LMBBS Conference Report 2008

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Editorial

Welcome to the LMBBS Conference Report for 2008! Attending the Conference year after year, you could be forgiven for wondering if perhaps there was anything new to learn, but every year Conference Organiser, Chris Humphreys, excels herself, putting together an impressive line-up of speakers. The highlight, for me, was listening to Professor Nico Katsanis. He answered so many questions about the more obscure aspects of the syndrome and dealt with complex issues in an easy to understand and entertaining way. Throughout the weekend there was much to see and experience, Trevor Frounks and James Humphries demonstrated their Aikido skills, Slimming World and Weight Watchers provided workshops, Ray Perry offered benefits workshops and private

discussion, Graham Longly and Steve Burge answered questions on living with LMBBS and there was a display of visual aids. The highlight was definitely the 'X-Factor' on the Saturday evening, organised and hosted by Julie Sales. Four volunteers took on the roles of the X-Factor judges and yes, we had our very own Mr Nasty! The contestants were brilliant and showed great courage and talent. My vote went to Alex and Harrison Clarke for their brilliant air guitar duet!

As a family we all really look forward to the Weekend Family Conference. The hotel is fabulous, the staff very helpful and friendly and the food this year was gorgeous. The boys always have a great time and we all relax knowing that for once we are no different to the other families. The knowledge gained from the weekend is taken home and spread amongst family and friends, which means everyone who knows our son, Dan, has a deeper understanding. Of course, the Conference doesn't just benefit those who attend, the Professors and Doctors who go to the Conference obtain vital information (not to mention nasal swabs, hearing tests etc) which they take back to their labs for further research, which ultimately impacts on everyone with LMBBS and their families. The Conference is a vital and invaluable source of support and information and must continue to thrive, so if you are impressed with what you read and would like to make a contribution, please follow the links on the LMBBS website, or contact Anne Crotty to make a donation.

If you have any comments regarding this Report, or have any stories, hints, tips or articles of interest, please, please contact me, your Winter LMBBS Newsletter needs you! I look forward to hearing from you soon.

Tonia

Update on research and study of LMBBS
Professor Philip Beales, Consultant Clinical Geneticist, Guys Hospital and Institute of Child Health, Gt. Ormond St. Hospital

Professor Beales welcomed a record number of delegates to the LMBBS family conference. He introduced the line-up of speakers, who had travelled from all corners of the globe to attend, setting a new record in terms of the number of miles travelled. Professor Beales began by talking about how the profile of the condition has been raised over the past few years.

"Jim Lupski and Richard Lewis found the location of the first gene back in 1994, but it wasn't until nearly a decade later that the first gene was identified. In 2003, the importance of cilia was discovered and, since then, the number of papers published has increased hugely, which is really good news for those with LMBBS and their families and good news for research in general.

There are a number of notable scientific advances that have occurred over the last year. Several more genes have been identified and it seems there may be problems with sensing temperature or stimulus of the finger tips. It has been shown that the BBS or LMBBS proteins actually work together, which explains the unusual genetics talked about over the years. It also helps to explain a little bit more about the way in which the syndrome actually arises and how the margins between LMBBS and

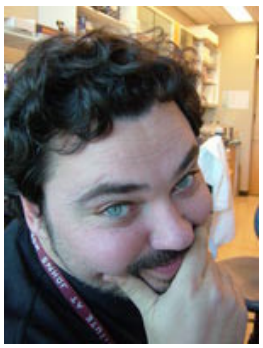
a lot of other conditions are now beginning to blur. Finally, I want to tell you about a study that has been done during the last three or four years by Peter Hammond.

With the help of those attending an LMBBS Conference, Peter was able to create an 'average' face for LMBBS. This has all come about because many of you have said that you are able to spot someone with the syndrome from a hundred paces. The data we have actually proves this is the case. The faces of about two hundred people *without* the syndrome had a three-dimensional face image taken, which has been merged together to form what we call the typical average face (male and female) of the British population. Peter was able to morph the image from the general population into the faces of those with the syndrome. The most visible differences, as the face morphs from 'typical average' to 'LMBBS average', are a flattening of the face and a distinct change in the nose. In fact, what was quite amazing, was that, if you were to take an image of the nose of someone with LMBBS and put it into Peter's computer database, where he has some three thousand images from fifty different syndromes, he can predict the presence of LMBBS, with ninety-one per cent certainty, which is pretty impressive. These facial differences have also been shown in LMBBS mice.

With humans, it is impossible to do a lot of the studies that we would like to do in the lab. These studies can be done using mice, however it would take a long time and a lot of money, so instead we use another favourite model of the geneticist and that is the zebra fish. We are able to alter or manipulate the genes in zebra fish, including LMBBS genes, and have a look at what happens with the bones in the head. In the manipulated fish, the jaw and a lot of the gill structure were missing and the fins were tiny. What we now believe is that there may be a number of cells very early on, when the embryo is developing inside the egg, or inside the womb, that have to move forward from the back of the developing brain, into the face. We know that the bones that develop in the face of a bird, a fish, a man, or a mouse, have exactly the same sort of trajectory and path, and use exactly the same genes and signals. It is possible that Cilia are involved in the movement of cells to the face, and this relationship needs investigating.

Finally, I would like to address something that many of you shared with me last year during a workshop. One of the parents asked 'Why does my son get so many chest infections?' Then another six hands went up saying 'It's the same thing for us as well.' We've talked over the last two or three years about the discovery that, at the cell level at least, the cilia seem to be involved in the syndrome. The cilia that we were interested in were the type that didn't move and we didn't think that the beating cilia, like the ones that line our lungs, were involved in LMBBS. However, after the workshop last year, I began to think that there may be some problems with those cilia and Heymut Omran will be talking about this later on."

Professor Beales finished his talk and introduced the next speaker, Professor Nico Katsanis.



