breakthrough

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Throwing light on severe ME/CFS

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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.

First published by ME Research UK, 2014

editorial

Bilbo Baggins in *The Lord of the Rings* warned of the dangers of stepping outside the front door, but we face dangers in the home as well, particularly in kitchens and bathrooms where thousands of people have accidents every year. These are personal risks, but what about the dangers faced by organisations? What about risks to charities?

There's a whole area of charity governance concerned with 'risk management'. Basically, it concerns the identification and management of possible and probable risks that a charity may face over its working life. Most are foreseeable and can be pre-empted by simple steps such as sound planning and close financial management. But some risks are unforeseeable – "*events, dear boy, events*," in Harold MacMillan's famous words. A recent example was the closure of the Chronic Fatigue Syndrome Research Foundation, following the unexpected death of its founder and driving force Anne Faulkner in 2013 (see page 14). Founded in 1992, it was a pioneer in its time, and its unexpected demise is a sad example of unforeseen circumstances.

The single most important risk faced by charities concerns their dependence on income sources which can vary greatly from month to month or year to year. Research charities are particularly vulnerable since they have to be ready to commit large amounts of money as potentially important projects come along. That's why we try to focus on creativity and innovation in securing income

in a consistent manner, and why we've targeted legacies for particular consideration in this issue of *Breakthrough* – a legacy pledge form is enclosed with this issue.

Although it is a sensitive subject, legacy giving has the potential to enhance considerably our income and future success. Research projects are expensive, but they do deliver scientific results that are so beneficial for changing attitudes and increasing awareness. By leaving a legacy you can make a direct and lasting contribution towards our vital work. As John F Kennedy said, "*There are risks and costs to action. But they are far less than the long-range risks of comfortable inaction.*"

Jan McKendrick
Trustee, ME Research UK

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this issue

Throwing light on severe ME/CFS

Around 10 to 25% of ME/CFS patients are reported to be housebound or bedbound, yet we still understand very little about the origin and outcome of their severe illness. We know, however, that the cumulative impact of profound illness over many years, where there is no sense of improvement, can be profound. Because of all this, it is astonishing that even the most basic clinical or scientific work has not been carried out on this important subgroup of people with ME/CFS.

Prof. Newton and colleagues at Newcastle University are leaders in the assessment of autonomic nervous system dysfunction in a range of diseases, and since 2006 they have received six project awards from ME Research UK to advance our understanding of ME/CFS. In an impressive series of scientific papers, they have uncovered a range of biological anomalies, and their main finding has been that autonomic nervous system dysfunction contributes significantly to the symptom burden and quality of life of ME/CFS patients, affecting standing, blood pressure regulation, muscle function and cognition.

Their research culminated in an award from the Medical Research Council to explore the relationship between autonomic nervous system impairments and the neurocognitive symptoms (including deficits in memory and attention) that are some of the most frequent and disabling symptoms associated with ME/CFS.

For many years, ME Research UK and Prof. Newton have been concerned about the chronic lack of research interest into severe ME/CFS, and the serious void that exists in the scientific knowledge-base about this group of patients. So, when ME Research UK awarded a large programme grant to the researchers in Newcastle in 2014 (see the story opposite), it was decided to initiate a specific project investigating housebound or bedbound individuals who are unable to attend clinics or take part in research projects (which often require hospital attendance and multiple clinic visits).

The two-year project will be conducted day-to-day by the newly funded ME Research UK Research Associate. The first task will be to identify severely affected ME/CFS patients from a variety of sources, including the records of the Newcastle Clinical Service, local patient support groups, and national registers. This will give an indication of how common severe ME/CFS is in this particular area of North-East England, and identify specific patients to be included in the investigation.

For the investigation proper, the Research Associate will make home visits to patients, and will undertake a series of specific assessments, including:

- Recording of demographic information, such as length of illness, mode of onset, provision of social care, receipt of benefits, etc.
- Autonomic testing at rest to gauge the presence of autonomic nervous system dysfunction.
- ME and CFS diagnostic criteria assessment, using the DePaul Symptom Questionnaire.
- Neurocognitive testing (e.g. memory, concentration and executive function) using software-based tools, since neurocognitive symptoms are some of the most common and worrying.
- Assessments of muscle strength, using dynamometer and manual physical techniques.
- Activity monitoring using a 24-hour actimeter.
- Assessment of symptoms, including information from sleep and activity diaries.
- Recording of patients' own experience of illness and treatment, and the impact of the disease.

Overall, the aims of this exploratory study are to throw light onto this severely overlooked group of patients, define their clinical characteristics, gauge the level of unmet clinical need, and determine the relationship, if any, between autonomic nervous system dysfunction and other clinical variables.

Subsequent progress will depend on what these investigations uncover and where the science leads. Crucially, however, a start will have been made on the serious scientific investigation of housebound and bedbound people with ME/CFS.

Prof. Julia Newton with ME Research UK chairman Dr Vance Spence

Programme Grant to Newcastle

In May 2014, the trustees of ME Research UK gathered for a visit to Newcastle University Medical School. The visit was to hear about the progress of research studies they are funding, and to unveil a plaque marking the charity's latest award – a Programme Grant to Prof. Julia Newton to advance biomedical research into ME/CFS.

The funding awarded will be used mainly to advance scientific investigation into severe ME/CFS (see the story opposite), undertaken by a newly appointed ME Research UK Research Associate. Some of the grant award will also be directed towards pump-priming smaller 'proof-of-concept' or early experimental investigations, as it can be very difficult for researchers to obtain funds for these initial studies. As Dr Vance Spence said, "*ME/CFS is an 'orphan' illness in terms of clinical recognition and research, and Prof. Newton leads one of the most successful and dedicated teams researching the condition anywhere in the world. In fact, she initiated this research herself after observing the profound impact of the illness on patients! This is the first ever Programme Award made by ME Research UK, and it is a measure of our confidence in the research undertaken by Julia and her impressive team of senior collaborators at Newcastle University.*"

After the unveiling, there were a range of research presentations, some from researchers engaged in work funded by ME Research UK. Dr Audrey Brown described her fascinating studies into abnormalities in muscle cells of ME/CFS patients; her *in vitro* model involves simulating 'exercise' in isolated skeletal muscle cells using a C-Pace EP multi-channel stimulator, and observing changes in a variety of cell signalling molecules. Dr SarahJayne Boulton of the Institute of Cellular Medicine described her collaborative work developing intracellular nanosensors for the investigation of muscular dysfunction; in the context of ME/CFS, she and Prof. Mark Birch-Machin are using spectrophotometry of cultured cell samples to examine the complexes of the mitochondrial electron transport chain.

Dr Joanna Elson of the Mitochondrial Research Group at the University, who specializes in population genetics and computational methods, described her studies on mitochondrial DNA mutations and their relevance to ME/CFS. Dr Andreas Finkelmeyer of the Institute of Neuroscience, whose expertise is in functional magnetic resonance imaging, described his efforts to tease out the role of autonomic nervous system dysfunction in the illness, with particular emphasis on changes in blood flow to the liver.

