

breakthrough

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**Genetic Markers:
the quest continues**



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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 conferences.

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Editorial



In the scientific buzz and bustle to find treatments or even a cure for ME/CFS, the experience of the individual — the real person living day-to-day with the illness — is often overlooked. Patients often find themselves in a Kafkaesque nightmare involving physical illness compounded by the scepticism of healthcare professionals and the disbelief of family and friends. Many haven't been to a GP for years; most (it seems) haven't been properly physically examined for a long, long time (if ever); and their quality of life is poor — literature reviews have shown that substantial improvement is uncommon (less than 6%) and that, in fact, full recovery is rare.

My own story is somewhat similar to thousands of others. As a senior bank manager in my 40s, I expected to continue working for another 20 years in a fulfilling job. However, progressive weakness and rapidly declining ill-health, probably with an infectious beginning though that was never proved, left me bed-bound for months, during which I was spoon-fed and virtually helpless.

Fortunately I had the support of my wife, family and close friends, but recovery was slow though never

satisfactory and certainly never complete. In the end, early retirement on health grounds was the only solution, though for me this was just the start of years of chronic illness and searching for cures that have never arrived.

So, the decision in 2000 to co-found ME Research UK with Dr Vance Spence and Roger Jefcoate CBE was the culmination of a long and personal journey — the drive to uncover the biomedical causes of this illness is no mere academic matter, therefore: it has a deep personal importance.

In a way, my intellectual journey is very similar to the one described by a US patient, John Herd, at the International IACFS/ME Research and Clinical Conference held in Reno, Nevada earlier this year. John described how, 20 years ago, he had great hopes that advocacy for greater recognition and understanding of ME/CFS would lead to a revolution in public understanding of the illness. But as he said, "*Now, it seems, we would have been better off focusing the bulk of our concentration and energy on raising funds for ME/CFS research.*"

After many years of illness, and reflection, this is also my view: nothing is more important than the rock-solid research which, alone, can provide the hard data needed to answer sceptics and provide the breakthrough we all want to see.

At present, ME Research UK provides funding to the Universities of Newcastle, Dundee, Strathclyde, Brussels, London (St George's and Hammersmith), Glasgow and Calgary. Yet, we all recognise that there is so much more that could and should be done. As biomedical research is expensive, a team effort is essential if we are to succeed. We need your help; together we can make a difference.

Mr Bob McRae
Co-founder/Secretary of
ME Research UK



this issue

Exercise and interleukin-6 levels.....4-5

The effect of exercise on this important immunological cytokine

Cover story.....6-7

The search for a genetic biomarker for ME/CFS

A Royal visitor.....8-9

A visit to MERUK headquarters by HRH Prince Edward

Recent research.....10-13

Studies from around the world, including research on somatisation, the brain, diagnostic issues, B-cell depletion therapy, and genes and exercise

Friends of ME Research UK.....14-15

The new £1 million “Just Four Quid” campaign, and recent and upcoming fundraising activities, including skydiving, tattooing and a half-marathon

How to help ME Research UK.....16

Please complete our standing order form to help support the work of ME Research UK



The effect of exercise on levels of interleukin-6

Muscle pain, fatigue and malaise after exercise — sometimes developing 24 to 48 hours later — are considered to be characteristic of ME/CFS. There have been some suggestions that the “fatigue” in the illness could be associated with limitations in the use or supply of fuel by the tissues. If so, an understanding of interleukin-6 (IL-6) and its associated receptors could be important, since IL-6 is produced by working skeletal muscle and is also a key component of the body’s response to the illness.

Some studies have indicated that ME/CFS patients do not have raised levels of IL-6 and other cytokines in the blood at rest. However, IL-6 requires receptors to be biologically active, so it is important that both IL-6 and its receptors are investigated. As it is exercise that brings on symptoms in most people with ME/CFS — at least in the early stages of the illness — perhaps researchers ought to be looking at changes during exercise rather than at rest?

It was this aspect that particularly interested Professor Myra Nimmo of the Strathclyde Institute of Pharmacy and Biomedical Sciences in Glasgow. Prof. Nimmo is a metabolic physiologist who is internationally renowned for work in exercise physiology, and she says, “Exercise offers the opportunity to examine patients in an exacerbated state, yet many studies to date have not clearly categorised the exercise regimen and, since incremental maximal tests are essentially limited by cardiorespiratory fitness, metabolic limitations may be more clearly identified through the use of a sub-maximal exercise protocol.”

