nerve of hearing and the brainstem on its way to the cortex. The recording is done by means of electrodes attached to the scalp. Since they are placed at some distance from the ear (ie quite far) the response is known as a *far-field response*. In children with type III GD, the interval between generating the signal in the inner ear and recording it is prolonged. Sometimes the response to a particular frequency may even be absent even though the PTA at the same frequency is normal. So as you can see, this test doesn't tell you

anything about hearing, just the way sound travels between two points ie the inner ear and the brainstem.

Special tests maybe to be used to pick up the range of hearing problems seen in type III GD patients. Some of these tests are included in the Central Auditory Processing Battery. For example, speech discrimination in quiet surroundings versus speech discrimination in noise e.g. classroom, cafeteria or shopping centre background noise. Another test measures the ability to fill in the blanks in what one is hearing. We all do this all the time i.e. we don't hear everything we listen to, but can fill in the gaps. So this test uses filtered words delivered to the ear through head phones. Another test would be to present words in a multi-talker background noise. Children with Type III GD can't hear these words properly. So they have difficulty in hearing against a noisy background as well as hearing poor quality speech.

*Mismatch negativity (MMN)* has been used in the past to test some children. This is a test that is used to test the *cortical* response to sound (as opposed to the brainstem which is used to test the brainstem response and doesn't tell you anything about cortical function). It is a sort of testing at the pre-conscious level. It tells you about the ability to *discriminate* between different sounds. For example, if you hear the sound "ba" repeatedly ie ba-ba-ba-ba, and then you hear "da" the cortex recognizes the difference and a different waveform is generated. The waveform is a negative one, and because it is

generated by the mismatch between two sounds (in this case "ba" and "da") the phenomenon is known as mismatch negativity. The ability to discriminate in this fashion is impaired in patients with type III GD.

You can see that patients with type III GD have certain common audiological features. They have normal outer hair cell function, normal audiometry, absent stapedial reflexes, abnormal auditory brainstem responses. Collectively, these features are referred to as the *Auditory Neuropathy Spectrum (ANS)*. It used to be known as auditory neuropathy / auditory dyssynchrony (because the neural pathways don't fire synchronously). The reason it is a spectrum is because the degree to which the individual features are affected vary. So at one end of the spectrum, for example, you may see someone who has perfectly normal hearing thresholds but difficulty in hearing in noisy, while at the other end may be someone who has great difficulty and so may behave as should they are profoundly deaf. Patients with type III GD tend to fall at the better end of the spectrum.

All this has important implications for affected children. They have normal outer hair cell function and abnormal brainstem responses, so they have auditory neuropathy spectrum. On the other hand they have normal pure tone audiometry but difficulty in hearing when there is background noise which suggests an auditory processing disorder. They have to strain to listen and understand in the classroom. They may do this, but on the other hand they may not bother, and might start

chatting to their neighbour. Such behaviour is often interpreted as being disruptive and may result, in some cases, in the child's exclusion from school. They are often very tired when they come home, as they have to strain so hard at school.

In the average UK classroom, the teacher's voice level at one metre is about 60 decibels. Background noise is also can be about 60 db, So there isn't much difference between the two even at one metre. As one moves towards the back of the class, the teacher's voice fades away and gets completely "swamped" by the background noise. Children need a difference of about 16 db to hear the teacher's voice properly. A normal child will be able to suppress the background noise sufficiently, but a child with type III GD will not. The management of this problem is twofold-firstly, to amplify the teacher's voice by the use of speakers on the classroom walls or small devices, such as the Edulink, in the child's ear (in which case the teacher wears a microphone), and by minimizing the background noise (non-echoing environment), and seating the child at the front of the class.

In summary, children with type III GD have normal hearing. Their presentation is identical to those with an auditory neuropathy and also with auditory processing disorder ie difficulty with background noise and poor sound discrimination. This results in significant difficulties in the classroom. The problem can be managed by a combination of improving classroom acoustics and amplifying the teacher's voice."

## Neuronopathic Gaucher Disease: more questions and the search for some answers

*Dr Nicholas Smith, Lysosomal Diseases Research Group, University of Cambridge described his proposed research into the LIMP-2 protein (see also his article on page 4);*

"Gaucher disease was first described by the French physician Philippe Gaucher in 1882, although it was not until the early twentieth century that the acute and later the chronic neuronopathic forms were identified as belonging to this same disorder. Subsequent characterisation of the disease course faced by patients led to the clinical classification of

disease as either non-neuronopathic (type 1) or neuronopathic (types 2 and 3) disease.

More recently it has become necessary to reconsider this categorisation; by definition type 1 disease is typified by an absence of primary neurological manifestations (involvement of the brain or nerves that is a direct result of the disease itself). However, in a small group of patients initially considered free of neurological disease, late onset neurological problems have been recognised. In the majority these symptoms are identical to those of



Dr Nick Smith

Parkinson's disease (a disorder of movement) including tremor, dystonia (stiffness of the body and limbs) and difficulties of movement and balance. In some cases features of cognitive decline or dementia have also been seen. This has led the majority of clinicians and researchers to reconsider the classification of disease as it now seems likely that a spectrum of neurological involvement exists ranging from a complete absence of nervous system involvement (classic 'type 1' disease) at one extreme to acute onset infantile disease (classic 'type 2' disease) at the other.