The site visit ended with a tour of the clinic area of the Falls and Syncope Unit in which some of the clinical studies take place, and the Cardiovascular Laboratory which is one of the largest autonomic testing labs in Europe and has all the necessary equipment and expertise for comprehensive autonomic testing. As Julia said rounding off the day, "*For the past 8 years, ME Research UK has provided the pilot funding for many distinct projects, which have produced the data on which our successful applications to the MRC were based and which have resulted in a range of scientific papers. This shows what can be achieved by biomedical researchers and research charities working collaboratively to drive science forward.*"

Vitamin D and vascular function

When people think of vitamin D deficiency, they think of rickets and its devastating effects on human populations. Yet, rickets is now recognised to be merely the extreme end of a spectrum of possible disorders; in effect, the tip of the vitamin D-deficiency iceberg.

Recent scientific work – centring on the discovery that 'vitamin D receptors' are widely distributed in the body and can be found in most cells and tissues – has thrown new light on this vitamin and its role in a variety of key functions. In particular, there is great interest in the part played by vitamin D (or its deficiency) on the risk of chronic illnesses, including autoimmune and infectious diseases, common malignancies, and cardiovascular disease.

Why might this be important in ME/CFS? Well, as a chronic illness with immune, infectious and cardiovascular aspects, there is at least a possibility that vitamin D deficiency/insufficiency could somehow be involved. Also, vitamin D inadequacy has been linked with impaired neuromuscular functioning and chronic pain, two important facets of the day-to-day experience of ME/CFS patients.

Given the possibility of links between vitamin D and ME/CFS, ME Research UK awarded funding to Dr Faisel Khan of the Institute of Cardiovascular Research in Dundee – who has worked for many years on cardiovascular factors in a number of diseases – to test vitamin D levels in already-collected samples from two studies previously funded by our charity.

The results of these preliminary studies were published in the *International Journal of Cardiology* in 2014. In the 41 patients for whom full data were available (their mean length of illness was 9.7 years, and all were of white European descent), levels of the main circulating form of serum vitamin D ranged from 7 to 108 nmol/L. Circulating vitamin D levels correlated significantly with age but not with sex or body mass index. Most importantly, the researchers found significant correlations between circulating serum vitamin D levels and markers of inflammation, oxidative stress, endothelial function and arterial stiffness.

As the authors point out, observational studies like this one cannot prove that vitamin D deficiency is causing impaired vascular function or the symptoms of ME/CFS, particularly as the interplay between the vitamin and physiological function is complicated.

Nevertheless, the results are intriguing. In other illnesses, such as type 2 diabetes, high-dose vitamin D has been shown to improve endothelial vascular function. To see if this is also the case in ME/CFS, we have funded Dr Khan and colleagues to undertake a clinical trial of high-dose vitamin D supplementation, and the results of this larger study will be published shortly.

Dr Faisel Khan

Vitamin D deficiency

The major cause of vitamin D deficiency is inadequate sunlight coupled with insufficient dietary intake, but medical conditions that limit its absorption or impair conversion of vitamin D into active metabolites (e.g. liver or kidney disorders) can also be responsible. Deficiency/insufficiency can affect tissues or processes, such as:

Bone metabolism
Protein or mineral content of bone can be reduced (osteoporosis), or there can be a loss of bone (osteopenia), leading to osteomalacia and weakness.

Muscle function
Skeletal muscles have a vitamin D receptor and may require vitamin D to function optimally since a deficiency is associated with muscle weakness.

Immunity
Vitamin D deficiency tends to increase the risk of infections, such as tuberculosis and influenza.

Cancer risk
Vitamin D regulates the expression of genes associated with cancers, but whether its deficiency *per se* increases the risk of cancer remains unproven.

Cardiovascular dysfunction
Low levels of circulating vitamin D are associated with important cardiovascular risk factors, such as high blood pressure, increased vascular resistance, increased heart left ventricular mass, and increased calcification of the coronary vessels.

£1 million research overview goes online

This year, ME Research UK reached a milestone, topping the £1 million mark in grants awarded to researchers. The results of the 35 specific biomedical projects have now been published as 58 research papers in peer-reviewed scientific journals. To mark this achievement, we produced a special 32-page edition of *Breakthrough* magazine, entitled *£1 million of biomedical research* and over 3,000 copies were distributed to friends and supporters with the previous issue of *Breakthrough*. We've now put an electronic copy on our website for everyone to see, so please share it with family and friends.

Written in plain English, the aim of the overview is to give non-scientists an easily digestible overview of the research we have funded over the years, alongside a list of the particular projects and the scientific papers published. As our Chairman Dr Vance Spence says, "*We are proud of our record, but we know that none of it would have happened without the hard work and generosity of our supporters. I am so grateful to you all.*"

So, what does our overview reveal? Well, the most important take-home message is that physiological abnormalities and biological anomalies can be found in ME/CFS patients if scientists have the funding – and the drive – to uncover them. For too long, the prevailing wisdom among some policy makers and healthcare professionals was that scientific investigation was largely unnecessary, since the primary disturbance in people with ME/CFS was psychological.

We now know this to be false: scientists can certainly find physical abnormalities (e.g. autonomic nervous system dysfunction, neutrophil apoptosis, arterial stiffness, impaired recovery from exercise, increased oxidative stress) and non-specific psychological therapies are not curative, though they may help to manage symptoms.

The overview also points up a crucial fact: that biomedical research is a long-term enterprise, involving decades-long commitment by researchers and funders. This is particularly true for ME/CFS which receives a fraction of the research interest and funding given to other chronic illnesses. Most often, it's only after a critical mass of investigators has produced a critical volume of biomedical data that patterns begin to emerge, and this is why we've tried to provide continuing project-on-project support to researchers early in their investigations when it can be particularly tough to get funding. In fact, funding is the key to progress. A significant proportion of research funding for all diseases comes from charitable sources (£1.1 billion each year in the UK alone) – this is what makes the role of ME Research UK so important.

We have we funded more specific biomedical projects on ME/CFS than any other organisation outside of North America, and are proud of what we have achieved. But we need to get cracking on raising the next £1 million. Please help if you can.

Problems with vision

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 few 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.

For that reason, ME Research UK awarded a grant to Dr Claire Hutchinson of the Vision and Language Research Group, University of Leicester to identify and quantify vision-related problems in the disease. To date, the group have published two robust scientific papers. In the first, they showed that ME/CFS patients were less able than healthy people to focus selectively on a specific target while ignoring other irrelevant information, and that patients were slower when it came to moving their attention to a target, slower at scanning, and more easily affected by 'distractors' on the screen (see *Breakthrough*, Autumn 2013).

Their second paper revealed that eye movement dysfunction was a prominent feature, and that patients performed worse than healthy people in tasks that required quick and accurate movements of the eyes. Intriguingly, the visual deficits seemed to be related to age in the ME/CFS patients but not in the healthy people, suggesting that older

