

# breakthrough

News of the ME research YOU are helping to fund



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**Putting the picture together**  
*Clarifying ME/CFS diagnosis*

# Breakthrough

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

When I presented a bouquet of  
flowers to Betty McRae to mark  
her retirement as a founding trustee  
after 12 years of hard work, I was  
struck by how quickly the years  
have gone. It seems like the twinkle  
of an eye since we sat around a  
table with coffees deciding whether  
or not to set up a charity to fund  
biomedical research into ME.

One was certainly needed,  
and 12 years on ME Research UK  
has funded more specific research  
projects on ME/CFS (34 to date)  
than any other single organisation in  
the world outside North America. To  
all our supporters, I am happy and  
proud to say that ME Research UK  
has almost topped the £1 million  
mark in funding committed to research.

I think we have done well, but ME/  
CFS is still an 'orphan' in research terms,  
and much more needs to be done. That's  
why we need your help. With this issue  
of Breakthrough we have included  
three easy ways for you to help us.

First, there are raffle tickets for our  
Spring Prize Draw, with a 1st Prize of £750,  
which will be drawn on 17th July 2013.

Second, our Home Collection Box  
is an easy way for you to raise money



for us; each box can hold about £5 –  
proving that every penny does count!

Finally, it would be marvellous if  
you could consider making a donation  
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by scanning the code in the box below.

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**Dr Vance Spence**  
**Chairman**  
**ME Research UK**

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# Does diagnosis matter?

## Two new studies comparing criteria for ME and CFS

### The Belgian investigation: an experimental study

One of the most animated debates surrounding the diagnosis and treatment of ME/CFS concerns the name of the illness and how it is diagnosed. At present, a range of possible definitions exist (see the table below), but each is different, and today the terms ME, CFS and their various combinations mean different things to different people.

Does this matter? Absolutely – because the different ways of diagnosing patients ('diagnostic criteria' in the parlance) capture different kinds of patients, and this in turn influences the types of clinical research carried out, the treatment options that are offered, and the perception of the illness by employers, benefit agencies and the public generally.

How did this messy situation come about? Well, the term myalgic encephalomyelitis (ME) originally referred to potentially chronic illness characterised by profound, generalised post-exertional loss of muscle power (fatigability); muscle pain that could include tenderness and swelling; a range of neurological or cognitive symptoms; and a tendency to relapse. Early reports dating from 1934 described apparent epidemics of an ME-like illness – such as the famous 1955 outbreak at the Royal Free Hospital in London – and the illness is thought to result from a continuing or persisting viral infection in most cases.

After 1988, however, chronic fatigue syndrome (CFS) arrived on the scene. This

was a diagnosis given (after other possible diagnoses had been excluded) to patients with six months of fatigue plus a number of other non-specific symptoms, such as sore throat and unrefreshing sleep. Since there was (and presently remains) no specific diagnostic test for ME, and since post-exercise fatigue was one of its prominent symptoms, people who would previously have been given a diagnosis of ME began to be diagnosed with CFS.

Today, the term CFS has been adopted by doctors, healthcare professionals and scientific journals, while



the term ME is seen largely as a lay term used by campaigning patients' organisations and some patients themselves.

In recent years, however, there has been a growing recognition that CFS is a very broad diagnostic category that could well contain a range of very different kinds of patients. In short, CFS is thought of as an umbrella diagnosis, and probably more of a holding bay for complex cases rather than a final destination. For this reason, a range of alternative definitions have been suggested, some using combination terms ME/CFS and CFS/ME, as the table shows.

The two most commonly discussed definitions are the 1994 Fukuda definition of CFS (used in the majority of scientific studies) and the 2003 Canadian definition of ME/CFS (designed by consensus to help health professionals make a diagnosis effectively). In addition, there are various ME criteria in existence, proposed by individual ME theorists; none are recognised by modern medicine or science today, but may become useful if properly operationalised and standardised.

In the final analysis, only experimentation is capable of cutting through the suppositions and preconceptions surrounding the relative effectiveness of this or that diagnostic definition.

### Current definitions of ME and CFS

Definitions of ME	
ME/postviral fatigue syndrome (Ramsay)	1988
London criteria (various)	1994+
'Nightingale' definition (Hyde)	2007
International consensus criteria	2011
Definitions of CFS	
CDC definition (Holmes)	1988
Australian case definition	1990
Oxford case definition	1991
CDC definition revised (Fukuda)	1994
CDC empirical case definition	2003/2005
'Combined' definitions	
Canadian consensus definition (ME/CFS)	2003
NICE guideline clinical criteria (CFS/ME)	2007

For this reason, ME Research UK has funded a 24-month investigation, led by Prof. Nijs of the Department of Human Physiology, Vrije Universiteit, Brussels to compare the 2003 Canadian, 1994 Fukuda and ME definitions. Patients fulfilling these different criteria will be examined with respect to several characteristics of both ME and CFS, including physical behaviour, muscle recovery following fatiguing exercise, psychomotor speed, cognitive performance,

symptoms of autonomic dysfunction, and inhibition of the descending nerve pathways.

In addition, patients will be compared with a control group comprising individuals with an established, severe and fatiguing illness such as multiple sclerosis, and patients will also be compared with a group of healthy sedentary controls. A secondary aim of the Belgian study is to examine the diagnostic overlap between groups, and whether they differ with respect to the

proportion of patients fulfilling the diagnostic criteria for fibromyalgia syndrome.

The clarification of the case definitional morass surrounding ME and CFS is an urgent challenge. Other chronic diseases, such as rheumatoid arthritis and systemic lupus, have previously overcome similar case definition difficulties. Success is therefore certainly possible – and the benefits in terms of diagnosis, research and treatment could be considerable.

## The Newcastle investigation: the DePaul Symptom Questionnaire

The University of Newcastle houses the most active ME/CFS biomedical research group in Europe, and one of the most active in the world. Since 2006, the group has received three separate grants from ME Research UK to look at the autonomic nervous system, muscle bioenergetics, and systems analysis (see pages 8 and 9). However, our largest grant to the group (awarded in conjunction with the John Richardson Research Group and the Irish ME Trust) was to investigate muscle and heart function in a large cohort of patients who attended the Newcastle Clinical Service and who were referred to the research programme.

Over the succeeding years, the researchers have collected a large volume of clinical, autonomic and symptom data from this ME Research UK cohort, and full data sets are available for over 200 patients to date.

