

MERGE breakthrough

News of the ME research YOU are helping to fund

2005

PAGE 2

Research into young people with ME/CFS will answer fundamental questions

PAGE 3

Exploring possible therapies for reducing pain in ME/CFS

PAGE 4

New experiments looking at cholinergic abnormalities in ME/CFS

PAGE 5

A review of muscle abnormalities in patients with ME/CFS

PAGE 6

Published research sponsored by MERGE

PAGE 7

The Individual, Corporate and ME Group Friends of MERGE schemes

PAGE 8

How you can help support MERGE



Energising ME research

MERGE's primary role is to identify and fund scientific (biomedical) investigation into the causes, consequences and treatment of ME. Recognising that much of the existing research into ME has concentrated on psychological interventions designed to "manage" the illness, we believe that a programme of biomedical research is what is needed, and is what most patients and carers want to see. To achieve this, researchers with fresh, novel ideas have to be recruited and encouraged to undertake research in this field, and it is at this leading edge that MERGE sees its role: to give help to biomedical scientists for novel research projects, including seedcorn projects.

We also aim to **energise ME research** in the broadest sense, and so our in-house team also publishes scientific papers; presents at meetings and conferences; and produces high-quality professional reviews and reports on biomedical aspects of the illness, including the recent workshop, "New Developments in the Biology of ME/CFS" (the speakers at which are pictured above).

Considerable progress has been made in establishing the research charity and in pursuing our aims. We have bold plans for the future, based on our strong in-house team, an advisory panel of professional scientists, and a core group of trusted volunteers who form the Friends of MERGE. From this strong start, we are committed to being a major force for change that will make a real, long-term difference to the lives and prospects of people with ME. ●

ON THE WEB



www.mereseearch.org.uk

MERGE's website has been online since 2002. Its purpose is to be 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 **LIBRARY**, 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 a selection of research papers from work sponsored by MERGE or undertaken by our own staff.

The **SOCIAL CARE** 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 recent Friends of MERGE fundraising ventures.

ME research in young people

Unique new study will answer some fundamental questions

A unique study into biochemical and blood flow aspects of ME/CFS in children and young people is to begin in 2005 at the Vascular Diseases Research Unit at the University of Dundee. Funding for this study has been provided by MERGE, in conjunction with the national charities "The Young ME Sufferers (TYMES) Trust" and "Search ME".

Estimates vary, but there are probably around 20,000 children with ME/CFS in the UK alone, yet biomedical investigation is almost non-existent. Attitudes are changing, however, and in a recent report the UK Chief Medical Officer highlighted the fact that research in children with ME/CFS is an urgent priority.

The aim of this newly funded study is to investigate a group of children with well-defined ME/CFS (in whom there is the possibility of long-lasting chronic ill-health), to see for the first time whether there exist similar biochemical abnormalities to those observed in adults with the illness. If so, these children may have signs of a chronic inflammatory disorder. This study is unique in that it is the first to investigate biomedical markers in children with ME, and fits well with the Chief Medical Officer's recommendation in 2002 that a "programme of research on all aspects of ME/CFS is required".

Dr Gwen Kennedy explains, "We will recruit 25 children with well-defined illness, along with 25 age and gender-



Dr Gwen Kennedy in the laboratory at the University of Dundee

"Do children with ME/CFS have the same biochemical abnormalities in their circulation as adults with the illness?"

matched 'control' children. Each child will have a medical examination, as well as blood tests consisting of a standard full blood count and measurements of oxidative stress, cholesterol, C-reactive protein

and apoptosis. We will also examine blood flow responses to acetylcholine using a scanning laser Doppler imager."

