

MERGE breakthrough

News of the ME research YOU are helping to fund



WINTER 2005

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Oxidative Stress, Symptoms and Genes

The body contains highly reactive molecules called free radicals. These are normally kept under control by natural processes which remove them from the circulation. However, when an imbalance occurs they can be left unchecked to cause damage. This damage is called oxidative stress. In particular, free radicals can change our normal “good” cholesterol into something more harmful, leading to heart and circulation problems.

A recent issue of the scientific journal *Free Radical Biology & Medicine* has published results of a MERGE-funded study showing — for the first time in ME/CFS patients — raised levels of F₂-isoprostanes, which are a standard indicator of oxidative stress. Increased isoprostanes were also associated with clinical symptoms such as joint pain and post-exercise illness.

These are important findings because they suggest that normal processes which control free radicals are not working properly in patients with ME/CFS. Increased oxidative stress is implicated in a range of disorders, including neurological diseases, as well as in ageing. These new results might well be relevant to the symptoms that characterise ME/CFS, and might also help to explain some of the peripheral vascular consequences of being upright, as recently discussed in our review in the magazine *Biologist*.

The importance of the work is underscored by new studies on the genes of people with ME/CFS. In the past few months, scientists have reported upregulation of the genes ABCD4 and PEX16 (suggesting improved defence against oxidative stress), and alterations to genes involved in the formation of isoprostanes. Clearly, biomedical research into ME/CFS is entering an exciting phase. ●

ON THE WEB



www.mererearch.org.uk

MERGE's website is a source of news, education and information on ME/CFS research and other issues of interest to biomedical researchers, healthcare professionals, people with the illness and their carers, and the general public.

The **RESEARCH** pages contain summaries and explanations of MERGE-sponsored projects, reviews of the scientific literature, recently-published MERGE articles, and details of our funding procedures.

In the **INFORMATION** section, you can find a collection of literature on ME/CFS and its consequences, a database of abstracts of all ME/CFS research papers from 1956 to 2005, and MERGE's own documents discussing and analysing important issues.

The **SUPPORT** section contains information and advice on accessing social care support for people with ME/CFS.

The website also keeps you up-to-date with the latest ME/CFS research news, and with Friends of MERGE activities.

Free Radicals and Oxidative Stress

New study raises important questions

Circulating in the bloodstream are highly reactive molecules called free radicals, which can cause damage to the cells of the body. This damage, which is called oxidative stress, is implicated in cardiovascular disease, most neurological diseases and ageing. With funding from MERGE, Dr Gwen Kennedy (pictured right), Dr Sandy Hill and Professor Jill Belch at the Institute of Cardiovascular Research, University of Dundee, have been studying oxidative stress and lipid peroxidation in ME/CFS.

They found that F₂-isoprostane levels (a measure of oxidative stress) were higher and HDL ("good" cholesterol) was lower in 47 ME/CFS patients than in healthy subjects. This was true both for patients who were obese and had high blood pressure (which are independently associated with oxidative stress) and for patients without these conditions, who would normally be considered low-risk. In the low-risk group, higher F₂-isoprostane levels were associated with worse joint pain and post-exertional malaise. In addition, isoprostane levels were higher in patients with the most severe joint pain;



similar results were reported for post-exercise malaise.

What might be the source of the excessive free radicals? Exercising muscle is a prime contender, and recent evidence points to an association between muscle pain/fatigue and oxidative injury in CFS patients, as well as viral persistence in the muscle tissue of some patients. ME/CFS is also associated with immune activation, and excessive free radicals may be generated by activated white blood cells as a consequence of persistent infection or environmental stressors.

ME/CFS patients have a lipid profile and oxidant biology consistent with cardiovascular risk, and high levels of F₂-isoprostanes may explain some of the symptoms. Importantly, obesity and hypertension represent a potential additional burden to CFS pathology, an issue of which patients should be aware.

The importance of these findings cannot be overstated. F₂-isoprostanes are now recognised as one of the most reliable approaches to assessing in-vivo oxidative stress. In the past few months, upregulation of the genes ABCD4 and PEX16 (suggesting enhanced defence to oxidative stress), and alterations to genes involved in the formation of isoprostanes, have provided a tantalising new context for these novel results. ●

HOW IS IT DONE?

