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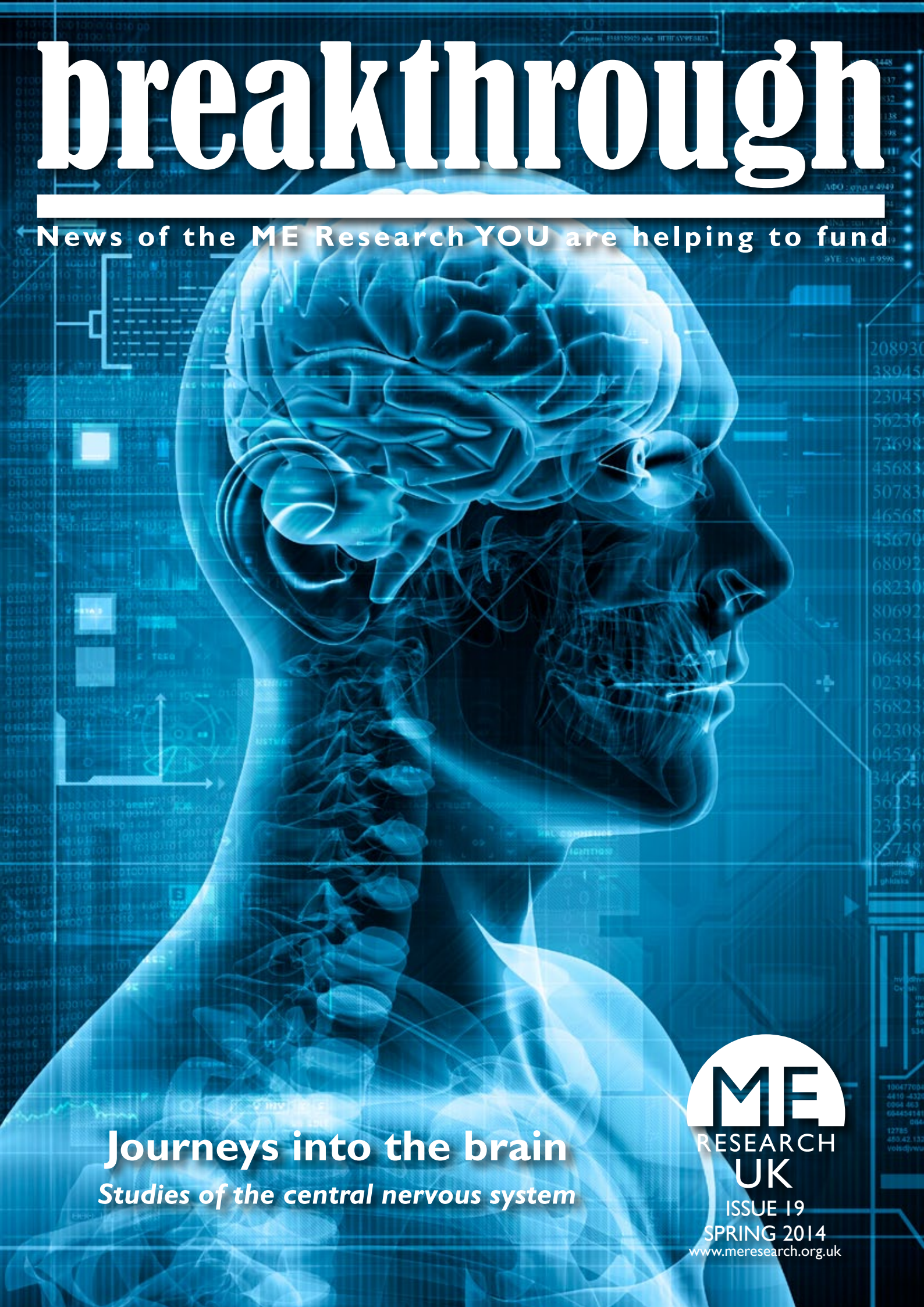

Journeys into the brain

Studies of the central nervous system

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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

Welcome to the spring 2014 edition of *Breakthrough* magazine – the 19th in the series – which explains the research work funded by your donations and other research from across the world. To mark ME Research UK's award of £1 million in grants to scientific researchers, we've also produced a 32-page booklet '£1 million of biomedical research' describing some of the results of our funded projects – a copy is enclosed with this issue.

The aim of this booklet, written with the lay person in mind, is to let you, our supporters, see the breadth and range of the scientific work which has been made possible by your donations. We hope you like it, and that you will spread the news about our work to your family, friends and colleagues.

We are proud of what we have achieved, but research is an expensive business and so much needs to be done. We now need to get cracking on raising the next £1 million – and for this we need your help. To harness the talents of all our friends, we are launching our Ambassadors scheme.

With this issue of Breakthrough, you'll find an appeal from Betty McRae, Founding Ambassador of ME Research UK, asking you to consider joining this exciting scheme. The aim of the initiative is to widen our fundraising base and boost the profile of the charity by building a network of Ambassadors promoting and supporting ME Research UK's work.

As Betty says, "*There are no targets to reach, no pressure to undertake anything that you do not wish to do, and you can choose how to contribute. All I would ask is to be able to count on your enthusiasm and skills.*" Please do read her letter, and think about getting involved.

Of course, there are other ways to help us and, as a new addition to our funding family, we enclose a freepost recycling bag for you to raise funds by recycling your used inkjet cartridges. Let's all work together to raise the next £1 million!

Ed Dunkerley
Trustee, 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.

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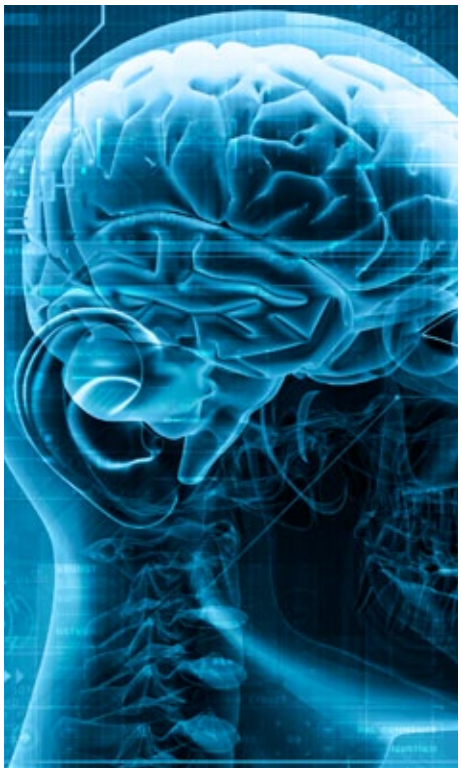


this issue

Interrogating the brain

Experiments with laser-evoked potentials and cerebral blood flow

There are good reasons for thinking of ME/CFS as a disorder of the nervous system. Symptoms such as fatigue, non-refreshing sleep, short-term memory problems, sensitivity to bright light and chemicals, and widespread pain certainly suggest central nervous system involvement. In fact, symptoms consistent with central nervous system pathology were reported with regularity in historical publications on 'epidemics' of ME, as Sir Donald Acheson pointed out as long ago as 1959 in his famous review.

