

breakthrough

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of the autonomic
nervous system



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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



Despite 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. Published research has demonstrated that the quality of life of patients can be seriously disrupted — more impaired than in MS, according to one Australian report — and the social consequences, as regards schooling, employment, relationships, financial security, future plans and personal worth can be severe; one estimate puts the cost of ME/CFS in terms of treatments, lost taxes and benefit payments at £3.4 billion per year in the UK.

In 2002, a report to the Chief Medical Officer of England said that ME/CFS was '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.' Unfortunately, seven years on from the CMO's report, little has changed for patients on the ground; the condition continues to be shrouded in mystery and metaphor, and remains invisible to all except the immediate family, largely unnoticed by health care professionals.

Most importantly, the illness is also ignored by the biomedical research community. Despite the seriousness and extent of the condition, comparatively little serious biomedical research has been conducted or is presently being undertaken anywhere in the world.

Given the extent of the problem — the recent NICE guideline gives a mean prevalence of 193,000 people with ME/CFS in the UK alone — this situation is bizarre, not to say tragic, particularly as some studies have already uncovered biological anomalies that might well help to explain many of the clinical features associated with the illness and indicate areas for therapeutic intervention (the findings of increased oxidative stress and neutrophil apoptosis at the University of Dundee, and dysfunction of the autonomic nervous system at the University of Newcastle are two examples).

Something that concerns me is the problem that exists at a funding level. Biomedical research is expensive: one medium-sized clinical trial can cost £300,000, while a major programme of research can last 5 years and cost £1 to 2 million. The ideal scenario would be for central (e.g., MRC and NHS R&D) funding of biomedical research to be provided through ring-fencing, making it easier to entice good established biomedical researchers into the field — so that a 'critical mass' of investigators could be encouraged to produce the 'critical mass' of biomedical data necessary to set the field alight. But this alone is not the answer. Experience has convinced me that the funding strategy for ME/CFS must mirror that of other illnesses which obtain most of their research revenue from private sources and ground-level fundraising. It is a huge task, but one that ME Research UK is determined to pursue.

Dr Vance Spence
Chairman of ME Research UK



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Autonomic nervous system dysfunction: a new 2-year investigation

The autonomic nervous system controls cardiovascular, digestive and respiratory functions, and has a range of other important roles. When it goes wrong, the consequences can be severe. One of the key difficulties faced by ME/CFS patients is standing, especially standing still without experiencing symptoms such as dizziness, altered vision, nausea, fatigue, etc. The possibility therefore exists that there could be a problem with the autonomic nervous system in the condition.

Professor Julia Newton (pictured below, between nurses Katharine Wilton and Jessie Pairman) of the School of Clinical Medical Sciences, University of Newcastle, received a grant from ME Research UK and the regional Clinical Service in 2007 to examine a large group of patients using a battery of tests of heart rate and blood pressure. The Cardiovascular Laboratory in which the tests were done is one of the largest autonomic testing labs in Europe, with all the necessary equipment and expertise for comprehensive autonomic testing.

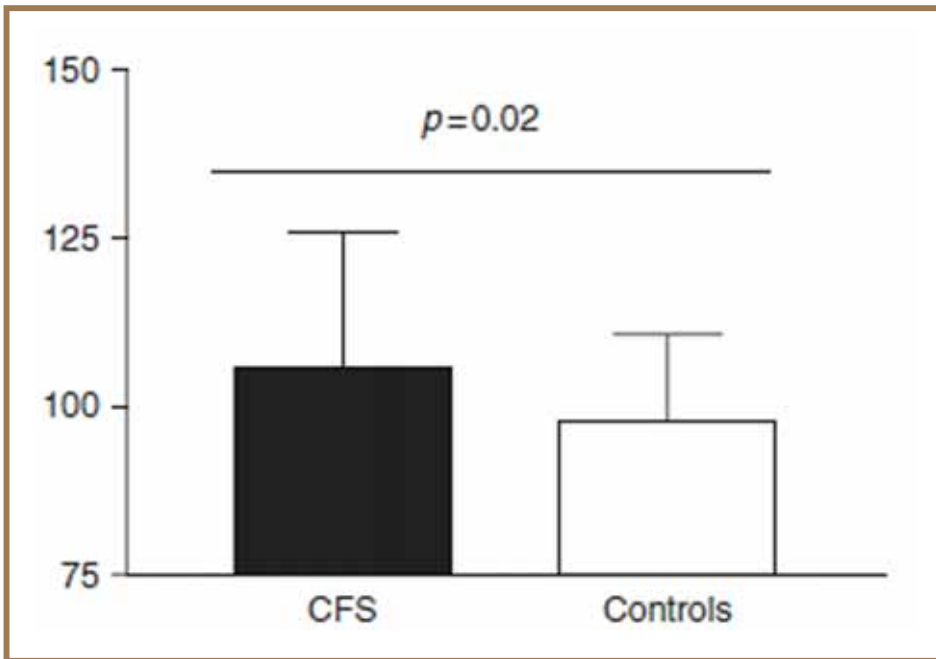
Professor Newton's results — published in the *Quarterly Journal of Medicine* (August 2007) — showed that autonomic dysfunction was present in three-quarters of the patients studied, a very unexpected finding. Furthermore, in a separate study (see the opposite page), she has reported that a simple-to-measure assessment of the heart rate response to standing was abnormal in a significant proportion of patients.

