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# Neuronopathic Gaucher Disease Day Agenda:

- 9.15 *Registration and Coffee*
- 9.45 *Conference - Introduction by Tanya Collin-Histed*
- 9.50 *Type 3 Zavesca Trial feedback session (families only)*  
*Elin Davies, Great Ormond Street Hospital*
- 10.45 *Causes and Pathophysiology of nGD \**  
*Dr Ashok Vellodi, Great Ormond Street Hospital, London*
- 11.15 *Coffee*
- 11.30 *Auditory Involvement and Learning \**  
*Dr Pauline Campbell, Speech & Hearing Science Dept, QMU Edinburgh*
- 12.15 *Neurological Features and Complications \**  
*Dr Catherine DeVillie, Great Ormond Street Hospital, London*
- 12.45 *A Personal Story \**  
*Laurenna Simpkin*
- 1.00 *A Father's Story \**  
*Abdul Waheed, Father of Hajira Waheed*
- 2.00 *Lunch*
- 2.15 *OGT 918 Clinical Trial in Type 3 Gaucher disease*  
*Dr H el ene Peyro-Saint-Paul, Actelion Pharmaceuticals and Dr Ashok Vellodi*
- 2.45 *Blood Brain Barrier \**  
*Dr David Begley, Kings College, London*
- 3.15 *Tea*
- 3.45 *Future Directions \**  
*Dr Ashok Vellodi, Great Ormond Street Hospital, London*
- 4.15 *Panel - Questions and Answers*
- 4.45 *End of Conference*  
*(The talks marked with an \* are reported below and on the following pages)*
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## Causes and Pathophysiology of nGD

*Dr Ashok Vellodi FRCPCH, is Consultant Metabolic Paediatrician at Great Ormond Street Hospital, London one of the four national designated Gaucher centres in the England. Dr Vellodi looks after the majority of neuronopathic Gaucher disease children in the UK and is a member of the European Cerezyme Access Programme (ECAP) medical advisory board.*

*'Why does nGD occur? In other words, why do some people with Gaucher disease develop the neuronopathic form and others not? We need to*

*understand this first before we are able to develop suitable treatments.*

*'As we know there are three subtypes of Gaucher disease; 1, 2 and 3. Historically Type 1 is known as non-neuronopathic and types 2 and 3 as the neuronopathic forms of the disease. We know that people with nGD have less residual enzyme than those with Type 1 Gaucher disease. In general the lower the residual enzyme the more severe the disease.*

*'The source of the substrate, Glucosylceramide, may be important. Outside the nervous system it is derived from*

*Continued on Page 3*

blood cell membranes, while inside the brain it is derived from gangliosides which are only found in the brain. In all forms of the disease, there is insufficient enzyme to break down the glucosylceramide derived from blood cells, while in type I disease there is enough enzyme in the brain to break down glucosylceramide derived from gangliosides. However, in nGD the enzyme level in the brain is not enough, and glucosylceramide therefore accumulates in the brain.

'The form of enzyme may be important. There are three different forms of beta-glucosidase, each with a different molecular weight. In Type 1 GD all three of these forms are present; however in types 2 and 3 one of the forms is missing. Nobody knows what this means but it may be important.

'It is important to understand that in the brain, the distribution of enzyme activity is uneven. This may explain why the disease does not affect all parts of the brain equally.

**Question: Where does glucosylceramide accumulate in the neurones?**

'If a lysosomal enzyme does not work properly or is missing, then the substrate will accumulate in the lysosome. But oddly in nGD there is no lysosomal accumulation of glucosylceramide in the neurons and very little in other cells. Why is this?

We know that glucosylceramide is the last step in the breakdown pathway of many metabolic processes. Therefore glucosylceramide is being produced in large quantities in the body. If little or no lysosomal accumulation is seen in nGD then it means that excess glucosylceramide must move out of the lysosome without being broken down. Therefore it must accumulate somewhere else.

