

breakthrough

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Our charity reaches a milestone


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Breakthrough

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ME Research UK funds research into Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (also known as ME/CFS). It has an international remit, and its principal aim is to commission and fund high-quality scientific (biomedical) investigation into the causes, consequences and treatment of ME/CFS. It also aims to 'energise ME research' by identifying potentially important areas for future biomedical research, producing high quality professional reviews and reports, presenting research at meetings and conferences, and hosting international conferences.

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editorial

ME Research UK reached a milestone recently, when it topped the £1 million mark in grants it has awarded to researchers. The 35 specific biomedical projects this represents are listed in the insert to this issue of *Breakthrough*, and 52 research papers have been published from these projects to date. We can be proud of this record, but we know that none of it would have happened without the hard work and generosity of our supporters who share our belief that only biomedical research can defeat ME/CFS.

When I read on our Facebook page and in *Breakthrough* of the numerous, imaginative ways that our friends find to help us – from the 'Walk for ME' scheme to running marathons, and from swimming the Channel to abseiling – I am truly amazed, and grateful to you all.

In the year 2000 when Bob McRae and I launched this charity, we could not have dared imagine how it would grow, nor the contribution it would make to the science of ME/CFS. I believe that the outlook is improving for research into this disease, and have been heartened by several recent advances, including the award of \$1.5 million to our ME/CFS Biobank, and the £1.6 million allocated by the Medical Research Council after many years of lobbying.

We can be rightfully proud of what we have achieved, but we must also look to the



future. Building on this £1 million milestone, we intend to continue our core function of commissioning and funding scientific research projects across the world. But we also want to harness the talents of our friends, and in spring 2014 we will launch our Ambassadors scheme in order to widen our fundraising base and boost the profile of the charity. Please consider helping us with this – many hands make light work!

Dr Vance Spence
Chairman
ME Research UK

Free to you, but costly to produce

Breakthrough is posted out free of charge to all our supporters, and is an invaluable way of highlighting the work that YOU are helping to fund, and attracting new supporters.

If you wish to contribute towards the cost of *Breakthrough*, please scan the 'code' on the right with your smartphone to donate £2 to us in a flash! Apps to do this are free and widely available.

No smartphone? No problem – just text **'MEUK01 £2'** to 70070 to donate £2.





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Fundraising by the Friends of ME Research UK: Walk for ME, pyjama party, tough mudder, ladies' lunch, dreadlocks, 1920s night, and more



Abnormal visual attention in ME/CFS

Around three-quarters of people with ME/CFS report problems with their eyes and vision – but you wouldn't know it from the mainstream scientific literature. Apart from a small group of observational studies, there is very little formal published evidence that these symptoms exist, despite the fact they greatly affect quality of life and can be easily measured. This means that there is no solid, evidence-based scientific data to back up patients' reports of their disabling visual disturbances.

In order to redress the balance, Dr Claire Hutchinson and Dr Steve Badham of the Vision and Language Research Group, University of Leicester have been busy trying to identify and quantify vision-related problems in the disease, with funding from ME Research UK and the Irish ME Trust. They are part of a multidisciplinary group of researchers working on key issues in vision, visual cognition and language comprehension, with access to a range of start-of-the-art techniques.

Based on the visual and vision-related symptoms most commonly reported by people with ME/CFS (summarised in the table opposite) the researchers



Dr Steve Badham and Dr Claire Hutchinson

initially set out to examine two main categories of visual impairment.

The first concerns heightened visual awareness (including hypersensitivity to light and difficulty suppressing irrelevant background visual information), and the second consists of eye-movement problems, such as difficulty focusing on images or tracking objects. The first scientific paper reporting their findings has just been published (*Optometry & Vision Science*, June 2013), and it makes fascinating reading.

Their report describes the specialised and quite intricate measurements undertaken on 29 ME/CFS patients and 29 matched healthy controls across three specific aspects of vision.

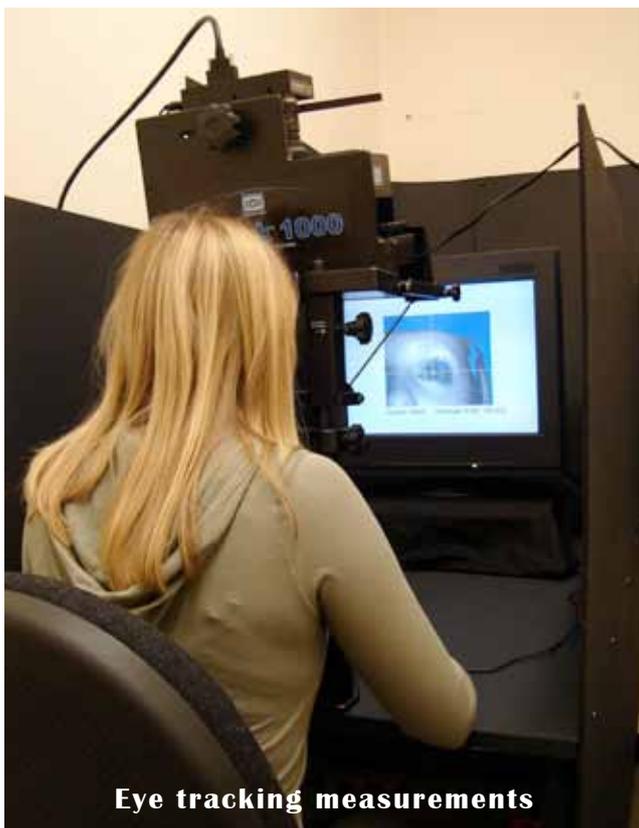
The first of these was visual processing speed, divided attention and selective attention – all of which involve assessment of the 'useful field of view', which is the visual area over which information can be extracted at a brief glance

without eye or head movements. The other aspects were 'spatial cueing' (the ability to shift attention from one thing to another), and 'visual search' which involves the ability to locate a target in a field of 'distractors'.

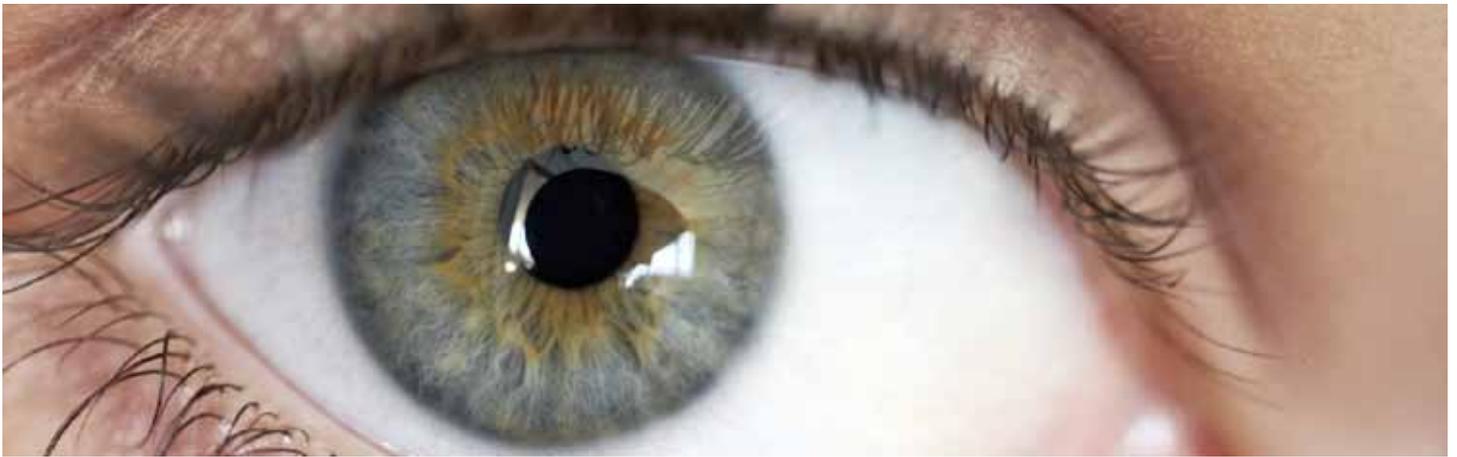
Overall, patients performed worse than healthy people in each of these specific areas – they were less able to selectively attend to a specific target while ignoring other irrelevant information; they were slower when it came to moving their attention to a target (see the graph on the right), particularly a target appearing at an unexpected (invalid) location; and they were slower at scanning visual stimuli and more easily affected by 'distractors' during a visual search.

