

Gauchers NEWS

October 2010

Gauchers ASSOCIATION

Report on the first Gauchers Association London to Cambridge sponsored cycle ride



Gauchers Association members visit Genzyme's 'Fill Finish Facility' in Waterford, Ireland



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Chairman's Chat

Dear Friends,

Welcome to the Autumn 2010 Edition of Gauchers News. This time last year we were all trying to come to terms with the shock announcement of the interruption of the availability of Cerezyme. We didn't expect then that the supply shortage would go on for as long as it has nor did we know that within the year that Shire would gain product approval for Velagucerase (now called Vpriv). Protalix/Pfizer also are pressing ahead seeking approval of the FDA and EMA for Taliglucerase (Uplyso). So although the situation with regard to Cerezyme supply remains uncertain as we go to press there are fortunately other alternatives to consider.

I have said before how fortunate we are in the UK to have the structure in place which ensures that the patients in the UK are treated on a national basis and are seen at National Centres of Excellence. This structure has proven to be vital in ensuring that the most needy patients in the UK continued to receive treatment whilst those on reduced (or no) treatment were kept informed and had their conditions monitored. We read in the press daily of budget cuts and we remain vigilant to ensure that this national service remains centralised around the countries experts.

Since our last edition we have held our members conference which was a great success. You will read about the presentations in these pages. In June the European Working Group on Gaucher disease was held and as you can imagine there was much discussion on managing the shortage of therapy as well as hearing about research into further understanding Gaucher disease and on the emerging treatments. The EWGGD is now restructuring itself into a formal body and among other topics will be focussing on seeking to establish a European Disease registry and looking at ways to collaborate with industry in the provision of Humanitarian Aid. The European Gaucher Alliance is publishing a booklet of all the presentations at the meeting and if you would like a copy please let us know.

Over the last few months we have had some major fundraising activities. We have had our marvellous marathon runners and of course the London to Cambridge cycle ride details of which are reported in the following pages. Fundraising has always been part of our activities and will continue to be so. Please look out for opportunities in the future to help us.

Next year will mark the 20th Anniversary since the formation of the Association. The Gaucher world has changed so much in the last 20 years. It will be a cause of reflection and celebration. I look forward to seeing you at the events that we are planning, details of which will follow.

Best Wishes

Jeremy

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Front page photo (top to bottom): Prof Timothy Cox congratulates Jeremy Manuel on completing the cycle ride; Alan Rosen, Director of the UK Gauchers Association crosses the finishing line; The Gauchers Association visits Genzyme 'Fill Finish Facility' in Waterford, Ireland.

Blockbusters and Niche Busters in Gaucher Disease

Professor Timothy Cox of the University of Cambridge and Addenbrooke's Hospital, provides an up to the minute review on the treatment possibilities for Gaucher patients and looks to the future:

Gaucher disease remains a prominent focus of attention in the orphan drug field, with several long-term projects coming to fruition. At the same time, there are unprecedented changes in the pharmaceutical industry, with increasing involvement of the world's largest makers of drugs in what is seen as a niche market. Gaucher disease remains at the forefront of these developments.

Specific treatment for Gaucher disease was first introduced by the Genzyme Corporation in collaboration with Dr Roscoe Brady and colleagues at the US National Institute of Health and with support from the National Gaucher Foundation.

The product of this work was a macrophage-targeted protein which is taken up in the principal tissues involved in the disease; pharmaceutical development of the agents later known as Ceredase and Cerezyme by the Genzyme corporation has been a prodigious success. This success, coupled with a vigorous international marketing strategy, has made the Genzyme Corporation the world's third largest biotechnology company.

At the same time, the orphan drug legislation in the US has approved over 350 drugs for about 200 rare diseases – and recently more than half the approvals of all drugs are classed as orphan medicinal products. Sixteen orphan products are among the 200 best-selling medications in the US, with annual sales ranging from \$200m to \$2bn; Cerezyme is at the higher end of this range.

For orphan agents revenues are earned from relatively few patients, and in the case of Cerezyme, until the Summer of 2009 this amounted to just over 5,000 worldwide – including those receiving the free drugs through several compassionate aid programmes organised by Genzyme. The catastrophic vesivirus 2117 infection in the bio-reactors that generate Cerezyme at the Alston plant in June last year stopped production; only now (October 2010) has manufacture been fully re-established so that stocks can

be gradually restored for full distribution and supply.

Our readers will have observed the emergence of competing enzyme preparations, velaglucerase-alfa and taliglucerase-alfa, respectively developed by Shire Human Genetic Therapies and Protalix. While it might be admitted that until recently the exact role for competing drugs of this kind with a very similar basis of action, despite small chemical and molecular differences from imiglucerase (Cerezyme) were initially unclear, the Cerezyme supply crisis has created an entirely different therapeutic environment.

There are strong reasons for optimism, not only on behalf of patients with Gaucher and other rare diseases, but also for the companies. As a result of the Cerezyme shortage, the regulatory agencies, and particularly the Food & Drug Administration (FDA) in the United States, took active steps to consult Shire Human Genetic Therapies and Protalix to accelerate their programmes of development and supply off licence.

As a result, both companies have sought to provide treatment for Gaucher patients where the supplies of Cerezyme have been wanting around the world. The Actelion Company, which supplies Zavesca, as well as Shire Human Genetic Therapies and Protalix have looked to their inventory and distribution mechanisms and where possible have informed physicians about the availability of their particular agents for Gaucher disease.

In Europe, these measures have mitigated the worst of the effects of the Cerezyme crisis. In Great Britain, with the concerted effort of Dr Edmund Jessop, the Medical Director of the National Commissioning Group, pharmaceutical company representatives and clinical directors of the national treating centres and physicians decided on the priorities for best distribution and delivery of the drugs.

Faced with this crisis, Genzyme management, its scientists, as well as those in manufacturing, quality control and personnel



in other parts of the company have all pulled together to repair any perceived damage to the company's reputation and to assist in the distribution of residual supplies of Cerezyme over this long period. We all hope that the supply problems with Cerezyme will soon resolve completely.

New Oral Agent for Gaucher Disease

At the same time, Genzyme has pushed ahead as far as possible with the development of its orally active agent, formerly known as Genz-112638, but now known as eliglustat tartrate.

In 2007, a landmark paper reported this agent which had been in in-house development following initial discoveries in academia by Dr James Shayman, a former colleague of Dr Norman Radin at the University of Michigan. In Genz-112638, Genzyme had discovered an extremely potent inhibitor of another molecular target in Gaucher disease – the enzyme that leads to the formation of the principal storage material observed in Gaucher disease, glucosylceramide.

It was found that Genz-112638 and related chemicals were extremely potent inhibitors of this drug, with an inhibitory range at least one hundred fold more potent than that seen in the studies of Dr Terry Butters and Professor Fran Platt with N-butyldeoxynojirimycin (miglustat). The new Genzyme chemical was also highly selective for its molecular target and in vitro studies, as well as studies in experimental animals, revealed a favourable ratio between the level at which it would inhibit formation of the storage material and that which led to toxicity. Genzyme has forged ahead with clinical development in human Phase 1 and Phase 2 studies and with ongoing Phase 3 clinical trials.

In August, the results of two years of

continued on next page...

Phase 2 clinical trial data were published. The company chose a composite point based on two of the three major clinical features of Gaucher disease for the endpoint of the trials (spleen volume, haemoglobin concentration and platelet count). Of the 26 adult studied patients recruited from centres all over the world, 22 completed the trial at one year, and of those, 20 had obtained the composite primary endpoint.

The two-year findings showed continued improvement across all the endpoints, compared with baseline, and 20 of the original 26 studied participants had completed – with the majority continuing even beyond the original two years. Spleen and liver volumes had decreased by one half and one quarter respectively and there was a significant rise in haemoglobin by an average of more than 2gms per decilitre (indicating a strong effect on the anaemia in Gaucher disease).

There was also a gratifying increase in platelet counts (more than 80% from baseline). Apart from salutary changes in blood counts, liver and spleen volumes and biomarkers, there was another potential benefit. There was a significant and continued improvement in the density of the bone in the lumbar spine and hip, and an improvement of the so-called ‘dark marrow’ signal that is believed to predict adverse outcomes of Gaucher disease in the skeletons in several of the patients. So far, eliglustat tartrate appears to be well-tolerated and relatively safe.

Given these favourable results rival those seen in full-dose enzyme replacement therapy trials, several additional Phase 3 clinical studies of eliglustat tartrate, based on the clinical proof of concept have been set up. With the Cerezyme shortage, there are challenges for enrolment on these trials and heroic efforts are being made to recruit suitable participants.

The first trial is designated ENCORE and is a randomized open-label study to compare the safety and efficacy of eliglustat with Cerezyme. A second trial, ENGAGE, which is a randomized placebo-controlled trial for patients with a confirmed diagnosis and for patients who have not been treated for at least 12 months for Gaucher disease may be eligible, and a final trial (EDGE) has been initiated which seeks to compare the effects of once-daily dosing of eliglustat tartrate with twice-daily administration of the drug.

Despite competition and recent misfortune, it is gratifying to see Genzyme investing so hard in this product – the concept of which must have been stimulated by the advent of the first orally active and now licensed drug for Gaucher disease, Zavesca (miglustat).

Marketing Approval of Velaglycerase-alfa (VPRIV)

Recently, the most exciting pharmaceutical event for the Association has been the granting of marketing authorisation in Europe by the European Commission for the first alternative enzyme therapy in Gaucher disease, velaglycerase-alfa, now termed ‘VPRIV’.

Whilst local pricing and reimbursement has to be agreed in each of the constituent countries, the drug is now approved for use across Europe. This will simplify a great deal of paperwork required for those patients who have been treated with the unlicensed agent when they have not had access to Cerezyme since the shortage of June 2009. An accelerated approval process also led to the approval of velaglycerase-alfa by the FDA earlier in the year.

