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breakthrough

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ME RESEARCH UK

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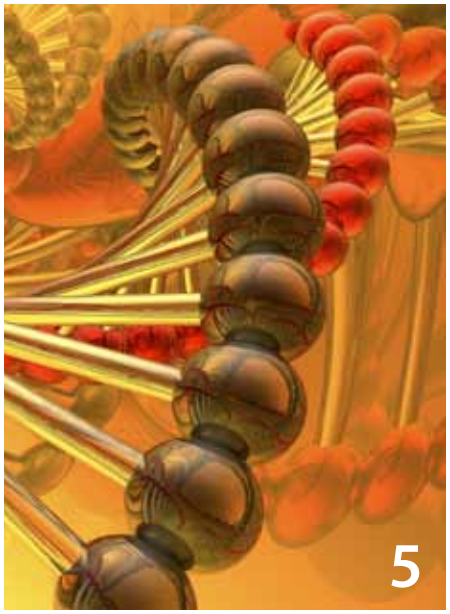


Welcome

Breakthrough magazine is published by ME Research UK, a Scottish Charitable Incorporated Organisation that funds research into Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (also known as ME/CFS). The charity 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. *Breakthrough* is an open access publication and, with the exception of images and illustrations, the content may be reproduced free of charge, subject to the terms and conditions found at www.meresearch.org.uk/bt-terms.

The Gateway, North Methven Street, Perth, PH1 5PP, UK
Tel: 01738 451234, **Email:** meruk@pkavs.org.uk

This issue

In the spotlight

What's happening in the world of ME research and funding

Prof. Mady Hornig from Columbia University

Signature move

Robust evidence of immune dysfunction in ME/CFS

Two robust scientific studies made the headlines earlier this year, both led by Prof. Mady Hornig from Columbia University, and supported by a world-class team of scientists including virus hunter Prof. Ian Lipkin and Prof. Nancy Klimas. In the first report, published in *Science Advances*, 51 immune biomarkers were measured in blood samples collected from 298 ME/CFS patients and 348 healthy controls. The headline finding was that there were "distinct plasma immune signatures" in the early stages of ME/CFS: patients who had the disease for up to three years had a specific pattern of immune biomarkers that was not present in healthy controls or in patients who had been ill for more than three years. Those with a shorter duration of illness had increased amounts of many different types of immune molecules called cytokines, including interferon gamma which has been linked to the fatigue that follows many viral infections.

"The immune response becomes like a car stuck in high gear."

Mady explains that ME/CFS patients seem to be flush with cytokines until around the three-year mark, at which point the immune system shows evidence of exhaustion and cytokine levels drop. The results support the idea that ME/CFS may reflect an infectious hit-and-run. Patients often report getting sick, sometimes from something as common as glandular fever, and never fully recovering. These infections throw a spanner in the immune system's ability to quieten itself down after the acute infection; the immune response becomes like a car stuck in high gear.

Prof. Ian Lipkin comments, "This study delivers what has eluded us for so long: unequivocal evidence of immunological dysfunction in ME/CFS and diagnostic biomarkers for disease… The question we are trying to address in a parallel project on the microbiome [the bacteria that live in the gut] is what triggers this dysfunction."

Mady's second study, published in *Molecular Psychiatry*, identified a unique pattern of immune molecules in the cerebrospinal fluid of people with ME/CFS (this is the clear liquid which bathes the brain and spinal cord, circulates nutrients and chemicals filtered from the blood, and removes waste products from the brain). Using samples from two US biobanks, the scientists measured levels of 51 cytokines in the cerebrospinal fluid of 32 ME/CFS patients who had been ill for about 7½ years on average, 40 multiple sclerosis (MS) patients, and 19 controls without obvious disease. Fatigue is an important symptom of MS, and cytokine abnormalities are known to occur in the cerebrospinal fluid of these patients.

Levels of many pro- and anti-inflammatory cytokines (including interleukin 1) in the cerebrospinal fluid were lower in ME/CFS patients than in healthy people, although CCL11 (eotaxin, which is involved in the recruitment of some kinds of white blood cells) was very strongly elevated. Importantly, immune profiles differed between the ME/CFS and MS patients, and the immune activation in the central nervous system was greater in the ME/CFS group. In particular, markedly higher levels of TGFβ (which controls cell growth) and CCL2 (which recruits cells to the sites of inflammation) were measured in ME/CFS patients than in individuals with MS, while some other cytokines, such as VCAM1 (which helps cells adhere to blood vessels), were significantly reduced. Most interesting, perhaps, was the finding that the ME/CFS patients could be categorised into three distinct immune groups, which may help to clarify diagnosis in future.

"We now know that the same changes to the immune system recently reported in the blood of people with ME/CFS with long-standing disease are also present in the central nervous system", Prof. Hornig says, and she suggests that they may contribute to symptoms such as muscle weakness and brain fog.