These important findings provide much-needed experimental evidence of visual impairments in ME/CFS, and support patients' own reports about some of their vision symptoms. But what are the causes of these abnormalities?

These remain to be teased out, but it could be that processing speed is impaired, particularly as we already know that reaction times are significantly slower in people with ME/CFS (see page 14 of this issue). However, the researchers suggest that problems with eye movement itself might underlie some of these findings, and their next scientific paper, due out shortly, will address this particular aspect.



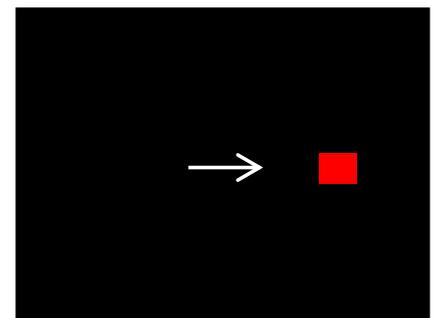
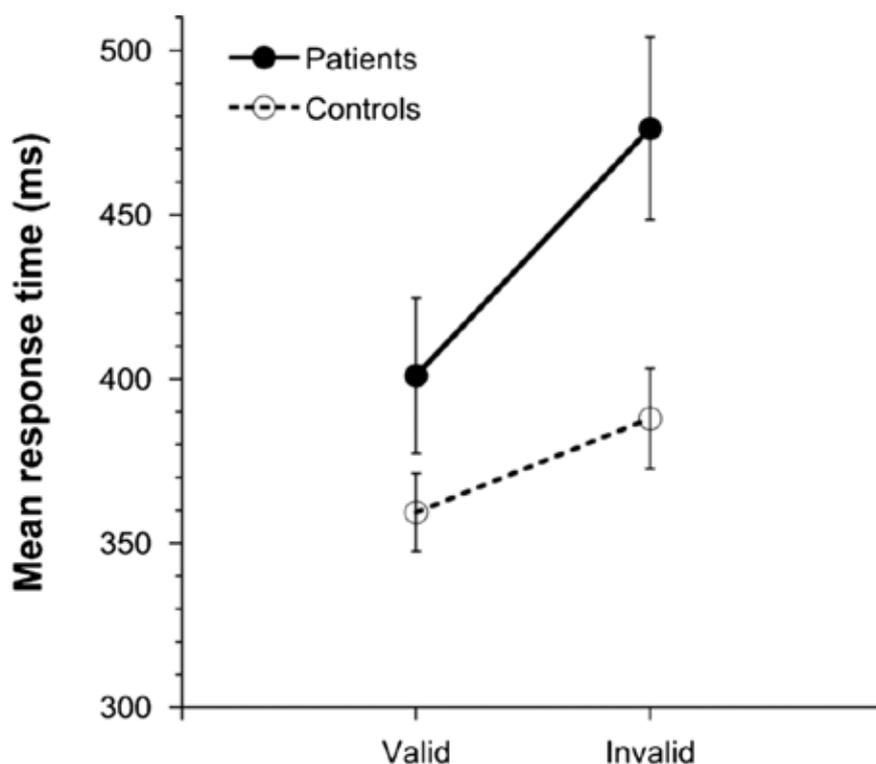
Eye tracking measurements



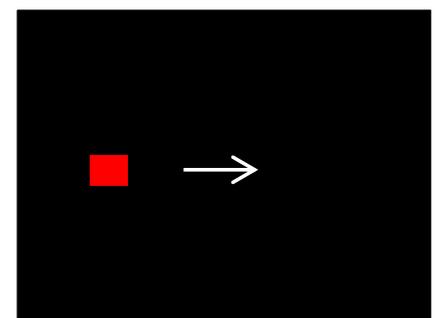
Common vision-related deficits in ME/CFS

Symptom cluster	Self-reported subjective visual symptoms
Heightened visual awareness	Hypersensitivity to light Difficulty suppressing visual information or directing visual attention
Eye-movement and tracking problems	Difficulty focusing on images Slow eye movements Difficulty tracking object movement
Reading difficulties	Confused or distracted by irrelevant print Difficulty tracking lines of print

Patients are slower at shifting attention



Valid cue



Invalid cue

UK ME/CFS Biobank project awarded £1 million grant

The dramatic news in July was that the National Institutes of Health in the US had given a large award of £1,029,411 (\$1,588,225) over three years to the pioneering ME/CFS Biobank project at the London School of Hygiene & Tropical Medicine. Dr Eliana Lacerda, one of the lead researchers on the project, said, "The grant provides a huge boost to the Biobank, which will enable more research into the causes of ME/CFS and ultimately help those affected."

Since 2011, a consortium of charities – ME Research UK, the ME Association and Action for ME, plus a private donor – has been funding the 'establishment phase' of the Biobank, which is the only one in the UK and the first in Europe aimed at the study of this disease.

In providing initial funding, our hope had always been that a major funder would contribute funding for a project to allow analysis of the samples, and help with the continuation and expansion of the Biobank resource. So it was marvellous to hear that the prestigious National Institutes of Health had stepped up to the plate, under a funding call issued by its Department of Health and Human Services.

The grant will enable important research on the immunology and genetics of ME/



Dr Erinna Bowman, Dr Luis Nacul and Dr Eliana Lacerda

CFS, and help to expand the Biobank to store samples from over 500 participants, which will be made available to medical researchers internationally. The hope for the longer term is that this vital piece of research infrastructure will become a repository for blood and tissues from many thousands of people with ME/CFS.

Dr Neil Abbot from ME Research UK, who was another significant contributor supporting the NIH grant application, said, "The creation of a Biobank infrastructure – linking bio-specimens with clinical, disease and other data over the long term – couldn't have been done without collaboration between charities.

The award of this grant from the National Institutes of Health shows the success of this approach, and the whole Biobank team deserve congratulations on this tremendous news."

What is a biobank?

Biobanks are large collections of biological specimens (tissue, blood, etc.) from patients or healthy people who have volunteered their tissues for research. Every sample is linked with comprehensive clinical information about the donor, making biobanks particularly useful for medical research.