Although measures such as physiotherapy, special education interventions and the use of medication including anticonvulsants and drugs to improve parkinsonian symptoms are available and in many cases of great value, it must be recognised that these are supportive only. To date, efforts to develop specific therapies (most notably enzyme replacement therapy) whilst of benefit in visceral disease have proven disappointingly ineffective in combating neurological involvement and the development of targeted treatment strategies for the nervous system and ultimately a curative intervention continue to elude us.

In order to achieve this outcome

we must first improve our knowledge of the disease process within the nervous system. A number of research groups around the world are employed in this endeavour, however many obstacles are faced, not the least being the availability of an experimental animal model which reproduces the disease seen in humans. Of great benefit to research in the field such a model has been developed by Professor Stefan Karlsson from Lund University in Sweden. Our research group in Cambridge is privileged to collaborate with Professor Karlsson's laboratory and we are undertaking a number of studies with these animals with the objective of determining the mechanisms of neuronal dysfunction in Gaucher disease.

We are also very interested as to why individuals with seemingly identical genetic origins of disease display such wide variation in their clinical features. For example, patients with the same disease causing genetic abnormality may present with or without nervous system involvement. This suggests that additional factors may modulate the disease course in individual patients. A number of factors may play a role in this observation including genetic changes in unrelated, though disease associated

genes, termed 'modifier genes'.

One potential candidate in this modifier gene category has followed from the recent work of Professor Paul Saftig's research group in Kiel, Germany and his scientific colleagues at Genzyme who have identified the important role of the Lysosomal Integral Membrane Protein type 2 (LIMP-2) gene. This gene codes for a protein that has been shown to play an important role in the intracellular trafficking of the enzyme glucocerebrosidase, which is absent or dysfunctional in the lysosomes of patients with Gaucher disease. Interestingly, this protein plays a greater role in certain tissues including the brain and moreover its absence has been implicated in another rare disease that displays overlapping features with the more severe forms of neuronopathic Gaucher disease. This observation has led us to question whether variation in the LIMP-2 gene and subsequently an alteration in the LIMP-2 protein predisposes to neurological involvement in patients with Gaucher disease.

It is hoped that answering this question will provide a means of better determining those patients at risk of neuronopathic disease and more importantly allow early implementation of future therapeutic interventions and neuroprotective measures."

## Complementary Medicine in Gaucher Disease

*Dr Sara Eames, Director of Education and Women's services at The Royal London Homeopathic Hospital, looked at the possibility of complimentary treatments for nGD patients, she did this by posing a series of questions and providing answers;*

"As most people are not really familiar with complementary therapy. So this talk is really for beginners.

### What is complementary medicine?

- It is a holistic system, looking at the whole body and characterized by a linking of mind, emotions and body. It is well known, for example, that on some days we don't feel so well, for no particular reason, but clearly the way our mind works can influence the way our body feels and vice versa.
- Most systems address an energy balance. This concept is best illustrated in traditional Chinese medicine (yin and yang) and

acupuncture (positive and negative balance).

- Stimulation of the body's own healing powers. The body is quite good at doing this, but we don't always take this into account when taking treatments that may suppress the body's own mechanisms rather than stimulate them.

### What is Homeopathy?

- It is a complete system of medicine based on the principle of 'like cures like. In other words, a particular medicine when given in a small dose may cure the symptoms that the person is suffering from if they are similar to the symptoms the substance can cause. eg: Homeopathic Onion for certain types of runny eyes and noses.
- Homeopathic remedies can be made out of anything; they use dilute substances of animal, vegetable and mineral origin.
- There are thousands of remedies.



Dr Sara Eames

Information about their symptoms come from

- Toxicology
- Provings
- Clinical Experience.
- Theories of chronic disease – Inherited predisposition to disease.

### So how can complementary medicine help in Gaucher disease?

- We are all limited by our genetic potential. So we should try and

maximize this. Complementary therapy aims to help with doing this. In homeopathy, for example, we might prescribe a constitutional remedy, which is an overall remedy covering both emotional and physical symptoms. This can help with how someone feels overall and can make their condition easier to accept and live with. Other systems of treatment would have a similar objective.

Homeopathic remedies can also be used for bothersome local symptoms for example rita and euphrasia for eye problems.

- One can also consider remedies to help during treatments such as injections, for example Arnica, Ledum, Staphisagria.

- It can also be helpful in the treatment of intercurrent illness.

#### What should one be wary of?

- Any practitioners who claim to be able to cure you or make statements that sound exaggerated. Unfortunately there is little or no regulation, although there are some steps being taken towards achieving this.
- Any practitioners who are not willing to share your care with other health professionals.
- Claims and products via the internet always need further research and information.
- Don't forget that Complementary Therapies are just that – designed to be used alongside the best of conventional medicine.

#### How does one find well-qualified practitioners?

- The Homeopathic Hospitals are part of NHS and staffed by conventionally trained doctors. In London, Tunbridge Wells, Bristol, Liverpool and Glasgow. Referral is by GP or consultant letter.
- The Faculty of Homeopathy is an international body of qualified health professionals who practice homeopathy and some other therapies. Lists of practitioners are available from [www.trusthomeopathy.org](http://www.trusthomeopathy.org)
- Word of mouth from families and/or doctors you trust, but always bearing in mind the suggestions to be wary of."

