LMBBS Conference Report 2009

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Introduction - Chris Humphreys

Every year, as Conference Co-ordinator, I wonder how we can build on the success of the LMBBS Family Conference, because every year seems to surpass the one before. This success is, of course, down to a large collection of people who always give their all to ensure that everyone has a fantastic weekend:

The Hilton Hotel, Northampton, make every effort to ensure that our guests are made welcome from arrival to departure. Precision planning by managerial staff ensured the smooth running of the weekend. (A special mention this year goes to Chef, who provided fantastic and varied menus, with superb presentation, throughout the weekend.) The thoughtful touches were very much appreciated, such as support for our blind delegates, ensuring that their needs were met at all times, and bowls of water provided for their guide dogs.

A big 'thank you' must go to our eminent speakers, who willingly gave up their time to inform and update us on the latest medical discoveries in LMBBS. During the afternoon, the speakers facilitated workshops, allowing for more 'personalised' help and support and their value cannot be overestimated. They provide a unique opportunity for an exchange of information between professionals and members, from which both parties can benefit. Members are sometimes torn as to which workshops they should attend and, frequently, the time available seems too short, when it is necessary to call a halt to discussions that are taking place, ready for the next item on the programme. The workshops were followed by a moving Family Perspective by Margaret Begley. In addition, Guide Dogs for the Blind were represented by Jill Baterman, who came along on Friday evening and Saturday afternoon to chat to members interested in becoming owners in the future. Ray Perry provided benefits advice and Sue King set up a resource table for the blind and visually impaired, and demonstrated sighted guiding for our carers, to prepare them for the weekend.

Grateful thanks go to our loyal band of volunteer carers, who have been coerced onto the 'team' over the years and are now 'part of the family'. A large group of carers took the older children and young adults to Drayton Manor Theme Park, where they enjoyed the thrills and spills of the rides, returning to enjoy social and craft activities in the evening. A small group of carers did a fantastic job of looking after our younger members in the LMBBS Creche. In addition, one of our members, Richard Zimbler, along with two of his friends, Joe Bentley and Martin Rhodes, all of whom are blind, provided entertainment with an evening of African Drums, with hands on participation, karaoke and disco. A fantastic time was had by one and all. Richard later sang a few songs from his CD, which he is selling to raise funds for LMBBS. If you would like to buy a copy, contact Richard on richard.r.zimbler@btinternet.com.

As usual, there was a resource table, which, as well as LMBBS material, provided useful information about education, holidays, visual aids and support for the visually-impaired and blind, which had been brought from Sight Village, Birmingham, for people to take home. There was great interest in the LMBBS clothing, bags and teddies on the merchandise table and the photographs on the display board. The tombola provided a source of amusement for all and the raffle was very well supported. Our grateful thanks to everyone who helped out with the resource table, raffle and tombola, and to everyone who donated items, including the Hilton, who provided the star prize of a Weekend Break at the Hotel.

As Trustees of the Society, we are totally committed to the annual organisation of the LMBBS Family Conference, (planning for Conference 2010 is already underway), and regard it as the highlight in the Society's calendar. We receive a lot of interest, worldwide, and we were pleased, this year, to welcome two visitors from Norway; however, it is you, the members and professionals, who actually make the Conference such a resounding success. Your continued support and appreciation of the weekend, as reflected in the evaluation reports and thanks received, makes all the work worthwhile and we look forward to seeing you all next year.

Update on Research and Study of LMBBS

Professor Philip Beales
Professor of Medical and Molecular Genetics
Wellcome Trust Senior Research Fellow in Clinical Science
Honorary Consultant in Clinical Genetics, Molecular Medicine Unit, Institute of Child Health, Gt Ormond Street Hospital for Children and Guys and St Thomas' NHS Trust.

Professor Beales opened the LMBBS Family Conference with a welcome to everyone, in particular the seven families who were attending for the first time. He went on to outline what was a particularly packed schedule and hopefully, he said, an exciting one. Professor Beales introduced a new member of his Lab to the delegates, Aiofe Waters. Aoife is a kidney specialist, a consultant in paediatric nephrology, and is undertaking a PhD with Professor Beales' team for the next three years or so. He then went on to talk about what has been happening over the past year:

"We have, in the last year, been trying to work on, or to develop, therapies to treat aspects of LMBBS. Last year, we talked about some of the work we've been doing, looking at testing specific drugs. We found a drug, for example, that may help with kidney cysts in fish. We use a number of animal models to try and work out what is going on in the disease, and one of those is zebra fish, which is a little animal that lives in the rivers at the foot of the Himalayas. The zebra fish is particularly useful in genetics, firstly because we know the whole of the genetic code, and secondly we can play around with its genes. It has most of the genes, if not all of the genes that we as humans have. We are undertaking relatively big drugs screens using fish at the moment, which is being done by Dan Osborne. So what Dan is doing is rather tediously going through trays and trays of little baby fish, adding different drugs to those, and seeing which ones actually make things better. We also have a complementary study going on at the moment where we're looking at mice that have been bred to have LMBBS. These mice have visual loss and some of the weight maintenance issues as well, and so what we do is any drugs that we particularly study in the fish to begin with, we then go and try them out in mice because, believe it or not, mice are actually much closer to us, genetically. We are also doing a lot of work on cell biology and a lot of work on diabetes as well. Also, Kate Baker, a neuroscientist, has got some very interesting things to tell us, so that is a brief outline of our ongoing research.

So, in terms of general things that have been happening in the last year or so, there is a couple of highlights that I think are important to you as a group, which come from a couple of papers which have been published. Val Sheffield's group, in Iowa, have discovered that the BBS proteins are central to the way all of us maintain our weight, so they are really quite critical. This gives us quite a lot of insight into thinking about potential therapies, which would be based on the part of the brain that tells us when we're full, at least that is what we thought when this paper came out earlier in the year. But then Hélène Dollfus, who many of you will know from the French LMBBS group, published a very nice paper just a few weeks ago, where she's saying that BBS proteins are important for the fat cells. So really there is this whole conflict, if you like, between whether or not the weight issue is a consequence of what's going on in the hypothalamus (a complex region of the brain) or to do with the way the fat cells accumulate energy, and fat, and this kind of thing. At the moment these two are kind of conflicting, and I've always felt it was a combination of the two, which may well be the situation, so watch this space. We have asked Hélène to come back and speak to us about this specifically next year.

I want to update you on the study that many of you took part in during last year's conference, which was the nasal brush test conducted by Heymut Omran who came over from Germany. The procedure involved brushing the inside of the nostril with a little wire brush and taking some cells from the back of the nose and putting them onto a slide. These were looked at under a microscope in an attempt to measure the frequency with which the cilia were beating. Many of you will know that there are two types of cilia: those that beat, the ones that line your airways and

then there is the other type which sort of just sit there on top of cells, and it is these ones that we think are the ones not working correctly in LMBBS. The results of the analysis showed that, essentially, there is nothing wrong with the cilia that are beating in your chest or in your nasal cavity, so that really brings us to the question as to why some of you are experiencing all of these increases in chest infection and various other infections. Robin Quinlan, many of you will know from last year, has been looking at mouse lungs and preliminary data suggests that there might be something going on with the way the sacs, the air pockets in the lungs, are forming.

The very last thing I want to talk about is a new initiative that members of the LMBBS group have been working with me on, which is to develop some National Clinics. One message that I get from you guys, year in and year out, is the frustration you have experienced when your children are younger; for example, you go to a doctor, they don't know what's going on, they've never heard of the syndrome, and I guess, throughout life, as you get passed from pillar to post to see different specialists, you're always having to explain what is Bardet Biedl syndrome and what is LMBBS. That, I can understand, is frustrating, so what we're trying to do is to redress that in some way, to have a centralised service to make things somewhat easier. The possibility of doing this comes out of an initiative from the Department of Health called the National Commissioning Group, which has funding set aside from the NHS to spend on rare conditions. Before Christmas, we put an outline bid in to see whether or not they would be interested in funding BBS, and they told us in March that we had been successful. Out of the twenty bids, I think there were about six that had been short listed and we were one of those six.

First of all, what is the aim? What are we trying to do here? Well, diagnosis is one of those aims, that's a given, if you like. What we want to do is to be able to have a central service whereby we can monitor the progression of the syndrome, if you like. As you all know, certain things happen at certain times of your life, and what we want to do is try and provide an integrated service. We want to be able to co-ordinate care, to provide a centre where local healthcare professionals can come to when they're in trouble and want to know more about what's going on. Another element of this, which is really quite exciting, is to hopefully be able to provide a national genetic testing service, which we're building into this particular endeavour. We are going to have four centres, two hospitals in Birmingham, Queen Elizabeth Hospital for adults and Birmingham Children's Hospital for children. In London, the equivalent will be Guy's Hospital, where I already run the clinic, the only existing clinic, and the other will be at Great Ormond Street Hospital for Children. Integral to this whole thing, and really pulling it all together, is the LMBBS Society because the LMBBS Society will run this clinic. They will work with you guys, and they will invite you to the clinics, tell you when they are happening, and they will help to arrange your transport and overnight accommodation.

So the shape of the service that's intended is an outpatient-based service. So what that means is that, when you turn up to clinic, you will be seen by up to six specialists, and amongst them will be an endocrinologist, an ophthalmologist, a nephrologist, a clinical psychologist, myself and a dietician. And then there will be a representative in every clinic from the LMBBS Society so that at least you have a familiar face there. There will be a dedicated nurse specialist for each clinic as well, and one you can contact outside of the clinic if there are any specific medical issues you wanted to bring up. The model that I've proposed will be one that we already use for some other clinics that we're doing at Guys. There will be a general meeting area, and then, for the actual consultation, you will remain in a particular room that's allocated to you for the day. The various specialists will come and see you in turn and this has a lot of benefits for us because then we can also meet together in another conference room and discuss what might be the best overall care plan that is designed and tailored to individual people.