As part of their clinical examinations, each patient has been assessed on the basis of the 1994 CDC revised definition (Fukuda), the 2003 Canadian Consensus Definition and an ME definition. The research group is keenly aware, however, of the limitations of each of these diagnostic criteria (listed in the table opposite), and the difficulties that can arise if they are applied differently in different settings.

For example, the most widely used case definition (Fukuda, 1994) uses polythetic criteria (i.e., patients are only required to have four out of a possible eight symptoms), but the same symptoms do not have to be present in all patients!

Again, the 2003 Canadian definition requires specific ME-like symptoms such as post-exertional malaise and memory/concentration problems to be present, but this case definition tends to be more



Prof. Julia Newton (centre) with nurses Katharine Wilton and Jessie Pairman

complex to apply and has been used relatively rarely for diagnosis or research purposes.

Fortunately, through the timely development of the DePaul Symptom Questionnaire (DSQ), an opportunity arose in 2012 to compare the clinical diagnoses of patients in the Newcastle ME Research UK

cohort with those derived from the structured DSQ instrument, and ME Research UK has agreed to fund this comparison study.

The DSQ is a standard questionnaire developed and refined by Prof. Leonard Jason and colleagues at De Paul University, Chicago. Prof. Jason has been in the forefront of research into the application of diagnostic criteria for ME and CFS for many years, and he devised the DSQ as a

way of identifying core symptoms of ME and CFS in a structured manner, ensuring that symptoms are assessed in a consistent way across settings to aid in diagnosis.

Importantly, the DSQ comes in a format which scores symptoms and Short Form-36 data, and produces a 'diagnosis' based on several of the more common definitions of ME, CFS and ME/CFS. Prof. Jason has made his questionnaire available to other research groups across the world for operational testing on existing ME/CFS cohorts.

Considering the importance of the ME Research UK cohort and its well-characterised nature, the results could throw valuable light on diagnostic categories and on the utility of the DSQ in practice. If the DSQ is found to be sufficiently sensitive, it could greatly assist patient diagnosis, saving time (as it can be completed in the patient's home and brought to the clinic for scoring) and improving confidence in the diagnosis.

*“The questionnaire could greatly assist patient diagnosis”*

# ME/CFS Biobank – funding the second phase

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

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

Over the past decade, a large number of disease specific biobanks have been formed across the world, for illnesses such as cancer, schizophrenia and heart disease. In that time, two biobanks have been created to house samples from ME/CFS patients: the SolveCFS BioBank (part of the Genetic Alliance BioBank) run by the CFIDS Association of America, and the Whittemore Peterson Institute repository. Both are located in the USA, however, and it was felt that the UK needed an ME/CFS-specific biobank of its own, given that around 200,000 of its citizens



Dr Eliana Lacerda and Dr Luis Nacul

are affected by the illness at any one time.

In 2011, a consortium of charities – ME Research UK, Action for ME and the ME Association, with the help of a private donor – joined forces to fund the establishment phase (Phase I) of the UK's first biobank of human blood samples for research into ME/CFS.

The project is led by Dr Eliana Lacerda and Dr Luis Nacul from the London School of Hygiene and Tropical Medicine, and the biobank itself is situated at London's Royal Free Hospital where

it links with the extensive research facilities at University College London.

During Phase I, the researchers achieved their target of banking samples from 60 well-characterised, clinically assessed ME/CFS patients and 30 healthy people (controls). For each person assessed, the UCL/RFH Biobank now holds approximately 46 aliquots of blood sub-products (including whole blood, serum, plasma, red blood cells, peripheral blood mononuclear cells, and preparations for RNA extraction), alongside key data information (see the box below), anonymised so that confidentiality is preserved

Thus, the fundamental infrastructure has been put in place to underpin a disease-specific biobank for ME/CFS.

At the end of 2012, the consortium of charities agreed to fund the next, expansion phase of the UCL/RFH Biobank. The aim of Phase II is to increase the number of stored samples to 200 (patients and controls), representing around 9,200 aliquots of blood sub-products available to medical researchers for specific research studies in the future.

In the process, other GP networks will be recruited, and the researchers will put in place a procedure so that other scientists can apply to access the samples for research purposes. The hope for the longer term is that this vital piece of research infrastructure will become a repository for blood and tissues from many thousands of people with ME/CFS.

## What information is collected about each donor?

- Detailed history and clinical measurements
- Demographic (age, gender, etc.), socio-economic and other exposure variables
- Clinical data (phenotype), including disease severity
- Confirmation of an ME/CFS diagnosis (Fukuda, Canadian) according to study criteria
- Fatigue Severity Scale and Energy Fatigue Scale
- Pain Analogue Scale – pain severity
- MOS Short Form-36 data – function and quality of life
- General Health Questionnaire-28
- Epworth Sleepiness Score
- Laboratory tests, including full blood count, blood chemistry, liver function tests, erythrocyte sedimentation rate, C-reactive protein, rheumatoid factor, thyroid function tests, tissue transglutaminase antibodies, serum vitamin B12, red cell folate, and urine analysis

# Expansion of the ME/CFS Disease Register

Disease registers hold key information on patients with a particular illness. Unlike biobanks, which store clinical tissues and samples, registers generally contain information alone, and can be very important reservoirs of demographic and clinical data.

As one review has pointed out, in chronic diseases “an accurate well-maintained register is a prerequisite to providing comprehensive and coordinated care”. For example, there are twelve Cancer Registries in the UK at present, and these are used to explore patient follow-up after therapies, to evaluate services, to help with health service planning, and to answer a range of other questions.

The ME/CFS Disease Register is the first systematic attempt to develop a population-based disease register for the illness. Led by Prof. Derek Pheby, it was housed initially alongside the ME/CFS biobank at the London School of Hygiene and Tropical Medicine.

At present, the Disease Register contains the details of over 300 ME/CFS patients; most were originally identified from GP

practices in the UK, while others are severely affected patients originally on a database of housebound and bedbound patients.

All patients have had their diagnosis determined, and completed a range of assessment instruments, including Short Form-36 (which measures health

to case identification, data processing, transmission, storage and analysis.

For logistical reasons, the ME/CFS Disease Register is moving to new permanent premises at Buckinghamshire New University, from where it can begin expansion of its operations. A consortium

of charities – ME Research UK, Action for ME and the ME Association – is sponsoring this relocation and expansion.

As soon as the register has bedded down, the recruitment of larger numbers of patients will begin, and a publication will be prepared on the experiences of the most severely ill patients.

The expectation is that the Disease Register will, from these positive beginnings, develop into a repository of

high-quality information on many thousands of patients. In particular, long-term follow-up data may be of considerable use to clinicians and researchers, especially when they are linked with samples in the ME/CFS Biobank or, ideally, to a post-mortem tissue archive of pathological specimens.