## Behavioural Issues

**Dr Paramala Santosh of Great Ormond Street Hospital, gave an in-depth talk on behaviour issues in patients with lysosomal storage disorders;**

"This is an area that is not often addressed at metabolic meetings. It is important to try and understand why the assessment of psychopathology is a fundamental part of the overall assessment protocol. The reason for this is that difficult behaviour is just as important a factor as physical problems in determining quality of life, and the ability of children and their families to cope.

I lead the Centre for Interventional Psychopharmacology at GOSH. We run four clinics

- Complex Developmental Neuropsychiatry Clinic
- Childhood Dementia Clinic (most LSD referrals fall into this group)
- Childhood Traumatic Brain Injury Clinic
- Complex Paediatric Psychopharmacology Clinic

There is a complex assessment process which is different from the normal clinic referral. Various questionnaires as well as Web-based assessments are necessary prior to the clinic appointment. The reason for this is that it is important to have a detailed idea of the problem so that the interview can be structured accordingly.

As far as treatment is concerned, we are never prescriptive. One of the reasons for this is there is very little evidence for the treatment of many rare disorders. Information sheets about the medicines are provided and the parents are asked to opt into treatment. At this point the evidence or lack of it is discussed in detail. Once treatment is started, the child is stabilized and monitored over the next 12-16 weeks. Much of this is based on telephone conferencing. In addition there is routine clinic follow up. Care is shared with local professionals. Emergencies are dealt by telephone.

It is important to stress that treatment is never commenced at the doses recommended in the books. There is in fact good evidence now that in organic brain conditions, medication must be given in low doses. We start with small doses (roughly 1/6-1/8 of the dose) and increase slowly (roughly 5-10 half-lives of the drug). So if it is a short-acting drug, the dose needs to be increased roughly every 3 days. If it is a longer-acting drug, we increase every 7 days. This is known as the Minimum Effective Dosing (MED) strategy. After each increase the family is contacted to check on side effects and symptoms. We don't go to the next dose if the child has developed side effects that can't be tolerated. We wait till these settle (they usually do with time) and then only go to the next dose. The result is that the child is



*Dr Paramala Santosh*

treated only with the minimum dosage needed to control the symptoms. Ideally, of course, one would aim for minimal side-effects and maximum response.

#### **Gaucher Disease**

What is the current evidence of psychopathology in Gaucher disease? There is no published data. The closest is a single case report of Niemann-Pick disease in which the Mini Mental Scale was used. This is not a useful scale to use. However, there are some general points that one can make. Firstly, there is a 10% chance of any child having a mental health issue. The presence of a medical condition that does not involve the brain increases the risk to 20%. In the presence of a chronic condition that involves the brain, it increases to 40-45%.

In a survey of 28 patients with type I GD in 2006, the Minnesota

Multiphasic Personality Inventory was used. Unfortunately this is an outdated profile. The researchers found that the patients had a tendency to deny psychopathology, had depressed mood and somatic concerns, and they showed psychological turmoil and felt isolated. This was perhaps not surprising, and has been shown with chronic diseases in general. In other words, the findings were non-specific.

In our study of the mucopolysaccharidoses, which was postal and internet-based, 160 patients were contacted. The findings were quite unexpected. For example, whereas only 1% of the general population would be expected to have autistic spectrum disorder (ASD), 65% of children with MPS III were found to have it. Importantly, none of the parents or careers had had any instructions on how to deal with ASD. There are three core deficits to look for in ASD- impairment of social skills, language and communication (these children tend to use language and communication to collect information rather than socialization), and repetitive behaviour. It is important to be aware of all three when it comes to management. An important finding in this study was that parent-child relationships could be predicated by behavioral problems. Similarly, social networks can be severely affected by difficult behaviour. Finally, it can lead to poor educational support, as a result of lack of understanding by educational authorities. All these can

result in a poor quality of life for child and family.

Treatment approach is based on symptoms rather than disease. Essentially there are three groups of symptoms:-

- Those that respond to medication alone
- Those that need behavioural modification as well as medication
- Those that require specific remedial approaches to retraining skills

One can make a rough guess as to which type of molecule might help, based on the underlying physiological disturbance. This method was published in the Lancet in 1999. We look at three basic neurotransmitter systems ie noradrenaline, dopamine and serotonin. For example, if one wants to reduce obsessive-compulsive behaviour, increasing serotonin should be the target. If depression is the problem, then one tries to increase noradrenaline and serotonin, and so on. So if a child has multiple problems, we try and map out the molecule that might work best. Of course, most drugs have side-effects, but they might be acceptable. In this way, the parents can make an informed choice.

It is worth briefly mentioning the syndrome of pseudodementia; this is common to most of these conditions. In this, the child starts losing skills and it looks as though dementia is setting in. In fact, the real problem might be severe depression. When this occurs in someone who has some

developmental delay, they may not be able to express it properly. The reason for this is that those parts of the brain that monitor mood may not be functioning very well. So it appears as though the child is losing skills, whereas in fact treatment with antidepressants might produce a good response.

It is also becoming apparent that treatment with some of these drugs may have a neuroprotective effect.

Finally, I would like to show you a few slides relating to the online system that we have developed. The intellectual property is owned jointly by GOSH and Guy's. This is an online system. It uses six cartoon characters that we bought from another company and animated. Child actors play the roles of each character. They "talk" to children and take them through various scenarios online. It fulfils security standards for the EU, and cost about £1,000,000 to produce. There are six computer games which look at various aspects of cognitive function. The audio function is particularly suitable for children with dyslexia. Responses are recorded "behind the scenes" on a database.