ME Research UK, the John Richardson Research Group and the Irish ME Trust have provided funding for the next phase of the work: a two-year project exploring some of the mechanisms behind these autonomic problems in ME/CFS patients. The investigation has two broad aims. The first is to examine fully those individuals attending the Newcastle CFS/ME Clinical Service, and develop a database of patients who can be followed up over the long-term.

The second aim is to begin to answer the following question: 'Does the autonomic dysfunction in people with ME/CFS arise in association with abnormalities of the brain, muscle and liver, as has already been shown in patients with other illnesses?'

For this investigation, a series of linked studies will examine muscle bioenergetics, and structural and functional abnormalities of the brain and liver. These investigations will use state-of-the-art magnetic resonance techniques, including assessment of liver fibrosis and percentage fat. ●





Graph of maximum heart rate (in beats per minute) after standing, showing the difference between ME/CFS patients and matched controls

Previous studies: what did the results show?

The most recent scientific paper (Quarterly Journal of Medicine, December 2008) from Professor Newton's group at the University of Newcastle described the prevalence of one simple-to-measure aspect of autonomic dysfunction, namely postural orthostatic tachycardia syndrome (POTS), in a group of patients recruited via the specialist CFS/ME service in Newcastle.

POTS is defined as symptoms of orthostatic intolerance associated with an increase in heart rate on moving from lying to standing.

Importantly, the major finding was that significant POTS could be measured in a high proportion (27%) of the patients but in only 9% of healthy control subjects. Moreover, the POTS observed in the ME/CFS group was characterised mainly by an increase in heart rate to more than 120 beats per minute on standing (see

the graph above). This increase in heart rate was significantly associated with increasing fatigue.

The central finding is important: POTS is a frequent finding in patients attending the clinic, suggesting that the clinical evaluation of patients presenting with ME/CFS should include heart rate responses to standing, an obvious and easily measurable clinical sign.

It remains unclear, however, whether the observed POTS should be viewed as a clinical entity distinct from ME/CFS, or whether patients with POTS represent a particular subset of ME/CFS patients with the most marked symptoms.

Whatever the case, the authors remark that the diagnosis of POTS (a potentially treatable condition) may currently be missed in ME/CFS patients attending clinical services. And they suggest that, at the very least, a haemodynamic assessment of the response to standing should be included in the clinical assessment of patients attending ME/CFS clinical services.

POTS is the most common form of orthostatic intolerance without orthostatic hypotension, and can produce substantial disability among otherwise healthy people. One large series of

patients with POTS reported the symptom burden to be significant and to include weakness, and muscle aches and pains. Its findings also suggested a neuropathic basis for at least half the cases of POTS, and an autoimmune component for a substantial percentage of cases.

Other studies have shown POTS to be accompanied by a range of autonomic nervous system abnormalities, including vagal withdrawal and enhanced sympathetic modulation, and that it can be associated with findings consistent with pooling in the lower limbs, similar to pathophysiological mechanisms occurring in a proportion of people diagnosed with ME/CFS.