Isoprostanes absorb certain wavelengths (or colours) of light more strongly than others, and this pattern is characteristic of these molecules. By shining light through a blood sample and measuring what comes out, Dr Kennedy and her colleagues are able to determine by how much these wavelengths have been attenuated, and thereby measure the level of isoprostanes in the blood.

Nerve Activity in Exercising Muscle

How do exercise and fatigue affect muscle activity?

One of the cardinal signs of ME is marked muscle “fatigability” or loss of power, often in response to quite minor degrees of exercise. Muscle cramps, twitching and extreme muscle tenderness are also common findings, but how many ME patients have received a proper clinical examination of their affected muscles? Very few, in fact.

However, patient reports suggest that observable muscle abnormalities might be more common than is often supposed, and there is also scientific evidence of anomalies in the muscles and nerves. Muscle fatigue produces alterations in muscle membrane excitability in ME patients, possibly associated with increased muscle oxidative stress.

Building on their ongoing investigation of pain in ME patients, Dr Les Wood and Dr Lorna Paul at Glasgow Caledonian University — with their research team of Lindsay Day and Gillian Sutherland — have designed a new study of how exercise and fatigue can affect muscle activity. MERGE is funding their investigation of how nerves control the calf muscles, and what happens to this control after exercise.

To do this, they record what happens to the muscle when they stimulate one of the nerves in the back of the leg behind the knee using a short, non-painful electric shock. This is then repeated

after a short exercise designed to fatigue the calf muscles. This involves patients pointing their toes as hard as possible against a footplate which records the force.

Dr Wood explains, “What we’re doing is investigating the effects of fatiguing contractions on the excitability of spinal motoneurone pools using the Hoffmann reflex as a tool to measure this. Following this exercise, we stimulate the nerve again to observe any effects of the exercise on nerve control. This nerve stimulation is repeated several times for up to four hours after the exercise has finished.”

From this initial investigation of the influence of delayed recovery on “reflex excitability”, the investigators hope to find out the status of spinal motoneurons in subjects with ME/CFS during the recovery phase following fatigue. The findings may lead to a large programme of research on muscle and nerve function in ME. ●

“Very few ME patients have received a proper clinical examination of their affected muscles.”



WHAT IS ME/CFS?

Myalgic encephalomyelitis/encephalopathy (ME) is characterised by a range of neurological symptoms and signs, muscle pain with intense physical or mental exhaustion, relapses, and specific cognitive disabilities.

During the 1990s, the term ‘chronic fatigue syndrome’ (CFS) came into vogue. Since there was no specific diagnostic test for ME, and since post-exercise ‘fatigue’ was one of its prominent symptoms, people with ME began to be diagnosed with ‘CFS’. At present, efforts are being made to revise the definitions of both ME and CFS, and meanwhile the term ME/CFS is used.

ME/CFS affects 120,000 to 240,000 people in the UK, and it is classified by the World Health Organisation as a neurological illness (ICD10: G93.3). Most people with ME/CFS are unable to work to full capacity, and 25% are severely disabled, some house or bed-bound. Little support is available to their families and carers. The cause of the illness is unknown, and no cure or universally effective treatment has yet been found.

A report to the Chief Medical Officer of England in 2002 states “ME/CFS is a genuine illness and imposes a substantial burden on the health of the UK population. Improvement of health and social care for people affected by the condition is an urgent challenge.”

FUTURE PROJECTS

MERGE-funded research has raised interesting questions and helped reveal key areas for further, urgent investigation.

Exercise & oxidative stress

This is an important feature of ME/CFS, and we would like to fund projects on the source and role of post-exertional free radical generation in the peroxidation of lipids, and the generation of post-exercise pain and symptoms.

Orthostatic intolerance

A key element in the generation of ME/CFS symptoms is the abnormal cardiovascular response to being upright. We would like to fund a study on arterial stiffening, the cardiovascular risk profile and blood vessel regulation.

Cellular energy in muscle

Many ME/CFS patients report a reduction in muscle force, and we would like to investigate muscle metabolism.

Novel treatments

One study on our wish-list investigates the effects of vibration and resistance exercise on neuromuscular performance.

These are some examples from the wish list of projects we would **LIKE** to fund. As a medical research charity, we support only good quality projects based in established research institutions. MERGE relies entirely on donations for its survival, so we need **YOUR** help, and **YOUR** donations for the work to continue.