Ongoing responses to medication can be recorded using this programme and displayed graphically, enabling the team to make changes in an informed manner. Of course, the more data that is collected the better. But this approach is probably the way forward."

## New Approaches to Targeting the Brain

*David Begley from Kings College, London explained how the blood brain barrier works and described possible delivery mechanism to treat LSD's;*

"My talk will be in three parts:

- A description of the BBB
- Work that has been done on targeting large molecules to the brain
- Plans for the future, especially within Europe (Brains 4 Brains)

**What is the BBB?**

- The blood-brain barrier is formed by the smallest blood vessels in the brain, the capillaries.
- The capillaries of the brain are

unlike those of most other body tissues in possessing this barrier.

- It prevents the free movement of small and large molecules from blood to brain and vice versa.
- Molecules that the brain needs are transported across the barrier.
- The barrier is a physical barrier to free diffusion.
- The barrier is a transport barrier, both in and out.
- The barrier is also a metabolic barrier in that it can detoxify drugs.

**Why does the brain need this barrier?**

- The brain needs to maintain an extremely stable internal fluid environment which is an absolute requirement for reliable synaptic



**Dr David Begley**

communication between nerve cells.

- The Blood-Brain Barrier is also a

protective barrier which shields the central nervous system from circulating neurotoxic substances in blood which are produced by metabolism or are ingested in the diet or otherwise acquired from the environment.

- Most fully differentiated neurones are unable to divide and replace themselves and thus any acceleration in the normal daily rate of attrition of neurones (cell death) will become prematurely debilitating.
- There are a lot of diseases of the brain for which current therapy is inadequate.
- Neurological diseases constitutes one of the top five causes of disease and suffering (*WHO statistic*)
- Most drugs under development for CNS disease fail as they do not cross the BBB

#### **What is the importance of the BBB in lysosomal storage disorders?**

- Current substrate reduction therapy (SRT) and chaperone therapy needs to cross the BBB to be effective.
- Currently available enzyme replacement therapy (ERT) does not appear to cross the BBB in therapeutically significant amounts.

#### **Why do we need to know more about the BBB?**

- Damage to the BBB may contribute to the neuropathology of LSDs.
- At present we do not know what factors determine the entry of SRT and chaperones into the brain
- In order to design new small molecule therapies we need to understand the process of brain

penetration in order for them to be effective

- The BBB contains a number of transport process which take large molecules such as proteins into the brain
- We need to understand these transporters for macromolecules so that we can adapt ERT to cross the BBB and treat the brain

#### **Recent Developments in Delivering Large Molecules to the Brain**

A paper published in 2004 showed in mice that the BBB has a transport mechanism for taking up lysosomal enzymes using the mannose-6-phosphate receptor. In very young mice this seemed to function quite effectively. However, by the age of 7 weeks, this transport mechanism had disappeared.

An interesting paper that appeared this year showed that if enzyme was modified using certain chemicals (in this case sodium metaperiodate followed by sodium borohydrate) it could cross the BBB and clear neuronal storage.

There are several receptors in the BBB that are capable of transporting large molecules across into the brain. So if an enzyme can be fused to one of these, creating a *fusion protein*, the large molecule uses its transporter to get across the BBB and takes the enzyme with it. This approach has been used successfully in experimental models, but is nowhere near human trials yet.

We have recently carried out an experiment. In collaboration with colleagues in Frankfurt, in which human albumin particles were aggregated into a small sphere about 250 nm in diameters. We have added ApoE to this, and shown that this complex can cross into the brain, something which no one had shown before.

Brains 4 Brain: European Task Force

on Brain and Neurodegenerative Lysosomal Storage Diseases.

- Because LSDs are rare diseases the resources in individual EU countries in terms of scientific manpower and finance for research are limited
- By forming consortia extra resource is generated both in scientific manpower and the funding for research
- Scientists and financial support can be concentrated into larger more effective groups
- Lobbying of the EU to influence calls can be more effective

Along with Dr Maurizio Scarpa, I have put together a proposal for the 7th EU Cooperative Working programme. Calls were in September 2008, and the deadline is December 3rd 2008, these are;

**RARE DISEASES HEALTH-2009-2.4.4-1:** Rare neurological diseases. *Collaborative Project (Small or medium-scale focussed research project 6M•)*

*Lysosomal Storage Disorders as Models for the Understanding and Therapy of Rare Paediatric Neurological Diseases 13 Partners 6 countries "Brains 4 Rare"*

**BRAIN AND BRAIN-RELATED DISEASES HEALTH-2009-2.2.1-4:** Understanding the blood brain barrier (BBB) to improve drug delivery to the brain. *Collaborative Project (Small or medium-scale focussed research project 3M•)*

*Understanding the BBB to Treat CNS Disorders: New Efficient Brain Drug-Delivery Systems. 7 Partners 5 Countries "Drugs 4 Brain"*

## My beautiful, loving son Daniel

**Kerry Hannaway, Mother of Daniel who has type 3 Gaucher disease gave a personal account of her journey with her son;**

"I wanted to start my story today by showing you this holiday snap taken in August this year. It is a photo of my mum and dad taken with their six grand children and captures the lovely day we all enjoyed at Land's End. One of their grandchildren suffers from type 3 Gaucher disease. I would suggest that for anyone looking at this photo that does not know me

and my family it would be very hard to tell which one that is. Now look at this second photo taken on the same day.... can you guess which is my son. Yes of course he is the one on his own to the left, there with the others but he's not really joining in. This is my son Daniel he is seven years old and he has type 3 Gaucher disease.