There is now good evidence of hypersensitivity of the central nervous system – called 'central sensitization' – in ME/CFS patients (discussed in the Autumn 2012 issue of *Breakthrough*). In fact, its presence would explain much of what we know about the illness, from the influence of infectious agents and immune dysfunctions, to the inability of the brain to activate the normal pathways of pain inhibition during and following physical activity.

However, there is still no direct evidence of central sensitization; direct monitoring of brain responses to harmful (noxious) stimuli has never been performed in patients with ME/CFS, and such direct evidence is crucial if the scientific world is to be persuaded.

For this reason, ME Research UK has funded a consortium of researchers specialising in neurology, cardiology and rehabilitation at Vrije Universiteit Brussel – led by Prof. Jo Nijs who has been at the forefront of ME/CFS investigation for a number of years (see the box opposite) – to undertake two related studies. Both aim to unravel the abnormal response of people with ME/CFS to exercise and, specifically, the inability of the brain of these patients to activate pain inhibition during and after physical activity.

The first investigation involves directly monitoring the brain responses of ME/CFS patients to (painful) stimuli, a crucial step if the presence of central sensitization is to be confirmed. The team will use a laser to provoke responses in the brain (laser-evoked potentials), allowing them to visualize on EEG how the brain processes harmful stimuli. Previous studies have relied on self-reports of pain, but using these objective methods permits the assessment of brain responses independent of the person's subjective interpretation.

For the study, 20 ME/CFS patients (Canadian 2003 criteria), 20 people with chronic pain but not ME/CFS (patient control group), and 20 healthy sedentary people will be recruited. Stimuli will be delivered to hand and foot by a CO_2 laser, and laser-evoked potentials recorded from two EEG electrodes on the skull.

The researchers' hypothesis is that the size of the laser-evoked potentials will be greater in ME/CFS patients than in the other control groups, a finding which would provide objective evidence of hyper-excitability of the central nervous system in the illness. Interestingly, laser-evoked potentials are

currently used in the diagnosis of neuropathic pain, and could become a standard assessment technique in the assessment of ME/CFS too.

The second study will examine blood flow to the brain. A number of previous studies have suggested that blood flow to the brain at rest is reduced in ME/CFS patients. For example, in 1995 researchers found reduced blood flow to the brainstem, and more recent studies have found cerebral blood flow reductions using a variety of techniques, such as arterial spin labeling (2011) or SPECT imaging (2006).

The Belgian researchers intend to examine what happens to flow during exercise; it may be, for example, that changes in blood flow account for the inability of the brain of ME/CFS patients to activate pain inhibition during physical activity. Part of the experiment will involve assessing the contribution of the autonomic nervous system, which has a central role in the regulation of blood flow to the brain.

This study will have a randomized, cross-over design, and will include 20 ME/CFS patients and 20 healthy, sedentary and pain-free controls. Each participant will have cerebral blood flow measured in the internal carotid arteries using a colour-coded ultrasound system, with autonomic nervous system monitoring and measurement of pressure pain thresholds.

All patients will undergo several dynamic challenges during which the measurements will be taken. These challenges include a Valsalva manoeuver (a standard test of autonomic function); a submaximal exercise test on a seat ergometer bicycle; and an emotional stressor (to control for the potential complicating effects which emotions can have on physiological measurements).

Prof. Jo Nijs

The researchers' hypothesis is that ME/CFS patients may be unable to increase cerebral blood flow sufficiently during exercise, something that might account for the abnormal pain inhibition processing during and following exercise.

Each of these studies has great potential. If objective testing in the first study finds that pain processing in the brain is impaired, or if the results of the second study show that cerebral blood flow really is impaired in response to exercise and is related to post-exertional malaise and/or dysfunctional pain processing, the hunt will be on to discover the underlying mechanisms in the context of ME/CFS.

Scientific progression at Vrije Universiteit Brussel

The research programme led by Prof. Jo Nijs in Brussels is one of the very few examples, anywhere in the world, of a consistent, on-going, progressive approach to tackling ME/CFS.

In most chronic diseases, real breakthroughs come only after years of painstaking work by specialist groups of researchers across the world, so if the scientific enigma(s) of ME/CFS are ever to be solved, the disease must become the main focus of a wide range of investigative programs like the one in Belgium.

Since 2007, the group has received four separate grants from ME Research UK. These investigations have resulted in a series of scientific papers and reviews showing that, compared with healthy people, ME/CFS patients can have:

- Increased sensitivity to pain throughout the body ('central sensitization').
- Abnormal central pain processing linked to post-exercise symptoms.
- Immune abnormalities with similarities to cancer.
- Dysregulation of intracellular immunity which impacts on daily functioning.
- A lower peak isometric muscle strength and a reduced physiological exercise capacity.
- Pain after both experimental and 'self-paced' exercise, even after 24 hours.
- Slower recovery in upper-limb muscle strength after exercise.
- Increased oxidative and nitrosative stress, which may be involved in chronic widespread pain.

As Prof. Nijs says, "*The funding provided by ME Research UK was of prime importance, helping the work of our 'Pain in Motion' research group to expand and helping us to obtain funding from other sources, including the European College for Decongestive Lymphatic Therapy, the Research Foundation Flanders, and the International Association for the Study of Pain (the largest scientific pain society in the world) which awarded a prestigious Early Career Research Grant to Dr Mira Meeus, ME Research UK Fellow*".