Gene Research: A Scientific

Glasgow team engaged in the search for

Dr John Gow and colleagues at the University of Glasgow's Department of Neurology are seeking to identify genes specific to ME/CFS using novel microarray technology. MERGE has contributed interim funding to the group for the first phase of their project, in which they will verify the importance of genes which have shown the greatest difference between patients and controls. The next phase will focus on the development of diagnostic biomarkers. The project will use peripheral blood mononuclear cells isolated from patients with ME/CFS and matched healthy controls.

As reported in a series of articles in the press in the Autumn of 2005, pilot data obtained by Dr Gow's team have suggested alterations to genes controlling the metabolism of prostaglandin and those regulation-specific immune cells. This is interesting work which deserves to be supported into its mature phase when a specific 'gene signature' for particular proteins may be revealed.

The Glasgow team is one of a number of worldwide research groups investigating the genetic characteristics of people with this illness. One group, led by Dr Jonathan Kerr at St Mary's Campus, Imperial

College, London, have just published some early results (in the *Journal of Clinical Pathology*): they compared levels of gene expression in the white blood cells of 25 healthy individuals with those in 25 patients, and found differences in 35 of the 9,522 genes analysed using DNA chip technology. Using real-time PCR, 15 of the genes were up to four times as active in people with ME/CFS, while one gene was less active. Dr Kerr is shortly to study 1,000 ME/CFS patients and healthy controls, this time looking at 47,000 gene products.

Another group, led by Suzanne Vernon of the Centers for Disease Control and Prevention's molecular epidemiology programme in Atlanta, USA, has been investigating gene expression profiles in the large Wichita clinical data set. Their preliminary findings suggest dysregulation of genes involved in immune pathways, supporting the many reports in the literature of immune dysregulation in the development of the illness. This team has been able to show differences among people with ME/CFS, confirming that the broad diagnostic category ME/CFS contains different kinds of patient groups. Examining 3,800 genes in 23 women, they found that those with sudden-onset illness

(developing in one week) had a different gene expression profile to those with gradual onset (developing over several months), and they may find particular patterns that are specific to other subgroups as well. While their hope is that the microarray could become a routine diagnostic tool for ME/CFS, they



'Signature' for ME/CFS?

potential diagnostic biomarkers

realise that finding effective treatment for CFS is the long-term goal. Dr Vernon says, "With a better understanding of the disease process, specific therapeutic interventions may one day be possible."

These developments are welcome: few areas of biomedical research into ME/CFS can boast more than two separate research groups simultaneously engaged on a common quest. But it is a long complicated process. Experience from the use of genome-wide scanning technologies for cancer screening has shown that

discovery and validation of biomarkers requires multiple phases of research over some years. Nevertheless, this work is one of the most exciting recent developments in ME/CFS, and could open the door to the development of pharmacological interventions. As Dr Russell Lane, a neurologist at Charing Cross Hospital in London, has said of the work on genes, if the researchers succeed and identify "clear physical changes in people with CFS, the lingering opinion that it is 'all in the mind' could finally be laid to rest." ●

THE RESEARCH CHALLENGES

The same problems that confront all researchers in ME/CFS also apply to those using microarray technology. 'Diagnosis' of the illness is often based on common non-specific symptoms, resulting in a diverse group of patients. As Jason and colleagues pointed out in an excellent recent review, "Subgrouping is the key to understanding how CFS begins, how it is maintained... and in the best case, how it can be prevented, treated and cured." It is unlikely, therefore, that any single biomarker or cluster will be able to detect all cases as currently defined, although microarray technology does have the potential to make diagnosis more precise in the long term.

Another problem is that obtaining and maintaining funding haunts the efforts of all biomedical researchers in ME/CFS, and it is particularly acute in these gene biomarker studies which will require millions of dollars to come to a definitive conclusion. In the Parliamentary members' business debate in June 2005 (motion S2M-2852), Alex Fergusson MSP said, on the subject of a cure for ME, that it is entirely unacceptable that major funding bodies seem uninterested in novel gene research, particularly when large tranches of money have been allocated to research on non-curative psychosocial strategies designed to 'manage' symptoms.