'New genes, new pathways for LMBBS'
Nico Katsanis Ph.D. Associate Professor, Institute of Genetic Medicine, Depts of Ophthalmic Molecular Biology and Genetics, John Hopkins University School of Medicine, Baltimore

Professor Nicholas Katsanis welcomed everybody and said how pleased he was to be back, his last visit being four years ago. He added how energised he felt to see some new faces, as well as more familiar ones, and stressed that Societies like the LMBBS are 'worth their weight in gold', especially for families going through diagnosis.

He began, "What are we all about? When I start thinking about why we are doing this and what the goals are, I really break it down to four increasingly optimistic goals, but I think we are on our way to achieving most of these. We really need to have what I call a molecular prognosis of the disorder. I think it is vitally important that we are able to provide accurate, definitive and inexpensive pre-natal and post-natal diagnostics for BBS. We need to have a better understanding of the clinical prognosis and management of the disorder and we really need to understand the tremendous variability that we see in patients."

“It seems to me, that a major challenge we face, is being able to predict what is going to happen in the future, in the next five and ten years, and start preparing the family and also appropriate medical intervention, whenever possible. I think we have been largely unsuccessful at this until very recently; however, now that we are beginning to understand what the molecular base of the disorder is and how the different mutations of different genes we have been talking about over the years are implicated in this, we are beginning to see that we will be able to offer a more personalised diagnosis and a more personalised treatment. But let’s not kids ourselves; the bottom line and the end game is to cure the thing, but, until we really understand the cilia defect, on an organ by organ basis, we will not be able to do this.”

“Also, we need to start thinking about selective intervention. It is my view that there is not going to be one magic bullet that is going to get rid of all the ailments that are associated with BBS. It seems to me that a more rational approach is one where we will be able to attack the deterioration of vision, kidney problems, weight problems and so on, separately. I think it would be a mistake to try to approach a very complex problem in a very simplistic way. In order to achieve this, we really have to understand what is going on at the level of each individual tissue, because obviously the liver is very different from the kidney, in terms of biology and biochemistry.”

“So how do we achieve these goals? The first path is to try to get the genes. If you get the genes, you get the proteins; if you have the proteins, you have the tools to study what is going on. The genes are coming thick and fast now; at this moment we are cloning genes at the rate of about two to three per year. Our only limitations are technology; we are no longer limited by concept, the concept is right. Also, we really want to understand the relationship between mutations in the different genes and what aspects of LMBBS each individual will carry. I don’t need to explain how diverse the presentation is. It seems now we are making some significant progress in this arena because we are now beginning to understand how there is this interaction between the different genes that contribute to the disorder and it is a matter of how many mutations and what type of mutations, that dictate which aspect of the syndrome will happen. Of course, we want to understand the normal function of the genes as well, because we need to understand how to correct them. Finally, we need to develop therapeutic targets. I think that my lab and Phil’s lab and our other colleagues around the world, are working very hard at this and we have made remarkable progress. I’m an eternal optimist, but I think finally my optimism can be found in some realism.”

Professor Katsanis produced a graph which showed the number of BBS genes found to date. This was, he said, already out of date as they were close to finding some more. He continued, “We’re getting very close to getting all of them. I’m not sure we will have all of them, but at least we will have greater than ninety percent. We expect there to be about thirty or forty genes, but it doesn’t really matter how many genes there are; what really matters is what they do and being able to offer diagnostic testing to individuals. What is the proportion of people that are able to unambiguously say they have a mutation in gene A, or gene B, or gene C? These numbers are going up, but we are currently at around the seventy percent range.”

“I want to remind you that, until 2001, we viewed this as a single gene disorder. You have loss of function on gene x, you’re Bardet Biedl 1, you’ll develop Bardet Biedl syndrome. Now, our understanding has changed profoundly because we now know it usually takes the co-operation of two or more genes, or mutations in two or more genes, to actually develop the disease and also determine what is going to be the clinical spectrum of the disease. We thought initially, until 2003, that the second gene was necessary to give rise to BBS. Now we know that it can modify the severity of the disorder. I think this is one thing that is very, very important, because this is one area of research that gives us the opportunity to look at the individual, as opposed to looking at BBS as a broad umbrella, and to start making predictions about what aspects of the disorder are going to come up.”

Professor Katsanis went on to talk about cilia; he said, “through a large number of studies, we now understand that most, if not all, of the problems associated with a clinical presentation of BBS are actually attributable to cilia. What we are beginning to understand, and this is a major revolution in the field, not just in BBS but in general, is that these organelles are extremely important in all major developmental decisions of the embryo, because they seem to contain the machinery that enables the cell to communicate with its outside environment. When cells are not able to communicate with

the outside environment in an efficient and orderly fashion, tissue architecture becomes significantly problematic."

Professor Katsanis showed a picture of the eye in cross-section and explained how light enters and hits the back of the eye and is then translated to an electrical impulse, which the brain translates into a picture. The outside piece of the photoreceptor (the light sensing cell), is in fact a modified cilium. He explained, "initially, people used to say there was a connecting cilium in the middle of the photoreceptor, but now the prevailing view is that the entire light sensing machinery in the back of your eye, is nothing other than a modified cilium. Now we can begin to understand how, if you have a cilia defect, you are going to have progressive loss of vision."

Professor Katsanis continued by talking about a study that delegates participated in during a previous conference, investigating the sense of smell.

"It turns out that the most heavily ciliated organ in your body is your nose. The primary cilia in your nose are required to sense every single odorant and every single chemical. Because of this, some time ago, we got a group of you to take part in a test using scratch and sniff cards. What we understand now is that about half of you are unable to smell efficiently."

Professor Katsanis showed the delegates a slide of BBS mice with a depleted layer of nasal cilia. He explained how the cilia transport the key molecules required for smell and, if the cilia layer is depleted, the sense of smell is affected. He then went on to talk about how hearing may also be affected, although there is an element of confusion, as some patients say they cannot hear very well, yet some parents say their children can hear too well. Professor Katsanis explained that there are bundles of cilia in the inner ear that are required for sound. If the organisation of the bundles of cilia is not quite accurate, then the sensing of the sound waves will not happen. When BBS proteins are missing, the organisation and orientation of these bundles, with respect to each other, becomes highly defective. This will cause a number of hearing defects. Delegates were shown pictures of affected mice with defective cilia in the ear.