From the patients' perspective, the information they provide can be used in many studies over many years, even though samples are donated once only. For the scientist, there exists a valuable database of well-characterised samples, with individual privacy and confidentiality maintained, that can be accessed for approved research projects.



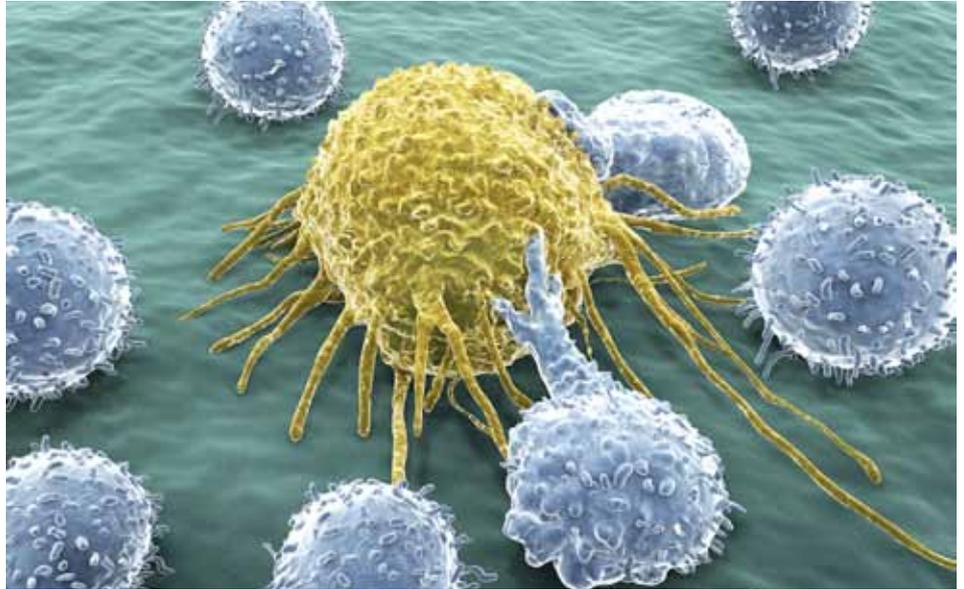
The Biobank Steering Group

Immunological mechanisms in ME/CFS and cancer: a newly funded study in Leeds

ME/CFS is not well understood nor, in many cases, properly recognised, and there is great debate about its underlying causes. Early symptoms include severe fatigue, sore throat, raised lymph nodes and pain in joints, similar to those associated with viral infections, so it is possible that an abnormal immune response to the initial viral infection is responsible for the continued symptoms.

The immune system of ME/CFS patients has been the target of medical researchers for many years, and the abnormalities found have included reduced natural killer cells, and increases in various types of cytokines (which regulate the immune system) such as interleukins and interferons. In fact, some of these immune abnormalities are similar to those found in cancer (see the table on this page). There is still much more to learn, however, and an immunological ‘smoking gun’ remains to be found.

Immunity in ME/CFS can also be studied in comparison with other chronic illness in which patients suffer from similar related symptoms such as debilitating fatigue and pain. For instance, 70 to 90% of breast cancer patients treated with chemotherapy have fatigue that can, in some cases, be severe and persist long after treatment, greatly affecting their quality of life. No-one is quite sure why this chemotherapy-induced fatigue happens, but chemotherapy is known to cause widespread alterations to lymphocytes (white blood cells that fight infections), and this may play a role. Could it be that changes in white blood cell populations underlie the



fatigue experienced by ME/CFS patients *and* post-chemotherapy breast cancer patients?

Given this possibility, ME Research UK has actioned funding for an investigation by a team at St James’s University Hospital, Leeds, involving a range of complex immune tests to assess the type and functional competence of lymphocytes, focusing on activated and regulatory cells (T and B cells). In particular, the team plans to recruit 25 ME/CFS patients and 40 breast cancer patients to observe how lymphocyte surface proteins (and the cytokines released by lymphocytes) change before and after treatment.

In the case of breast cancer patients, treatment refers to chemotherapy; for ME/CFS patients, the treatment centres around their clinical care. All participants

will complete outcomes questionnaires before and after treatment, and ME/CFS patients will be requested to complete the DePaul Symptom Questionnaire which assesses core symptoms of their illness and helps diagnostic classification.

The main aim of the investigation is to shed light on any major common immunological mechanisms that might be responsible for the catalogue of symptoms shared by people with cancer or ME/CFS. The study could well reveal novel and immunologically important information, leading to new treatment options to protect against fatigue and increase the quality of life, particularly for the ME/CFS patients who presently have few treatments available to them.

Immune abnormalities in ME/CFS and cancer

Factor	ME/CFS	Cancer
Ribonuclease L	Increased activity leading to increased apoptosis	Decreased activity leading to decreased apoptosis
Nuclear factor kappa beta	Increased activation	Increased activation
Natural killer cells	Decreased activity	Decreased activity

Source: Meeus et al, *Anticancer Research*, 2009

Postural orthostatic tachycardia and ME/CFS

One of the key difficulties facing ME/CFS patients is standing, especially standing still, which can bring on symptoms such as dizziness, altered vision, nausea and fatigue. So it is certainly possible that some dysfunction of the autonomic nervous system is involved in the disease.

Since 2006, with the financial help of ME Research UK, Professor Julia Newton and her team at the School of Clinical Medical Sciences, University of Newcastle have been investigating autonomic nervous system function in ME/CFS. In fact, their scientific papers have reported autonomic dysfunction in three-quarters of ME/CFS patients, and that their blood pressure is lower and its regulation abnormal compared with healthy people.

A new scientific paper from Prof Newton's group (published this year in the *Journal of Internal Medicine*) describes postural orthostatic tachycardia syndrome (POTS), an aspect of autonomic dysfunction that can produce substantial disability among otherwise healthy people.

POTS is defined as symptoms of orthostatic intolerance (problems with standing), and it is easily diagnosed by observing the increase in heart rate on

moving from lying to standing (a person with POTS has an abnormally large increase). The team wanted to test a large group of ME/CFS patients for the presence of POTS, and to look for clinical differences between those with and without the disorder. If differences exist, it might be possible to treat and manage POTS patients as a distinct clinical subtype of ME/CFS, since we already know that this diagnosis includes a wide range of different kinds of patients.

In total, 179 consecutive patients from the Newcastle CFS Clinical Service were examined, and they underwent a series of demographic and symptom assessments, as well as autonomic function tests including heart rate variability (HRV) and left ventricular ejection time of the heart. The patients had been ill for just over 7 years on average and, overall, the prevalence of daytime sleepiness and orthostatic symptoms was high, as was physical and cognitive impairment.