Virus hunter, **Prof. Ian Lipkin**

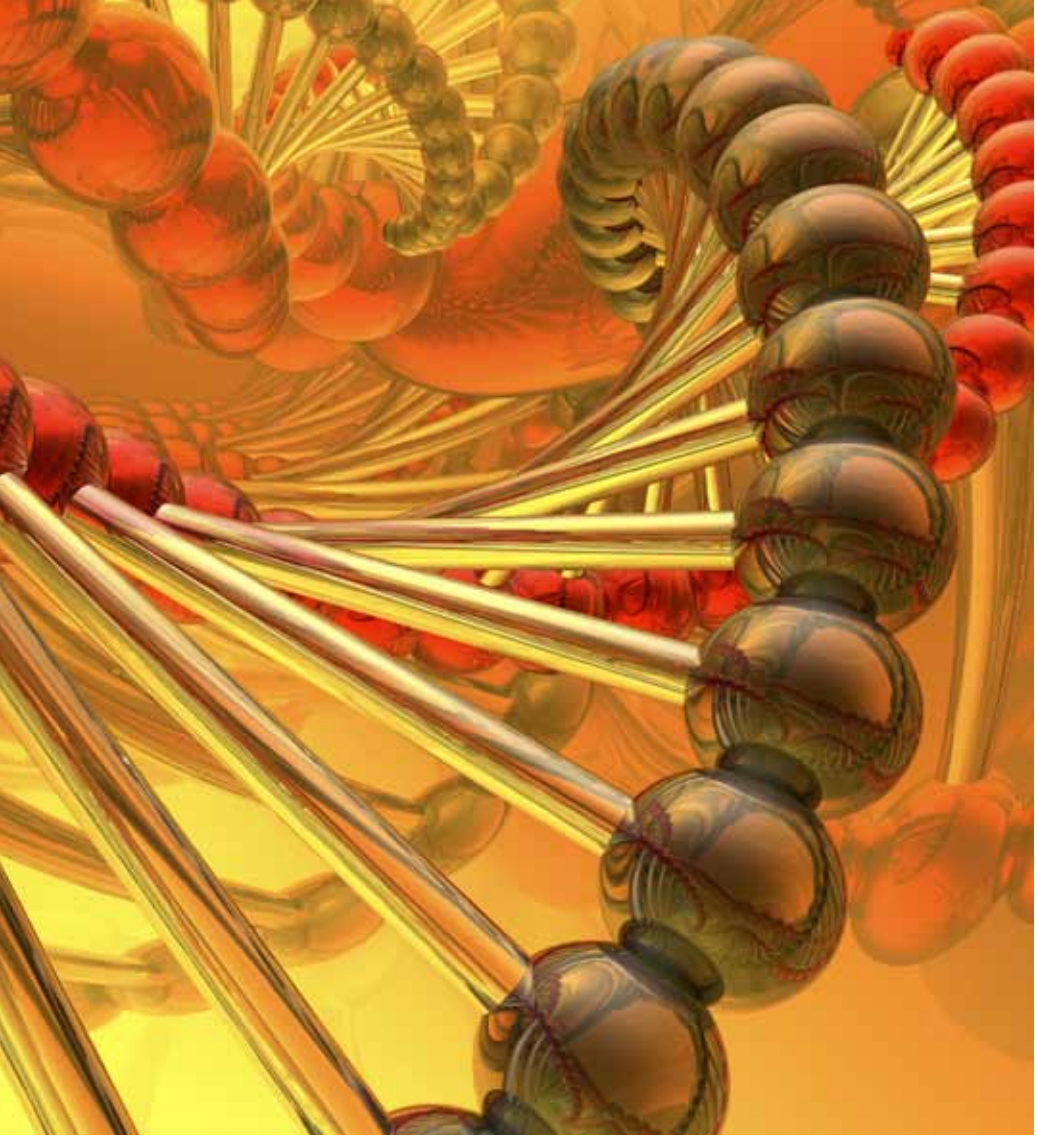
Both studies were widely reported in the world's media. As Dr Neil Abbot of ME Research UK said in the *Daily Mail*, "A biological signature or thumbprint for ME is the holy grail – it's what we all want to see. If the immune changes reported in these studies can help, it would be a great step forward."

ME Research UK funding has an impact

The real impact of scientific research is hard to gauge. Promising leads can hit a brick wall, while seemingly insignificant findings herald major breakthroughs. So, how can we know if research funding is having an effect? The usual way is to look at citations – the number of times a published research paper has been referenced by other scientists – which give an indication of the effect of research findings on the scientific world in general.

Since 2000, ME Research UK has awarded 41 specific grants, totalling £1.3 million, to research institutions in the UK, as well as Australia, Canada, Belgium and Sweden. The most important findings have centred around the autonomic nervous, immune, circulatory and musculoskeletal systems. The results of these studies have been published in 69 research papers in peer-reviewed scientific journals. At July 2015, these studies had been cited 1134 times by other researchers, and the tally can only increase with time.

Biomedical research is a long-term enterprise, and the real influence of the scientific reports published with ME Research UK's funding will not be known for many years. Nevertheless, the high level of citations is a very promising start, and is particularly important given the chronic lack of research into ME/CFS across the globe. We have to bring this disease to the notice of scientists and opinion-formers, and citations by other researchers is an important element in spreading the word to these professionals.



Out of sequence

Exploring the genetics of ME/CFS

Human beings are 99.5% identical as regards their DNA gene sequences. The remaining 0.5% consists mainly of single nucleotide polymorphisms (SNPs, pronounced *snips*), which are small genetic changes in DNA that vary between individuals. Most SNPs are silent, but others have important consequences; a single SNP mutation in the APOE gene, for example, is associated with an increased risk of Alzheimer's disease. At the moment, scientists across the world are involved in identifying particular SNPs and linking them with particular diseases.

To date, only a handful of studies have attempted to examine individual SNPs or patterns of SNPs in ME/CFS patients. One was an ME Research UK-funded investigation at the University of London, which found significant differences in the distribution of a small number of SNPs between ME/CFS patients and healthy people. Another study, from Japan, examined SNPs in genes involved in the monoaminergic system but did not find an association overall, while an investigation by the Center for Disease Control in Atlanta, Georgia found that genes associated with neurotransmission and sleep–waking cycles might be associated with ME/CFS.

The latest report on SNPs in ME/CFS is a pilot study from Australia, and it focuses on the transient receptor potential (TRP) superfamily of ion channels involved in many key biological processes. TRPs are impaired in a range of diseases, including chronic pain and motor neuropathy, so it is certainly feasible that there might be specific variations in SNPs associated with TRP ion channel genes in people with ME/CFS.

"Complex diseases such as ME/CFS are likely to be the result of large numbers of SNP variants."

When the Australian researchers compared 115 ME/CFS patients and 90 non-fatigued controls, they found that 13 SNPs were present at significantly different frequencies. Nine of these SNPs were associated with the TRPM3 gene, which makes a protein involved in cellular calcium signalling and in maintaining physiologically stable conditions. Of the others, two were associated with TRPA1 (a sensor for pain, stretch and environmental irritants) and two with TRPC4 (which plays a part in the regulation of blood vessels and cell division). As the researchers point out, the results of this pilot study are essentially preliminary, although they do imply that genetic alterations at TRP ion channels have a role in the development or maintenance of ME/CFS.

