European Conference on Rett Syndrome - October 2010, EDINBURGH

A Report For Family Members by a Family Member
Dave Hewetson 14th December 2010
INTRODUCTION

The event brought together genetic science researchers, behavioural science researchers, and families, from across the world to share in the most up to date knowledge of Rett Syndrome - of whereabouts we are on the path to a cure, and what can be done to improve the lives of our girls until that cure arrives.

I listened to a number of speakers, and spoke personally to some of them; I read a large number of posters describing research projects. Since the Conference, I've asked questions of a number of the researchers, who have provided clear answers for the most part. I also met family members from UK, US, Poland, Germany, Greece, Russia, and Holland. This is my personal take on what are the most important developments for Rett families to be aware of. It is not a review of the complete programme.

HEADLINES

Scientific Research at Conference

1. Adrian Bird assesses where we are, with optimism. Gene therapy planned.

2. Rett reversal success, and further behaviour studies – James Eubanks

3. Rett reversal success – Univ. of Aberdeen

4. Gene therapy success with SMA (spinal muscular atrophy) – Elisa Dominguez

5. ANT1 gene implicated in Rett Syndrome study – Nicoletta Landsberger

6. – 10. Drug treatment successes

Scientific Research outside Conference

11. Huda Zoghbi lab successfully targets Rett in a subset of the brain

12. Alysson Muotri demonstrates Rett reversal using human skin biopsy – and proves biopsy can be used to screen anti-Rett drugs.

13. Jonathan Kipnis pioneers bone marrow transplant of Rett symptoms

14. Julian Paton & John Bissonette correct respiratory defects

Clinical Research & Guidelines at Conference

1. Things every parent should be aware of, including gallstones, leg length discrepancy, and physiotherapy - Sarojini Budden

2. Fighting Nutrition Problems – Irène Benigni

3. Measuring the eye gaze of Rett patients – Cristina Martins

4. Scoliosis successfully reversed – a case study plus Conductive Education – positive results – Meir Lotan

5. Reversing scoliosis with physio Overnight sleep test available – Hilary Cass

6. Breathing irregularities in all Rett girls – Peter Julu

7. High pain threshold in Rett girls – Jenny Downs

SCIENTIFIC RESEARCH AT CONFERENCE - DETAIL

1. Prof. Adrian Bird (Univ. of Edinburgh, UK). His lab was the first to reverse Rett Syndrome in mice in 2007. Adrian contributed to several sessions including a Q. and A. session with a small group of families. Adrian said that this field of research is progressing rapidly now, and families should be assured that a great deal of work is being done across the world to advance the cure of Rett Syndrome. We know that Rett Syndrome has 1 source gene; by comparison, autism and schizophrenia each may have hundreds. And there is a good chance that most treatments will be generic to all MeCP2 mutations.

Since 2007, several other scientists have independently replicated the reversal of Rett, and this is important in science: it means that his results have been verified universally.

There are at least 6 labs worldwide trying to get to gene therapy in the lab (i.e. in mice). He estimates his own lab is about 1 year away, and is sure that within 2-3 years we'll know if gene therapy can be effective. Gene therapy will consist of delivering a virus containing MECP2 to the brain. Much of the research will focus on getting the right level of MECP2 to deliver to the brain. It's important not to upset working cells. (for instance, there may be 50% of cells where MECP2 is at precisely the correct level). Research into Battens Disease (see www.bdsra.org) has shown the model to follow. This year Prof. Ron Crystal at Cornell University in USA has

moved beyond lab tests to begin Clinical Trials on Battens patients.

In 2007, following his reversal success, Adrian had said he would be disappointed if there wasn't a human therapy within 10 years. He still feels it is realistic to hope for a therapy by 2017. I asked about how long it might take the various approaches to progress through clinical trials to an effective treatment. He said

a) Gene therapy could be complex. The EU has 800 pages of Guidelines on managing a clinical trail of gene therapy. (see also 5. below)

b) MECP2 reactivation via drugs – if a drug is discovered that can replace the missing MECP2, and that drug is already one that's been approved by FDA (Food & Drugs Administration), that would be brilliant, and things could move quickly. Otherwise it will be expensive.