Given these associations, it is important that POTS be recognised and managed, whether in ME/CFS or in other groups of patients. Professor Newton's findings suggest that current treatment regimes (which can include a range of pharmacological and non-pharmacological strategies) for the management of orthostatic hypotension and POTS should be incorporated into ME/CFS management programs.

The NICE Clinical Guideline: convincing evidence?

For the Judicial Review of the NICE Guideline on CFS/ME on the 11th and 12th of February 2009, at the High Court in London, Dr Neil Abbot provided an Expert Witness statement on the evidence base underpinning the main 'treatment' recommendations. In this article, he summarises his conclusions, mainly with reference to cognitive behavioural therapy (CBT), though many points also apply to graded exercise therapy (GET).

The National Institute for Clinical Excellence (NICE) is rightly respected for basing its treatment recommendations on evidence. In the case of the illness ME/CFS, its principal recommendations were cognitive-behavioural approaches for the specialist management of the illness because 'currently these are the interventions for which there is the clearest research evidence of benefit'.

However, cognitive-behavioural approaches are widely recognised,

including by the NICE Guideline itself (section 6.3.8, page 252), to be non-curative for ME/CFS; and in other physical illnesses these approaches are used as adjuncts to but not substitutes for mainstream treatment. So, what was the evidence base for the central role of these approaches in the clinical management of the illness?

The table opposite shows that the evidence base for these cognitive-behavioural approaches consists of a small group of randomised controlled trials on adults (ten trials in all; seven with mild-to-moderately positive results and three with negative results). Focusing in on CBT (a form of psychotherapy used to treat a variety of psychological impairments), the first thing to note is that two out of five trials have a negative overall result (Whitehead, 2002; Lloyd, 1993). The remaining three trials have overall positive effects, and moreover have high 'validity scores', indicating that they are likely to have been well-designed and conducted. Nevertheless, the 'gold

standard' evidence-base consisted of three mild-to-moderately positive randomised controlled trials only. It is instructive to compare this with the evidence base available for NICE Guideline 8 on multiple sclerosis, with many hundreds of trials.

Other key points to note are the following:

Patient numbers

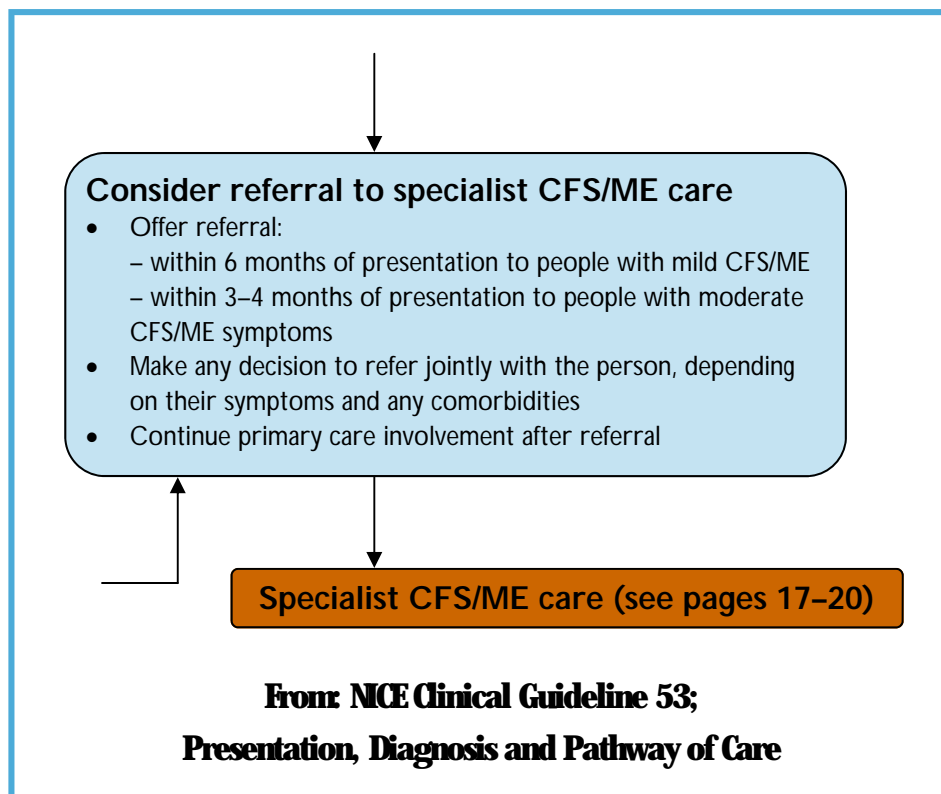
The trials of CBT have relatively small numbers of patients; in four of the trials, analysis was performed on no more than 30 patients in the CBT groups, while the largest trial (Prins, 2001) analysed 92 patients in the CBT arm. Since only two of the trials (Deale, 1997; Prins, 2001) reported making a power calculation to determine the adequacy of sample size to determine a treatment effect, it is entirely possible that some samples were too small to determine a true effect.