Eye movement dysfunction

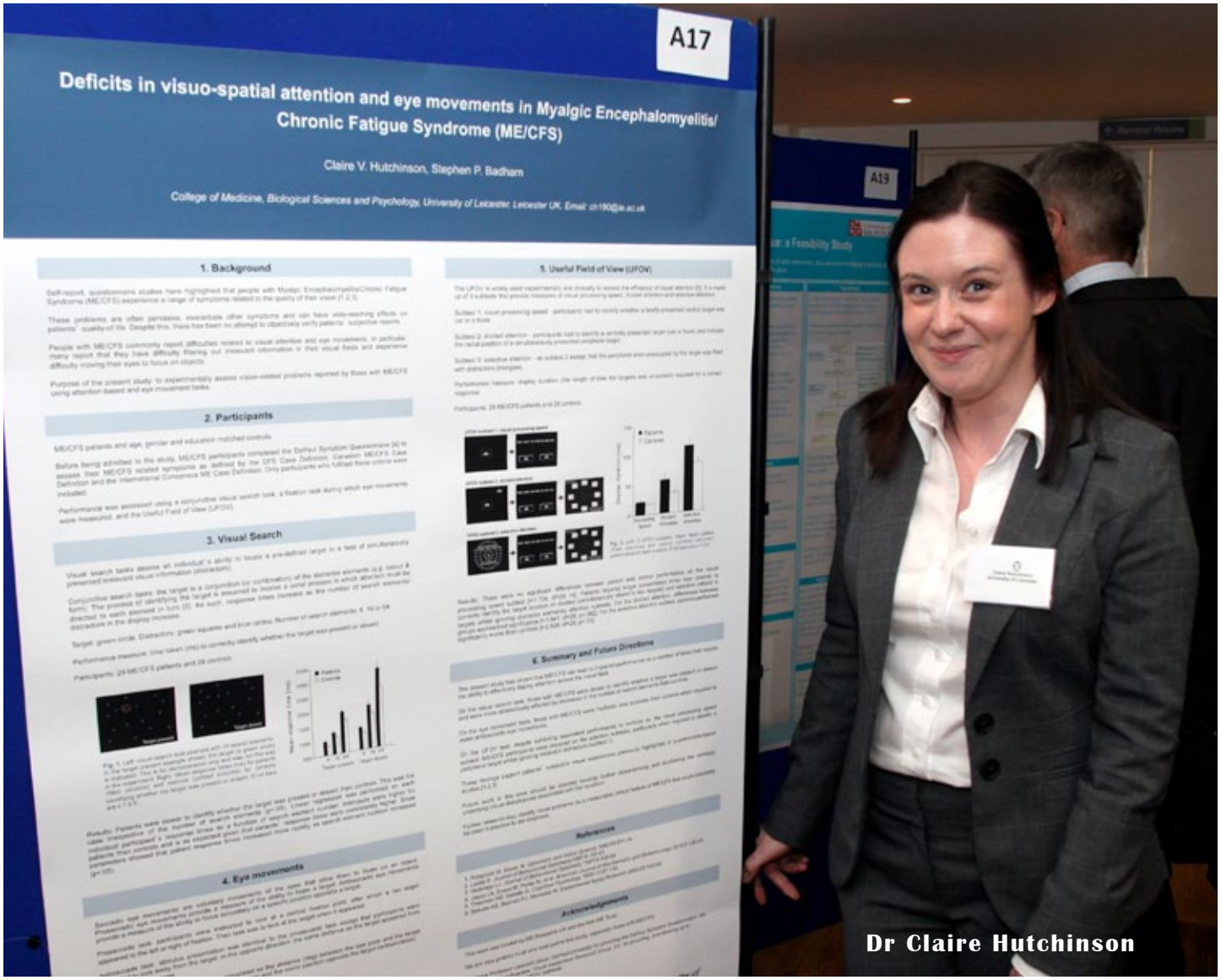
Problems with eyes and vision are common in people with ME/CFS. In fact, around three-quarters of the 2,073 consecutive patients described in one report specifically said that sensitivity to light and dullness of vision were significant problems.

However, apart from a small group of observational studies (see the box opposite), there is very little evidence in the scientific literature that these symptoms exist, even though they greatly affect quality of life and can easily be 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.

Based on the visual symptoms most commonly reported by people with ME/CFS – such as light sensitivity, difficulty focusing and reading problems – the researchers initially set out to test patients' visual awareness (including hypersensitivity to light and difficulty suppressing background visual information). In the last issue of *Breakthrough*, we explained the results of their first scientific paper, which showed that ME/CFS patients were less able than healthy people to focus selectively on a specific target while ignoring other irrelevant information. It also revealed 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.

Now, Claire and Steve have published a second scientific report, describing their experiments on eye movement tracking during 'smooth pursuit' of a slowly moving object, and on voluntary eye movements towards (prosaccade) or away from (antisaccade)



Dr Claire Hutchinson

visual targets on screen. Although the ME/CFS patients and matched healthy controls (20 in each group) were similar in many respects, patients generally performed worse than healthy people in tasks that required quick and accurate movements of the eyes.

In particular, the ability to perform eye movements opposite a target was more impaired in ME/CFS patients, and associated with high positional errors (i.e. discrepancies between the final eye gaze position and the desired fixation point).

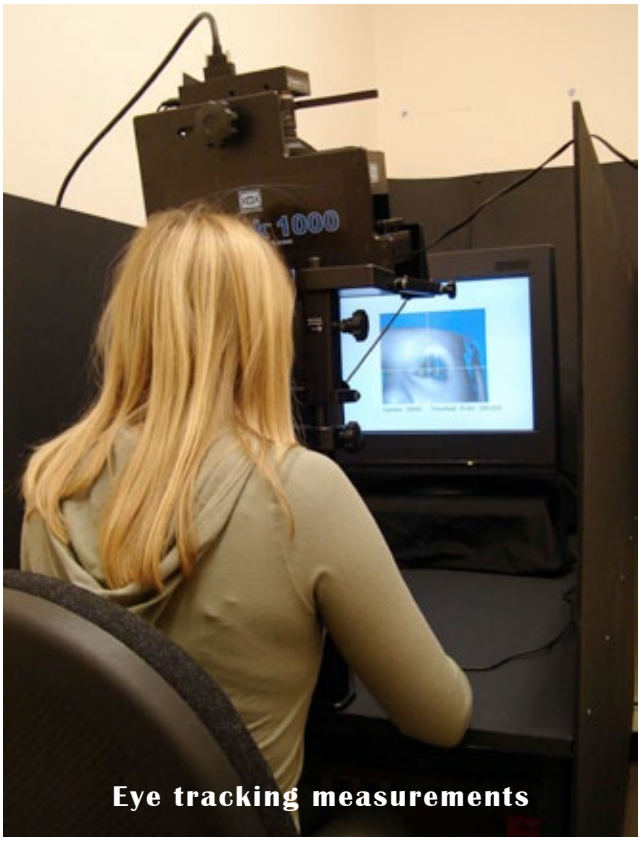
In addition, patients were deficient in their ability to track closely a moving target during 'smooth pursuit' with the eyes, and their performance deteriorated as the testing session went on, something not seen in the healthy people. As the authors point out, it may be that patients are susceptible to fatigue even at these very short timescales – the 'smooth pursuit' requires sustained musculature activity for 30 seconds, and the three test-runs take only 5 to 10 minutes.

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. In fact, the overall impact of ME/CFS may be proportionately greater in older patients, as a recent ME Research UK-funded research from Newcastle University has suggested (see *Breakthrough*, Spring 2013).

In that study, there were distinct physiological and clinical differences between older and younger patients, even though they had been ill for the same length of time.

Older patients not only had more fatigue and depression (and a poorer quality of life), but they had a significantly greater burden of autonomic nervous symptom problems too!

These observations could be very important clinically, as a sizeable proportion of people with ME/CFS present with symptoms for the first time over 50 years of age, and a significant number are aged over 60.


Eye tracking measurements

"Patients performed worse at tasks that required quick and accurate movements of the eyes"

Signs and symptoms in the eyes

In the early 1990s, two reports appeared in the scientific literature reporting ocular (eye) symptoms in ME/CFS. In the first, in 1992, a research group in Boston, Massachusetts surveyed 190 patients and 198 healthy controls by written questionnaire and found a range of eye-related symptoms, which they grouped into categories: functional (related to accommodation and convergence); neuro-sensory (such as headaches, sensitivity to light, and central-peripheral integration disturbances); entoptic phenomena (such as "floaters"); and anterior segment (such as tear-related). In this study, 24.7% of patients had reduced or stopped driving because of eye problems compared with only 3% of controls.

In the second study in 1994, all 25 ME/CFS patients reported eye symptoms; the most common clinical findings were abnormalities of the pre-ocular tear film and ocular surface (19 patients), reduced accommodation for age (18 patients) and dry eyes (9 patients).

Later in the decade, two more reports appeared, both in 1997. One presented three in-depth cases for an audience consisting largely of practising optometrists, concluding that ME/CFS patients can experience symptoms ranging from mild accommodative dysfunction to debilitating disability, while the other report reviewed the visual and ocular signs and symptoms of 141 patients and discussed several management options, including yoked prisms, progressive lenses, tints and ocular lubrication.