Professor Katsanis continued, "finally, I want to talk very briefly about cilia in the kidneys. We all know about the challenges with renal disease, both in LMBBS and also in other allied syndromes. We understand that there are cilia on the surface of the renal tubules that can sense salts and pressure, as well as other things, and they seem to be critical in the development of the function of the kidneys. Once again, we can begin to think about how defects in these structures of the kidneys might correlate to some of the kidney problems that patients have. This understanding is the first step; without understanding we have nothing."

"One thing I would like to impress upon you today, is that, as we understand more and more, we can begin to address new questions and begin to appreciate the complexity of the syndrome in a way we were unable to do so before. Let's start thinking about the nervous system. Nerve cells transport proteins from the centre to the tip, in a way that is very similar to the way cilia operate. We also know that nerve cells themselves have primary cilia. What we do not know is what primary cilia are doing on nerve cells; however, we are beginning to get some idea. This is going to be very important. We can start thinking about fingers and toes, which is important from a developmental standpoint because, if we can start understanding how cilia are required in sensing the position of the digits while they form, we might understand how all the defects in these structures might lead to polydactyly. We now know that the nerves that populate the skin mediate the communication of the individual with the outside world. Is it hot or cold? Is there pressure? Is there vibration? It turns out that these nerves, as well as the cells that cover your skin, both of them have primary cilia. Defects in these are giving rise to defects in sensing the environment."

"What's next? What are we up to? We are now in a position to identify, essentially, all the genes required for the function of cilia. I'm not going to sit here and tell you that we'll get every single one of them but I think we'll achieve better than ninety percent. These are not the genes for BBS, these are the genes required for the function of cilia. By definition, what that means is we will have all the BBS genes and most of the modifiers. In that collection we'll have, essentially, all the genes that cause BBS and most of the genes in which mutations will serve to modify the clinical presentation of the disorder. Who is going to get renal cystic disease? Who is not? How fast is a retinal degeneration going to progress? When do you need intervention A, B, C, D, and so on?"

“We have created a resource called the cilia protein database, which is nothing more than a collection of data that we believe describes, very accurately, the entire molecular content of primary cilia. This comprehensive resource has been converted to a searchable website that can be used freely by the entire community and we are getting at least five thousand unique hits every month. So how can we use this type of resource to investigate all the cilia genes for BBS? Can we do that? Not quite. It’s not because we don’t know how, just because it’s too expensive, the technology needs to become cheaper. It’s no longer an intractable problem. This is the key. This is what I call the VCR principle. The first betamax video recorder cost an arm and a leg; now you can pick them up for fifty quid, if you can find them. The same principle applies to this. To sequence an entire human, circa 2000, cost a huge sum of money – millions and millions of pounds. A company in California recently sequenced a human for sixty thousand dollars, which is about thirty thousand pounds. That’s two orders of magnitude cheaper, in the space of just five or six years. So what are we doing? We are beginning to set up a way to investigate every single gene involved in ciliary function and try to understand its potential involvement in cilia disease. It used to be that we would query one gene at a time, which was very tedious and very expensive. We are now in a position to start looking at gene sets in sets of two dozen and it is because of this that the new genes for BBS are coming thick and fast. We are only limited by how many sleepless nights the people in the lab are willing to invest, how fast we can run our machines and how much money we have to run them. This is no longer a conceptual problem; it’s not even a technological problem, because there is a technological solution; it’s just too big and too bulky. Make no mistake, this will happen and it will happen in the next twelve to twenty-four months. We’re not looking at the distant future anymore. In the past year, we have cloned two more BBS genes, BBS 13 and 14 and we have cloned one more modifier. Through work we have been doing with Phil (Beales) and other colleagues there are at least four or five modifiers in the pipeline.”

Professor Katsanis explained how they have discovered that genes which cause BBS can also contribute to other disorders. Clinically, these disorders are vastly different; however the molecular basis is very much the same. This is important because it moves the research out of the realm of rare, obscure disease, which has huge implications with regards to interest and funding. Professor Katsanis explained, “the possibility that we could actually attack the lot in one fell swoop is something that is massively exciting and I hope it pans out that way. We’ll see how it goes.”

Professor Katsanis moved on to talk about the sense of touch and how those with BBS seem to have a high tolerance to pain. He said, “we have been hearing about BBS kids with a burst appendix, or with a twisted ankle, who were not complaining about it very much. The question I asked was whether there is an issue with the ability of the neurons that innervate the skin to sense stimuli like heat, touch, and vibration. We know that the neurons in the spine are ciliated, so it could be that in BBS we actually have a defect in these cilia.”

Professor Katsanis described different experiments, using BBS mice, the results of which suggested that they have a higher tolerance to external stimuli than non-BBS mice. This also means that amplified stimulus is required to obtain the same reaction as would be seen in non-BBS mice. He explained, “For those of us who always used to think that these types of problems were because of issues of brain development or brain function, we have unequivocally shown this is not the case. This has significant ramifications, because we are now beginning to believe that some of the behavioural challenges associated with some of the symptoms have nothing to do with central brain function. They have to do with a difficulty in communicating with the environment because, if you cannot sense, accurately, environmental cues on a day to day basis, then behaviour will be modified. We are beginning to see some of these defects in some very serious conditions such as profound autism.” Professor Katsanis showed the delegates some data generated from a study by Professor Phil Beales. Among the various things tested were sense of touch and pain and it was found that some sensory modalities are defective in BBS patients.