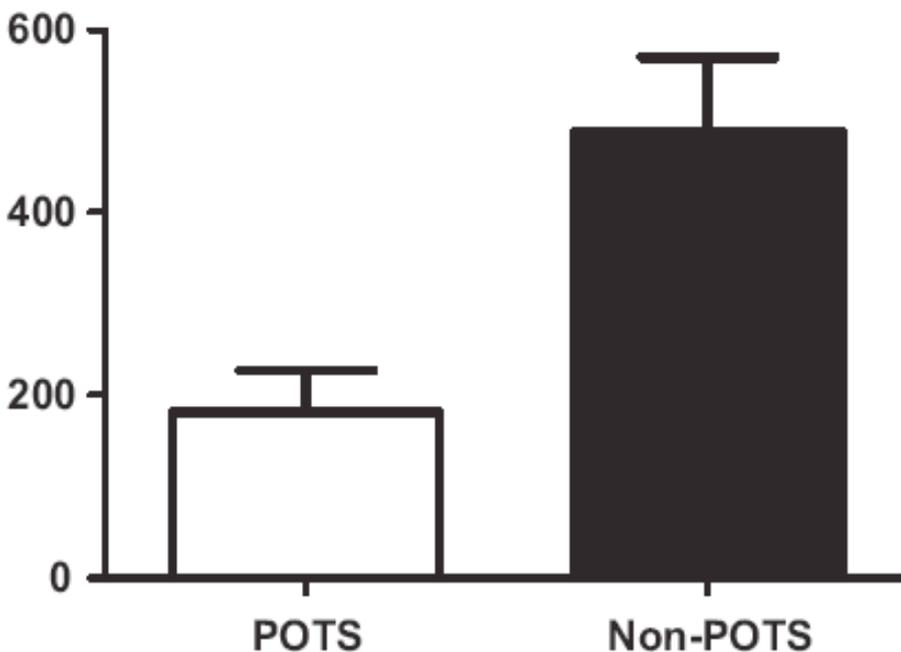


Prof. Julia Newton

In total, 24 patients (13%) had POTS, and they were younger (average age 29), less fatigued, less depressed, and reported less daytime sleepiness than the 155 (87%) without POTS. Crucially, they also had greater orthostatic symptoms and autonomic dysfunction. In fact, it was possible to predict which patients would be in the POTS group with 100% accuracy from a combination of high orthostatic intolerance and low daytime sleepiness. Of particular interest was the significantly lower HRV in the patients with POTS (see the graph on the left), indicating a greater level of autonomic nervous dysfunction in this subgroup.

These interesting results were the subject of an expert commentary in the same issue of the *Journal of Internal Medicine* by Prof. Jo Nijs and colleagues from Brussels. They point out that the investigation provides compelling data for a novel subgroup within the ME/CFS population, and that the results support the view of ME/CFS as a central nervous system disorder. Clearly, it is important that POTS be recognised and managed, whether in ME/CFS or other groups of patients, since treatment can improve functional impairment and quality of life.

Difference in heart rate variability



The science of ME – what do we know?

There are more than four thousand scientific publications on ME, many under different names, such as postviral fatigue syndrome, ME/CFS, chronic fatigue syndrome, chronic fatigue immune dysfunction syndrome, etc. Significant progress has been made in the scientific understanding of the disease, particularly in the last 20 years, and in the list below we summarise some of the headline findings.

Inflammation and immune activation are involved: Chronic T-cell activation, increased cytokines, raised oxidative stress and low natural killer cells point to a chronic state of low-grade immune upregulation.

Infection is important: Illness starts with an acute, infectious-like episode in many patients. The main agents implicated in causing or maintaining the disease include enteroviruses (such as coxsackievirus), Epstein-Barr virus, cytomegalovirus and human herpes virus 6.

Neurocognitive abnormalities are prevalent: It is well established that cognitive problems – mainly with memory, attention/concentration and reaction time – occur frequently.

Endocrine (hormonal) abnormalities can be found: Hypothalamic-pituitary-adrenal axis dysfunction is a well-recognised feature.

Symptoms are serious, and chronic illness is common: We now know that the most common symptoms of ME (pain, sleep disorders and vision problems) are daily challenges affecting the quality of life of patients, most of whom endure long-term illness. Between 10 and 25% of patients are severely affected – housebound, bedbound or immobile – and severely overlooked.

Psychiatry is not the answer: We know that the illness is not a form of depression, nor a primary psychiatric condition. As in other chronic diseases, psychological interventions can help some people to cope and to manage their symptoms until a cure is found.

Genetic factors play a part: This has been shown by family and twin studies.

Neurological abnormalities can be detected: There is good evidence of autonomic nervous system dysfunction, including orthostatic intolerance which

causes problems on standing. Brain structure and blood flow abnormalities have also been identified, and central sensitisation, due to an abnormal increase in the firing of nerve cells in the spine, may be important.

Muscle function is impaired in some patients: This includes abnormalities to skeletal muscle and impairments to cardiac 'bioenergetics'.

Prevalence is high: Epidemiological studies show that ME affects around 200,000 people in the UK and 1 million in the USA. This makes the disease more prevalent than multiple sclerosis, systemic lupus and HIV infection.

Biomedical research has made significant progress, but imagine the advances that could be made by a concerted effort to fund programmes of research across the globe! Our strategy for ME has to mirror that of other illnesses, such as cancer, which obtains most of its revenue (£500 million per year in the UK) from private sources and ground-level fundraising. It is a huge task, but much can be achieved by a determined effort to mobilise the resources of the wider community.



Launch of the UK Research Collaborative

The UK CFS/ME Research Collaborative was launched in April 2013 at the Wellcome Collection building in central London. The aim of the Research Collaborative – the first of its kind in the world – is to promote the highest quality of research into ME/CFS by bringing together national agencies, ME/CFS charities and working researchers from across the UK. The importance of the event was underscored by the attendance of HRH The Duke of Kent and The Countess of Mar, one of our Patrons.

Annette Brooke MP, Chair of the All Party Parliamentary Group on ME, opened the meeting and spoke about the importance of research for patients. She explained that as there are around 200,000 ME/CFS patients across the UK, every MP will have a constituent who is experiencing difficulties in having their condition recognised and accessing services. “Our constituents are angry and frustrated,” she explained, “many want more than standard care and coping strategies, as useful as these can be. They want the causes to be understood, and they hope to be cured.”

Annette was followed by two speakers from national research funding agencies. Dr Joe McNamara of the Medical Research Council in London described the MRC initiatives established in recent years, which



The Duke with invited guests

“We welcome this attempt to dramatically alter the research landscape for the benefit of patients everywhere”



Trustee Sue Waddle gives the charities' presentation

culminated in the award of £1.65 million in 2011–12 for five discrete grants to ME/CFS researchers. Dr James Fenton of the NIHR Trainees Coordinating Centre described the training awards that were available for developing “research capacity” in specific areas.

The centre-piece of the morning was the talk by Sue Waddle, Vice-Chair of ME Research UK on the role of medical charities in ME/CFS research, which was given on behalf of all five research-supportive charities (Action for ME, the Association of Young People with ME, the CFS Research Foundation, the ME Association and ME Research UK). In the presentation, Sue pointed out that a significant proportion of research funding in the UK for many, if not all, illnesses comes from charitable sources – £1.14 billion in 2011–12 alone. In fact, if the charity sector did not exist, scientific research into all medical conditions would be much the poorer, and discoveries would be far less frequent.

Sue concluded by saying, “It augers well

for the future that all stakeholders, be they charities, scientists, funding bodies, government or industry, recognise that a collaborative approach to funding research offers the greatest chance of success. The only way we can achieve the level of change that we need is by working together to tackle this awful disease.”