**Neuronal Storage: how does this cause nGD?**

'Firstly we will look at the role of glucosylceramide. Is glucosylceramide toxic to the brain? When Professor Tony Futerman and colleagues at the Weitzman Institute in Israel studied hippocampal neurons from a rat (the hippocampus is a very active part of the brain and easy to study so it is widely studied) and incubated them with glucosylceramide, they discovered changes in the functional calcium stores. Calcium has a normal pathway in the nerve cells and has to be stored and be able to move in a normal fashion but if this is disturbed then neuronal death occurs. Interestingly when the enzyme glucocerebrosidase was added to the neurons neuronal death was reversed. This suggests that if we could get the enzyme into the nerve cells this mechanism might be reversed and cell death prevented.

'Now calcium channels in the brain are located in an area of the cell called the endoplasmic reticulum (ER). Therefore, in order for glucosylceramide to disturb these channels, it must accumulate in the ER (see above).

**The Role of Glucosylsphingosine**

'Glucosylsphingosine is a modified form of glucosylceramide. It has been shown that the brains of patients with nGD had much higher levels of glucosylsphingosine than from type 1 Gaucher disease, it was the highest in type 2 Gaucher disease. It therefore seems to be related to the neurological problems that are seen in Gaucher disease. It is also known to upset calcium transport in the cell (as does glucosylceramide but by a different mechanism).



**Dr Ashok Vellodi**

**What is the Role of Inflammation**

'It is thought that inflammation plays a major role in Gaucher disease. It tends to be more severe in types 2 and 3. It may not even need much storage to trigger inflammation. At the National Institute Health (NIH) a few years ago **Dr Rick Proia** developed a knock out mouse that was deficient in the enzyme. This mouse had massive inflammation in the tissues

but no Gaucher cells. Until recently it was not clear whether this was seen in the brain as well. In 2006 Korean scientists showed that there was upregulation (a surge) of pro inflammatory cytokines (chemical messengers) in the brain of type II Gaucher mice; these triggered inflammation in the brain of the Gaucher mouse. How inflammation causes neuronal damage is not clear.

**Conclusion**

'The mechanisms by which Gaucher disease can cause apoptosis (programmed cell death) may therefore include glucosylsphingosine, inflammation, or disturbances in intracellular calcium. So there may be more than one mechanism responsible. What is clear is that these are all secondary events; the primary event being storage resulting from enzyme deficiency. Once these secondary events are set in motion, other therapies may be necessary to control them, so it is important to try and understand them.'

# Auditory Involvement and Learning in nGD

*Pauline Campbell is a Lecturer in Audiology and Hearing Science at the Queen Margaret University College in Edinburgh. Pauline has been looking at the auditory involvement in patients with nGD for a number of years. Her talk focused on identifying the implications for patients and what can be done to support them on a daily basis. Pauline has been involved in recording the auditory brainstem responses by a sensitive test of brainstem involvement in nGD.*

'Sound comes in through the ear drum where there are three bones that help to mechanically 'push' the sounds through to the cochlea (inner ear). The cochlea is very important as it is here that the sounds are spilt into high and low pitch. These sounds are then sent to the auditory nerve. In clinic children will have a simple hearing test to see if the cells lining the cochlea are working. This test is called otoacoustic emissions. In the majority of cases the children can hear and respond to different tones.

'Sound in the auditory brainstem pathway is measured using a test called the Auditory Brainstem Response (ABR). It is assessed by placing 3 small sensors on the head and a clicking sound is heard through headphones. Audiologists analyse the ABR by looking at the presence of a five point peak. In most nGD patient's peaks I and II are seen, however peaks III, IV and V that measure the higher brainstem disappear or deteriorate over time in some patients. To get a five point peak the cells in the auditory nerve and brainstem need to fire (or respond) at the same time. If the cells are not firing synchronously this may tell us that there is a timing difficulty.'