Professor Katsanis continued, “I want to tell you a couple of things, just to close, about what is around the corner. Firstly, BBS and the immune system, this is something we really have not explored at all. There is a very bright colleague in my lab, who decided to start growing some cells from the bone marrow, from the spleen and from the thymus. These are three sites of major production of cells, critical to fighting infections and it turns out that most of them have cilia. If they have cilia, what do ciliary defects do to the immune system? Some preliminary data in one mouse model with BBS suggests there are some subtle but significant defects in the maturation of specific sub-sets of

immune cells, which might have profound ramifications to the way in which BBS patients can combat infection. We really need to understand this. The second thing is function of the skeletal muscle. Muscle tone, is it good? Is it bad? We don't really have good data, so we need to look at this." Professor Katsanis referred to data from lab work with mice which showed that muscle damage takes much longer to repair and recovery from injury is much slower. There is also some evidence that there might be issues with the speed and quality of wound healing.

Finally, Professor Katsanis said that they were now at a stage where they could ask the question, 'Can we improve the ciliary pathways?' The ultimate goal, he explained, was to screen approximately 150,000 chemical compounds, because using known drugs cuts down the time involved, before embarking on clinical trials. However it would still be a long process, improving the BBS pathway in cells, fish, mice, and then, finally, in people.

What is the role of respiratory cilia to clear our airways?
*Professor Heymut Omran***,** *Professor of Paediatrics, Vice Head of the Department for Paediatric Neurology at the University Hospital of Freiburg.*

Professor Omran began by thanking Chris for inviting him to speak and said how happy he was to be there. He said that he would be talking about the "moving world of cilia" and produced many slides and video clips to illustrate his talk.

Professor Omran said that most cells have cilia – non-motile cilia. However, motile – or moving – cilia can be found in the lining of the respiratory tract, the fallopian tubes and the ventricles of the brain. Sperm are also moving cilia and there are also cells with one cilium in the developing embryo which can move. Professor Omran showed highly-magnified cilia and pointed out the 'motors' that made the cilia move.

Professor Omran then talked about a disease called Primary Ciliary Dyskenesia (PCD). He described PCD as a rare, recessively-inherited disease in which the motor proteins in the cilia are defective and do not move properly. Patients have respiratory tract infections in the upper and/ or lower airways. Half of those affected have Situs Inversus, where the heart and stomach are on the opposite side of the body and there are also other problems such as male infertility. There are other rare disease manifestations like Hydrocephalus and Retinitis Pigmentosa. In patients with this disease, the motor proteins are missing and the result is that they have immotile cilia. Professor Omran said, "We found, many years ago, a gene that is responsible for most defects in Primary Ciliary Dyskenesia, which is a large motor protein gene" (*DNAH5*). He showed a picture of a cilium in which the motor was absent and pointed out that cilia like these would be completely immotile which would explain why patients with this disease cannot clear their airways properly.

Professor Omran described some of the problems experienced by people with PCD such as bronchitis and pneumonia. As they get older, usually in their twenties, thirties or forties, they develop bronchiectasis, a destructive lung disease. He showed CT images of lungs, parts of which were completely destroyed; these parts have to be removed sometimes to avoid repeated infections. He said that chest physicians sometimes miss the signs as X-rays do not always show the true extent of the disease and the severity of the patient's cough is underestimated. Professor Omran said that sinusitis is also very common in patients with PCD and that this is another aspect that is sometimes underestimated. He said, "Another fairly specific thing in Primary Dyskenesia is that, after birth, the children do not go immediately home with the family but stay a little bit longer because the respiratory system needs time to adjust." He added that about fifty per cent of patients with PCD are affected in this way.

Professor Omran asked those present if they had any comments to make about similar respiratory problems in BBS. Several members described symptoms in their children such as chest problems e.g. cough, infection, bronchitis and pneumonia, chronic runny nose, ear infection, use of grommets, and removal of tonsils and adenoids. Professor Omran said that he would like to investigate the problems mentioned by taking some nasal brushing samples later on.

Professor Omran then addressed the problem of reduced male fertility. Using video clips, he compared normal, active sperm with those of many patients with PCD who were experiencing reduced male fertility. The sperm tails of these patients had no motor proteins, causing sperm immotility. He asked whether something similar is observed in Bardet Biedl Syndrome and offered to discuss it privately with anyone who was interested.

Then Professor Omran spoke in more detail about Situs Inversus. He compared two girls, one of whose heart and stomach were normally situated on the left side of the body with the liver on the right; the other's heart was on the right with the liver on the left. He described this more as a variant than a medical condition, which is not normally a problem unless the person experiences a medical situation such as appendicitis! He said, "Even in modern times, people tend to overlook and not to trust their ears when they listen to chests. Sometimes it can be a problem." Professor Omran showed pictures of an early embryonic node, with nodal cilia that could move. These embryos move in a clockwise direction, causing a flow from right to left and it is this flow that determines the left/right asymmetry. If there is no flow, randomisation of left and right occurs.

Professor Omran went on to talk about a family in which mutations were identified in a gene called OFD1, which is found at the base of the cilium. These patients had cognitive impairment, polydactily and most had obesity. They also suffered from severe respiratory tract infections which caused most of the males to die. Their cilia were not immotile but had a motility defect, which meant that their cilia were not moving properly. He also spoke about another family whose males were affected by blindness due to RPGR mutations, most of whom had severe problems of the respiratory tract. Professor Omran said that there is a strong suspicion that the protein involved in the photoreceptor cilium is also involved in the respiratory cilium and that they play similar roles. " We believe that similar things happen in patients with Bardet Biedl Syndrome."

Professor Omran proceeded to talk about a disease called Nephronophthisis in which patients' kidneys shrink and develop cysts, which is similar to kidney problems experienced in Bardet Biedl Syndrome. He said that the genes involved in this disease very often cause Retinitis Pigmentosa and that the protein is also located in the base of the cilium. He said, "When you look more closely at this network of genes responsible for nephronophthisis, you see that all these proteins interact and… it's very likely that these proteins all have a role in the common pathway."

In closing, Professor Omran said that a diagnosis of nephronophthisis (NPHP1, most common type)can be made by just analysing respiratory cells, taken by nasal brushing, avoiding unnecessary renal biopsies. "....so this simple test might help to speed up with novel diagnostic strategies." He concluded by describing how the 'nasal brushing test' was carried out and invited those present to participate later on.