Prof. Stephen Holgate, Collaborative Chair and MRC Professor of Immunopharmacology, University of Southampton, gave a lively talk on why a UK Collaborative was needed, drawing on his previous experience of organising a successful Research Collaborative in respiratory illnesses. He described the background to his own interest in ME/CFS, the burden on patients that the disease represents, and why he thought the time was ripe for a collaborative approach to overcoming the many issues surrounding the illness.

During the lunch break, researchers' posters could be perused and discussed. It was a particular pleasure for ME Research UK to have some of the researchers it has funded in attendance and presenting posters, and they included Dr Claire Hutchinson (University of Leicester), Dr Clive Carter (Leeds NHS Trust), Dr Eliana Lacerda and Dr Erinna Bowman (London School of Tropical Medicine & Hygiene), Dr Faisal Khan and Dr Gwen Kennedy (University of Dundee), Prof. Julia Newton and colleagues (Newcastle University), and Prof. Derek



Trustee Jan McKendrick at our stall

Pheby (Buckinghamshire New University).

The main focus of the afternoon session was the work of some of the groups which had received grant awards from the MRC. Dr Wan Ng (Newcastle University), using primary Sjogren's syndrome (an autoimmune condition with several clinical features similar to ME/CFS) as a disease model, described

his comprehensive analysis of the immune system to identify biological fingerprints, and to explore whether these biomarkers are present in ME/CFS patients. Prof. Julia Newton (Newcastle University) outlined her plans to explore the pathogenesis of autonomic dysfunction and its relationship with ME/CFS, using functional magnetic resonance imaging to measure changes in blood flow to the brain.

Dr Carmine Pariante described his immunological model of fatigue, and his plan to follow patients undergoing interferon-alpha treatment for hepatitis C to identify biological measures useful for the prediction of the development of ME/CFS. Prof. Anne McArdle's group at the University of Liverpool will use newly developed, sensitive laboratory techniques to study mitochondria within muscle cells, with the aim of identifying interventions to reverse or halt further damage.

As Jan McKendrick, speaking for the other trustees of ME Research UK, said, "Our hope in joining this venture is that the success of the UK Respiratory Research Collaborative – which saw grant funding for respiratory medicine research increase 10-fold between 2005 and 2012 – can be reprised for ME/CFS, which has been a poor orphan in research terms for far too long. It is because we are all people directly affected by ME/CFS – either as patients, family members or friends – that we welcome this attempt to dramatically alter the research landscape for the benefit of patients everywhere."



Dr Gwen Kennedy and Dr Faisal Khan (Dundee) with Dr Clive Carter (Leeds)

Research bites from around the world



NORTHUMBRIA

Sleep abnormalities

Sleep problems affect a large majority of people with ME/CFS, and they can have a very great impact on all other aspects of patients' lives. For this reason, scientists in the Centre for Sleep Research at Northumbria University decided to look for objective evidence of severe sleep disturbance in the disease, including the range and variety of problems experienced.

The researchers analysed data from 343 Fukuda-defined patients from the Netherlands, who all underwent a single night of polysomnographic investigations (all-night recording of EEG, electromyography, electrooculography, ECG and respiration) at a specialist sleep clinic. Overall, there were two major findings.

First, 104 of the patients (a full 30.3%) had a 'primary sleep disorder' (mainly sleep apnoea) which might, in itself, explain some of their symptoms, including muscle aches and pains, fatigue and problems with concentration. Second, the remaining 239 patients could be grouped into four different sleep categories

each with a distinct 'sleep profile'; two of these groups have mainly insomnia-like symptoms, while two are characterised by poor quality of sleep – showing that different types of sleep dysfunction can exist, even though all patients have the same diagnosis.

There seems to be no consensus as yet on the science behind sleep derangement in ME/CFS, though the most common research findings include problems with initiation of sleep (i.e., dropping off – no surprise to readers!) and also reduced slow-wave stage (non-REM) sleep. The causes, however, remain a mystery – and one that needs to be unravelled.

Source: Gotts et al., BMJ Open, 2013

CHICAGO

Spotlight on definitions

There are a number of possible definitions of ME and CFS but each is different, and the terms ME, CFS or their various combinations mean different things to different people today (see lead article in *Breakthrough*, Spring 2013).

Many different views and opinions exist about which definition might be 'best', but hard data is thin on the ground. Fortunately, there are ongoing attempts to compare definitions, and the latest comes from Prof. Leonard Jason's very active research group at DePaul University, Chicago, which has compared the most widely used CFS criteria (Fukuda 1994) with the relatively new International Consensus Criteria for ME (ME-ICC 2011).

Their main finding is that people who meet both Fukuda and ME-ICC criteria have poorer function (lower physical function, more physical pain, etc.) and more severe symptoms than those meeting Fukuda criteria alone. This is no real surprise, since it is probably easier for patients with milder symptoms or lower levels of disability to meet the Fukuda criteria than to meet the ME-ICC criteria which are more stringent. The unexpected finding was that levels of psychiatric illness seemed to be higher in the ME-ICC group; as the authors say, "*While the ME-ICC criteria are an improvement over the vague and minimal guidelines of Fukuda... it is possible that the ME-ICC criteria select for individuals with increased psychiatric symptoms and functional impairment.*"

This is a preliminary report, and its results may be overturned in subsequent investigations. However, it illustrates that we cannot just assume that this or that definition is 'better' than another; each will have its strengths and weaknesses, and only experimentation can draw these out.

Source: Brown et al., North American Journal of Psychology, 2013

BELGIUM

Intestinal bacteria

Recently, scientists have begun to focus on the hidden yet extensive world of microbes that live in our bodies (the 'microbiome'). In fact, most bacterial cells are located in our gut – about 1.5 kg of bacteria per person. It is now clear that gut bacteria can influence health in a variety of ways, such as by synthesising nutrients, inhibiting microbial and viral pathogens, and detoxifying food. But they also contribute

to the optimal functioning of the immune system; 70% of all immune cells are located in the gastrointestinal tract, for instance.

Gastrointestinal problems are very common in ME/CFS patients, so it is at least plausible that some abnormality of gut bacteria could be linked to the development of the illness. Belgian researchers have now used high-throughput gene sequencing to search for different species of bacteria in stool samples of ME/CFS patients from Belgium (18 patients) and Norway (25 patients), and from local healthy people.

Compared with Norwegian controls, Norwegian patients had decreased percentages of some *Firmicutes* sub-populations (*Roseburia*, *Syntrophococcus*, *Holdemania*, *Dialister*), a strong 20-fold increase of *Lactonifactor*, and a 3.8-fold increase of the *Bacteroidetes* genus *Alistipes*. Belgian patients showed fewer differences compared with local controls, but *Lactonifactor* was again strongly increased (45-fold) while *Asaccharobacter* was decreased.

Scientific study of the relationship between the microbiome and human disease is still rudimentary, so we and the authors can only speculate about what these results might mean. *Roseburia*, for example, are thought to contribute to the production of energy and

to protect against gut inflammation, while there is some evidence that increases in *Alistipes* are also related to gut inflammation (the bacteria were first identified in appendicitis tissue). It is certainly possible, therefore, that these findings are consistent with increased intestinal inflammation.