To explore whether IL-6 and its receptors might be involved in the reduction in exercise performance and

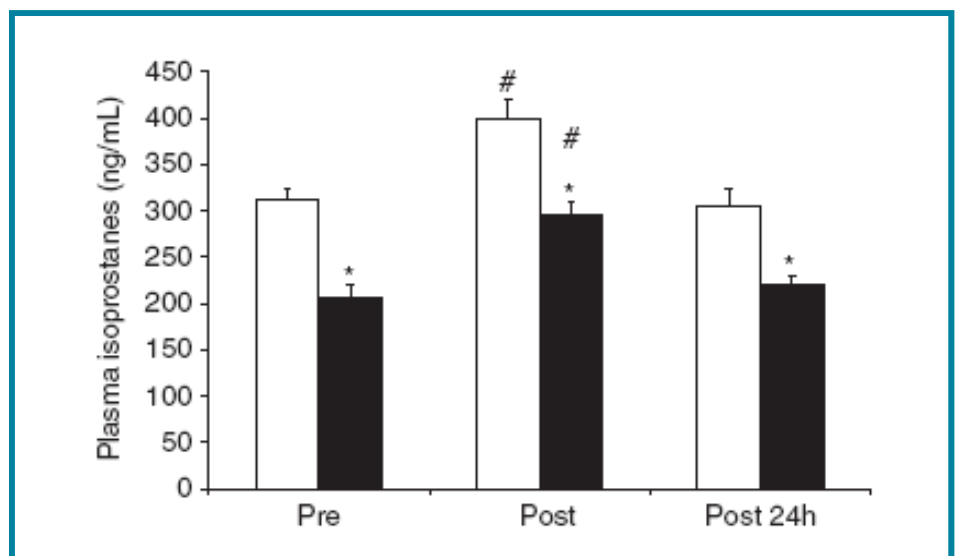


poor recovery from exercise seen in these patients, Prof. Nimmo and Mark Robinson conducted an ME Research UK-funded pilot study of six men with ME/CFS and six healthy control subjects matched for age, physical activity and body mass.

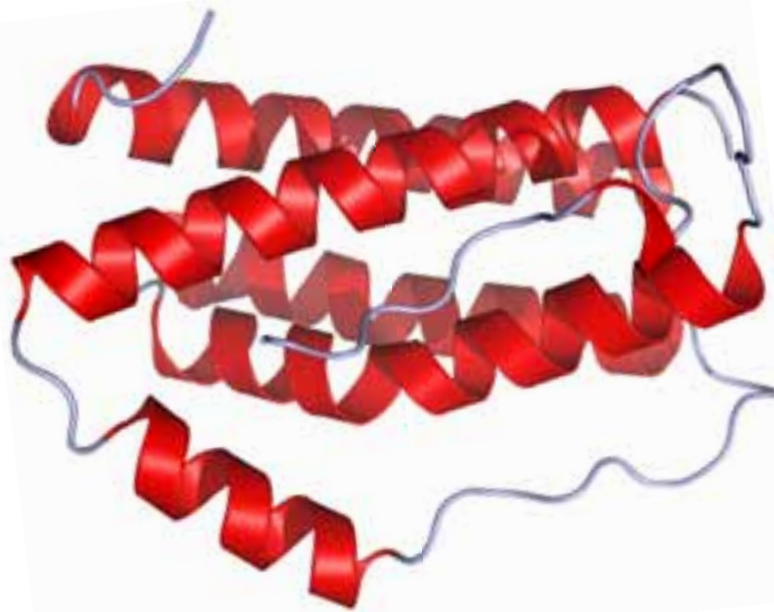
Each participant undertook an

exercise bout at 90% lactate threshold, allowing a “matching” of the metabolic load between controls and patients — a refinement missing from previous studies. All volunteers were required to visit the laboratory twice, the first visit for identification of the lactate threshold. On the second occasion, subjects were exercised at their identified exercise load in the morning before eating. Subjects were then given standardised meals for the following 24 hours (not very palatable, we’re told!) and blood samples were taken before and after exercise, and at regular intervals throughout this period. A further 33 CFS and 33 healthy control participants gave a resting blood sample for measurement of IL-6 and soluble IL-6R levels.

The results have just been published in the *Scandinavian Journal of Medicine and Science in Sports* (2009). During the incremental exercise test, the physiological responses of both groups were closely similar, except that the power output at the lactate threshold was 28% lower in the ME/CFS group than in the matched controls ($p < 0.05$). In



Oxidative stress markers are higher in ME/CFS patients (open bars) than in controls (black bars) at rest and after exercise



The crystal structure of interleukin-6

addition, F2-isoprostanes — which indicate oxidative stress — were higher in patients than in controls at rest ($p < 0.05$), as well as after exercise and after 24 hours (see the graph opposite).

However, the study found no differences in IL-6 or its receptors between patients and controls at any time point, and in the larger study there were no differences in resting IL-6 levels or its receptors.

What are we to make of these findings? Well, the lack of a difference in either IL-6 or its soluble receptor at rest or during exercise suggests that “transignaling” is unlikely to be involved in the pathology of ME/CFS. This is a negative result yet an important one.

However, the results do confirm previous ME Research UK-funded work (by Dr Kennedy in Dundee) showing raised levels of F2-isoprostanes in ME/CFS patients at rest, and Prof. Nimmo has now shown that these levels remain high during exercise and in the recovery period. Indeed, the level of isoprostanes in the “rested” ME/CFS patients was as great on average than that reached by the healthy controls *after* exercise!

As isoprostanes also act as vasoconstrictors, their presence, accompanied by additional free radicals during exercise, may be responsible for some of the clinical symptoms seen in ME/CFS, such as joint pain and post-exercise illness. ●



Interleukins and their uses

The interleukins are naturally occurring proteins important in the immune system, particularly in the activation of lymphocytes to ward off infection. The best-known interleukins are IL-1 and IL-2, which together ensure a plentiful supply of T-lymphocytes to fight specific infectious agents.