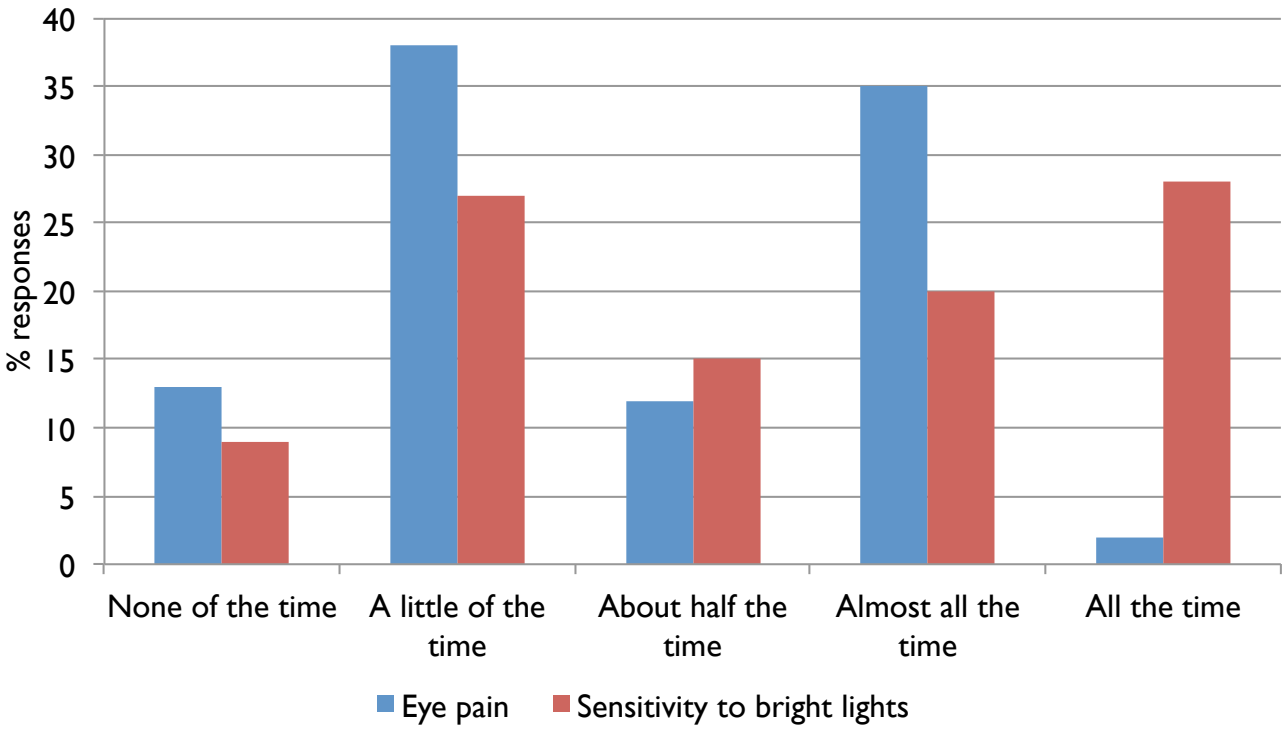
adults with the illness are less able than young adults to compensate for ME/CFS-related vision deficits (see *Breakthrough*, Spring 2014).

The researchers have just published a third, descriptive report describing the visual symptoms (eye pain, sensitivity to bright lights, problems with focusing or attention, and loss of depth perception) experienced by their ME/CFS patients. To record these symptoms, they used the recently developed DePaul Symptom Questionnaire, a standardised measure designed to assess core symptoms.

All 59 ME/CFS patients (39 women and 20 men) included in the study reported having no history of eye disease, yet 92% had some degree of sensitivity to bright lights; 88% were unable to focus vision and/or attention; and 86% experienced eye pain (see the graph below). Fewer people reported loss of depth perception, but this symptom was still present in around 60% of the group. Each of these symptoms was severe or very severe in more than 30% of the patients, and there was a close relationship between severity and frequency of symptoms.

The researchers' aim in publishing this report in the *British Journal of Ophthalmology* is to increase awareness among healthcare professionals, including ophthalmologists, of the importance of problems with vision in ME/CFS.

As they point out, their report "*adds to an emerging body of evidence that vision-related symptoms represent a significant clinical feature*," that might be useful for diagnosis. Yet these symptoms are not presently included in clinical and diagnostic guidelines, such as the NICE Guideline in the UK.



Information on ME/CFS: what's out there?

ME/CFS is a potentially chronic illness experienced by approximately 200,000 people in the UK and one million in the USA. This makes the disease twice as prevalent as multiple sclerosis, systemic lupus or HIV infection. A number of reports and guidelines have been written on the disease over the years.

Some are more useful than others and none are ideal, but all contain at least some information that can be put to good use in certain contexts: to inform GPs, to support advocacy, to quote to journalists, to share with families and friends, etc.

The documents below are those that we have found most useful, for a variety of purposes, over the past decade. Copies of each are widely available on the Internet, and some can be obtained from ME Research UK. Our website contains many more documents, however, including earlier literature on epidemics of myalgic encephalomyelitis.

ME/CFS: A Primer for Clinical Practitioners, 2012
(IACFS/Myalgic Encephalomyelitis, Chicago, USA)
Developed by clinical consensus, this primer was written for the clinical practitioner, and it contains advice on diagnosis and on possible therapies.

Myalgic Encephalomyelitis – Adult & Paediatric: International Consensus Primer for Medical Practitioners, 2011
(*Journal of Internal Medicine*, 2011; 270: 327–38)
Using the Canadian Consensus Criteria (below) as a starting point, the International Consensus Primer uses more recent knowledge to develop clinical criteria and provide clinicians with a "one-stop, user-friendly reference".

Diagnosis and Management of CFS/ME in Adults and Children, 2007
(National Institute for Health and Clinical Excellence, London)
This official NICE guideline, with recommendations, concludes, "*The physical symptoms can be as disabling as multiple sclerosis… congestive heart failure and other chronic conditions.*"

Scottish Good Practice Statement on ME-CFS, 2010
(The Scottish Government, Edinburgh)
This document provides GPs with guidance to assist with differential diagnosis and clinical management. It underpins two other summary documents – a quick reference clinical guide and a guide for patients.

ME/CFS: Clinical Working Case Definition, Diagnostic and Treatment Protocols, 2003
(*Journal of Chronic Fatigue Syndrome*, 2003; 11 (1): 7–116)
The 'Canadian Consensus Criteria' document outlines a working clinical case definition, and reviews research to 2003 and available symptomatic therapies. A useful 'short version' has been produced and printed, and copies are obtainable from a variety of sources.

Report to the Chief Medical Officer of an Independent Working Group, 2002
(CFS/ME Working Group, Department of Health, London)
One of the first attempts to bring together what was known about ME/CFS, the report concludes that ME/CFS is "*a relatively common clinical condition, which can cause profound, often prolonged, illness and disability, and can have a very substantial impact on the individual and the family*".

The Clinical and Scientific Basis of ME/CFS, 1992
(Nightingale Research Foundation, Canada).
This 725-page reference book is still available in hard or electronic form from the Nightingale Research Foundation.

As different names have been used to describe the disease (postviral fatigue syndrome, ME/CFS, chronic fatigue syndrome, etc.), these publications use an array of different terms and sometimes confusing acronyms. But don't be put off – each, in its own way, emphasises the seriousness of the illness and points up the need for action.

Widespread neuroinflammation?

There are good reasons for thinking that problems with the central nervous system are involved in the development of ME/CFS, and it is certainly possible that inflammation of the brain (neuroinflammation) has a key role. However, proving the existence of neuroinflammation requires specific neuroimaging methods, and these had never been applied to ME/CFS patients – until Japanese researchers bit the bullet earlier this year.

The team at Osaka City University in Japan, which has been studying ME/CFS for many years, used PET brain imaging to try to obtain direct evidence of neuroinflammation. They measured the density of 'translocator protein' produced when certain brain cells are activated – it is the activation of these cells which indicates that inflammation is taking place. In this case, the particular brain cells were microglia (thought to be the main form of active immune defence in the central nervous system) and astrocytes (the most numerous brain cells, with functions including nutrient supply, repair, and nerve impulse transmission).

