

breakthrough

News of the ME Research YOU are helping to fund

**Investigating
visual symptoms
in ME/CFS**



RESEARCH
UK

ISSUE 15

SPRING 2012

www.meresearch.org.uk

Breakthrough

Breakthrough magazine is published twice a year and is available free of charge.

To subscribe, contact:

ME Research UK, The Gateway,
North Methven Street, Perth PH1 5PP, UK

Tel: +44 (0)1738 451234

E-mail: meruk@pkavs.org.uk

Web: www.mereseearch.org.uk

ME Research UK is a Scottish Charitable Incorporated Organisation, charity number SC036942

We encourage your comments and suggestions for future articles.

Chair of Editorial Board: Dr Neil Abbot

Editor and Design: Dr David Newton

Publisher: ME Research UK

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.

This is an open access publication and, with the exception of images and illustrations, the content may, unless otherwise stated, be reproduced free of charge in any format or medium, subject to the following constraints: content must be reproduced accurately; content must not be used in a misleading context; ME Research UK must be attributed as the original author and the title of the document specified in the attribution. The views and opinions expressed by writers within Breakthrough do not necessarily reflect those of ME Research UK or the Editor. No responsibility is assumed by the publisher for any injury and/or damage to persons or property as a matter of products liability, negligence or otherwise, or from any use or operation of any methods, products, instructions or ideas contained in the material herein.

First published by ME Research UK, 2012

© ME Research UK

editorial



Over the past few years, steadily and progressively, there has been a sea change in how charities are regulated. It may not have made newspaper headlines, but the changes have been as profound as those in the financial sector. The goals of regulation are simple – to protect the public from financial loss, engender confidence in the system, and ensure a sustainable future.

As a Chartered Accountant, and presently a Trustee of a major public company's pension fund with duties including chairing its audit and governance committee, I have seen the evolution of regulation and governance in the financial sector and now, as honorary Finance Director of ME Research UK since 2006, in the charity sphere.

In Scotland, the Office of the Scottish Charity Regulator (OSCR) was established to be both a regulator and also a champion of good governance. It encourages, and if necessary requires, charities to improve and evolve continually in order that they remain relevant and effective, encouraging innovation but also emphasising compliance with best practice.

As part of this approach, linking regulation with better governance, OSCR has introduced the "Scottish Charitable Incorporated Organisation" (SCIO) – a new legal device that allows Scottish charities to change legal form and take advantage of liability protection previously available only with company status, whilst avoiding administrative complications. Within the next 18 months, charities in England and Wales will also be given the opportunity of converting to Charitable Incorporated Organisation status.

After very careful consideration, the trustees of ME Research UK decided that conversion to a SCIO was in the best interests of the charity. It was the most effective way of securing our long-term future, continuing to be at the forefront of funding innovative and vital research. With OSCR's consent, we became a SCIO on 8th November 2011. Indeed, ME Research UK was one of the very first charities to make this conversion. The change to a SCIO was also an opportunity to examine carefully our internal governance and to ensure that our policies were robust, relevant and "fit for purpose".

Supporters may ask what difference this will make to ME Research UK. Our purposes remain the same, our ethos and drive are unaffected, but we are now able to plan for the future with more certainty, in the knowledge that our legal structure and governance are now up-to-date and robust.

Governance and regulation may be arcane concepts to supporters, but they are the bedrock upon which trust is based. A well-run charity, which is open and accountable, is also an effective charity, and one which delivers what its supporters desire while being best placed to have a sure and certain future.

David Macdonald
Honorary Finance Director
ME Research UK



this issue

More than meets the eye?4-5

New study assessing visual function in ME/CFS

MRC grant awards..... 6-7

Details of the ME/CFS biomedical research studies awarded MRC funding

XMRV update..... 8

Are research findings due to contamination?

Vascular endothelial damage.....9

New study indicating increased cardiovascular risk in ME/CFS

Projects funded by ME Research UK..... 10-11

An overview of research supported by the charity

Recent research..... 12-15

Underdiagnosis in school children, XMRV not found in blood supply, orthostatic intolerance, rituximab therapy, Lyme disease, and more

Taking a dive..... 16-19

Fundraising by the Friends of ME Research UK: skydive challenge, wheelchair push, historic wedding, marathons in Cardiff, Reading and Belfast



MORE THAN MEETS THE EYE?

ASSESSMENT OF VISUAL FUNCTION IN ME/CFS

People with ME/CFS often have problems with their vision; in fact, around three-quarters of the 2,073 consecutive patients described in the Canadian Consensus Document 2003 specifically reported sensitivity to light and dullness of vision to be significant problems.

Yet, apart from a group of smallish observational studies (see the box on the opposite page), there is very little formal evidence in scientific literature that these symptoms exist, despite the fact they greatly affect quality of life and, moreover, can be easily measured. Furthermore, because no attempts have yet been made to quantify objectively the nature or extent of visual symptoms in the illness, there remains no solid empirical evidence-base to back up patients' individual reports of disabling visual disturbances.

To begin to redress the balance, ME Research UK and the Irish ME Trust have jointly funded a one-year pilot study that aims to determine quantitatively and objectively the main visual symptoms that people with ME/CFS experience. The study will also determine their rate of occurrence and establish whether the types and extent of visual symptoms experienced can be correlated with the severity of the condition and the specificity of other (non-visual) symptoms.

The investigations are being organised at the Vision and Language Research Group at the University of Leicester, which consists of a multidisciplinary group of researchers all working on key issues

in vision, visual cognition and language comprehension. The laboratories house a range of techniques including psychophysics, electrophysiology, computational modelling and eye movement recording, to study sensory and cognitive processing in the brain from the level of individual neurons to the behaviour of the organism as a whole.

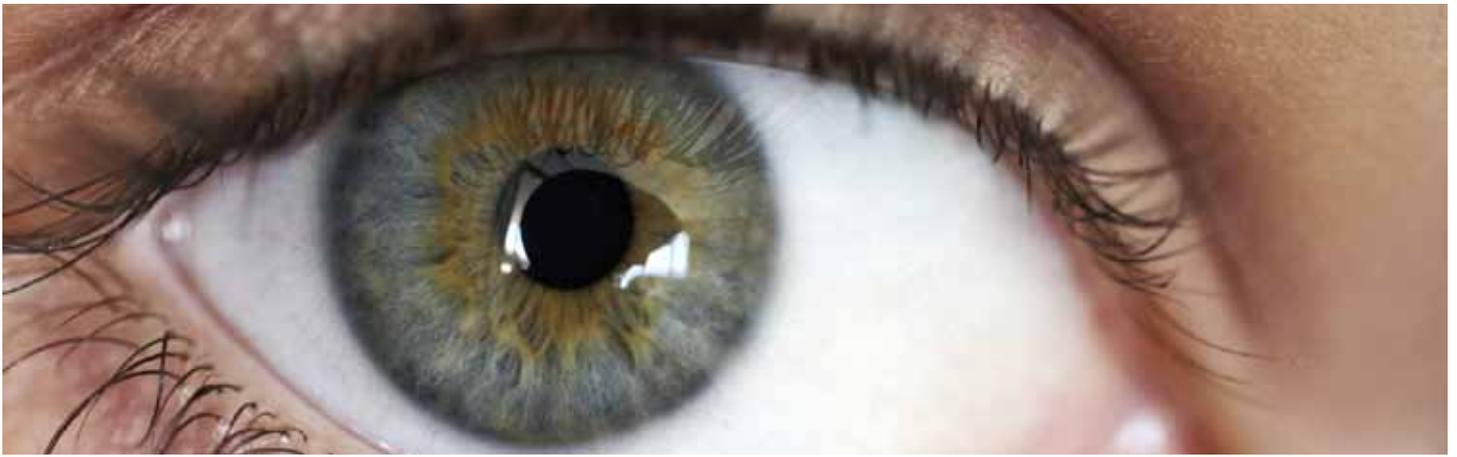
Based on the most commonly reported visual and vision-related symptoms (see the Table opposite), project leaders Dr Claire Hutchinson and Dr Steve Badham (pictured below) aim to examine two main categories of visual impairment with specialist ophthalmic techniques used in the Vision and Language Research Laboratory. The first concerns heightened visual awareness (including hypersensitivity to light and difficulty suppressing irrelevant background visual information), and the second consists of eye-movement problems (such as difficulty focusing on images or tracking objects).