*“An accurate well-maintained [disease] register is a prerequisite to providing comprehensive and coordinated care.”*

status and quality of life) and visual analogue scales for pain and fatigue.

Importantly, Prof. Pheby and colleagues have undertaken a pilot project (published in *BMC Research Notes*, 2011) in East Anglia, East Yorkshire and London, which confirmed the feasibility of their approach

## What are disease registers?

- Disease registers aim to identify, as far as possible, all cases of a particular disease or condition in a defined population.
- In the main, they are used for chronic conditions, such as diabetes, coronary artery disease, asthma or cancer, which consume a high proportion of healthcare resources.
- Many hundreds of disease registers now exist in the USA and Europe, where they have a significant record of contributing to medical knowledge and health care.
- Their main uses include epidemiological research, health needs assessment, and contributing to improvements in patients care and service quality.
- A report commissioned by the UK's Department of Health in 2000, 'Saving Lives: Our Healthier Nation' gave a commitment to “... strengthen the information base on chronic diseases in the population by establishing a series of disease registers in different parts of the country”.



Prof. Derek Pheby

# Is ME/CFS different in elderly people?



It is estimated that around 9,300 people develop ME/CFS every year in the UK, and that around 200,000 are living with the illness at any one time. We also know that most become ill between the ages of 30 and 50, but does age itself make a difference? For instance, do people who are older when they first become unwell have a different type of disease than people who first become ill at a younger age?

The issue is important scientifically because there is now quite good evidence to suggest that abnormalities of the autonomic nervous and vascular systems underpin at least some of the symptoms of ME/CFS. These abnormalities are, however, also a complication of the ageing process itself, so it is certainly possible that older people who develop ME/CFS are at additional risk of these complications, over and above the effect of ageing itself.

An ME Research UK-funded study has been examining this aspect, and the results (published in the *European Journal of Clinical Investigation*, 2013) make interesting reading. For this investigation, patients aged over 50 years were matched, on a case-by-case basis, by sex and duration

of illness to a group of younger patients. This matching was particularly important to disentangle the effects of ageing from the effects of illness duration, which itself critically affects the type and severity of symptoms experienced by patients.

Of the 179 consecutive patients who had attended the Northern Regional CFS Clinical

*“The effects of age and illness combine to create even more severe autonomic dysfunction”*

Service in Newcastle between November 2008 and June 2011, 52 (29%) were over 50 years old. Twenty-five of these patients (aged between 51 and 70 years; who had been ill for 93 months on average) were matched case-by-case to 25 patients (aged between 16 and 29 years; ill for 91 months on average).

In addition to a full clinical assessment, the volunteers underwent assessment of symptoms, and autonomic nervous system

function was tested by measuring heart rate variability as well as the sensitivity and effectiveness of the baroreflex mechanism, which is involved in blood pressure control.

Overall, there was no difference between the younger and older patients as regards pain, cognitive function, sleepiness or anxiety. However, older subjects had more fatigue, more depression, and a poorer overall quality of life.

The most intriguing differences between the two groups were found in the measurements of autonomic nervous system function. Compared with the younger patients, the older group had significantly increased ‘low frequency’ but reduced ‘high frequency’ heart rate variability. This suggests an imbalance between the two complementary parts of the autonomic nervous system, the sympathetic (‘quick response’) and parasympathetic (‘rest-and-digest’) divisions.

Additional support for the relative impairment of parasympathetic function was seen in the RR ratio (an indicator of the inter-beat interval of the heart) which was significantly reduced in the older subjects (see the figure opposite). Resting heart rate was significantly lower in older patients, who also had an impaired ability to maintain blood pressure.

One of the most interesting findings concerned the left ventricular ejection time (the time interval from the opening to the closing of the aortic valve in the heart), which was significantly longer in older than in younger patients (286 versus 275 ms).

In both groups, however, left ventricular ejection times were much shorter than the 374 ms measured in healthy people by a previous study. This supports other findings from Newcastle University of a reduced left ventricular performance and impaired cardiac function in ME/CFS patients.

Now, some of these observed effects are certainly due to the ageing process itself because autonomic nervous system function, including heart rate variability, is known to deteriorate with age. However, since

# Bringing the evidence together

## Funding a systems approach to modelling symptom data

Since 2006, researchers at Newcastle University have collected a large volume of clinical, autonomic and symptom data from patients recruited to studies funded by ME Research UK and its partners, the John Richardson Research Group and the Irish METrust.

Full sets of data are available for over 200 patients to date, and the very large amount of data available (plus information collected from every patient attending the Newcastle ME/CFS Clinical Service) represents a very valuable longitudinal resource of clinical and biological information on people with the illness.

While their scientific papers published to date have reported key headline findings, Prof. Newton and colleagues recognise that mining this rich dataset has the potential to reveal even more about the illness, including the relationships between demographic, clinical and biological parameters.

The power of modern computing and, in particular, a scientific approach called

'systems biology' allows the development of multi-dimensional models of how a large number of different measurements link with each other. Such models might allow the identification of processes causing disease and, crucially, allow formal estimation to be made of how changes in one or more symptom might be expected to impact on the overall burden of disease.

Of course, these models can never replace studies involving patients, but they can allow prediction of which patient studies are most important and indicate the direction of future research and treatment.

An example of such a systems approach to a complex clinical problem is the work on the cell biology of ageing by Prof. Kirkwood and colleagues at Newcastle University (*Nat Rev Mol Cell Biol*, 2003). Their modelling of the interactions between multiple molecular mechanisms believed to contribute to the ageing of cells led to a novel prediction of the interaction between mitochondrial dysfunction, oxidative stress

and chromosomal erosion in human cells, something that was subsequently confirmed experimentally.

The aim of this new ME Research UK-funded investigation, headed by Prof. Newton but involving other colleagues in a cross-discipline collaboration, is to apply similar computational and mathematical tools to the rich dataset on ME/CFS patients which now exists at Newcastle University.

There are four elements to the study: identification and phenotyping of the study cohorts; development of the ME/CFS symptom model; testing of the ME/CFS symptom model; and indicative application of the model in ME/CFS to explore the possible effects of treatments for fatigue or other symptoms ('in silico trials' to identify potentially valuable interventions for 'in vivo' testing).