Interleukin-6 (IL-6) is a fascinating member of the family which is secreted by T cells and macrophages to stimulate an immune response to trauma, especially burns or other tissue damage leading to inflammation.

However, it also has an important part to play in exercise. IL-6 is produced from muscle and becomes significantly elevated with exercise. It can both stimulate inflammation (for example, when produced by blood vessels) and act as an anti-inflammatory through its inhibitory effects on cytokines such as tumour necrosis factor-alpha.

Clinically, inhibitors of IL-6 (including oestrogen) have been used to treat postmenopausal osteoporosis, and blockade of IL-6 by its natural antagonist has been shown to inhibit the progression of arthritis, a disease expressing not dissimilar symptoms to those seen in ME/CFS patients.

Gene Research: the quest continues

In a recent issue of the scientific journal *BMC Medical Genomics* (2009), Prof. John Gow and colleagues from Glasgow Caledonian University report the initial results of their efforts to identify genes involved in ME/CFS. Since 2005, with funding from Scottish Enterprise and ME Research UK among others, these researchers have been using DNA chip microarray technology to try to identify a specific gene expression “signature” that could become a diagnostic biomarker for ME/CFS, a development that could revolutionise diagnosis and treatment.

The Glasgow team took blood from male patients who had developed ME/CFS after an infection, as well as from matched healthy control subjects. Peripheral blood mononuclear cells were isolated so that levels of gene expression could be measured by genome-wide Affymetrix GeneChip array technology. This allowed rapid comprehensive analysis of 39,000 transcripts derived

from 33,000 gene sequences (see the box opposite).

Significant differences in gene expression between patients and healthy people were observed for 366 genes. Closer analysis revealed a “gene signature” for ME/CFS that highlighted changes in gene expression in three main areas: oxidative stress, apoptosis and viral-like immune dysfunction (see the table opposite). Interestingly, previous ME Research UK-funded scientific studies have reported increased oxidative stress and neutrophil apoptosis in ME/CFS patients, and there are many reports in the literature of immune dysregulation being involved in the development of the illness.

The team at Glasgow Caledonian University is just one of a number of research groups worldwide investigating gene expression in people with ME/CFS. The number of published scientific reports in this field has been steadily increasing in the past few years, a welcome development as few areas of

biomedical research into ME/CFS can boast more than two or three separate research groups simultaneously engaged on a common quest.

In 2007, one group in the UK, led by Dr Jonathan Kerr at St George’s London, reported their identification of a putative “gene signature” for ME/CFS consisting of 88 human genes, the top functional categories being haematological disease and function, immunological disease and function, cancer, cell death, immune response, and infection. Notably, three of the commonly over-expressed genes identified in the most recent work by the Glasgow Caledonian group had also been identified previously by the St George’s Group: CXCR4, upregulated in infection and reported to be high among patients with arthritis; EGR1, associated with infection; and PRKARIA, a gene associated with a variety of disorders.

While the putative “signature” identified in the current research seems promising as a potential biomarker for diagnosis and treatment, relating genetic findings in the laboratory to applications in the clinic can be a long, complicated process. Experience in the use of genome-wide scanning technologies for cancer screening has shown that discovery and validation of biomarkers requires multiple phases of research over many years.

Nevertheless, work on gene expression by various groups across the world 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*”. ●



ME/CFS — the research problems

The same problems that confront all researchers in ME/CFS also apply to research groups using microarray technology. One is that “diagnosis” of the illness is most often based on a ragbag of common non-specific symptoms, resulting in a diverse group of patients. As Jason *et al* (2005) have pointed out in an excellent review of the subject, “*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 a single biomarker or gene cluster will be found able to detect ALL cases as currently defined, although microarray technology does have the potential to make diagnosis more precise. As Steinau *et al* (2004) have pointed out, “*Biomarkers... could contribute to precision in case ascertainment, identify heterogeneity in the population to clarify contributing pathways to disease, suggest novel therapeutic targets, and provide indicators of disease progression and prognosis.*”

The other major difficulty is obtaining and maintaining funding — a problem that haunts the efforts of all biomedical researchers in ME/CFS, and it is particularly acute in these gene biomarker studies which require major investment — millions of pounds over many years.

The three main areas showing changes in gene expression (with some specific up-regulated genes)

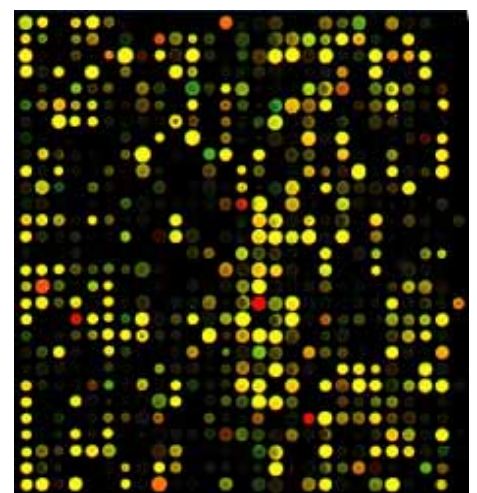
Oxidative stress genes	Prostaglandin Synthase: COX-1 and 2, haemoglobin gamma A and gamma G
Apoptosis genes	<ul style="list-style-type: none"> • Annexin-A3 • Annexin-A5 • Serine/threonine kinase 17b • Histones 1 and 2 • Protein S (alpha) • Serum deprivation response (Phosphatidylserine binding protein) • Caspase 1 • Transforming growth factor-β1 • Death effector filament forming CED4-like apoptosis protein • Complement 3a receptor 1 • Early growth response 1 • Tumour necrosis factor-AIP3 • Tumour necrosis factor-RSF17 • Tumour necrosis factor-SF4
Immune dysfunction genes	<ul style="list-style-type: none"> • Decay accelerating factor (CD55) and CD46 • Antigen processing via MHC class II (MHC II DP α1 and DR α) • Interleukin-12, 13 and 6 biosynthesis