We are delighted with this outcome for the clinical trial programme conducted with Shire Human Genetic Therapy’s agent. It has been perhaps the largest ever conducted for an enzyme replacement therapy and involved four independent studies over six years. These include patients who had never received any enzyme replacement therapy (naïve), and those who had moved on (‘transitioned’) from imiglycerase. Of key importance was the inclusion of children in the trials, which is a vital aspect of the use of the agent, particularly for those severely affected.

All of us observing this field for a very long time had been wondering how long it would take before velaglycerase got to market. We were delighted that faced with all the difficulties and with the encouragement of the FDA, velaglycerase-alfa could be made available to patients in need. There have been several abstract publications reporting the results of these trials and it is encouraging to see that data showing at least five years’ follow-up from experience with the agent have also been made public.

At the European Working Group for the study of Gaucher Disease meeting held in Cologne in July 2010, the response of bone parameters, including bone mineral density and specific bone scores in the femur and hip of patients receiving velaglycerase for at least five years were presented.

There were improvements in the parameters which were maintained, even though patients had had dose reductions as part of their trials. To view a professional peer-reviewed publication, the four-year findings from the initial Phase 2 trial appeared in the prestigious journal *Blood* in June 2010.

Professor Ari Zimran and his colleagues in Jerusalem are well known to the Association and they have been instrumental in this clinical programme and use of velaglycerase-alfa. It is also pleasing to

note that in the difficult trial environment, patients have been recruited from all over the world, including South America, India and Russia.

Many readers have given a great deal of support to Shire Human Genetic Therapies. I would like to pay particular tribute to those at SHGT who made a particular effort in Europe to step-up supply and secure the drug for European patients in need during the Cerezyme crisis, and especially when their own production facilities were not expecting to ramp up until later next year.

All parties, including the National Commissioning Group and Genzyme, as well as the clinical directors of the Gaucher centres in the UK have cooperated to consolidate clinical demands and make drugs available as far as possible, both with velaglycerase-alfa (now VPRIV) and taliglycerase-alfa.

Protalix: taliglycerase-alfa trial results and a new partnership

It is appropriate here for to provide a further update on the activities of Protalix. As many of you know, Protalix is an Israeli biotech company that has developed its own enzyme therapy for the treatment of Gaucher disease with a protein expressed in plant cells, taliglycerase alfa.

Protalix have also responded rapidly to the problems faced by patients previously treated with imiglycerase, but for whom the dose has been reduced or discontinued as a result of shortage of the product since summer 2009. Protalix has initiated an open-label expanded access trial of taliglycerase-alfa in patients with Gaucher disease who required enzyme therapy and for patients who are older than 18.

This study was designed to address the need for treatment in the United States based on the request from the FDA who were faced with some responsibilities for the Cerezyme shortage. Eleven centres in different states have recruited in the US and the study was also opened at four different centres in Israel. At the same time, programmes were opened to address the shortage of Cerezyme worldwide, including:

1. A named patient programme, where at the request of a treating physician, treatment with taliglycerase-alfa is provided to patients in several European countries, including the UK, Germany and Holland.
2. A similar programme of compassionate treatment was opened at the request of the needs of patients with Gaucher disease in France.
3. A compassionate programme was started in Australia at the request of treating physicians there.

4. In Brazil a compassionate treatment programme was also opened.
5. Finally, in Israel a compassionate programme with taliglucerase-alfa was provided on request to treating physicians.

Mindful of the need to treat children with this condition, Protalix has initiated a safety and efficacy study of taliglucerase-alfa in subjects from 2-18 years of age with Gaucher disease, who would randomly be assigned to treatment with one or two doses of the agent. The duration of this trial is one year; thereafter eligible patients would be offered enrolment in an open-label extension study if at that point taliglucerase is not commercially available.

Other trials are under way, including a switch-over trial in young patients aged 2-18 to assess the safety of taliglucerase-alfa in patients who were previously treated with imiglucerase. This was originally designed for 15 adult patients with stable disease and has created some difficulties of recruitment due to the Cerezyme shortage and the request to the FDA. There are a few opportunities for patients to be recruited to this study which is now under way.

Finally an important trial, known as a Phase 3 trial to assess the safety and efficacy of taliglucerase-alfa, has been completed by Protalix and was also presented at the WORLD meeting in Miami in February, and the 9th EWGGD meeting in Cologne in July by Professor Zimran.

This was a multi-centred, double-blind parallel group dose-ranging trial in 31 patients with Gaucher disease, carried out at eleven treating centres in nine countries over a nine-month period of enrolment, and thereafter an open-label extension study at two doses of the drug given every two weeks.

The trial had no serious adverse events, although two of the 32 patients developed a hypersensitivity reaction. In both dose groups, it was pleasing to see that the primary endpoint (change in spleen volume) had been met by six months; other important endpoints, including the rise in haemoglobin even in anaemic patients was met, and there was a significant rise in platelet count, as well as other parameters of disease activity, including biomarkers.

The study included an important examination of the magnetic resonance bone marrow signal, conducted by Professor Mario Maas at the Amsterdam Medical Centre, and showed salutary effects and improvement in the important 'fat fraction' at the end of the study.

These encouraging results have been

found right out to two years of follow-up – as hoped for and expected. Clearly these are all very encouraging findings and one envisages soon that taliglucerase-alfa will also gain marketing approval in the US through the FDA and in Europe through EMEA (COMP: Committee on Orphan Medicinal Products). In line with my earlier remarks about the interest of large pharma in orphan medicinal products, Protalix and US giant Pfizer have recently established a strong collaboration. This may contribute to medical and scientific understanding of Gaucher disease but also was introduced as part of their global marketing and patient support infrastructure; it will be interesting to see how the different expertise of Pfizer will combine with that of Protalix and we wish the marriage well.

Reflections

This is 'no easy life' – but it is certainly a busy one, especially in the field of Gaucher disease!

As a person involved in the treatment of this condition for over 20 years, it is heartening to see not only what is now available but what is becoming available for Gaucher patients of all ages. At the same time, one has cause to reflect on previous opinions and concerns – for example, about the development of alternative enzyme therapies.

The vesivirus 2117 infection affecting Genzyme's Alston Plant has created a crisis not only for the company, but for the patients on a scale previously unimagined. This crisis has persisted for over a year and is also affecting other products from Genzyme's manufacturing facility. Never was the need for a safe licensed enzyme replacement therapy as an alternative to Cerezyme more necessary.

The consequences of the infection were unimagined at the time when patients and their physicians were undergoing the delicate contract of enrolment for clinical trials with alternative enzyme preparations – and especially when Cerezyme was already available.

We accepted that competition is more likely to reduce prices but we had no idea that it would add a crucial element to supply and thus continued access to treatment. Velaglucerase-alfa (VPRIV) owes its origin not to Chinese hamster ovary cells, but to a modified human cell line. Of course, these lines might also be susceptible to other mammalian viruses, but one hopes that the state-of-the-art production facility being installed at Shire's production plant in Lexington, US will be able to minimise such risks. Coming then to the question of

'the third man', the enzyme, taliglucerase-alfa: this is manufactured as a slightly altered human enzyme expressed in genetically-engineered plant cells. Here we have the opportunity for a large scale production, and as previously stated by the company, the chance of a lesser price within this competitive orphan drug market.

But there is another difference: taliglucerase-alfa is a different molecule from Cerezyme and VPRIV, and perhaps more importantly it is generated in a cell system that will not be susceptible to human or mammalian virus or other infections. Moreover, with three enzyme preparations in live competition in the market (currently there are two – the licensed oral drug, Zavesca is a substrate inhibitor), there will be a strong element of clinical competition too. I predict that there will be intensive further analysis of therapeutic responses of Gaucher disease to the various preparations which will refine our choices – and, in the end, can only improve the outcome for patients.

Finally, in the face of all of this, we see Genzyme actively building up its inventory, and in particular investing a great deal in the development of eliglustat tartrate, for which an extensive trial programme is underway to general what appears to be a more powerful orally active agent for patients with Gaucher disease.

This drug is not yet licensed, and the programme to obtain marketing approval is a challenging one; but we have every indication that it will be revealing for those patients with Gaucher disease who would wish to explore this as a potential avenue of treatment.

There is an additional aspect to the continued development of drugs in the eliglustat class. Although the pre-clinical data indicate that Genz-112638 (eliglustat tartrate) does not remain in the brain at sufficiently high concentration to alter its molecular target in neurological tissue, there are analogues which are likely to have such properties – and themselves could be developed to tackle perhaps the last remaining critically important clinical aspect of Gaucher disease: its neurological features, particularly in young patients and children.

This field perhaps remains the 'Holy Grail' of medicinal and clinical research in Gaucher disease and it is one where collaborations between patients, their doctors and researchers - together with our successful biotech companies as partners – will be instrumental.



“SAVE THE DAY” – Gauchers Association 20th Anniversary Celebration – Saturday 5th November 2011. Details will be available in the New Year.

Professor Atul Mehta



In August 2010, Dr. Atul Mehta was appointed Professor of University College London.

Professor Mehta is Clinical Director of the Lysosomal Storage Diseases Unit, Consultant Physician and Haematologist at the Royal Free Hospital in London and has treated Gaucher patients for more than two decades. He is, and has always been, accessible to and a champion of the Gauchers Association.

As director of one of the nationally designated centres for the treatment of patients with lysosomal storage disorders and a world recognised expert in Gaucher disease, he and his colleagues have played a crucial role in developing the adult Gaucher service in London and more recently in management of the recent Cerezyme shortage. In addition, he has over the years participated in clinical trials for novel

therapies for Gaucher disease with all the major pharmaceutical companies in the Gaucher field and has played a important role in the development of these new therapies. As has been reported in previous editions of Gauchers News, he has been instrumental in initiating vital research on Gaucher disease and its possible links with other conditions in an effort to lead to a greater understanding of those conditions and their possible causes. He has been closely involved with the development of a humanitarian aid programme in India and is a member of the Medical Advisory Board of the Indian Cerezyme Access Programme (INCAP).