I chose this picture because I think it represents how the disease really affects him, not all the medical science, but how he is affected on a day to day basis. All Daniel strives for is to be able to do the things his



Kerry Hannaway

friends take for granted but his body constantly fails him and he is becoming increasingly isolated both at school and in other social settings because of it.

Daniel can't write, he can't draw, he can just about colour at the level of a three year old. He can't play with lego, computer games, build his marble run or his car track, in fact he even really struggles to put a car on the track when it is built. He can run but he can't keep up with other children and constantly falls over, he can jump but he can't play on a trampoline with others because he can't balance. He can climb but not as well as his peers who now enjoy monkey bars and fireman poles. Last year we went on holiday with friends from school, and I was really excited because I knew that Daniel had finally mastered the beach and was able to walk and run on it with the others. But what happened as soon as we arrived at the beach, all the children wanted to do was go rock climbing and yes you've guessed it Daniel couldn't do that!

#### **With a smile on his face**

How does Daniel deal with all this? Usually with a smile on his face and sheer determination. Daniel is the most caring selfless child you could ever meet. He is also an extremely happy child who has always loved the things life has to offer. However he is a child who also desperately wants to fit in and in the last year the disease is even starting to rob him of these special qualities. We have seen increasingly frustrated and aggressive behaviour towards his dad and myself and his siblings and tears and tantrums over little things.

#### **The beginning**

It wasn't always like this in his first year of life Daniel's development appeared normal. He rolled over at three months, sat up before six months, crawled at nine months although never robustly and looked like he was about to walk at 10 months walking along happily holding one finger. However at 13 months he was still holding onto one finger.

By this time Daniels health had deteriorated. At eleven months he started being violently sick on a regular basis, on examination of his stomach it was discovered his liver and spleen were more than significantly enlarged. We spent about six weeks

that summer back and forth to our local hospital being told maybe it was just a virus but it could be something very serious. We were very up and down during this time but by the end we just wanted to know what was wrong with our son. Finally we were referred to Great Ormond Street Hospital and Daniel was within a week diagnosed as having Gaucher disease.

#### **Embarking on a clinical trial**

When we first met Dr Vellodi in September 2002 he told us the diagnosis but also talked about the Zavesca drug trial that was about to start and the hopes that this drug would really help children with this condition. Daniel indeed might benefit from it eventually although at 14 months he was too young to go on the trial.

Five months later in February 2003, we were now told that because the trial had been delayed it might be feasible for Daniel to take part in it. Having discussed the pros and cons and feeling that we could opt out at any point we decided for Daniels sake to attempt the trial.

One of the reasons we made this decision was because of what we saw happening to Daniel that second year of his life. His physical development started to fall significantly behind his peers and we started to realise Daniel was on the more severe side of the type 3 spectrum..... Although he was walking at 14 months he didn't progress to running and jumping, this was the first sign of his ataxia.

At 13 months when we first met Dr Vellodi it had been difficult to detect whether Daniel's eye movement was affected or not, indeed Dr Nischal examined Daniel and said his movement was fine, by the summer we were told that his eye movement was now typical of the older children with his condition. Daniel also started to develop an intention tremor that year. Both Ian and I were concerned how much he could deteriorate in the next few years and therefore felt that by putting him on Zavesca we might be able to keep him stable. Indeed it is that very belief that kept me going in those early days.

As the build up to the drug trial progressed I personally found an unexpected benefit of participating. I was definitely at the lowest point I have ever reached as we entered 2003. Through the drug trial I met two

very special people who really supported me and showed me that it is possible to be happy and have a child with Gaucher disease. Elin haf Davies barely saw me without tears in my eyes and not only provided a shoulder to cry on but always took the time to talk through the problems I was facing and Jo Bardoe, who was the only mother in the world that I had found that really understood everything I was going through. Mia, Jo's daughter was only 18 months older than Daniel and at that time her symptoms appeared to be very similar. Another thing happened of course, I fell pregnant with my daughter Rosie and at 12 weeks of pregnancy found out she was not affected by the condition, I honestly don't know where I would have been today if she had been.

Daniel turned two in the July and started the trial about the same time. The tremor tests were bad enough with wires glued to his head and heavy weights placed on his hand. But the real killer was the eye movement test. Daniel was two years old, he sat there all morning with wires on his head and around his eyes..... I think .... watching a square move backwards and forwards, this would have been difficult for any two year old but one with Daniel's problems it was a great strain. At the end of the morning we were told that the software had failed to make any recordings and that we would have to repeat the test in the afternoon. Not surprisingly we tried but Daniel was just too tired to follow that square. So we came back the next morning and somehow bribed him to carry it out. I will never forget my little boy just turned two sitting their all wired up and trying to follow that black square for about an hour and all the time tears were rolling down his eyes.

If I hadn't really believed that Zavesca was going to save his life I would have stopped it there and then.

#### **Challenges**

In August we felt we had won the lottery Daniel was one of the children given the drug. Our next challenge was to get Daniel to actually take it. I remember lying in bed every morning listening to Daniel screaming as Ian tried various ways to get him to take it. I refused to come down until it was over and will be eternally grateful to Ian for taking over that responsibility

for me. I probably shouldn't admit it but in the end Daniel took the contents of the capsule in honey every morning without a fuss until at the age of three, when he was able to swallow it whole. Anyone who ever tasted that drug will know that is quite a remarkable feat for a two year old.