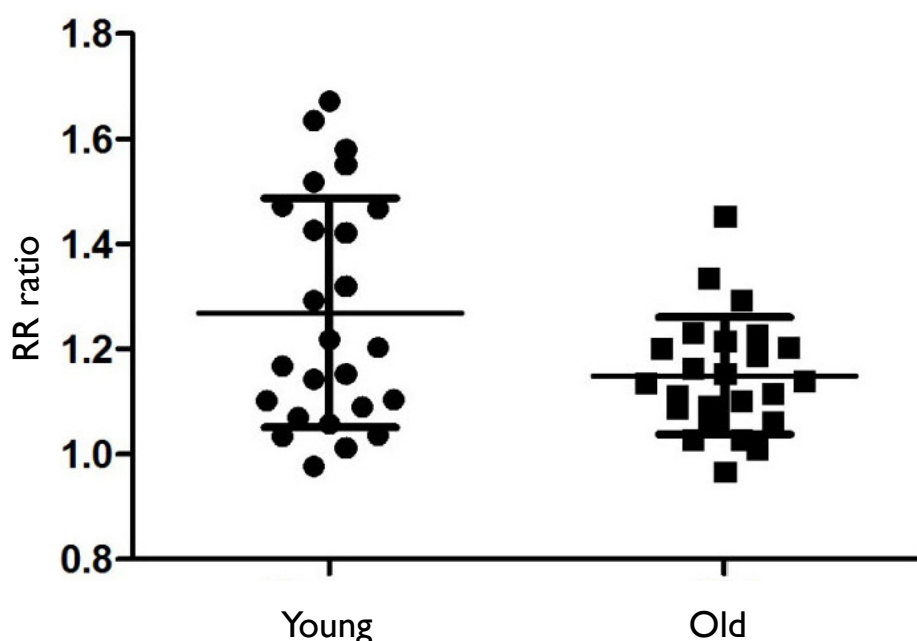
The work may yield novel insights and hypotheses that can be tested subsequently in clinical or biomarker studies.

autonomic dysfunction is a consistent finding in people with ME/CFS of any age, it may be that the effects of age and illness combine to create even more severe autonomic nervous system dysfunction in older patients. It is even possible that the underlying disease process differs between older and younger patients.

Overall, the results show that there are distinct physiological and clinical differences between older and younger people with ME/CFS, even though they have had the illness for the same length of time. Not only do older patients have more fatigue and depression, and a poorer quality of life, but they also have a significantly greater burden of autonomic dysfunction.

The importance of these findings lies in the fact that a sizeable proportion of people with ME/CFS present with symptoms for the first time aged over 50, and a significant proportion are aged over 60. It is important to be aware that the combination of underlying ME/CFS disease mechanisms and the normal physiological effects of ageing may result in a greater disease impact (particularly on the cardiovascular system) in these people who are older when they become ill.

## Parasympathetic function is reduced in older patients



# Funding the breakthrough



Prof. Julia Newton



Prof. Jonas Blomberg



Dr Gwen Kennedy



Dr Derek Pheby

The primary aim of ME Research UK is to fund biomedical research into ME/CFS, to find its cause, to develop effective treatments, and ultimately to discover a cure.

We have invested more than £950,000 in 34 specific biomedical projects based in the UK or overseas; some of the most recent are listed here, and fuller details, including the resulting scientific papers, can be found on our website.

Money is the platform which supports all biomedical research. But it is expensive: one clinical trial can cost half a million pounds, while a major programme of research can last for years and cost millions of pounds. So, unravelling the causes and finding cures for ME/CFS will require big money over a long time.

Major central funders like the MRC in the UK or the NIH in the USA can help, but the money they have available is thinly spread across all types of research into all diseases. Even the £1.65 million recently provided by the MRC for ME/CFS research

is only a small part of the biomedical activity needed to set the field alight.

In fact, a significant proportion of research funding for all illnesses comes from charitable sources – if the charity sector did not exist, scientific research into all medical conditions would be much the poorer and discoveries far less frequent.

Across the board, UK charities spent £1,137 million on research in 2011/12 – an astonishing figure. In the same period, the income of Cancer Research UK alone was £492,627,000.

Much of the income for research into cancer and other illnesses comes directly or indirectly from public donations. We have to do the same for ME/CFS. As most patients are too ill to fundraise themselves, our strategy has to be to raise awareness of the need for biomedical research into the illness, to ensure that our organisations are worthy of the trust and support of patients and the wider general public, and keep the research community on-side for the long march ahead.

## Long-term research programmes are vital

Funding one-off investigations is useful since these can provide pilot data for subsequent grant applications, or spark off interest in other researchers. But in modern science real breakthroughs come at the end of a programme of painstaking work by a specialist group of researchers.

One of the few examples of such a programme on ME/CFS, anywhere in the world, is the work at the Vascular Diseases Research Unit, University of Dundee, which has received a number of grants from ME Research UK and its funding partners.

In a step-by-step progression involving both adults and young people with the illness, the group has uncovered:

- unusual sensitivity of blood flow responses to acetylcholine (a neurotransmitter),
- increased levels of isoprostanes (a

gold standard marker of oxidative stress in the bloodstream),

- an unexpected increase in dying (apoptotic) white blood cells, consistent with an activated inflammatory process or persistent infection,
- increased cardiovascular risk factors with arterial stiffness in patients, and
- biochemical anomalies in children mirroring those found in adults with the illness.

Such a progression – whether towards positive findings or away from negative ones – is the norm for scientific investigation.

The burning need in this illness is for there to be many groups undertaking programmes of research across a range of basic and clinical sciences fields so that a 'critical mass' of investigators can produce a 'critical mass' of biomedical data.

# Recent projects funded by ME Research UK

## **Lymphocyte phenotype and cytokine production**

Dr Clive Carter, Leeds Teaching Hospital NHS Trust

## **ME Disease Register: transfer and implementation**

Dr Derek Pheby, Buckinghamshire New University

*(co-funded with the ME Association and Action for ME)*

## **The sensitized brain: experiments using laser-evoked potentials and cerebral blood flow**

Prof. Jo Nijs, Vrije Universiteit Brussels, Belgium

## **Development of a rational diagnostic system based on microbiological biomarkers**

Prof. Jonas Blomberg, Uppsala University Hospital, Sweden

## **DePaul Symptom Questionnaire: evaluation in the ME Research UK cohort**

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

## **Assessment of visual function**

Dr Claire Hutchinson, Vision and Language Group, University of Leicester

*(co-funded with 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

*(co-funded with the ME Association and Action for ME)*

## **Adopting a systems approach to modelling symptom data**

Prof. J 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

## **Muscle bioenergetic abnormalities**

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

## **XMRV in Swedish patients**

Prof. Jonas Blomberg & Prof. Carl-Gerhard Gottfries, Uppsala University Hospital, Sweden