How is gene expression measured?

Gene expression is the way in which the information inherited from our parents (usually ‘recorded’ as a gene, a sequence of DNA) is translated into a product, such as a protein or an RNA molecule, that can be used by the body.

A key component of gene research is the use of microarray technology to analyse the genetic material of an individual. Researchers take a sample of blood or tissue and apply it to a silicone slide, called a microarray, which contains more than 20,000 gene identifiers. From this, they are able to determine which genes in the sample are being expressed — that is, turned on or off, or turned up or down.

If a particular gene is very active, it produces many molecules of messenger RNA which hybridise to the DNA on the microarray and generate a very bright fluorescent area (as seen in the picture below). Less active genes generate dimmer fluorescent spots, and inactive genes none. The gene expression profile generated provides a window into the disease process under examination. ●



Gene expression pattern on a microarray

A Royal Visitor

On 7th April 2009, ME Research UK was honoured with a visit from His Royal Highness The Prince Edward, who met the team and was introduced to the work of the Charity. His Royal Highness spent the morning at the headquarters of the Black Watch at Balhousie Castle in Perth, and was shown the chief's room dedicated to his grandmother, the late Queen Mother. He then toured the grounds in which stands had been prepared by local primary schools, and a display was put on by Black Watch cadets.

In the afternoon, His Royal Highness, accompanied by the Lord Lieutenant of Perth and Kinross, Brigadier Melville Stewart Jameson, attended a function in the recently completed Perth Concert Hall, and then came to visit the Gateway Centre, the base of Perth and Kinross Voluntary Services and home of ME Research UK.

A display of some of our research projects had been prepared, and Prince Edward was welcomed by Dr Vance Spence, Chairman of ME Research UK, who made the introductions to each member of our team, pictured below.



Dr Vance Spence welcomes Prince Edward

The Prince showed a keen interest in the range of biomedical projects funded by the charity, and the fact that we now provide funding to the Universities of Newcastle, Dundee, Strathclyde, Glasgow, Brussels and Calgary, and the London Medical Schools (St George's and Hammersmith).

Dr Spence explained that contrary to its popular perception as 'Yuppie Flu',

ME/CFS is a serious, often disabling, chronic illness, causing impaired mobility and disability in the majority of cases.

Despite this, comparatively little serious biomedical research has been conducted or is presently being undertaken anywhere in the world, making ME Research UK one of the very few international charities focusing on and funding biomedical aspects of the illness.

He continued that the ideal scenario is for a 'critical mass' of investigators to be producing the 'critical mass' of biomedical data necessary to set the field alight — a huge task, but one that ME Research UK is determined to pursue.

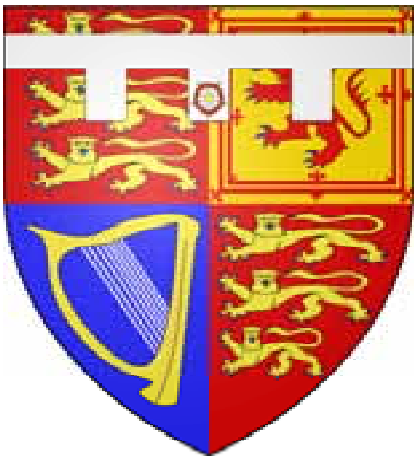
The visit ended with tea and cakes at the Gateway centre with elderly service users and invited guests.

As Dr Vance Spence said, "It was a delight to welcome His Royal Highness The Prince Edward, who each year visits every part of the United Kingdom at the request of Lord Lieutenants, charities and other organisations.

"His visits cover the whole spectrum of enterprise and initiative involving every aspect of life in the country each year, so it was marvellous to see the work of ME Research UK recognised in this way." ●



The team introduced to Prince Edward: Dr Neil Abbot, Sara Cornwallis, David MacDonald, Priscilla Wares & Dr Vance Spence



Prince Edward Earl of Wessex

Prince Edward, currently seventh in line to the throne, was born at Buckingham Palace in March 1964, the fourth child of Queen Elizabeth II and Prince Philip, Duke of Edinburgh. In 1999, on the day of his wedding to Sophie Rhys-Jones, he was created Earl of Wessex and Viscount Severn.

The Earl carries out a full schedule of royal duties on behalf of the Queen, and is President of the Commonwealth Games Federation and plays an active role in The Duke of Edinburgh's Award, the programme for young people set up by his father in the 1950s.