Illnesses are most easily accepted when they have a specific clinical or scientific 'signature' — a biochemical test, a cluster of specific symptoms or signs, etc. — that confers legitimacy in the eyes of healthcare professionals. Until then, patients are in a no-man's land between the living and the well, subject to a variety of quasi-therapeutic interventions. ME/CFS has been called the "disease of a thousand names", but it has also been the disease of a thousand false dawns and broken promises. The discovery of a clinical or scientific 'signature' for ME/CFS would transform this situation at a single sharp stroke. In the longer term, work using genome-wide scanning technologies has the potential to reveal such a 'signature': to quote Steinau and colleagues in 2004, "Biomarkers characteristic of CFS could contribute to precision in case ascertainment, identify heterogeneity in the CFS population to clarify contributing pathways to disease, suggest novel therapeutic targets, and provide indicators of disease progression and prognosis."

MERGE ARTICLES



MERGE produces reviews of scientific research into ME/CFS, and publishes general articles on the topic to raise awareness of issues involved. Recent examples include:

A Scientific 'Signature' for ME/CFS?

An essay on current developments in genetic research in ME/CFS.

The Muscle in ME: It Isn't All Deconditioning!

A "research update" overview, originally published in the magazine *Interaction*, in 2005.

New Developments in the Biology of ME/CFS

Our report on the Royal Society of Edinburgh Workshop in 2004.

Severely Overlooked by Science

An overview with the 25% ME Group (which has close links with MERGE) in 2004 of research on the most severely affected ME/CFS patients.

Advances in the Biomedical Investigation of ME/CFS

Describing some recent developments in biomedical research, as well as some of the problems.

SETTING THE AGENDA

MERGE's publications and presentations offering analysis and discussion of public policy issues.

Unhelpful Counsel?

MERGE's response to the CMO's report into the research and treatment of ME/CFS.

Research into ME/CFS in the UK: Can the NRR inform future policy?

MERGE's analysis of ME/CFS research funding sources.

Who Cares?

MERGE's submission on care pathways to the Scottish Executive's Short-Life Action Group on CFS/ME.

Shattered — Life with ME

by Lynn Michell, who collaborated closely with MERGE during the writing of this book. Contains a Foreword and Appendix by MERGE.

Cross Party Parliamentary Group on ME

Presentation given in 2005 to the Scottish Parliament by our Chairman Dr Spence.

Database of Research Publications

Contains more than 3,000 research abstracts on ME/CFS, from 1956 to the present.

Most of these and other documents can be found at the MERGE website. See the sidebar on page 2.

Loss of Brain Gray Matter in ME

Implications of new research findings

There is no doubt that central nervous system symptoms are part of the ME/CFS spectrum; indeed, they are as characteristic as the post-exercise malaise, myalgia or myriad of other symptoms that people experience. They were discussed in the famous review by Acheson in 1959, and, half a century later, they form a key element of the Canadian definition (2003), which insists that patients must have at least two of a list of six “neurological/cognitive manifestations”, including impairment of concentration and short-term memory, difficulty with information processing, and disorientation or confusion.

To date, no-one has established for certain what causes the cognitive dysfunction in ME/CFS, though a variety of structural and functional studies — including SPECT imaging and MRI scans — have been conducted. The jury is still out on the meaning of these reports, but it is entirely possible that well-conducted studies might yet be able to provide diagnostic information in place of the present deduction or guesswork about what might be going on in the brain.

There have been two very interesting reports recently. One by de Lange in the journal *Neuroimage* (2005) found a significant 8% reduction in brain gray matter volume. Gray matter, which looks gray to the naked eye, refers to the areas of the brain that are mainly composed of the heads of nerve cells. The reductions were related to the level of physical activity in ME/CFS patients, but not in the control group, and importantly were unrelated to age or duration of illness. The authors comment that their results “corroborate and complement previous studies that observed cerebral abnormalities associated with CFS”.



Importantly, these results accord with another recent study by Okada (2004) in Aichi, Japan, which reported an average 11.8% reduction in gray-matter volume in the bilateral prefrontal cortex, a volume reduction which paralleled the severity of the fatigue of the patients.

Why should gray matter be reduced in ME/CFS? De Lange and colleagues speculate that reduced gray matter volume might be the “cause” of the illness and the ensuing physical inactivity. They comment that since the volume reduction is not related to the length of time patients have been ill, it is unlikely that the reduced physical activity causes the gray matter reduction. Alternatively, oxidative stress may be involved. Animal work shows that metabolically active gray matter of the brain appears more susceptible to oxidative stress than white matter, and is the likely primary target of oxidative stress at all ages. This supports a number of reports linking ME/CFS with raised levels of oxidative stress in the tissues.