*(co-funded with the Irish ME Trust)*

## **Vitamin D supplementation and cardiovascular disease risk**

Dr Faisel Khan, Institute of Cardiovascular Research, University of Dundee

## **Autonomic nervous system dysfunction – a clinical cohort study**

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

*(co-funded with the Irish ME Trust and the John Richardson Research Group)*

## **Biochemical and blood flow aspects in children**

Dr Gwen Kennedy, University of Dundee

*(co-funded with The Young ME Sufferers Trust and Search ME)*

## **Evaluation of pain and therapeutic interventions**

Dr Lorna Paul and Dr Les Wood, Glasgow Caledonian University



Dr Faisel Khan



Dr Les Paul & Dr Lorna Paul



Dr Jo Nijs



Dr Claire Hutchinson

# Research bites from around the world



## NETHERLANDS

### The vaccination question

Whether or not ME/CFS patients should have vaccinations has been a hot topic for many years. The question is reasonable since if the illness involves immune dysfunction, as we suspect, then patients' responses to vaccination might be very different from those of healthy people.

At Radboud University, Nijmegen, researchers have been investigating ME/CFS patients' responses to the seasonal flu jab. Overall, the influenza vaccination fulfilled its function: patients were able to mount a protective antibody response and a cellular immune response seven days after a single shot. The degree of protection against flu was similar in patients and healthy controls, leading the authors to conclude that "Standard seasonal influenza vaccination... when indicated, should be recommended..."

So, is that the end of the story? Well, the authors report no follow-up assessments of clinical outcomes, such as adverse effects on symptoms or even relapses, in the days and weeks after the flu jab. This is important because some patients say that vaccinations, including for flu, significantly worsen their condition. In one review of

patients' experiences of vaccinations, 20% of patients said that the flu jab provoked a marked flare-up in their symptoms, while other respondents reported a variety of reactions to other vaccines, although most reported little or no adverse effects.

Ideally, for a more complete picture, research studies on vaccination and ME/CFS should include both immunological outcomes and clinical outcomes over time.

*Source: Prinsen et al., BMC Immunology, 2012*

## NEVADA

### Human endogenous retroviruses

Human endogenous retroviruses (HERVs) are remnants of ancient retroviral infections, and are thought to be involved in autoimmune diseases such as multiple sclerosis and systemic lupus.

As ME/CFS involves symptoms that overlap with autoimmune diseases, including gastrointestinal problems which affect 80 to 85% of patients, could HERVs be involved in this illness too?

Researchers at the University of Nevada, Reno have just reported finding 'immunoreactivity' to HERV proteins in the gut (duodenal) biopsies of 8 out of 12 people with ME/CFS, but in none of 8 healthy people.

And they implicate specific immune cells, plasmacytoid dendritic cells, in the process.

It is far too early to say what this novel 'observational' finding really means, if anything – particularly as measurements were made on surplus clinical biopsies and unmatched control specimens. As the authors say, HERV protein expression might have a central role in the pathology of ME/CFS, but it might also be common to many inflammatory diseases. And the association of HERV with autoimmune diseases might turn out to be a blind alley. We await replication by other research groups... watch this space.

*Source: De Meirleir et al., In Vivo, 2013*

## BELGIUM

### Personality disorders not a factor

CDSM-IV axis II personality disorders involve 'maladaptive personality traits', such as obsessive-compulsive disorder. A study from Belgium reports no increase in such personality disorders in ME/CFS patients compared with people in the community (prevalence 16.3% in each group, in contrast with 58.7% in a comparison group of psychiatric patients). No surprise there then, particularly as the results accord with a previous study in 2009 (prevalence 12% in both patients and controls).

The interesting thing is that both of these 'negative' investigations used the ADP-IV questionnaire to assess personality disorder, whereas other 'positive' studies (reporting moderate differences between ME/CFS patients and controls) have tended to use the PDQ questionnaire which, as the authors point out, gives high rates of false positives and overestimates the prevalence of personality disorder. Such matters are important, particularly when the results of research studies affect the lives of real people, and impact on healthcare professionals' views of the illness!

*Source: Kempke et al., Int J Behav Med, 2012*

## NEW YORK

### XMRV controversy laid to rest

Since 2009, the controversy over the retroviruses XMRV/pMLV and their role in ME/CFS has involved a rollercoaster ride for scientists and patients. More than 50 scientific papers have now reported finding no association between the viruses and ME/CFS or other diseases, and the final act came on 18 September 2012 with the publication of the results of a multicentre study coordinated by Columbia University's Prof. Ian Lipkin.

This blinded analysis used blood samples from 147 ME/CFS patients and 146 matched healthy controls recruited using rigorous criteria at six sites of excellence across the USA. Each of the samples was divided and sent to three different research groups, including those which had described the original association. All the labs used procedures, including polymerase chain reaction (PCR), which had previously been optimised for molecular or serological detection of the viruses.

The table below encapsulates the stark message: none of the 293 patients or controls tested positive for the viruses using PCR, and the paper concluded that there was no evidence of infection with either virus.

While this definitive outcome is a blow to us all, Prof. Lipkin is adamant that research on the causes of ME/CFS must continue; "We've tested the XMRV/pMLV hypothesis and found it wanting," he said, "but we are not abandoning the patients. We are not abandoning the science. The controversy brought a new focus that will drive efforts to understand CFS/ME and lead to improvements in diagnosis, prevention and treatment."

Source: Alter et al., mBio, 2012



## AUSTRALIA

### Faecal transplants

Faecal microbiota transplantation (FMT) – the infusion of faecal matter from a healthy person into the colon of an ill person, usually by enema – aims to re-establish a "balanced intestinal flora" to a digestive system where there may be an imbalance.

Now, a review has suggested that FMT might benefit chronically ill patients with autoimmune-related conditions, such as irritable bowel syndrome and ME/CFS. The problem is that the review can point to just one small, uncontrolled study on CFS patients published only in abstract form 17 years ago, so there is a long evidential journey to be undertaken before FMT can be rolled out as a specific therapy for ME/CFS patients (with or without gut problems).

Nevertheless, although the idea behind FMT is at least 50 years old, interest in the technique has been reinvigorated by recent scientific discoveries about the importance of the human microbiome, the hidden yet extensive world of the microbes that live in our bodies.

You never know, further revelations about the importance of the microbiome in human health and disease might bring FMT suddenly and dramatically to the fore as a treatment.