To demonstrate this point Pauline asked the audience to number themselves off as number 1, 2 and 3. In the first exercise all numbers 1, 2 and 3 standing up in sequence and calling out their number. She then asked number 1s to sit down and repeated the exercise with just number 2s and 3s. Finally number 2s sat down and it just left number 3s to call out. This demonstrated how the timing of different sounds could upset the flow of information.

## **What is like in a classroom?**

In another exercise to recreate the environment of a child with nGD Pauline asked the audience to put their fingers in their ears. She then divided the room in half and asked one group to talk among themselves. While this was happening she walked away from the microphone and continued talking. After a short period she asked the audience to remove their fingers from their ears and whether they had been able to hear what she had been saying? The response was that the audience could not hear and she explained that this is the experience of what a child with nGD hears in a classroom and demonstrated how difficult it may be for them to understand what is happening.

Pauline recited a poem by Hall and Mueller (1998) which describes what it is like to have auditory processing deficits.

"Words coming in seem foreign; I catch them as I can. Catch a few, hold them tight, watch the rest continue flight. Take a few, turn then 'round', fitting pieces until they sound."

She highlighted that many nGD children of these children may have short term memory issues which is not surprising if they are unable to "catch" all of the words being said to them.

## **Evidence to support learning in the classroom**

Pauline emphasised the need to collect the evidence on auditory processing deficits and have it published so that parents can use this to access support for their children in school and college.

There are some new tests that look at the brainstem response and try and identify why nGD children do not understand speech when there is background noise, or the child can not see the teachers face. These portable tests can be taken into the child's home or school and carried out. These tests look at:

- How they use consonants and vowel sounds and is able to identify which part of the word may be absent and therefore cause the problem.
- The onset (start) and offset (finish) of sounds and how the brain recognises when these stages happen.
- Startle response to see if the brain can learn, i.e. to simulate a loud noise and then next time it happens to see if the brain has learnt to react to it in a less startled way.

Pauline talked briefly about neural plasticity and some environmental modifications that can help nGD children at school. Finally she also showed a list of websites which might be useful for parents to look at. These are programmes, auditory integration techniques and listening exercises that can be used to train the brain.



**Dr Pauline Campbell**

- Earobics (Cognitive Concepts, Inc 1997, <http://www.earobics.com/>)
- FastForWord (Scientific Learning Corporation, 1997) <http://www.scilearn.com/>
- Phonomena (Isis Innovation, the technology transfer arm of Oxford University <http://www.mindweavers.co.uk/>)

# Neurological Features and Complications of nGD

**Dr Catherine Devile is a neurologist at Great Ormond Street Hospital (GOSH), London. Catherine looks after all of the nGD children and young people seen at GOSH. Catherine spoke of the huge clinical variation in nGD and its heterogeneity and how manifestation can vary in patients.**

## **Spectrum of neurological features**

'The neurological features in nGD include; horizontal gaze palsy, squint, disorder of muscle tone, movement and co-ordination, feeding and swallowing difficulties, reduced clarity of speech, learning difficulties and seizures.

## **Abnormalities of Movement**

'Abnormalities in movement are caused by different neurological pathways. Those movements seen in nGD include; Ataxia causing poor co-ordination of the voluntary muscles, issues with balance which may affect motor skills and cause a tremor at the end of a movement; Spasticity which cause increase muscle tone in the hamstrings and ankles and is noticeable when there is a quick movement or a change in direction of movement; Extra pyramidal affects the control and movement of voluntary movement and some involuntary movement causing a resting tremor and rigidity with increased resting muscle tone and finally; Bulbar Impairment which affects the muscles of the tongue, face, throat and swallowing causing muscle stiffness, lack of facial expression, chewing and swallowing problems and problems with the production of speech.

## **Clinical Presentation**

'All nGD patients present with horizontal gaze palsy which is the failure to move your eyes quickly from side to side and adjust them to fix on a target which can cause difficulties in a busy area such as a school playground. Eye movements are a very complicated area and we know that the main function of that comes from the brainstem. In all nGD patients there



**Dr Catherine Devile**

is the presence of horizontal gaze palsy and in some patients there may be vertical involvement affecting the movement of the eyes up and down.