Between 2000 and 2010, two further reports appeared. The first was a case–control study in which the 37 patients had significant eye impairments compared with controls; the impairments included foggy/shadowed vision and sensitivity to light, and there were associated problems of eyeball movement (oculomotor impairments) or tear deficiency. The second, from Russia in 2003, reported vascular pathology of the eye in 70.2% of the 218 ME/CFS patients studied, and 'dystrophic pathology' in 52.8%.

It's amazing that that these six smallish reviews and studies represented the sum total of research on eye problems in ME/CFS prior to our recent funding of the vision study in Leicester. Time marches on but sometimes it can seem to stand very still indeed where research into ME/CFS is concerned!

Delayed recovery of muscle strength

The fact that muscles take longer to recover after exertion is characteristic of ME/CFS. In fact, the term myalgic encephalomyelitis (ME) originally referred to a potentially chronic disease characterised by profound, generalised, post-exercise loss of muscle power (fatigability); and, even today, the UK's NICE Clinical Guideline insists that GPs should look for post-exercise symptoms before making a diagnosis.

However, experimental studies showing a loss of power after exercise have been few and far between over the past 30 years, which is why the new scientific paper from Kelly Ickmans, the ME Research UK research fellow at Vrije Universiteit Brussel, is particularly welcome.

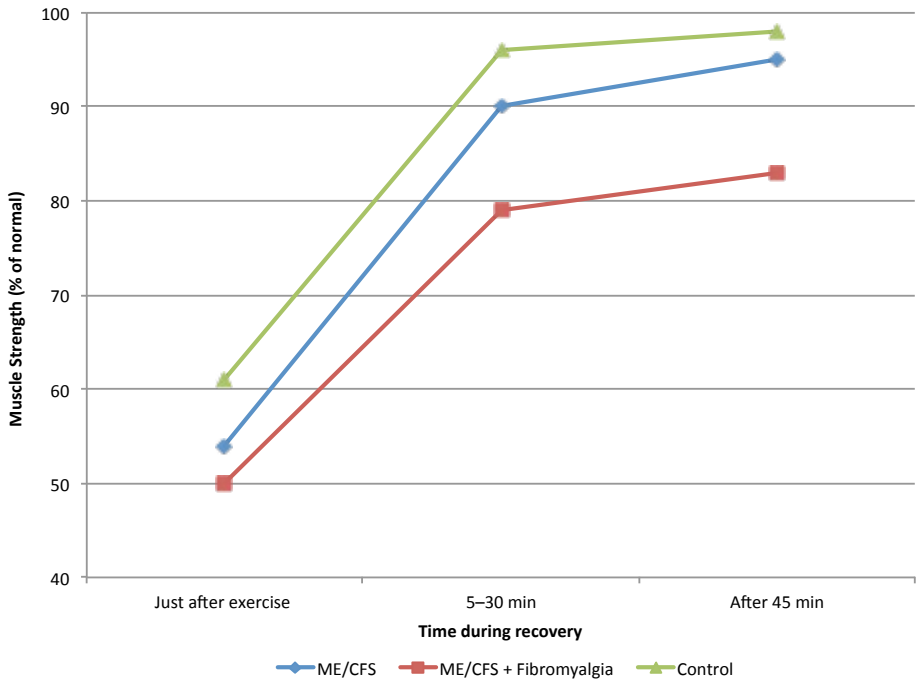
In her report in the *European Journal of Clinical Investigation*, Kelly points out that muscle recovery in the upper limb has never been subjected to detailed research in ME/CFS patients, even though they complain of muscle fatigue in the arms and use these muscles most frequently for everyday activities such as combing and washing hair, ironing and cooking. So, Kelly decided to test muscle function in the upper arm during and after exercise using a simple hand dynamometer which measures force and strength.

The participants (48 ME/CFS patients and 30 healthy, inactive control subjects) were instructed to grip the dynamometer as hard as possible several times to obtain a pre-exercise 'isometric maximum voluntary contraction' value for their non-dominant hand (usually the left). After this, they performed an exercise challenge of 18 maximal contractions, and the recovery in muscle strength was measured over the next 45 minutes.

As the graph below shows, she found that muscle recovery was significantly slower in ME/CFS patients than in healthy people (muscle strength was still recovering 30 to 45 minutes after exercise). However, this was only true for patients who also fulfilled the 2010 criteria for fibromyalgia; i.e. who had a high degree of "widespread pain" as well as other symptoms shared with ME/CFS.


Kelly Ickmans

Recovery of muscle strength was slower in ME/CFS patients



As 43 to 70% of ME/CFS patients also meet the criteria for fibromyalgia, this test could be a low-cost, easy-to-perform way of objectively measuring delayed muscle recovery in a substantial number of people.

We're still not sure why upper limb muscle recovery is delayed in patients. It may be that intracellular acid, which builds up in muscles during exercise, is removed less efficiently, as previous ME Research UK-funded research in Newcastle has suggested (See *Breakthrough*, Autumn 2011). Again, the problem might lie with the circulation, particularly the microcirculation consisting of the smallest vessels, which impacts upon the muscles' ability to remove waste products.

Whatever the underlying physiological reasons for the delayed muscle recovery, Kelly recommends that ME/CFS patients make sure to alternate between physically and mentally demanding tasks in their everyday life, and that they remember not to perform the same physically demanding task for extended periods. Importantly, she points out that these recommendations should be respected by healthcare professionals working with ME/CFS patients.

Severe ME/CFS – what do we know?

Ignored and invisible! When the authors of the Chief Medical Officer's report coined that phrase in 2002 they were referring to the exclusion of the most severely ill people with ME from community and social care provision. But the same description also holds true for mainstream scientific research.

The scientific literature on ME/CFS contains around 6,400 publications, but vanishingly few focus on severely affected patients, who are "ignored and invisible" by science as well. So, what do we know about this important group of ME/CFS patients?

It's thought that between 10 and 25% of patients have severe ME/CFS – housebound, bedbound or immobile. However, the real proportion may be higher: in a members survey by Action for ME in 2000, 34% described themselves as severely affected. This means that they can be counted in thousands in the UK and in millions worldwide – though their voices are rarely heard.

The consequences of severe illness are also severe. In 2002, the Chief Medical Officer's report made clear that severe physical disability with serious mobility restrictions has "*profound effects on personal and social functioning, which in turn substantially affects the patient's ability to access health and social services… These patients suffer from additional problems of invisibility, barriers to accessing all forms of care, variable responses to treatments, and under-representation in research.*"

Prospects for recovery are almost certainly worse for the severely affected than for other mobile, functioning patients, whether adults or children. Apart from anything else, the cumulative impact of *any* severe chronic illness, such as rheumatoid arthritis, MS or ME/CFS, can be profound.

No specific treatments are available. The NICE Guideline of 2007 stated that patients' symptoms can be just as "*disabling as multiple sclerosis… congestive heart failure… and other chronic conditions*", yet it could offer little guidance on the specific care of patients with severe ME/CFS, other than to say that management is "*difficult and complex, and that healthcare professionals should recognise that specialist expertise is needed*".

Biomedical research studies on severe ME/CFS are extremely rare, so we know very little about the biomedical basis of severe illness or its long-term consequences.