I asked Adrian what he thought of the recent work by Jonathan Kipnis (see 12. below) who is pursuing the theory that Rett Symptoms may be improved via bone marrow transplant. He is following Dr. Kipnis' progress with great interest, but cautioned that, even if positive results are obtained in the lab, human bone marrow transplantation is a complex and difficult road to travel, and with an unpredictable level of success.

Until now, glia had been regarded as just like plastic wire around the neurons, almost like polystyrene packing (there are 10 times as many glial cells as neurons). But recent work in the US has shown that they are a major player, which just illustrates that, with the brain, we are learning all the time, and continue to do so. MeCP2 study is teaching us things about the brain that were previously unforeseen. Since recent work has shown that MeCP2 exists in glia as well as neurons, it may well turn out that we can target glia for therapeutic approaches, and that is good news, as glia are seen as being receptive to a wider range of therapeutic options than neurons.

- *Some definitions:*
- *Neuron: Nerve cell - an electrically excitable cell that processes and transmits information by electrical and chemical signalling*
- *Glial cells: Or glia (Greek for 'glue') non-neuronal cells that provide support and protection for the brain's neurons. There are 10 glia to every neuron.*
- *Astrocytes: Star-shaped glial cells in the brain and spinal chord*

2. Dr. James Eubanks (Univ. of Toronto, Canada.) James' work has firstly been an independent confirmation of the 2007 reversal of Rett Syndrome in Adrian Bird's lab, which is very important. It is essential to independently validate any scientific study to show the result is general and not only seen in a specific climate. However, his results appeared to reveal a correlation between the stage of MECP2 reactivation and the degree of the recovery from Rett-like behaviour in mice. This was a cause for concern among Rett families at the Conference - concern that it implied symptoms might not respond to treatment in older girls. I have since asked James to clarify this point. He told me "...As for the severity at the time of reversal, in our study, we actually let the mice get more severely affected on average before reactivating MeCP2 than in the original (Adrian Bird's) study, and the effect was still preserved... The most severely affected mouse we (and Adrian's group) have tested showed a robust improvement in its gross phenotypic severity score." This reassured me.

The behavioural characteristics that have been studied for improvement in the mice during James' and Adrian's work to date have been diminished inertia, irregular breathing patterns, abnormal gait, hind limb clasping, presence of tremors, and general poor appearance (grooming, ruffled fur, etc). James plans to assess some of the other behaviours that need to be assessed, such as learning and memory, seizures, cardiac rhythm, temperature regulation, gastrointestinal motility (moving food through the digestive system), to name only a few.

3. Lianne Robinson, Univ. of Aberdeen, UK. Together with Gernot Riedel, and in collaboration with Univ. of Edinburgh (Jackie Guy, Adrian Bird, Jim Selfridge), This study successfully reversed impairments in the motor ability of mice after MECP2 re-activation.

4. Dr. Elisa Dominguez y Salmeron (Institut de Myologie, Paris, France) Elisa has shown that the injection of a virus can be used to target areas of the central nervous system. She then tested its use as therapy for a mouse suffering from SMA (spinal muscular atrophy). This disease is caused by mutations in a single gene, smn. She showed that a single injection at birth of a virus containing the smn gene prevented the SMA symptoms. This is obviously an encouraging pointer for gene therapy in Rett Syndrome. Elisa has since told me that her team has just started the project of clinical development for SMA, and hope to be able to begin clinical trials in humans around 2013-2014. Since Rett researchers have a year to go to reach where Elisa is now with SMA, it suggests that clinical trials of gene therapy for Rett may not start till around 2015. Elisa further told me that she expects to begin a collaboration with colleagues in Marseilles in 2011 developing gene therapy for Rett Syndrome.

5. Nicoletta Landsberger, San Raffaele Scientific Institute, Milan, Italy This poster showed a number of things. Firstly, MECP2 interacts with the protein YY1 to repress the ANT1 gene. Both in a mouse model, and using skin biopsies from Rett patients, it was shown that, when MECP2 is removed, both the ANT1 protein levels, and the genetic instructions fired by ANT1, are

increased. Secondly, the MECP2 - YY1 interaction led to the discovery of the de-repression of another gene FRG2. The data indicates that mutations in MECP2 might cause certain genes to be over-expressed in error, and that such genes may be part of the cause of Rett Syndrome. ANT1 is a likely candidate, because it is known that other human diseases have been associated with mutations in ANT1 and over-expression of ANT1.