Source: Borody & Khoruts, Nat Rev Gastroenterol Hepatol, 2012

## WASHINGTON

### Shortness of breath

Dyspnoea is shortness of breath or 'hunger for air', and is most often seen in cardiac and respiratory disorders. It is also commonly reported by people with ME/CFS. In fact, 80% of the 2,073 consecutive participants in a Belgian study of 2001 reported dyspnoea after exertion, and because of this finding the symptom was later included in the Canadian consensus criteria for ME/CFS.

In a new study by researchers at Georgetown University, Washington, significant dyspnoea was reported by 54% of 257 ME/CFS patients compared with only 3% of 456 healthy people with sedentary lifestyles.

Furthermore, the patients' shortness of breath correlated with exertional exhaustion, pain, severity of rapid heart rate, muscle spasms and dizziness. However, pulmonary function testing was normal overall in both patient and healthy subject groups. For example, there were no reports of asthma or obstructive pulmonary disease.

The unusual thing was that the patients reported more sensory complaints, such as dizziness and chest pain, following laboratory measurements that required deep breaths in and out.

Apparently, the sensation of shortness of breath is a very complex process. It involves nerve inputs to and from the brain, airway pressure sensors, respiratory muscles and a host of physiological mechanisms, so unpicking which is disordered will not be easy.

The authors suggest that the breathing difficulties in ME/CFS could well be the result of an increased 'sensory hypersensitivity', such as an imbalance between the elements of the nervous system sensing inspiration and those sensing when air intake has been sufficient.

Source: Ravindran et al., Global Journal of Health Science, 2013

### Testing for XMRV/pMLV by three research groups

Laboratory	Sample	ME/CFS cases (no. positive/total)	Controls (no. positive/total)
CDC, Atlanta	Plasma	0/147	0/146
FDA, Bethesda	Plasma	0/121	0/110
FDA, Bethesda	Peripheral blood cells	0/121	0/111
Mikovits, Ruscetti & Hanson labs	Peripheral blood cells	0/117	0/126

## BOSTON

### Qualitative study of the lightning process

There are many views about the Lightning Process (LP) as an alternative treatment for ME/CFS, and the internet hosts a range of patients' anecdotes – some reporting lightning cures, some reporting no success at all. So, it was refreshing to see some published information from Harvard University, Boston on the experiences of young people with LP.

Nine youngsters, members of the Association of Young People with ME, answered a call to share their experiences of LP with researchers. As the authors report, *"The experience of effectiveness split the young persons in roughly three categories: instant healing, gradual improvement, and no improvement at all."*

A qualitative interview study like this cannot tell us anything about clinical effectiveness, yet its 8,000 words certainly throw a spotlight on the youngsters' experience of illness. The positive aspects of LP, as reported by the children, include

positive and encouraging staff, practical assignments, the one-to-one setting, and the setting of specific goals.

The negative aspects included the secrecy surrounding LP, the high cost, the apparent lack of honesty about true success rates, and the perception that patients can be left feeling guilty and blamed if the treatment is not a success.

As this article points out, LP aims to address dysregulation of the central nervous system by breaking the 'adrenaline loop' that keeps the systems' stress responses high. The core scientific question is whether this rationale stands up to scrutiny – and only experimentation can answer it.

**Source:** Reme et al., *British Journal of Health Psychology*, 2012

## NEWCASTLE

### A patient's journey

The *British Medical Journal* publishes occasional articles by patients about their experiences that offer lessons for doctors.

The latest is by Matilda Hale in conjunction with Professors Julia Newton and David Jones of Newcastle University. Matilda has primary biliary cirrhosis, an autoimmune

liver disease with fatigue as a prominent symptom, and some elements of her journey will be recognised by ME/CFS patients, particularly the day-to-day struggle and the scepticism of GPs and hospital doctors.

It was Prof. Newton and Prof. Jones' experiences of primary biliary cirrhosis as an illness and its effects on patients like Matilda that sparked off their interest in fatigue as an overarching symptom common to many different illnesses. This, in turn, led to their involvement in ME/CFS, which they have shown to involve far higher levels of total fatigue than other comparable conditions.

For example, the investigations have shown that ME/CFS has a total fatigue impact score of 102, compared with 41 in primary biliary cirrhosis and 18 in primary sclerosing cholangitis.

**Source:** Hale, Newton & Jones, *British Medical Journal*, 2012

## ITALY

### Cadmium poisoning?

Heavy metal exposure, such as with mercury in dental amalgam, has been suggested as a cause of ME/CFS in some people. A new hypothesis paper suggests that cadmium (a

widespread occupational and environmental pollutant) might be involved in the illness, based on the similarity between the neurological symptoms and the known effects of cadmium on the human body.

For instance, brain grey matter has been shown to be decreased in ME/CFS patients compared with healthy people, and cadmium is said to induce neuronal death in cortical neurons in the brain. Again, ME/CFS has been associated with reduced cerebral blood flow, and cadmium has disruptive effects on the creation of new blood vessels.

This is all speculation, of course, but if high levels of cadmium were indeed measured in these patients, the hunt would be on for therapies capable of limiting or reversing cadmium exposure.

**Source:** Pacini et al., *Medical Hypotheses*, 2012



## Recovery of participants in the PACE trial

ME or CFS diagnosis	Percentage of PACE participants who 'recovered'			
	Adaptive pacing	CBT	GET	Standard medical care
Oxford criteria (i.e. all participants)	8	22	22	7
CDC empirical case definition (2005)	9	19	22	6
London ME criteria (1994)	11	21	21	10

### LONDON

## Biomedical research comes into its own

In 2012, the UK's Medical Research Council allocated £1.65 million for biomedical projects into ME/CFS – to widespread congratulations from patients and charities. But several years before, it had funded two large, expensive clinical trials (FINE and PACE) of cognitive behavioural approaches for ME/CFS, and the consequences are still reverberating.

The FINE trial found that 'pragmatic rehabilitation' of severely affected patients had some benefits in the short-term, but these

were not maintained after one year, and the cost-benefits of treatment were minimal (*BMC Family Practice*, 2013).

When the PACE trial was finally published in the *Lancet* in 2011, it reported improvements in fatigue and physical functioning in some ME/CFS patients after cognitive behavioural therapy (CBT) or graded exercise therapy (GET), compared with medical care alone. Overall, around 10 to 15% of patients benefitted over and above the beneficial effects of standard medical care – an unsurprising finding since we already know from surveys that some patients can be helped by non-specific therapies. For instance, the ME Association's survey of 2010 found GET to "improve/greatly improve" symptoms in 22.1% of respondents (906 responses), while the equivalent figures were 25.9% for CBT (997 responses) and 53.7% (1675 responses) for meditation or relaxation techniques.