He also works on behalf of a number of charities and organisations, particularly those connected with the arts, sport and young people. ●



Our patrons

The Royal visit was the culmination of a decade of help and support from our patrons, The Countess of Mar and Roger Jefcoate CBE, who are pictured below.

Margaret of Mar, the 31st Countess of Mar and the 24th Lady Garioch, is a crossbench member and one of the 92 elected hereditary peers in the House of Lords, and holder of the original Earldom of Mar, the oldest peerage title in the United Kingdom. She has held many positions within the House of Lords, including Deputy Speaker from 1999 to 2007, and is an indefatigable campaigner against ignorance and injustice. She has a long-standing interest in ME/CFS and related illnesses, and is a stout advocate of the need for research and support.

Roger Jefcoate CBE, our founding Patron, was instrumental in the creation of ME Research UK in 2000. Roger gives nationwide help to severely disabled people who need adapted computers for educational needs or community work. He is also co-founder of the National

Association of Toy and Leisure Libraries, and Canine Partners, and founder of the AIDIS Trust, the Disability Aid Fund and the Mobility Trust. Roger is a Liveryman of the Drapers' Company, and in 1998 was made CBE for services to disabled people. ●



The Countess of Mar



Roger Jefcoate CBE

Recent research from around the world

BELGIUM

The unbearable lightness of somatisation

Do you think you are suffering pain or other physical symptoms, and are you seeking medical help for them? Well, you might be “somatising” — experiencing and communicating somatic (bodily) distress in response to psychosocial stress.

This claim will come as no surprise to many ME/CFS patients, who are used to being told that their “unexplained” symptoms might be psychological in origin. Now, however, a recent systematic review (*Pain* 2009) provides strong evidence that the concept of somatisation is scientifically flawed when applied to pain research.

The authors identified 116 research studies investigating the relationship between somatisation and pain in adults over the age of 18 years. In most cases, the frequency and/or intensity of somatic symptoms were measured using

standardised questionnaires administered during a structured interview. However, the review revealed serious problems in the measurement of somatisation in these studies.

Most did not investigate whether the reported pain was unaccounted for by pathological findings, whether the individuals attributed their pain to a physical cause, or whether they sought medical help for it. No study properly fulfilled the criteria for somatisation as described in the accepted definition, and current misuse of this concept in patients with pain “places an inappropriate focus on presumed patient psychopathology, and risks misdiagnosis and rupture in the physician-patient alliance”.

As the authors point out, their review provides evidence that the construct of somatisation, at least as it is applied in pain research, is scientifically imperfect — or perhaps we can use the term “light” since the title of the article is borrowed from Kundera’s famous novel (*The Unbearable Lightness of Being*) — and that its current operational use may unduly lead to a “psychologisation” of physical complaints.

Makes you wonder about its usefulness generally, doesn’t it?

HISTORY CORNER

Low blood flow at brainstem

Scientific interest in researching ME/CFS is low — you could say that the illness is the Cinderella of chronic conditions. For example, the number of clinical trials listed in the MEDLINE database over the past 10 years is only 204 for ME and CFS together, compared with 2,314 for the broad subject area rheumatoid arthritis, to choose just one other chronic illness. One consequence of the lack of scientific interest in ME/CFS is that whatever research is, in fact, done tends to be piecemeal and discontinuous, as an example from 1995 illustrates.

In that year, researchers from the Institute of Nuclear Medicine, UCL Medical School, London looked for brain blood flow abnormalities in ME/CFS patients (*Quarterly Journal of Medicine* 1995). After an initial pilot study revealed widespread reduction in regional brain perfusion in 24 patients compared with 24 normal volunteers ($p < 0.0001$), the unit tested whether perfusion to the brainstem itself was different in 43 ME/CFS patients with no psychiatric disorders compared with 40 healthy controls, 29 patients with major depression, and 10 with epilepsy.

Imaging was performed with single-photon emission tomography, and in this enlarged patient group a reduction in flow (hypoperfusion) to the brainstem was confirmed in all ME/CFS patients. Furthermore, the ME/CFS patients had significantly lower brainstem perfusion than depressed patients ($p < 0.0001$), and the authors pointed out, “There could be a relationship between hypoperfusion of the brain, particularly the brainstem, and direct neuronal damage by a viral agent.”

The finding could have real clinical significance but has never been reproduced with equivalent methodology. Indeed, in the 14 intervening years only one other scientific





paper (*American Journal of Medicine* 1998) has reported imaging of the brainstem, and in that investigation, which used PET scanning, an anomaly was also found: a significant hypometabolism in the brainstem.

NEW YORK

Brain lactate

A sensitive biomarker is the holy grail of scientific discovery for all diseases, and no more so than in ME/CFS which many see as a diagnostic black box that needs unpacking. Could brain lactate concentration serve as a potential diagnostic marker? To examine this, doctors at Cornell University in New York examined brain lateral ventricular volumes from MRI scans, and cerebrospinal fluid lactate concentrations in 16 people with ME/CFS, 14 with generalised anxiety disorder and 15 healthy volunteers matched for age, sex, body mass index, handedness and IQ (*NMR in Biomedicine* 2008).