6. Laura Ricceri (Istituto Superiore di Sanità, Rome, Italy) Laura injected CNF1, a bacterial protein, directly into the brain of Rett- affected mice (i.e. with MECP2 suppressed), and observed that motor skills were restored to normal, with substantial improvements in other areas. Also, she observed that astrocytes that had atrophied in MECP2-deficient mice were dramatically improved after CNF1 treatment. She observed that it may be that astrocyte abnormalities in MECP2-deficient mice may have diluted the benefits of CNF1 treatment. I have asked Laura if she has plans to start clinical trial of CNF1 treatment, and await her reply.

7. Dr. Omar Khwaja (Children's Hospital, Boston, USA) IGF1 (insulin-like growth factor 1) is an FDA-approved drug used to treat children with short stature. Recent studies have shown that injection of an IGF1 peptide (i.e. small protein) appear to restore a range of functions in mice. Omar believes that it may help to improve some Rett symptoms, including breathing irregularities, and brain development function. He has told me that he is planning a clinical trial, which will run for a year. He expects to report by the end of 2012 unless the interim analysis is striking, in which case he will report before that. He believes this is the first trial that aims to treat Rett by targeting the underlying neurobiological disorder.

8. Dr. Eva Gak (Univ. of Tel Aviv, Israel) Eva presented on behalf of her colleague Manuela Vecsler. This study proposed the trialling of a new drug to treat Rett patients with nonsense mutations of MECP2. Skin biopsies were taken from Rett girls with different nonsense mutations of MECP2, and the cells treated with a newly developed low-toxin drug NB54. This achieved more than 30% correction of the abnormal - truncated MeCP2 protein. This is promising, but Eva has since told me that NB84, a more potent variant of NB54, has now been developed. NB84 is currently undergoing extensive tests both in Rett mouse model (Peter Huppke), Rett patients skin biopsies (Eva Gak), Cystic Fibrosis (mouse model), Retinitis Pigmentosa (Germany), and cancer (both mouse models and human cancer cells). Note that all these diseases are genetic diseases in which nonsense mutation is the underlying cause of a disease, which represents about 12% of all types of mutations in all the genetic diseases. Clinical trials should be possible, as NB84 is so much less toxic than gentamicin, a related drug that has been used in previous clinical trials and proven to be too toxic to be an effective treatment. Funding is needed. Prof. Timor Bassov from the Israeli Technion is the originator of these new NB substances and their application in various human genetic disorders.

9. Shih-Ming Weng (Univ. of Glasgow, UK) Shih-Ming's poster showed that the impairment in the brain's ability to transmit messages, as well as in its memory and learning, increases as Rett symptoms increase. The impairment was corrected by application of a drug, memantine. This study suggests that progressive functional synaptic impairment is a key feature in the Rett brain, and also that it may be amenable to pharmacological intervention.

Definition: Synapse A junction box in the brain that allows electric or chemical signals to be transmitted from a neuron to another cell.

10. Katherine Barnes, Children's Hospital Boston & Harvard Medical School Katherine's study treated adolescent Rett girls with the drug escitalopram, and observed improvements in motor function, as well as measuring both improvement in their mood and reduction in their anxiety. (Adolescent Rett girls are at risk of developing mood disorders and anxiety.)

SCIENTIFIC RESEARCH OUTSIDE CONFERENCE - DETAIL

11. From the lab of Huda Zoghbi, Baylor College of Medicine, Houston Texas, USA. Huda discovered MECP2 mutations as the source of Rett Syndrome in 1999 – the landmark that has launched all subsequent research into the condition. In November 2010, Hsiao-Tuan Chao, a postdoctoral fellow in the lab, demonstrated that removing MECP2 from the small group of neurons that produce GABA, (which control the strength and timing of information transfer in the brain), reduced GABA production by 30%, which was enough to induce some Rett symptoms, including paw clasping. This is an important step in linking some symptoms to a subset of neurons, and suggests that targeting GABA-producing neurons may derive future therapies for Rett Syndrome.