The very last thing I want to talk about is the possibility of implementing a DNA diagnostic service off the back of this. It's something that we've been doing for several years now but we're doing it on a research only basis, and we rely on donations and research grants to do this - the NHS has no equivalent at all and so we are asking the NHS to step up and help us deliver this. This will certainly be the first in Europe and, quite possibly in terms of its comprehensiveness, the first in the world as well. The real reason for that is because we are looking at so many different genes. There are fifteen different genes now, and counting, associated with LMBBS. So that is technically challenging, as well as very costly to do. Why have a DNA diagnostic service? Well,

diagnosis is just a small part; we will be able to tell relatives if they are carriers and a lot of parents may want to avail themselves of prenatal testing as well.

What's the timetable? The timetable is that we have until the end of April to finish the application. On June 7th the NCG panel will sit to discuss our application. On July 14th another panel will meet, who have the final say in many senses, so that's the real high hurdle to get over. If we are successful, and we've had fairly good indications thereof, we will start the process in April 2010. At this meeting next year, hopefully we'll be able to say we're up and running, or about to start. So that really leaves me just to thank the Committee members of the LMBBS Society who have been working really hard with me over the last few months."

Retinitis Pigmentosa and emerging treatments

Dr Andrew Webster
Consultant Ophthalmologist at Moorfields Eye Hospital, London
Senior University Lecturer at the UCL Institute of Ophthalmology

"I am an ophthalmologist and I work at Moorfields Eye Hospital; I have a special interest in retinal disorders and also genetics. I see a lot of patients with retinal problems and I have a small lab that looks at the genetics of patients and families with these problems. Although I've been asked to talk about treatments, I want to begin by explaining some of the terms that we use to describe the eye problems that people with Bardet-Biedl have. These terms are often complicated but, if I demystify some of these terms, you will find they are very straightforward.

I want to talk first about retinal dystrophies and then come on to treatments and how that applies to helping people with retinal problems. The retina is the clever photo sensitive layer in the eye. It is the bit of the eye that absorbs light and transduces it into an electrical signal, which can then be interpreted by cells of the retina. This is then fed back to the brain, where it is interpreted further and impinges upon our consciousness. The retina has a number of specialist cells in it. The most important, and possibly the most interesting cells, are the ones that go wrong in many of the genetically determined retinal problems and those are the photoreceptors.

The photoreceptors are a collection of cells in the retina that do the important job of absorbing light and transforming it into electrical energy. In all vertebrates, including the zebra fish, which Phil was talking about, there are two fundamental types of photoreceptor. The reason for this is to enable us to see in different lighting conditions. In order to see in dim light, you need very specialist cells called the rod photoreceptor, which can pick up even a single photon. A single signal of energy from light can be picked up by one of these cells, and so they have to be

specialised. They are packed full of protein that can absorb this light, and capture any stray light that's going. They are also wired in such a way that there's convergence of the photoreceptor cells into the next cells in the retina called the bipolar cells, meaning any small signal will be amplified and actually have an effect in the retina.

The second type is the cone photoreceptors, which don't capture as much light and are not as sensitive. You have to put a lot of photons in for a cone photoreceptor to work, and they are wired in a very accurate way, such that there's a one to one correspondence between these cone cells and the rest of the signalling cells in the retina. They see detail, they see colour, and they see bright lights. Very often, in retinal dystrophies, particularly retinitis pigmentosa, it is the *rod* photoreceptors that are affected first and so people tend to have problems with seeing in the dark. They may also have problems with the peripheral field because the majority of the rod photoreceptors are at the anterior part of the retina, which sees towards the outside of our field of vision. However, there are other disorders that affect the *cones*, specifically, and, when that happens, the sort of visual problems that people have are quite different. They are fine seeing in the dark but they are usually averse to bright lights. They either find bright light difficult and painful or they can't see as well in bright light. They lose the ability to see accurately, so very often they can't read as well or they can't recognise faces and so on. Any fine visual tasks are difficult and discriminating colours is difficult. So those are all cone problems. In some of these retinal disorders, just one of those two things happen, and they're a set of disorders called stationary disorders, in which there's a problem with the retina but it doesn't progress; so people have night blindness throughout the whole of their lives but the cone cells still work okay and they do fine. The opposite to that is when people have colour blindness, achromatopsia it's called, where people can't see accurately, they can't discriminate colours, they don't do very well in bright lights but they're excellent in the dark. That's a stationary disorder and they do fine, too. They have to get used to the fact they don't have detailed vision but there are ways to get round that. Unfortunately, in retinitis pigmentosa and the retinal dystrophy that occurs in Bardet-Biedl Syndrome, it is a progressive disorder. It is something that gets worse very gradually throughout a person's lifetime, and those progressive disorders do affect both the rod and the cone systems, so people will have difficulties that relate to the rod system – seeing in the dark and seeing things in their peripheral vision – and also very often the cone system, which sees detail.

I've mentioned the photoreceptors, which are important cells; however there's another type of cell, the retinal pigment epithelium cell, which is the pigment cell. This cell maintains the photoreceptors and is responsible for keeping the photoreceptors working normally. The reason I mention this cell is that gene therapy, so far, is directed towards those disorders that are due to problems with the pigment cells of the retina. In Bardet-Biedl Syndrome, however, it is always the photoreceptors that are affected and it is primarily a disorder of the cilia. It isn't immediately obvious what cilia would be doing in the retina. Some of them waft about and some of them don't, however, cilia are extremely important because all photoreceptors are derived from a specialised cilium.

Photoreceptors have two bits: they have an outer segment and they have an inner segment. The inner segment has got all the machinery that most cells in the body have. It has the nucleus and mitochondria, which make energy, and all the other processing structures. It is the outer segment that is the specialised bit that sees the light and turns it into an electrical signal. In the outer segments of both rods and cones, very specialist proteins have to be packed together to perform that role. The outer segments are entirely built from a specialised cilium and so any ciliopathy may damage photoreceptors, because they have the specialist equipment that all cilia have. This explains why the twelve or more proteins that have been discovered so far that cause Bardet-Biedl Syndrome also have an effect on the retina. They affect the photoreceptors.

Many of you will have had the misfortune to go to eye clinics for investigations, so I would now like to talk a bit about that. One thing that is good in ophthalmology is that we can usually investigate the retina without becoming too invasive. Some might disagree with this because we have to put drops in to enlarge the pupils and they sting. I apologise for those drops but they haven't made any non-stinging drops yet. Once we've dilated the pupil, we can usually get a nice clear view of the retina without having to do difficult scans or inject people with contrast. We can take all sorts of photographs to tell us about what the retina is doing, whether it's working normally, and which bits of the retina aren't working. There's another mode of investigation that

people may be aware of, may be even fearful of, because, in some hands, it can be quite a stressful test, but it needn't be, and that's an ERG, an electroretinogram. An ERG measures the electrical output of the retina. We flash a light at the eye and a little electrode placed near the eye measures the changes that occur around the eye. This can give us an awful lot of information. It can tell us about the rod and the cone cells, and it can tell us about those cells in the middle part of the retina called the macula, which see detail. One very important use of the ERG is that it is sensitive to people with very early disease. If a member of a family needs to know whether or not they will ever get retinitis pigmentosa that has affected other members of the family, an ERG performed in the early teenage years or later can completely exclude people from having the disorder.

Where does that leave us with treatment? I'm going to mention two main developments, gene therapy and retinal implants, and bring people up to date with developments. Gene therapy is all about replacing a missing vital gene, however some people with RP have what is known as *dominant* disease in which the gene is still there but produces a protein that has a toxic effect. This is difficult to fix because replacing the gene won't help, we have to knock out the gene that's causing the toxic protein. Bardet-Biedl Syndrome, however, is a *recessive* disease, which means the gene just doesn't work and therefore we just need to replace the gene. Very often we can't treat people with retinal disease. Many of the retinal disorders I see are like a car crash where every bit of the car has gone wrong, which makes treating it quite difficult.

With retinal dystrophy, in every family, and including families with Bardet-Biedl, it's just one component that has gone wrong, so it's simpler. We know what the gene is and we can work hard on replacing that one gene. Also the eye is particularly applicable to gene therapy because both the eye and the retina are accessible. As I've said, we can see it when we look through the dilated pupil, we can take photographs of it and we can easily get a needle to it. Secondly, the cells in the retina are stationary. You're born with your photoreceptors, you're born with these pigment epithelium cells and all the other cells in the retina, and they stay there for the rest of your life, which is good and bad. Bad, because it's difficult to get them back if you lose them, but good, because if we can get the gene into the cell, then that's likely to stay there. In Cystic Fibrosis, a common genetic disorder that affects the lung epithelium and other organs, those cells are continually being replaced, so gene therapy is particularly complicated there because you have to try and aim the gene at the stem cells that produce the new cells all of the time, but we don't have that problem in the retina. It's just one layer of cells, it's there for the whole of the person's life, and we just need to get the gene in.