Source: Frémont et al., *Anaerobe*, 2013

NORWAY

Clinical review of young people

Very little is known about the clinical characteristics of young people attending ME/CFS clinics, so a review of cases at Haukeland University Hospital, Norway between 2002 and 2011 was interesting. Clinicians examined the records of children referred for “fatigue symptoms”, finding 33 eligible cases – not a huge number, but referrals had been growing, with 25 patients referred since 2009. Of the total, 6 were given other diagnoses (mainly epilepsy, sleeping disorders and hypothyreosis), while 27 received the diagnosis ‘G93.3 post viral fatigue syndrome’.

Symptoms had started at age 11 on average, and in all children had begun after an infection. All tested positive for antibodies to infectious agents, mainly Epstein-Barr virus (74%) but also cytomegalovirus or *Borrelia*. None of the patients was found to be suffering from anxiety or depression, and most were referred for additional medical investigations, including magnetic resonance imaging of the cerebrum or chest X-ray, which were mostly negative. Intriguingly, 12 young people (44%) were found to be clinically underweight for their age, though whether this was related to their post-viral illness is unknown. The authors report that many of the adolescents had additional gastrointestinal symptoms, which might help explain the low bodyweight, though another reason could be the loss of muscle mass due to inactivity.

What is missing from this report is any information about outcomes – i.e., who improved or recovered and what effect any treatment interventions might have had – and perhaps a future study will throw light on this aspect. The authors are correct, however, in calling for European-wide guidelines on the diagnosis, assessment and treatment of young people with post-viral fatigue syndrome – such guidelines are long overdue.

Source: Elgin et al., *International Journal of Pediatrics*, 2013



Photo by Milan Jurek

BALTIMORE

Lessons from the XMRV fiasco

Between 2009 and 2012, the controversy over the retroviruses XMRV/XMLV and their role in ME/CFS involved a tumultuous roller-coaster ride for patients and scientists around the world. More than 50 scientific papers reported no association between the viruses and ME/CFS or other diseases, and the final act in the drama came when Columbia University's Prof. Ian Lipkin published the negative results of a definitive multicentre study in which none of the 293 patients or controls tested positive for the viruses using polymerase chain reaction.

So what can we learn from this controversy? Well, a recent review article outlines the major take-home message for working scientists – the need for practical precautions in the laboratory. As it points out, the finding that XMRV was a “cell culture contaminant” as opposed to a clinically important pathogen highlighted an important fact: that murine endogenous gammaretroviruses were infecting commonly used laboratory human cell lines. In fact, since XMRV was discovered, many additional cell

lines have been shown to harbour these gammaretroviruses, threatening not only the invalidation of experimental results but also the cross-contamination of uninfected cell lines grown in the same laboratory.

Today, all laboratories should be aware that additional precautions are needed, including routine testing for XMLVs in human cell lines developed by transplantation from one species to another, or any cell lines cultured in laboratories concurrently growing transplanted or known XMLV-infected cell lines.

Source: Hempel et al., Frontiers in Oncology, 2013

AUSTRALIA

Slowing of information processing

Neurocognitive problems are one of the most frequent and disabling symptoms associated with ME/CFS. In fact, around 90% of 2073 patients in one large study reported having memory/attention deficit problems, and patients often say that physical or mental exertion makes their cognitive problems worse. The latest results from

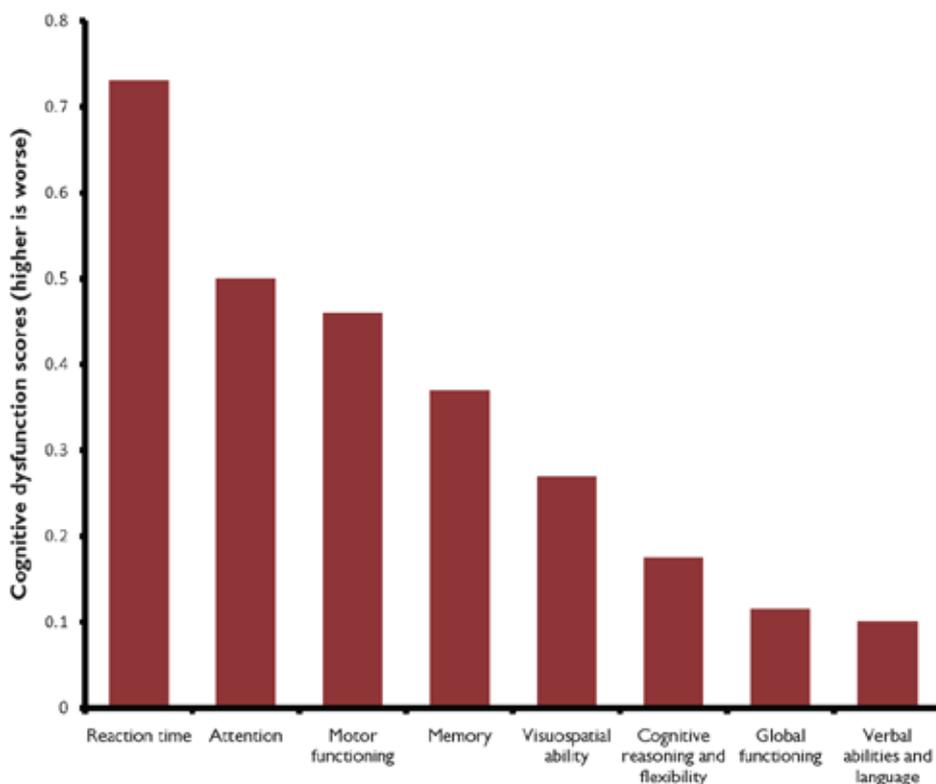
researchers at the University of Adelaide on cognitive performance in ME/CFS confirm some patients' reports, and go further.

In 50 patients, they found that the main cognitive deficit was in ‘reaction time’ (assessed as reaction times to both simple and complex choices presented on a computer screen) – which was about 50 milliseconds slower on average in patients than in the control group of 50 healthy people. They point out that a basic slowing in information processing speed seems to be the cause, rather than a deficit in more complex decision making. Interestingly, the slowing of reaction time was not related to psychological status (including depression or anxiety), the number or severity of ME/CFS symptoms or everyday functioning.

This very active Australian research group also published, in 2010, an excellent overview of all relevant clinical trials examining cognitive functioning in people with ME/CFS. Their meta-analysis found convincing published evidence (see the graph on the left) of deficits in reaction time, attention (encompassing attention span and working memory), and memory (assessed by verbal and visual memory tests, mostly memory for word lists). Moreover, the deficits in performance of ME/CFS patients were around 0.5 to 1.0 standard deviations below those of healthy people, a fact which helps to explain the significant impact cognitive problems have on patients' day-to-day activities and quality of life.

Source: Cockleshell & Mathias, Neuropsychology, 2013

Cognitive deficits in patients with ME/CFS



MANCHESTER

Black and minority ethnic patients

It seems that people from the black and minority ethnic population are two to three times more likely to suffer from ME/CFS than white groups, but (bizarrely) are less likely to be diagnosed with the illness. A group from Institute of Population Health, University of Manchester has been examining why this might be – and what barriers might be in the way.