'Looking at the motor aspects of clinical presentation, the presence of gait ataxia which may or may not present with a tremor which may cause difficulties with fine motor skills are the most common found in nGD patients.

'Learning may be affected in nGD with some cognitive impairment and a lower IQ, however the cognitive assessment is only one area of our assessment and it is important to recognise that there may be areas of strengths and weaknesses. It is therefore crucial to recognise any learning impairment to ensure that these children are able to get help and support at school and that this support is assessed on a regular basis.

'Some children with nGD may develop seizures. Seizures are essentially an abnormal electrical discharge from brain neurons (cells). Epilepsy is a name for recurrent seizures. In nGD there are a number of different types of seizures, these are:

- Myoclonic seizures which are usually very small and very brief but can over time become more frequent and may build up to be more severe.
- Generalise seizures, more commonly known as Grand mal seizures, these affect the whole body causing stiffness of the arms and legs and the person will become unconscious.
- Partial seizures that cause a blank vacant facial expression, odd jerks and stiffness with partial unconsciousness.

'It is important to try and be as accurate when identifying the type of seizure to ensure that the correct management and treatment are given.

## **Functional Impact**

'The neurological complications described in nGD can have an impact on day to day functions and they may also delay some aspects of development earlier on in life. However it is important to highlight that the challenges and stresses of tasks over time may seem like the disease may be getting worse, however the underlying disease may not be changing but the tasks are getting more challenging.

## **Practical Management**

'Our aim is always to maximise potential and function so by identifying the goals we can put interventions in place where necessary in the areas of physical and motor skills, feeding and nutrition and seizures.

## **Summary**

'There is a wide spectrum of neurological features and how these affect children functionally. It is essential to monitor and neurology and learning accurately as changes maybe slow and we need to be clear and accurate about disease progression. This will enable evaluation of potential responses to treatment and target management and support to the child and family.'

## **Future Developments**

Catherine described the development of a severity scoring system for the neurological aspects of nGD looking at all of the neurological features with the aim of having a systemic tool that can be used across centres.

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# A Personal Story

**Laurenna is 23 years old and has Type III Gaucher disease, here is talks about the challenges that she has faced since her diagnosis in 1986;**

'My name is Laurenna some of you may know me or might have heard of me. I would like to share my story with you.

'I was born in 1984 and in January 1986 doctors discovered I had Gaucher disease; my parents were told and they had no idea what it was. The doctors at Kings College explained that there was no cure and that my bones would deteriorate and I would be in a wheel chair by my early teens and dead by my late teens.

'As we were leaving a doctor suggested we contact the Westminster Children's hospital where we met a very nice doctor they called 'The Professor'. He explained to my parents that all they could offer me was a bone marrow transplant (BMT) and that the risks were high but that this was my only option. There wasn't any enzyme replacement therapy then.

'In March 1986 all of my family were tested to see if they were a match for me but none of them were suitable donors, so we asked the Anthony Nolan Trust for help. They found one possible donor out of 40,000 people.

'In August 1986 my spleen was very large and I was unable to walk so I had a splenectomy, this operation had to be done anyway so that I could have a BMT.

'In September 1986 my Gaucher disease had accelerated and doctors told my parents that I must have a BMT. We went to the Anthony Nolan Trust and asked to use the donor they had identified as a possible match, even though with this random match the success rate was low.

## **Preparing for my BMT**

'In 1986 I went into hospital to prepare for my BMT, they bathed me in a special soap and placed me in a small cubicle. This was to be my home for two months. I was given many drugs for my BMT, these made me loose my hair and stooped me from eating.

'In January 1987 we found out that the BMT had failed and that we needed to find a better donor. A few months later in April 'The Professor' retired and new doctors arrived but still no donor. Throughout 1987 and then in 1988 new doctors came to the hospital but many of them left as the Government were closing down hospitals and Westminster Children's Hospital was one of the hospitals they wanted to close.