Ken Ridley and his best friend Jake

Ken has Retinitis Pigmentosa and has been registered as blind for several years. He attended the conference with his wife, Jean, to give a talk about life with his best friend, 'Jake', his Guide Dog. Unfortunately we did not have the opportunity of hearing Ken speak during the conference due to time constraints; however, delegates had the opportunity of talking to Ken on Friday evening and Saturday afternoon and were able to take away a wealth of information and leaflets about the services provided by Guide Dogs for the Blind. Our warmest thanks go to Ken, Jean and Jake for attending and we hope they will visit us again in the future.

Synopsis of Bardet-Biedl Society, France
Francis Lestel, Vice President Bardet-Biedl Society, France

Professor Beales introduced Francis Lestel to the delegates as the President of the equivalent LMBBS Society in France. Francis would talk about their progress and also about some unification they have been able to make across various borders, which is something that our Society could perhaps learn about and implement in the future.

Francis thanked Professor Beales for his introduction and upgrade to President of LMBBS in France, but he is in fact Vice President. Bertrand Lasbleis, who himself has the syndrome, is their President, He went on to say that BBS has no frontier and is in all countries. Francis has a 15 year old daughter, who was only diagnosed three years ago by an external nephrologist and ophthalmologist, as the medical consultants in his area were not aware of the syndrome.

Whilst visiting Cannes, Francis met some friends, one of whom is an ophthalmologist, and one who is a nephrologist. He talked to them about his daughter's Retinitis Pigmentosa and kidney problems and, after further discussion, it emerged that a similar case had been seen where two brothers, who had poor vision, kidney problems and polydactily, like his daughter, had been diagnosed with Moon Syndrome. With that information, Francis 'Googled' Polydactyly, Retinitis Pigmentosa and Kidney, and up came Laurence-Moon-Bardet-Biedl Syndrome. Google gave Francis a diagnosis where Doctors had failed. "Perhaps Doctors do not have 'Google'?" said Francis. When he was 99% sure of the syndrome, Francis went to Strasbourg to meet Professor Hélène Dollfus, who spoke at our conference four years ago. Hélène made the DNA analysis and, one year later, found the BBS gene. The reason for the delay in diagnosis was that, although Professor Dollfus was aware of one of the mutations, the second one was new to her. Francis said that, although France has many doctors who specialise in the syndrome, to his knowledge, only two have actually conducted studies, Professor Hélène Dollfus for adults and, in Paris, Professor Alain Verloes for 16 years and under.

Francis talked about their BBS Association, which was founded in 2003 and, as of 2007, had 30 families registered on their database. The venue of their meetings is changed annually; in 2007 they met in Cannes and 2008 will see them meet in Strasbourg. Francis gave an open invitation to anyone who wished to attend, with an assurance of a warm welcome. Francis went on to speak about a Rare Diseases Forum organised in France in 2007, with 6000 rare diseases registered. France has referenced one hundred and seventy four associations of rare diseases and, as a result, acquired a wealth of information about BBS Associations. Francis talked about a parent led Multinational Discussion Group (spoken language English), of which he is a member, giving an opportunity to exchange ideas on the day to day coping with the syndrome, especially behaviour.

Francis ended his presentation by telling the delegates of an American database, www.genetest.com, where you can find an excellent description of LMBBS by Professor Philip Beales.

Annual General Meeting
The Hilton Hotel, Northampton
Saturday 26th April 2008

Minutes of previous AGM
The Minutes of the AGM on Saturday 21st April 2007, previously circulated, were agreed and signed.

Election of officers
The current officers, Phil Humphreys (Chairman), Terry Crotty (Vice Chairman), Julie Sales (Secretary) and Kevin Sales (Treasurer), were all eligible for re-election and, in the absence of any further nominations, were elected unopposed.

Election of Committee
The current committee members, Craig Barrass, Anne Crotty, Jackie Farrington, Tina Hickey, Chris Humphreys, Tonia Hymers and Julian Thomas were all eligible and willing to stand for re-election and, in the absence of further nominations, were all elected unopposed.

Chairman's Report
On behalf of the society, I would like to extend sincere condolences to Andrew Merchant and family on the sad loss of his wife, Elaine, who passed away on 8th January this year after a long illness. Those of you who knew Elaine will know what a wonderful caring wife, mother and friend she was, who thought of only others before herself.

As you're aware, 2008 sees LMBBS celebrate its 21st anniversary and we are pleased to welcome Drina and Michael Parker here today.

I am pleased to announce that Ryan Jones, who captained the Welsh team to triple crown and six nations grand slam success, has accepted our invitation to become patron of the society. I am sure Ryan is going to be an active patron and will bring awareness of the society to a wider circle. Due to short notice, Ryan was unable to be with us today; however the date for next year's conference is already in his diary, matches permitting.

Congratulations are in order to Helen May-Simera for successfully gaining her Ph.D. Helen will be leaving Professor Beales' team in the next few days to take up a post in America but has promised to visit us and update us on her research. We wish Helen every success and look forward to future visits.

With regard to fundraising, our greatest thanks must go to our loyal band of supporters, members and friends, for their generosity and hard work throughout 2007. We thank Anne Crotty, who has worked tirelessly, trying to obtain grants this year. The Coventry Building Society Charitable Trust donated two thousand pounds, which is very much appreciated. Although further grants have been awarded since the New Year, 2007 was a particularly difficult year. Four people showed interest in running the London Marathon, on behalf of the society, but our usual source of obtaining golden bonds was changed and we were unable to have anybody running this year. There was a small response to our appeal to join the weather lottery but we need to have many more people joining the scheme to make it worthwhile. It's worth visiting the website to see how the weather lottery has helped many small charities like ours. This year has started well with the grants and there are several new ideas of fundraising in hand. We're hoping for more success in 2008.