Different kinds and duration of treatment

There is a difference between trials in the type and content of CBT delivered, as well as in the number, frequency and length of intervention sessions given. This makes it impossible to say that like was being compared with like as far as type and delivery of 'treatment' was concerned.

Diagnostic definitions

Case definitions of CFS differ, raising the question of whether homogeneous groups of patients are being compared between trials. Two of the positive trials recruited patients using the Oxford criteria (1991) which focuses on unexplained chronic fatigue and does not require additional symptoms. Given that the NICE Guideline itself recommends that post-exertional malaise and other symptoms such as cognitive difficulties,



sleep disturbance and chronic pain be present for a diagnosis to be made, it is entirely possible that new patients diagnosed by their GPs using NICE guidance constitute a different — most probably more sick — clinical group than those who took part in the original trials.

Comparison groups differ

As each trial employed a different comparison group (placebo injection, relaxation, standard medical care, guided support/natural course and no intervention), it is impossible to say that the CBT delivered was having a 'specific' treatment effect. For example, some people (including the authors of the Canadian Consensus document of 2003) wonder whether a program of formal CBT or GET adds anything to what is available in the ordinary medical setting under a good and concerned medical practitioner.

Long term effects

In four out of five trials, follow-up was relatively short, and so the relevance of the findings over the longer term remains unknown. This is particularly important in an illness which is a long-term condition, and tends to be chronic with serious debility in some; a moderate treatment effect in the short term might not show treatment-specific gains in the longer term. For example, the one trial (Deale, 1997) in which five-year follow-up results were reported revealed no significant difference in physical functioning and fatigue between CBT and a relaxation control group after five years, though other parameters were improved.

Serious commentators might consider that the conclusions about efficacy one could draw from this small group of trials are suggestive and tentative only. A recent Cochrane review (Price, 2008) found fifteen studies of CBT (including

controlled clinical trials) for CFS/ME, and took a far more measured, cautious view of the evidence and its limitations than the authors of the NICE Guideline, as did a second recent review (Malouff, 2008).

The practical consequences of NICE's recommendations can be seen in the 'Quick reference guide' to the NICE Guideline, which (unfortunately) is the only part read by most healthcare professionals and GPs. On page 6, the Pathway of Care ends at a category called 'Specialist CFS/ME care' (see figure opposite), inside which CBT and/or GET are the principal 'treatments' alongside activity management.

Whatever the merits of these therapies in themselves for psychological illnesses, can it be reasonable for them to be enshrined in established national guidelines which feed into clinical care and government policy — at a potential cost to the country of £45.2 million over a five-year period — on the evidence available? ●

Summary of randomised controlled trials in adults

(source: Appendix 1, NICE Guideline; and Bagnall et al, 2007)

Author and year	Case definition	Treatment	Patient numbers	Comparison group	Overall effect of "treatment"
Lloyd, 1993	Australian	CBT (+ DLE injection)	90	Placebo injection only	None
Deale, 1997 & 2001	Oxford	CBT	60	"Relaxation"	Positive
Sharpe, 1996	Oxford	CBT	60	Standard medical care	Positive
Prins, 2001	CDC, 1994	CBT	270	"Guided support" and "natural course"	Positive
Whitehead, 2002	CDC, 1994	CBT by GP	65	"No intervention" control	None
Wearden, 1998	Oxford	GET & fluoxetine	136 (4 groups)	Review of activity diaries/placebo capsule	None
Fulcher, 1997	Oxford	GET	66	Flexibility exercises and relaxation therapy	Positive
Powell, 2001 & 2004	Oxford	GET	148 (4 groups)	Standardised medical care	Positive
Moss Morris, 2005	CDC, 1994	GET	49	Standard medical care	Positive
Wallman, 2004	CDC, 1994	GET	61	Relaxation/flexibility therapy	Positive

Working towards a breakthrough



Dr Gwen Kennedy



Dr Jo Nijs



Prof. Julia Newton



Dr Faisal Khan

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

We fund the work of a growing number of scientists in the UK and worldwide, whose research covers several different areas of interest. Our priority is to support innovative clinical and biomedical studies, based in established research institutions with a successful scientific track record.