All the investigations on SNPs in ME/CFS that have been published to date can best be described as hypothesis-generating rather than conclusive in themselves. Their aim is to pin-point specific areas of the genome that future investigations might examine more closely. However, complex chronic illnesses like ME/CFS are most likely to be the result of very large numbers of SNP variants working in concert. So, in reality, large studies using genome-wide scanning methodologies and complex analytical methods will be required to obtain definitive results, as are currently underway in a range of other illnesses.

A big splash

Promising effects with rituximab treatment

In 2011, a scientific report by Øystein Fluge and Olav Mella of the Haukeland University Hospital in Bergen suggested that the symptoms of ME/CFS could be improved with rituximab treatment. The results made a big splash in the ME world, and received widespread coverage in the press and social media. Rituximab is a monoclonal antibody against the CD20 protein on the surface of B-lymphocytes, a type of white blood cell. The drug wipes out these B-cells, and has been used to treat diseases such as some cancers and autoimmune disorders, in which these cells are malignant, overactive or too numerous.

The results showed "lasting improvements in self-reported fatigue" over 12 months in 67% of ME/CFS patients on rituximab compared with 13% of those on placebo. Rituximab was also associated with significant improvements in quality of life, and no serious adverse events were reported. The Norwegian researchers described their results as preliminary and indicating only a proof of principle, but were intrigued enough to plan further experiments.

Drs Fluge and Mella have now published the report of their next study with a group of 29 ME/CFS patients with illness levels ranging from mild to severe. The idea was to explore the effect of rituximab over a longer period, as well as the types of responses and any adverse effects. Each patient was given two infusions of rituximab two weeks apart, followed by maintenance infusions after 3, 6, 10 and 15 months, with follow-up for 36 months. The trial also gave patients in the placebo group from 2011 the chance to have rituximab treatment.

Focus on funding

The taxman can help

It's not easy to get funding for research. The National Lottery doesn't give grants for scientific investigation, and the charitable giving of most companies is for community-based schemes. However, by 'giving smart', the taxman can be surprisingly generous. Here are two tax advantageous ways to give – see our website for more details.

The **Gift Aid** scheme allows charities to claim an extra 25p for every £1 donated. Most donations qualify but you need to make a Gift Aid declaration (which can also cover past and future donations). You will qualify as long as your are a UK taxpayer and donate no more than four times what you have paid in tax in any tax year. That's why our donation and Standing Order forms all have Gift Aid declarations – just tick the box to allow us to increase your donation by a quarter.

Payroll Giving is a flexible scheme which allows anyone who pays UK income tax to give regularly to charities on a tax free basis. It is also known as Give As You Earn or workplace giving. It allows your regular donation to be taken from your pre-tax salary – meaning that part of your donation comes from money that would have otherwise gone in tax. So each £1 you give will only cost you 80p. Ask your employer about Payroll Giving or employee donation matching schemes.

Drs Øystein Fluge & Olav Mella
of Haukeland University Hospital

Amost two-thirds of patients experienced lasting improvements in fatigue. There was a delay before the treatment had any effect, and the responses lasted between 69 and 105 weeks. Importantly, the patients who responded to treatment also had significant improvements in quality of life and substantial improvements in their ME/CFS symptoms. Dr Fluge says, "Eleven of the 18 responders were still in remission three years after beginning the treatment, and some have now had no symptoms for five years… Suddenly, their limbs started to work again and their hands were no longer cold or sweaty."

These are very promising results. The Norwegian researchers point out that the lag times and patterns of responses to rituximab seen in this study accord with response patterns to rituximab in some established autoimmune diseases. They also suggest that autoimmune disease may underlie ME/CFS in a subgroup of patients. It could be, as Dr Fluge notes, that an infection can trigger the body to produce antibodies that then turn against a person's own tissues, possibly affecting the circulation. It may be significant that 12 patients in the study had first-degree relatives with an autoimmune disease, although a genetic predisposition has not been established. Rituximab was relatively safe overall, although two patients had an allergic reaction to the drug and two had an episode of uncomplicated late-onset neutropenia.

The next phase of this work on rituximab in ME/CFS has been launched: a randomized, double-blind, placebo-controlled phase 3 study of 152 patients from five centres in Norway, who are being followed up for 24 months. The authors are also conducting a smaller study on patients with severe or very severe ME/CFS, using the same rituximab treatment protocol. As the authors "do not encourage the use of rituximab for ME/CFS outside of approved clinical trials", and as no equivalent treatment trials are ongoing anywhere else, we await their results with great interest.

cellular workout

A fascinating new ME Research UK-funded study from Newcastle has found **abnormalities in the muscle cells** of ME/CFS patients

In the early scientific literature, the hallmark of myalgic encephalomyelitis was muscle fatigue and weakness, often after relatively mild exercise. Muscle cramps, twitching and tenderness were also often present. Today, patients diagnosed with ME/CFS frequently highlight peripheral fatigue – such as impaired muscle power in the arms and legs – as a particular practical problem.

The biological mechanisms underlying muscle fatigue and weakness are currently being investigated in a number of different diseases. For almost a decade, ME Research UK has provided the pilot funding for distinct projects at the University of Newcastle designed to explore these mechanisms in ME/CFS. One of these projects using magnetic resonance scanning of peripheral muscle (a scanning technique that looks at how muscles work) revealed significant abnormalities in the way acid is handled – suggesting that acid build-up during exercise may be due to a problem with muscle cells themselves.

Muscle cell cultures

To explore these and other interesting leads, ME Research UK awarding further funding in 2009 to Prof. David Jones and Prof. Julia Newton to undertake laboratory studies involving assays and cultures of isolated muscle cells (myocytes) from ME/CFS patients and healthy individuals. The first scientific paper from this series of investigations was published recently in the journal *PLoS ONE*, and it makes fascinating reading.

For these experiments, cultures of isolated skeletal muscle cells were obtained (by needle biopsy of the muscle on the outside of the thigh) from ten people with ME/CFS and from seven age-matched healthy people. Electrical pulse stimulation was then applied to the cells for up to 24 hours to simulate an exercise challenge by inducing contractions in the cultured muscle fibres. In

"The lack of activation of AMPK during exercise in ME/CFS patients points to a muscle abnormality."