During the drug trial Daniel grew from a toddler to a little boy attending school. At two and a half, six months into the trial Daniel's walking became very unsteady due to side effects of the drug but then settled down a few months later although his balance was still significantly affected by the disease. By the age of three he was given one to one support for fifty per cent of his time at nursery. At three and a half I bought a huge trampoline for Daniel because I was told by other mothers with children with special needs how much it had helped their balance, within two months he broke his leg on it!

The fall was at the end of November, the cast came off in January, he started walking in February and in March he had eye surgery to correct a squint that had developed due to the Gaucher disease. Daniel missed a lot of nursery that year!!! During this time we were also fighting to get Daniel into his local school and get an appropriate statement for him both of these were achieved by May and things settled down. His class teacher and his teaching assistant were both fantastic so I knew he was going to be looked after in a way that I had never dared hope for. All I wished for now was that Daniel would be able to make just one special friendship with another child for at the age of four I can honestly say despite great efforts on my part he hadn't actually formed any friendships like his peers and I started to become a bit obsessive about this probably worrying about it more than anything else at that time.

Daniel was only four years and 2 months when he started school and for the first two terms he attended mornings only as did all the children his age. However three weeks into his first term he had a horrendous fall and banged his head just above his eye on his way to school, I was standing right next to him at the time and had only looked away for a second. The school

nurse used an ice pack but was unable to stop the swelling so I took him to casualty. Daniel was being so chirpy I didn't bother worrying as I thought I could cope with Daniel and Rosie and just get him checked out. Two hours later I asked Ian in tears to come and join me..... Daniel was by now very upset, his whole head had swelled up and his left eye was closed and down to the tip of his nose. Daniel was off school for the next ten days until his eye was starting to open but unfortunately for me he felt better within 2 days.

### **Making friends**

To my amazement we had two years that for me have been the happiest of Daniel's life. He settled down really well at school, I was devastated that he had had so much of the first term off because I felt that would really hinder him in making friends, but by the summer term Ian and I were the happiest we had been since Daniel had been diagnosed. Most of his friends birthdays were in the summer and as we went to party after party with him we found something truly amazing had happened, he had friends and all the children at school loved him and looked out for him. I can remember watching with tears in my eyes as his friends not me helped him down the steps and picked him up when he fell over on bouncy castles.

So things were good. At the end of year one at school something else I never thought I would see happened when we went to a fun run day at the school. I stood there nervously as Daniel lined up but when the children started running there was my little boy running too. Somewhere around the age of five and a half he had started to run I had waited for it for so long I almost didn't want to believe it but there he was. A third of the way round the track he fell far behind the others and walked most of the way but the cheer he got and the hug from his headmistress when he finished says it all. At this point I really thought Daniel is going to be all right we are going to beat this disease!!!

### **The need for a new treatment**

Unfortunately over the last year my hope has started to fade. Last January he developed epilepsy. When he had his first fit I just sat there stunned. This



*Daniel*

was not meant to happen to my precious little boy. He was only six years old, he has also developed reflux and started drooling again. He has so many different types of tremor his body is never still for more than one minute, so even when I am cuddling him I am constantly reminded of it. He now has night splints which he does complain about and we have to incorporate daily stretches into both the morning and evening routine along with an ever increasing cocktail of medications. He can barely use a spoon any more and most of the time he uses his fingers or we feed him. Recently he has developed some sort of involuntary jerking of his head and body which has caused him to fall under water whilst in the bath and off the bed the other day whilst looking at a book ...fortunately I managed to catch him —I am getting better at that. All these changes in the last 18 months have made me very frightened for Daniel's future.

To all of you today I would say that I believe Daniel's most stable time was when he was on the Zavesca. I know Zavesca was too toxic for him but I believe a better small molecule drug could really help him and others with this condition. I think in Daniel's case because his progression is relatively fast it is easier to see how Zavesca benefited him, my only wish now is that we can find another small molecule drug or some other treatment in time for my very special little boy. Thank you."

# Severity Scoring Tool and Quantifying Neurology

*Elin Haf Davies, PhD Student, Great Ormond Street Hospital, London, describes the work she is developing to assess and monitor patients with nGD;*

"There are three aspects to my current studies

## The Severity Scoring Tool

### What is the Severity Scoring Tool?

- It is an eleven domain tool developed to assess and monitor nGD.
- It has been fully validated
- It allows for individual assessment and cohort comparison in a quantitative way.
- It offers qualitative and quantitative data.
- It has demonstrated feasibility, easily applied by physicians, 20-30 minutes.
- There are no cultural or economic constraints.

### Why do we need such a tool?

Quantifying neurology can be very subjective eg when we say that the reflexes are "brisk" as opposed to "normal". A much more objective system is needed.

The SST for nGD was developed and published in 2007. It contains 11 domains eg ataxia, seizures etc. Some domains are more important than others, in that they may have more impact on day-to-day living, and these domains need to be weighted accordingly. For example, epilepsy has a much higher weighting than speech. Scoring of the domains was done using a Nominal Group Technique through WebEx teleconference involving five international experts. Each expert was asked to score each domain from 1-10. This approach had distinct advantages:-

- A more focused discussion was possible, compared to traditional (free for all) meetings

- Allows for equal participation of all members of the group (lessens dominance of the discussion by more senior individuals)

Interestingly, horizontal gaze palsy, which was used in the Zavesca study as a primary endpoint, was not thought to be the least burdensome domain on disease severity.