For this initial study, a large group of ME/CFS patients will be recruited from the Leicester area, and each will be assessed on their fulfilment of both the Fukuda 1994 and

Canadian 2003 criteria. To prevent sampling bias, recruitment will be drawn equally from local ME support groups and via clinics in the Leicestershire NHS Partnership Trust which take referrals from GPs in the area.

For all studies, the participants with ME/CFS will be compared with a group of control subjects matched for factors such as age, education level and gender. As well as undergoing ophthalmic examinations, participants will complete a variety of outcome measures, including symptom severity and quality-of-life measurements, allowing associations to be examined between clinical status and any objectively identified visual deficits that are uncovered. The results could surprise us all, and might help delineate ME/CFS from other chronic illnesses and help improve diagnosis.





VISION-RELATED DEFICITS REPORTED BY ME/CFS PATIENTS

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

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 (published in *Optometry and Vision Science*, 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 four categories: functional (related to accommodation and convergence); neurosensory (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 (*Journal of the American Optometry Association*, 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 the same volume of the *Journal of Behavioural Optometry* 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 accommodation dysfunction to debilitating disability. 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.

Then, between 2000 and 2010, two further reports appeared. The first was a case-control study (*Annals of Ophthalmology*,

2000) in which the 37 patients had significant eye impairments compared with controls; the impairments included foggy/shadowed vision and sensitivity to light, as well as problems of eyeball movement (oculomotor impairments) or tear deficiency. The second, from Russia (*Vestnik Oftalmologii*, 2003), reported vascular pathology of the eye in 70.2% of the 218 ME/CFS patients, and “dystrophic pathology” in 52.8%.

The astounding thing is that these six smallish reviews and studies (probably) represent the sum total of observations on, or research into visual dysfunction in ME/CFS in the past 30 years, even though eye symptoms are a concern for a majority of patients.

As we have said before, time marches on but sometimes it can seem to stand very still indeed where research into ME/CFS is concerned!



MRC grant awards: a significant achievement

The award by the Medical Research Council (MRC) of almost £1 million to Professor Julia Newton, Dr Fai Ng and colleagues (Newcastle Biomedicine, Newcastle University, UK) for two biomedical projects is a great boost for research into ME/CFS in the UK. In total, the MRC has made five discrete grant awards under the “Understanding the Mechanisms of CFS/ME” call, at a cost of approximately £1.65 million (more details are at the top of the opposite page).

The research at Newcastle University represents one of the very few research programmes anywhere in the world on ME/CFS – and a rare example of a consistent, directed, problem-solving approach to tackling the illness. Since 2006, the group has received three separate grants from ME Research UK to look at the autonomic nervous system (2006), muscle bioenergetics (2009) and systems analysis (2010). In addition, the researchers received a large grant (2007) from ME Research UK, the John Richardson Research Group and the Irish ME Trust for “Autonomic nervous system dysfunction: a two-year investigation” to examine muscle, liver and heart function in a large patient cohort.

These investigations have resulted in a series of novel, incremental, scientific papers showing that, compared with healthy people, ME/CFS patients can have a range of measurable disorders, including dysfunction of the autonomic nervous system (three-quarters of patients), an abnormal heart rate response to standing, lower blood pressure

and abnormal blood pressure regulation, substantially slower recovery from skeletal muscle exercise, and impaired cardiac function.

Prof. Newton commented, “I am delighted at this outcome, which arrives after many years of hard work by my colleagues and myself. I’d like particularly to thank the charity ME Research UK. Since 2006, the charity has provided the pilot/seedcorn funding for four distinct projects, which have allowed us to accumulate the data on which these successful applications to the MRC were based. In addition, ME Research UK has supported our research programme in a variety of ways, not least by providing formal support letters for our grant applications to the MRC. The success of these applications shows what can be achieved by biomedical researchers working closely with medical research charities in a supportive and collaborative way.”

The issue of MRC funding for ME/CFS research has been a “hot potato” for a long time. Patients, support groups and charities have been unhappy that most of the MRC’s inadequate grant-spend in the past has been allocated to researching “biopsychosocial” aspects at the expense of truly biomedical research into the causes of the underlying physical illness, the reverse of the situation in other illnesses such as multiple sclerosis or rheumatoid arthritis.

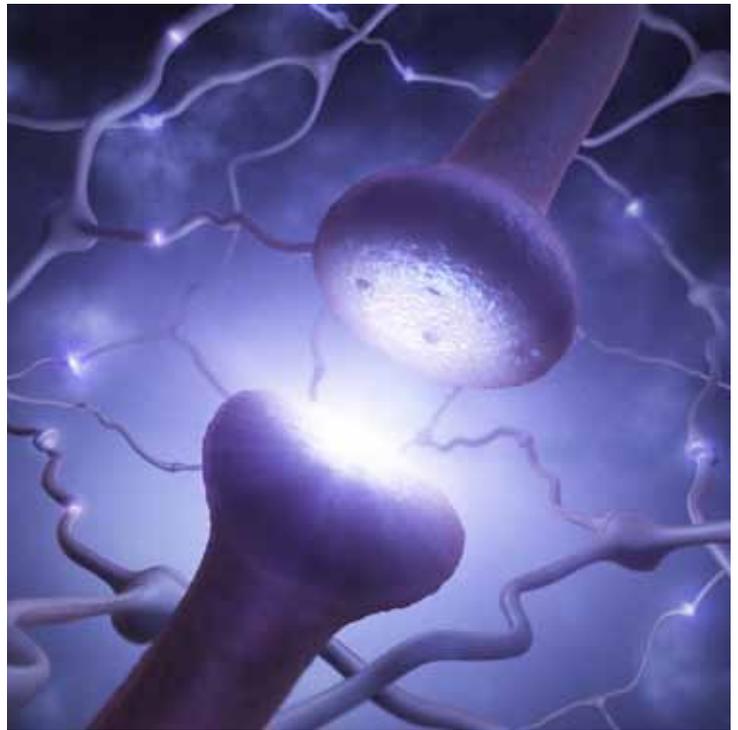
Since 2008, however, there has been a much greater level of engagement between the MRC and ME/CFS charities at a professional level. First, the arrival into the field of Prof. Stephen Holgate (MRC

Clinical Professor of Immunopharmacology at the University of Southampton School of Medicine), who has previous experience of organising a successful research collaborative in respiratory illnesses, brought new momentum, not least through his chairmanship of a novel “MRC CFS/ME Expert Group” to consider how new high-quality research might be encouraged.