12. Dr. Alysson Muotri, Univ. of CA., San Diego, USA reported in November 2010 the results of his work with IPS - induced pluripotent stem cells. (This just means that, from the skin biopsy of a Rett patient, you can take a cell that has already differentiated, and reprogram it back to a more naïve state resembling a human embryonic stem cell). This technique was discovered a

few years ago in Japan, and allows scientists to track the processes of genetic mutations in a human cell as it differentates into other cells outside the body. Dr. Muotri has now used it to produce the following outstanding results using cells taken from patiemnts with 4 different mutations of Rett:

1. He demonstrated the reversabilty of some Rett characteristics
2. This was true for all of the mutations, indicating that a single drug may reverse all
3. He administered a drug, IGF1, which has been shown to have had some success in addressing some Rett symptoms in mice. He demonstrated its beneficial effect using the cells from all the patients.

The result of all this is that IPS will be many factors quicker and less expensive than mouse models to screen potential drugs. Hundreds of thousands of compounds can be efficiently and quickly screened, and using human, not mouse, cells. Dr. Muotri will now focus on making his system more robust, and extend it to test against more Rett characteristics. Ultimately he wants to use the system to test libraries of drugs that previously failed clinical trials for other diseases. Drug repositioning, as this concept is called, is attractive because repurposed drugs can bypass much of the early cost and time needed to bring a drug to market.

13. Dr. Jonathan Kipnis, a neuroimmunologist at Univ. of Virginia, USA reported in July 2010 that he has become heavily involved in Rett-related research. Microglia are brain cells that are not formed in the brain, but in bone marrow. If you transplant bone marrow into a Rett mouse, eventually the microglia in the brain will be replaced by the new microglia grown in the new bone marrow. Following this through, Dr. Kipnis transplanted bone marrow from a mouse with Rett symptoms to a healthy mouse, and that healthy mouse then developed Rett symptoms. Dr Kipnis is working as fast as he can to discover if a bone marrow transplant from a healthy mouse to a Rett-affected mouse can improve or cure some aspects of Rett in the affected mouse. This is a new door that has opened - that doesn't involve working directly on the brain, which scientists like Adrian Bird admit is still largely a mystery to us.

Definition: Microglia Glial cell residing in brain and spinal cord. 20% of glial cells in the brain are microglia. Microglia (and astrocytes) are distributed in large non-overlapping regions throughout the brain and spinal cord. They act as the first and main form of active immune defense in the central nervous system (CNS). Microglia are very, very active participants in the brain but are not made in the brain; they come from hematopoietic stem cells in blood or bone marrow.

14. Prof. Julian Paton (Univ. of Bristol, UK) and Prof. John M Bissonette, (Oregon Health & Science Univ. US) co-authored an October 2010 paper, showing how they were able to completely correct the breathing defects of MeCP2-deficient mice, by using techiques to increase the levels of 2 types of neurotransmitter - namely GABA and serotonin - in the body. For those interested, see here for an independent commentary on this work.

Definitions

- *Neurotransmitter: Chemical produced by the body which transmits signals from a neuron to a target cell across a synapse.*
- *Synapse: A junction box in the brain that allows electric or chemical signals to be transmitted from a neuron to another cell*

CLINICAL RESEARCH & GUIDELINES AT CONFERENCE - DETAIL

1. Dr. Sarojini Budden, Portland, Oregon has worked with many Rett girls over many years. Her talk provided the following insights for me:

- There has been increased identification of reflux, gallstones, and fractures as the reason for pain and discomfort in girls.
- If there is obvious pain around meal time, it may indicate reflux or gallstones. 11% of all girls had gallstones (between 8 and 22 years of age). Girls should have ultrasound scan for gallstones, but, even if this shows negative, parents should pursue a HIDA scan, which can evaluate whether the gallbladder is diseased. Alan Percy, Prof. of Paediatric Neurology at Alabama, USA, confirmed that this is essential, and has been required in a number of cases.

- Standing should be extended to at least 30 minutes to 1 hour daily – beneficial in the fight against scoliosis (together with calcium and vitamin D in the diet), excessive wind, constipation (together with fibre / vegetable diet)
- Sitting - methods of sitting should be explored that could be beneficial to the spine
- Physiotherapy is vital. Daily stretches should maintain the range of movements of the muscles and joints. Local physio should suggest types of stretches and for how long.
- There is incidence of leg length discrepancy, which should be checked, in case correction is required for standing or walking
- Girls have shown potential for improving skills, e.g. hand function
- Siblings reactions are very important
- PLEASE keep talking to the girls

2. Irène Benigni (Paris) talked about nutrition in Rett Syndrome She made the point that parents must mobilise the health professionals to allow the girls to express their full health potential. If care of the Rett girls is improved, secondary handicaps (e.g. scoliosis) can be prevented or delayed. Some specific points

- Try and brush the teeth at least twice a day (post breakfast & dinner.