While ventricular volumes were not different between the groups, the average lateral ventricular lactate concentrations were increased almost three-fold in the ME/CFS patients compared with generalised anxiety patients, and 3.5-fold compared with healthy volunteers (both $p < 0.001$), even after controlling for ventricular volume.

What can be causing this novel and unusual finding? Well, the authors says that their observations are consistent with an emerging theory that implicates oxidative stress and its effects on cortical blood flow and/or mitochondrial function, citing ME Research UK-funded research that showed increased levels of isoprostanes (indicators of oxidative stress) in ME/CFS patients. The theory goes that oxidative stress vasoconstricts the vasculature, decreasing cerebral blood flow and increasing brain lactate, the end product of glycolysis.

UK

Fatigue in different diseases

“Fatigue” is a disabling consequence of a wide range of chronic diseases; indeed, it was a main symptom of past outbreaks of ME, including the Royal Free Hospital outbreak in 1955, and its occurrence in conjunction with a constellation of symptoms forms the basis of present-day ME/CFS. But is the nature of fatigue different in different illnesses?

Prof. David Jones and colleagues at the University of Newcastle explored this issue by examining data from 600 people across five chronically ill disease groups (*Quarterly Journal of Medicine* 2009). The diseases studied were non-alcoholic fatty

liver disease, vasovagal syncope, primary sclerosing cholangitis, primary biliary cirrhosis and ME/CFS (using patients recruited during an ME Research UK-funded project). Each patient had completed a generic Fatigue Impact Scale (FIS) from which scores on 3 subscales (physical, cognitive and psychosocial) were derived.

The overall conclusion was that the nature of patient-reported fatigue was similar between all 5 patient groups, suggesting that symptoms such as fatigue arise due to generic disease processes shared by chronic illnesses. However, as regards severity, the 82 ME/CFS patients had much higher levels of total fatigue than any of the other patient groups (total FIS score of 102, compared with the primary biliary cirrhosis group which was next highest at 41). This was reflected in higher subscale scores, since, as the researchers point out, the larger the direct impact of physical limitation, the greater are the subsequent knock-on effects on other aspects of higher cognitive and social functioning.

CALIFORNIA

Low-dose naltrexone

Naltrexone hydrochloride has been used clinically for many years to treat opioid addiction. Recently, there have been suggestions that naltrexone at 3 to 4.5 mg per day (low-dose naltrexone, LDN) might be beneficial for chronic pain and autoimmune disorders, and open-label pilot trials of LDN for Crohn’s disease and multiple sclerosis have been conducted. A recent paper (*Pain Medicine* 2009) reports its use for fibromyalgia, a chronic pain disorder with a diagnostic overlap with ME/CFS.

Ten women with fibromyalgia received a placebo for 2 weeks followed by LDN 4.5 mg for 8 weeks, and then a two-week “washout” period. They completed reports of symptom severity every day, and also visited the lab every two weeks for tests of mechanical, heat and cold pain sensitivity.

Overall, LDN seemed to have a beneficial effect: key symptoms of fibromyalgia were reduced by 32.5% with



LDN compared with 2.3% for placebo ($p=0.003$). Not all patients responded, and only six out of ten showed more than a 30% decrease in symptoms. However, women with evidence of general inflammatory processes had the greatest reduction in symptoms.

While it's impossible to conclude much from a small pilot study in which only some of the patients responded to the drug, the findings are certainly intriguing. And the proposed mechanism of action (reduction of inflammation by suppressing central nervous system microglia cells) suggests that a clinical trial of LDN for ME/CFS patients might be worthwhile, given that there is evidence of an ongoing inflammatory process in some patients.

MINNESOTA

Lessons in herding zebras

Proper diagnosis is a key issue in ME/CFS. In the absence of a full clinical assessment (which most patients have either never undergone, or last had many years ago), the diagnosis of ME/CFS can easily become a terminal stop for clinically complex patients with a variety of different illnesses.

Two examples illustrate the problems that can arise if investigations to exclude other conditions are not performed

before the ME/CFS “diagnosis of exclusion” is given to the patient.

The first is an audit of 100 outpatients with CFS in the University of Dundee in 1993: of these, 21% were found to have other organic illnesses (e.g., muscle, connective tissue or endocrine disorders), 12% had a psychiatric disorder alone, and 7% had fibromyalgia. The second example is an audit of service in 2007 after three years at the CFS/ME CNCC in Newcastle, England: CFS was confirmed in 56% of referrals, but alternative diagnoses were provided in 28%, sleep apnoea was diagnosed in 9%, and depression and anxiety in 7%. This shows that in around 40% of patients referred in the UK from primary care with a diagnosis of ME/CFS, alternative exclusionary diagnoses can be found after investigation at a specialist clinic.

A fascinating commentary in a recent issue of *Minnesota Medicine* (November 2008) describes the difficulties experienced at a clinic seeing patients with fatigue, exercise intolerance and weakness (i.e., patients very like those with ME/CFS in the UK). The authors report three recent cases, all adolescent patients experiencing fatigue and weakness, to illustrate how patients with common symptoms can end up with very different, sometimes unusual, diagnoses.

In the first case, an almost housebound 15-year-old girl with fatigue for 18 months following fever was eventually diagnosed with postural orthostatic tachycardia syndrome, which

the authors say probably accounts for most cases of chronic fatigue during adolescence.