Thank you to Craig Barrass and Jackie Farrington, who, no thanks to the Royal Mail who failed to deliver our packs until the last day, successfully manned the LMBBS table at Sight Village in 2007. They made many new friends and are looking forward to assisting again this year, hopefully with all the information in place.

Our thanks also to Lance French, who continues to manage our web site at no cost to the Society. Lance and Julie (Sales) are currently working on updating the design of the web page, which, at the end of 2007, had 15,337 unique visits, 22,555 return visits and a total of 80,399 hits (this means that people have put in a word from our title and come up with our site). The USA is still the most popular visitor, followed by the UK.

Merchandise – we have T-shirts of all shapes and sizes available, along with Christmas cards designed by our children. Also, new this year, we have promotional gifts in the shape of teddy bears, sports bags, key rings and so on.

Our database has a steady number of family and professionals, with the database standing now at 280 families and 185 professionals. Thank you to Chris Humphreys for managing the help line – the first point of contact for many of our newly diagnosed families – along with the day to day emails. Thanks also for her continued role as conference coordinator. There has been a steady increase in delegates attending the conference over the years and 2008 is no exception. This year, including carers and children, we have 225 here, our highest ever.

Thank you to Tonia Hymers, who produces twice-yearly Newsletters and the Conference Report, which are available in print, on audio CD and to download from our website. I am sure you have enjoyed the Conference Report 2007 and Spring Newsletter and I'd like to remind you that without your snippets of information, stories and photographs, there would be no newsletter. Please contact Tonia at toniahymers@btinternet.com and you, too, will have your name in print. I will leave our treasurer Kevin Sales to give his report on this year's accounts but thank him for his continued tight rein on the spending of the society.

Treasurer's Report

The accounts have been balanced and audited for 2007, by Mr Michael Bannister of Thompson and Co. The two Barclays accounts are running smoothly, with the 'Friends' account increasing every month. During the year, we were only successful in obtaining one grant of £2000 from the Coventry Building Society. However, donations and fundraising nearly doubled throughout 2007 and a big thank you goes out to all those who contributed to the society.

As indicated in the accounts, we made a financial loss of £3735.65 during 2007, which will have a major impact on the 2008 accounts. We will have to use the majority of the money held in the Friends Account and the Number One Account for this year's conference, which will virtually wipe the society out of funds.

Without your continued support and tireless fund raising efforts, we would struggle to continue, so just keep up the good work and we will see you again next year.

Appointment of Auditor

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

Any Other Business

It was proposed and seconded that, with regard to Clause 4(a) in the Constitution, those persons on the Committee holding the positions of National and Conference Co-ordinator, Fundraising Co-ordinator and Newsletter Editor were amended to become Honorary Officers, in order to facilitate continuity in the management of Society activities. In the absence of any objections, the amendment was accepted. 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.

Louise Martin -Tears and Triumphs: A parent's perspective

"When Chris Humphreys first asked me to consider giving a parent's perspective, my heart thudded down to my boots. Yes, I was happy to give my perspective to Chris, but to give it to all of you, all at once, was more than a little scary! In previous conferences, this particular section has made me shed a tear. I hope that, as I take you through my journey, this won't happen, but who knows? There have been so many tears along the way… and so much unexpected joy watching a special child growing into a very special adult.

I have two children, Genny and Alex, born 18 months apart, so different from each other, but both very special. Alex was a toddler-star! developing much earlier than his sister. Two weeks old and he had teeth! He never left a drop of milk in his bottles, no matter how much I put in. At 3 months he was eating my food and feeding himself as soon as his hands could grasp. I had the ridiculous situation that Alex would sit in the high chair feeding himself, whilst his older sister would sit on my knee being fed, because she couldn't feed herself.

Alex and Genny are now 17 and 18 years old, different from each other in every way possible. They have grown up both loving and loathing each other, as is only possible for a close sibling to do. I have brought them up for the most part on my own, but that is another story. I now have the loving support of my partner Roger, who lives 180 miles away, but travels to London every weekend to be with us.

I knew before Alex was born there was something wrong. I was told he had an enlarged kidney and would need antibiotics from birth, until he was old enough to have a special scan and test for reflux. The day of his birth came, there was even more fun just waiting to happen. The midwife immediately removed him from my sight, and the trainee nurse asked 'what is wrong with his feet?' They would not give him to me until I screamed at them. I was then told to expect a visit from an orthopaedic consultant. It turned out that Alex had Talipes or a club foot, as it is so charmingly called.

There followed months of painful physiotherapy and three major operations, all before he was barely a year old. I still have Alex's first surgical gown. It looks like dolls clothes, and is handmade, probably by the nursing staff. I don't know why I kept it – I suppose so that one day I could look back and remember how I felt then, knowing that now he is alive and well and things are a little better. Except sometimes they aren't. Alex came through the surgery and we were delighted that he could walk and run as well as any toddler.

I recall Alex's first picnic, he liked to run, and once running, would not stop. I took one bite of my sandwich and, as I looked up, saw a dot disappearing into the distance. It was Alex; he didn't look back then and has not looked back since. Later that year, Genny was in hospital, fighting off pneumonia and Alex visited every night. The children's ward was arranged in a circle and Alex would run around in a continuous circle until visiting time was over and we were all exhausted – apart from Alex.

Alex attended toddler group, play group and, eventually, nursery school with no problems, just like his sister had done a year ahead of him. Unfortunately, things were not destined to go smoothly forever. When Alex was four years old, I went to his sports day. At the end of the day, all the other children from his class went walking in a line back to the classroom. Alex remained on the field. 'Why wasn't he going with all the other children?' I asked the nursery nurse. Sensitive soul as she was, she replied: 'Oh, didn't you know, Alex is not like the other children.' This was the first of many disturbing statements from teachers. Every parent thinks their child is special. But when does special become a label, which means something very different?