Prof. Julia Newton speaking at the launch of the UK ME/CFS Research Collaborative in 2013

this way, the direct effect of exercise on the cells themselves could be observed. As the researchers point out, the attraction of using muscle cell cultures is that conditions can be standardised, so that any differences reflect changes in the cultured cells rather than personal or social differences between patients.

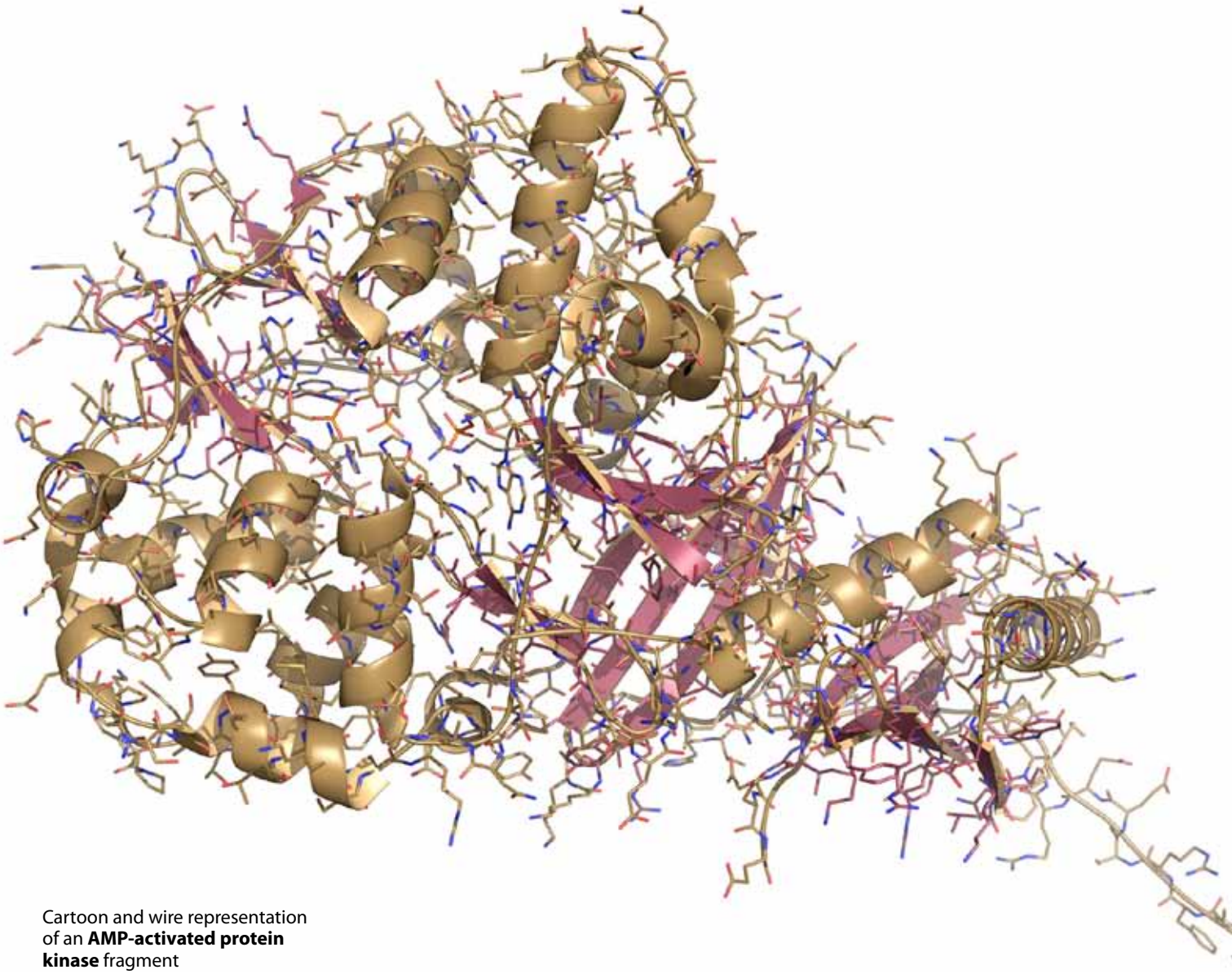
Exercise challenge

The main findings of the experiments were that, after 16 hours of this simulated exercise, muscle cell cultures from the healthy individuals had increased levels of AMP-activated protein kinase (AMPK) phosphorylation, as well as a higher rate of glucose uptake. In contrast, cultures from ME/CFS patients showed no such increases after exercise. In addition, the secretion of interleukin 6 (which is involved in inflammation and fighting infections) in response to exercise was significantly lower in cells of ME/CFS patients than in those of healthy individuals. Finally, even without exercise, the muscle cells of ME/CFS patients had a higher than normal expression of myogenin (which co-ordinates skeletal muscle development and repair).

AMPK activation

The impairments in AMPK activation and glucose uptake in the muscle cells of ME/CFS patients are particularly intriguing. The fact that the cultures were unable to increase the rate of glucose uptake in response to exercise most probably reflects the impaired activation of AMPK. This complex enzyme plays a key role in monitoring the use of energy in cells, sensing whether cells' 'batteries' are charged or discharged at any particular moment (see the box opposite for a more detailed explanation). As the authors say, the lack of activation of AMPK during exercise in muscle cells from ME/CFS points to a muscle abnormality at the level of AMPK (which is normally activated during muscle contraction) or in other regulatory enzymes further up the biochemical pathway. They plan to investigate these as well, using the system they have developed to analyse the workings of isolated muscle cells in the lab.

Overall, the evidence from this important study points to an exercise-related, primary abnormality in the muscle of ME/CFS patients. Because this occurs in cultured isolated muscle cells, it may well have a genetic or epigenetic basis. Exciting results, without a doubt. ●



Cartoon and wire representation of an **AMP-activated protein kinase** fragment

In more depth
What is AMP-activated protein kinase?

AMP-activated protein kinase (or AMPK) is an enzyme that has a key role in the regulation of the supply of energy inside cells. It is particularly active in tissues with high energy requirements, such as the liver, brain and skeletal muscle.