On hearing of this announcement, Gauchers Association Chairman Jeremy Manuel said, "This is great news not just

for Atul Mehta and his family but for the whole Gaucher community. On behalf of all our members I send him our congratulations. I remember first talking to Atul in the early 1980's when he contacted the Association to seek our help on behalf of a patient who was trying to access enzyme replacement therapy and we have worked very closely together for the benefit of patients ever since. Our members are delighted that his contribution to Gaucher disease has been recognised and we all remain very grateful for his care and compassion. We look forward to continuing this close relationship and wish him every success in the years ahead."

Aunty Day – July 2010

As part of the Gauchers Association's ongoing commitment to support young girls with Type III Gaucher disease, a small group of girls travelled to London on July 17th. Niamh Finnegan and Victoria Crook, Clinical Nurse Specialists from Great Ormond Street Hospital report on the day:

Well it was 'Aunty Day' time again. At our previous transition workshop in November 2009 the girls had expressed anxieties about travelling on public transport, specifically in London. We suggested a tube trip around London and everyone was enthusiastic about this idea.

We met the girls and their parents at 11:00 at Great Ormond Street Hospital on a lovely sunny Saturday morning in July and although a little apprehensive, all were in good spirits. We abandoned parents and headed off towards Holborn, tube maps in hand! We tasked the girls with finding a bus that would get us to Waterloo and from there a tube that would get us to Bond Street. We gave no prompts or assistance and were completely directed by the girls on where we were going and when to get on and off whatever mode of transport we were on.

There was lots of discussion, route planning and teamwork and the correct route was eventually worked out and we got to Bond Street station without any problems. We got off the tube at Bond Street and just had to have a little detour

into Primark on Oxford Street! We then asked the girls to take us back to Holborn station. We walked to Marble Arch and got on the Central Line back to Holborn. This was the most difficult part of the journey as the tubes were extremely hot and very busy with standing room only. This was the part of the day the girls found most challenging as the crowded trains and platforms made them nervous. We advised them to stand aside and wait for the next train if they were too crowded.

We all arrived in Holborn in one piece and were very pleased with our achievements. The girls should be very proud of themselves for working together to overcome nerves and getting us all around London without any problems. They expressed that they found it a very useful exercise and would like to do it again. The day ended with pizza and a good time was had by all!

Radhika said: 'I have enjoyed the 'Aunty Day' very much because I met up with the girls after a long time. I enjoyed spending time with the other girls. I learnt how to



Left to right: Radhika, Irma, Maddie and Nadia

travel on the trains to different locations. We also enjoyed when we had to buy each other a gift(s) especially unknowing it was something that they wanted. I hope we can meet up more often'.

Maddie said: 'I really enjoyed the day we went on the underground. Before I was always worried about going on the trains but now I am more confident. It really helped'

Nadia said: 'I have enjoyed this experience so much, although I was a little bit nervous... but with the support of Niamh and Victoria I've gained so much confidence in using London underground. I love Aunty Day, it gives us opportunity to explore fun and also useful things. Since then I've used London Underground to go to a summer Art school during the summer holiday. Thank you so much.'

Editors Note: The funding for the day was provided by a grant received from Children in Need to support this ongoing project.

Professor Carla Hollak receives the Sixth Alan Gordon Memorial Award

On Sunday 13th June 2010 at the Association's members conference, Robert Gordon, son of the late Alan Gordon the Association's founder Treasurer presented Professor Carla Hollak with the sixth Alan Gordon Memorial Award in recognition of her significant commitment to Gaucher disease, its treatment, management and patient welfare.

Robert Gordon said: "Professor Hollak was recently appointed a Full Professor at the University of Amsterdam on the basis of her work in Lysosomal diseases and in particular, Gaucher disease, which has achieved international recognition. This is no mean achievement for a faculty member in such a prestigious European university. Professor Hollak left her field of internal medicine and haematology to concentrate on metabolic medicine. She has an interest in metabolic disease generally, but especially Fabry disease and Gaucher disease – the latter is the subject of her PhD thesis and most of her subsequent publications. She is a senior academic and has developed a prestigious career.

In her research, Professor Hollak discovered chitotriosidase as the first biomarker of Gaucher disease, which she did with the advice and supervision of Professor Hans Aerts. In later years, Carla has become a dominant figure in Gaucher disease and she has worked internationally with many investigators including Stephan vom Dahl, studying the effects of enzyme dosage and other areas of practical importance for patients. She pioneered home treatment for Gaucher disease in The Netherlands and has adduced many principles for clinical practice, gaining wide respect from investigators the world over.

Professor Hollak's commitment to improving treatment for Gaucher patients will ever remain an advocate for them in times of need. This was vividly demonstrated by her performance at a meeting in Bad Honnef in Germany in September 2009 where she played a leading role in the publication 'Force Majeure: Therapeutic measures in response to restricted supply of imiglucerase (Cerezyme) for patients with Gaucher disease'. She also played a leading role in the correspondence relating to the Cerezyme emergency access programme in relation to the cessation of the Cerezyme supply for all Gaucher patients worldwide from June 2009. This is an indication of

both her initiative and her ambition to be a driving force from Europe, working with the European Gaucher Alliance (EGA) for the betterment of Gaucher patients.

Thank you

Professor Hollak was unable to receive her award in person but sent a message to the Association by video. She said:

Dear Jeremy, Tanya and members, it is my pleasure and honour to accept the Alan Gordon Memorial Award and I am very grateful. I must say that I was completely surprised! I am aware of the fact that in receiving this honour I become part of a team who have made important contributions to the care and research for Gaucher patients. I know all of them personally and it makes me feel proud and humble to have my name linked to them.

I realise also that I share this honour with many friends and colleagues who have worked with me. From the Academic Medical Centre in Amsterdam Hospital, I especially want to mention Professor Hans Aerts with whom I've worked with for almost 20 years and who was my predecessor in receiving this award. Hans and I almost always disagree and we are both persistent on being proved right which usually leads to new and interesting ideas. I want to thank him here as his support has been crucial to my achievements.

Next, to the researchers and nurses at our centre and my greatest appreciation goes to the patient organisations. The Gauchers Association has taken the lead in launching the EGA; I admire the energy and dedication of all those patient relatives and parents of Gaucher sufferers who give their time and energy to improve the quality of lives of those who need it. It is with your help that access to treatment can be provided to patients who, for example, live in Eastern Europe. Susan Lewis has been a driving force in the past and in remembrance of her dedication you have set up a fellowship to



provide grants to healthcare professionals from developing countries to allow them to be educated in the management of Gaucher disease. If we at the Amsterdam Medical Centre can help in hosting and educating them I would like to offer this opportunity to you now.

We face tremendous challenges with the shortage of enzyme for treatment and the early access of new drugs on the market, so how do we deal with this? How do we ensure that the patients that need it the most will be able to profit the most? The next few years are crucial, e.g. establishing sustainable ways of evaluating outcome of therapies. I am an advocate of independent disease registries over drug registries to avoid data fragmentation and achieve better outcomes. Also I think the roles of the Government and the pharmaceutical industry need to change to improve these outcomes.

In the past years I've experienced a high level of collaboration between Gaucher physicians and researchers within the European Working Group on Gaucher Disease and the EGA and I cannot stress enough how important and powerful your organisation has been and will be in the future. With your help we have published guidelines for emergency treatment and set up a programme that is shared with other patient organisations throughout Europe.

These achievements make me feel confident that together we will be capable of pointing the current developments in the right direction. I regret that I can't be with you today; apart from a physician and researcher I am a mother, and my two sons Thomas and Robert mean everything to me and it is because of them that I am unable to travel to be with you, I hope you will forgive me.

I would like to end by once again expressing my sincere gratitude for the honour that you have bestowed on me. Thank you'.

Trip To Genzyme's Waterford Facility

In May 2010, Tanya Collin-Histed, Don Tendell, Alan Rosen and two Irish Gaucher patients travelled to Waterford in Ireland to visit Genzyme's fill finish facility to learn about the process of Cerezyme production. When planning the visit members of the Gauchers Association who live in the Republic of Ireland were invited to join the visit. Patricia Fox and Margaret Farrell give their impression of the day:

On arrival the group met Paul Condon, Genzyme's Supply Chain Director, who gave a brief description of the facility:

The Genzyme Ireland manufacturing plant is a multi-phased biopharmaceutical facility employing 465 personnel. It is a state-of-the-art facility for finishing of biopharmaceuticals, including Cerezyme and employs a high level of automation.

It was designed to increase the plant's capacity – is part of Genzyme's commitment to supply product to patients, particularly poignant during Cerezyme supply restrictions'.

Patricia Fox who travelled from County Meath tells her story of the day:

'As a Irish Gaucher sufferer, I have not had many opportunities to meet other patients so when Tanya invited me to come along to the Waterford plant, I gladly accepted.

Genzyme got the ball rolling by getting in touch with Tanya to invite them plus any patients receiving Cerezyme to give them a tour and provide an opportunity for a Q&A session.

On arrival, I questioned why I had come and what I could get from the day, other than a visit to a clinical workplace.

When I arrived I met with everyone from Genzyme, Tanya, Don and Alan and Margaret Farrell and her friend Mary Cork.'

We then had lunch that gave us all a chance to mingle and see what everyone's roles were. It was great to meet Margaret and Don and chat with them about their life with Gaucher. It made me feel very normal, which was great!

I was impressed by how personal the company was and there was a genuine interest in the patient as opposed to just distribution. They wanted the patients to trust them again after the Cerezyme shortages because Genzyme has invested years in understanding the value of this treatment and how it contributes to a sufferer's chance of having a good quality of life.

The tour of the plant involved 'clean room' outfits, heavy duty boots and goggles. We were where the process takes place and the complexity of the machine functions were amazing, checkpoints at each stage of the process right from the cleaning of the vials; filling of the substance; freeze drying of the drug and the air tight capping of the bottle.