Many of the disorders that we see in the clinic have animal models. For diseases affected by the pigment cells, and diseases affected by the photoreceptors, it is clearly possible that, in the mouse retina, we can use methods to get the gene into the cells that need it and for that gene to do the work of producing the protein that's missing. The way that has been done so far, the most successful way, is using a virus. This is using a virus that has the propensity to infect cells, deleting out those bits of the virus that would cause damage and perpetual infection, and putting in the gene that is missing. This is all possible with modern technology. The most popular virus for the eyes is rAAV virus, which is a very small virus, and not very effective. That has been done in many animal models and it has been shown that we can do that both with the pigment cell and also with the photoreceptors. The photoreceptors are more difficult because it has this outer segment bit that absorbs all the light. You want to get the virus into the inner segment, which is where most of the cell processes happen. That particular hurdle has been overcome, which is great.

Recently, you may have heard that testing has actually moved into humans and, so far, there have been three trials, one in London and two in the States. The trial is for a form of RP called RP65, which is a recessive disease. It affects children and is a severe and rare form of retinitis pigmentosa, rarer than Bardet-Biedl Syndrome. Because of its rarity, we are struggling to find families to treat, but, so far, results have been encouraging. RP65 is due to a problem with the gene needed by the pigment cells which makes things a bit easier for us, because it is easier to get the gene into the pigment cells. So far, four or five patients have been treated in London and at least six patients in the States, probably more now. The main issue with any of these trials at the beginning is safety. The gene that we're putting in is making a protein that the body has never seen before, so one of the main worries is whether there will be an immune reaction to that

protein? So far it seems that this isn't a major problem at all, so that's a good thing. There doesn't seem to be any other toxic effects, so that's great too, and of the nine patients published so far, in seven of them, and this is a bit of a bonus, there has been evidence that vision has improved.

One of the main aims of gene therapy is to stop these progressive disorders from getting worse. It is nice to see that, in the trials, at least seven out of nine had improved vision, so the sensitivity to light and dark in seven of those patients got better to some degree. I am hoping that, in my working lifetime, this will be applied to other recessive disorders, including Bardet-Biedl Syndrome. It is a photoreceptive disorder, it is recessive, and so it may be the subject of gene therapy in the future. However, these things move slowly and we are unable to predict exactly when gene therapy will be available to people with other retinal dystrophies.

I am now going to talk about retinal implants. Retinal implants have been called the 'bionic eye', as media people try to make them sound more interesting than they are. These implants are arrays of electrodes that are placed in the back of the eye. Careful surgery is done to take out the jelly from the back of the eye, which is the vitreous and just gets in the way, and then a small implant, which is no more than a centimetre and a half in its greatest diameter and contains sixty electrodes, is actually tacked onto the retina. There needs to be two things to go into that implant for it to work. You need to put electricity in and you need to put in digital information. This is achieved very much like your electrical toothbrush. You have your toothbrush without a lead; you put it on the holder and it charges up without there being any connection between the toothbrush and the charger. It does that through two coils that make a magnetic field, which is a very clever way of charging something electrically without a connection. So, there is a coil on the side of the eye and there is a coil on the person's spectacles. A microprocessor receives a signal from a camera on the pair of glasses, and feeds the information to the implant inside the eye and also charges and powers the device.

The aim of this is to try and represent what the camera sees by stimulation of the retina, such that people get some idea of what the world contains. There are two companies that are going for this at the moment and are leading the technology. One is a company called Second Sight, who are based in California, and the other is a company called IMI, Intelligent Medical Implants, that are based in Hamburg in Germany. Both of them are conducting international trials and we are doing this at Moorfields. If anything, Second Sight is more advanced. They've operated on more patients so far. The initial trials are only for patients with no vision. The aim is to start with a person with a very low baseline of vision to try and get them to see something. If the technology improves, it may be available to those folks with a bit of vision left. So far, four patients have been operated on and three have been looked at carefully. The details haven't been published, but it is positive. At least two out of the three find it a much better experience with the glasses on. They can see very basic things, for instance, edges of door and windows, if there's high contrast, lines on the ground. One patient can actually sort different coloured socks, which is fantastic. It's a very basic technology, but it will improve. This therapy looks promising for people with very poor vision, however there is a limit to that. The limit is that the implant is stimulating a whole load of cells on the inner retina called the ganglion cells and the bipolar cells that don't normally react to light, so there is a limit to the degree in which we'll be able to get people to discriminate. You can only get a certain number of electrodes there without causing damage to the retina, due to the amount of electrical energy that has to be supplied, so there are absolute limits; however it does look promising.

Those are the two main things that are happening. There is another trial called a trial of growth factors, which we'll be getting the results of very soon. This is a different type of retinal implant which goes in the eye and contains cells that make a molecule called a growth factor. The particular molecule that's being favoured for this work is something called CNTF (Cilial Neurotrophic Factor) and the aim is to try and delay the process by which cells die in the retina. It is of interest that, in some forms of retinitis pigmentosa, we know for sure that the only cells that are compromised by the single gene defect that patients have are the rod photoreceptors. The cones are fine but they still die anyway. There's a bystander effect that, if a cone cell is sitting next to a dying rod cell, then it suffers too, and so the aim of this sort of approach is to try and keep those cells from dying, and growth factors are one of a set of molecules that might achieve that. This has been tested in animals before and there's a small pilot study going on in the States

of very severely affected patients to see whether or not there's any effect of that approach. That will be interesting to see.

Finally, people always ask me about stem cells because that has been in the news such a lot. I think it has been in the news a bit too much because there's a lot of work still to do, at least in the eye, to get that working. There's a lot of work going on in the laboratory in animals to try and work out ways in which we can replace the cells that have died in the retina and in other organs, but that's going to take a while. In the retina, we would have to replace the pigment cells, as well as the photoreceptors, get the photoreceptors connecting up to the cells that are already there, and to develop all the very specialised proteins that are required for photoreceptors to work. There's some great preliminary work that has been done but that's a long way off, I think, and further than the growth factors, the implants, and gene therapy."

Questions

What is the optimum time, within the natural history of the syndrome, that you should be administering gene therapy?

"In any organism, any target, in order for gene therapy to work, the cells you want the gene delivered to have to be there. If there's complete death of the cells then gene therapy won't work. Very often, in retinitis pigmentosa, the cells don't work to start with and the photoreceptor outer segments may have gone but there may still be the nuclei there. In animals there is a period of time in which the cells aren't working but they're still there anatomically. The reason the RP65 disease was targeted first was because it was peculiar in that respect, in that there are many years in animal models, and in humans too, in which the photoreceptors remain living in the retina but they just don't work. The reason they don't work is they can't regenerate the important molecule that actually changes its shape in the light, called retinal vitamin A. That's why it was targeted first. If it didn't work in that disease, then we would be quite upset by that because it wouldn't work in the more difficult diseases. Gene therapy will only be helpful to folks before the cells have been lost and probably before the vision has been lost. It's a preventative treatment that will only be useful when the cells are still available to receive the gene. That window of opportunity will vary for different disorders."

Should any siblings with the syndrome be automatically tested to see if they have retinitis pigmentosa?

"If there was ever a doubt that a sibling has the disorder, then an ERG can give us that answer. Some people want us to do ERG's very early, but we don't tend to do that because it's not so sensitive at that time, so a person can develop the disease later and we did not detect it with an ERG in a young child. I'm talking before fifteen or sixteen really. Secondly, that data isn't very clean when we perform an ERG in a young child. We can ask very basic questions about why a child may be non-seeing but to detect early signs of a disorder is more difficult. Sometimes that goes wrong and we misinterpret the ERG, which is a bit noisy, and wrongly label a child as having the propensity to get a retinal problem. So we tend to leave it till later, but it is useful to do in siblings if there is doubt they may have the disorder."

How Your Money Helps

Lisa Pettifer
Communications Manager, Jeans for Genes

Lisa began her talk by explaining that, before she started working for Jeans for Genes, she was a journalist. Her job with Jeans for Genes involves communications and PR and she spends her time talking to journalists, newspapers and making fundraising packs. She stressed that those working for Jeans for Genes are not scientists and, apart from the Chief Executive who has a son with a genetic disorder, are not affected families. Lisa explained how fantastic it was to meet everyone and also to learn more about the conditions people live with because, as she said, they 'are not at the coalface'.

"So for those of you that don't know a great deal about Jeans for Genes, we are a national children's charity, although, as you can tell from this event, adults are benefiting from the funding that we offer as well. We originated in 1996 as a national campaign, primarily to raise money for the Chronic Granulomatous Research Trust, which is a condition that leaves children with very little immunity to bacterial and fungal infections. The first Jeans for Genes day raised three quarters of a million pounds, and obviously from that they thought 'Oh, this is quite a good idea.' They brought an additional three charities on board, including Great Ormond Street Children's Hospital charity, and much of the funding that Great Ormond Street receive from us goes into research at the Institute of Child Health.

So, Jeans for Genes Day this year will be our fourteenth and to date we've raised over thirty million pounds for children, families, and research. In 2000, we decided that we wanted to widen the impact of what we can do, so we invited charities like yourselves to come on board and benefit from funding. The first one we worked with was the Cystic Fibrosis Trust, and we've gradually expanded until last year we had fourteen guest charities. Although we had perhaps reduced the size of the grants that we could offer, we could offer funding to a much wider range of charities and impact on many more families than we perhaps would have previously. Certainly, we are very pleased to be helping to fund this event; the children are having a fantastic day at Drayton Manor with some of our funding. I remember the days of Drayton Manor when it was just swings and a zoo, so it has come a long way since then, it is very different now.