She continues, "We will find out if young people and adults share the same kind of immunological abnormalities, such as altered neutrophil apoptosis and oxidative stress. And in children and young people with ME/CFS, in whom there is the possibility of long-lasting, chronic ill-health, we may detect a pattern of abnormalities in cellular behaviour and vascular responses which might become targets for further investigation and future interventions." ●

Pain in ME

Glasgow researchers explore possible therapies

Dr Lorna Paul and Dr Les Wood (pictured right), lecturers and lead researchers in physiotherapy and physiology at Glasgow Caledonian University, have received funding from MERGE to part-fund a PhD studentship for three years to evaluate pain and therapeutic interventions in people with ME/CFS.

Post-exercise pain and malaise/fatigue are the two most common and often most disabling symptoms experienced by ME patients. Within the CDC diagnostic criteria for "CFS", five of the eight minor criteria are pain-based (e.g., myalgia, arthralgia, headache, abdominal pain).

Although pain may affect many areas of the body, some 90% of patients report persistent musculoskeletal pain.

Some researchers have proposed mechanisms to explain the pain experienced by ME/CFS patients — for example, reduced levels of corticotrophin-releasing hormone affecting pain modulation — but little is really known about their pain experience.

Shockingly, there have been no studies comprehensively examining patients' pain and its effect on daily functioning, and no studies have been performed to evaluate the effectiveness of any pain-relieving (non-pharmacological) therapy in this group of patients.

As Dr Paul explains, "While researchers attempt to unravel the biology of the pain mechanisms, patients require



symptomatic relief, and something has to be done. A number of medications may be effective in reducing the patient's pain:

from simple analgesics, through low-dose tricyclics, to anticonvulsants. However, as with any forms of medication, potentially serious side-effects may occur. It has been recognised that there is a need to assess 'a wide range of potential therapeutic

interventions including symptom control measures' (CMO Report, 2002), and physiotherapists are ideally placed to examine and treat patients presenting with significant pain."

Over the next three years, this long-term exploratory project will investigate aspects of pain. "The aims are to comprehensively examine the pain presentation in a group of ME/CFS patients, to determine appropriate instruments, to evaluate pain presentation and the effectiveness of a therapeutic intervention for pain control within a subgroup of these patients," explains Dr Wood. "The chosen intervention may involve acupuncture, manual therapy, TENS or other electrophysical agents such as heat; all currently used to control pain in other patient groups." ●

"Pain affects many areas, but 90% of patients with ME/CFS report persistent musculoskeletal pain."

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.

Vascular sensitivity

New series of experiments into cholinergic abnormalities in ME/CFS

Acetylcholine is an important chemical in the nervous system, and many of the symptoms associated with ME/CFS — such as fatigue, muscular pain, intestinal problems and neural disorders — can be linked to abnormalities in the regulation of acetylcholine.

Over the last three years, Dr Faisal Khan and his colleagues in the Department of Medicine at the University of Dundee have found that the skin blood vessels of patients with ME/CFS have an apparently increased sensitivity to acetylcholine, which is a most unusual, if not unique, observation.

To dilate a blood vessel, acetylcholine attaches itself to special muscarinic receptors on the endothelial lining of the vessel wall. Soon after the receptor is activated, an enzyme called cholinesterase removes the acetylcholine molecule, and its dilatory effects then die away very quickly. The researchers have postulated that patients with ME/CFS have less of this enzyme on their blood vessel walls, or that it is less active, so prolonging and increasing the effects of acetylcholine.

In a separate series of experiments, Dr Khan has uncovered further evidence that the blood flow abnormalities in ME/CFS may indeed be a result of problems with endothelial acetylcholinesterase, and that the finding may be unique to ME/CFS (i.e., patients with Gulf War syndrome and those exposed to insecticides have normal blood flow responses).

To unravel the biology of the illness further, MERGE has recently funded a continuation of this series of experiments. The new study (also under the auspices of Dr Khan) is examining the roles of nitric oxide, prostacyclin and endothelium-derived hyperpolarising factor in the blood flow response to acetylcholine in ME/CFS patients and matched control subjects. To achieve this, the research teams will use a variety of chemicals to block the activity of these substances, and test the subsequent effect on blood flow responses to acetylcholine.