Then, a Research Workshop was held in November 2009, at which established researchers and scientific representatives of charities – including Dr Vance Spence and Dr Neil Abbot of ME Research UK – met to set research priority areas. The culmination of this process was the “Call for proposals: Understanding the Mechanisms of CFS/ME” in February 2011, under which five projects have now been funded.

Medical research funding of £1.65 million for ME/CFS is not a huge sum; the MRC’s gross research expenditure was £758.2 million in 2009 to 2010 (see the box on the opposite page). However, the allocation of these monies under a “pathophysiology” call, culminating in the award of grants for research that is overwhelmingly “biomedical” rather than “psychosocial” in nature, is a significant achievement for which Prof. Stephen Holgate, the ME/CFS charities and the MRC itself deserve congratulations. The task now is to ensure that Class I funding continues to be available, year-on-year, for biomedical research into a disease that has been overlooked for far too long.

New MRC-funded programmes in ME/CFS



Understanding the pathogenesis of autonomic dysfunction and its relationship with cognitive impairment

Prof. Julia Newton

Clinical Professor of Ageing & Medicine, Newcastle University

Dysfunction of the autonomic nervous system, characterised by problems while standing, is present in many people with ME/CFS. The researchers will use functional MRI to measure changes in blood flow to the brain and how this relates to cognition and nervous system dysfunction.

Identifying the biological fingerprints of fatigue

Dr Fai Ng

Clinical Senior Lecturer in Rheumatology, Newcastle University

(The photo opposite shows the research team, from left to right: Christine Downie, Jessica Tarn, Andini Natasari, Philip Stocks, Shereen Al-Ali, Dr Ng and Katie Collins.)

Using primary Sjogren's syndrome (an autoimmune condition with several clinical features similar to ME/CFS) as a disease model, the researchers will undertake a comprehensive analysis of the immune system to identify biological fingerprints, and explore whether these biomarkers are present in ME/CFS patients.

Modulation of aberrant mitochondrial function and cytokine production in skeletal muscle by supplementary polyphenols

Prof. Anne McArdle

Institute of Ageing & Chronic Disease, University of Liverpool

A defect in mitochondria, the energy-producing cells of the body, may be present in ME/CFS patients, significantly reducing the energy supply to the muscles. The research team will use newly developed, sensitive laboratory techniques to study mitochondria within muscle cells, with the aim of identifying interventions to reverse or halt further damage.

Can enhancing slow wave sleep improve daytime function?

Prof. David Nutt

Neuropsychopharmacology Unit, Imperial College London

As sleep disturbance is a core symptom of ME/CFS, the researchers at Imperial College will use a drug to increase deep restorative sleep in ME/CFS patients and measure its effect on brain function during waking hours.

Persistent fatigue induced by interferon-alpha: a new immunological model

Dr Carmine Pariante

Centre for the Cellular Basis of Behaviour, King's College London

Interferon-alpha is produced as a protective response to viral infection, but it also causes fatigue and flu-like symptoms similar to those experienced by ME/CFS patients. The researchers will follow patients undergoing interferon-alpha treatment for hepatitis C to identify biological measures useful for the prediction of the development of ME/CFS.

What is the Medical Research Council?

- Incorporated by Royal Charter in 1920, the UK's MRC supports medical research, from fundamental laboratory-based science to clinical trials, in all major diseases.
- It invests in world-class scientists, and has produced 29 Nobel Prize winners, most recently the 2009 Nobel Prize in Chemistry awarded to Dr Venkatraman Ramakrishnan, MRC Laboratory of Molecular Biology, Cambridge.
- The MRC's core funding allocation comes from the Government's Department for Business, Innovation and Skills (BIS), though it receives additional funding from other partners for collaborative projects and joint initiatives.
- Gross research expenditure by the MRC was £758.2 million in 2009 to 2010: £288 million on around 1,100 grants to researchers in universities, medical schools and research institutes; £375 million on over 500 programmes within the MRC's own research units and institutes; and £78 million on almost 2,000 studentships and fellowships.
- The health categories receiving most support include neurological and mental diseases (20.5% of research programme expenditure); infection (16.1%); cancer (8.1%); blood, cardiovascular and stroke (6.3%); and inflammatory and immune system diseases (6.3%).
- ME/CFS research is currently designated a high priority area for the MRC, and the £1.65 million allocated in December 2011 to five research projects followed a specific "call for proposals" for research applications.

XMRV: GAME, SET AND MATCH TO CONTAMINATION?

It has been 30 months since the prestigious scientific journal *Science* published startling evidence (Lombardi et al, 2009) of a link between the virus XMRV and ME/CFS. Unfortunately, no other researchers across the world have been able to reproduce the original dramatic findings, and none of their 23 distinct scientific papers has reported finding significant levels of the virus in either ME/CFS patients or healthy controls.

One of the teams attempting to confirm the original report was headed by Prof. Jonas Blomberg at the University of Uppsala, Sweden, which had received grant funding from ME Research UK and the Irish ME Trust for a thorough investigation in Swedish patients. Their task was not easy, and several methodological difficulties related to murine gamma-retroviral diversity had to be resolved. This work involved tracing the recombinant origin of XMRV/HMRV strains and determining the sensitivity of various polymerase chain reaction (PCR) techniques to detect portions of the gamma-retroviral spectrum. In the end, they found three major groups of murine endogenous gamma-retroviruses and developed two sensitive PCRs capable of detecting them.

After clarifying the methodological aspects, they turned their attention to clinical samples, recruiting 85 patients via the Gottfries Clinic from the Gothenburg area of Sweden: 48 had ME/CFS (Canadian 2003 criteria, similar to patients in the Lombardi report), 30 had both ME/CFS and fibromyalgia, and 7 had fibromyalgia alone. Interestingly, irritable bowel syndrome was found to occur in 40% of the total group of patients, and the patients' mean score on the FibroFatigue scale was 41 ± 9 points – indicating a moderate to severe level of symptoms. Both RNA and DNA were extracted from white blood cells and plasma in the patients, and blood serum from 168 consecutive anonymous blood donors was obtained from the blood bank at Uppsala Academic Hospital, Sweden. Samples were interpreted as “positive” if



repeatable signals with at least two different XMRV/HMRV PCRs were obtained.

The group's findings (published by Elfaitouri et al in *PLoS ONE*, 2011) were that XMRV/HMRV could not be detected in white blood cells or plasma from Swedish patients with ME/CFS or fibromyalgia, or in blood sera from Swedish blood donors, using the sensitive PCR techniques specifically developed.

In a separate expert review (*Advances in Virology*, 2011), Prof. Blomberg suggested two reasons for the large number of “negative” studies from across the world. First, XMRV/HMRVs might just be very hard to detect, particularly if chronic illness establishes a low-grade infection with a waning immune response – a phenomenon seen in experimentally XMRV-infected macaques and, apparently, not unknown in HTLV and HIV infections. Alternatively, the high levels of XMRV found in the Lombardi report might have been the result of contamination rather than true infection in patients; as he said, “if this were the case, it would be a sad outcome of a fascinating and important story”.

Since these words were written, the original Lombardi manuscript has been retracted by the editors of *Science* (and

partially retracted by some of its own authors) due to the weight of contrary evidence, in particular, the inability of other researchers (including the Swedish team) to reproduce the original results, coupled with separate, robust evidence for contamination of samples.