Sometimes called the cellular fuel gauge, AMPK is activated by a drop in the energy status of the cell, such as when energy is being used up faster than it is being produced. During a bout of exercise, for example, AMPK activity increases as muscle cells experience the stress caused by the increased demands for energy. Such activation of AMPK during exercise involves a cascade of processes, including the stimulation of glucose and fatty acid uptake and oxidation.

Overall, the effect of AMPK activation is to switch off pathways that use energy and switch on pathways that generate energy, helping to restore the energy balance within the cell.

Although much remains to be discovered, AMPK is thought to be an important player in conditions such as type 2 diabetes, metabolic syndrome and obesity, which are all associated with disturbances of energy metabolism. AMPK-activating drugs are already used to treat type 2 diabetes.


DOUBLE
TRIPLE

double word score

Patients' **symptoms and their severity** can be just as important as the definitions used to diagnose their illness

Diagnosis is the basis of all medical research, and is usually guided by clearly defined criteria. But there are many definitions of myalgic encephalomyelitis (ME), chronic fatigue syndrome (CFS) and their combinations (see the table over the page), and much debate about which might be best. What is more, any diagnosis is only as valid as the soundness of the initial clinical assessment and the efforts of doctors to exclude other conditions that might be causing the symptoms. If the examination is cursory (and the clinician sceptical or uninterested), the diagnosis of ME or CFS can easily become a convenient lay-by for complex cases that do not fit easily into any other category.

The term ME originally referred to chronic illness involving a profound loss of muscle power after physical exertion, muscle pain, neurological and/or cognitive symptoms, and a tendency to relapse. Today, there are a number of definitions of ME, but none are recognised by modern medicine. The term CFS appeared in the 1990s and was applied to people who would previously have been given a diagnosis of ME. However, the most widely used definition of CFS (published in 1994) relies on a number of vague, ill-defined symptoms shared with many other illnesses, and it has become an catch-all diagnosis that can include very different kinds of patients. ME/CFS is the combination term used most commonly today. Confusingly, some patients can equally be given the diagnosis of fibromyalgia, a condition characterised by chronic widespread pain and sharing many symptoms with ME/CFS.

Ultimately, only experimentation can throw light on the merits of this or that definition, and that's why ME Research UK funded an investigation

Prof. Jo Nijs outside the Atomium in Brussels

led by Prof. Jo Nijs of the Department of Human Physiology, Vrije Universiteit, Brussels.

Comparing symptoms

Prof. Nijs recruited a group of 48 patients who all satisfied the broad 1994 criteria for a diagnosis of CFS. In addition, there were 19 multiple sclerosis (MS) patients and 39 healthy individuals for comparison. The CFS patients were screened to determine whether they also fulfilled criteria for ME or the Canadian consensus definition of ME/CFS, and whether a diagnosis of fibromyalgia might also apply. All participants completed questionnaires assessing the severity of standard ME/CFS symptoms, as well as factors such as quality of life, fatigue, memory and concentration. Other measurements included daily activity levels, muscle strength, recovery time following exercise, and neurocognitive function.

Overall, the people who fulfilled the 1994 criteria for CFS had more severe symptoms than did the MS patients or healthy individuals (see the chart opposite), as well as a much lower quality of life and poorer cognitive performance. CFS patients also had lower muscle strength and a slower recovery after exercise, but daily activity levels did not differ between these patient groups.

Comparing definitions

Half of the CFS patients also fulfilled the Canadian consensus criteria for ME/CFS (as reported in previous studies), while more than three-quarters also fulfilled

Definitions of ME, CFS and their combination

A bewildering array of definitions of ME and CFS are currently in use, with no agreement among patients and academics as to which are the most accurate or appropriate. There is much speculation but very little hard data.

Definitions of ME

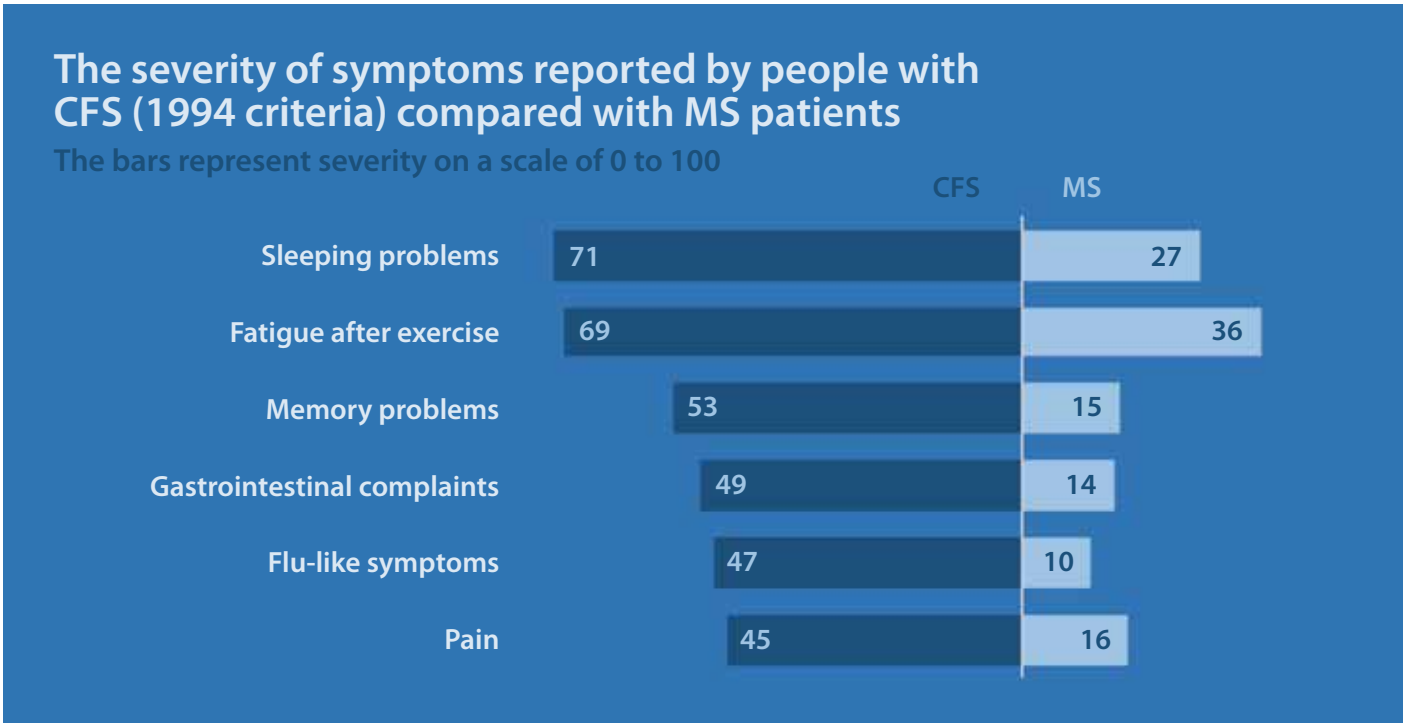
1988 ME/post-viral fatigue (Ramsay)
1994 London criteria (various)
2007 Nightingale definition
2011 International consensus criteria