The second case was a 14-year-old boy with exercise intolerance who was at times overwhelmed by weakness, palpitations and headaches. After full investigation, a renal ultrasound revealed masses near the kidneys, and the child has done well after surgical excision of these pheochromocytomas.

In the final case, a 14-year-old boy presented with a three-month history of fatigue, weakness and weight loss, which finally resulted in a diagnosis of previously undiagnosed dermatomyositis and secondary bronchiolitis obliterans organising pneumonia, with the comment from the authors that “*a thoughtful and thorough physical exam can sometimes reveal otherwise hidden diagnoses*”.

In their conclusion, the authors say, “*Sometimes in our clinic, we feel as if we’re wandering through a herd of zebras... Not all the ‘stripes’ on the animals are the same, and not every animal in the herd is actually a zebra... Navigating through clinical complexities is difficult, and we’re still learning how to best diagnose and manage our patients.*” Commentaries like this do raise the question of which alternative treatable diagnoses might be uncovered if all patients currently parked in the ME/CFS diagnostic terminal were examined intensively at a specialist Centre of Excellence by thoughtful and thorough physicians.

NORWAY

B-cell depletion therapy?

In 2004 and 2005, doctors in Bergen noticed that a patient who had been ill for seven years with ME/CFS had an unexpected, marked recovery from symptoms during and after cytotoxic chemotherapy for Hodgkin’s disease. They reasoned that the transient recovery was related to methotrexate treatment, which affected the immune system, partly through depletion of B-cells (which produce proinflammatory cytokines and are regulators of other effector cells in the immune system). Could other people with ME/CFS also

benefit? In a case series published in *BMC Neurology* (2009), the researchers describe the case above and two others in which ME/CFS patients were B-cell depleted by infusion of the monoclonal anti-CD20 antibody rituximab.

All three patients had improvement of symptoms: two had major amelioration from six weeks after treatment, while the third improved markedly from 26 weeks. The symptomatic effect lasted for 16 to 44 weeks. After relapsing, all patients were re-treated with rituximab, and again had marked symptom improvement mimicking their first response, and a further cycle of treatment followed.

What are we to make of these findings? Well, one swallow doesn't make a summer, nor one case series a cure. However, the researchers are presently conducting a phase II/III randomised trial in Norway to investigate further the safety and efficacy of this apparent therapeutic strategy, on the hypothesis that at least a subset of CFS patients have an activated immune system involving B-lymphocytes, and that B-cell depletion may alleviate symptoms. We await further developments.

SALT LAKE CITY

Exercise affects gene expression

Across the world, there are at least five different teams of scientists, from Japan to the USA, investigating the role of genes in ME/CFS. While most of these research groups are using gene expression microarrays to explore the genetic causes of the illness (see page 6), one team at the University of Utah has followed a different strategy by employing gene expression to determine useful biomarkers (*Journal of Pain* 2009). They have focused on genes that might contribute to fatigue, and on two of the most common additional symptoms, muscle pain and long-lasting post-exertional worsening of symptoms.

Using real-time, quantitative PCR, the researchers showed that expression of white blood cell β -2 adrenergic receptors was lower in 19 ME/CFS patients than in 16 healthy subjects, but that otherwise there were no differences between the

two groups before exercise. However, after 25 minutes of moderate exercise, patients showed greater increases ($p < 0.05$) in gene expression for muscle-produced metabolites (ASIC3, P2X4, P2X5), for genes that are essential for sympathetic nervous system processes (adrenergic α -2A, β -1, β -2 and COMT), and for immune function genes (IL10 and TLR4). These increases were highly correlated with symptoms of physical fatigue, mental fatigue and pain.

Given that healthy control subjects did not show any significant increases, it is possible that post-exercise alterations in the expression of genes extracted from circulating patients' white blood cells might become important diagnostically. Around 90% of ME/CFS patients could be distinguished from healthy controls using just four of the genes, suggesting that a blood test could be devised as an objective biomarker for sensory muscle fatigue and muscle pain.

HAWAII

Anticardiolipin antibodies

In 2008, a Japanese group at the University of Hawaii at Mānoa, Honolulu

noticed the presence of the phospholipid cardiolipin in blood samples from a small number of patients with ME/CFS, suggesting that "acute phase lipids" may be part of the disease process in the illness. The latest scientific report from this group (*Journal of Clinical Laboratory Analysis* 2009) extends the investigation to 40 blood samples obtained from patients' physicians from various regions of the United States.

Using an enzyme-linked immunoassay for anticardiolipin antibodies (ACAs), the immunoglobulin M isotype of ACA was found to be present in 38 out of the 40 (95%) samples tested. Apparently, this is a higher proportion of positive tests than might be observed in the healthy general population (approximately 16%), and points to an autoimmune basis for the illness that could potentially be treated by suppression of the ACA or by diminishing the antigen cardiolipin in serum.

In Honolulu, further experiments are underway to elucidate why anticardiolipin antibodies at relatively high titres — which are suggestive of alterations to the inner membranes of liver mitochondria — are produced in people with ME/CFS, and these studies will include investigations of the effects of specific chemical agents, marine toxins and anticardiolipin antibodies on mitochondrial metabolic pathways.