We also met Pat O'Sullivan, General Manager. Like others at Genzyme, Pat had a genuine interest in the patient and was considerate to the hardship endured by patients in the last year due to drug shortages.

Although I had anxieties, they were promptly laid to rest.

Everyone was positive and there was a sense of transparency that made me feel more comfortable. The opportunity to chat and question was there not only by Tanya and the team but also for Margaret and I that made the experience personal, which was great.

Margaret Farrell writes: 'I'm Margaret Farrell and I live in southern Ireland. I was diagnosed about 23 years ago and I have received enzyme replacement therapy since 1997 in a local hospital.

I received an invitation to visit the Genzyme factory in Waterford where my drug is finished and packed. My friend Mary and I travelled down to Waterford where we were welcomed by both Genzyme and by members of the Association.

After lunch we toured the factory which was most enjoyable. A highlight of the day was meeting Tanya from the Association and other Gauchers sufferers. As a result of the trip I hope to start home treatment soon.

Thank you to Genzyme and the Gauchers Association for all their help'.



Members of the Gauchers Association with members of Genzyme in Waterford, Ireland



Mary (left), Margaret (centre) and Patricia (right) prepare to enter the fill finish plant

Tanya commented after visiting the facility "being the mother of a Gaucher patient I have been receiving Ceredase and then Cerezyme monthly for the last 13 years. In all that time I never understood the complexity of the process that it went through until I went to Waterford. I would like to thank Genzyme for their past and ongoing commitment to Gaucher patients worldwide".



Fill Finish facility

Results of a Three year study on understanding the molecular mechanism underlying cell death in nGD

In 2007 the Gauchers Association awarded Professor Mia Horowitz of the Department for Cell Research and Immunology, Tel Aviv University, Israel a three year grant to understand the molecular mechanism underlying brain cell death in neuronopathic Gaucher disease. The funds to support this research had been raised by the family of Ellie Carter who died in 2004 aged seven months; Ellie had Type 2 Gaucher disease. This research project completed in August, Professor Mia Horowitz outlines her research findings and possible ideas for further study –



Research objectives:

1. To establish a correlation between endo-H sensitivity of glucocerebrosidase (Gcase) in different cell types and neuronopathic Gaucher disease severity .
2. To identify interactors of mutant glucocerebrosidase variants, that participate in its Endoplasmic Reticulum Associated Degradation (ERAD).
3. To test whether Endoplasmic Reticulum (ER) stress caused to brain cells in patients with type 2 or 3 Gaucher disease leads to their death through apoptosis (cell death) or autophagy(degradation of a cell's own components).

The Results:

1. Our results strongly indicate that the L444P mutant GCase variant, which is associated, in homozygosity, with type 3 Gaucher disease, is retained in the Endoplasmic Reticulum (ER) and undergoes extensive Endoplasmic Reticulum Associated Degradation (ERAD). In this process mutant molecules that enter the ER are recognized as misfolded and after several attempts to refold them they are degraded. Therefore, there is very little mutant enzyme that reaches the lysosomes. The severity of the disease is determined by the fraction that reaches the lysosomes and has some activity there.

Unfortunately, enzyme replacement therapy (ERT) cannot reverse or alleviate neurological signs since the administered enzyme does not cross the blood brain barrier. To overcome this difficulty enzyme enhancement therapy (EET) has been developed. EET uses small molecules, known as

pharmacological chaperones (PCs), to stabilize the native conformation of a mutant enzyme as it folds in the ER, allowing more functional molecules to form and evade the ERAD pathway by instead being passed on to the ER transport machinery, resulting in increased amounts in the lysosome.

We found that Ambroxol, a known expectorant, lately described as a chaperone for mutant GCase, removes the L444P mutant GCase variant from the ER and transports it to the lysosomes, where it has some activity.

2. An association has been established between Gaucher Disease (GD) and Parkinson's disease (PD). Namely, the prevalence of PD was found to be higher among GD patients than in the general population. It was also documented that the prevalence of GCase mutations among individuals suffering from Parkinsonism is much higher than in the general population, suggesting that the presence of mutant GCase contributes to a vulnerability to Parkinsonism. Parkin, mutated in autosomal recessive, juvenile form of PD, is an enzyme that plays a role in tagging proteins for degradation. As GCase mutant variants undergo different degrees of ERAD and are eliminated in the proteasome, we tested the possibility that the concurrence of GD and PD reflects an association between parkin and misfolded mutant GCase variants.

Tests indicated that mutant GCase forms were less stable in the presence of parkin, indicating that parkin mediates degradation of mutant GCase. Mutant GCase variants underwent "Degradation tagging" and proteasomal degradation in the presence of parkin.

We hypothesize that, due to its occupation with mutant GCase variants, parkin is unable to efficiently degrade its natural

substrates in cells in the mid brain, involved in movement. This leads to accumulation of these substrates and death of these cells, namely, development of PD.

3. Mutant glucocerebrosidase variants undergo ERAD due to their inability to properly fold. Ample evidence strongly indicates that when the amount of unfolded protein exceeds the capacity of the ERAD, ER-stress related apoptosis commences. ERAD, as well as the productive folding mechanism, is induced in response to ER stress, an imbalance between the load of unfolded proteins that enter the ER and the capacity of the cellular machinery that handles this load sets. These are two processes, regulated by a transcriptional program termed the unfolded protein response (UPR), leading to degradation of unfolded proteins and accelerated refolding. Since UPR leads to changes in gene expression, it can be followed by testing the RNA levels of several key genes in this process.

We chose 12 different GD derived cells in tissue culture to test the level of UPR in neuronopathic versus non-neuronopathic GD. Surprisingly, we found that in a major part of the cells studied there was UPR. However, there was no direct correlation between the level of UPR and GD severity. We still have to examine whether growth rate of the cells in tissue culture or the number of passages influence the level of UPR.

Editors Note: The Association as delighted to learn that a poster giving the details of this work was given an award at the 9th EWGGD meeting in June 2010.

London to Cambridge Cycle Ride nets £50,000 for the Association

Over 100 riders took part in the first ever Gauchers Association Cycle Ride on Sunday 5th September 2010.

The route from Hampstead in North West London (home of the Royal Free Hospital) to Addenbrooke's Hospital in Cambridge was designed to link two of the Nationally Designated Lysosomal Storage Disease Centres and took in the quiet roads of Hertfordshire and Cambridgeshire. The weather was dry and sunny – perfect for cycling – and the riders were well fed and hydrated at the four refreshment stops en route.

More than one rider complained that the cakes were so good that the Gauchers Association ride will have the reputation of being the only sporting event where the participants put on weight! All riders were welcomed to cheers and applause at the finish line at Addenbrooke's Hospital and received their 'Finishers Medal' from Professor Tim Cox.

The ride was the idea of Association Chairman, Jeremy Manuel who writes, "Congratulations and thank you to all our riders for their physical efforts and thanks to their individual sponsors and the platinum event sponsors, Genzyme and Shire. Thanks also to all those who volunteered and gave us services, supplies and facilities free of charge".

"This event would not have happened and been the success that it was without the hard work of countless dedicated members and friends who manned the marshal points, encouraging riders on their way and who were the welcoming party at the refreshment stops. We also had support teams from the

hospitals, volunteers in cars and on motor cycles, and a St John Ambulance crew. We nearly had as many volunteers as we did riders but it was the sheer energy, enthusiasm and hard work of the volunteers that helped made the day the success it was."

Space does not permit me to thank all involved by name as I would like to, but I do however want to pay a special tribute to Liz Morris and all her colleagues who took responsibility for the riders once we crossed into Cambridgeshire from the final refreshment stop to the finish line. In addition, this event would simply not have happened without our dedicated organising committee of Charles Barnett,



Registration



The Official Start with Prof Atul Mehta and Councillors Monroe and Suzette Palmer

University College School kindly allowed their playing fields to be used as the starting point and for riders to register and have their bikes checked by our mechanic. After a safety briefing from route planners, Cycle Support Services, riders were then sent on their way by Professor Atul Mehta and local Councillors Monroe and Suzette Palmer.

Although not a race, the first riders crossed the finish line in less than four hours. Most riders completed the ride in less than six hours although some riders took longer enjoying the quality and quantity of the refreshments!



First over the line



Riders head off

Quotes from the day:



Ian (Parent) and Elin (Nurse) congratulate each other

Lawrence Gould, Ian Bennett, Liz Manuel and Alan Rosen. Each brought special skills to ensure that all details were covered and worked incredibly hard to ensure the success of the day in all respects. I cannot thank them enough."

The Association has received a deluge of letters and emails from riders and volunteers – a selection are reprinted on this page.

The feedback from riders has been so positive (and so many people have said "see you next year") the Association will hold a 2nd sponsored cycle ride on the 4th September 2011. Please email Sarah at admin@gaucher.ok.uk to register your interest. Full details of the event will be available soon.



Dr Patrick Deegan from Addenbrooke's Hospital

"We had a wonderful day, our marshalling point was very early on in the ride and so over very quickly but we then went on to meet our two riders at the refreshment stops along the way and at the finish. Everyone was having a great time eating all the cakes provided. Our two riders who have taken part in several other rides thought this was one of the best organised and certainly the one with the best food. It was a pleasure to take part."

Evelyn and Mick Ashdown

*"It was a pleasure to help. I wish I could have done it. Some information re. point 22: 5 people, 3 men and 2 women went by at 8.55; 13 by 9.30 and 29 by 10; 50 odd went through between 10 and 10.30. Some notable comments: not another bloody hill, my a*** is killing me!"*

John Gerszt

"Cycling is certainly a new thing to me. I'd been on the road just the once in recent memory (and that was on the previous Saturday, in the form of a training ride). Therefore, to say that I was a little apprehensive about this event was an understatement! As it transpired, I shouldn't have been so anxious. Across a glorious Sunday, the organization was first-class from start to finish, and with regular pit stops along the route, I was able to not only refuel at my leisure, but to meet others in the same predicament as me and gain in confidence. The encouragement of riders, marshals, sweepers and supporters was tremendous. Two special mentions: the little girl (Liz Morris' daughter) who was giving out cups of water to the in-coming cyclists at the finish, and to whomever it was that made the apple and raisin pudding cake at stop four. Wonderful! It was a pleasure for me to be part of such a fabulous event, raise monies for such a worthwhile cause and to meet the people that bring the Gauchers Association to life. I wish the Association all the very best in its fundraising endeavours."