Andrew has talked very well about gene therapy, and certainly that had some involvement from Jeans for Genes in its very early days. We helped the very early stages of gene therapy; although that has been largely funded subsequently by a number of other bodies because of the limited amount we raise every year, but funding from us has certainly helped to get that research off the ground. Rhys Evans was the very first little boy to receive gene therapy for an immune deficiency. He had what was known as 'baby in the bubble syndrome', where he had no natural immunity to infection at all and his environment had to be very sterile. Many children with this condition, certainly up until now, were lucky to live until their first birthday. Rhys is now eight-years-old. I spoke to his mum a couple of weeks ago and this little boy in Wales is now enjoying dancing and is doing very well. Because he's growing so fast, he still needs top ups to support his immune system, but on the whole he's doing really, really well, and, since then, another nine children have benefited from gene therapy for that condition, which is fantastic.

So this year, for Jeans for Genes Day, we have a number of guest charities on board again. I'll give you some examples of those charities. We're working this year with an organisation called 'Amy and Friends'. Amy is a seventeen-year-old girl who has Cockayne Syndrome and the organisation is run more or less by her parents. Up until we provided funding, their 'Family Weekend', which, as you know, has great value, was largely funded by her parents, so we're delighted that this year Jeans for Genes can pay for their weekend, to the tune of around ten thousand pounds. The family have done some fantastic work in getting specialists from across the world to converge on Merseyside for that event coming up in a few months time, so that is fantastic.

We are also working with the Primary Ciliary Dyskinesia support group this year, which is a condition that affects the cilia. The children are very vulnerable to chest infections, they need daily physiotherapy, and often children are born with their vital organs, particularly their heart, on the other side of their body. Genetic conditions, as you know, can be very complicated to explain, not only to the children themselves but to grandparents, parents, aunts and uncles. You need time to digest this and you need the information to refer to. For the PCD support group, we are providing funding so that they can update their website. They can produce DVDs so that families can take them home, digest the information, learn about managing their condition, and then, when they go back to their specialists, they know the questions they want to ask. We are also supporting the Scottish Huntingdon's Association. Many children living in families with this condition, the association tell us, can be sole carers for parents at times. Amy, who is fourteen, is the sole carer for her mum who has Huntingdon's disease and, with this condition, they have a 50/50 chance of the condition manifesting itself in them at some time in their life as well. We're helping them to fund a five day summer camp, in which the children can have the chance to be children, which day to day is something they don't often get. They also get the chance to make friends. Usually, this would be two days, but, with funding from us, they've got that opportunity to spend more time together.

Another of our key roles at Jeans for Genes is education. We see having charities like yours on board as very much a part of our education programme. We tend to think of ourselves like Debenhams. So you might be Dorma bed linen and you've got a small shop in a small town, and you get a few people that come past and look in your window, whereas, if Debenhams sells your Dorma bed linen, you get an awful lot more people coming by, they get to know your name, they get to know your product, so we like to think that we're an avenue for charities like yours to have more of a voice. For those long difficult names that perhaps otherwise wouldn't get the attention that they need, we hope that through Jeans for Genes we can help to give you a voice, we can make people more aware of you, both at a clinical level as well as amongst the general public, and certainly in schools we provide free educational materials. This year, we've developed interactive whiteboard activities. We're also producing films with families, so children get to tell their own stories of what it's like living with their conditions, and then classroom discussions are based around those films. They are key stage specific so that helps to not only understand genetics and genetic disorders but to make children more accepting of children that are different. We are all different, but sometimes our differences are more than others. There are more specific needs that children need to be aware of and understanding of, and that is very much a part of what we want to do at Jeans for Genes.

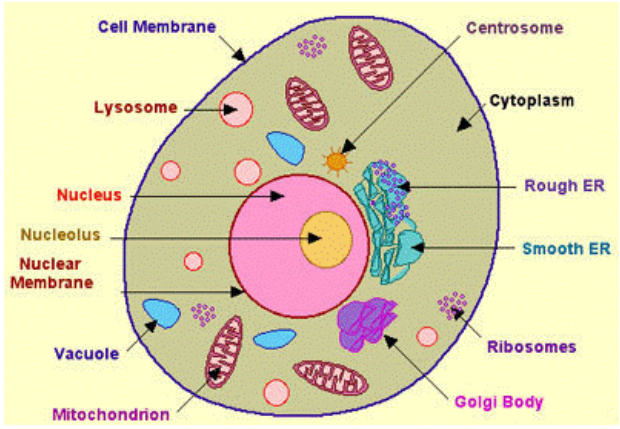
To finish, Jeans for Genes day this year takes place on Friday 2nd October. It's the day when you can organise a Jeans for Genes day at work, at school or you might want to have a coffee morning at home or at the sports club. Invite people to wear their jeans and make a donation. Schools tend to pay a pound, adults two pounds. There's usually a bit of cake selling, wig wearing, or whatever you feel like doing. We are aiming to raise around three million pounds this year; we know it's a difficult year financially for a lot of people, but we hope that two pounds each will still be something that everybody can afford, especially when we can tell stories, as we did last year with some of you as families, to illustrate how much that money is needed."
If you would like to register for a fundraising pack or would like to find out more about the work of Jeans for Genes, please visit their website at www.jeansforgenes.com

Immunity and Cilia: Is there a link?

Professor Gillian Griffiths
FMedSci. Professor of Immunology and Cell Biology
Wellcome Trust Principal Research Fellow, Cambridge Institute for Medical Research

"I am going to try and address the question, 'Is there a link between immunity and cilia?', but first, just to start off, I would like to tell you a little bit about who I am and what I do. The first thing to note is that I am not a clinician. I'm a PhD and I have spent my entire working life in medical research. I did my PhD in the Medical Research Council's lab in Cambridge, and, from there, I went off to Stamford in America, then to Switzerland, UCL in London, Oxford, and now, just recently, back to Cambridge. All of my work has been on medical research and, over the last ten to fifteen years, we have focussed a lot on genetic diseases which are immunodeficiencies rather than ciliopathies. That work has brought us to wonder whether there might be a link between ciliopathies and, potentially, some increased immune problems.

I work now at the Cambridge Institute for Medical Research, which is really aimed at trying to understand genetic diseases in parallel with the underlying cell biology. I am both a Professor of Cell Biology and Immunology and I want to start by explaining to you what those two things are and exactly what it is that we do. Cell biology really means looking into what is happening inside of individual cells. Your body is made up of lots of different types of cells, all of which work together, and do very different things, very effectively, to make your body work.



Let me first describe the rough layout of a cell. First of all, the nucleus is where the genes and DNA are, and that is what codes everything. Surrounding it is the cytoplasm, which is all bounded by an outer membrane that keeps everything in shape. In the cytoplasm are different organelles, and these all do very different and very important things. There are mitochondria, which produce energy in the cell. The golgi stacks are where proteins are made, which are then secreted out of the cell and I am going to focus on two separate compartments of these. Secretory granules store up the protein in these little bags and release them just at the right moment, when it receives the right signal from outside. They move around on long tracks that are known as microtubules or the cytoskeleton. The microtubules, which you could regard as the motorways of the cell, allow these little secretory compartments to move around. Of course, the microtubules have to be tethered, and they are all tethered around an area known as the centrosome, which contains two centrioles and these are involved in cilia formation.

There are lots of different cells in the body and they all look different; some of them have cilia, and others, like the cells of your immune system, don't have cilia, which you might think is rather strange, considering that I'm saying there might be a link between cilia and immunity. If you asked people who work on cilia, they would say that every cell has a primary cilium, except for immune cells. They don't have anything like that. What our research has shown in the last few years, though, is that there may well be a link between cilia and immunity, which is what made me go to Phil Beales when I was last in Great Ormond Street and say 'You know, people with ciliopathies, do they ever get any increased level of infection that might suggest that there's something not working optimally with their immune cells?' I want to explain to you, in terms that I hope you can understand, what I found out and why it might be interesting.

The first and biggest component of the immune system is probably the skin and there are several layers of skin cells which act as a physical barrier to prevent the body from getting infections. The skin not only acts as a physical barrier but it has, within it, some cells of the immune system that can already begin to capture these foreign pathogens as they try to get in, to try and show them to the rest of the immune system, to kick start it, so that the body can fight it off as quickly and as effectively as possible. In the same way, ciliated cells in the trachea physically try and push out any foreign particles that come in via the airways. Within the immune system, if things do get into your body, then there are a whole variety of cells that can very effectively try and get rid of those bacteria and viruses that try and invade and replicate themselves within the body.

You could classify one group of these cells as cells that capture and engulf the infectious agents, or pathogens, and, in this case, neutrophil cells capture bacteria. Neutrophils have lots of secretory granules within them. When they are activated, by seeing something that needs to be captured outside, they actually throw out some of these granules, a bit like a fisherman throwing out his nets, which allows more pathogens to be captured and engulfed by the cell, where they are digested and then shown to other cells in the immune system.

Macrophages are a similar cell type; they can recognise different bacteria and other pathogens and they can also engulf them in a very similar way. Macrophages are often thought of as being the scavengers of the immune system. If there is any debris, they will go and pick it up, and engulf it, and digest it so that you don't have lots of dead bits of cells, that have been destroyed by other immune cells, floating around in your body. All of these cell types, not only pick up and begin to digest the pathogens themselves, but the key to getting everything working right is that they show it to other cells in your immune system that come in with a very specific way of destroying those pathogens very quickly, and the best cells at doing this are dendritic cells. They are what is known as the professional antigen presenting cells. If you like, they are the professional guard that pick up and show everything to the immune system and say 'these are the pathogens you've got to go for,' so dendritic cells can't be missed.
So the macrophage cell has picked up invading bacteria, takes it inside and shows it to a different type of immune cell, known as a B cell or a B lymphocyte. What B cells do, is they make antibodies. Once the B cell has seen the pathogen from the macrophage, or the dendritic cell, or other antigen presenting cells, then it becomes activated and it starts producing antibodies and secreting them from outside of the actual cell, so they can absorb all the bacteria and neutralise the threat. They can be then be picked up by other cell types and destroyed.