Constipation pain is common in the girls. Fight against it by

- standing,

- abdominal massage,
- adequate fluids, and fibre intake at meals (fruit and vegetables every day, ground vegetables in soup every day, and pulses twice a week)

GOR (Gastro oesophageal reflux) has been seen in 50% of Rett girls studied. This is an abnormal reaction of stomach acid to the passage of food from the gullet. It can cause burping, vomiting, regurgitation, and nausea. Additional signs may be

- Coughing during and after meals
- Profuse throat secretions
- Pulmonary, ear, nose and throat infections
- Asthma
- Food refusal
- Sleep problems
- Hyper-salivation and drooling
- Anemia
- Hands or clothes in the mouth
- Irritation around the mouth
- Teeth grinding
- Pain

There are a number of ways to fight GOR, including

- Anti-acid treatment
- Sitting position after meals
- Raise the head of the bed
- Prevent spinal deformations
- Increase time between meals
- Adapt food texture to chewing abilities
- Prevent and treat constipation
- Use clothes that do not compress the abdomen

Chewing and swallowing problems. You can mince meat, crush vegetables, and grind fresh fruit with apple sauces or milk desserts. You need to optimise the girl’s sitting posture – knees and hips flexed, and support for the feet and elbows

Worried about fluid intake? You could try gelified water (preferably flavoured) taken as a drink or with a spoon as a jelly; also savoury and / or sweet smoothies and soups, or milkshakes. Add Vitamin C, proteins, calcium, and fibres.

Malnutrition. Enrich the food with proteins (concentrated milk, powdered milk, cheese, milk as a drink, eggs), carbohydrates (almonds, nut powder, starchy food, cakes), and lipids (butter, margarine, oil, cream).

3. Cristina Martins, Rett Syndrome Centre, Montefiore Medical Centre, New York, USA studied Rett girls eye gaze using the latest eye tracking technology, to see how strongly the girls use their gaze to indicate preference. The study showed that Rett girls were able to use eye gaze accurately in order to activate visual stimuli, in a way comparable to healthy adults. They preferred pictures of real people to cartoons, and they did recognise novelty stimuli. The technology allowed the focus of the gaze to be represented by a red laser guided dot on the target object, and the study showed that it can provide reliable and quantifiable outcome measures. Eye tracking can therefore be used for cognitive assessment and non-verbal testing in Rett girls.

4. Meir Lotan, Israeli Rett Centre presented a case study of a Rett girl whose scoliosis was reversed by a rigorous daily routine of exercise. Measurement of the angle of curvature was observed, and several physio aids constructed by Meir himself, each of which was designed to counteract the angle of the curve. These included a seat for floor sitting, the seat in the girl's chair for performing activities, the girl's standing frame, and a special pillow for sleep time. Over an 18 month period, the angle of curve in a standing position was reduced from 30% to 20%, which is all the more remarkable when you consider that the expected progression of the curve is an annual increase of over 10%, according to previous studies. This seems to me an important contribution by Meir, who is currently working with a family in Ireland on a similar exercise. He has told me he is happy to discuss with physios who contact him.

In a separate poster, Meir reports improvement in the gross motor skills of 3 girls placed in a Conductive Education environment over 24 months. CE may serve as an enabling educational environment for Rett girls. To find out what CE services are on offer in the UK, visit here

5. Dr. Hilary Cass, Paediatric Neurodisability Consultant Guy's and St Thomas, London, UK. Among other things, Hilary emphasised that scoliosis can be reversed through physiotherapy. The physiotherapy should be most proactive at the most difficult times, like puberty and young adulthood, in order to prevent a secondary handicap (e.g. scoliosis) and preserve bone health. I asked Hilary how to find out why a girl might seem exhausted during the day, and she suggested a sleep test called an actigraph could be done. This involves attaching a device like a watch to the wrist overnight, and obtaining a readout, which can then be analysed.