Surveys of severely ill patients by the 25% ME Group and Action for ME show that:

a) More than half are unable to attend their GP surgery, yet only a minority of these ever get a GP home visit.
b) One-third waited longer than 18 months for formal diagnosis.
c) Many feel suicidal because of their illness.
d) The overwhelming majority suffer severe pain.
e) Around one-third use a wheelchair.
f) Many say that psychological strategies, such as cognitive behavioural therapy or graded exercise, have not helped or have worsened their condition.
g) Improvements in health can occur – but over time.

For further information, the late Emily Collingridge's book 'Severe ME/CFS: A Guide to Living' (available at severeme.info) is a good reference point for people with severe ME, their loved ones and professionals caring for them. Also, the film 'Voices from the Shadows' (available at voicesfromtheshadowsfilm.co.uk) is a moving documentary about severely ill ME patients. And please remember that 8th August each year is 'Severe ME – Understanding and Remembrance Day', when patients, carers, families and charities undertake events to raise awareness of severe ME and the plight of people with disease, many of whose stories remain untold.

Immune responses to heat shock protein 60

A majority of ME/CFS patients can point to an acute, infectious-like episode as the start of their illness, so the scientific investigation of infection is particularly important. A range of viruses and bacteria have been implicated in ME/CFS at some time, though no single agent has been found to be the 'smoking gun' in a majority of cases.

With funding from ME Research UK and others, Prof. Jonas Blomberg and colleagues at the University of Uppsala in Sweden have been looking for evidence of persistent or past infection in people with ME/CFS. The aim of ME Research UK's support is to 'pump prime' the initial work, which is part of a larger investigation the Swedish group would like to undertake on the development of biomarkers in ME/CFS.

The research group has just published the first report of its findings in the scientific journal *PloS ONE*. Their paper describes the identification of antibodies (which are made by the body in response to an infection) to heat shock protein 60 (HSP60), one of a number of 'stress proteins' made when cells undergo physiological stresses, such as excessive heat, disease or infection. It seems that HSP60 is an element of the 'cascade' of danger signals which results in an immune response by the body.

In a complicated series of experiments on blood taken from ME/CFS patients, other patient groups (including people with multiple sclerosis or systemic lupus) and healthy blood donors, the researchers measured immune responses to HSP60 peptides obtained from different kinds of infection-causing agents.

Their main finding was that levels of antibodies to specific parts of HSP60 were relatively high, both in ME/CFS patients and in control samples. However, significant levels of antibodies to *Chlamydia pneumoniae*-derived HSP60 were present in around a quarter of ME/CFS patients – a far higher proportion than in the patients with other illnesses (0.003%).

Prof. Jonas Blomberg

Chlamydia pneumoniae is a bacterium that infects humans and is a major cause of pneumonia. While the precise meaning of this finding is unclear at present, it is possible that immune responses to certain synthetic HSP60 peptides will come to have a role as biomarkers of ME/CFS – at least in a subset of patients.

In a short article in the Swedish newspaper *Upsala Nya Tidning* earlier this year, Prof. Jonas Blomberg said, "*We know from experience that it is common for patients with diabetes, multiple sclerosis and other autoimmune diseases to have antibodies in their blood that target any part of the HSP60 protein.*

"*A hypothesis based on our findings is that antibodies generated in response to an infection may contribute to symptoms by disrupting the endogenous HSP60 protein's normal functions in mitochondria… However, this is something that needs further exploration.*"

A bedside diagnostic tool?

At present, testing for autonomic nervous system dysfunction is done in a clinical setting – usually in a state-of-the-art assessment laboratory – so there is a need for a simple assessment method that can be used at the bedside or in the patient's home. In fact, a wide range of bedside techniques will have to be developed if severely affected patients are to get the scientific attention they deserve (see page 9).

Prof. Julia Newton, Prof. David Jones and colleagues at Newcastle University are leaders in the assessment of autonomic nervous system dysfunction in a number of diseases. Since 2006, the group has developed one of the few research programmes in the world on ME/CFS, with the support of organisations like the MRC and ME Research UK (which has awarded it five grants).

In an impressive series of scientific papers, the researchers have shown that autonomic dysfunction, in all its aspects, contributes significantly to the symptom burden and quality of life of ME/CFS patients. It affects standing, blood pressure regulation, muscle activity and cognitive functions, such as the memory and attention problems which are frequent and disabling symptoms.

Prof. Newton has amassed a multi-disciplinary team of clinical collaborators, and one of them, Dr James Frith of the UK NIHR Biomedical Research Centre in Newcastle, has been assessing the role of measures of blood pressure variability, which is controlled by the nervous system, in the assessment and diagnosis of ME/CFS.

In a scientific paper in the *Quarterly Journal of Medicine*, Dr Frith has described his attempts to derive simple markers of autonomic dysfunction using a Task Force Monitor, a device which gives beat-to-beat data for heart rate, blood pressure and other key areas of the vascular system using non-invasive, easy-to-use technology.

The researchers found striking differences between ME/CFS patients and the matched controls in diastolic blood pressure variability in the resting state. Importantly, they observed that a combination of three particular aspects – resting low frequency, high frequency and total power spectral density variability – differentiated between ME/CFS and controls with a sensitivity of 77%, though specificity was lower (53%).

The fact that these measures can be made at rest (unlike many autonomic assessment techniques) raises the possibility of assessing autonomic nervous system dysfunction at the beside, using appropriate portable technology. The researchers' next step is to validate their findings in other groups, and to explore their diagnostic usefulness, in combination with other potential diagnostic markers.

Prof. Julia Newton (second left) with ME Research UK trustees

Brain blood flow and autonomic symptoms

As many ME/CFS patients have autonomic nervous system problems, particularly problems with standing (orthostatic intolerance) and with memory or concentration, there has been speculation that blood flow to the brain might be impaired, at least in some people.

With our support, Dr Jiabao He and colleagues at the Newcastle Magnetic Resonance Centre have been exploring whether the autonomic abnormalities in ME/CFS patients seen at the unit (particularly abnormal acid accumulation in leg muscles during exercise) are mirrored by changes in blood flow to the brain.

They did this by using magnetic resonance imaging to measure brain blood flow, and magnetic resonance spectroscopy to probe skeletal muscle during two challenges: an exercise of the foot and a standard autonomic function challenge called the Valsalva manoeuvre, in which the patient takes a deep breath and holds it for 16 seconds.

They found a correlation between brain blood flow and the accumulation of acid in the skeletal muscles: lower blood flow to the brain was associated with a reduced accumulation, while higher flow was associated with higher acidity.

Given this relationship between brain vascular control and skeletal muscle acid regulation, both at rest and when responding to challenges, the researchers speculate that autonomic nervous system dysfunction might underlie changes to brain blood flow.

As they point out, it is possible that ME/CFS itself is driven by a primary abnormality at the periphery of the body (e.g. skeletal muscles) which has secondary effects on the brain or other organs.

Research bites from around the world

LONDON

Lyme disease guidance

Public Health England has announced that it will coordinate the development of new UK guidance on the diagnosis and treatment of Lyme disease. A multi-disciplinary team – involving infectious disease specialists, microbiologists, neurologists, GPs and patient groups – will carry out the work.