The researchers recruited 9 people with ME/CFS (Fukuda 1994 and ME-ICC 2011 definitions) and 10 healthy controls, all of whom underwent PET scanning involving the injection of a tracer followed by dynamic scanning over 60 minutes. Participants also completed questionnaires about symptoms, including fatigue, pain and neurocognitive problems.

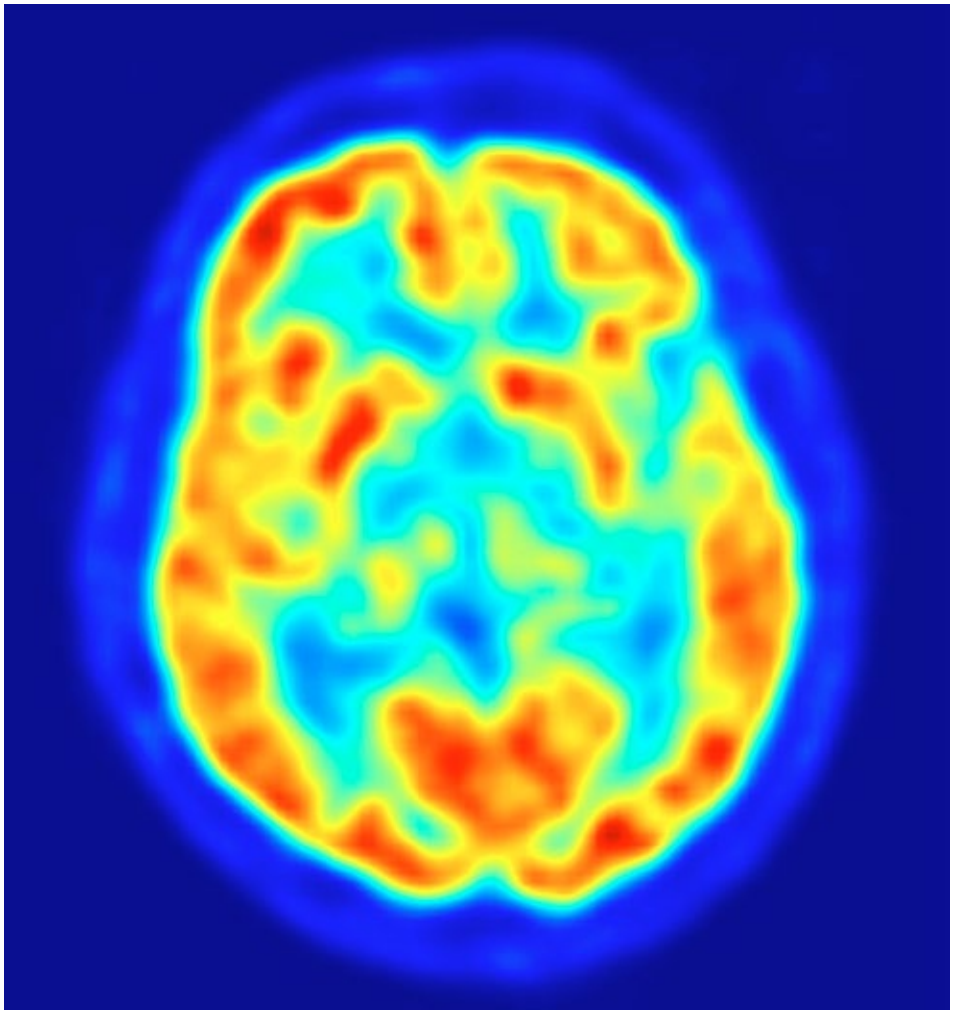
The researchers' report in the *Journal of Nuclear Medicine* revealed that protein levels (indicating inflammation) were higher in ME/CFS patients than controls in "widespread brain regions", including the cingulate cortex (199% higher), hippocampus (81%), thalamus (66%), midbrain (47%) and pons (45%). Intriguingly, protein levels in some brain regions were significantly associated with the severity of particular symptoms; some of these associations were quite striking despite the small number of patients, as in the correlation between protein level and cognitive impairment scores ($r=0.94$, $p<0.0002$).

The authors conclude that "*neuroinflammation is present in widespread brain areas*" in ME/CFS patients compared with healthy people. They point out that this may be due to an immune response to an underlying infectious process, or possibly to over-activation of nerve cells (for whatever reason).

There are several things to bear in mind, however. First, patient numbers were small, so the findings in this pilot study will need replication – one swallow doesn't make a summer, and one scientific report does not convince, though it might fascinate. Second, protein levels were relatively low in absolute terms, raising intricate methodological issues associated with standardisation in PET imaging. The authors are to explore this particular aspect in the next phase of their work on ME/CFS patients, an international collaboration study that will use a different, second-generation tracer and have a refined methodology. Lastly, inflammation (as measured with PET imaging from higher-than-normal translocator protein density, as in this report) occurs in many conditions. Similar PET findings have been reported in patients with brain injury, cancer or peripheral inflammation, as well as in more chronic inflammatory conditions like Parkinson's disease and MS.

So, the importance of this study is probably not that the evidence of inflammation is 'specific' to ME/CFS, but that it has been demonstrated so clearly. For instance, these results will have come as a surprise to anyone – including some healthcare professionals – sceptical about the 'reality' of the illness.

If these dramatic and fascinating results can be reproduced, objective evidence of an inflammatory process in the brain of people with ME/CFS may become readily available for incorporation into diagnostic protocols and for treatment-monitoring purposes, with enormous consequences for patients and their families.



IACFS/ME conference 2014

The 11th Biennial IACFS/ME conference, "Translating Science into Clinical Care", was held in San Francisco in March 2014 and recorded just under 400 attendees, the highest number in the past 15 years. Part of the reason for the success may have been the pre-conference research meeting on ME/CFS at Stanford University Medical Centre, and the presence of speakers such as Prof. Ian Lipkin, Prof. Abraham Verghese and Prof. Noel Rose.

ME Research UK was one of thirteen external organisations supporting the conference, and our booth in the exhibition hall was manned by our Development Director. Attendees were able to visit our booth and have a chat (and some candy) during the breaks and exhibitions. One was De Paul University's Prof. Leonard Jason, and others included researchers from ME Research UK-funded institutions such as Laura McLachlan and Andreas Finkelmeyer from Newcastle University, and Eliana Lacerda and Erinna Bowman from the UK Biobank.

In his opening address, IACFS/ME President, Dr Fred Friedberg, explained that the aim of the conference was to provide fresh, updated perspectives on ME/CFS, hence the Patient Conference and a series of specialist workshops which overlapped with the joint sessions at key moments.

The first keynote lecture was by Prof. Ian Lipkin – described by Discover Magazine as the "world's greatest virus hunter" – who has extensive experience of HIV, SARS and pandemic influenza, and who was lead investigator of the definitive study that disproved the link between ME/CFS and the XMRV virus.


© Louis Grenier

Later in the opening day there was a keynote lecture by Stanford physician and author, Abraham Verghese, on the importance of the doctor–patient relationship in the genomic era, and presentations on medications, including antivirals (Dr Jose Montoya) and immunomodulators (Prof. Nancy Klimas), and workshops on severely ill patients (Dr Charles Lapp) and legal aspects of disability (Dr Steven Krafchick).