The other arm of the immune system that can be activated, is one on which my lab really focuses its research, and these cells are natural killer cells called cytotoxic T lymphocytes. They are killer cells of the immune system and what they do is recognise and destroy those cells in our body that have been infected with viruses. So viruses are different from bacteria because they infect inside the cell and, from there, start producing lots more viruses and secreting those from out of the cell, so that they can infect other cells. The best thing the body can do is to try and get rid of the infected cell, but how does a cell know which one has got a virus in and which one hasn't? It is very clever. The killer cells that we work on have special little receptors sticking out from their surface and these receptors recognise another receptor that is on every single other cell in the body. What this receptor does is it sits out on the surface of all cells and, if it is virally infected, it will contain a little bit of something made by the virus, which means the killer cell will know that this cell has got a virus infection. It's incredibly specific, it's incredibly accurate, and that is really important because you don't want these cells going round killing cells when they are not virally infected.

When a killer cell recognises a cell that is virally infected, the microtubules converge to the point where the killer cell meets the virally infected cell and all of the secretory granules, which contain the proteins that can kill this target, move down in the same direction. Within those granules are special proteins, called perforin, which can punch holes in the membrane of the virally infected cell. The perforin inserts into the membrane of the virally infected cell and binds to another perforin protein and they bind to form a little circle with a donut-shaped core in the middle. With that donut- shaped core, all the other proteins from those granules can enter and can trigger a very rapid form of cell death known as apoptosis.

What my lab has really been interested in is how do you control that? Over the last ten years or so, we have researched how these killer cells work by looking at patients who have had genetic diseases which affect the way in which their killer cells function. There are a number of diseases which are autosomal recessive genetically, and many of the genes that have been defective in these diseases have been identified. In collaboration with the immunologists at Great Ormond Street, we have looked at a number of these diseases because we know their killer cells aren't working, but why? To find out is incredibly simple. All we need is a single blood sample from a patient. We can then separate out the killer cells, which we plate out and grow by giving them something that looks like an infected cell. This encourages them to proliferate, to make more of themselves to mount a good immune response and means that, in our tissue culture dishes, in our incubators, we can suddenly get lots of cells and we can do a lot of experiments.
I will now describe examples of some of the things we've found. In one patient, where they lack a protein called Rab 27A, all of the secretory compartments were there but they were not able to get to the membrane and release their content, so the killer cell didn't work very well and the target wasn't killed. Another example is one where the secretory granules get all the way to the point where they should release their contents but then they get stuck and so, again, can't kill. So what happens when the killer cell can't kill? It chases, and chases, and chases, but the virus infected cell is still there and so there is increased infection in some of these patients. What I was able to do then, having looked at lots of different patients and learnt what I could, I realised that we could then begin to identify what normally happens. How do the microtubules get to the right place? It could be either that there are some tiny slip roads, if you like, that they would come down, or maybe the centrosome does something special.

What we found, when we looked, which was the big surprise, was that the convergence spot, the centrosome or the centriole, which is the point from which cilia are formed, is the same point where the killing has to take place. Just like when a cilia needs to be formed, it is this centriole within the cells that comes to the point where the cilia needs to be formed. In killer cells, they might not form cilia but they are using the same machinery to do something else which is very important, they are putting their centriole at the point where these secretory granules need to come and release their contents to kill the virally infected cell.

This docking of the centrosome or the centriole is actually very, very rare. It really only occurs during cilia formation and in a rather different process called cytokinesis. It was this similarity with cilia formation that made me begin to read all the papers about cilia and to begin to look at the pictures of cilia. When we compared the pictures we were looking at in our killer cell with the pictures that were produced of how cilia, and, in this case, flagella, form, the more we looked at them the more similar they looked. So to me, what it looks like is as though killer cells may have adapted the machinery that your other cells use to make cilia as a way to deliver what they need to deliver in a very direct fashion. So the question arises, are they using the same sort of machinery, and is there a link where, if you've got a problem sometimes with the way the cilia are formed, is there possibly a problem sometimes with the killer cells not working quite as well as they might normally?

That is what took me to Phil Beales to ask 'is there ever an increase in infection'? He said 'It's funny you should ask that. Come along to Northampton.' We rely a lot upon our collaborators, particularly at Great Ormond Street, where the immunologists Adrian Thrasher and Graham Davies are based. I've collaborated with them for a long time, and we're hoping, in collaboration with Phil and with help from some of you, we can begin to look and see whether ciliopathies might have some differences in the way their killer cells work."

Learning Difficulties in Bardet-Biedl Syndrome
What, When, Where, How and Why?

Dr Kate Baker
Academic Clinical Fellow, Developmental Cognitive Neuroscience Unit, UCL Institute of Child Health

"I am a junior doctor, a junior paediatrician, and I'm interested in learning more about the sorts of problems that children with genetic syndromes have, so that I can help more in the future. I'm going to talk about learning difficulties in LMBBS; what, where, when, how, and why? Now, that's a lot of questions, and I don't really have the answers. I do, however, think they are important questions to ask, questions about learning problems, problems with thinking, feeling, acting, remembering, and all those sorts of things and nobody in the medical or scientific world, at the moment, really has the answers. For some of the questions like 'what are the problems?', 'when do the problems happen?', 'how are the problems different for different people with LMBBS?', it is those with LMBBS who have the answers. I want to learn about experiences of LMBBS as a child, as a teenager, as an adult who has the syndrome, or as family members who live alongside individuals with the syndrome, and, even though I don't have the answers to the questions, being a neuroscientist, of sorts, I have access to methods and tools, which will enable me to ask these questions in new ways.

I am also a scientist who works on understanding the brain, so I have the best possible job. I get to try and help look after children a bit when they are not well, and then I get to try and understand a bit about how the brain works and, particularly, how the brain develops and changes, which is the best fun in the world. I get to meet little babies when they are first born. They're the apple of their parents' eye; they feed when they're meant to feed, then they go to sleep; they gurgle, they smile, so all their parents have to do is tickle their toes and stare at them adoringly. By the time the babies are six months old, they are sitting up and looking around the world. A few months later, they're off crawling, exploring, putting everything in their mouths and learning about the world. Then, at about a year old, they're tottering up on their feet, realising that, if they stand up, they can reach more stuff, break more stuff, throw more stuff, and then they are off running, so they can escape from their parents, which is very important when they are that old. By the time they are two or three, they know everything there is to know. They're talking, learning and think they are the centre of the world and it's all great. Then, at five to six, they are skipping off to school, happy as anything, full of the joys of life, delighted to be at school. Then they are pretty much ready to go off into adolescence, becoming a teenager, and it just doesn't get any better than that.

Now we all know life is just not quite like that for any child. It never goes quite like that. Yes, we learn to do a lot of those things, but, for all children, it's a challenge; there are parts of that process that are different, where things can be a bit more of a struggle for the child and their family. For lots of children, the problems might begin before they are born. If a mother is unwell during pregnancy, or around the time of delivery, then that can make things difficult. It is a really dangerous thing, being born; it's not to be recommended at all, lots of problems can happen. If everything went according to plan, I wouldn't have a job, there wouldn't be any special care baby units and I wouldn't have to work nights, which would be great. It's not easy at all in those first few weeks and lots of illnesses can happen in the first year or so. Every time there's a problem with an aspect of physical development or wellbeing, it has a knock on effect on the brain and on development for all children. What is incredible is that everybody has what we call compensation, so children encounter all sorts of challenges through those first weeks, months, and years of life, and, amazingly, they manage to pick themselves up, get back on their feet, more or less, and carry on.

So that is what is supposed to happen in the first ten years or so of life, and we know it's a challenge, but, for individuals with a genetic syndrome, it can be a big challenge, sometimes just for one period of time, sometimes not until later in adolescence, but there are reasons why there

are difficulties and we want to understand that much more. The brain starts off as a tube of cells, and then the top end of the tube expands and thickens, and becomes so big that it folds up on itself in very clever ways that we really don't understand. It's a bit like origami but we really don't know how it works. By the time the baby is born, the grey cells and white matter connections are all ready and waiting to start getting organised and start processing information about the world. Then you might think that it's all finished by the time the baby is born, but it really isn't. More and more, we are learning about how the brain carries on growing, and changing, and developing, at least until about twenty years old and possibly longer. So all the different parts of your brain that need to work together to process information and interact in the world need to be wired up. The outline scaffolding is there, but it's how those connections become really well organised that we think is most important to things like thinking and speaking.

There has got to be some instructions that tell you how to build your brain in the first place and a lot of those instructions come from the genes. The genes that build the molecular machines, and the proteins, go on to build your brain cells and connect them all together and we are really just at the outset of understanding what those genes are and how they work. So you've got all your instructions from your genetics and then you've got the world, because most of your learning comes from things you encounter in the world; the information and the experiences you have, and the mapping together and the matching of the genetic instructions from your inside, and your information and experiences from the outside world are contributing to building and shaping your brain for your whole life.

So, why are we interested in starting to think about these questions in LMBBS? Because, in LMBBS, we know a little bit about the genetics, thanks to the work of Phil and other colleagues, and we know a bit about how the genetic differences in LMBBS change the function of cilia and can contribute to the building and the function of different organs in the body, but what are the cilia doing in the brain? They must be doing something, they've got to be, it just makes sense, because they are present and so important to other parts of the body. However, at this point, we have very little idea of what the cilia are doing in the process of building a brain and helping the brain to change through childhood and adult life.