It is too early to say whether tests of acetylcholine sensitivity could become diagnostic markers for ME/CFS *per se*. Given that the vascular endothelium is a dynamic organism, such tests are rather

blunt instruments for the assessment of specific disturbances. However, it may be that — conjoined with other biological anomalies in these patients, such as novel 'markers' of oxidative stress or neutrophil apoptosis — these tests could help to distinguish ME/CFS patients from others currently included in the diagnostic 'black hole' that is the diagnosis of 'chronic fatigue syndrome'. ●



Dr Faisal Khan, Senior Lecturer in Medicine

Muscle in ME

Dr Vance A Spence, Chairman of MERGE

In the historical literature, the hallmark of myalgic encephalomyelitis was marked muscle fatigability, often in response to minor degrees of exercise. Muscle cramps, twitching and extreme muscle tenderness were also common findings. Today, how many ME/CFS patients have had a proper clinical examination of their affected muscles? Very few, judging by recent MERGE-funded clinical research. Yet, if a full clinical examination was conducted, muscle abnormalities might be more common than is often supposed.

What abnormalities have been found in the muscles of these patients? Well, researchers in Glasgow have shown that 80% of patients with post-viral fatigue syndrome — an alternative name for ME/CFS — have abnormalities of mitochondrial structure. In a more recent study, there was evidence of impaired mitochondrial structure and function in skeletal muscle tissue. One explanation for these findings is that they might be caused by a persistent viral infection affecting the metabolic machinery of the muscle cell without causing any obvious inflammatory changes or cell destruction.

Viruses have been isolated from the muscle of patients in epidemic incidences of ME/CFS, and abnormalities in the part of the muscle responsible for movement have been reported from recordings of muscle jitter. These findings are supported by subtle changes in muscle tissue and structural damage to the muscle fibre.

These studies are very useful in that they provide evidence of physical muscle disease in well-defined ME/CFS patients. They should not be considered as diagnostic tests, but as a starting point for additional research that might well be



important in terms of operational criteria for ME proper.

What can we learn from studies such as these? We discover that a subset (20–30%) of ME/CFS patients have abnormal mitochondrial structure and enzyme function, and that about the same proportion, but not necessarily the same patients, have evidence of viral activity in skeletal muscle tissue. Clearly, the persistence of viral particles may well interfere with the muscles' ability to carry out specialised functions. Interestingly, some researchers contend that a diagnosis of ME/CFS should not be entertained without the most dominant and constant feature of the illness: muscle fatigability and myalgia.

Finally, it is worth asking how and why these patients feel muscle pain. What is clear is that most muscle disorders are not painful. While the mechanisms of pain may not be the same in all ME/CFS patients, it is possible that lack of oxygen in muscle tissue will give rise to pain, and so post-exertional myalgia may well be driven by an inadequate blood supply, a state of energy depletion during exercise, and the development of noxious free radicals.

This is a peripheral explanation for pain, but it is important to understand that chronic pain causes changes to the central nervous system. So the pain experienced by ME patients is likely to involve the brain and central nervous system, as well as the part of the body that feels sore! ●

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:

Broader Lands and Better Days

MERGE's comprehensive report on the 6th International Conference of the AACFS in Washington, 2003.

Database of Research Publications

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

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 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 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.

Royal College of Paediatrics & Child Health Guidelines 2004

A report from MERGE was submitted on the draft of the guidelines.

National Institute for Clinical Excellence 2005

MERGE is registered as a stakeholder in a process to develop guidelines for the effective treatment of ME.

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

What is MERGE?

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 and Dr Gordon Parish as patrons, our official opening was in May 2001.

Since then we have accomplished much with our strong in-house team: Betty

McRae (Administrator), Dr Neil Abbot (Director of Operations) and Dr David Newton (Communications Officer). In its first year, MERGE was instrumental in forming a Cross Party Group on ME at the Scottish Parliament, to provide a forum for the concerns of patients and carers.