David Podbur, Genzyme

"We were really happy to be involved and were hugely impressed by the whole event – the planning and attention to detail was amazing but it was also great fun to be involved with as well as helping a good cause. Congratulations to all involved and to your tremendous dedication."

Tina McLean and Family who helped out at one of the refreshment stops

"...delighted it was so successful, roll on next year."

Judi Newman marshaled at the London end

Paul Cox, Ken O'Reilly, Aidan Gill and Hilary Baseley joined the ride from Shire Pharmaceuticals and much to their surprise managed to finish in good shape, though Addenbrooke's was a very welcome sight at the end. The hills coming out of London nearly finished Paul, but the big surprise was 6'6" Dr Aidan Gill, who you would think might suffer from increased air resistance when cycling, but instead powered up the hills! In addition to Shire's overall support for the event, we're really pleased to have raised another £1,300 plus in our personal sponsorship efforts and thank all who have contributed plus the great organisation and support on the day. Our efforts and training were however put in perspective by Dr Patrick Deegan who, as we flagged, flew past us peddling furiously on his collapsible travel cycle...

"I have participated in many 'bike events' and I must say that this was one of the finest. The people involved in managing the ride were incredibly friendly and accommodating. When I was not there at the official start time they took the initiative to call me just to find out I was lost in London; a few good directions and 10 minutes of riding and I was there. In addition, being from the US (where people drive on the correct side of the road!) I thought for certain I would have difficulties following the route; this was not the case. The route was well marked with marshals at exactly the correct locations. Overall it was a great ride, on a great day, with wonderful people for a very worthwhile cause. I fully plan on making the trip from New York, along with my bike, for next year's event. I cannot thank the Gauchers Association enough for such a memorable day."

Rider, Ray Urbanski, Pfizer

"It was good fun & a great challenge – and I'm very pleased it was such a success. It was really well organised with excellent sign posting & refreshments."

Simon Waddington and Steven Howe, from the Royal Free Hospital, London and Institute of Child Health, London respectively not only cycled there, but they also cycled back home again!

"Thank you for such a terrific event - it was so well organised, including thinking of providing wet-wipes at the refreshment stops. Of course the cakes were amazing - many thanks to all the volunteers, who were so cheerful and supportive."

Liz Begley

Photographs: Ling Arzeian

Marathon runners raise £20,440

This year's London Marathon took place on Sunday 25 April with 36,550 runners taking part. Of these, Andrew Bloom, Paul Gold, Alex Frost, Simon White and Lee-Anne Tartoosie who all completed the 26.2 mile course on behalf of the Gauchers Association. Read below how our magnificent runners describe their experience of the day.

Andrew Bloom writes, "In October 2008 I was diagnosed with Type I Gaucher disease. After spending seven months on an unsuccessful trial I decided it was time to move to the tried and tested enzyme replacement therapy. From leading a very active lifestyle I found the deterioration in my health very frustrating.

When I found out that the Gaucher Association had places available for the Marathon, I thought 'what better way to raise money for a worthwhile cause and improve my fitness'.

After only two weeks of training, my running partner pulled out through injury. As I was already committed, I ploughed ahead with the training by myself.

After four months of training the big day arrived. Supported by my wife Della, my children Oliver, Alex & Charlotte and other members of my family, I completed the course in 4h 15m. More importantly, I was overwhelmed by my sponsors' generosity and I was extremely pleased to raise £8,500 for the Association."



Andrew Bloom

Simon White creatively writes in verse on behalf of himself, Paul Gold and Alex Frost:

THE ULTIMATE DASH

*Si, Al and Po stand at the start
26.2 miles to show they have heart
Legs and feet are also required
An injection for Po, his knee had misfired
But stand at the start, the three did achieve
Painkillers and isotonic made us believe
We ran past the start line, proud and together
Then Po stopped to empty his bladder
The first six miles were no trouble at all
Go Al, Si and Po, they're having a ball
Now up from Greenwich, towards Surrey Quays
Si turns to Po 'How are your knees?'
'Fine and dandy' Po does reply
We look up, and find Al, leaving us behind
And now Tower Bridge comes into sight
A half way marker leaves a bit of a bite*

*On Al, who is now short of breath
Don't worry; it did not lead to an untimely death.
But Po and Si were sent on in front
Al hits the wall, to be very blunt
Now through the narrows, and onto the Wharf
We are overtaken by one of the dwarfs
By mile 18 it's a game of some pain
But desire still burns, like a boilers' flame
Back towards town, and crowds start to rise
'Go Po, Go Si' shout's a man from the side
But 'Go' is now hard, and feels like a stop
Keep going now though, we don't want to drop
We then see Al's brother, also his dad
'We left him behind, please don't be mad'
And as I turn to set off once more
Po is already on his way to the door
Of Buckingham Palace, to complete the race
And I am trying to save a little face
And not let Po lead us up winner's row
And have to deal with him telling us so
Finally I catch up and say in a state
'Ar-e y-ou - al-rig-ht th-ere mate?'
'I thought you were ahead of me'
Sure you did Po, he was trying to flee
But back now together,
and the finish line is in sight
Legs are burning but we continue to fight
And we turn on the power one last time
Nothing now to leave behind
It's done; it's over, FEELING UNREAL
Medal's now worn at each and every meal
4.58 is the time for Si and Po,
Don't judge unless you have given it a go
Al came in just five minutes later
We met, embraced and the feeling's now greater
As family and friends met their marathon runners
Photo time 'Look at those three stunners'
Special thanks to Gauchers,
for whom we raised lots of cash
And who helped us to celebrate our ultimate dash*

Lee-Anne Tartoosie reports, "After running last year's marathon and enjoying the experience so much, I had high hopes for this year's event. In the months leading up to the race, training was going well and all looked good for a new personal best.

However, on the morning of the race, I woke with a really bad case of nerves. Out at Greenwich the nerves developed into



Lee-Anne Tartoosie



Alex (left), Simon (centre) and Paul (right) celebrate their triumph

something more, requiring several trips to the portaloos! I was starting to question whether I should continue to the start or take the train home, but my heart overruled my head and to the start line I went.

The first stages of the race went OK. I had started with a pacer from Runner's World, but dropped off the group quite early on. I figured that I would still be able to improve on last year's time, just not as much as I had hoped. But just after halfway round, I didn't just hit the dreaded wall, I was carrying it! I was running on empty and the pocket full of energy gels that I had been diligently taking were just sitting heavy in my stomach. It was going to be a very long 2nd half.

The crowd is such a big factor in the London Marathon, and the support that I received in that 2nd half was the reason that I managed to keep going. The never-ending supply of Jelly Babies, Starbursts and biscuits through the Docklands area gradually lifted my energy levels. Even though there seemed to be people walking faster than I was running, I knew that I would be taking a medal home with me.

I shuffled down the Mall and across the finish line in well over 6 hours, but I didn't care. I was so pleased to have finished considering how I felt at mile 15 – when I had seriously considered throwing in the towel when it all appeared to be getting 'a bit too hard'.

I am grateful for the opportunity to have run for Gauchers, and for the support that my family and friends gave me, in sponsorship and on the day."

The Association would like to thank all its members, friends and supporters who helped raise £20,440 for the Gauchers Association. Special thanks go to our 5 fabulous runners who endured the 26.2 mile course to help us in our work.

The Association is delighted to announce we already have a few runners who are interested in running in the 2011 London Marathon for the Association. If you would like to take part in 2011 or put your name down for 2012 please contact either Tanya or Sarah on 01453 549231 or e-mail admin@gaucher.org.uk

Report on Research into Transport of Zavesca into the brain



Dr David Begley

In the July 2009 edition of Gauchers News, we reported on a grant to Dr David Begley from Kings College, London to support work being undertaken to study how Zavesca gets into the brain. Dr Begley reports on the outcome of this study and offers some observations:

The so called blood-brain barrier is created by the smallest blood vessels in the brain – the capillaries – and regulates very closely what gets into and out of the brain. This barrier makes sure that the environment of the brain is kept very constant so that the brain can work at optimum efficiency. It also protects the brain from harmful substances that might be circulating in the blood. Unfortunately this blood-brain barrier also severely limits the access of many drugs to the brain that we might want to use to treat brain disease. Until this study was done we had no detailed knowledge of how Zavesca might cross the blood-brain barrier. Zavesca is clearly very useful in treating peripheral storage in Gaucher disease but we didn't really know whether it easily reached the brain.

Studies were carried out in mice and in human brain endothelial cells, the cells that form the blood-brain barrier. We had Zavesca specially made with a radioactive label incorporated into the molecule by GE Healthcare. The results clearly show that Zavesca does enter the brain but at a

relatively slow rate. This rate is some two and a half times faster than sugar sucrose (the sugar we cook with) but compared to a drug like the alcohol in beer it is some one thousand times slower.

Zavesca is itself a sugar, first extracted from mulberry leaves by Chinese herbalists, but it's a specialised plant sugar which cannot be metabolised by mammals or humans. Our studies indicate that Zavesca does not use a sugar transporter to get into cells and movement across the cell membrane is largely by simple diffusion (dispersion). However the movement of Zavesca into cells is partly dependent on the sodium outside of the cell and thus it might have a very low affinity for the sodium-dependent glucose transporter (SGLT); a transporter which both carries the sugar glucose across cell membranes and is the sugar which is used to power our cells.