The researchers conducted semi-structured qualitative interviews with 35 ‘key stakeholders’ in North-West England, including 11 black and minority ethnic patients with ME/CFS and 5 community leaders, 2 carers, 9 GPs and 5 practice nurses. Overall, several barriers were identified, including a

lack of awareness of ME/CFS among black and minority ethnic respondents. Also, religious beliefs and family and community expectations were found to be important, since patients from ethnic minorities may be more likely to manage their symptoms outside primary care using alternative therapies, prayer or spiritual healing.

Language barriers may also make a diagnosis of ME/CFS harder to obtain. One aspect highlighted by the patients themselves was the importance of an ongoing relationship with a GP, something which could be difficult in inner city practices with a high turnover of doctors.

The need for additional training for health professionals is stressed by the authors, who say, "Patients, carers and community leaders described how they believed that some GPs may hold stereotypical views of people from certain cultures such as being 'lazy', 'complainers' or 'work shy'", views which might prevent a proper diagnosis. There is also a need for culturally sensitive, educational resources for patients to explain symptoms and encourage them to come forward for help.

Source: Bayliss et al, Primary Health Care Research & Development, 2013

MASSACHUSETTS

Vagus nerve infection?

Given the evidence of the involvement of infectious agents (virus or bacteria) in ME/CFS, the prevailing view is that its symptoms reflect an ongoing immune response to infection, possibly because of immune system dysfunction. However, a recent hypothesis paper article goes much further, speculating that infection of the vagus nerve itself might be the cause of the illness.

Dr VanElzakker from Tufts University in Massachusetts postulates that a viral or bacterial infection causes activation of glial cells (which support and protect nerve cells) somewhere along the vagus, which is a long, highly branched nerve travelling throughout the visceral organs, including the gastrointestinal lining, lungs, lymph nodes, spleen, liver and heart. Glial cell activation then produces inflammatory substances which bombard the sensory vagus nerve, sending signals to the brain to trigger a range of involuntary symptoms, including myalgia, fever, fatigue, sleep architecture changes and



cognitive abnormalities. Importantly, when glial cell activation becomes pathological, as in neuropathic pain, the signals can be intensified and intractable, leading to chronic illness. According to the author, variation in ME/CFS between patients could be explained by the location of infection along the vagus nerve pathway, the severity and duration of the body's response, and the type and severity of infection.

One advantage of this theory is that it simplifies the quest to find specific infectious causes of ME/CFS – since any pathogenic infection of the vagus nerve can trigger the symptoms of the disease. But is the hypothesis true? Well, only experimentation can answer that question, and possible strategies include basic biomedical imaging of the vagal nerve pathway from the peripheral to central nervous system, or even functional neuroimaging studies if these are feasible.

Source: VanElzakker, Medical Hypotheses, 2013

BRISTOL

Treatment outcomes

More than 8,000 adults are assessed and treated by specialist NHS 'CFS/ME' clinical teams every year in the UK, but little is known about the outcomes for patients. Fortunately, a longitudinal cohort study has just been published, using data from six 'CFS/ME' specialist services between

January 2005 and December 2009. In the 5 years, 1,643 patients had been seen, but follow-up data 12 months after the initial consultation was available only for 834 (51%).

Overall, there were significant improvements in fatigue (of 6.8 points on a 0–33 scale), physical function (4.4 points on a 0–100 scale), anxiety (0.6 points on a 0–21 scale) and pain (5.3 points on a 0–100 scale). Importantly, patients who were less physically able at the initial assessment had higher levels of fatigue, depression and pain at follow-up. Similarly, patients who were in more pain initially, had worse scores for all outcomes at follow-up.

The NHS specialist 'CFS/ME' services in England follow the 2007 NICE Guidelines in offering cognitive-behavioural or graded-exercise therapy, along with activity and sleep management. These strategies are mainly intended to help patients better cope with their situation, not to cure the underlying disease, so it is perhaps not surprising that the outcomes seen in this study were relatively modest overall. Indeed, they appear to be less effective in this 'real world' setting than in formal clinical trials. As the authors point out, while these NHS services are moderately effective in improving fatigue in patients with ME/CFS, they seem to be much less effective in improving physical function than similar treatments delivered in clinical trials, something that they say requires urgent investigation.

Source: Crawley et al., QJM, 2013

RAZZLE DAZZLE

Recent fundraising for ME research



Modus pop-erandi

Anna Pearson and fellow Fashion Retail Management students at Birmingham City University put on a spectacular 'Take a seat in the 1920s' event at the Custard Factory Theatre, Birmingham on Tuesday 26th February 2013 in support of ME Research UK.

Organised by Modus Events, the evening promised class, razzle-dazzle and a little bit of sunshine – and it gave all three, plus a showing of the movie Chicago, a raffle and, of course, popcorn.

We applaud their marvellous fundraising efforts, and we also thank Birmingham Rotary Club for their additional donation, and the fashion retailer Gap which may generously provide matching funding.

Pyjama party

Victoria Anderson kept her pyjamas on all day on Sunday 12th May, but she wasn't having a long lie. "My dad suffers from ME," said Victoria, "and this year a bunch of us thought it would be a great idea to do

something to mark ME Awareness Day, raise awareness and raise funds for charity."

Victoria and her friends Lynsey and Anne Marie, all from West Lothian, came up with the idea of having a sponsored pyjama day, wearing their pyjamas from 9 am to 9 pm. If they needed to go out, they were allowed to wear coat, shoes, hat, scarf, gloves etc., but to keep their PJs on underneath. The day was great fun and very successful, so thank you Victoria, Lynsey and Anne Marie.

Going, going, gone

Too late to turn back now, Jono! On Thursday 4th April, Jono Hoskins sacrificed his two-years-in-the-growing dreadlocks to raise funds for ME Research UK. Jono's mum has ME, and as he explains, "she had to retire from her job and was housebound and often in a wheelchair. While she is much better, she still suffers from constant pain, balance problems, concentration and memory issues and is overwhelmingly tired."



He soared through his initial fundraising target – the basic level needed for his dreadlocks 'sacrifice' to be worthwhile – so his head was shaved, leaving his hair short for the first time in nearly a decade. Thanks to Jono and all his supporters at the University of the West of England's Bower Ashton Campus!



65th birthday

To Anne Baxter, a belated 65th birthday greeting and massive thanks for her staunch support of ME Research UK. Anne held her birthday 'bash' at The Wooden Doll, North Shields to raise funds for us. Many happy returns to you, Anne!

Craigmore viaduct lights up for ME

The members of the Newry & Mourne ME/FM Group are great supporters of our charity and they managed to get the longest railway viaduct in Ireland illuminated in blue to raise awareness of ME.

At 9.20 pm on 25th May 2013, the Mayor of Newry, Councillor John McArdle, 'flicked the switch' to light up the 126-foot Craigmore Viaduct (an Tarbhealach Craig Mór) near Bessbrook in County Armagh. The bridge suddenly turned deep blue, bathing the surrounding area in a warm 'ME' glow, and remained lit for 3 weeks. The story we put on our Facebook page was our most 'viral' single posting ever – seen or shared by 5528 people – thanks to the stunning photograph opposite by Noel Moan published in the Newry Democrat. We thank both him and the editor, Patrick Ryan, for allowing us to reproduce it in *Breakthrough*.