## **My second BMT**

'In 1989 we met a new doctor, he wanted to give me a second BMT and a new donor, a woman was found. My first donor had been a man and we hoped with the second donor being a women this may give me a better chance. In June 1989 I prepared for my second BMT, the operation took place but things didn't go well. Nobody knew why I wasn't getting better and I had to stay in hospital for five months.



**Laurenna**

## **Coming Home**

'In January 1990 I went home but couldn't go to school so I had to have home tuition. By September 1990 I was able to go to school for two or three days a week but all of the teachers knew that if anyone in the school had a bad infection I had to be sent home and have an injection.

'During my primary school years the teachers understood that I had problems, that I was slow at doing things. When I was 11 years old the teachers said that I was not capable of going to secondary school, but I did go and I did struggle but I had a teaching assistant to help me. At the age of 14 I was preparing for my GCSE's, again the teachers said I couldn't do them, but I achieved six out of the seven I took. I am now at college and on a Saturday I work in a shop called 'New Look' for three hours.

## **Life is Good**

'I know some of you think that you have been dealt a bum card in life but I have come here to tell you my story to show you that life isn't that bad. You should all be happy to be alive and living life to the full despite everything. Even though I am epileptic now and take a lot of medicine, it really helps.

'Before I go I would just like to thank someone who has helped me stand here today and tell you all about myself. Back in 1990 a young doctor did stay at Westminster Children's hospital and helped me through my second BMT, even though the hospital was going to close. He never walked away, he found me a new hospital and looks after me today. You all should like me be glad that he looks after you all, I am of course talking about **Dr Ashok Vellodi.**'

# A Fathers Story

**Abdul Waheed is the father of nine year old Hajira who has Type III Gaucher disease, here Abdul talks about his precious daughter Hajira;**

'Today my daughter asked me what I was going to talk about, I said that I was going to talk about her. She said promise me that you won't say anything sad, only the good things.

'Hajira was born on 3 May 1998 at Queen's Medical Centre, Nottingham, at a time of great stress to our family. She was a precious gift to our family. One of my sisters was in the late stages of Ovarian cancer, my father was struggling with leukaemia and my mother had for several years been living with renal failure.

'Sadly the leaf of hope that had come into our life in the form of Hajira was diagnosed with neuronopathic Gaucher disease in November 1999. This was a very testing time for our family, the diagnosis was very difficult, and being so rare the doctors were clueless. Initially Hajira's large abdomen was diagnosed as excess wind! Scans, tests and trips to Queen's Medical centre and then to Manchester confirmed our worst fears. However it was during this time that the human compassion and support came as a sign from God not to lose hope. Friends and family rallied around us and gave us support at a time of uncertainty.

'Friends organised charity events and fundraising activities including the 'Gaucher Cricket Cup'. I remember the look of great delight in Hajira's face as she sat at the controls of a train organised by a friend of mine who works for the Midland Mainline. Even the boxer **Amer Khan** came round to our house to see Hajira.



**Hajira Waheed**

## **Support**

'The greatest support came from my brothers and sisters who looked after the rest of the family for our never ending trips to hospital in Manchester, London and Plymouth.

However amazing support that we received and will treasure for the rest of our lives came from two complete strangers. The first was a pony tailed stranger wearing jeans, a t-shirt and sandals. This was **Dr Ed Wraith** who became Hajira's Consultant at Manchester Children's Hospital. He gave us his personal mobile number and told us we could call him at any time if we needed to talk.

'The second person was our own **Tanya Collin-Histed** who simply offered help and one day appeared on our doorstep all the way from Watford. She spent the whole day with us reassuring us and providing information in Gaucher disease.

## **Our Brave Daughter**

'Despite a total of 186 infusions to date and various problems with administering Hajira's enzyme replacement therapy, Hajira continues to be an inspiration to us, with her beaming smile and maturity beyond her years.