Friends of ME Research UK

Ongoing event



£1 million campaign needs YOU

ME Awareness Day 2009 saw the launch of a £1 million appeal to raise funds for much-needed biomedical research into ME/CFS. This appeal will run for one year — yes, a whole calendar year! — until May 2010.

Specially designed for the recession, the campaign invites people with ME and their friends and family to join in a year of cleverly saving money so that they can donate a bit of their saving to research. And its name is “Just Four Quid”, to reflect how achievable the £1,000,000 target is — if each of the estimated 250,000 people in the UK with ME/CFS donated £4, the target would be achieved!

The idea is simple. Each week, the “Just Four Quid” dedicated daily blog reports on totals raised already, and suggests a new tip for saving cash. If, for example, that tip saves you £10, you might consider making a £5 donation. By the end of the year, you will be better off AND you will have donated to the campaign. The key idea is that lots of people donating little and often will add up to a huge amount over the year.

People can donate to either or both of the charities taking part: ME Research UK, and the Ramsay Research Fund of the MEA. And all of the donation goes

directly to the charity chosen — Just Four Quid receives none of the money raised.

If you're not already involved, you can start straight away. Visit the Just Four Quid website (justfourquid.com) to get the latest fundraising tip, and if you think it can save you money give a little back to us. And why not tell other people about the campaign so they can join in too? After all, 250,000 donations of £4 equals that elusive £1 million!

Recent events

Rhiannon in free-fall

Rhiannon Jones, who was 60 earlier this year, wanted to celebrate her birthday by doing a sponsored skydive to raise funds for our charity. After several cancellations due to bad weather, she finally made her dream come true on 31st May when she went WHOOSH and jumped from the plane.

The photo below shows Rhiannon at the moment of free-fall, and thrilling video footage of the dive — talk about hair-raising! — can also be seen at her Justgiving page.

As Rhiannon says, “I was overwhelmed that so many people visited my Justgiving page and that over £1,500 has been raised. To everyone, your kindness and generosity are greatly appreciated!”

Congratulations and thank you, Rhiannon, from all of us at ME Research UK on your tremendous achievement.



Spotlight of the Gods

There's an old Iban proverb from Borneo that says that "a person without tattoos is invisible to the Gods". Well, Cath Roberts must really be in the heavenly spotlight — as her awareness and fundraising event of 2009 was to have a tattoo!

As an ME sufferer for over 11 years, Cath knows the devastating effect it has on lives and families. And her aim was to have a tasteful, feminine and floral tattoo design that incorporated the ME "blue ribbon" — blue swirls to represent the ribbon, with three pink flowers.

The venue for tattoo D-day was the Chameleon Tattoo Studio in Lancaster (which donated to Cath's campaign), and the photo, courtesy of the Lancaster Guardian, shows Cath, her daughter Jennie Keighley and tattooist Mark Goulding from the Studio looking very pleased with their efforts, as well they should.

As Cath explains, "The ankle is healed up now and I'm none the worse, luckily! I'm so glad I did this as £440 has been raised for the cause."



Rotary Shakespeare Half Marathon

A fearless mother–daughter duo, Mary and Shonagh Hill (pictured on the right in their ME Research UK t-shirts) did a marvellous thing by running in the Rotary Shakespeare Half Marathon to raise money for both the 25% ME Group and ME Research UK.

They undertook the daunting task of the half-marathon, a full 13.1 miles, because family member Sarah (Mary's daughter) has had chronic ME for 19 years, and during that period little money has been invested into biomedical research into the illness.

Mary crossed the finishing line in a lightning 02:27:48 while Shonagh was one second slower at 02:27:49 (we think they synchronised their times, don't you?).

Thanks to both Mary and Shonagh, and their supporters, around £1,800 will have been raised, from which both charities will benefit. A great achievement and a wonderful day! At the AGM of the Shrewsbury ME Group meeting in May 2009, Mary formally presented the cheque to our Chairman Dr Vance

Spence who had travelled down to give a talk on the science of ME/CFS.



Sandie's Great Manchester Run

Sandie Fisher achieved a personal best of 68.37 minutes when she completed the Great Manchester Run earlier this year, and smashed her fundraising target in the process, raising almost £2,000 with more still coming in through her Justgiving page. As she says, "It's amazing, really. What can I say? Everyone has been so generous."

The photo below shows Sandie with her sister Laura (right) who is 24 and has suffered from ME for over four years, with an enormous impact on her life. Sandie's aim is to have Laura running the 10k with her as soon as she's well, which we all hope is just around the corner!





Standing Order Form

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

ME Research UK 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:

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

Tel: 01738 451234
Email: meruk@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 ME
Research UK, a/c no. 50419466

Bank reference number:

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 PHI 5PQ, UK
Account: ME Research UK, Account no: 50419466, Branch code: 82-67-09

If you are a UK taxpayer, under the Government's Gift Aid scheme ME Research UK can reclaim the tax you have already paid on your gift. This means that your donation can increase by nearly a third at no extra cost to you. It doesn't matter what tax rate 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 indicate below if you would like ME Research UK to reclaim the tax on your gift.

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

Signature _____ Date _____

Thank you for your support