Contamination, it turns out, can occur via four main routes: from infected cell-line DNA, from infected cell-line virus particles, from mouse DNA, and from plasmid DNA. Furthermore, it has been known to occur even in laboratories with considerable experience in virology. For example, an “envelope-defective retrovirus” reported to infect rheumatoid arthritis patients in 1997 was found to be the result of laboratory contamination with a rabbit beta-retrovirus.

Although we still await the final piece of the jigsaw – the results of a \$2.3 million investigation funded by the US government to be published in 2012 – the case for the involvement of XMRV infection in human diseases, including ME/CFS, looks increasingly threadbare. Most scientific researchers now believe it is game, set and match to contamination – if true, a sorry end to a story which held so much promise for patients all over the world.

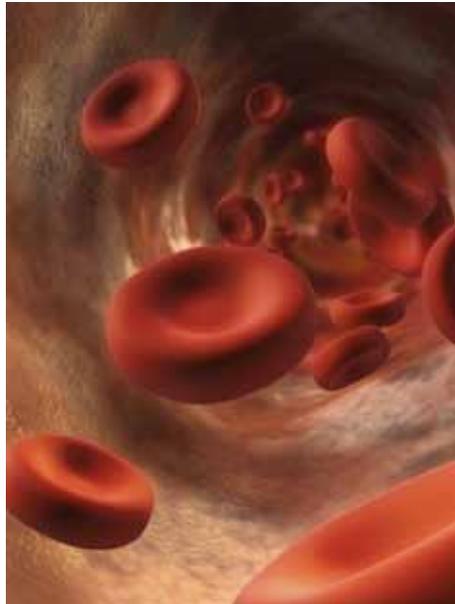
Vascular endothelial damage in ME/CFS?

ME/CFS is associated with cardiovascular symptoms including autonomic and cardiac dysfunction (see page 6), and impaired blood pressure regulation. In addition, several research groups have reported raised levels of oxidative stress, low-grade inflammation and increased arterial stiffness. These different evidential strands form a picture of increased cardiovascular risk in people with the illness, something of great potential importance to patients and healthcare services.

One potential site of oxidative injury – cumulative cell damage caused by oxygen “free radicals” – is the vascular endothelium, the thin layer of cells that lines the inner surface of every blood vessel. The vascular endothelium in fact lines the entire circulatory system, from the smallest capillaries to the arteries and all the way to the heart, and has very distinct and unique functions that include the movement of hormones, the maintenance of blood vessel tone, and the recruitment of white blood cells.

Damage to the vascular endothelium would be expected to lead to dysfunction of the endothelial cells themselves and a reduced ability of the blood vessels to open to full capacity. Could the vascular endothelium be damaged in ME/CFS patients?

Building on their previous programme of cardiovascular research in adults and children with ME/CFS, Dr David Newton and colleagues at the Vascular and Inflammatory Diseases Research Unit, University of Dundee decided to investigate both



large-vessel and small-vessel endothelial function, both of which are known to be related to cardiovascular risk and outcome. Large-vessel function was measured using flow-mediated dilatation (see the box below), and small-vessel (microvascular) function was measured by laser Doppler flowmetry of the forearm skin after cuff occlusion of blood flow to the arm.

Flow-mediated dilatation was significantly lower in the 30 CDC-defined patients than in the 27 age and gender-matched control subjects (median of 5.99 versus 9.24%, respectively, $p < 0.001$). Importantly, after glyceryl trinitrate was given to patients and controls, there was no significant difference between the groups, demonstrating that

the impaired flow-mediated dilatation was most likely to be due to endothelial dysfunction and not to some other cause (such as damaged smooth muscle).

As regards the small vessels, ME/CFS patients had a significantly lower blood flow response in forearm skin than did control subjects (peak flow 38.33 versus 69.80 arbitrary units, respectively, $p = 0.002$). ME/CFS patients also had significantly higher levels of serum hs-CRP and triglycerides, and lower levels of HDL cholesterol in blood samples – all indicative of increased oxidative stress and cardiovascular risk.

The importance of this investigation was that it was the first ever to measure and demonstrate vascular endothelial dysfunction directly in ME/CFS patients. Since the experiments measured the response of the vascular endothelium to a “shear stress” (i.e., the stopping and starting of blood flow), the reduced vascular responses support the hypothesis that some functions of the endothelium are damaged in ME/CFS patients, both in large vessels and in the small-vessel microcirculation.

The authors of the scientific paper (Newton et al, *International Journal of Cardiology*, 2011) say that their findings “build on previous work reporting indirect markers of endothelial dysfunction, such as increased oxidative stress, inflammation and arterial stiffness”, and that these results taken together with previous evidence “point to an increased cardiovascular risk in ME/CFS patients”.

What is flow-mediated dilatation?

- When blood flow increases through a blood vessel, the vessel dilates (or increases in diameter) – this phenomenon is called flow-mediated dilatation.
- It is the most widely used research technique for assessing the health of the vascular endothelium, the layer of active cells which lines the entire circulatory system and participates in the regulation of blood flow in response to the needs of tissues and organs.
- To measure flow-mediated dilatation, arterial blood flow (usually to a limb) is temporarily stopped and then restarted, causing blood flow to overshoot (reactive hyperaemia) as the vessels dilate. The resultant increase in blood vessel diameter can be measured using an ultrasound probe.
- In patients with dysfunction of the endothelium – seen in cardiovascular diseases and in inflammatory conditions such as systemic lupus – the blood vessels are less able to dilate, and so flow-mediated dilatation is lower than in healthy people.
- Flow-mediated dilatation has become a valuable assessment tool, since a disturbance of endothelial function is now considered to be a key event in the development of atherosclerosis.

Some projects funded by ME Research UK



Prof. Jonas Blomberg



Dr Claire Hutchinson



Prof. Carl-Gerhard Gottfries



Dr Paula Ansley

Since 2000, we have funded the work of a number of scientists in the UK and overseas, whose research covers a range of different areas of interest. Grants totalling almost £770,000 have been awarded for 32 specific investigations on ME/CFS patients (some are listed below), and we are particularly grateful to those ME organisations that have provided larger donations to help us fund some of these investigations.

Our priority has always been to support innovative clinical and biomedical studies, based in established research institutions, investigating the causes of ME/CFS and the effectiveness of potential treatments. All our grants are competitive and are subject to peer review. To date, 44 scientific papers have been published from funded projects, and details of these (with abstracts and essays by ME Research UK) can be read in the research section of our website.