'This has been evident in the last three years and has helped us to bear the loss of my father, my sister and recently my beloved mother. Hajira has been a precious gift from God, she reminds us of God's creation, her resilience and the way she has coped with her condition has been a true inspiration.'



**Abdul holding the Gaucher cricket cup**

# Blood Brain Barrier

**Dr David Begley is co-Director of the Blood Brain Barrier Research Group at Kings College London. In November 2004, David spoke at the first European nGD Family Conference in Leicester on the blood brain barrier (BBB). "I was working in a BBB laboratory was working on the transport of substances in and out of the brain across the BBB. That meeting in 2004 changed the direction of the work that goes on in my laboratory and since then I have started studying aspects of the BBB and its importance in lysosomal storage disorders including Gaucher disease. The nGD meeting in 2004 was therefore a critical meeting for me and for my work."**

Dr Begley introduced Dr Charlie Pontikis who is now working alongside him at Kings College, London and said;

'The BBB was discovered by Paul Erlich who was working on infection and later developed the first treatments for Syphilis. It was in his laboratory that the first sign of the BBB appeared. Whilst he was working on sleeping sickness caused by parasitic Trypanosomes he noticed that when rats were injected with a blue dye their bodies went blue but their brains did not. At the time he thought that the dye had not stuck to the rat's brain. One of his students Edwin Goldmann repeated Erlich's experiment and got exactly the same result. He then injected the dye into the blood of the rats and observed that it didn't get into the cerebral spinal fluid (CSF). At this point Goldmann went onto do a second experiment which was to inject the dye straight into the brain and observed that the brain went blue. He concluded that it wasn't that the dye had not stuck to the brain in the first place it just did not get there. More importantly when the dye got into the brain he observed that it didn't leak out of the brain and back into the blood. As a result the BBB was discovered.

'The BBB is a very effective barrier to many things in the blood including many medicines and drugs we take, including enzyme replacement therapy, and stops it getting into the brain.

## **'Why does it do this?**

1. The brain requires a very stable environment. The constitution of our blood varies, it goes up and down all the time, each time we eat, drink, and don't drink. Nerve cells couldn't work if this was the case, they have to have a stable background as they rely on generating nerve impulses in order to work, and they have to talk to each other by chemical transmissions.

2. The BBB protects the brain from nasty things in the blood which would damage the nerve cells. Many foods contain neurotoxins which would kill nerve cells. Each day we lose nerve cells. If the BBB was leaky then more nerve cells would be destroyed.

'Because of the BBB there are a large number of diseases that effect mankind where treatment is currently unavailable, including the lysosomal storage disorders. Many lead drugs under development by pharmaceutical companies for

central nervous system (CNS) diseases might do the job they are designed for but they don't reach the brain in sufficient quantities, therefore they are dropped during development and never reach the market. Therefore we need to understand now how these drugs react with the BBB to be able to treat these diseases better.

## **Laboratory Studies**

'In Dr Fran Platt's laboratory at Oxford experiments have been carried out on mouse models for Tay Sachs disease, Sandhoff disease and Gangliosidosis. Blue dye was injected into blood of the mice. In the normal mouse model and the Tay Sachs mouse no dye was observed in the brain, however in the Sandhoff and GM1 mice large amounts of dye were seen to leak into the brain. This would conclude that in Sandhoff disease and GM1 the tight junctions are damaged or that the cell membrane



**Dr David Begley**

properties have been altered and therefore are not acting as a barrier.

'In my laboratory at Kings College we are looking at Sanfillipo syndrome (MPS III A/B). These studies are looking to see if the BBB is damaged in MPS III A/B, how the damage occurs; does the damage contribute to the CNS pathology; can we do anything to cure or reduce the defects in the barrier; and do current treatments like Miglustat improve the barrier function? Apparatus has been developed over a period of one year to carry out these studies and will look at the mouse brain to see how much of the drug test substance gets into the mouse brain and which area of the brain, hindbrain, cerebellum, hemispheres, midbrain and olfactory lobes. These studies are being funded by the UK and Spanish MPS Societies.