The idea was first raised last October at a Lyme disease conference, at which The Countess of Mar applauded the agency's willingness to involve patients. As Lady Mar pointed out, the experience of patient support groups would contribute to the resolution of uncertainties that remain about Lyme disease; in particular, the effectiveness of diagnosis methods, and the differences of opinion about the usefulness of long-term antibiotic treatment.

Lyme disease is caused by *Borrelia* bacteria transmitted by tick bites. There have been suggestions for many years that a subgroup of people with ME/CFS have undiagnosed Lyme disease, particularly those who live in areas of the world where tick-bites are common. Equally, there have been other concerns about misdiagnosis or overdiagnosis of Lyme disease by non-specialists.

Given the many uncertainties about Lyme disease, the creation of the multi-disciplinary group is a welcome development.

WASHINGTON

Committee on diagnostic criteria

The first meeting of the Institute of Medicine's 'Committee on Diagnostic Criteria for ME/CFS' took place on 27th January 2014 in Washington DC. The open session was filmed (and can be viewed at the Institute's website) and included presentations by organisers and committee members, followed by submissions from ME/CFS patients, advocates and members of the public.

The committee consists of fifteen well-respected scientists, and includes several well-published ME/CFS researchers, such as Prof. Nancy Klimas, Prof. Ben Natelson and Dr Peter Rowe.

One of the most animated debates surrounding the diagnosis and treatment of ME/CFS concerns the name of the illness and how it is diagnosed. At the moment, around twenty possible definitions can be identified, but each is different and the terms ME, CFS and their various combinations mean different things to different people.

The aims of the committee are to evaluate comprehensively the current definitions, develop consensus 'clinical criteria' and make recommendations for their implementation. It is a big task, and the challenge is to arrive at a sensitive and specific definition of real practical value to patients and clinicians.

SWEDEN

Sleep loss can hurt the brain

An article in the scientific journal, *Sleep*, received wide media coverage recently. It showed that a lack of sleep, even in healthy young people, produces chemical changes in the brain similar to being hit hard on the head!

Specifically, the young men tested had 'spikes' in the molecules NSE and S-100B after the loss of just one night of sleep. Other research has shown that the brain needs sleep to cleanse itself of toxins, and the lead researcher, Prof. Christian Benedict, was quoted as saying, "*Our results indicate a lack of sleep may promote neurodegenerative processes.*"

Sleep problems affect many people with ME/CFS; in fact, in one investigation of 1,578 patients, 92 to 94% reported sleep disturbances with a high degree of severity. We also know that different patients experience different kinds of sleep difficulties, and that these impact greatly on all aspects of life.

So, these new findings may help to explain some of the difficulties patients have with 'brain fog', memory, concentration/attention and information processing, and the importance of clinical sleep assessment and treatment.

Source: *Benedict et al., Sleep, 2014*

AUSTRALIA

Illness in youngsters

Many thousands of young people in the UK have a diagnosis of ME/CFS. As the Chief Medical Officer's report (2002) made clear, the illness "*potentially threatens physical, emotional, and intellectual development… and can disrupt education and social and family life, at a particularly vulnerable time of life*". Yet, there is surprisingly little scientific information about ME/CFS in young people, which is why the recent report from the Murdoch Children's Research Institute in Australia is particularly valuable as a reference point.

The clinicians audited the medical records of all young people attending their clinical service during 2012, and found that 59 patients had been diagnosed with ME/CFS, while 20 others had received another diagnosis. They found a high occurrence of important symptoms in these children.

For instance, 92% of the group reported pain (mainly headaches and muscle pain), 80% post-exertional malaise, 86% sleep disturbance, and 76% autonomic effects (mainly dizziness but also POTS and palpitations). Importantly, the illness was triggered by an infection in two-thirds of patients, and by 'immunisation' in two cases (3%), confirming the occasional reports of vaccination/immunisations as a triggering factor. Overall, 14% were severely affected (housebound), and, shockingly, it had taken more than a year for more than half of the young people to be seen at a specialist clinic.

The value of an audit report like this is that it crystallises for other clinicians and researchers the seriousness of the impact of ME/CFS in children and young people.

Source: *Knight et al., Journal of Paediatrics & Child Health, 2013*

KENTUCKY

Early multiple sclerosis?

A recent scientific paper has revealed an intriguing fact. Apparently, people can be labelled with a 'fatigue-related' illness – sometimes for years – before finally receiving a confirmed diagnosis of multiple sclerosis (MS)! Over half of MS patients say that fatigue is one of their worst symptoms, and researchers from the University of Kentucky were particularly interested in whether fatigue had been present as an early symptom.

Using retrospective databases, they found that 28.9% of 5,305 MS patients had been given an earlier fatigue-related diagnosis. Most had received the general label 'other malaise or fatigue', but 73 people (1.4% of the group) had been given the label 'chronic fatigue syndrome' in the three years before their re-diagnosis with MS.

The researchers' aim was to show that "*fatigue may herald MS, often by years*", since awareness of this fact might help physicians to detect the initial stage of MS and start treatment earlier. They also point out that "*careful history and physical examinations should be performed in all patients presenting with fatigue for the presence of clues to the possible diagnosis of MS*", and that a more comprehensive neurological examination than is routinely performed on patients with 'fatigue' may also be required.

Source: *Berger et al., Multiple Sclerosis Journal, 2013*

MASSACHUSETTS

Gluten sensitivity

The protein gluten is mainly found in wheat, but it's also a constituent of rye, oatmeal and barley. Gluten-related disorders (encompassing a range of conditions from marked coeliac disease to a more simple gluten allergy) are increasingly recognised in developed countries, and one specific type – 'non-coeliac gluten sensitivity' – was reviewed recently by an international group of researchers.

Non-coeliac gluten sensitivity is associated with a variety of symptoms, including gut discomfort (abdominal pain, bloating), and more systemic problems such as brain fog, fatigue, headache, joint and muscle pain. Some of these are also well-recognised symptoms of ME/CFS, so might a gluten-related disorder (however defined) be at the root of ME/CFS itself?

Well, one argument against is that symptoms of gluten sensitivity usually occur soon after gluten is eaten and "*disappear with gluten withdrawal within hours or a few days*", whereas the symptoms of ME/CFS tend to be ongoing and chronic. Another is that relatively few ME/CFS patients are rediagnosed with a primary gastrointestinal disorder (including coeliac disease) at specialist clinics.

Despite this, we know from the many e-mails and phone calls that ME Research UK receives that some patients' symptoms are helped by excluding gluten from their diet – in fact, some people have been helped greatly, though not cured. So, going gluten-free is certainly worth a thought, and worth talking over with a GP.

Source: *Catassi et al, Nutrients, 2013*

BRISTOL

Experiences of graded exercise

In surveys, between 39 and 57% of ME/CFS patients say that graded exercise therapy (GET) worsens their symptoms, while the scientific literature paints a picture of moderate benefit and rarely alludes to adverse effects. Where does the truth lie?

One way of exploring the issue is to dig deeper into survey data, so researchers at North Bristol NHS Trust have been re-analysing 'qualitative' responses given by 76 patients during Action for ME's online survey of rehabilitation therapies in 2010.

Overall, 56% of the patients reported a worsening of symptoms with GET. The 'negative themes' thrown up by these encounters include poor communication and support from the therapist; a sense of being pushed; worsening of symptoms after treatment, leading to short and long term setbacks; and being blamed for treatments not working.