Now a second report, this time in *Psychological Medicine*, has been published on the numbers of people who 'recovered' from illness after treatment in the PACE trial. 'Trial recovery' was defined as occurring when a patient was in the normal ranges for fatigue and physical function, no longer met the Oxford case definition of CFS, and had ratings of 'very much' or 'much' better on the Clinical Global Impression scale. As the table above shows, around 15% of participants derived extra benefit from CBT and GET over and above standard medical care, reiterating the previous findings.

But what about the 85% of patients who did not derive this additional benefit from the therapies, or the 90% or more of patients who had not recovered from ME/CFS after 12 months of basic care?

The authors themselves recognise this problem when they say, "The relatively small proportion of recovered patients...should also spur us on both to enhance currently available therapies and to develop new and better treatments."

Exactly. Patients with chronic illnesses such as ME/CFS have a variety of useful non-specific psychological approaches available to them. However, these cannot substitute for the whole clinical and therapeutic armoury required to treat and (ultimately) cure the underlying disease, and this is where biomedical research comes into its own.

Source: White et al., *Psychological Medicine*, 2013

### MARYLAND

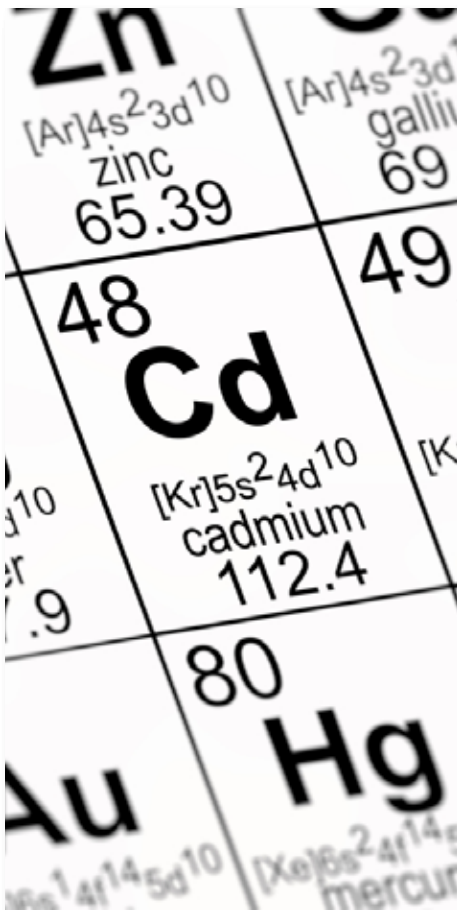
## Human herpesvirus

Human herpesvirus 6 is thought to play a role in several neurological diseases. A recent technical report from the National Institutes of Health, Bethesda describes the development of novel techniques capable of detecting antibodies to HHV-6 infection, and the use of these techniques to examine blood serum samples from ME/CFS patients and healthy controls.

Overall, seropositive HHV-6A antibody responses were found in 13.5% of control samples and 9.7% of ME/CFS samples, while the equivalent figures for HHV-6B were 76 and 75%, respectively. There was, therefore, no evidence of increased infection with (or serum antibodies directed against) HHV-6 in CFS patients compared with healthy people, although immune responses to HHV-6B were highly prevalent in the general population.

Does this mean that we can exclude HHV-6 as a causal or maintaining factor in ME/CFS? Well, no – we're still far from that stage. Results of studies can differ depending on whether testing is for active infection, for the presence of antibodies only, or for reactivation of latent infection. In fact, the real importance of HHV-6 might lie in how it associates with other co-infecting viruses, such as parvovirus B19, to impair the immune function of the patient, as Latvian researchers suggested earlier this year.

Source: Burbelo et al., *Am J Transl Res*, 2012



# Our Friends 101 DONATIONS

*Recent fundraising for ME research*



## Simmons's skydive

Taking support for ME Research UK to new heights (13,000 feet, in fact), Simone Bell and friends from the Newry & Mourne ME/FMS Support Group leapt at the challenge to skydive to raise funds. A big hug to all who took part in the event, hosted by the skydive centre in Garvagh.

As Joan McParland, one of the founder-organisers of the group, said, "We were delighted with the turn-out, and all very proud of Simone's bravery in jumping from that plane. Simone says that the instructor tells you to SHOUT as you jump out of the plane. I think I would be screaming all the way down and that's only if my heart didn't stop. Brave girl, our Simone!"

The complete DVD of the fall shows Simone laughing and smiling the rest of the

way down... wow! Our thanks to everyone in the group, who helped raise almost £3,000.

## Walk for ME

For this year's ME Awareness Week (6–12 May 2013), ME charity supporters have launched a 'Walk for ME' campaign. The hope is that as many people as possible, especially the family and friends of patients, will do a sponsored walk no matter how small, and it need not be over ME Awareness Week either!

As they say, "We hope this will be a fun but poignant event. The whole idea is that the friend or family member is doing something that their loved one would like to do but can't."

There is a dedicated web page where you can choose which charity to walk for, so please visit [walkforme.co.uk](http://walkforme.co.uk) and choose ME Research UK as your charity.

## 9,000 frames

Stevie Laws, a second-year animation student at the University of Central Lancashire, was diagnosed with ME recently, and says that at her worst she barely has the energy to eat and drink.

Determined to help ME Research UK, she set herself the task of animating a 6 minute film – quite a task, since every second of film consists of 25 separate frames of animation. "I know I can't run a marathon or swim the channel but I still want to make a difference, and this is my way of doing that."

In total, Stevie aims to complete the 9,000 frames needed within a year – 25 frames per day for the next 360 days! She set her initial goal at a modest level, asking her Facebook friends to donate £1 each for the first 100 frames. Her first milestone has been reached, and she is now asking friends to help her reach her target frame by frame, with each frame raising funds for us.

She has created a blog so people can track her progress and see clips of the final animation – have a look at [9000frames.tumblr.com](http://9000frames.tumblr.com).

## 75th birthday swim

Gues what Janet Baker did to celebrate reaching the age of 75? Shortly after her birthday, she swam 75 lengths for ME Research UK, simply because she believes that basic research into ME is urgently needed, and that something should be done to help.

Janet says, "I have chosen ME Research UK as one of my charities as my daughter Heather has ME and very little is known about it. Even though at least 200,000 people suffer from it in the UK very little research has been done into what causes it and what is actually happening in the body. Until it is better understood, there is scant chance of finding a cure."