As a child, Alex was interested in everything around him. I once held an earthworm in my hand to show him; he grabbed it and tried to eat it. He had never been fussy with his food! Even now, he will try anything. Alex never learnt by trial and error. He studied the stair gate for months, and, then, just went up and undid it, whereas his sister had been trying for years and failed. Potty training, and Alex went straight from nappies to using the toilet and washing his hands afterwards, all in one smooth move, at his grandma's one Christmas. For a long time, I used a tandem buggy as Genny would not walk in straight lines. She always got in the back of the buggy (meant for babies to lie flat in), and went to sleep. Alex always sat in the front, taking in the world around him. Even now, years after he has been registered blind, he always knows where he is.

It was a long time before I actually believed Alex had serious problems. I began to notice that, when Alex was not holding my hand whilst out walking at night, he was unable to see. When he was three, we were returning home after a party at a friend's house, he walked into someone's garden wall, and was unable to see the curb. I took him to see an optician, but, as Alex didn't know his letters, it was difficult to test him, but we persevered. Eventually the optician tested his eyes by means of 'reflection off his retina'. I was told his eyes were normal. I took him regularly for check ups and was always told he was OK, though I knew he wasn't. School were unable to teach him to read, so I taught him myself with flashcards. He learned really quickly and seemed so bright. I couldn't understand why he wasn't reading at school – I didn't know he was unable see the blackboard. Alex didn't know either; he had got used to pretending he could see the same as everybody else. He still pretends. He doesn't want to upset anyone.

Attending clinic appointments can be upsetting, especially when a naïve young nurse will ask, 'Can you see this?', (Alex will never let her down and so always says, 'Yes,') followed by 'Look in that mirror and read the chart.' I can almost read Alex's mind as he thinks, 'What mirror? What chart?' We continue to attend the appointments, but now they bring the chart to Alex, and hold it inches from his face. It is two feet tall, with letters the size of my hand. Sometimes he can see one if he's having a good day. It breaks my heart each and every time. Every six months, we spend a day travelling to Moorfields hospital in the city. We see someone different each time and, as they have usually not had time to read the notes, we go through the same upsetting routine. 'Have you had drops in your eyes before?' they ask and I think to myself 'Just a couple of hundred times'. I always arrive home after these appointments feeling as if I've been in a train crash. It's mentally and physically exhausting, although Alex just takes it in his stride. Each time I tell Alex we have a hospital appointment, he calmly says, 'What's this one for then?' He has endured so much pain, and so many clinical investigations, that he thinks it's normal. When I have an appointment for me and get nervous, he doesn't understand what all the fuss is about.

Alex treats each appointment as an exciting opportunity, wondering if *this* is the time I will cave in and get him an edible treat, like a McDonalds or an ice cream out of the vending machine. I rarely cave in, but he is forever hopeful, and finds lots of different ways to ask. 'Shall we have a snack, Mum?', 'Have we had lunch yet, Mum?', 'I could do with a little something.' One day, I will compile a thesaurus of all the ways there are of talking about, and asking fo, food.

Alex made his way through primary school, not learning very much, but causing more than his fair share of concern. We had six-weekly meetings at school to discuss IEP's, behaviour problems and, eventually, Education Statements when the school realised they weren't making any progress. It never occurred to anybody that Alex could not see, that he got bored in lessons, so misbehaved. Alex was diagnosed with Bardet-Biedl syndrome when he was about 9 years old. Suddenly he wasn't just another child; he was 'special'. Alex was registered blind and given extra equipment at school, but he was increasingly set apart from the other children. Alex was no longer invited to parties, or to have a kick around in the playground; he hated school and started having tummy aches to avoid going.

Eventually, it was time for secondary school transfer. I was unhappy with the school offered by the local authority; they had a reputation for the 'rougher element' and I didn't think that Alex would survive the playground. We were told it would have a special needs unit, but there was not one in existence at that time for us to visit. I refused to send him and campaigned to get him into a local special school. Eventually, after seeking advice, the director of education saw things my way.

Alex soon made friends in his new school and settled down into a routine where little was expected of him. As Alex's sight deteriorated, his teachers completed all his practical work. Alex brought home

fantastic works of art, including carved pieces of wood, amazingly complex metalwork, and exotic dishes from the cookery class, and would quite openly tell me that the teacher had made them, and he had no idea how he would do it by himself. Time to re-think schools. After some research, visits and without too much fuss, I managed to get Alex a place at Linden Lodge, a school for visually impaired children in Wimbledon. Alex made friends, learned Braille, became an amazing touch typist, and is learning Independence and Living Skills. Although Alex still brings home amazing cakes that the teacher has made, it's hard to complain when they are so delicious!

Learning to become independent is great for Alex, but a nightmare for me! One weekend last December, Alex decided it was time he did his own washing, but decided not to mention this to anybody. Although I suppose I was given a clue two weeks previously when he said that I didn't do the washing quickly enough, as the clothes he wanted were still in the wash. On this particular Sunday night, I was just winding down for bed and Alex was finishing his evening bath. I switched off the TV and headed for bed, calling in to check on Alex. I found that the bathroom had turned into a swimming pool, with a trail of water between the bathroom and Alex's bedroom. On his radiator was a large amount of very wet clothing. When I asked what on earth had happened, he told me that he had washed his clothes in the bath. When I asked him' Why?', he replied 'I wanted to see what happened.' His Dad, who does not live with us, hasn't got a washing machine and had told the children that he washes his clothes in the bath, so from Alex's point of view, he was only being logical, not realising that a week's worth of wet laundry would not dry and be ready to wear overnight. Fortunately, the water did not drip into the mains socket directly below the radiator and blow the house up. A quick wash and spin in the washing machine and all was well again, but this was only a minor incident compared with the previous October….

It was before the October half term; Alex had an inset day. I was in 'gym mode' and reluctant to miss the last exercise class before the half term holidays, knowing that I would not have the opportunity that week. I told Alex the night before I would be up early and where I was going. He never gets up before midday anyway at the weekends, and is always happy to stay in bed until called down for food. He said that was fine by him.