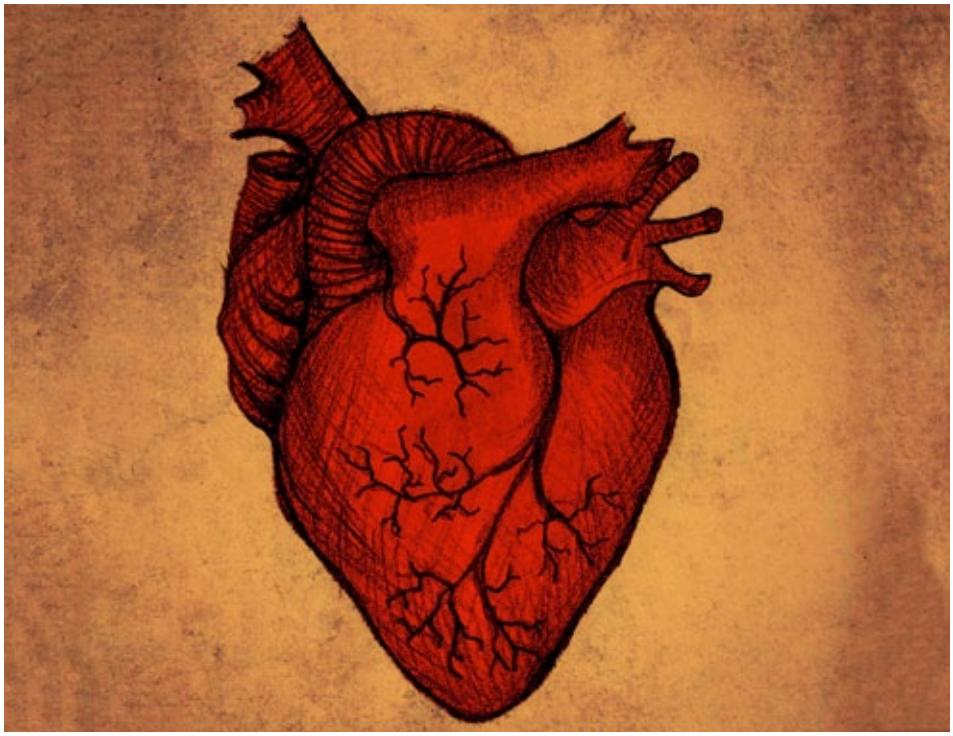
Dr Kenneth Friedman, IACFS/ME board member

The keynote lecture on the second day came from Prof. Noel Rose, an expert on autoimmune disease from Johns Hopkins, followed by presentations on immunological research, including allergy-related immune signatures, plasma cytokines, natural killer cell degranulation and subset distribution, and genome-wide analysis. A later session on virology research contained work on chronic pelvic pain, markers of human parvovirus B19 infection, and chronic enterovirus infection. Long-standing ME/CFS researchers Dr Dan Peterson and Prof. Nancy Klimas chaired meetings on treatment studies and methods of diagnosing difficult clinical cases.

In his 40-minute summary concluding the conference, Dr Anthony Komaroff of Harvard Medical School highlighted the ME/CFS-specific biobanks which now exist in the USA and UK; the evidence from immunological studies, including the Stanford inflammation studies; the relevance of studies on virology and infectious agents; the potential role of exercise provocation studies; and issues surrounding investigations in paediatric patients.

ME Research UK was delighted to have been a supporter of the conference. As our Development Officer said, "*The whole event went splendidly, and the Board of the IACFS/ME deserve congratulations for bringing off another engaging meeting – the most important conference of its kind in the field of ME/CFS anywhere in the world.*"

Research bites from around the world



SOUTHAMPTON

NHS provision for severely ill patients

"Ignored and invisible" – that's how the Chief Medical Officer's report described the most severely ill ME/CFS patients in 2002. Have things improved in the intervening 12 years?

The Department of Primary Care and Population Science in Southampton recently undertook an assessment of current NHS provision for severely ill patients, and their report has just been published. The researchers contacted all 49 English NHS specialist 'CFS/ME adult services' in England with a questionnaire about their methods.

The main research question was how closely these units were adhering to current NICE guidelines for severe ME/CFS. All 49 specialist CFS/ME services replied, and amazingly one-third said they provided no service for housebound patients. Only 55% of services treated patients with severe illness, and their interventions followed the NICE guidelines, while the remaining services offered only occasional or minimal support. In the whole of England, there was only one NHS unit providing relevant, specialist in-patient provision. Clearly, there is a long way to go before housebound or bedbound patients get the recognition and treatment they deserve, which gives added urgency to our study on the severely affected (pages 4 to 5 of this issue).

Source: *McDermott et al., BMJ Open, 2014*

JAPAN

Orthostasis and heart abnormalities

We now know that many ME/CFS patients have orthostatic intolerance – the inability to stand upright for long without symptoms such as dizziness, altered vision, nausea, fatigue, headache, etc. In 2011, researchers at the Miwa Naika Clinic in Toyama, Japan described a subgroup of ME/CFS patients with relatively small hearts in whom orthostatic intolerance was associated with a low 'cardiac output' (the amount of blood pumped by the heart in a certain time). The same team has just finished a new study on 40 ME/CFS patients (ICC-ME 2011 criteria) and 40 healthy controls, with interesting results.

Orthostatic intolerance was assessed from self-reported symptoms, plus blood pressure and heart rate changes during a 10-minute standing-up test, along with measurements of cardiac function. Almost all of the patients (97%) were found to have orthostatic intolerance on the stand-up test and, in many, orthostatic intolerance took the form of POTS (i.e., an increase in heart rate of 30 beats/min or more, or a heart rate of at least 120 beats/min during the standing-up test).

As regards measurements of the heart and circulation, most were significantly smaller in the ME/CFS group than in the healthy people. In fact, compared with healthy people, it was far more common for the left ventricle of the heart to be smaller in patients than controls (less than 40 mm in diameter) in the 'end-diastolic' phase just before a contraction (45 versus 3%), and for the patients to have a low cardiac index (53 versus 8%), which is a measure of the heart's performance relative to the size of the person.

The high incidence of orthostatic intolerance found by the Japanese research group is no great surprise; orthostatic symptoms are also found in many Western patients, though, sadly, their presence has not yet been incorporated into official clinical and diagnostic guidelines, such as the NICE Guideline in the UK. It is the cardiovascular measurements that are particularly intriguing, however. Other investigators have also reported a reduced cardiac volumes in ME/CFS patients, and it is certainly feasible that an impairment of flow, particularly to the brain, could underlie fatigue and other symptoms.

Source: *Miwa et al., Heart and Vessels, 2014*

LONDON

Post-mortem brain and tissue bank

Along with other charities, we helped to establish the UK ME/CFS Biobank at the London School of Hygiene & Tropical Medicine for the storage of blood and blood

products. The ideal over the long term, however, would be a tissue bank of other kinds of samples, accessible to researchers all over the world. There are many difficulties in setting one up and, fortunately, the Biobank team in London have just developed and published a good protocol outlining the elements needed to set up a UK ME/CFS repository of high-quality human tissue.

The researchers reviewed the operation of existing tissue banks from a range of sources, arriving at a protocol designed to meet high technical and ethical standards and legal requirements based on recommendations of the MRC UK Brain Banks Network and the Brain Net Europe II network.

They found that the facility would be most cost-effective and efficient if incorporated into an existing tissue bank, and that tissue collection should be "*rapid and follow robust protocols to ensure preservation sufficient for a wide range of research uses*". A central tissue bank would need resources both for wide-scale recruitment of potential donors and for there to be a rapid response to a donor's death to allow prompt 'harvesting' and processing of tissue.