SGLT is mainly found in the intestine and the kidney but is present in all cells to a limited extent. We also discovered that the movement of Zavesca across the cell membrane is dependent on the acidity of

the solution in which the cells are placed. At normal body acidity the movement of Zavesca across the cell membrane is fastest. Once inside the cells the environment is more acid and the Zavesca does not come out as quickly as it goes in. We were able to confirm with the human endothelial cells that the Zavesca enters the cells faster than it leaves until the concentrations inside and outside become equal. Inside the lysosome it is very acid and once inside this the Zavesca would be almost trapped. This observation suggests that cells exposed to Zavesca for long periods might eventually build up high concentrations of the drug. We also showed that Zavesca is not subject to any active transport out of the cell.

Given the chemical properties of Zavesca we would not have predicted that it would enter cells so slowly, so it remains an enigmatic drug. Other sugars related to Zavesca such as miglitol and isofagomine may have different properties in this respect and may be useful in the treatment of neuronopathic Gaucher disease, and should therefore be investigated.

Dr Begley has been invited to visit Actelion in November to deliver a full report on this research and it is hoped that this may lead to further support for this work.

Examining the link between Gaucher disease and Parkinsonism

In the March 2010 edition of Gauchers News, we reported on a study into the possible relationship between Gaucher disease and Parkinson's disease. Dr Alisdair McNeill, a Clinical Research Fellow in the Institute of Neurology and Royal Free Hospital, London provides details of this study:

In partnership with the Institute of Neurology, the Lysosomal Storage Disorders unit at the Royal Free Hospital has begun a major research project examining the link between Gaucher and Parkinson's diseases.

An increased prevalence of Parkinson's disease amongst sufferers and carriers of Gaucher disease has been confirmed by recent studies (see below). The current project aims to understand why Gaucher disease patients and carriers have an increased chance of Parkinson's disease. To do this we will assess a large group of people with Gaucher disease and carriers for signs of early Parkinson's disease. We will be inviting all people with Gaucher

continued on next page...

...research continued from previous page

disease attending the Lysosomal Storage Disorders unit at the Royal Free Hospital to participate and additionally, patients will be asked to tell their relatives (parents, siblings or children) about the study and ask them to contact the research team if they would like to participate.

Participants are interviewed for about 40 minutes, either at the Royal Free Hospital or at a convenient time at their home, and will involve testing the sense of smell and speed of hand movements. These tests do not enable us to detect early Parkinson's disease in an individual but instead, by using statistical tests to compare the scores from groups of Gaucher patients and carriers with people

who do not have mutations, we will be able to detect signs of early Parkinson's disease in the group as a whole. Participants will also be asked to give blood and urine samples. In the Institute of Neurology research laboratory these samples will be tested for alterations in levels of certain chemicals to see if this explains the predisposition to Parkinson's.

A small number of participants with Gaucher disease will be asked to have a skin sample taken. This is a simple procedure done under local anaesthetic in which a piece of skin less than half a centimetre across is taken using a sterile instrument. The skin cells will be grown in the research laboratory and these skin cells will be studied

for chemical changes which might predispose to Parkinson's disease. If you would like to take part please contact Dr Alisdair McNeill (email a.mcneill@medsch.ucl.ac.uk or leave a message with Ann Stone on 020 7794 0500 ext 34363).

References: Velayati A. The role of glucocerebrosidase mutations in Parkinson's disease and lewy body disorders. Curr Neurol Neurosci Rep 2010; 10: 190-198; Multicenter analysis of glucocerebrosidase mutations in Parkinson's disease. New England Journal of Medicine 2009; 361: 1651-1661.

Severity Scoring Tool for nGD

Elin Haf Davies became involved in the Gaucher world when she was recruited to co-ordinate the Zavesca clinical trial for Type III at Great Ormond Street Hospital, London. She identified a need and looked to fill it.

During her work on the trial she noticed how hard it was to have an assessment measure that children could comply with, but which gave meaningful data. It was from this experience, and through gaining knowledge about clinical research while studying for her Masters degree that she decided to develop a new means of assessment that was specific for Type III Gaucher patients. This led to her current PhD studies where she is exploring the use of a Severity Scoring Tool (which she has developed in collaboration with European experts), gait analysis and brain MRI data. Her research is almost complete and will be written up for publication before the end of the year. Elin provides a brief report on her research –

In 2007 the European Task Force for Neuronopathic Gaucher Disease (nGD) published a review of 55 patients from four European countries; Germany, Poland, Sweden and the UK. As part of this work, a Severity Scoring Tool (SST) was developed in an attempt to provide physicians with a means of monitoring the neurological progress of patients in a uniform way. The SST is a simple way of attributing a score

to disease severity based on 11 neurological manifestations commonly seen in nGD.

Through incorporating the views of experts worldwide, further work has been done to modify and validate the SST. In a bid to "test" the value of the modified SST (mSST) and to report on the progress of the patients initially assessed, a follow up review was arranged. This work was supported by the Gaucher Association in the UK by way of a travel grant to cover my costs to visit Germany and Poland. Unfortunately it was not possible to arrange visits to Sweden at this time.

Thirty nine of the patients originally assessed were reassessed nearly four years later. By using the mSST it was possible to report on the disease status of the patients assessed. Overall there had been progress in neurological involvement which was made evident by the overall increase in the mSST score. This increase was generally small which is reflective of the slow progressing nature of neurological disease in most nGD cases.

The mSST was able to detect a difference when comparing disease status and rate of progression in various genotypes. It appears



Elin Haf Davies

that patients who are L444P homozygous and those with a D409H and L444P combined genotype were much milder with a slower rate of progression than those with heterozygote genotypes.

The SST is currently included in the revised recommendations for the management of nGD. It is hoped that through continued and expanded use, the SST will offer an improved insight into neurological outcome of the disease in the enzyme replacement era, and ultimately offer a means of monitoring the value of any new emerging therapies that may become available in the future.

My heartfelt thanks go to the UK Gauchers Association, Dr Ashok Vellodi, Dr Eugene Mengel and Professor Anna Tytki-Szymanska for their generous support of this work.

Royal Free Team awarded £470,000 from the MRC for research into Type II Gene Therapy

In the March 2010 edition of Gauchers News, we reported on the work of Simon Waddington and his team from the Department of Haematology at the Royal Free Hospital, London, which had some positive outcomes.

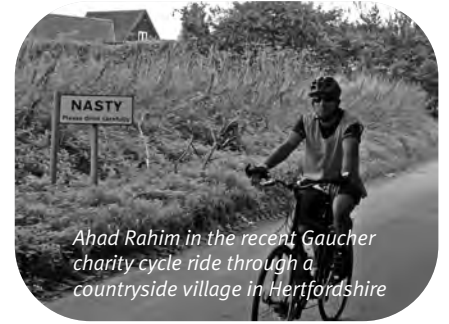
In 2009 the Association gave a small grant to the team to purchase some viral vectors for use in gene therapy research in Type II Gaucher disease. Simon provides an update on this work which has gone from strength to strength:

On purchasing the vectors we injected these into foetal and neonatal mice and found that we could deliver a marker gene very efficiently to the central and peripheral nervous system. This is an important finding because in Type II – neuronopathic – Gaucher disease the damage to the nervous system is impossible to treat using enzyme replacement therapy.

I am delighted to report that based on preliminary results, we applied to the UK Medical Research Council to do more extensive studies, initially with marker

genes, but then using a gene therapy vector for glucocerebrosidase to treat a mouse model of Type II Gaucher disease which was kindly given to us by Stefan Karlsson from Lund in Sweden.

A month ago we learned that the Medical Research Council has awarded us a grant of £470,000 to perform this work. This will pay for Dr. Ahad Rahim (pictured right) to concentrate his activities on gene therapy for Type II Gaucher disease for three years. We are extremely excited to be embarking upon these studies, particularly given the fast pace at which preclinical and clinical gene therapy is moving. For example, earlier this year, an incurable mouse model of the disease spinal muscular atrophy was completely cured by neonatal injection of a similar gene therapy vector



Ahad Rahim in the recent Gaucher charity cycle ride through a countryside village in Hertfordshire

which we are planning to use.

We are extremely grateful to the Gauchers Association and the family of Ellie Carter who died from Type II Gaucher disease who initially supported our work through a grant to purchase the initial vectors.

Gordon Conference on Lysosomal Storage Diseases

Professor Tony Futerman of the Weizmann Institute in Israel, Professor Fran Platt of the University of Oxford in the UK and Dr Steve Walkley of the Albert Einstein College in New York, USA announce a prestigious Gordon conference on lysosomal storage diseases (LSD) to be held in Texas, USA.

This world class conference aims to bring together the academics and clinicians working in the field. The LSD conference will have sessions on topics including the basic science of lysosomal biology and function (but with strong emphasis on pathogenic mechanisms of lysosomal disease), the relationships of lysosomal diseases to other neurological diseases, pathogenic cascades, biomarkers, recent advances in therapy and clinical trials and design. Gordon conferences are generally recognized as the premiere academic conferences, and about 150 are held annually. It is therefore

recognition for the field that lysosomal diseases have been chosen as a topic to be sponsored by a Gordon conference.

The conference differs from other conferences in the area as many of the other conferences are sponsored by Industry. In contrast, although the Gordon conference has received generous support from a number of companies, the companies do not have any input into the program. The scientific program will be determined by academic considerations. Moreover, discussions at Gordon conferences are 'off the record', which results in the free-flowing

exchange of ideas. It is hoped that this meeting will lead to wide-ranging discussions of exciting and novel data that will eventually lead to development of new therapeutic options.

The UK Gauchers Association is delighted to have been able to sponsor six bursaries to young scientists to attend this conference. This funding has been given to the organising committee who will allocate this through the application process.

For more information go to: www.grc.org/programs.aspx?year=2011&program=lysosomal.

2010 Members Conference: Choices and Challenges

On Sunday 13 June 2010, the Gauchers Association held a members conference at the Royal Free Hospital, London. The title of the conference reflected the challenges that had faced the Gaucher community in the course of the previous year, and the new choices that Gauchers patients will face. The conference was well attended and was judged to be a success. Brief summaries of the key presentations are below and on the next two pages –

Professor Timothy Cox opened the proceedings by addressing ‘The impact of the Cerezyme Shortage, What Can We Learn?’