All grants are competitive, subject to peer review, and rigorously assessed before award and after completion.

To date, we have invested over half a million pounds to support biomedical research, and are particularly grateful to some of the ME organisations which have provided larger donations to help us fund specific projects, some of which are shown below. Full details of these and other projects, including the resulting scientific papers, can be found on our website: www.mereseearch.org.uk.

Evaluation of pain and therapeutic interventions

Dr Lorna Paul, School of Health and Social Care, Glasgow Caledonian University

Autonomic nervous system dysfunction — a clinical study

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

The effect of exercise on the immune and sensory systems

Dr Jo Nijs, Dept of Human Physiology, Vrije Universiteit Brussel, Brussels, Belgium

Non-invasive neuroimaging of the brain

Prof. BK Puri, MRC Clinical Sciences Centre, Imperial College London
(with ME Solutions and the MRC Clinical Sciences Centre, Imperial College)

Plasma vitamin D status in ME/CFS

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

Interleukin-6 and its receptors

Prof. Myra Nimmo, Dept of Applied Physiology, University of Strathclyde, Glasgow

Biochemical and blood flow aspects of ME/CFS in children

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

Gene expression studies

Dr Jonathan Kerr, St George's Hospital, University of London
(with co-funding from the Irish ME Trust)

Exercise tolerance and post-exertional symptoms

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

Chronic inflammation and apoptosis

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

Characterisation of differential gene expression

Prof. J Gow, University Department of Neurology, Glasgow

Elucidating novel mechanisms of fatigue in ME/CFS

Dr P Ansley, Northumbria University, Newcastle upon Tyne

The funding challenge

Money is the platform which supports all biomedical research. But it is expensive: one clinical trial can cost half a million pounds, while a major program of research can last for years and cost 2 million pounds or more. So, unravelling the causes and finding cures for ME/CFS will require big money over a long time.

When people think of medical research funding in developed countries they think of 'Class 1' funders, such as the MRC in Britain or the NIH in the United States. But the money available from these central sources does not go far given the many demands, and even if ME/CFS got its 'fair share' of Class 1 funding, that share would fund only a small part of the biomedical activity that is necessary.

In fact, a significant proportion of research funding for many, if not all, illnesses comes from charitable sources: the Association of Medical Research Charities estimates that some £791 million was spent on projects in 2006/7 by its members. And the annual income of Cancer Research UK alone in the same period was £468 million — an instructive comparison figure for ME Research UK's grant spend of half a million pounds in its entire lifetime.

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

Some recent publications from funded projects

Physiological cost of walking in those with CFS. *Disability and Rehabilitation* 2009; in press

Postural orthostatic tachycardia syndrome is an under-recognized condition in CFS. *Quarterly Journal of Medicine* 2008; 101(12): 961–5

Low grade inflammation and arterial wave reflection in patients with CFS. *Clinical Science* 2008; 114: 561–6

Symptoms of autonomic dysfunction in CFS. *Quarterly Journal of Medicine* 2007; 100: 519–26

Is CFS a hypercoagulable state associated with platelet activation? *Blood Coagulation and Fibrinolysis* 2006; 17: 89–92

Chronic fatigue syndrome. *Lancet* 2006; 367: 1574–5

Oxidative stress levels are raised in CFS and are associated with clinical symptoms. *Free Radical Biology and Medicine* 2005; 39: 584–9

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

Acetylcholine mediated vasodilatation in the microcirculation of patients with CFS. *Prostaglandins, Leukotrienes and Essential Fatty Acids* 2004; 70: 403–7

Increased neutrophil apoptosis in CFS. *Journal of Clinical Pathology* 2004; 57: 891–3