There are also logistic, technical and ethical issues surrounding the physical establishment of a tissue bank, but the keystone, of course, is sustainable funding, ideally involving research councils, health services and charities.

Source: *Nacul et al., BMC Research Notes, 2014*

CHICAGO

A rational basis for diagnosis?

An intriguing report was published recently in the *International Journal of Machine Learning and Computing* – an unusual home for a scientific paper on ME/CFS. The researchers from DePaul University in Chicago used 'unsupervised machine learning' (a series of statistical techniques for finding hidden structures in data) to examine information on ME/CFS patients collected using the DePaul Symptom Questionnaire (DSQ).

They brought together information collected at three different sites: data collected during an ME Research UK-funded study on the use of the DSQ in patients at the UK's Newcastle University; data collected by DePaul University itself; and BioBank sample data from the CFIDS Association of America. All 515 patients and 176 controls were classified according to their fulfilment of three case definitions originally developed by consensus but not by experimentation (Fukuda 1994 CFS, Canadian 2003 ME/CFS, and ICC 2012 ME), and the raw data was then put through 'machine learning' techniques.

The upshot was that an 'empirical' definition based on the selection of eleven specific symptoms seemed to provide greater diagnostic accuracy than any of the three consensus-based criteria. The symptoms included fatigue/extreme tiredness; next day soreness or fatigue after non-strenuous, everyday activities; minimum exercise causing physical tiredness; feeling unrefreshed on waking; and muscle weakness. If this intriguing attempt to establish a rational, experimental basis for a diagnosis is found to be valid, it could end arguments over the relative merits of the many consensus definitions (of CFS, ME, ME/CFS, CFS/ME) that currently exist, and simplify diagnosis at the bedside or clinic.

Source: *Watson et al., Int J Machine Learn & Comput, 2014*

CANARY WHARF

ME/CFS and market failure

Recently, there was a short but insightful essay on the Reuters website by Edward Hadas outlining the case for ME/CFS to be taken far more seriously – from an economic perspective. He points out that modern economies work to meet consumers' needs. Yet, when it comes to healthcare, sometimes unhelpful ideologies get in the way of economics delivering the goods.

In the case of ME/CFS, the economic benefit of treating this difficult condition should be obvious to drug-makers and society, yet treatment is poor and symptoms are sometimes "*dismissed as physical manifestations of psychological difficulties*".

He explains that ME/CFS is the sort of complicated condition that high-tech, high-expense healthcare systems are supposed to address effectively, but are failing so to do. In his view, the main reason that the physical condition ME/CFS has been left so long to the "*psychological crowd*" is that it does not fit with the traditional model of infectious disease. If it did, there would be far more interest from the healthcare industry.

He sees some improvement in the situation, though. Some scientists are taking an interest, and some leading researchers now see the disease as a complex and multi-system failure. Their work could lead to a medical, intellectual and economic triumph, but the severe lack of mainstream financial support is holding them back. In his words, "*That makes no sense, even on the crassest and narrowest economic calculation. Treatments or vaccines for CFS are likely to turn out to cost less than the value of the labour that is currently lost to the disease.*"

Source: *Hadas E, 11 June 2014, blogs.reuters.com*

RICKMANSWORTH

Fond farewell to CFSRF

The closure of the Chronic Fatigue Syndrome Research Foundation (CFSRF) following the unexpected death of its driving force Anne Faulkner, on 7th November 2013, marks the end of a chapter in the history of ME/CFS research. Founded in 1992 by Anne and her late husband Hugh, the CFSRF was, like ME Research UK itself, one of the very few organisations anywhere in the world dedicated to funding biomedical research into ME/CFS.

In its lifetime, the foundation's total research spend was £1,970,000 on 20 different projects, from which 20 papers were published in the scientific literature. The bulk of its projects (15) were initiated in the decade 1992 to 2002, and those focused on virus, muscle and mitochondria. Later, the CFSRF targeted most of its funding (£961,000) towards studies of gene expression in ME/CFS at St George's University of London, and it was fortunate to be able to rely on wealthy independent backers to fund this expensive programme of research. While the putative ME/CFS 'gene signature' discovered was eventually found to be too insensitive for use as a broad diagnostic test for the illness, the attempt was valiant, and the CFSRF deserves credit for supporting this ambitious programme of work.

The CFSRF was a pioneer in its time, and its success, particularly in its first decade, was due to the street-level fundraising efforts of patients, their families and friends who wanted simply to get biomedical research off the ground. The landscape for scientific research charities has changed dramatically since 1992, yet commitment – the ability to keep going forward through the ups and downs – is as vital as it always was. Anne and Hugh understood that, and the CFSRF and its work is a fitting testament to their vision and commitment.

CALIFORNIA

OMF's vitamin B12/folate trial

The Open Medicine Foundation and Institute is starting a collaborative study, led by Dr David Kaufman and Dr Andreas Kogelnik, of the effects of vitamin B12 and/or folate supplementation in ME/CFS patients. Although there has been very little recent research into this topic, one report from 1993 found low folate levels in half of ME/CFS patients, and another in 1997 linked B12 levels with fatigue. In fact, some doctors treating ME/CFS patients prescribe B12 injections to help with 'brain fog' and fatigue, and some patients report improvements over time using the therapy. Over a decade ago, Dr Charles Lapp authored an essay, "Using vitamin B-12 for the management of CFS" which still makes interesting reading; as he said, "*The mechanism has yet to be defined, but in my clinical experience, large doses of B12 provide improvement in energy and well-being in a majority of CFS patients.*"

In the new study, B12/folate will be given to ME/CFS patients with and without *MTHFR* gene mutations. As the researchers' point out, if this mutation (commonly found in neuro-immune patients) is present, people may also need to take folate for B12 to work effectively. A successful outcome could open the way for this relatively simple, low-cost treatment to be made more widely available. It may also encourage healthcare systems to include the treatment in new published guidelines on ME/CFS.