What we do know a little bit about, are some of the problems with the development and the function of the brain that you have already told Phil and colleagues about over the years. Back in the late 1990's, when Phil first carried out his survey, he asked about a hundred and twenty people in the UK about the kind of problems experienced. The first range of problems that you told us about, were to do with motor development. One of the basic things the brain has to learn to do is to control the movement of the arms and legs and the survey showed that this happens in a delayed way in at least half the individuals with LMBBS. Babies in the UK, on average, will start to walk at about a year old, but there is a range. Some babies walk a bit earlier than that and a lot don't walk until eighteen months and that's fine. In LMBBS, maybe about half of individuals with LMBBS walk even later, so that shows us that some of those initial developments that have to happen in the brain are happening with some difficulty, something is making that process challenging in LMBBS. This might then translate in adulthood into having some difficulty in co-ordinating complex movements that need both hands, or balancing, for example; I think that there's some evidence that some of those aspects of the way the brain has to co-ordinate arm and leg movements carries on being difficult into adulthood.

The next area that you told us about was that lots of aspects of language and learning may be more challenging for at least some individuals with LMBBS. If you think about it, language development is one of the most amazing things that children achieve. From very early on, they start babbling, listening to sounds, copying, gradually understanding which words pair with what objects and, by the time they are two, they've learnt the only two important things they need to say, which is 'I want' and 'No.' Once you've learnt that, you're sorted. Obviously, it gets more complicated than that and you learn lots of words, and sentences, and grammar, which is a pretty amazing process that uses all of the brain. Early speech development, according to the survey, was delayed in at least half of the individuals with LMBBS. Again, it's fine that things take more time, but, sometimes, when things come online a bit later, it gives us an idea that the way the brain is organising itself isn't happening as efficiently. So the fact it takes longer to learn to speak, and longer to build up these stages, just shows us that some aspects of that learning are more

challenging. Once children have learnt to produce the basic speech sounds, that's obviously not the end of learning language. It goes on and on.

Learning to understand complex language, and learning to use language appropriately, that's something we all carry on learning right through into adulthood and beyond, and, possibly, it may be the case that some of those more complex aspects of language learning remain difficult for a lot of individuals with LMBBS. It would be very easy if people just said what they mean, but a lot of the time, people don't say exactly what they mean, and you have to be very good at reading between the lines and thinking about what other people are thinking about, to work out what they want. It's very difficult for everybody, but I wonder if some of those things are a bit more difficult in LMBBS. So that's language and learning.

After Phil did his first survey and found out what the areas of difficulty were, another psychologist at the Institute of Child Health did some puzzles and games tests with twenty teenagers and children, some of whom may be here. The main thing that I think was important from that study was realising how wide a range there is in LMBBS. Some individuals have no difficulties at all with these thinking skills, and memory skills, and understanding skills, and other individuals have a lot of problems. There isn't, on the surface of it, one pattern that fits all, and I think that's really important, not just scientifically, but clinically. We think that what might be happening in LMBBS is that aspects of the brain development are happening maybe inefficiently but in a different way for each individual. Some are affected more severely than others, and, where individuals are affected, it will actually affect their development in different ways, which is kind of complicated.
The last thing I'm going to talk about, which is also to do with the brain, although maybe not traditionally to do with learning difficulties, are other really important aspects of bringing up a child, which is how they feel about things, how they react, how they behave. The survey indicated that there seemed to be problems that were encountered by some, but not all, children with LMBBS. The first thing was liking fixed routines, needing to have their timetable, needing things to be quite the same and predictable. That's not unusual because a lot of children aged two, three, four, five are like that. Some children don't mind what plate their toast comes on and are happy to eat anything, and happy to be looked after by anybody, but a lot of children, regardless of whether they've got any genetic syndrome, like what they know and they like to stick with what they know, because they feel safe with what they know. What might be unusual in LMBBS is if that carries on a lot through primary school and secondary school, so you're not that flexible about trying different things. That might be a bit unusual. It's not necessarily a problem because it just depends on how you feel about it as an individual, and how your family and the people around you feel about it, but it might be a bit unusual. The other thing that was noted in the survey was that, sometimes, some children seemed to have quite unpredictable reactions to things, either some reactions one might call tempers or outbursts, being angry quite easily about things that don't seem to bother other people. Again, lots of children are like that. It all depends how you manage it and how you manage, as you grow older, to modify those reactions.

The other term that is used is 'inhibition of responses'. We all have to make choices and have to decide what we want, and whether we want it right now or if it can wait. Some people, like me, are impatient and are not very good at waiting. If there's something I want, I'm very, very bad at waiting until it's my turn. Again, that can be normal, but maybe that is something we all have to learn. I'm still trying to learn when is the right time to stop and wait, and, quite often with me, I have to try and keep my mouth shut and wait for other people to talk, as I'm not very good at waiting until it's my turn to speak, or I might say something and it might not be the appropriate thing to say at the time. That, possibly, might be what some people with LMBBS are like. I don't know. Again, it's not necessarily a problem.

Something I think is really important to think about is what happens as teenagers. Being a teenager is rubbish. I didn't like it at all. Moody, didn't know whether my friends liked me or not, always thought everyone else was having more fun than me, always thought everyone else was better than me at stuff, which they probably were, and it really wasn't always a happy time. It was an exciting time and a challenging time but it wasn't always a happy time. That's what being a teenager is like – it's rubbish. It gets better once you get a bit older. Now, as I said, feeling like that as a teenager, or even as a young adult, is part of the normal experience of growing up. It's a tough time. For individuals with a genetic syndrome, I think being a teenager is really the toughest time and tougher than it is for others. That's because you start to realise that you're a bit different

to other people. In LMBBS, your vision might be getting worse and that's really, really difficult and challenging. Having met a couple of teenagers with LMBBS, whose vision is moderately impaired, I can see what a traumatic time it is for them and their families, and how they have to re-learn so many of the skills that they've struggled to acquire already. I think that's really tough. I wonder whether, in LMBBS, some of those feelings are more difficult to deal with, feeling unhappy, or worried about being a teenager and growing up, and that is an important thing to look at.

Those are all the things we think we know about, but what do we know about the brain in LMBBS? I hope I'm not speaking out of turn to say we really don't know anything very much at the moment. We know a little bit about mice, which is great, but mice and humans are not quite the same. Mice aren't known for talking, and thinking, and all those sorts of things, so, until we really look at the brain in LMBBS, we're not going to know. So that is what we are going to do, we are going to do something that has never been done before, which is to do some MRI brain scans on young adults and teenagers with LMBBS, to look at how the brain is maybe developing differently. That's not going to answer all those questions but I think it's an important start.

I am going to briefly talk about the sorts of things we can learn about the brain by doing MRI brain scans. An MRI is a big arch-shaped magnet. It doesn't hurt, you don't feel anything when you're inside it, it doesn't use any radiation and it doesn't change anything inside, it's just noisy. So by scanning, using an MRI scan, we can look at the brain in LMBBS, and just find out for the first time whether the brain has been built differently. If those scans look totally normal, then what can we do? Well, then we can use some very clever analysis, where you take brain scans from a whole group of people, maybe ten or twelve people with BBS, and average them all together and make a kind of average BBS brain to compare with an average non-BBS brain, but, again, we may find absolutely nothing at all. So then, using a very special kind of magnetic resonance imaging sequence called 'diffusion weighted imaging' we can, for the first time, look not just at the volume of different structures within the brain, but at the connections. We want to look and see whether there are any patterns in BBS, not just in terms of motor development, but also in pathways that you need for learning language. That may be completely normal as well because that is what happens in science. You set out with questions, you say 'Is this going to be different?' and, usually, the answer is 'No'. It is just the same, so you have to ask another question. The last question we will ask in our MRI scanner is what is called a functional MR question. How is the brain using oxygen differently when it is doing different tasks? We give people in the scanner a word like 'football' and ask them to think of an action word, which may be 'kicking'. Using the scanner, we will take a picture of the brain when the person is not thinking of anything, followed by a picture when the person is thinking about 'kick', and then we can see where the brain is active.

So that is what we are going to do. It sounds like a lot of work, but it means we are going to put this complicated pattern together. How do your genes influence how your brain is built and how it interacts with the world, and what might the cilia be doing to influence that? So, a big puzzle, but all we need is an hour of your time. If you have LMBBS and happen to be between the ages of thirteen and thirty-five, we'll pay for you to come to London for one day, to have a scan, and do some very short puzzles of learning and language, and then you'll be able to contribute to answering these questions. I hope very much that this has been of interest to you, and, secondly, that, by doing this project, we're going to find out some things that will be very interesting and, hopefully, useful, for individuals with LMBBS, and also for other people who have learning disabilities."

If you would like to participate in this study, please contact Kate at:
Dr Kate Baker, Academic Clinical Fellow in Paediatric Neuroscience and Mental Health,
Developmental Cognitive Neuroscience Unit, Institute of Child Health, 30 Guilford Street, London, WC1N 1EH,
or email: k.baker@ich.ucl.ac.uk

Annual General Meeting 2009

The Hilton Hotel, Northampton, Saturday 18th April 2009

Minutes of previous AGM
The Minutes of the AGM on Saturday 26th April 2008, previously circulated, were agreed and signed.

Election of officers
The current officers, Phil Humphreys (Chairman), Terry Crotty (Vice Chairman), Julie Sales (Secretary), Kevin Sales (Treasurer), Chris Humphreys (Conference and National Co-ordinator), Anne Crotty (Fundraising Co-ordinator) and Tonia Hymers (Newsletter Editor) were all eligible for re-election and were elected unopposed.