Definitions of CFS

1988 CDC definition (Holmes)
1990 Australian case definition
1991 Oxford case definition
1994 CDC definition revised (Fukuda)
2005 CDC empirical case definition

Other and combination definitions

2003 Canadian consensus definition (ME/CFS)
2007 NICE clinical guideline criteria (CFS/ME)
2015 Systemic exertion intolerance disease (SEID)



criteria for ME (a higher proportion than that reported previously). Importantly, measures of symptom severity, muscle strength, neurocognitive function, etc. were broadly similar between these diagnostic groups, suggesting that the different diagnostic criteria commonly used for ME or CFS patients may not be sensitive enough to select symptomatically different groups of patients, particularly when their symptoms are severe.

A key finding was that three-fifths of the CFS patients also fulfilled current diagnostic guidelines for fibromyalgia. These individuals had markedly worse symptoms (more pain, fatigue and problems sleeping) and a poorer quality of life than did CFS patients without fibromyalgia, although there was very little difference in the objective measures (such as muscle strength and recovery time). Indeed, the co-occurrence of chronic pain (which defines fibromyalgia) was a far more important factor in determining the severity of illness than the specific definition used for diagnosis.

Focus on patient wellbeing

The major take-home message from this study concerns the everyday experience of patients and how they are treated. While clarifying the definitions of ME and CFS remains a challenge, it may be less important to patients than ensuring that their core symptoms, such as pain, are recognised and treated. Around 190,000 people in the UK live with ME/CFS, with approximately 9,300 new cases each year. Healthcare professionals and clinicians need to be aware that (as the results of this study illustrate) these people can be highly disabled, sometimes to a greater degree than patients with established chronic illnesses such as MS. Their quality of life, physical and social functioning, and daily activities are often restricted, and chronic widespread pain is a common problem.

Instead of being disbelieved or ignored, these patients need to be taken seriously and their symptoms targeted by appropriate treatments. In the short term, continuing education for GPs should be beefed up – ideally with input from ME/CFS charities and experts. In the longer term, the problem could be resolved by creating ME/CFS Centres of Excellence offering biomedical assessment, proper diagnosis, treatment and onward referrals, all under one roof. ●

"These people can be highly disabled, sometimes to a greater degree than patients with established illnesses such as MS."

Research bites

Our round-up of recent research from around the world

© Sagol Center for Hyperbaric Medicine and Research, Zerifin, Israel

Hyperbaric oxygen and the brain

Efrati et al., PLoS One, 2015

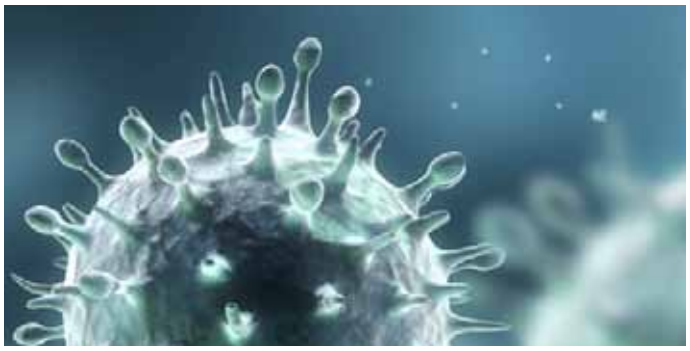
Hyperbaric oxygen therapy is a recognised treatment for deep-sea divers experiencing the bends, as well as for carbon monoxide poisoning and some soft-tissue wounds. The technique involves breathing oxygen via a mask in a pressurised hyperbaric chamber like those pictured above. Many multiple sclerosis national therapy centres in the UK have hyperbaric chambers because of the anecdotal evidence that hyperbaric oxygen can help the symptoms of that condition. Lots of ME/CFS patients have also tried the therapy, and some say that it helps particular symptoms, such as brain fog or concentration difficulties, while others report no benefit from the treatment. Two smallish experimental studies have reported varied results, but overall there is little convincing evidence (anecdotal or experimental) that hyperbaric oxygen is useful as a specific treatment for ME/CFS. And that's why the results of a new scientific study from the Sagol Center in Israel are so surprising.

The researchers found that hyperbaric oxygen had a dramatic benefit in fibromyalgia – a condition which shares many symptoms with ME/CFS, including pain, and overlaps diagnostically. As well as improvements in physical function and quality of life in the 48 women who took part, there were intriguing results from SPECT imaging of the brain: hyperbaric oxygen seemed to rectify the abnormal functioning of specific areas of the brain related to pain. It would be fascinating to see the experiment reproduced under similar conditions in a large group of ME/CFS patients.

ME/CFS is not simply chronic fatigue

Klimas et al., Fatigue: Biomedicine, Health & Behavior, 2015

The Chronic Fatigue Initiative was set up to search for the causes of ME/CFS and to find treatments. Its work includes a large multicentre investigation at five US sites linked to a national biorepository, and the first results have just been published looking at more than 400 ME/CFS patients and controls. Fatigue-related symptoms were present, but cognitive problems, inflammation, pain and autonomic dysfunction were also common and severe, and seven clusters of symptoms could be recognised. Lead author Prof. Nancy Klimas (pictured above) points out that ME/CFS is clearly not simply a state of chronic fatigue as is sometimes believed – there are many other clinical features that have to be taken into account, and taken seriously.