On my return home, happily sweaty and tired, the house was strangely quiet. I went up to wake Alex to tell him I was back and would be starting to make breakfast soon. He was not in bed. I went and looked again downstairs, but there was no sign of him. I went back upstairs and this time checked all the rooms to see if he was hiding behind any doors – he likes to stand quietly and listen at doors – he gathers secret intelligence this way sometimes! But he was not there. I came down and sat in the chair wondering what on earth was happening. I then went around the house bizarrely checking under all the beds and in all the cupboards and wardrobes, and behind the curtains in some kind of crazy one sided hide and seek game. Having established that Alex was not in the house, I went downstairs; I noticed that his long cane was on the window ledge and his coat was still hung up on the end of the stairs. I went into the lounge to call the police, convinced that he had been stolen. As I picked up the phone, I heard a key in the lock and in walked Alex very matter of factly, holding a carrier bag. He told me he had been shopping. I didn't even know he knew how to use his key! He always had one in his school bag for emergencies just in case I got caught in traffic and couldn't get home in time to meet the school bus. It had only happened twice in four years and then the escort had seen him into the house for me. I yelled and shouted in utter panic and fear, telling him how I was going out of my mind with worry, not knowing where he was – it was not as if he had left a note or anything. He promised me he would not do it again, and I promised him that we would start mobility lessons and train him up to go out by himself.

The following week, during half term, we walked into town three or four times, with Alex using his cane to guide himself. I talked the route over with him as we walked. About a week later, Roger and I slipped out for an hour to shop, whilst Alex was engrossed in listening to a football match on TV. When we got back, he was gone. There was a tiny scrap of paper on the dining room table saying 'to shops'. I sent Roger off on the route I had been practising with Alex, whilst I waited for Genny to come home. I then went out and asked in the two nearest shops whether they had seen Alex – a small boy with a white stick – quite distinctive. Yes, they had seen him heading off down to Whitton – the route we had practised. Roger phoned me, he had seen Alex and was trailing him back towards home. Alex was using his stick and had crossed several roads and was safe. I walked up to meet them, watching as Alex negotiated the side roads and then the zebra crossing, missing all the roadworks we had practised going round the previous fortnight. He then went into the corner shop

and spent half an hour or more choosing about 10 packets of sweets and chocolate bars. We signalled to the shopkeeper that we were watching to see what Alex did.

After that, I let Alex go on his own to the corner shop, with me trailing him from a distance. I have arranged for a mobility officer locally to do some routes with him and this is happening in the holidays, as he now boards at school weekly. Alex has known all along what he wanted. But it is so hard for me to let him do his own thing. On Sunday 28th January, Alex did his first (official) solo outing. We all got up late, and were in our dressing gowns, too hungry to get dressed before breakfast. But disaster….there was no bread! Alex was as dismayed as the rest of us, but then perked up and said 'I'll get some!' I thought and thought, but could not think why he could not get the bread. …Except that it usually takes him an hour to get dressed! But I thought, 'Give him a chance.' I told him we were all very hungry, but tha,t if he could get dressed and be ready to be out the door in five minutes, he could get the bread for us. Amazingly, he did just that. I gave him £2.00 and got him to repeat what we needed, 'ordinary sliced loaf.' Off he went. Even if I chickened out, I could not follow him – I was still in my dressing gown. I paced the house for 10 minutes and then the door bell rang. It was Alex, proudly displaying a carrier bag containing a loaf of bread. He was all smiles. I said 'How did that feel?' A man of few words, he said 'GOOD!' in the strongest loudest voice I have ever heard him use.

Last month, Alex was offered a place at Dorton College in Kent. It is a residential course, and he will have three years there, learning how to cook, shop and take care of himself. After that, the college will help Alex to move into independent accommodation. I feel that I am coming to the end of a long and hard career as a parent carer. I am sad, but happy, and am looking forward to being a normal parent again, with a kid in college, who comes home some week- ends, and brings his dirty washing for me to do! except I hope he'll be able to do his own washing, hopefully in the machine. It's been a long journey for all of us. I have watched my baby grow into a fine young man, and I feel we are all, at last, arriving at a very good place."

The Chairman thanked Louise for her perspective and said he was sure that many of the delegates present could equate with her journey. Throughout the presentation, Louise showed us photographs of the children as they were growing up.

Helen May-Simera

As mentioned in the Chairman's report, Helen left for the States shortly after the Conference weekend. Proving we are never far from Helen's thoughts, we have had an email from her, bringing us up to date with life overseas.

"I thought I should send you an e-mail to let you know how I was getting on and to say 'thank you'. First of all I really wanted to thank you for all the lovely cards and gifts you gave me at the conference. It was such a surprise and I felt very touched. Yesterday, I finally moved my stuff into my new room and my LMBBS bear takes pride of place on my desk. I have been here for almost a month and it feels like the time has just flown by, it has been crazy. I started my job straight away and it is fun. I love the lab and the people seem very friendly. I am still trying to work on BBS as much as possible."

Before she left the UK, Helen completed the Bath to Paris bike ride, to raise funds for the Society, and already she is planning another fundraising event with an 'English Tea Party', complete with cucumber sandwiches and scones. We look forward to hearing more from Helen in the future.

Delegates Comments:

"The quality of childcare was excellent, everyone had such a wonderful time."

"More of the same and twice a year please!"

“Excellent mix of speakers - enjoyed the workshops.”

“Nico Katsanis was excellent, I learned more than I could ever have dreamed of; bring him back!”

“The children’s activities at the hotel were excellent.”

“The workshops this year were excellent, I only wish I had time to do them all, make the conference longer!”

“The hotel staff were superb, plenty of help plating food, carrying luggage and generally ensuring that everyone was well looked after. “

“The family quiz was excellent as always. Highlight of the evening.”

“Food was excellent this year, much better arrangement to be in the restaurant for all meals. “

“The carers are the unsung heroes of the conference, allowing parents an opportunity to network with other like minded people and have an opportunity to speak to eminent professionals in a relaxed atmosphere.”

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