The truth is that whether gray matter reduction is a primary feature of ME/CFS, related to the underlying pathophysiology, or a finding secondary to other processes remains to be discovered. But the report of reduced gray matter by two separate research groups is interesting, more so because (unusually) both research groups have found correlations between loss of gray matter and patients' symptoms. ●

MERGE and Friends



The Myalgic Encephalomyelitis Research Group for Education and Support (MERGE) was founded in 2000 by Dr Vance Spence and Mr Robert McRae, who recognised the need for a national UK charity to fund biomedical research and inform the agenda. With Roger Jefcoate CBE as founding patron and The Countess of Mar as patron, our official opening was in May 2001.

Our Friends of MERGE scheme provides the core support needed for our work to continue. There are three categories of membership: Individual Friends, Corporate Friends and ME Group Friends, all sharing our medium to long-term aim of a medical breakthrough in ME/CFS, and representing many thousands of patients and carers across the globe. Individual Friends can give their support in a variety of ways, such as fundraising, regular donation by standing order, taking a MERGE collection box, or by just spreading the word — word-of-mouth is

one of the most efficient ways of getting our work known.

Events undertaken in the past few months alone include the Junior Fresh 'n' Lo Run by eight youngsters, a large "Tea at the Ritz" garden party in Hampshire, the Stonefest festival and the Aberdour Arts Exhibition.

The recently formed Group Friends of MERGE is for local ME support groups and organisations across the world that share our medium to long-term aim of a medical breakthrough in ME/CFS, and recognise that only biomedical research can achieve this goal. The Groups range from Castleford to Solihull & Birmingham, and from Aberdeen to Warwickshire, and the full list can be found on the Friends of MERGE section of our website.

With the help of all our Friends, MERGE can continue to be a force for change, and a source of real hope for the thousands of people with this debilitating illness. ●



A MESSAGE FROM OUR PATRONS

"ME is a substantial medical and social problem, yet relatively little research has been conducted into its causes and consequences.



The Countess of Mar

"A recent report to the Chief Medical Officer said that a programme of research on all aspects of the illness is urgently needed, and that improvement of health and social care is an urgent challenge.



Roger Jefcoate, CBE

"Given the recent sea change in the public perception of ME, and the possibility that ME patients will now be encouraged and supported rather than derided and scorned, we hope that MERGE's scientific and policy research will lead the way towards a treatment and cure for people with ME. Please help us to make a real difference to the lives of people with ME."

To allow us to press ahead with our mission to Energise ME Research, please consider responding to our Standing Order appeal.

MERGE receives no public money and relies entirely on donations from ordinary people. It is vitally important that all our supporters understand that we are one of the very few charities in the world funding biomedical research into ME/CFS, and raising awareness of the issues in a truly professional manner.

Help us to make the breakthrough that patients need and deserve by completing the standing order form on this page, or by donating through the online giving facility via our website.

Please send this form to:

MERGE Headquarters
The Gateway
North Methven Street
Perth PH1 5PP, UK

Tel: 01738 451234
Email: merge@pkavs.org.uk
www.mereresearch.org.uk

For office use only:

Clydesdale Bank
 23 South Methven Street, Perth
 (82-67-09) for the credit of
 MERGE, a/c no. 50419466

Bank reference number:

Standing Order Form

1 Name _____

Address _____

Postcode _____

Telephone _____

Email address _____

2 To the Manager

Bank/Building Society _____

Branch address _____

Postcode _____

3 Name of account holder(s) _____

Account number _____

Branch sort code _____

4 Please arrange to debit my/our account with the sum of £ _____

On the _____ day of each month until further notice

Starting on _____

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

Account: MERGE, Account number: 50419466, Branch code: 82-67-09

6 If you are a UK taxpayer, under the Government's Gift Aid scheme MERGE can reclaim the tax you have already paid on your gift. This means that your donation can increase in value by nearly a third at no extra cost to you. It doesn't matter what rate of tax you pay as long as you pay an amount of income or capital gains tax equal to the tax we reclaim on your donations in that financial year. Please inform us of changes in your tax status. Please tick the box below if you would like MERGE to reclaim the tax on your gift.

Please treat this and any future donations I make to MERGE, and all payments I have made to MERGE since 6th April 2000, as Gift Aid donations.

7 Signature _____ **Date** _____

Thank you for your support