# Cardiff Half Marathon

Beth Whittingham was supposed to run the Cardiff Half Marathon in support of ME Research UK, but sustained a stress fracture of her femur and so was unable to take part. But all was not lost because her brother Tom took up the cudgel and ran instead.

Tom did absolutely brilliantly and finished in 1 hour 34 minutes, with Beth cheering him on at the 2 and 7-mile points and again at the finish line.

As Beth said, "I certainly couldn't have asked for a better replacement and I'm really proud of him, and pleased with what we have both managed to raise for ME Research UK."

You can still donate using their JustGiving page.

## Life with Art

Life With Art is a charity which works with local communities and organisations providing free workshops in art, photography and drama – and ME Research UK is one of the organisations it has chosen to support.

For a few weeks, its extensive photographic exhibition was open to the public in Dundee at The Vision Building near the centre of town. We were there with an information display to meet visitors coming to view the exhibits, which included 70 photos (including the one pictured below) from two shows about the invisible nature of ME: 'A diagnosis of exclusion' and 'Unpredictable patterns' by photographic artist Juliet Chenery-Robson.

Life with Art has ambitious plans to launch Juliet's show in a range of other venues round the UK – all inside empty offices and businesses. The other charities in the exhibition are the Riding for the Disabled Association and the Teenage Cancer Trust.

## Stranger and Stranger

Many thanks to Robert McMullen, author of 'Stranger and Stranger' who has very generously donated his Kindle royalties from the sale of his book to ME Research UK.

As our own resident reviewer said, "The arrival of



a mystery e-mail sparks an exchange that illuminates a dark place but takes up his available energies and has an emotional cost.

"Like the illness ME itself, the story takes unexpected turns, with quizzes, challenges and quotations, and the outcome is a most surprising one, leaving a questioning reader."

The Kindle Edition is available on Amazon but please remember to shop through our website to help us even more.



## Public talk by Dr Vance Spence

Our Chairman, Dr Vance Spence, has given over sixty public talks over the years, and his most recent took place at the end of 2012, in the Soutar Theatre, Perth.

Entitled, 'ME/CFS – 21st Century Issues and Challenges', his wide-ranging

discourse was accompanied by a PowerPoint presentation, and he discussed a range of research findings, highlighting in particular the research projects that ME Research UK has funded. The afternoon ended with a stimulating Q&A session.

Many thanks to the Perth ME Support Group, which meets on the first Tuesday of every month in Perth, for jointly organising this event.

Particular thanks go to member Alison Ferguson who encouraged her colleagues at Perth & Kinross Council to donate the money raised from their Dress-Down-Friday, and also held a cake and candy stall, raising £300 in the process.

## Cross-Channel swim

Unfazed by bad weather, Sam Stevens and friends Jon Bury, James Goymour and Dave Glasgow completed the 35-mile cross-Channel swim in support of ME Research UK in 13 hours and 13 minutes. Even more amazingly, they did it all without wetsuits in the cold water.

Sam's friend, Martin, who was a fellow student at Reading University, has been fighting ME/CFS for the past four years.

As Sam says, *"I share Martin's love of all things connected with the ocean, so thought it was fitting that my friends and I should raise some money for research by swimming the English Channel!"*

The guys had to complete a two-hour qualifying swim in Dover harbour, but their training paid off – and what can we say except congratulations and thank you for raising over £8,000 for our biomedical programme.



## Redcar Half Marathon

Gemma Wilson and running partner Laura Iles (pictured below) successfully ran the Redcar Half Marathon for us, with great smiles and enthusiasm, albeit with aching legs afterwards.

Before the race, Gemma said, *"I'll be running 13 miles, that's more than I've ever walked, and facing more pain than I've ever*

*been in... and I've had to give up Dominoes pizza! If you know me, you know that this is a massive deal for my inactive, unsporting body and I'm having to work really hard. But I'm determined to do it without walking, and finish in an un-embarrassing time, and raise as much money as possible on the way."*

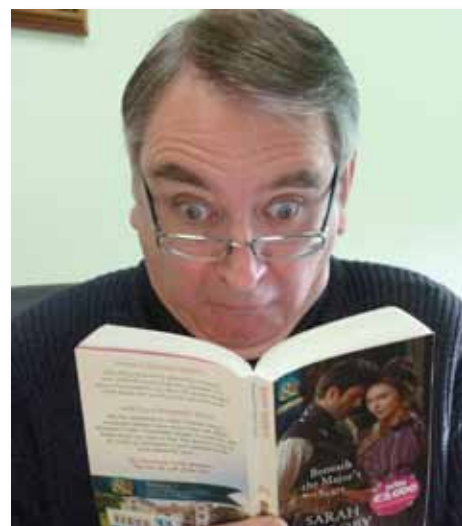
In fact, Gemma and Laura completed the course in a very respectable time, raised a grand total, and learned one key lesson: to wear thicker socks next time!



## Read with ME

Amy Christian is encouraging people to sponsor her to read or listen to as many books as possible, or to undertake their own sponsored read over a 3-month period. In her blog, Amy gives full details of how to join in, and there is a specific ME Research UK JustGiving page too. Amy says, *"As someone with ME/CFS, I'm not able to do many physical activities, but one thing I enjoy and which makes me feel better is reading."*

Our own Dr Neil Abbot is helping Amy's campaign by reading his first Mills and Boon romance, *Beneath the Major's Scars*. As the cover says, *"Major Dominic Coale's formidable manner is notorious, but Zelda shows no signs of fear..."* Phew!



# Standing Order Form

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

Name \_\_\_\_\_

Address \_\_\_\_\_

Postcode \_\_\_\_\_

Telephone \_\_\_\_\_

E-mail address \_\_\_\_\_

To the Manager, Bank/Building Society \_\_\_\_\_

Branch address \_\_\_\_\_

Postcode \_\_\_\_\_

Name of account holder(s) \_\_\_\_\_

Account number \_\_\_\_\_ Branch sort code \_\_\_\_\_

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

Starting on \_\_\_\_\_

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

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

*giftaid it* ☐

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

Signature \_\_\_\_\_ Date \_\_\_\_\_

**Thank you for your support**



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Can there be any easier way to earn money for our charity? If you are buying from Amazon, then just click through the link on the Amazon page on our website, and 5% or more of your purchases could be making its way back to ME Research UK. It really is that simple.

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

Visit our website for more details: [www.mereseach.org.uk/support/shopping.html](http://www.mereseach.org.uk/support/shopping.html).

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