Plasma endothelin-1 levels in CFS. *Rheumatology* 2004; 43: 252–3

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

Neurophysiologic analysis of neuromuscular symptoms in UK GW veterans. *Neurology* 2003; 61: 1827

Prolonged acetylcholine-induced vasodilatation in the peripheral microcirculation of patients with CFS. *Clinical Physiology and Functional Imaging* 2003; 23: 282–5

Recent research from around the world

USA

Vitamin D deficiency and chronic pain

We get vitamin D from our food (particularly fatty fish), and from sunlight which stimulates its production in the skin. But due to reduced dietary intake and exposure to sunlight, vitamin D deficiency seems to be becoming more common in the general population, and might be involved in a number of chronic illnesses, including autoimmune and infectious diseases, cancer, and cardiovascular disease.

It may also be important in ME/CFS, since this illness is thought to involve immune, infectious and cardiovascular aspects, and ME Research UK-funded work is currently underway to investigate whether there is a link between vitamin D and vascular function in the illness. Meanwhile, the prevalence of vitamin D deficiency in patients with chronic pain (a key symptom reported by a majority of people with ME/CFS in surveys) was the subject of a recently published paper (Pain Medicine, 2008) from the USA.

The investigators measured vitamin D levels in 267 patients admitted to a pain rehabilitation centre for chronic musculoskeletal pain (ME/CFS was not specifically mentioned as a diagnosis, but 66 participants were reported to have fibromyalgia). Over a quarter of patients were determined to have vitamin D deficiency, and these individuals tended to have worse symptoms, poorer health and to have taken pain relief for longer than those with normal vitamin D levels.

Interestingly, in people using opioid medication, those with low vitamin D were using almost twice the morphine-equivalent doses of pain killers than patients with adequate blood vitamin D levels. These results implicate vitamin D deficiency as a potential factor in chronic musculoskeletal pain, but it remains to be

seen whether it is an important factor in the pain profile of ME/CFS, or indeed whether pain itself can be reduced by vitamin D supplementation.

UK

Bayesian biomarkers

Bayesian biomarkers? Markov Chain Monte Carlo computation? The world of genetic research is full of these seemingly impenetrable terms and phrases, but dive beneath the jargon and there are some fascinating findings that may one day aid the diagnosis and treatment of ME/CFS.

Biomarkers, of course, are one of the holy grails of research: biological measurements of various kinds that can be used to distinguish individuals with diseases from those without. Genetics is a fertile area for the discovery of biomarkers, and a team in Scotland (Genomics 2008) recently set out to identify markers specific to fatigue that may also be exclusive to ME/CFS.

They looked at genetic mutations known as single nucleotide

polymorphisms (SNPs) in patients with Fukuda-defined CFS, as well as in individuals classed as having insufficient symptoms of fatigue and those who were non-fatigued.

As in most clinical research, statistical methods were necessary to determine whether there were any differences between these subject groups. Bayesian modelling is a type of statistical analysis which is often considered to be particularly suitable for this type of work because it takes into account prior knowledge and uncertainties about this kind of complex information.

The investigators managed to identify a number of SNPs which occurred at varying frequencies in the different subject groups. But perhaps most significantly, some of these SNPs were associated with the angiotensin-converting enzyme (ACE) gene. ACE is involved in the cardiovascular system in which abnormalities have been identified in ME/CFS, and ACE polymorphisms have been found previously in Gulf War veterans with CFS.

The methodology may be impenetrable, but if it helps to unearth another piece of a complex jigsaw, so much the better.





SPAIN & UK

Mitochondrial malfunction?

The mitochondria are small organelles (or subunits) found in most animal and plant cells. They are often described as the power plants of the cell because their main job is to generate chemical energy, although they also have other roles in signalling and cell growth.

Mitochondrial dysfunction seems to be implicated in a number of diseases, including mental disorders and heart problems, as well as being involved in the ageing process. Since ME/CFS is characterised by a profound, generalised post-exertional loss of muscle power, it seems reasonable to suggest that mitochondrial dysfunction may be involved. Indeed, over the years, there have been diverse smaller investigations exploring this aspect, ranging from the first study by Byrne et al (1985) to the following two recent investigations.