Recently, we have produced several professional documents aimed at informing the national agenda (see sidebar). We have also commissioned and funded a number of biomedical research projects, some now completed. In addition, we have established close working relationships with other ME/CFS organisations in the UK and overseas.

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

MERGE-sponsored research

Plasma endothelin-1 levels in chronic fatigue syndrome. *Rheumatology* 2004; 43: 252–253

The specificity of the CDC-1994 criteria for chronic fatigue syndrome: comparison of health status in three groups of patients who fulfil the criteria. *Annals of Epidemiology* 2004; 14: 95–100

Enhanced sensitivity of the peripheral cholinergic vascular response in patients with chronic fatigue syndrome. *American Journal of Medicine* 2000; 108: 736–739

Peripheral cholinergic function in humans with chronic fatigue syndrome, Gulf War syndrome, and with illness following organophosphate exposure. *Clinical Science* 2004; 106, 183–189

Standing up for ME: cardiovascular mechanisms of orthostatic intolerance. *The Biologist* 2004; 51: 65–70

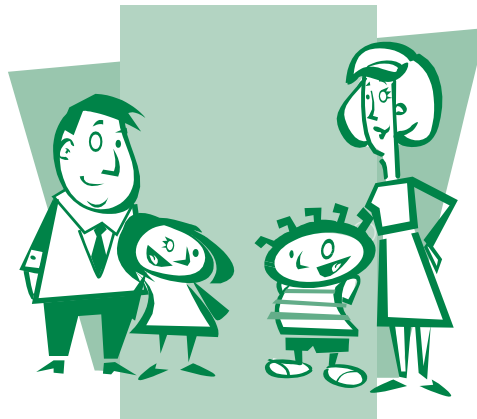
Prolonged acetylcholine-induced vasodilatation in the peripheral microcirculation of patients with chronic fatigue syndrome. *Clinical Physiology & Functional Imaging* 2003; 23: 282–285

Acetylcholine mediated vasodilatation in the microcirculation of patients with chronic fatigue syndrome. *Prostaglandins, Leukotrienes and Essential Fatty Acids* 2004; 70: 403–407

Is chronic fatigue syndrome a hypercoagulable state associated with platelet activation? *Blood Coagulation & Fibrinolysis*

Increased neutrophil apoptosis in chronic fatigue syndrome. *Journal of Clinical Pathology* 2004; 57: 891–893

Friends of MERGE



The Friends of MERGE scheme lets you help us energise ME research, stimulating real advances in the understanding of this much neglected illness. It also provides the core support needed for our research work to continue. There are three categories of membership: Individual Friends, Corporate Friends and ME Group Friends.

The Corporate Friends category is designed for any larger independent organisations — corporations, larger registered charities, companies, businesses — 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. It is also a vehicle for the increasing number of companies that recognise ME/CFS as an illness, the incidence and cost-of-care of which have important implications for their customers and employees. Corporate Friends brings collective power, representing many thousands of patients and carers across the globe. Current members include the Alison Hunter Memorial Foundation, Australia; the Danish ME/CFS Association; the ME Association of America; the Irish ME Trust; the Young ME Sufferers Trust (TYMES Trust); and the Associated New Zealand ME Society.

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. Recent events undertaken by Friends on our behalf have included the BUPA Great South Run 2004 (by runners associated with the Warwickshire Network for ME), the Fresh 'n' Lo Great Scottish Run 10K 2004, the Thames Path Walk 2004, the Belfast ME/CFS Conference 2004 (organised by The Northern Ireland Campaign for ME/CFS Healthcare), the Syntegra Edinburgh Marathon 2004 (with the help of the cross-party group at the Scottish Parliament), Tesco supermarket collections (by the NE Fife ME Support Group), the Britannic Asset Management Women's 10K Race 2004, the Flora London Marathon 2004, several football bucket collections, and sheep dog trials on Culloden Moor.

These are only some of the events — more details can be found on the Friends of MERGE section of our website. ●



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.mereseearch.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