Some of the patients' comments are particularly revealing: "*The therapist wasn't listening. Just patted out the same old lines.*"; "*They push you to do more without listening to what you are telling them. I have had ME for years; I know when my body is tired.*"; "*I was treated like an army cadet on an assault course.*"; "*It also made me feel guilty about being physically ill, as if it was my fault.*"

The report stresses that rehabilitation therapy can be of low quality or high quality, and that high-quality therapy is characterised by empathetic patient–therapist collaboration and a plan for setbacks. The authors say that poor-quality rehabilitation gives rise to negative experiences, and suggest that publicly available criteria should be made available so patients can identify whether they are receiving low-quality or high-quality rehabilitation support.

Source: *Gladwell et al, Disability and Rehabilitation, 2013*

SERBIA

Multivitamin supplements

Scientific research often tends to focus on the complicated, so it's refreshing to see a simple experiment for a change. With funding from the Ministry of Science in Serbia, researchers at the University of Novi Sad recruited 38 women with ME/CFS who agreed to take a multivitamin mineral supplement for two months. The supplement was Supradyn, chosen for composition, wide availability and affordability (the women bought it themselves). Before and after treatment, women completed symptom-based questionnaires, and had the activity of the enzyme superoxide dismutase (SOD) – a marker of oxidative stress – measured from blood samples.

After two months of multivitamins, SOD activity levels increased from 71 to 314 mEq, a positive finding (higher SOD activity is associated with lower oxidative stress). Also, the women reported significant improvements in some specific symptoms – fatigue, sleep, autonomic nervous system problems and headaches – but not in overall health-related quality of life.

Although this was an uncontrolled study (there was no group taking a sham vitamin tablet to control for placebo and other effects), the results are interesting, and back-up the findings of ME charity surveys which show that significant numbers of people with ME/CFS say they benefit from vitamin supplements.

Source: *Marci et al, Medical Science Monitor, 2014*

SOUTHAMPTON

A dozen different diseases?

The Chair of the UK ME/CFS Research Collaborative (CMRC), Prof. Stephen Holgate, gave a presentation to the Countess of Mar's Forward ME group in late 2013, followed up by an interview with *Health Rising*'s Simon McGrath.

Each was a fascinating tour de force, as Prof. Holgate explained his view that ME/CFS – which he referred to as 'a spectrum of disorders' – might consist of 12 to 15 different diseases, each with a different 'causal pathway'. Indeed, he pointed to the case of breast cancer, believed to be a much more uniform illness than ME/CFS, in which around 14 different causal pathways have been identified.

Of course, some of the causal pathways in ME/CFS might be interlinked, resulting in only 5 or 6 underlying disease mechanisms – but that's still a lot of different diseases currently grouped under one umbrella.

He also pointed out that medical research has struggled to tackle chronic illnesses in the past 30 years. However, the effort has to be made, and the only option is to track down and understand the individual causal molecular pathways – knowing the pathway is key to dealing with the disease, and to getting the drugs industry involved in research.

The thing he most loves as a scientist is a new challenge, particularly helping others who deal with "*complex issues around complicated diseases*" – a nice summary of ME/CFS, which he gave as an example. He believes that patients must be partners in research, so he is encouraging patients and the public to come to the CMRC's Annual Scientific Conference in September 2014. ME Research UK and the many research groups it has funded will also be attending – so we'll see you there!

Prof. Stephen Holgate

MARYLAND

The voice of the patient

Patients' views are not often heard – at least, not in formal publications such as scientific papers or official reports. So, it is refreshing to read the newly-released US Food and Drug Administration (FDA) document, which summarizes the input from patients and patient representatives at a meeting in 2013. The discussion focused on two key topics: disease symptoms and daily impacts that matter most to patients; and the patient perspective on treatments.

Overall, the FDA's conclusion was that ME/CFS is a "*debilitating disease that can severely affect a patient's day-to-day functioning and have a devastating impact on a patient's life*". And key themes from the patient consultation exercise included the following:

- Many patients can pinpoint a specific time in their life when they contracted the disease.
- Patients struggle daily with their symptoms, and the most frequently mentioned included severe fatigue or exhaustion, impairments in cognitive functioning, chronic pain, sleep difficulties, and susceptibility to infection.
- Post-exertional malaise is a severe exacerbation of those cognitive and physical symptoms.
- Patients use or have tried a complex regimen of drug and non-drug therapies to treat their disease and manage their symptoms. These treatments have been met with varying degrees of effectiveness; for some, none is effective.
- The illness takes a devastating toll on the lives of many patients and their families, including loss of careers, decreased quality of family life and social isolation.

Source: *The Voice of the Patient Report: CFS and ME, fda.gov 2013*

Like Comment Share

Recent fundraising for ME research

Facebook shutdown

Richard Gardner is a Facebook aficionado: "*I feel that I use Facebook far too often – I check for new notifications and home page stories posted by my friends every hour that I am not sleeping!*"

He realised that he would be isolated without Facebook, but this got him thinking about people who have to deal with real social isolation. One of these is his sister, Emma, who is 21 years old, has had ME for almost a decade, and is now almost completely housebound. "*Thousands of people like my sister have been robbed of the normal life so many of us take for granted.*"

Richard has started a sponsored 'One year off Facebook' campaign, and will be regularly updating his JustGiving page with video diaries documenting his experience of social network withdrawal. You can contribute to his Justgiving campaign at www.justgiving.com/richardgardnerme.

Donna's weight loss

Donna Reynolds has battled with her weight for a long time, but she decided recently to lose 6 stones. As she says, "*I'm 36 now, and the extra weight is affecting my health. I could blame lots of factors though, ultimately, it's down to me. But there are people out there who are seriously ill through no fault of their own, and one of them is an old friend of mine, Nichola.*"

Donna and Nichola have little contact since the day they both left school nearly 20 years ago, but Donna has been very affected by Nichola's story in ways she never could have imagined.

"*Here I am eating all the pies, and feeling sorry for myself – and there she is, with her beautiful family and every day a struggle.*"

So she has dedicated her weight loss journey to Nichola by raising funds for ME Research UK; as she exclaims, "*Give me a high five when you see me and my beetroot face on the gym treadmill!*"

Amsterdam marathon

The first marathon in Amsterdam was held on 5th August 1928, during the 1928 Summer Olympics. The event has grown in size since, though the route still starts and finishes at the original Olympic Stadium.

Fast forward to 2013, when two Scots lads, Daniel McGuire and Sean Anderson, ran the TCS Amsterdam Marathon for us. "*Good grief, what a hard slog it was,*" says Daniel, "*but I managed to finish with a time of 3:48:26.*"

In fact, given that the distance is 26.2 enormous miles, Daniel's time was not so far behind that of the first winner of the race, Boughera El Ouafi, in 1928! Well done, Daniel and Sean!

Afternoon tea for ME

Jenny McNeill and Janice Templeman put their thinking caps on about the best way to fundraise for us, and decided on an 'Afternoon Tea for ME' event. Janice has had ME for many years, but, as she points out, "*There are virtually no facilities for the 7,000 ME sufferers in Northern Ireland, and nowhere near enough research to find a cure. So we thought we'd do something ourselves to help the cause.*"

The idea behind the event was to mobilise 'girl power', to come along with their goodies and have a laugh at the same time. Supporters brought their sister, mum,

aunt or friend to have a good catch-up, a bit of craic, and to celebrate female friendship.