Development of a rational diagnostic system based on microbiological biomarkers

Prof. Jonas Blomberg
Uppsala University Hospital, Sweden

Assessment of visual function

Dr Claire Hutchinson
Vision and Language Group, University of Leicester
(co-funded by the Irish ME Trust)

Establishment of the UK ME/CFS Biobank

Dr Luis Nacul and Dr Eliana Lacerda
London School of Hygiene and Tropical Medicine
(with co-funding from Action for ME and the ME Association)

Adopting a systems approach to modelling symptom data

Prof. Julia Newton
School of Clinical Medical Sciences, University of Newcastle

Comparison of criteria for ME and CFS: neurocognitive, physical and autonomic manifestations

Dr J Van Oosterwijck and Prof. Jo Nijs
Artesis University College Antwerp, Belgium

Exercise, pain, and the immune and sensory systems

Dr Jo Nijs, Vrije Universiteit Brussel, Brussels, Belgium

Muscle bioenergetic abnormalities

Prof. David Jones
Institute of Cellular Medicine, University of Newcastle

XMRV in Swedish patients

Prof. Jonas Blomberg and Prof. Carl-Gerhard Gottfries
Uppsala University Hospital, Sweden
(with co-funding from the Irish ME Trust)

Autonomic nervous system dysfunction – a clinical study

Prof. Julia Newton
School of Clinical Medical Sciences, University of Newcastle
(with co-funding from the Irish ME Trust and the John Richardson Research Group)

Vitamin D supplementation and cardiovascular disease risk

Dr Faisal Khan
Institute of Cardiovascular Research, University of Dundee

Evaluation of pain and therapeutic interventions

Dr Lorna Paul and Dr Les Wood
Glasgow Caledonian University

Interleukin-6 and its receptors

Prof. Myra Nimmo
University of Strathclyde, Glasgow

Biochemical and blood flow aspects in children

Dr Gwen Kennedy
Institute of Cardiovascular Research, University of Dundee
(with co-funding from The Young ME Sufferers Trust, and Search ME)

Gene expression studies

Dr J Kerr
St George's Hospital, University of London
(co-funded by the Irish ME Trust)

Non-invasive neuroimaging of the brain

Prof. Basant K Puri
Imperial College London
(with co-funding from ME Solutions, and the MRC Clinical Sciences Centre, Imperial College).

Exercise tolerance and post-exertional symptoms

Prof. Brian MacIntosh and Dr Eleanor Stein
University of Calgary, Alberta, Canada

Chronic inflammation and apoptosis (programme)

Prof. Jill Belch
Institute of Cardiovascular Research, University of Dundee

Differential Gene Expression

Prof. J Gow
University Department of Neurology, Glasgow

Novel mechanisms of fatigue in ME/CFS

Dr Paula Ansley
Northumbria University, Newcastle upon Tyne

Effects of muscle fatigue on H-reflex excitability

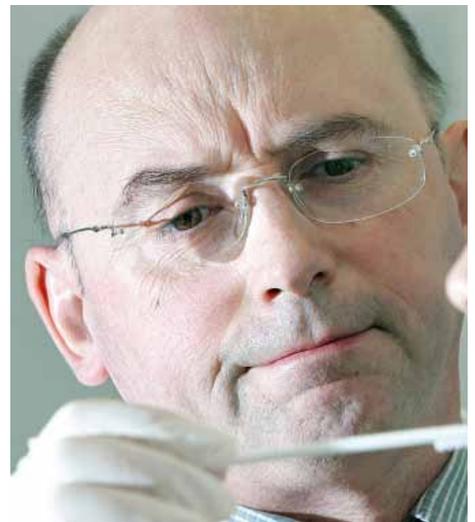
Dr Les Wood
Glasgow Caledonian University



Dr Jo Nijs



Dr Eliana Lacerda



Prof. John Gow



Prof. Jill Belch



Recent research from around the world



BEIJING

High transforming growth factor

Abnormalities of the immune system are frequently found in ME/CFS, and there is evidence that the “cytokine” transforming growth factor beta (TGF- β 1), a protein molecule which regulates a wide variety of cell processes, might be involved. In fact, ME Research UK-funded work on ME/CFS at the University of Dundee found high concentrations of active TGF- β 1 in addition to increased neutrophil apoptosis (an important process that controls infections and removes cells that have reached the end of their natural life), suggesting an association between TGF- β 1 activity and abnormalities in immune cells.

Because of such evidence, researchers in Beijing (Zhang et al, *Journal of the Formosan Medical Association*, 2011) funded by the National Natural Science Foundation of China investigated TGF- β 1 production (mRNA expression) in white blood cells, which have a role in fighting infection.

They recruited 63 ME/CFS patients, 50 healthy people, and 50 control subjects with other diseases such as liver or lung cancer, diabetes mellitus, systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis, and primary Sjögren’s syndrome. They found that mean TGF- β 1 mRNA expression was significantly higher in ME/CFS patients (1.17 ± 0.58) than in disease controls (0.07 ± 1.08) or healthy people (0.00 ± 1.63), with no significant differences between disease controls and healthy controls.

Given that TGF- β 1 is found in many tissues such as blood, brain and cerebrospinal fluid, and is heavily involved in the complex processes surrounding apoptotic programmed cell destruction, the authors suggest that the abnormally high levels – not found in the comparison group containing people with the range of other diseases – point to underlying disease processes in ME/CFS, such as a persistent or reactivating infection, or a toxic state indicated by accelerated apoptosis.

BRISTOL

Under-diagnosis in school children

We do not really know how many youngsters are affected by ME/CFS, but with rough prevalence figures of 60 to 70 cases per 100,000, it is likely that around 9,000 people under the age of 16 in the UK meet the criteria for the illness which – according to the report to the Chief Medical Officer in 2002 – “represents a substantial problem in the young” and “can disrupt education and social and family life, at a particularly vulnerable time of life”. We know, however, that many of them remain undiagnosed and under-investigated, which was why researchers at the Centre for Child and Adolescent Health in Bristol (Crawley et al, *BMJ Open*, 2011) wanted to examine whether school-based clinics could be used to identify these children.

The investigators examined records of children aged 11 to 16 years enrolled in three state secondary schools in the south west of England, to determine the number of children newly diagnosed with ME/CFS. Attendance officers identified those children who had

missed 20% or more of school in a six-week term without a known cause. Children with fatigue were referred to a specialist “CFS/ME” service for further assessment, and outcomes were evaluated after six weeks and six months. All children given a diagnosis of ME/CFS were screened for other medical and emotional causes of fatigue.

Of the 2,855 enrolled children, 461 (16%) had missed 20% or more school over a six-week period, and 28 children, representing around 1% of the school population, fulfilled the criteria for ME/CFS. Importantly, only 3 of these 28 children (10.7%) had previously received a diagnosis and accessed specialist treatment. Of 19 children followed up, 6 had fully recovered at six weeks and a further 6 at six months. As might be expected, children who were detected through school-based clinics were less severely affected than those referred via health services, and appeared to do well once treated.

The key lessons of this study are the high degree of under-diagnosis of ME/CFS among school children, and the important, though underappreciated role the illness has in “unexplained” absence from school. School-based clinics should be aware of the problem and of the option to refer these ill children to specialist services.

MARYLAND

XMRV not found in blood supply

Following the report in October 2009 of XMRV infection in some ME/CFS patients, there were also suggestions that blood supplies might be contaminated with the virus. In fact, over the next year, various regulatory authorities across the world either banned blood donations from ME/CFS patients or discouraged them from giving blood.

A new report in *Transfusion* (Dodd et al, 2012), which is the official journal of the American Association of Blood Banks, has described the examination of routine blood donor samples and samples from a linked donor–recipient repository, for evidence of infection.

Samples were tested for the presence of antibodies to XMRV-related recombinant

antigens and/or XMRV RNA using validated, high-throughput systems. Overall, in 17,249 blood donors or recipients, the presence of antibodies to XMRV could not be confirmed (0% positivity). Also, 1,763 samples tested were found to be non-reactive for XMRV RNA (0%), and there was no evidence of infection in blood samples taken from 109 recipients after transfusion from 3,741 donors.

The fact that XMRV and related murine leukaemia virus markers were not present among a large population of blood donors, and that evidence of transmission by blood transfusion could not be detected, is surely good news for the general population.