Election of Committee
The current committee members, Tina Hickey and Julian Thomas, have a further year to serve on the committee. Craig Barrass and Jackie Farrington retire this year, having served over and above their two years, and we thank them for their contribution over this time. Nominations were received for Jackie Farrington, Steve Burge and Allan Clarke. The votes were counted by Robbie Hymers and verified by Terry Begley and Steve and Allan were elected for a period of two years.

Chairman's Report
Phil Humphreys, Chairman, gave his report: "What a difference a year can make. As I stood here last year, I wondered if we'd be able to afford a weekend conference in 2009, such was the state of our bank balance. As you will see from the accounts, January to December 2008, there has been a dramatic improvement in our finances. I'll leave that to our treasurer. Craig Barrass and Jackie Farrington retired from the committee. The committee extend their thanks to Craig and Jackie for their invaluable contribution and wish them well in their future endeavours. I would at this time like to pass on condolences to Craig, Beverley and family, on their recent bereavement.

With regards to fundraising, a huge thank you to everyone who has raised funds, donated, and helped in any way to accumulate over £25,000 in 2008. What an amazing year you've had. Anne Crotty has been more successful in her application for grants in 2008 and the amounts received were as follows: Bellinger Donnay Charitable Trust £1,000, Goldsmiths' Company Charity £2,000. These grants, together with that received from the Coventry Building Society Charitable Foundation, enabled us to have an excellent annual residential weekend and day conference that many of us enjoyed last year. Our heartfelt thanks go to these trusts. The Jeans for Genes Campaign 2008 granted us £4,900 for this year's weekend, and we are pleased to welcome Lisa Pettifer, Communications Manager, and her colleague, Danny Parry, Communications and Events Executive, here today. Unfortunately, two of our projects in 2008/2009 – an awareness day at the House of Lords, to be hosted by Baroness Helena Kennedy, and a charity ball in Cardiff, hosted by Ryan Jones, and attended by the Welsh squad – had to be cancelled through lack of support, but watch this space for another event to be organised in Cardiff in the Autumn of 2009.

On a more successful note, thank you to all those who took part in our other two new ventures, namely the sports raffle and the national coffee morning. This will give us something to build on in the coming years. I would like to thank Ryan Jones not only for his support during the year but for donating much sought after signed memorabilia. Ryan is unable to be with us today, due to match commitments. This exceptional year of fundraising has boosted our funds and taken us out of a somewhat desperate situation, but we cannot rest on our laurels. The Society still needs to raise at least thirty thousand pounds a year, so we constantly need your help. I thank all those who have taken part in the fundraising; without every single one of you, the society could not continue the valuable work that it does.

Thanks to Julie Sales and Lance French who manage our website at no cost to the Society. Lance and Julie are currently working on a redesigned web page, which, once finished, should be more interesting than our current one. At the end of 2008, we had 11,848 unique visits, 19,407 return visits, and a total of 160,255 hits. The USA is still the most popular visitor, followed by the UK. As well as managing the web and the merchandise, (we have t-shirts, polo shirts, rugby shirts, fleeces, hoodies, christmas cards, teddy bears, sports bags, keyrings and so on), Julie also manages the childcare at the conference, and, for this, we thank her. Our database has a steady number of families and professionals. It now stands at 300 families and 181 professionals. We are finalising the update of the LMBBS database, checking the information we hold is accurate and in line with the data protection act. Thank you, too, to Chris Humphries for her work as national coordinator; Chris is the first point of contact for many of our newly diagnosed families, professionals, and many other organisations, by telephone and email.

Conference numbers are slightly down on last year, due to the mix up of dates with the Hilton – their fault, not ours - nevertheless, we have 173 attending this weekend, including carers and children. You'll have recently received your bumper spring newsletter, produced by our newsletter editor Tonia Hymers. I'm sure you will agree that, along with the conference report, they made excellent reading. There is no office. Tonia produces the report from home, juggling family commitments, as we all do on the committee, along with an Open University Honours degree. Copies of the reports are available in audio, CD, print and are available to download on the website. Please contact Tonia on toniahymers@btinternet.com for any other requests. If you have received this year's newsletter, put pen to paper and send Tonia any photographs, snippets of news, fundraising, personal perspectives, or anything you could think would interest others within the Society and you too could have your name in print.

My thanks to Allan Clark for raising awareness in Scotland; Allan has attended the Scottish Parliament Rare Disease Day in March, as well as attending the first 'Sight Village' in Glasgow to promote awareness of the syndrome. Allan has been involved, and still is, in fundraising for the Society.

Thank you, too, to Robbie and Tonia Hymers, Tina Hickey, Jackie Farrington and Craig Barrass, who, on a rota basis, manned the LMBBS stand at Sight Village in Birmingham in 2008. It is an important date in the Society's calendar, enabling us to reach out to many professional organisations and those with a visual impairment. Sight Village, organised by Queen Alexandra College, Birmingham, is a premier European event, showcasing technology, support and services for people who are blind or visually impaired. Exhibitors from throughout the world take part and many thousands of visitors are welcomed over the three-day period. Admission is free. For further information, log onto www.qac.ac.uk.

Our aims and objectives for the coming year are as follows:

- To continue to actively seek sponsors to fund future conferences
- To support Professor Beales in setting up designated LMBBS clinics in Birmingham and London in 2011
- To finalise the update of the LMBBS database, checking the information we hold is accurate and in line with the Data Protection Act
- To build on the success of the LMBBS National Coffee Morning, making it a significant annual event aimed at raising awareness and funds
- To continue with fundraising and support our members in their fundraising activities
- To continue to produce a newsletter and conference report annually

We will strive to achieve our aims outlined above, and we will always work together to ensure the Society continues to go from strength to strength. I will leave our treasurer, Kevin Sales, to give his report on this year's accounts. My thanks to him for his continued tight rein on the spending of the Society. Finally, I would like to thank Professor Beales and all members of the committee for the continued unstinting work and dedication to the Society, and all our speakers for giving up their valuable time to attend our conference. Thank you very much."

Treasurer's Report

Kevin Sales, Treasurer, gave his report: "The accounts have been balanced and audited for 2008 by Michael Bannister of Thompson and Company, who has again agreed to stand next year. Michael

does the accounts free of charge, so we show our appreciation with a few bottles of wine. The two Barclays accounts that we've got are running smoothly with the 'Friends' account increasing every month. During the year, we were successful in obtaining three grants totalling £7,900. Obviously, the grant for Jeans for Genes for £4,900 is showing in the accounts as a restricted fund, as requested by them, and this is to be used for certain events throughout the year, including the conference. As you can visibly see, donations and fundraising throughout 2008 raised over £25,000 – a record year for the society compared with 2007, more than double. This was quite a remarkable achievement, taking into account the current economic climate, so a big thank you goes out to all those people who managed to raise money for the Society in 2008.

I would also like to say a big thank you to Jonny and Sharon Fegan for their support over the year and the people of Newry for the magnificent amount of twelve thousand pounds. I'm pleased to say we finished the financial year with just over £10,000 in 2008, which is a good start for the year to come. However, without your continued support and tireless fundraising efforts we would struggle to continue as a Society, so please keep up the good work. Thank you."

Appointment of Auditor
The Chairman confirmed that Michael Thompson has kindly agreed to continue as Auditor for another year and he was re-appointed.

Any Other Business
The Chairman had received no written notification of any other business but invited those present to raise any questions; in the absence of any such questions, the meeting was closed.



Day to Day Living With Two Young Adults with LMBBS
A Family Perspective

Margaret Begley

"My name is Margaret Begley; I am married to Terry and we have three children, Michelle, 28, Christopher, 27 and Terry, 24, and four grandchildren. Michelle and Terry both have LMBBS. Michelle was born with two extra fingers; they were only skin, so they tied them and they came off. Michelle was born with both feet turned in and was in plaster until she was about two and a half; she had a lot of operations. Michelle didn't like sleeping very much when she was a baby; we'd be lucky if she slept two hours a night, she was always hungry. Except for the night blindness, Michelle hasn't had a lot of problems with LMBBS. She is a care support worker at a local Hospital; she has been there for ten years. Michelle has a daughter called Victoria, who is nearly six. After Michelle, we had Christopher, no problems at all, and next came Terry. Before Terry was born, we were told that he had cysts on both kidneys. When Terry was born, they took him to the special care unit to check him over and he was nearly

two days old before I cuddled him, because I was ill; I had to have a blood transfusion. A student nurse brought Terry to me; she was looking at him and said 'Oh, I didn't know he had six fingers and toes.' I said 'Neither did we.' None of the doctors had checked him over. I cried and then thought better to have too many than not enough.

Terry was the image of Michelle. Terry was five days before we went home. He was always hungry and didn't like sleeping, like his sister. Lucky for us, Christopher enjoyed sleeping. We had to go to Singleton hospital for tests when Terry was six weeks old. The specialist called us into the office and told us that Terry had polycystic kidneys. He said he wouldn't live past three months. We were so upset and couldn't stop crying for days. We were then referred to Cardiff Royal Infirmary Hospital. They did a lot of tests on Terry. He stayed in there for two weeks. It was terrible watching him crying, with all the tests he had done. I just wanted to take him home and keep him safe from everyone.

Then, they referred us to Great Ormond Street Hospital. They did tests on Michelle, Christopher and Terry. They told us Michelle and Terry had Laurence-Moon-Bardet-Biedl Syndrome. We just looked at them. What do those words mean? We didn't know. They told us it affects the eyesight, kidneys, and weight. They were more interested in Terry's extra fingers and toes. Doctors came from everywhere to look and take photos. They asked if they could put the photos in a medical book, so Terry has famous hands and feet.