"*Everyone has given fantastic support to Janice over the years,*" says Jenny, "*and this was a marvellous way to get them all together for a day of great fun and laughter.*"

Cycling from coast to coast

Gareth Faull's wife has ME, so he thought he would put his love of cycling to good use by going 'Coast to Coast' from the Spanish Atlantic to the French Mediterranean on his bike.

It was a new experience, though. "*Actually, I've only ever done one touring adventure before, from London to Paris with a friend. This time I am travelling somewhere warm, and I've opted to camp out*". His trek took him along an approximate route from Bilbao to Narbonne, and the adventure was described with photos on his blog: cycling.garethfaull.com.

Pete Harris

Pete Harris enjoyed doing the BUPA Birmingham half-marathon so much in 2012 that he did it again in 2013, raising money for both ME Research UK and Verity PCOS. In addition, his employer, Salts Healthcare, decided to choose ME Research UK as one of its two sponsored charities for the year, and so far its employees have taken part in the 'Survival of the Fittest' event in Nottingham, and have organised a cake and samosa sale.

Thanks to Pete and all the staff of Salts Healthcare – corporate sponsorship makes a big difference to many charities, including our own; we couldn't do it without them.

London marathon runners 2014

Chris White (pictured right) ran the Windsor half marathon for us in 2013, finishing in 1 hour 44 minutes and 5 seconds, and he intends taking up the cudgels again, this time in the Virgin Money London Marathon on 13th April 2014.

Jessica Page and John Ritchie are experienced runners who are also using their individual places to raise funds. John last did the London marathon in 2012 and is running for his father "*and the many thousands like him (about 200,000 in the UK) who are affected by this chronic illness*".

So, if you spot a runner with an ME Research UK T-shirt on the TV, remember and give three big cheers!

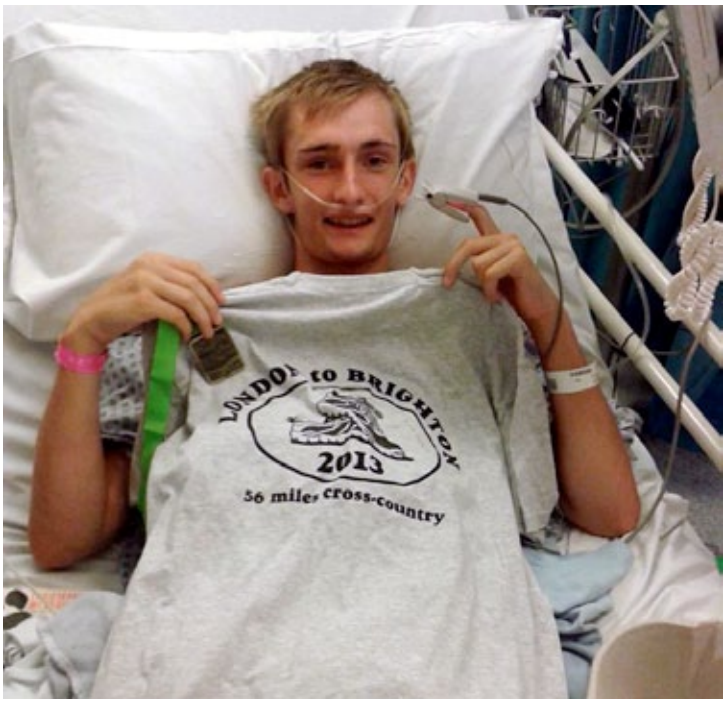
London 2 Brighton

On 22nd September 2013, Matt Rimmington did the 'London 2 Brighton' Ultramarathon, one of the UK's greatest endurance events.

Technically, the distance is 56 km, but after getting lost a number of times with his two other team mates, it stretched to 63 km!

Matt's mum has had ME for more than 12 years, and that thought kept him going. "*About 50 miles in, I really did begin to struggle, but all this meant too much for me to give up!*", he explained. In fact, he managed to finish in 14:20:22, becoming the youngest person to ever complete the race. However, the exertion took its toll, and he became very ill, ending up in A&E with kidney failure!

The photo below shows Matt in hospital after his ordeal, but proudly holding his race T-shirt. Matt is quite an athlete – and in 2013 alone completed the Keswick to Barrow (40 miles), the 4 Inns (40 miles) and Tough Mudder (12 mile assault course), all raising funds for ME Research UK.



Walk for ME 2014

ME Research UK is proud, once more, to have been chosen as one of Walk for ME's featured charities for 2014. Now in its second year, Walk for ME is determined to build upon the success of last year's event which raised almost £12,000 for charities focused on biomedical research into ME.

As well as the UK, supporters in Ireland, Spain, New Zealand and the US took part. Distances varied depending on participants' health. As there is no minimum distance set, no targets and no set dates (though ideally walks would happen during ME Awareness Week 11–17th May 2014), everyone can take part. As the organisers say, "*The whole idea is that a friend or family member is doing something that their loved one would love to be able to do but can't.*"

In 2013, Bill Haywood Smith (right) walked the entire length of the River Test by following the Test Way (44 miles). Beginning by the river's source in Berkshire on 4th May and reaching Southampton Water the next day, Bill raised a wonderful total for ME Research UK. He walked for all those affected by ME, but in particular for Emma.

You too can follow in the foot-steps of Bill and join the Walk for ME initiative. Our website has all the details and links to help you take the first step.

Vance at the viaduct

Our Chairman, Dr Vance Spence, attended the ME Therapy Week, which is hosted by the Irish ME Trust every year.

The venue is An Grianán (which means 'the sunny place') – a charming manor house and estate situated near the long sandy beaches of the Co. Louth coast and the River Boyne estuary.

This beautiful stately home was built in the late 18th century and still reflects the splendour of those years in its manicured grounds, ornate ceilings and domed central stairway.

The Irish Countrywomen's Association manage An Grianán with great efficiency and provide courses dealing with Arts & Crafts, Leisure, Personal Development and Self Care. Complementing these courses are Irish ME Trust-arranged therapies.

Dr Spence took the occasion to visit the viaduct, which had been lit in blue during ME Awareness week 2013.

Gillian's 50th birthday

Gillian Abercrombie knows that the most important gift in life is the gift of health and it's one we all take for granted until it's not there. She's been living with ME for 30 years, and knows that in that time advances in understanding the disease and in developing effective treatments have been shockingly inadequate. So, she's decided to use the occasion of her 50th birthday to ask for donations in lieu of gifts

Help us by recycling – free!

In this issue of Breakthrough, you'll find a freepost recycling bag so you can help us by recycling your 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). Most makes are acceptable (HP, Dell, Canon, Samsung, etc), but Epson and Kodak cartridges are not (our website has more information). Please note, however, that cartridges must not previously have been refilled, must not be damaged, or have additional holes or peeled-off labels. You can place up to 5 cartridges in the freepost recycling bag. Just post it to the address on the label (not to us!) and we will receive a donation from Recycle4Charity. You can also recycle your mobile phone as it still has a value even if it is broken, faulty or locked – up to 3 mobiles can be placed in the recycling bag.

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.

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