'The transport of Zavesca across the BBB is another area of work being carried out at Kings College. Evidence from Oxford shows that Zavesca penetrates the CSF however it is not yet know if it gets into brain tissue where it is needed. This is the first of the questions that need to be answered. If Zavesca does get into the brain tissue, to what extend and what is the mechanism by which it does? This current work is funded by Actelion Pharmaceuticals.'

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# Future Directions in nGD

***In this presentation Dr Ashok Vellodi presented a number of possible methods for future treatment of nGD and the challenges facing researchers. He started with a discussion on Enzyme replacement therapy;***

'There is, as yet, no evidence that intravenously administered enzyme crosses the blood-brain barrier (BBB). However, there is some evidence from work done in animal models that it may result in reduction of storage in the brain. So far, this has been seen in mouse models of alpha-mannosidosis, metachromatic leukodystrophy and MPS VII. In the MLD mouse, the storage reduction was accompanied by improved neurological status. Of particular interest in the MPS VII mouse was that there was no effect on storage when the mice were given 4 mg/kg/week for 4 weeks, but after giving them 20 mg/kg/week for 3 weeks there was a reduction. Thus, there may be a threshold beyond which an effect is seen. It is important to realise that clearing of storage may not be uniform. For example, in the MPS VII mice there was no clearing in the cerebellum. Whether any clearing is seen in humans is not known.

## ***Getting enzyme across the blood brain barrier***

'Several approaches have been found to achieve this in animal models:

- By packaging it so that it is carried across e.g. in liposomes. In particular, stealth liposomes have been found to escape capture by the lungs and enter the brain.
- By modifying the enzyme. Certain proteins can enter the brain easily. They do this by means of small areas called protein transduction domains (PTD). These can be transferred to other proteins enabling them to enter the brain as well. This approach has been successfully used in the mouse model of Parkinson disease.
- By direct administration

- a) Using a virus to carry the gene.
- b) Using cells that have been made to secrete the enzyme by a virus e.g. bone marrow cells
- c) Using neural progenitor cells
- d) Direct administration of enzyme into the CNS.

Of the methods listed above, the only one currently being trialled in patients is CNS gene therapy using a virus. Two trials are in progress, one in a lysosomal disorder, Batten's disease, and the other in a non-lysosomal disorder, Canavan's disease. Both are trials of safety rather than efficacy.

'A single patient with type II Gaucher disease has undergone direct CNS infusion of enzyme. Again, this was a safety study only; the procedure was tolerated well.

## ***Chaperone therapy***

'It is not possible to discuss the rationale of chaperone therapy in detail here. However, it is important to realise that different chaperones may be required for different Gaucher mutations. Most work has been done on the mutations responsible for type I GD. Effective chaperones (at least in the laboratory) have been for these mutations. However, very little progress has been made so far on the mutations responsible for type III GD. One reason for this seems to be that these mutations are located on a domain (area) of the enzyme that is not easy to access. Further research in this area is urgently needed, particularly since chaperones are small molecules that will probably cross the blood brain barrier.

## ***RNA interference (RNAi)***

'This is a relatively new and very interesting area of research. It was first observed in 1990 when Jorgensen, who was working with petunias, wanted to create a petunia of a deeper shade of purple by introducing the "purple" gene. Instead, a white petunia was created. Clearly, the "purple" gene had been switched off or silenced. It immediately became obvious that this phenomenon could be used to study the function of a gene by switching it off and observing the effect. However, it was only recently that Mello and Fire showed how this happened, using a microscopic roundworm as a model. They called this RNA interference or RNAi. In fact, RNAi is an ancient human trait and probably a defence against viruses. In this sense it is unique. There is potential for clinical applications, for example, switching off viruses such as hepatitis B. However, it does not cross the blood brain barrier and therefore may face the same problems as ERT.

## ***Conclusions***

'There are several promising areas of research, some more advanced than others. It is likely that no one therapy on its own is going to be effective; combination therapy may be the way forward.'