LONDON

ME/CFS is more than a meme

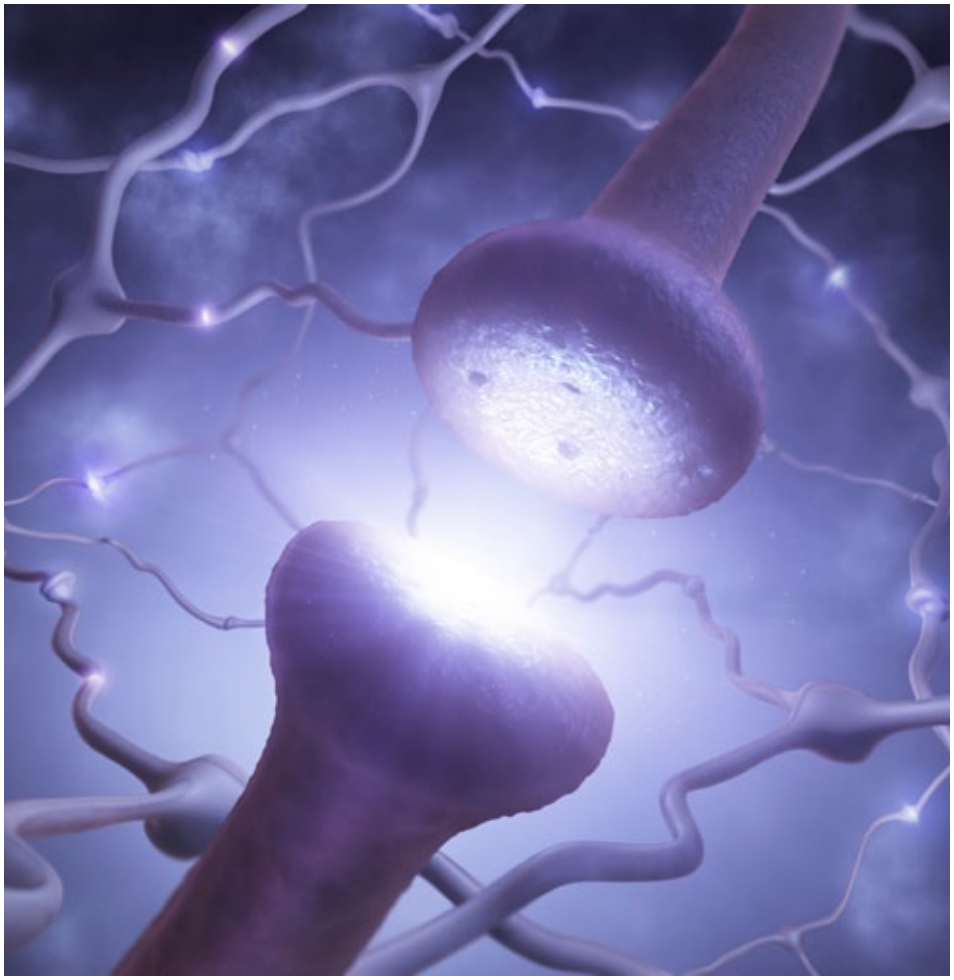
According to Richard Dawkins in his book *The Selfish Gene*, a meme is "*an idea, behaviour or style that spreads from person to person within a culture*". In June 2014, a piece on the *British Medical Journal*'s website asked how well 'chronic fatigue syndrome' fits the model of a meme-mediated syndrome – a "*dysfunctional culturally-transmitted idea-infection*". The authors concluded that "*characteristics of transmission and retention of CFS fit well the characteristics of meme transmission… Present mainstream treatments for CFS make sense when viewed as a process of de-meme-ing.*"

In a 'rapid response' published on the *BMJ* website, ME Research UK's Dr Neil Abbot pointed out that memes are ideas or groups of ideas; they have no independent existence outside of human minds. The things of the world are not memes, however. Leprosy, for example, is an infectious illness that would exist as a fact of the world whether anyone ever 'conceived' of it or not. Similarly, with ME/CFS. People meeting

the definitions of ME/CFS certainly exist (around 200,000 of them in the UK); their physiological illness is plain for anyone with eyes to see; and research frequently uncovers objectively existing biological abnormalities.

Examples from ME Research UK-funded studies over the past 14 years include dysfunction of the autonomic nervous system; impaired cardiac function, including reduced cardiac mass and blood volume; increased levels of oxidative stress, and increased apoptosis of white blood cells; the presence of cardiovascular risk factors with arterial stiffness; and biochemical anomalies in children. He concluded that "*ME/CFS is much more than a meme; it is very real, it should be taken as seriously as any other medical condition, and patients should be treated with respect.*"

Source: *Abbot NC, British Medical Journal, 2014*



MARYLAND

Movement restrictions in young patients

In biomedicine, a joint that has a reduction in its ability to move is said to have a limited 'range of motion'. The most common cause is a mechanical problem at the specific joint, most often seen in the arthritic diseases accompanied by swelling, stiffness and pain. In an unusual study, researchers at the University School of Medicine in Baltimore have examined 'ranges of motion' in the limbs of young people with ME/CFS – with fascinating results.

The study included 48 adolescents and young adults with ME/CFS and a control group of 48 healthy youngsters. Test manoeuvres included ankle dorsiflexion (where the toes are stretched upwards), passive straight-leg raising, a seated slump, an upper-limb neurodynamic test (assessing tension, particularly of the median nerve), prone knee bend, and prone press-up – all designed to examine how restricted participants were in particular bodily movements.

The young people with ME/CFS had a significantly greater number of body areas with impaired ranges of motion (5 areas in patients versus 2 in controls, $p<0.001$) at the start of stretch, and they were far more likely to have more than 3 areas where the range of motion was impaired. Also, patients were more likely to develop abnormal symptoms, such as fatigue, light-headedness or headache, after testing (44% of ME/CFS patients versus 0% of the controls).

The various physical examination manoeuvres used in this study to test range of motion add an 'elongation strain' to the nervous system and associated soft tissues. The authors speculate that ME/CFS patients, even at this young age, have a reduced compliance in their nervous system and connective tissue, and therefore an increased sensitivity to mechanical movement which limits their daily activities and contributes to symptoms. The next step is to tease out the mechanisms underlying these curious results.

Source: *Rowe et al, Journal of Pediatrics, 2014*

CHICAGO

Low nerve proteins

It is well known that levels of brain derived neurotrophic factor (BDNF), a protein involved in the development of peripheral and central nerve cells, are lower in patients with multiple sclerosis than in healthy people. This is no surprise, as BDNF is involved in supporting the survival of existing nerve cells and repairing damaged nerves. The real surprise comes from De Paul University, Chicago, which has found BDNF to be reduced to a similar level in ME/CFS patients as well.

For their pilot study, the team measured BDNF levels from a blood sample, finding that they were far higher in healthy controls (1114.15 pg/mL) than in either multiple sclerosis patients (573.33 pg/mL) or people with ME/CFS (404.71 pg/mL).

For the authors, this unexpected and novel finding suggests that the ability to maintain a normal nerve structure and function is reduced in ME/CFS patients. The extent of the reduction from normal levels (64%) in ME/CFS is also striking, and contrasts with smaller reductions in other groups of patients; for example, one investigation on 'burnout' patients found BDNF levels to be reduced by only 15% compared with normal values.

We already know that there are similarities between multiple sclerosis and ME/CFS as regards some disease characteristics and symptoms. If very low BDNF levels can be conclusively shown to be a shared characteristic, the processes of nerve survival and repair will become a key target for future ME/CFS research.

Source: *Sorenson et al, J Neurol Neurophysiol, 2014*

Shining a Light

Recent fundraising for ME research

Lighting up Belfast

ME Support Northern Ireland waved its magic wand again, and managed to have many buildings lit up in blue during ME Awareness Week in May 2014.

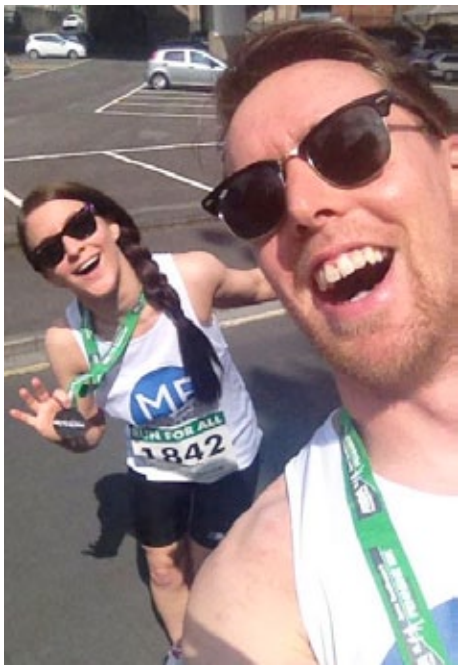
The Great Hall of Stormont, made entirely from Italian travertine marble, looked dramatic bathed in blue, as did Newry City Hall, Newry Arts Centre, Bessbrook Town Hall and the Craigavon Civic Centre. The great coup was to get Belfast City Council to light up Belfast City Hall; as Antoinette Christie says, "*The idea was to light up structures blue to 'Shine A Light on ME'.*" The city hall first opened its doors in 1906, but had never been ME blue before.