Is enterovirus active?

Chia et al., Open Journal of Gastroenterology, 2015

Gut problems are very common in ME/CFS, so it's possible that enteroviruses in the gastrointestinal tract are involved. In 2008, researchers in California found evidence of enteroviruses in stomach biopsies of over 80% of ME/CFS patients with chronic abdominal complaints. The same team recently examined 482 people with dyspepsia or chronic gastritis, 416 of whom also had ME/CFS. Again, enteroviral protein was found in stomach tissue in most cases, but there was also evidence of viral RNA, involved in the manufacture of viruses. The discovery of both protein and RNA suggests that an active viral replication process is still going on, and the authors suggest a large scale clinical trial to see if antiviral therapy helps relieve symptoms.

Post-polio syndrome

Baj et al., International Journal of Infectious Diseases, 2015

In the early literature on epidemics of ME-like illnesses, poliovirus infection gets a prominent mention. Since then *post-polio syndrome* has become a recognised separate diagnosis in polio survivors, who number 15 to 20 million worldwide. These people can develop central and peripheral fatigue, muscle atrophy and weakness, musculoskeletal pain, and new disabilities affecting body functions such as digestion and sleep. Also, there is no specific diagnostic test for their illness which can develop in different ways, and symptoms are often mixed and disabilities variable. It all sounds very like the clinical picture of the ME/CFS we know today, so you can see why many people suspect an as-yet-unidentified virus to be the root cause of ME or CFS.

Handgrip weakness

Miller et al., Journal of Translational Medicine, 2015

In 2014, an ME Research UK-funded study in Brussels showed that ME/CFS patients had slower than normal muscle recovery after a repetitive handgrip exercise. Prof. David Patrick and colleagues at the University of British Columbia (pictured above) have performed similar investigations, also examining tissue oxygen levels in wrist muscles during testing. Oddly enough, there was not a clear difference in oxygen use between ME/CFS patients and healthy controls, but the force produced by handgrip was 26% weaker in patients, supporting the Belgian results. One take-home message is that even simple tests like the change in handgrip strength over a short period can yield useful information on delayed muscle recovery in ME/CFS.

NIH report: advancing research

Green et al., Annals of Internal Medicine, 2015

A report from the National Institutes of Health in the USA confirms that ME/CFS "is a chronic, complex, multifaceted condition characterized by extreme fatigue and other symptoms, including pain, impaired memory, sleep disturbance, and insomnia that are not improved by rest". One million people are affected, it says, and the estimated economic burden is between $2 and $7 billion in the USA alone. Importantly, the authors say that, "Both society and the medical profession have contributed to the disrespect and rejection experienced by patients with ME/CFS. They are often treated with scepticism, uncertainty, and apprehension…" It recommends bench-to-bedside research; the funding of basic research by larger national funding agencies; and the setting-up of an international research network. And it points up the importance of training healthcare staff: "We believe that ME/CFS is a distinct disease that requires a multidisciplinary care team… a properly trained workforce is critical." As a concise summary of the current status of ME/CFS research and related issues, the report is a very positive development and a solid basis for action.

Misdiagnosis of multiple sclerosis and ME

Patient survey, MS Society, 2015

A survey of over 1,500 multiple sclerosis patients made waves in the media this summer. It showed that four in five people with the condition have been misdiagnosed in the past, and that 39% were left waiting a year or more for a diagnosis. Misdiagnoses included depression, anxiety or stress (14%) and stroke (11%), and 28% had been told incorrectly by their GP that they had a trapped nerve. This is all very reminiscent of the confused situation many ME/CFS patients find themselves in. Misdiagnosis is widespread there too, and four in ten people given a diagnosis of ME or CFS are eventually diagnosed with another condition after attending a specialist clinic. And in some cases, the rediagnosis is multiple sclerosis itself!

Comparison with breast cancer

Hall et al., Fatigue: Biomedicine, Health & Behavior, 2015

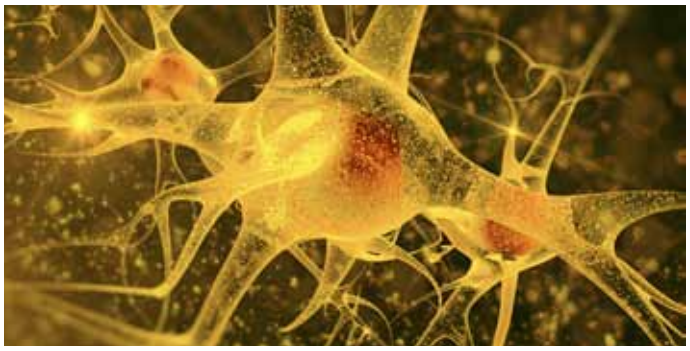
Fatigue is a particular problem in cancer survivors, and, like ME/CFS patients, they rank it as among the most distressing aspects of their illness. Researchers at the University of Miami found that fatigue interferes with daily activities to a greater degree in ME/CFS patients than in breast cancer survivors. ME/CFS patients also had more severe fatigue, as well as a higher level of self-reported depression, which may reflect the lower level of support available to them. ME Research UK is presently funding an investigation at St James's University Hospital, Leeds on immunological mechanisms that could be behind the symptoms shared by people with breast cancer or ME/CFS, so the comparison of the laboratory data will be fascinating.

"ME/CFS is a distinct disease that requires a multidisciplinary care team… a properly trained workforce is critical."

Environment influences immunity

Brodin et al., Cell, 2015

Immunity protects us against infection, but whether we have our genes or our lifestyle to thank for this remains a mystery. To explore this, scientists at the Center for Immunity and Infection at Stanford analysed data from 210 healthy twins, measuring many different aspects of immune function. They found non-heritable factors to be the most important influences on immune function, including previous exposure to toxins or pathogens, diet and vaccinations. In fact, well over half of the differences in immunity between twins was related exclusively to factors in the environment. Although these findings were on healthy twins, the Centre is also conducting a very large study on ME/CFS patients, and their results are eagerly awaited.