6. Dr. Peter Julu, working at the Swedish Rett Centre. Peter's study showed that all Rett patients have abnormal breathing, and fall into one of three categories:

- Feeble breathers - These are patients with Rett syndrome who have the habit of very shallow breathing. The movements of the chest and the abdomen are so small that sometimes parents and carers do not notice it at all and may be mistaken that the Rett person has stopped breathing altogether.
- Forceful Breathers - These are patients with Rett syndrome who forcefully inhale and exhale air, sometimes continuously and would often lose a great deal of carbon dioxide from the bloodstream.
- Apneustic Breathers - These are patients with Rett syndrome who take in air but fail to breathe out regularly. There are three types of breathing abnormalities in this category. They are long breath holds, repeated short breath holds and protracted inspirations.

Peter concludes that clinical assessment and categorisation of breathing pattern is essential, and should be carried out for all Rett patients, because rational approaches to clinical management are different and unique for each type.. Note: Work by Emma Brockett, Jacky Guy, Adrian Bird and Leanne McKay at Univ. of Glasgow, UK has shown in their lab that breathing abnormalities can be reversed when MECP2 is re-activated in mice.

7. Jenny Downs, Univ. of Western Australia. A poster presented survey data which indicates that Rett girls have reduced sensitivity to pain, i.e. have a high pain threshold. This is based on question responses by parents about situations likely to cause pain like injections, falls, trauma, and burns. Clinicians should be made aware of this when assessing potential injuries.

PEOPLE I MET AT CONFERENCE

Thomas Carroll, dad of a 4-year-old girl who was diagnosed 3 months before the Conference. Thomas was an extremely interesting guy. He is a practising brain surgeon in Sheffield, and had an infinitely better understanding of the neuroscience than me. He questioned why there weren't more clinicians at the conference, and questions whether the Rett community will be ready to

manage clinical trials if candidate therapies present themselves in the near future. Thomas has a 6-year-old son who has a condition even more rare than Rett - called Fanconi Anaemia - and that clinical community seems to be better organised and prepared to deploy clinical trials of candidate therapies.

His little girl was experiencing hundreds of absences per day. Thomas prescribed the drug paradoxin for her, and these have stopped completely. He feels there should be a network of clinicians / paediatric neurologists with whom this info can be shared.

Adam Aowerczuk, a clinical doctor at the Medical University of Gdansk, Poland. Excellent company, Adam has a little girl with Rett Syndrome. He is a very positive person, and not afraid to give his opinion to the scientists. He is setting up an organisation to raise funds for research in Poland. Website is www.rettsyndrome.pl

Tom Duncan, a golf professional who lives in Germany now, but hails originally from my home city of Glasgow in Scotland. Tom is dad to little Emma who has Rett Syndrome. He plans to run a fundraising golf event next year for Rett research. He and I spent a lot of time exchanging views on the world in the Glasgow vernacular, much to the confusion of fellow diners.

Catriona Moore, mum to 3-year-old Amy, who has Rett Syndrome. Catriona told me she spends several hours each day with Amy at meal times, which has taught her a lot about the challenges of nutrition in Rett girls. Catriona writes a blog at Living with Rett Syndrome Since Conference, I've been following it, and really enjoying Catriona and Amy's take on the world. It is a living testament to the resilient spirit of mums looking after Rett girls. I think they are a remarkable group of people.

Monica Coenraads is the Executive Director of the Rett Syndrome Research Trust, (RSRT) the world's largest private sponsor of scientific research into the treatment and cure of Rett Syndrome (which I like to refer to as "ATACRS"), and also mum of Chelsea, who is 13 and has Rett Syndrome. Monica had talked to me on the phone a number of times from her home in Connecticut, but this was the first time we had met. I'm full of admiration for the quality of the model she has set up to channel the global scientific effort towards the goal of a cure. It was obvious at Conference that she enjoyed the respect and friendship of the leading scientists in the field, including Adrian Bird, Gail Mandel and Huda Zoghbi. On a personal level, I found her to be modest about her achievements, good fun to be with, focused like a laser on raising funds to advance the science, yet always thinking about Chelsea's well-being, and how to maintain

her quality of life.