Grateful thanks go to Maeve McLaughlin, the MLA for Foyle, and members of the Committee for Health, Social Services & Public Safety who agreed to sprinkle magic on ME Awareness Day.

Smile, please!

Our supporters Elizabeth Ellis and Ashley Holt (pictured right) were obviously delighted after running the Lancaster Pennine 10k on 22nd of June. They completed the course – which starts and finishes in Burnley and takes in three of the town's pretty parks – in an impressive 58 minutes, well ahead of most of the other 1500 runners.

As Lizzie explains, "*A member of our family suffers with this condition and so it is a cause close to our hearts. Sadly, there is very little known about the illness, so we were running to raise awareness.*"



The Graticast

Chip Colquhoun and friends have been creating a series of YouTube videos, The Graticast (youtube.com/user/graticast), to raise awareness of ME. Their films are aimed at people who may never have thought about the illness but whose support is vital if we are to get research funded.

The videos aren't specifically about ME, but the illness always gets a mention, and the weekly updates aim to help viewers look on the bright side of life, based on all the frustrating things that happen to the presenter, Chip.

It's an ambitious and exciting project, and in the first episode Chip discussed questions such as "*Will Chip beat sunglasses dude to the supermarket checkout?*" and "*Will there be enough sausages to go round?*"

Trek around Pembrokeshire

Gwyn Hopkins had ME for 5 years, first bedbound then progressing to a reclining wheelchair and eventually to 100% recovery. She now helps to raise awareness of ME and raise money for research. In May, she set off on a 155-mile, 7-day trek round Pembrokeshire, and her JustGiving page gave daily reports of bluebell woods, spectacular views, and slurry pits she passed on the way. She also raised awareness of a newly formed Group for ME and FM in West Wales – contact us for further details.

The longest day

What a great idea and a terrific challenge: to cycle for a whole day and see how far you get! And that's just what Hal Bransby (pictured right) did, although he chose the longest day of the year (21st June) to do it.

Raising funds for ME Research UK all the way, Hal set off from Croyden at 4.43 a.m. and headed west to see how far he could get before the sun set at 9.21 p.m. His route took him through Sutton, Epsom, Basingstoke, Stonehenge (for a well-deserved Wiltshire pasty), Castle Cary, and into Exeter for 7 p.m. (for a cup of tea).

The ride ended on Dartmoor where Hal's wife, children and parents were waiting to congratulate him. How far did he travel? Well, he managed 211 miles in total, and his JustGiving page is still open for donations if you want to give him a push.

Virgin London Marathon 2014

Jessica Page has sent us a nice photo of herself (see below) celebrating her London Marathon run earlier this year. Jessica is an experienced runner who was using her individual place to raise funds for us.

We also had another runner that day, John Ritchie, who last did the London marathon in 2012, and who was taking part this year for his father "*and the many thousands like him who are affected by this chronic illness*".

John completed the 26.2-mile course in 3 hrs 48 min, and Jessica in 4 hrs 22 min. A big thumbs up for Jessica and John from all of us at ME Research UK.

Swimming Lake Windermere

"*One of my oldest friends and one of my newest friends have both been diagnosed with ME. I feel helpless watching how it drains and ravages their day to day lives, and I stand in awe of how they carry on bringing up families and getting through each day the best they can.*"

These are the words of Leigh Fleming, (pictured below with her family and ME sufferer Wendy Kachmarski) who completed the Great North Swim on Lake Windermere in 1 hour and 24 seconds.

It was a fantastic day, kicked off by Rebecca Adlington, in which 10,000 swimmers in wetsuits took part in the 3-day event. Leigh is also a researcher, so she wanted to help a research charity – and we're grateful that she did!

Stormont meeting

There was a very successful meeting for parliamentarians and decision-makers in the Parliament Buildings at Stormont earlier this year, attended by around 100 politicians, researchers, health professionals, civil servants and patients. The main speaker was Prof. Mark VanNess of the Pacific Fatigue Lab in California, who discussed the role of exercise and activity management for people with ME or CFS, based on his own experimental work.

Our chairman, Dr Vance Spence, gave the distinguished audience a very concise overview of the research to date under the title "*The science of ME/CFS: What do we know?*" And there were other presentations, including one from patient and campaigner, Horace Reid, who highlighted the desperate need for more research and better health services.

The event was organised by Joan McParland (below) of the Newry and Mourne ME and FM Support group, who gave the audience a very moving presentation about the daily challenges faced by ME patients. Our thanks go to Joan and her team for putting it all together, and for the £1,000 donation from the group presented to Dr Vance Spence for ME Research UK's research programme.

Guinness World Skydivers

They did it! In June, on the longest day of the year, 279 people completed a tandem skydive organised by Skydive UK Ltd and beat the previous Guinness World Record for the most people to skydive in daylight hours.

Among them were ME Research UK supporters Katherine Palmer (pictured above) and Amber Reanna Blackmore (below) who were also using their skydives to raise funds. Not only did Katherine and Amber help break the world record, but the jumps were the highest skydives possible without needing oxygen (15,000 feet) – no wonder the instructor can't bear to look!

Amazingly, Katherine was diagnosed with acute ME in 2009, but she counts herself lucky not to have been bedbound for many years as some patients are.

As she says, "*I did it and it was awesome, and I will definitely be doing it again. I'm glad Amber and I were both raising money for ME research, and we couldn't have asked for better weather! My advice to anyone thinking of doing it? Don't look down!*"

Hair-raising and fundraising experience

Around 20 chaps, including staff, students and family members, had their legs, chests and backs waxed at a charity male waxing event at Eastleigh College's Beauty Salon, Essence, in aid of ME Research UK and Fibromyalgia Association UK.

Pictured below are the beauty students and their lecturer, Vanessa Parker, who 'pulled off' (!) this great fundraising event, along with our Vice Chair Sue Waddle and Jayne Wallace of Fibromyalgia Association UK.

A delighted Sue said, "*This money means an awful lot to us because funding for research is shockingly low for an illness that affects around 200,000 people – efforts like this are essential to our activities. This donation will go towards research.*"

Beauty Lecturer Vanessa Parker said, "*We are delighted to welcome Jayne and Sue to the College to accept the cheques. It's great for the students to learn how their fundraising money will be used.*"

Please return your recycling bags before the end of October

In the last issue of Breakthrough (Spring 2014), we sent out freepost recycling envelopes to allow supporters to recycle their empty inkjet cartridges.

Only inkjet cartridges are recyclable – these are the ones that fit in the palm of your hand and have a circuit board and jet plate on the bottom (it's the circuit boards that have a recycling value when empty).

It seems that Royal Mail is due to change the Freepost address very soon, so we've been asked to let everyone know that the freepost recycling envelopes must be sent to Recycle4Charity before the end of October 2014.

So, if you have between 2 and 5 cartridges (HP or Dell, but not Epson or Kodak), please remember to post them off ASAP.

Recycle 4 Charity

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

giftaid it ○ 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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