Nerve cell discovery

Lee et al., Cell Reports, 2015

The sensational news reported in May was that scientists at McMaster University in Hamilton, Canada have discovered a way to grow nerve cells (neurons) from an ordinary blood sample simply by adding a gene. This means that they can create both central and peripheral nerve cells with the same genetic makeup as any patient, which will allow potential pain-killing drugs to be tested in the laboratory using an individual's own nerve cells. Chronic pain is debilitating and very common, and is a particular problem in people with ME/CFS, most of whom (80 to 90%) report severe pain, as well as muscle or joint pain. For them and millions of others, this discovery could well be life-changing.

Adam Parkinson crosses the finish line (courtesy of Badass Mucker)

Friends united

Some of the many activities undertaken by our supporters to raise funds for ME research.

Badass muckers

Including stages with names such as the *creepy crawl*, *mud pit*, *pine crawl* and *log carry*, Tasha Lord, Adrian Parkinson and Jay Richards probably knew that Halton Park, Lancaster wasn't going to be an easy 10-km event. In fact, it was part of the Badass Mucker family of events, so our t-shirts weren't going to have a great time either! Many thanks to Tasha, Adrian and Jay for doing this mad event and supporting a charity close to the heart of their friend, Sonia McDermott.

Tea is the logical thing

Many thanks to Logic Now's developer James Quayle for holding an event in his Edinburgh offices as part of our *Have a Cup of Tea for ME* campaign for ME Awareness Week. Our Founding Ambassador, Betty McRae, led the way by treating friends and neighbours to some delicious cakes and biscuits (and we had supplied copies of *Breakthough* magazine, so they left with a better understanding of ME, as well as a very sweet taste in the mouth). We raise our teacups to everyone, up and down the country, who helped with an event!

Sue speaks to the CAB

Sue Waddle, our vice-Chair, visited the office of the Fareham Citizen's Advice Bureau in June, at the invitation of the Manager, Bridget Mayo. The idea was to explain to CAB staff about the day-today difficulties faced by people with ME and about ME Research UK. In all, 15 staff attended the training session and had lots of questions.

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01 James Quayle produces some delicious cakes to accompany his *Cup of Tea for ME*

02 CAB Manager **Bridget Mayo** (left) with **Sue Waddle** from ME Research UK

03 Emma Anderson is a princess for the day!

04 Vance Spence (centre) meets **Beth & Tom Whittingham**

It transpired that one of the local CAB volunteers has had ME since 1987, while another person with ME volunteers on the telephone helpline. Sue came away inspired that there are so many people, including ME sufferers, who give freely of their time to help others.

Team Princess

The idea behind Team Princess is that everyone dresses as a princess for ME Awareness Day, raising money for the ME charity of their choice. This year there were 14 Princesses, making it an impressively regal team: "*United we all fight for the same cause and fairy tale, which is to raise awareness and recognition of this devastating illness.*" ME Research UK had the support of 4 princesses: Alison West, Emma Anderson, Helen Louise Mackay and Jenny Horner, and photos of them as Princesses in their royal attire can be seen on the Team Princess Facebook page. Alison says, "*I was hoping to have enough energy to get me through this special day, but I did it – along with my little daughter – and it was fun!*"

Well done, Tom!

Tom Whittingham, one of our Ambassadors, ran the Edinburgh Marathon for us, and completed the race in a stonkingly impressive time of 3 hours 29 minutes! His sister Naomi has had ME for over 25 years, since the age of 12, and has endured many years of intense suffering, confined to the same four walls at home, and deprived of so many things we all take for granted. In the days before the race, Tom and his sister Beth popped in for a visit to our headquarters at The Gateway in Perth to meet the team and our Chairman, Dr Vance Spence. Afterwards, they had a quick tour of the city. It was great to meet them, and we send our thanks to Tom and the whole family for their enormous support.

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05 Katherine Cheston with mum & friend on the Bath Beat

06 The first cut for **Abbie Pritchard** as she shaves her head to raise awareness

07 Rebecca & George May complete their Thames hike

08 Michelle Grimshaw (and friend) during her skydive

Walk for ME 2015

In ME Awareness week this year, a large number of *Walk for ME* events were held throughout the country. The campaign was supported by walkers from Caithness to the Isle of Man, and many places in between. There were short walks, long walks, fun runs, and not-so-fun-on-the-day runs. But wherever they were taking place, all of these events were helping to raise awareness of ME and of the need for research into the illness. The photos above include Ambassador Katherine Cheston and her mum, with best friend Heather, who walked 26.7 miles of the Bath Beat 2015. And you can also see Thames Travellers Rebecca May and George, who hiked 30 miles from Hampton Court Palace to Greenwich Pier.

Abbie's head shave

Abbie Pritchard from Fetcham in Surrey raised funds for ME Research UK by shaving off all her hair. Her aim, she said, was to make her illness visible and to raise awareness of ME in the UK. And Abbie's sacrifice brought in donations of more than £1,100.

Skydive record attempt

The Skydive UK's Guinness World Record attempt was scheduled for June, and 333 brave fundraisers were needed to jump in tandem over a 24-hour period to break the previous world record, held by the USA, for the most tandem parachute jumps completed within 24 hours. Unfortunately, bad weather caused this attempt to be called off, but we are proud to say that four intrepid souls, including Michelle Grimshaw, rebooked and then jumped for ME Research UK – thanks to them all.

Standing Order Form

To allow us to press ahead with our mission to Energise ME Research globally, 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 of account holder(s)

Address

Postcode

Telephone number

Name of Bank or Building Society

Branch address

Postcode

Instruction to your Bank or Building Society

To the Manager, Please arrange to debit my/our account with the amount detailed below, once every month until further notice.

Account number

Branch sort code

Amount (£)

Payment date each month

Date of first payment

Pay to: Clydesdale Bank, 158/162 High Street, Perth PH1 5PQ, UK, Account: ME Research UK, Account no: 50419466, Branch code: 82-67-09

☐ ***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 to which you donate 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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