As the accompanying editorial in *Transfusion* said, “over the past two years, XMRV has transformed from an agent of potential human disease association, and a possible threat to the national blood supply, to a laboratory contaminant without a current threat to humans. This revolution of ideas regarding XMRV could only have been made possible by the scientific method.”

NEWCASTLE

An objective test for orthostatic intolerance?

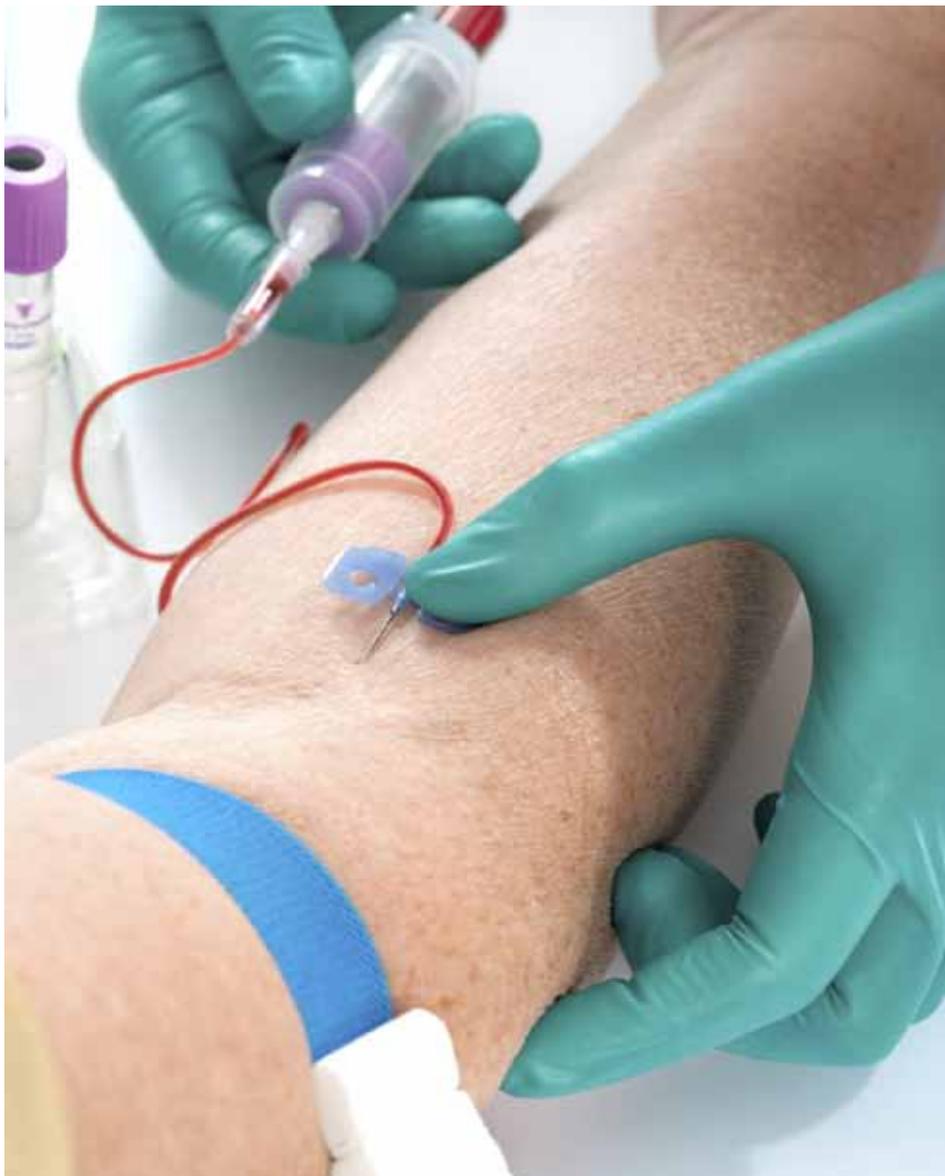
Symptoms of autonomic nervous system dysfunction are present in around three-quarters of ME/CFS patients. One of these symptoms is orthostatic intolerance, the inability to remain standing without ill effects. Many patients know from experience that standing can bring on dizziness, nausea, altered vision and fatigue. Yet, their reports are often discounted by doctors who attach more importance to “objective” findings.

For several years, Dr John Allen and colleagues in Newcastle have been developing photoplethysmography (PPG), a simple-to-use, relatively low-cost method of shining light onto skin to detect changes in blood volume. In their latest scientific report (Allen et al, *Physiological Measurement*, 2012), they describe the use of novel state-of-the-art multi-site PPG technology that takes measurements from sites on the ears, fingers and toes simultaneously in real time – a tool that is perfectly suited to the measurement of cardiovascular responses to standing.

In the experiment, multi-site PPG pulses were collected from tissue pads of the ears, fingers and toes of 14 people with ME/CFS and 14 age-matched sedentary control subjects during ten minutes of lying down followed by three minutes on a tilt table (head-up to 70°). Percentage change in pulse timing, and pulse amplitude at each site were calculated using beat-to-beat pulse wave analysis.

The results showed that the change in composite score measured on tilting was significantly less in the ME/CFS patients than in controls (26 versus 37%, $p=0.002$). Using both timing and amplitude measures, they could achieve a diagnostic accuracy of 82%.

The researchers say that these demonstrable pulse wave abnormalities have the potential to become a bedside diagnostic marker. They find it interesting that the predominant abnormalities of pulse wave form found in ME/CFS patients were at the ear rather than the fingers or toes, suggesting that reduced cardiac output or abnormalities of regulation of cerebral blood flow might underlie some of the symptoms experienced on standing.



NORWAY

Delayed response to rituximab therapy

The publication of a scientific report in October 2011 showing an improvement of symptoms in ME/CFS patients treated with rituximab (Fluge et al, *PLoS One*, 2011) made a big splash in the ME world, and received widespread coverage in the press. Rituximab is a monoclonal antibody against the CD20 protein which is mainly found on the surface of B-lymphocytes, a type of white blood cell. The drug eliminates these B-cells, and has therefore been used to treat diseases such as some cancers and autoimmune disorders, in which these cells are malignant, overactive or too numerous.

There is an interesting background to this investigation. Originally, the researchers at Haukeland University Hospital, Bergen noticed that one patient with ME/CFS experienced “unexpected and marked recovery of CFS symptoms lasting for five months during and after cytotoxic chemotherapy for Hodgkin’s disease”. Because of this, they conducted a pilot case series in 2009 to explore the clinical effects of rituximab in three more people with ME/CFS, and found a “significant clinical response”.

Building on these intriguing results, the researchers planned their newly published investigation – a double-blind, placebo-controlled phase II study – using 30 ME/CFS patients randomised to receive either rituximab or placebo (saline), given as two intravenous infusions two weeks apart. The participants were then followed up for a whole 12 months.

The predefined “primary endpoint” – self-reported fatigue score 3 months after treatment – was negative; i.e., there

was no significant difference between rituximab and placebo. As the authors point out, however, differences in fatigue between the two groups were actually most evident after 6 to 10 months, suggesting that 3 months was too short a time to evaluate the effects of rituximab on symptoms, something that subsequent investigations will take into account.

So, over the whole 12-month follow-up period, a major or moderate “overall response” (defined as lasting improvements in self-reported fatigue) was seen in 67% of patients on rituximab compared with only 13% of patients on placebo ($p=0.003$; see the Table below). Furthermore, rituximab was also associated with significant improvements in some quality of life measurements, and, what’s more, no serious adverse events were reported in patients receiving rituximab.