However, further work is required. Briefly, this consists of:

- Intra and inter reliability. The tool should yield the same scores when used several times in quick succession by the same person, and also by different people at the same time.
- Mean Important Clinical Difference. This refers to the amount by which a score has to change to be meaningful. For example, is a change from 5 to 10 as or more important than a change from 15 to 20.

However the SST can still be argued to have a deal of subjectivity in assessment. There remains a need to identify objective assessments which are clinically relevant to the disease, without being too lengthy and/or invasive, with normative ranges for paediatric patients.

This brings me to the second aspect of my studies, the GaitRite. When developing the SST, especially during the weighting we found that ataxia was felt to be one of the most important and consistent feature. So we felt that it would be good to be able to measure it in some way. Since ataxia affects gait, it followed that assessment of gait might be a way forward. The GaitRite is a sort of magic carpet that records footprints, but in a very clever way. It's a bit like when one comes out of the shower and leaves wet footprints on the floor. Differences (either improvement or



*Elin haf Davies*

deterioration) in step patterns can be seen. It has been used in other conditions; haemophilia and MPS-II. It is a simple, non-invasive method with the potential for picking up change - in many ways an ideal tool, but of course its value remains to be proven. We tested four children with nGD on the GaitRite and showed that the ones with the worst SST score had the most abnormal patterns on the GaitRite. When someone is ataxic, the body compensates in certain ways. For example, the base of support becomes wider, the hands are held up slightly, more time is spent in double support (both feet on the floor at the same time), and one takes faster, shorter steps. These are the sort of parameters that I'll be looking at. We are also very fortunate in that one of our colleagues, Lucy Alderson, has developed normal reference ranges for children, so comparison is possible.

The third aspect of the project is an MRI brain scan, using a new research method that measures some changes in the cerebellum, the part of the brain that is likely to be affected when one has ataxia.

Hopefully, using this combination of tools, we will be able to pick up significant and meaningful changes that will correlate with each other."

Visit our new website at [www.gaucher.org.uk](http://www.gaucher.org.uk)

# Pharmacological Chaperones

**Dr Ashok Vellodi, Consultant Pediatrician, Metabolic Unit, Great Ormond Street Hospital for Children NHS Trust gave this talk on behalf of Dr Derralyn Hughes, who was unfortunately unable to attend the meeting;**

“One should start by pointing out some of the components of a normal cell- the nucleus, endoplasmic reticulum (ER), Golgi apparatus and lysosome.

Lysosomal enzymes are all proteins so it is important to know a little about how proteins are made. All proteins are formed in the ER. The sequence of amino acids in a protein defines its primary structure. The blueprint for each amino acid is laid down by sets of three letters — known as base triplets — that are found in the coding regions of genes. These base triplets are recognized by ribosomes, the protein building sites of the cell, which create and successively join the amino acids together. This is a remarkably quick process: a protein of 300 amino acids will be made in little more than a minute. The result is a linear chain of amino acids, but this only becomes a functional protein when it folds into its three-dimensional (tertiary structure) form. Ordered protein folding in this cramped chaos is only possible under the supervision of specialized molecules, called *chaperones*, which accompany proteins and make sure that they do not clump together prematurely.

These naturally occurring chaperones are known as *molecular chaperones*. Correctly folded wild-type proteins meet the endoplasmic quality control system are quickly transported to the Golgi apparatus for further maturation and addition of sugars before trafficking to the lysosome for substrate degradation. Correctly folded wild-type proteins meet the endoplasmic quality control system are quickly transported to the Golgi apparatus for further maturation and addition of sugars before trafficking to the lysosome for substrate degradation. Properly folded proteins are also stable. On the other hand, misfolded proteins are unstable. They do not meet the ER quality control and do not reach the lysosome. Obviously, in this situation, substrate cannot be broken down and builds up, resulting in the signs and symptoms of a lysosomal storage disorder.

In most individuals with a lysosomal storage disorder, the enzyme is present but *misfolded*. *Pharmacological chaperones* (which should not be confused with *molecular chaperones*) are designed to help misfolded enzyme to fold correctly and take it to the lysosome. Once this has been achieved, the chaperone separates or *dissociates* from the enzyme and goes back for more misfolded enzyme.

*What are the desirable properties of a pharmacological chaperone?*

1. The process described above

should be reversible ie it should be able to dissociate from the enzyme once it has taken it to the lysosome.

2. Lower affinity for enzyme at the acidic lysosomal pH
3. It should be able to exit the lysosome
4. Mutant enzymes are stable and functional in the lysosome in the absence of chaperone
5. Substrate can be turned over even in presence of chaperone

However, not all misfolded enzymes respond to chaperones. The *active site* needs to be available.

AT2101 (Isfagomine tartrate) is a pharmacological chaperone that binds to the active site of glucocerebrosidase (GCase), the enzyme deficient in Gaucher disease. Using cell-based and animal models it has been shown that AT2101 increases cellular levels of glucocerebrosidase. Importantly, this effect was seen in the brain as well. Several Gaucher mutations have been found to respond to this drug.