We can learn many things, both scientific and medical from the shortage. We can learn the true predictive significance of biomarkers that might be investigated as a result of this gigantic, unexpected and unethical experiment. We can learn about the extent of reversibility of Gaucher disease and also about the variation of individual responses.

We can learn about the value of structured centres in the UK through the National Commissioning Group and the European Working Group on Gaucher Disease to assist in the negotiations and work together to develop back-up policies. All companies involved in this field have also learnt a lot. We learnt that there is not always one answer and that necessity is the mother of invention; that competition is good – at least in the pharmaceutical world.

We learnt about ourselves and our colleagues and that no one can be complacent in the field of health; we learnt how to communicate and build trust and we learnt how important it is to build teams that can work in unison.

We learnt what it is like to be anxious about one's health. We learnt that humans often only know the value of things (like health) when they are taken away. We learnt about loyalty, the value of transparency in communications and that the spirit of humanity, in all affected parties, is very difficult to put down completely. The future is not bleak.

Professor Atul Mehta gave an update on the progress of forth-coming treatment –



Shire HGT have been organising a series of multi-centre international trials assessing the safety and efficacy of Velaglucerase. Velaglucerase (which is to be marketed as V-PRIV) is the human enzyme that is deficient in Gaucher disease (glucocerebrosidase) which has been manufactured within a human cell line.

One of the trials has compared it with Cerezyme. Another trial has used two doses of the drug, 45U/kg every two weeks and 60U/kg every two weeks in a range of individuals including children, and a third trial has looked at the impact of continuing Velaglucerase in patients who had previously been receiving Cerezyme at various doses. The results of Velaglucerase therapy in a group of Israeli patients with Gaucher disease who have been receiving the drug for upwards of five years have also recently been published.

All of the results including those on nearly 100 patients in clinical trials are encouraging. The drug has met all of the end points which were specified in clinical trials. The drug has already been licensed in the US and there is now very considerable experience of its use in the UK. Twenty or so patients at the Royal Free Hospital were receiving it and no problems had been encountered. Taliglucerase, manufactured by an Israeli company called Protalix, is the human glucocerebrosidase enzyme manufactured in a carrot cell line. The results of a large multi-centre study on more than 30 patients with Gaucher disease had recently been presented. The drug had met all of the end points which had been specified in the clinical trials and there was demonstrable

safety and efficacy. In particular the drug led to improvements in blood counts, biochemical measurements and liver and spleen volumes in Gaucher patients.

There is considerable experience already from the UK and quite a few patients at the Royal Free were either in clinical trials or receiving the drug on a compassionate basis as a result of the Cerezyme shortage. No significant problems had been encountered and he felt the drug offered a real alternative to Cerezyme therapy.

Eliglustat is a tablet treatment for Gaucher disease being developed by Genzyme. The drug reduces production of the material that accumulates in Gaucher disease (in other words it works by substrate inhibition).

The Royal Free was one of a number of centres throughout Europe and around the world that are recruiting patients into phase three studies using this drug. Phase two studies have demonstrated safety and efficacy. In particular some of the results recently demonstrated that the drug could not only improve blood counts and organ volumes in patients with Gaucher disease but could also improve bone density.

It seems that maybe this promising alternative to enzyme replacement therapy. Professor Mehta ended by thanking all who had participated in the trials and all of the Gaucher community for their co-operation and patience during the Cerezyme shortage.

Dr Ashok Vellodi addressed the challenges of clinical trials for paediatric patients –



Firstly, it's wrong to extrapolate adult trial results to children and secondly, EU regulations now require evidence from

specific paediatric clinical trials before a drug is approved for clinical use. While RCTs (randomized controlled trials) are the gold standard for determining clinical efficacy, in children with rare disorders this is not always possible. The number of participants is small; age-appropriate, outcome measures are lacking, and interpreting results in growing children is difficult.

There may also be problems with recruitment. In addition to the small numbers, the cost may be higher because parents have to attend thereby incurring travel expenses. Finally, children often have difficulty taking the medication i.e. it may not be palatable.

Outcomes may be difficult to assess. There is often a lack of age appropriate and reliable outcome measures. Many diagnostic tools have not been tested in children and are not sufficiently sensitive to determine treatment effect. Children are 'moving targets' because they grow, so that each age group has its own physiological and psychological challenges.

Tests need to be standardised across age groups. Children get bored easily and can react badly to pain (e.g. blood tests). There may be time constraints due to limited concentration. Children are not small adults; they have different physiology, disease progression, response to intervention, etc. The effect of child growth and development on physical outcomes (e.g. strength) poses a number of statistical challenges. Objective endpoints often lack clinical relevance in children. In fact subjective measures such as pain, disability and happiness may be more important to parents.

There is the issue of child 'self reporting' which may not always be appropriate depending on age and the presence of developmental delay. Direct measures of pain/disability in young children are not reliable. On the other hand, parent/proxy reporting has its own problems; it is prone to bias, and may not always reflect the child's situation.

There may be ethical issues. In rare diseases, children are often 'over-researched'. Children seldom volunteer for a trial, but are strongly 'encouraged' by their parents to participate.

Specific issues in paediatric Gaucher disease are:

- Measurement of liver/spleen by MRI
- Age-dependent ranges for blood tests
- Need for intravenous canulation
- Assessment of symptoms such as pain & fatigue

Suggested solutions include:

- Multicentre involvement
- Dedicated paediatric clinical trial facilities
- Study design modified for children

In conclusion, Dr Vellodi reported that as a result of the Cerezyme shortage, in England, there were 33 children on Cerezyme (19 Type I and 14 Type III). All except three had been switched to Velaglucerase. The first two infusions were given in hospital. The infusions had been well tolerated so far with no reported problems.

Dr Patrick Deegan described the way the Cerezyme shortage was managed –



The UK group of lysosomal storage disorder specialist centres acted in a coordinated way that made the handling of the crisis somewhat easier and more effective than in other countries. All centres kept in close contact with each other through telephone conferences held by the National Commissioning Group. Thirteen such meetings were needed to respond to a situation that changed very frequently. The principles under which we tried to operate were as follows:

- Quick, accurate communication
- Reassurance based on earlier experience of drug holidays
- Equity – provision based on need
- Full coordination of UK response
- Coordination of European response – agreed principles, emergency supply
- Access to alternative treatment options

The problems that we encountered were related to the ever-changing supply of Cerezyme, recommendations from European Regulators that were not consistent with the best available knowledge and the very difficult decisions we had to make in deciding whose need for treatment was greatest. As it emerged, about 80% of adult patients had to go without treatment, starting from late summer 2009. Supplies of Velaglucerase, only recently licensed in September 2010 as V-PRIV, began to become available in October 2009 and a number of patients chose to switch to this treatment at that stage. A few patients switched to Taliglucerase, another enzyme treatment in development, made in Israel.

Improved supplies of Cerezyme began to become available in late January, but shortly afterwards further problems with production emerged. From March 2010 to now, supply of Cerezyme is at the 50% level. As increasing numbers of patients have now switched to Velaglucerase (V-PRIV), the 50% supply of Cerezyme allows the

patients who remain on Cerezyme to resume their normal dose. At present, supplies of both Cerezyme and V-PRIV are stretched, but taken together these treatments are meeting the needs of Gaucher patients in the UK.

Dr Simon Jones described the management of the Cerezyme shortage from a paediatric perspective –



The recent shortage of Cerezyme clearly posed a problem for those of us managing children with Gaucher disease as it did for the adult centres. While initially the children were protected from the shortage on the grounds that children were in general on smaller dosages and they may be more vulnerable, as the shortage deepened this became untenable.

After many hours of teleconferences between the National Commissioning Group (NCG) and the various consultants at lysosomal storage disorder centres (and including patient organisations), these approaches were agreed nationally. Due to the somewhat 'stuttering' nature, the supply issue revealed itself and there were many meetings and many plans.

For most of the Gaucher children, by the time there were significant dose reductions in place, other options became available. In a rolling programme from October 2009 we gradually introduced Velaglucerase to some of our Type I (and eventually Type III) patients. Initially this was done in a controlled setting in hospital but as we became more comfortable and experienced with the drug we felt able to make the switch in the home setting for the Type I patients at least.

Our experience so far has been that we have seen no significant safety issues with the use of Velaglucerase, and no obvious deteriorations. It remains too early for clear comparisons to be made between the drugs (Velaglucerase and Cerezyme) and we also have patients remaining on Cerezyme. Currently in Manchester we have 11 Type I and two Type III patients on Velaglucerase. Whilst this last year has been very challenging for the Gaucher community as well as the NCG centres, we at least have experience of an alternative enzyme replacement therapy and choice of the two drugs (and soon more) will undoubtedly benefit the community as time progresses.

continued on next page...

Dr Edmund Jessop, Medical Director, National Commissioning Group explained the National structure involved in the treatment of Gaucher patients –



The current system is working well so we're not expecting the review to bring any change but patient views and support for the current arrangement are very welcome.

Dr Derralyn Hughes discussed the links between Gaucher and Parkinson's disease and myeloma.



higher risk of Parkinson's. The cause for this is unclear and may suggest a 'gain of function' of the mutated enzyme resulting in carrier manifestations. There is funding for a study to take place at the Royal Free Hospital looking into the relationships.

Editors note: see page 13 'Examining the link between Gauchers disease and Parkinsonism'.

Emily Wallrock and Dan Brown both Directors of the Gauchers Association concluded the conference with a presentation on the future of the Gauchers Association.

The session started with a history of the Association and explored the extensive work that the Association undertakes, typically fundraising, research and member activities. These roles are fulfilled by the Association, but people were surprised to discover that the Association is also involved in so many things like liaising with the pharmaceutical industry and lobbying government at both a national and European level.