After two and a half weeks, we went home. Now we had a name for what Michelle and Terry had but still didn't know what to expect. The doctors would ask us about it because they hadn't heard about it. LMBBS had changed our lives. When Terry was eighteen months old, he had his extra digits cut off. He started nursery when he was three. He used to kick and scream because he didn't like going. Terry could only say 'mammy' and 'daddy' until he was about five. He makes up for it now. Terry started infants in a special class; he got on well. Then he went into an ordinary class but had one to one support and speech therapy twice a week. Terry did go through a lot of bullying. He had yoghurts poured over him, he was pushed, called names, made fun of, mostly because of his speech and his weight.

Once, Terry went on a school trip. He fell down a very steep bank into a stream. Luckily, it wasn't very deep. His body was black and blue. We went to the school to see what went on. Even though we informed the school, they didn't realise how bad Terry's eyesight was. Terry missed a lot of schooling. He was always in and out of hospital. Anything going around, Terry would get it. When he was seven, he had his tonsils out and grommets put in his ears, but the grommets damaged his ears and so he had to have another operation to repair it.

When Terry was about nine, his Doctor told us about a group of people who had LMBBS, that meet up. He gave us the phone number. As soon as we got home, we phoned the number. Drina Parker answered. She was really friendly and invited us to the day conference in Coventry. We didn't know what to expect, but at least now we knew we weren't alone. So we attended our first conference – it was great. We were made so welcome and it was good to meet people who knew what we were going through, because they were as well.

Terry was fifteen when he lost his sight altogether. He had his gall bladder removed but he didn't want to part with all the gallstones because he's still got some floating around. Terry never made a lot of friends in school. He played with his brother and sister, and his cousins, but he was much happier playing with his wrestling figures. Me and my husband went through blaming ourselves. I have cried so much in the last twenty-four years – not for me, but for Terry. It has been hard. He has been through so much and is still going through it. Terry loves to talk about his extra fingers and toes. He thought it was great, having more than others. Every year, we look forward to the conference. Terry loves coming to the conference, especially to see Phil, who always gets Terry shouting about Manchester United. No wonder he's got high blood pressure.

Terry has fallen down the stairs a few times, walked into doors, lamp posts. Terry did have cane training from our house to the shops, but Terry never had the confidence to go out by himself, no matter how hard we tried to get him to. When Terry was at school, one of the teachers, Mr Tanner, took Terry to do the Duke of Edinburgh award. He passed the bronze and silver but had left school before he could do gold. We got him in a few places that did it but they never included

Terry. He was always sat in a corner on his own, so Terry never finished it. One year, we came to the conference. Drina said 'We were worried about you', because we were late. It was ten o'clock when we got there. Terry shouted at the top of his voice 'We had to go back home because my mother forgot her purse and the money.' Thank you, Terry.

I can't remember a time when Terry hasn't been in pain. It has been so hard to watch a child suffering and there's nothing you can do except cuddle your child and tell him it will get better, but it hasn't. Terry has been having stents put in his drainage tube from the kidneys. The doctors have been talking about doing an operation, but it is risky. They don't really want to do it because Terry is so young. Terry's weight has always been a big problem since he was a baby, but the last eighteen months, Terry has lost over six stone and still losing it. We're so proud of him. We know how hard it has been for him to give up his favourite foods. If Terry had a life like other people his age, it would have been easier. Terry went to Swansea College for three years and then took a year out to have a rest. Terry now attends Swansea University, doing computer science. The university had a lot of problems, at first, trying to get things right for Terry. In the beginning, I think Terry wanted to give up. He felt they didn't want him there. He was so sad, that his lip used to quiver because he was so upset, but, now things are being sorted out, Terry is a lot happier there. Every night, Terry checks the windows and doors are all locked. He comes home from university in a taxi. He gets out by himself, comes down to the house, and lets himself in. Every night, he gets me and his father a cold drink, tells his father all about the news that is going on in the world. Terry is really loud himself, but, if anyone shouts or there are loud noises, he covers his ears and gets upset. He says it hurts his ears.

Terry has always had a lot of temper tantrums; he still has them now. I always worried about Christopher when the children were growing up, because Michelle and Terry needed a lot of my attention. If I could have done anything different, I would have made Terry less dependent on me. I would do everything for Terry, thinking I was helping him, but I haven't helped him, because I am so worried about what will happen to Terry when I am not here. You've got to let go. I never really did. Terry is a happy young man, so loving and caring. He never complains, with all he's been through. We're so proud of all our children but especially Terry. We all love coming to the conference every year. We learn something new. Thank you everyone, especially Chris, for all your hard work."

Phil Humphreys

"Thank you, Margaret. Some of the words that Margaret has spoken remind me so much of the times that we've had with James, especially with the weight loss and earlier days of tantrums and things like that. Terry is one of the reasons that I enjoy coming here every year.

Finally, I would like to thank you all for coming again to our conference. I hope that it has been invaluable to all of you. Each year, we seem to learn something new, meet new people, and learn of new experiences. As far as I'm concerned, every year, whatever it costs to come, and I don't mean monetary, whatever it costs has been worth it and it is, every year. I hope the new people that have come this year have found it worthwhile. If we can be of help to you over the next twelve months, you know where we are. Just get in touch with us. I hope I see you all again next year. Thanks very much. "

LMBBS Family Conference – Saturday Evening

We returned back from Drayton Manor, which was an absolutely fantastic day, all round. Laurie, who we looked after throughout the day, had great fun on the water ride and her parents said that she had never been on anything like it before. She said that she really enjoyed it.

After having dinner, we went down to the activity rooms. My daughters Melissa and Gemma helped the children make lots of different things at the craft table, like Easter pots, putting sticky foam onto bags, pencil cases, and notebooks, and also sewing, were a few of things they did. Myself and my husband helped between the craft table and the pool table, although I was not too good in helping on the pool table, as I was pretty useless! A bit later on, Gemma and her friend, Ellie, went to help in the karaoke room. They sat in the audience for a little girl while she was singing.

All the children really enjoyed the craft table and couldn't wait to go and show their parents what they had made and the evening went too quickly for them and us. After the crafts and karaoke, it was all back up to the reception area for the quiz. Once again it was great entertainment thanks to the variety of questions supplied by Dennis Clarke. The raffle was well supported with prizes such as a hamper and hotel break to name a few. Together with the tombola, it raised a whopping £655, so a big thank you to all who donated prizes or bought tickets.

All in all we think the parents, children and carers had a fantastic weekend.

Karen Masters
With a little help from Mick, Melissa & Gemma.

The Crèche

I have been asked to write a few words about my favourite topic, "The LMBBS Crèche". I think I can safely say we all had a lovely day. We were a team of four: Myself, Linda, Claire and Denise, with break-time help from my daughter, Tonia. We had five gorgeous little ones to look after and over the 10 years I have been a member of the LMBBS Crèche childcare team, I have been learning more and more about these special little people and how we can all enjoy our day together.

We had a craft table with various activities throughout the day; paints, play-dough and colouring plus other crafts for the older children. The babies had a corner with all the safe, noisy toys! We had a kitchen with lots of pots, pans and food, a pop up shop, tunnels to crawl through and ride on toys. We had DVDs and story-telling during the afternoon and I mustn't forget our walk in the hotel grounds, meeting the baby ducks!!!

One of our highlights was the assault course, constructed by Claire; round the chair, through the tunnel, on the ride-along and so on. I'm sure everyone must have heard the laughter and squeals from all of us. When the parents came to collect their little ones, they were given lots of paintings to decorate the walls at home! We had another happy day to remember and ideas to make next year even better.

Sandra Dale


Feedback

“Thank you very much for such a warm welcome on Friday night and then again on Saturday. Everyone we met was so willing to talk and share their own experiences of Living with LMBBS.”

“We both gained a lot from the weekend although mixed emotions I guess, if we are completely honest, as we saw a lot of the reality of living with BBS too.”

“The conference was a wonderful opportunity for me to meet families, and I have already had a number of completed questionnaires returned to me in the post from LMBBS families who picked them up at the conference. Thank you for giving me the chance to attend; it will be a great help to the research.”

“Many thanks to you all, you were so helpful and obviously do such a wonderful job with the conference.”

“The children had a great time and were looked after brilliantly, once again, by the excellent childcare team – you are all stars.”

“I Just wanted to thank you for organising such a terrific conference once again, it was the best conference yet. Everything seemed to go very smoothly from what I could see, the food was best ever, the workshops were informative and well attended and the speakers were inspiring.”

“I felt the support from the hotel was the best ever and we were extremely well looked after on the Sunday after everyone else had gone.”

“I can't begin to tell you how much we enjoyed the conference and how much it inspired us. For me to meet people with the condition and to listen to how others have coped was very beneficial. For my mum, it felt as though she had done her best and a weight had been lifted from her shoulders and that we were not alone.”
“It was an absolute pleasure and priviledge to attend the meeting on Saturday, I wouldn't have missed it for the world! Meeting the members of the society was inspirational, and I am so glad to be working with you on this project.”

“It was a pleasure to take part; I really enjoyed the day. In short, and you already know this, the annual conference does infinitely more for the welfare of the patients and families with BBS than the medical profession can ever do. Also, it stimulates more research into the disorder, which will always move things in the right direction.”

It was reported last year that the Conference Report was funded with the support of the Coventry Building Society, we would like to point out that they actually provided funding towards the Conference itself, not just the report. Our apologies for this error.

We hope you have enjoyed this conference report, don't forget, all of the contact details can be found at the beginning.