The Norwegian researchers suggest that the “delayed” responses to rituximab (starting after 2 to 7 months), in spite of rapid B-cell depletion, support the idea of ME/CFS as an autoimmune disease in which the gradual elimination of autoantibodies from the body leads to symptom improvement.

However, they describe their results as preliminary and indicating only a “proof of principle”. In fact, they were probably as surprised as anyone else by the spin given by the media to these tentative findings. The next phase of the work is at the planning stage: a Norwegian national initiative to undertake a randomized, blinded, multicenter phase III trial to verify or reject these findings.

Given the drastic action of rituximab (the destruction of B-cells which have an important role in immunity), and the cost of the drug (over £3,500 for a single course of two 1000-mg intravenous infusions), it is most likely that other research groups will await the results of the phase III trial before attempting their own investigations.

Clinical responses to rituximab and response durations during 12 months of follow-up

| Clinical responses | Rituximab group (15 people) | Placebo group (15 people) |
|-----------------------------------------|-----------------------------|---------------------------|
| Major | 9 (60%) | 1 (7%) |
| Moderate | 1 (7%) | 1 (7%) |
| Overall | 10 (67%) | 2 (13%) |
| Mean response duration in weeks (range) | 25 (8 to >44) | 41 (34 to >48) |

SALT LAKE CITY

Exercise and gene expression

The cardinal symptom of ME in the historical literature was profound, post-exertional loss of muscle power associated with muscle pain, tenderness and swelling. The NICE Clinical Guideline requires “post-exertional” symptoms (delayed with slow recovery over several days) for a diagnosis. Some researchers have therefore focussed on patients’ responses to exercise in a laboratory setting as a means of understanding the illness and improving diagnosis.

One of these research groups, at the University of Utah, has been investigating the role of molecular receptors in muscle pain and fatigue, and their most recent report (Light et al, *J Intern Med*, 2011) describes their efforts to determine differences in activity in the genes of ME/CFS and fibromyalgia patients before and after moderate exercise. The study included 48 patients with ME/CFS and fibromyalgia, 18 patients with fibromyalgia alone, and 49 healthy controls, and the genes examined were involved in signalling and modulating sensory fatigue and muscle pain. All participants underwent moderate exercise (one 25-minute session on a combined arm-leg cycle ergometer) and had blood samples taken.

In the healthy people and patients with fibromyalgia alone, there were no gene expression changes following exercise. However, in 71% of ME/CFS patients, moderate exercise increased the activity of most sensory and adrenergic receptor genes and one cytokine gene for 48 hours. These post-exercise increases correlated with measurements of fatigue and pain. In the remaining patients (who were more likely to have a history of orthostatic intolerance), genes were not altered apart from adrenergic α -2A receptor transcription, which was decreased at all time-points after exercise.

The fact that even moderate exercise led to increased expression of certain sensory ion channel, adrenergic and immune genes in a majority of ME/CFS patients brings an exercise-related “biomarker” for the illness closer. As the authors say, the post-exercise expression of four specific genes identified in their study meets published criteria (accuracy 0.80) for a “very good to excellent diagnostic tool”.

LIVERPOOL

Misdiagnosed with Lyme disease

The fact that the “umbrella diagnosis” of ME/CFS shares its symptoms with many illnesses will complicate diagnosis and research until a specific biomarker is found. One “overlapping” diagnosis is Lyme disease (caused by *Borrelia* bacteria transmitted via tick-bites); indeed, there have been suggestions for many years that a subgroup of people with ME/CFS do, in fact, have undiagnosed Lyme disease, particularly those who live in areas of the world where tick-bites are common.

The Tropical and Infectious Disease Unit in Liverpool has recently published the results of a case note review (Cottle et al, *QJM*, 2012) of patients referred with suspected Lyme disease, and it makes fascinating reading.

In the five years from 2006 to 2010, 115 patients had been referred. The commonest reasons for referral were fatigue (in 44% of patients), rash (32%), and neurological (19%) and rheumatological (17%) symptoms. After investigation at the Unit, 27 patients (23%) were diagnosed with Lyme disease. However, 38 patients (33%) were given a diagnosis of ME/CFS, since none of them had clinical features that were suggestive of active Lyme disease, or a positive reference laboratory serology.

The remaining patients were diagnosed with other medical conditions, or obtained no specific diagnosis. Intriguingly, almost half of people with ME/CFS had been labelled as having “chronic Lyme disease” by alternative practitioners and had been advised to take multiple and prolonged courses of antimicrobials. Overall, at least 53 unnecessary antibiotic courses had been given by non-NHS practitioners (and 21 given by NHS practitioners) to people who did not have Lyme disease.

Similar high levels of over-diagnosis of Lyme disease by non-specialists have been reported by other referral centres in the UK and North America, particularly to ME/CFS or fibromyalgia patients whose “disputed” illness is always susceptible to misdiagnosis.

As the authors say, “*the frustration expressed by these patients is compounded by the substantial costs of repeated attendances... of unvalidated investigations (often sent overseas) and of multiple lengthy courses of anti-microbial agents, with potential for toxicity*”.



LONDON

How many people have ME/CFS?

It's said that 17 million people in the world have ME/CFS – but this figure is no more than a rough guess based on crude prevalence estimates from developed countries (0.2 to 0.4%, including children) applied to the 7 billion inhabitants of planet Earth! In fact, rigorous, robust estimates of the occurrence of the illness in each country are needed, particularly to plan healthcare and allocate funding for research.

In the UK, a team at the London School of Hygiene and Tropical Medicine have recently concluded an investigation which used rigorous methods to estimate the prevalence (numbers of people) and incidence (new cases each year) of ME/CFS. Their work was part of the ME/CFS Observatory, a collaborative National Lottery-funded research programme involving a series of investigations and the piloting of an ME/CFS specific disease register.

They examined a population of 143,000 people, aged 18 to 64 years, covered by primary care services in three English regions: London, East Anglia and East Yorkshire. Recruitment of patients followed a staged approach for the identification

of cases, starting with a search of GP electronic databases, and ending with a clinical review and the classification of cases according to various definitions of ME and CFS, including the main CDC-1994 (Fukuda) and Canadian (2003) criteria.

In their report (by Nacul et al, publishing in *BMC Medicine*, 2011), the overall minimal yearly incidence (new cases) was 0.015%, implying that potentially around 9,300 people develop the illness in the UK each year. Furthermore, the estimated minimum prevalence rate of ME/CFS was 0.2%, which accords with previous estimates and implies (all things being equal) that a minimum of 125,000 people are living with ME/CFS (however defined) in the UK. About half of these patients (0.11% or potentially 68,300 people) also met the more stringent Canadian definition, and they had more – and more severe – symptoms, including higher pain scores than patients who met the less restrictive Fukuda definition. Whether Canadian-defined patients represent a different clinical subgroup of “true” ME/CFS patients, or are simply ME/CFS patients with a greater burden of illness than others less severely affected, remains to be determined.

The use of a robust methodology, involving the employment of specific diagnostic criteria and rigorously sequenced filter procedures prior to the confirmation of cases, improves confidence in the estimates of the number of people with ME/CFS.