Pharmacological chaperones have several attractive properties. They can probably be administered orally so, provided they are non-toxic and have long-term safety, they should have numerous advantages over ERT, including easier administration, greater affordability and convenience. Finally, unlike enzyme replacement therapy, they are small molecules that often can cross the blood brain barrier (BBB), and thus have a potential role in the treatment of nGD.”

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## Transition and Independence

**The session was facilitated by Dr Ashok Vellodi and attended by all the parents attending the conference. There were also two adult patients, as well as Sarah Long, who has Morquio’s (MPS IV, an LSD) disease;**

Dr Vellodi opened the session by welcoming everyone. “He said that the main areas that we wanted to cover were around growing up and transition to adult services.

One of the most important things we needed to know was how children affected by NGD were coping with the day to day stresses of life, not just at school but at home and also in other social settings. Current assessments consist mainly of neuropsychometric evaluation. While these are helpful for educational authorities, they do not really give an overall picture of how the child is coping. We are planning

a research study that will look at this.”

“He continued, there was also the issue of transition and how prepared children and parents were for this. There were two aspects to this. The practical one to insure the transfer was well coordinated but also how well prepared the child was for transition. Many children are used to their parents asking questions and dealing with all the issues surrounding clinics. They might not understand very much about their disease, and might not be prepared for the challenges of an adult clinic. This might involve for e.g., young persons spending some time on their

own with the clinical team in the clinic apart from their parents. Obviously, this would need to be carefully managed, as they were important issues around confidentiality etc. However, it is quite possible that many children might welcome such an offer.”

Sarah Long gave a talk on independent living which was inspiring. The challenges that she described and the way she had managed to rise to them, was indeed inspirational.

Rodney Bradbury, an adult type III Gaucher patient described his experiences of early childhood, and how he was coping with every day life.

The session ended with an agreement that functional assessment and transition arrangements were of great importance and needed to be urgently addressed.

# 7 runners for Gauchers Association in 2009 London Marathon

*The Association is delighted to have 7 people running in the 2009 London Marathon. Five runners will take our Golden Bond places and the other two have secured ballot places and will run for the Gauchers Association.*

Good luck to runners Sarah, Liz, Kate, Nathan, Alistair, Dan and Jake who over the next few months will be training hard up and down the country, each tell their story below. Please support them as much as you can. Last year the Association raised over £9000 through the generous support of our members, their friends and family.

The Association has now established a marathon fundraising page at [www.justgiving.com](http://www.justgiving.com) to make it easy to support our runners. To make a donation all you have to do is go to the Just Giving website and type in the 'Gauchers Association'. Once you get to our site you will be guided through the process.



**Dan Britten**

"My name is Dan Britten I am from Stamford Lincolnshire. This year's London Marathon will be my second London Marathon and hopefully my second Marathon of April 2009. I am hoping to complete the London and Paris marathons in preparation for a future fundraising event of the Marathon des Sables in 2010. I enjoy personal physical challenges and this summer I completed Lands End to John O'Groats on my bike and I now look forward to returning to my running training.

I am running for the Gauchers Association as my colleague's son, Henry Jameson has Gaucher disease and I wanted to support him and the association's future development. I am delighted to help Gaucher and look forward to raising awareness of the charity and plenty of money for the cause".



**Jake Britten**

"I am Jake and I believe more than anything that the London Marathon is massive challenge and an amazing occasion, for everyone that is involved. I ran the Great North Run a couple of years ago and it was an incredible experience, with a lovely atmosphere, one that gave me a real buzz and a desire to complete the full marathon distance. Having watched my brother partake in the London Marathon a couple of years ago it has since been a day that I have wanted to experience, for both my own sense of achievement, as well as for the thousands of people that benefit from the money raised. Gaucher Disease is not that well known, unless you have a friend or family member that suffers from it. By helping to raise money for the Gauchers Association I aim to help raise this awareness and support for people that suffer from it and the families that are affected as a result, so that they have every possibility of dealing with the symptoms that it brings".



**Alistair, Kate and Nathan Walsh**

"I am Kate and I will be running the London Marathon with my two brothers, Alistair (left) and Nathan. Alistair is a

Lecturer in Engineering, Nathan has a computer sales business and I run my own shop selling gifts and furniture. We live near Preston in Lancashire.

Nathan and I have acquired our places in the Marathon through the Gauchers Association and Alistair has gained his through the ballot.

Alistair's son, Sam, who is 8 years old, was diagnosed with Gaucher Diseases when he was 3. Sam will be cheering us on in London along with his little brother Oscar who, thankfully, has not inherited the condition. We are novice runners and this will be our first Marathon, so we have a lot of training to do!

We are looking forward to the challenge and to fundraising for the Association".



**Sarah Stansfield and Liz Begley**

"My sister, Elizabeth Begley (on the left), a GP in London and myself, Sarah Stansfield, an accountant in Worcester, both juggle full time jobs with looking after husbands and largely grown up children. We have been running for about 6 years and did the London Marathon in 2005 fairly slowly. We hope to be a bit faster this time although probably not competing with Paula Radcliffe. We heard about the Gauchers Association through my brother-in-law, David Begley, who gave a presentation at the recent neuronopathic Gaucher disease family conference in Northampton, and therefore we are really pleased to be able to support the brilliant work the charity is doing for sufferers from this disease. I have been lucky enough to be given one of Association's golden bond places and my sister, who got a place through the marathon ballot, has chosen to run for Gaucher as well. Hopefully we will get round in a personal best time but more importantly we want to raise money and awareness for Gauchers Association".