The future of the Association depends on members getting interested. Dan and Emily ended with suggestions as to how people can get participate, such as fundraising activity; patient support activities; joining a committee of the board or helping out with the newsletter or website. There are many ways to get involved and if you are interested, please contact Sarah at admin@gaucher.org.uk

The National Commissioning Group is to change its name to AGNSS (Advisory Group for National Specialised Services) and some of its responsibilities, in response to the Government's consultation 'Strengthening National Commissioning'. Patients should not notice any effect of this change in administrative structures. The new group will however have responsibilities for decisions on expensive therapies including new enzyme replacement therapies.

Following a recommendation from the EU, all member states are encouraged to develop a strategy or framework for Rare Diseases by 2013. This will cover both treatment and research and there is strong emphasis on involving the patient organisations. The Department of Health will be working on this, and Rare Disease UK is co-ordinating on behalf of patient organisations.

The designation of centres for the treatment of Gaucher disease and other lysosomal storage disorders is due for review in 2012.

There is an increased prevalence of myeloma in Gaucher disease but it is still a rare condition and it is not clear why there is an association. It may be due to immune activation by storage material and then selection of cells with myeloma potential.

Patients with Myeloma and Gaucher tend to respond less well to chemotherapy which seems to be poorly tolerated, probably also because of Gaucher involvement in the marrow. We are looking at how bone changes in Gaucher relate to the development of myeloma.

She explained that some people say the presentation of Parkinsonism symptoms is representative of the continuum in Gaucher disease but in fact whilst this is a neurological manifestation in Type 1, it is different to the neuronopathic effects of Types 2 and 3. Both carriers and patients seem to be at

Members' Fundraising

The Association relies on its members, their families and their friends who generously support the association's work through subscriptions, donations and the organisation of fundraising events (examples of which can be seen on pages 10 & 11 of this newsletter). We are extremely grateful for this support and would like to remind you of the various fundraising resources available to help you, such as t-shirts, balloons, stickers, posters and leaflets.

The family of **Clive Harries** who had Gaucher disease and passed away 21 years ago have donated £40 to the Association.

Thanks go to **Jeff Hammerschlag** who requested donations totalling £410 to the Association in celebration of his 60th Birthday this year.

Dyrham Park Country Club very kindly donated £70 after their lady golfers held a charity golf day.

Old Brentwoods Lodge held a Lodge Ladies Night after which they donated £125.

Joe Robinson who works for Studsvik very kindly donated his reward scheme of £50 along with a personal donation of £50 to the Association.

For more information on fundraising ideas and organisation, please call us on 01453 549231 or email ga@gaucher.org.uk.

Members Subscription Donations

We would like to thank all of our members who generously donated additional funds to the Association with payment of their annual subscription.

Donations Received £3,108

Generous donations have been received from EG Ansell; Carrie & David Norris; Kenneth Steel; Healthcare at Home; William Brake Charitable Trust; Debbie Isaac; Old Brentwoods Lodge; Alex & Gregg Kohansky; Frances Sloan and Hilda Adamson and many more.

European Gaucher Alliance (EGA) Meeting, Cologne, Germany, June 2010

On the 30th June, in Cologne, Germany, 40 people from 28 member countries of the European Gaucher Alliance (EGA) met to discuss the current challenges that Gaucher patients around the world face. Tanya Collin-Histed, reports on the day's events:

At the start of the meeting each national representative was given the opportunity to present the situation of Gaucher patients in their own country providing details of difficulties with access to treatment, dosage levels, communications, dealing with health ministries, access to humanitarian aid and financial support.

One concern echoed by everyone was the shortage of available treatment and concern over consistent access to therapy. All members felt that the bulk of their efforts had been geared towards supporting patients through the shortage and had felt it had been a very stressful experience.

Prof Stephan Vom Dahl the host of the EWGGD opened the proceedings and welcomed the representatives from the largest number of countries ever to attend a EWGGD.

Prof Carla Hollak presented on the need for the development of independent disease registries (rather than drug registries that are managed by the pharmaceutical companies).

After lunch, a series of workshops were tasked with identifying the future challenges for the Gaucher community and also to find better ways to work and communicate with each other.

Later in the day, representatives from Actelion, Genzyme, Protalix and Shire were

separately invited to make a presentation to the EGA, with time for a Q&A session at the end. Each company shared information on the availability of their product, drug shortage; future available technologies and dosage levels were discussed. A number of difficult and testing questions were asked by the delegates. The common theme of the pharmaceuticals companies was that patient well-being was their priority.

The full EGA membership has historically met every two years before each EWGGD workshop. The EGA now includes 28 countries including Associate members Jordan, South Africa and the USA. We are always looking for representatives from other countries to join, please contact Tanya Collin-Histed on: Tanya@gaucher.org.uk for further information.



Representatives from 28 member countries of the EGA

A full list of the EGA Country members is:

Austria; Belgium; Bulgaria; Czech Republic; Denmark; Estonia; France; Finland; Greece; Germany; Israel; Italy; Jordan; Latvia; Lithuania; Netherlands; Norway; Poland; Romania; Russia; Serbia; Slovenia; South Africa; Spain; Sweden; Ukraine; United Kingdom; USA

Editors Note: At the EGA meeting on the 30th June in Cologne, Germany, Jeremy Manuel and Tanya Collin-Histed were elected for a second term as Chairman and Director of the EGA respectively.

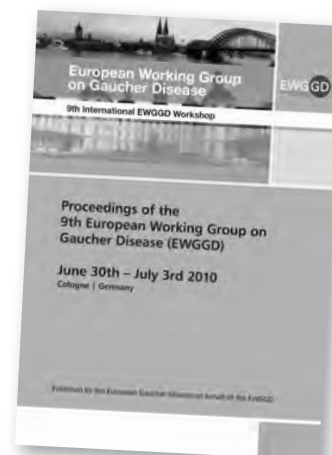


Representatives from 28 member countries of the EGA

Proceedings of the 9th European Working Group on Gaucher Disease (EWGGD)

The European Gaucher Alliance (EGA) has published the proceedings of the 9th EWGGD that took place 1-3 July 2010 in Cologne, Germany. This briefly summarises the presentations at the meeting which range from scientific research, results of clinical trials, and the clinical management of patients.

If you would like to receive a hard copy or PDF version of the proceedings (which is also available in German) please contact Tanya Collin-Histed on: Tanya@gaucher.org.uk or oo 44 1453 5492310r a copy will be available to download on the Gauchers Association website at: www.gaucher.org.uk



Become a Friend of the Gauchers Association

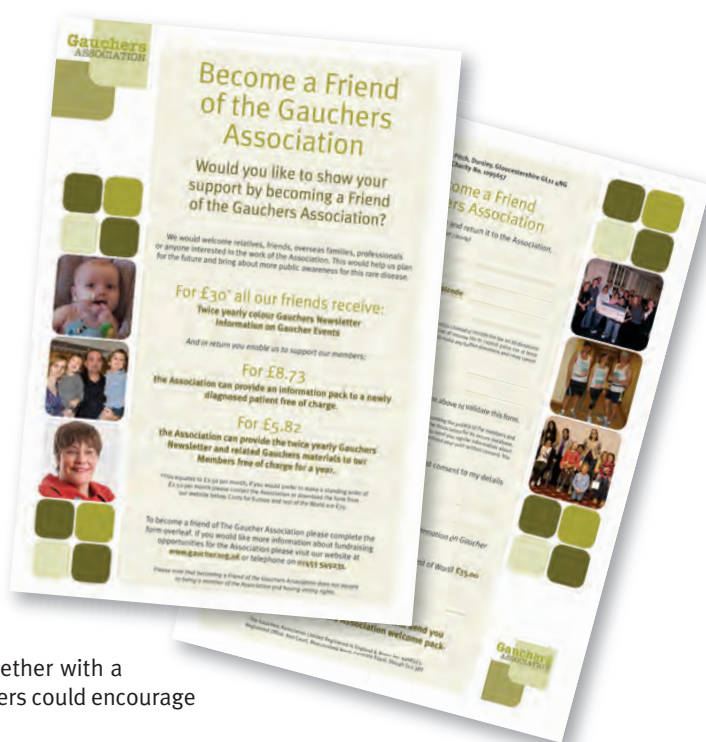
The Association announces the launch of its 'Become a Friend of the Gauchers Association' Scheme.

Sarah Allard, Administration Assistant reports: Our new scheme is designed to help us raise much needed funds, to enable us to plan our future activities, to support vital research and bring about more public awareness of Gaucher disease. We welcome relatives, friends, overseas families and indeed anyone interested in the work of the Association.

The cost of becoming 'A Friend' is £30 a year (equating to ONLY £2.50 per month). In return, all our friends will receive our twice yearly newsletter along with information on Gaucher events taking place together with a small gift of thanks. It would be really great if our members and supporters could encourage their family and friends to become members of the association.

You can download a form from our website at: www.gaucher.org.uk or contact either Tanya or Sarah on +44(0) 1453 549231 or email ga@gaucher.org.uk.

Please pass on a form to your friends and family and ask them to support our work.



Gauchers Association Golf Tournament

Following previous year's success, we are pleased to announce our fourth Golf tournament will be held at the beautiful Dyrham Park Golf Club, Galley Lane, Barnet, Hertfordshire on 18th May 2011 from 1pm. The golf will be followed by dinner.

- Open to anyone with a handicap
- Entrance fee £110.
- As we only have 80 places available early booking is essential.

If you would like to play either individually or with a team, please contact Sarah in the office on 01453 549231 or email her at admin@gaucher.org.uk

PRELIMINARY ANNOUNCEMENTS

2nd Gauchers Association Charity Cycle ride

SAVE THE DATE – Sunday 4th September 2011

To register your interest email Sarah at: admin@gaucher.org.uk

European nGD (Type III) Family Conference 2011

Will be held on 29 April – 1 May 2011

For details and a programme of the weekend please contact Tanya Collin-Histed on: 00 44 1453 549231 or Email: Tanya@gaucher.org.uk