Taking a dive for ME research



Skydive drama

Teresa Foss (pictured above) had always wanted to do a skydive, so in Autumn 2011 she undertook a tandem skydive to raise money for research into ME, which affects her sister Yvonne. She was joined by her nephew David Anderson and his girlfriend Eloise and brother Paul, and together they raised over £700 and had a dramatic and exciting day.



Talk at Edinburgh MESH

The Edinburgh MESH group is a very active support group with one of the largest memberships in the UK, and Dr Vance Spence, Chairman of ME Research UK, was the keynote speaker at its AGM on 15th October 2011 at Lammermuir Hall, Edinburgh.

Vance's hour-long talk was entitled "Taking research forward", and it included the results of some of our recent research projects, including developments in XMRV. The hall was full of Edinburgh MESH members and their families, and there was a very exciting and robust question and answer session on issues such as vitamin D supplements, the need for biomedical clinics, possible links with sick building syndrome, and the marginalization of ME/CFS as an illness.

The picture above shows Jo Bluett, who chaired the afternoon, presenting a cheque to Vance at the end of the meeting.

Push It for ME Research challenge

Rachel Groves can't get far under her own steam, and is certainly unable to compete in her local Lichfield 10K race! So, she simply devised her own 10K around the town, calling on a small army of family and friends for a wheelchair fundraiser "Push It on Sunday".

As she says, "It was a great day – I had nine people walking with me and helping to push! My husband Paul walked the whole 10k with me [Rachel and Paul are pictured right], while our friend Phil took photos, and neighbour Nick pushed me for the first lap of the Stowe Pool circuit. Then, Isobel, Michael, Hazel, Kate, Kay and Nick got involved, and brother Simon pushed for the fourth and final lap with some co-pushing from a couple of my neighbour's children (we had a sort of conga line!). There was a great atmosphere, everyone chatting and laughing together as we walked despite there being rain and wind." Thank you Rachel and team for a great idea, and for raising almost £900.



Historic wedding

In the historic setting of Stobo Kirk, Dr Beth Owen married Dr Robin Kerr in March. The couple (pictured right) asked guests to give donations to our charity through the John Lewis website in preference to gifts. In 2009,

Beth had cycled from Land's End to John O'Groats for ME Research UK in memory of her sister Lois. Lois had been a member of the 25% ME Group for Severe Sufferers, and died in March 2009 after battling with chronic, severe ME for 19 years. She was also very creative, and left behind numerous paintings, poems and writings.

Veronica's half marathon

Along with 15,000 other runners, Veronica McMahon took part in the Cardiff half marathon in October 2011, the biggest road race in Wales. She was running for our charity because a close family member has been suffering from ME for over 15 years now.

As Veronica says, "She is housebound and if she exceeds her limited energy ration, even by having visitors longer than an hour or so, she relapses with flu symptoms and pain and it takes days, weeks or even months to recover – the neurological illness ME is not simply fatigue."

On her Justgiving page, which is still open for donations, Veronica has raised £860, a tremendous achievement – and the photo to the right shows Veronica after having finished the marathon, showing the family her well-earned medal.



Trev keeps singing and running

Singer-songwriter Trev Williams released his first EP in September 2011, a fresh and innovative recording called "Keep Singing", which included four acoustic, pop-influenced tracks. Trev also teaches guitar and is very well known on the music scene in Oxford, playing

gigs throughout the year at a range of venues. However, April 2012 saw him at a most unexpected venue: the Reading half-marathon.

Trev's sister Zoe (the two are pictured below right) has had severe ME for 22 years, and as he explains, "There is still no cure and a great lack of understanding about it, particularly in the medical profession. At her worst, tiny activities, such as eating and even lying flat, were enough to trigger a very

painful collapse. Now she is well enough for occasional short wheelchair rides, while many of her friends remain bedbound."

As well as raising awareness and funds for research, Trev is running to help promote the new film, *Voices From The Shadows*, an intensely moving one-hour documentary by Natalie Boulton and Josh Biggs on the reality of ME/CFS, which is now available on DVD from: voicesfromtheshadowsfilm.co.uk.





Deep RiverRock Belfast marathon

The 2012 Belfast marathon is on 7th May, and over 20,000 runners are expected to hit the streets for charity. For several years, Antoinette Christie and her family (pictured above), who have a website at familyfights4me.blogspot.com, have been taking part in aid of ME Research UK, as well as organising other fundraising for our charity over the years.

Antoinette's son David has now been ill for eight years (David's story is on our website), but despite the harshness of the situation, Antoinette is determined to look on the bright side and is doing her best to raise awareness of the condition. As she says, "There is now a lot of scientific evidence that the illness is a complex physical disorder of the nervous/immune systems, possibly with viral cause, yet very little help is available. Sufferers and their carers are usually left to cope on their own whilst their lives fall apart." Antoinette and family's Justgiving webpage for the Belfast marathon (justgiving.com/antoinette-christie1) will stay open for a few more months; please support them by making a donation if you can.

Asda collection

The Perth ME Support Group, led by Elizabeth Moncrieff and Janet McEwan (pictured below), has only been going for less than two years, but has already had an impact in raising the profile of the illness.

During ME Awareness week 2011, it launched its campaign with an exhibition and information point in the AK Bell library in the city, which attracted the attention of many hundreds of passers-by over the five days and helped recruit members.

As a feature article in the local newspaper during that week pointed out, "ME can be a very solitary illness due to its debilitating nature... Sharing experiences of medical professionals, drugs, benefits and life in general can be very helpful."

Then, in September, the members hosted a collection in the Asda store in Perth, with each member taking turns to hold the stall, raising funds for ME Research UK. As Dr Vance Spence of ME Research UK says, "It's marvellous to see such an active group on our own doorstep."



Ways to help us

You can support ME Research UK by fundraising and taking part in sponsored and other events, and we hope the activities on the preceding pages have given you some inspiration. You can also help us by volunteering or simply spreading the word, and there are now several different ways to donate to the charity, either directly or via searching the web or shopping online. Here are a few of the most popular methods, but please visit our website for more ideas. We are very grateful for your invaluable support.



JustTextGiving

Through JustTextGiving, donations can now be sent to ME Research UK from your mobile phone. It is simple, quick and easy, and we receive ALL your donation without any commission being taken off. The maximum that can be donated in a single text is £10, and the money donated is deducted either from your call credit or added to your phone bill.

To donate, text "MEUK01" and the amount to 70070. The donation can be £1, £2, £5 or £10. For example, to donate £2 the message would read: "MEUK01 £2", and should be sent to 70070.

You will receive a thank-you message and an opportunity to add GiftAid to the donation.



Want to shop at all your favourite High Street and online retailers easily and raise funds for ME Research UK at the same time? With easyfundraising.co.uk it's simple. Register, nominate ME Research UK as your charity, and the retailers will donate as you shop online, in the knowledge that ME Research UK benefits also. Did we mention that there are exclusive special offers and deals too?



Shop at Amazon

If you are buying from Amazon, then just click through to Amazon from our website, and 5% or more of your purchase could be making its way back to ME Research UK.

Provided that you connect to Amazon via one of the links on our website, your shopping will qualify. It really is that simple.

The amount we get varies according to the type of product and the type of link followed. It won't cost you a penny more, and you won't lose out on other discounts, so please help us by shopping via ME Research UK's Amazon link.

Visit our website for more details: www.mereseach.org.uk/support/shopping.html.



Read about more Friends' activities and ideas for your own fundraising at our website www.mereseach.org.uk/support

E

F P

T O Z

L P E D



E D F C Z P