Monica gave a 60-minute talk at Conference entitled "Science for Non-Scientists: Understanding Pathways to a Cure". This was in the stream of talks for Clinical and Family conference-goers, but it spoke volumes about her standing that many scientists chose to attend in preference to the alternative stream for Scientists. There are a number of videos here of various talks Monica has given in the past, which I recommend any family members to watch.

Rachael Bloom is the Chair of Trustees of Rett Syndrome Research Trust UK and mum of Amber, who is 15 and has Rett Syndrome. Rachael has worked closely with Monica Coenraads to set up this UK Charity, which is supporting the work of RSRT. With the help of her fellow Trustees, she is galvanising the energies of Rett families across the UK to fundraise for research that will lead to a cure. Since Conference, the official launch event of the Charity, Reverse Rett London, on 18th November, raised around £140,000 (US$220,000). Rachael is a pint-sized powerhouse. When I told her that my granddaughter Clara had had her healthiest ever winter following her swine flu injection, Rachael told me that Amber had been virtually cold-free for 3 winters since she's been having an annual flu jab. This seems like a must-have for the girls to help them fight off predator bugs. So Clara has since had her first standard anti flu injection.

Claudia Petzold is a young Rett mum from Germany, who has had the drive and determination to set up Rett Syndrom Deutschland to support the efforts of RSRT. This website has just been launched now.

Melanie Ekless is Director of Rett UK which provides support to patients, their families and carers in the UK.

Marielle van den Berg attended the whole Conference with her husband and her little girl of 5, who has Rett Syndrome. The little girl's smile lit up the lecture hall during some very serious scientific presentations. Marielle is also an orthopaedic surgeon, and the Chairman of the Dutch Rett Syndrome Association
which supports Rett families, and promotes research.

Olga Timutsa is aiming to set up the Russian Rett Syndrome Foundation. Tennis star Vera Zvonareva (2010 Wimbledon and US Open finalist) famously donated much of her US Open prize money this year to help set this Foundation up, and has been co-opted onto the Foundation Board. I'm looking forward to seeing the Website being set up.

Emmett Harten and his wife attended form Ireland. They have a little girl Kayla who has Rett Syndrome. Emmett is on the Committee of Rett Syndrome Ireland which is an association of parents and families, and provides support and information.

Alison Kerr attended the conference as a guest of the organisers. While at Glasgow University before her retirement, Alison was for many years the most significant advocate of the importance of Rett Syndrome, and was more than anyone else responsible for keeping Rett Syndrome visible to scientists worldwide. She was invited to say a few words, and responded with these thoughts.

- The task goes on, and we should be aware of the amazing progress that has been made
- She gets the feeling that there are anxieties and disagreements among elements of the Rett community, and worries about funding. This is a cyclical phenomenon. We should remember that the most important driver has always been motivation, not funding. Most discoveries have been made "in a broom cupboard"
- Researchers - you must always keep the girls with you

Vania Broccoli, a research scientist at San Raffaele Scientific Institute, Milan, Italy, who presented his research into the CDKL5 mutation variant of Rett Syndrome. He told me his institute was set up to research solely into Rett Syndrome, and was funded by the Telethon in Italy. I asked how Rett Syndrome managed to attract 1 million euros of Telethon funding in a year. The answer is that the Telethon in Italy benefits only rare genetic diseases. Since then I've done a bit of digging on Telethons around the world. The main ones are

- France - 100 million euros last year. This was set up in 1987 originally for muscular dystrophy, but now benefits neuromuscular and other rare diseases
- Italy - 33 million euros last year. Set up in 1990. Benefits 200 rare genetic diseases
- Perth, Western Australia - AUS$ 6 million last year. Benefits therapy more than scientific research
- Good Friday Appeal, Melbourne, Australia. AUS$ 14 million last year. Benefits the Royal Children's Hospital in Melbourne
- Children in Need Appeal, UK. £39 million last year. Benefits children's therapy and care. Not research

I've written to Alastair Kent of Genetic Alliance UK, and Rare Disease UK to ask if there is any political push to start a Telethon along the lines of the Italian or French, and await his reply.

Gérard N'Guyen, Rett Syndrome Europe (RSE) – a tireless and inspirational campaigner on

behalf of his daughter and all Rett girls – he described the function of RSE as the “Dynamic acceptance of Diagnosis”. His final message of Conference to all Rett families was “Take care of yourselves now and then”