St Andrews University student charities

We had great fun earlier this year at the St Andrews University Student Fayre, where charities competed for the votes of the 3,000 students! The winners of the vote were chosen as 'charity partners' in the University Charity Campaign 2014, and we were up against stiff competition. In the end, the lucky organisations were Macmillan, Maggie's and Médecins Sans Frontières, but we still had a grand day speaking to the students about ME – and Dr Vance Spence even managed to meet a nice teddy bear (who was really Craig Anderson, the student who had suggested us for the competition).



Following the 'Test Way'

The 'Walk for ME' campaign in May was very successful indeed. The idea was that the family and friends of a person with ME would do a sponsored walk, which is something that their loved one would like to do but can't because of their illness.

We had 20 people, and a hamster, taking part in UK, Spain and the Blue Ridge mountains of Virginia, and one was Bill Haywood Smith, walking for 22-year-old Emily whose life was turned upside-down by this debilitating and devastating illness nearly 10 years ago.

Bill walked the entire length of the River Test, following the 'Test Way' which is 44 miles from the river's source in Berkshire to its mouth at Southampton Water. Thank you, Bill – a marvellous thing to do!

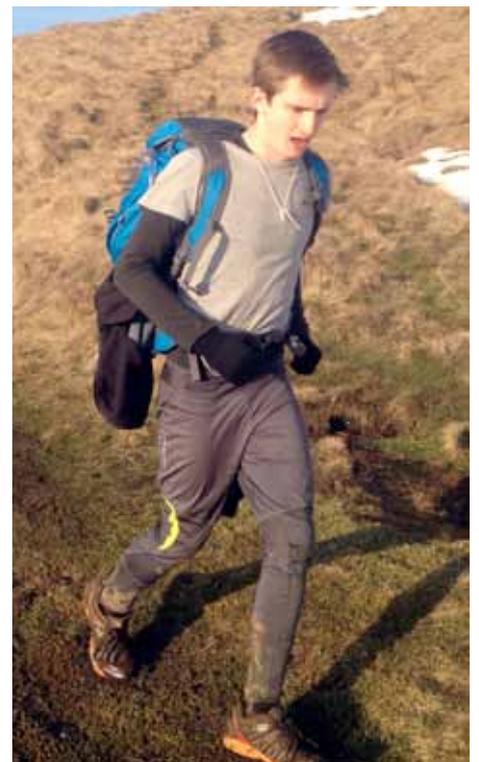
Ultra fundraising

Tough Mudder events are 12-mile-long, hardcore obstacle courses designed by the Special Forces to test all-round strength, stamina and mental grit. And 20 year-old Matt Rimmington (right) – whose mother has ME – is doing a Tough Mudder as part of his training for an Ultra Marathon which he's running on our behalf.

The particular Ultra Marathon is the 56-mile race from London to Brighton, which has to be completed in under 13 hours, and it took place on 22nd September 2013. Matt's JustGiving page at justgiving.com remains open for donations and messages, so please support him if you can.

Inaugural fundraising ladies lunch

The Royal George Hotel, Perth was the perfect venue for our first ever Ladies Lunch attended by supporters both old and new. The Very Rev Dr James A Simpson (pictured above with our team; photo courtesy of Angus Findlay Photography) regaled the company with wit and pearls of wisdom which set the tone perfectly for a most convivial lunch. Our raffle proved to be a tremendous success and, together with our special auction, raised a truly fabulous total for research purposes.





Stephen Fry tweets for research into ME

ME Awareness Week happens every year around the date of Florence Nightingale's Birthday (12th May), and it gives us all the opportunity to bring the disease to the attention of the general public. As we all know, ME/CFS affects around 200,000 people in the UK alone – almost twice the number with multiple sclerosis which receives far more attention – so we need to do all we can to get the message out to the widest audience!

Stressing the importance of biomedical research, ME Research UK decided to launch a 'Thumbs Up to ME Research' campaign on Facebook during ME Awareness Week. Each day, we added a new Facebook posting, covering aspects of the illness and the need for scientific investigation. And we'd asked supporters to get their friends and relations to 'like' our Facebook page and share the postings across the Internet – to let their fingers do the walking and give a 'Thumbs up to ME research'.

We were dramatically helped when actor, writer and polymath Stephen Fry agreed to start the campaign off by tweeting about

the need for research into ME. Stephen likes to tweet about issues rather than for individuals or particular charities, so his posting at 'coffee time' on Monday 13th May said: "Give a 'Thumbs Up' to ME Awareness Week and show that research matters", and linked back to our Facebook page.

Stephen has one of the largest Twitter fan-bases on the Internet – 5.76 million followers to date – so the potential for getting the awareness message across was enormous.

Buoyed by Stephen's publicity, our daily Facebook postings that week, such as "Let's be Aware of Severely Ill People with ME" and "Let's be Aware of the Science of ME", (see page 9) proved to be particularly popular, and reached the eyes of 52,000 people!

It was very hard to find major stars willing to 'tweet for ME' – so a big hug to Stephen for sensationally highlighting this disease.

Visit to Vrije Universiteit Brussel

From 5th to 7th June, Dr Vance Spence and Dr Neil Abbot visited Vrije Universiteit in Brussels at the invitation of Prof. Jo Nijs

(pictured below at the Brussels Atomium) for a series of seminars. Prof. Nijs leads one of the most active research groups on ME/CFS anywhere in the world, and has received several funding awards from our charity.

The group has investigated circulating protein levels during exercise, reported abnormal central pain processing linked to post-exertional malaise, and investigated the role of central sensitisation in pain. Most recently, with further ME Research UK funding, his team have been exploring definitional criteria (see *Breakthrough*, Spring 2013). Thank you, Jo and colleagues, for the invitation to discuss your findings and hear about your plans for the future!



Standing Order Form

To allow us to press ahead with our mission to Energise ME Research, please consider setting up a Standing Order by completing this form and sending it to ME Research UK, The Gateway, North Methven Street, Perth PH1 5PP.

Name _____

Address _____

Postcode _____

Telephone _____

E-mail address _____

To the Manager, Bank/Building Society _____

Branch address _____

Postcode _____

Name of account holder(s) _____

Account number _____ Branch sort code _____

Please arrange to debit my/our account with the sum of £ _____ on the _____ day of each month until further notice

Starting on _____

Pay to: Clydesdale Bank, 23 South Methven Street, Perth PH1 5PQ, UK

Account: ME Research UK, Account no: 50419466, Branch code: 82-67-09

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Tick if you would like us to treat this, any future donations to ME Research UK, and all payments in the previous 4 financial years, as Gift Aid donations until you notify us otherwise. You confirm you have paid or will pay an amount of UK Income Tax and/or Capital Gains Tax for each tax year that is at least equal to the amount of tax that all the charities or CASCs which you donate to will reclaim on your gifts for that particular tax year – 28p of tax on every £1 given up to 5 April 2008 and 25p of tax on every £1 thereafter. Please inform us of changes in your tax status.

Signature _____ Date _____

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Whether it's books, electronics or toys, Amazon has it all. Provided that you connect to Amazon via one of our links, your shopping will qualify. The amount we get varies according to the type of product and the type of link followed. It won't cost you a penny more, and you won't lose out on other discounts, so please help us by shopping via ME Research UK's Amazon link.

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