A Spanish study (Dolor, 2008) explored mitochondrial function in 15 patients, from the CIMA clinic in Barcelona, diagnosed with idiopathic chronic fatigue (but not with the full ME/CFS symptom complex). The researchers took medical and family histories to look for signs of mitochondrial impairment, conducted an exercise stress test, and performed an open muscle biopsy from

which a sample was obtained for electron microscopy.

The number of mitochondria was increased in 60% of patients, and mitochondrial function was abnormal in a similar number. In one third of patients, these abnormalities correlated with hearing loss, and with headache in their mothers (mitochondrial genes are passed on from mother to child).

While this study was relatively small (and had no matched control group for comparison), it does provide a glimpse of the kind of intriguing findings that could be uncovered from a battery of validated mitochondrial tests from a larger sample of patients and their extended families.

In another recent study from the UK (International Journal of Clinical and Experimental Medicine, 2009), 71 CDC-defined CFS patients provided blood samples from which mitochondrial function was assessed using an ATP profile test on white blood cells.

The major finding was a correlation between the degree of mitochondrial dysfunction and the severity of illness as assessed by a simple 10-step ability scale. However, we cannot say whether this correlation is meaningful clinically since simple correlations are notoriously open to confounder bias (in which other unidentified factors might be behind the relationship). Nor do we know if the results are specific to ME/CFS, since comparison mitochondrial function data from other chronic illnesses (such as neuromuscular disorders and frank

mitochondrial myopathies) is not presented.

A further complication is that the study used neutrophils, phagocytic cells of short life-span, which do not synthesise much ATP and are rarely used for mitochondrial research (which tends to use cells from high energy tissues such as muscle). Nevertheless, the results are intriguing and provide grounds for investigation of mitochondria in ME/CFS.

It is now almost 25 years since the first study of the modern ME/CFS era reported some aspect of mitochondrial physiology or function. Since then, a patchy and sometimes contradictory picture has emerged from the relatively small number of scientific investigations conducted. Yet, there remains a sense that not all is well with mitochondria in ME/CFS patients, and that the time is ripe for well-planned hypothesis-driven mitochondrial studies on well-characterised patients, using properly validated techniques and outcome measures.

JAPAN

Split nails

In 2006, a research group from Osaka University reported a putative diagnostic test for ME/CFS using visible and near-infrared spectroscopy of a blood sample. Now, the same group has just published another report (Clinica Chimica Acta, 2009) investigating structural changes of proteins in patients' fingernails. The researchers collected a sample from the nail plate of the free edge of the fingernail tip in 65 ME/CFS patients and 41 control subjects.

Even allowing for the influence of sex and medications (which can affect nails), ME/CFS nail plates had a secondary structural change of proteins (decreased α -helix content and increased β -sheet content) compared with healthy nail plates. Since the α -helix is supposed to contribute to the stabilisation of the protein structure, a decrease of α -helix may cause instability of proteins in nails.

Like the authors, we have no way of telling if this observation might become diagnostic, or if it has any clinical meaning or any specific relevance for ME/CFS patients at all. To find out, we have a nail-biting wait ahead.



HOLLAND

Lifestyle factors

Lifestyle factors are important risk factors for several diseases, such as cancer, heart disease and diabetes, but is this also true for ME/CFS? Well, academics at the Radboud University Nijmegen Medical Centre (*Journal of Human Nutrition and Dietetics*, 2009) explored the issue by collecting data from 247 ME/CFS patients on lifestyle factors, smoking, intake of alcohol, fat, fibres, fruit and vegetables, body mass index (BMI), fatigue severity, and functional impairments.

Of the patient sample, 23% smoked, 32% had a BMI greater than 25 (i.e., overweight or obese), and none had an alcohol intake that could be classed as unhealthy. In fact, 27% of ME/CFS patients abstained from alcohol altogether, compared with around 14% of the general Dutch population, confirming an earlier study from 2004 and patients' own reports of alcohol intolerance.

Only 5% had a healthy fibre intake and approximately 70% had an 'unhealthy' lifestyle with respect to fat, fruit and vegetable intake, though the eating habits of the general Dutch population also reveal a similar 'unhealthy' pattern, and overall the researchers found that patients tended to lead a healthier lifestyle than the general Dutch population.

But were there differences between patients with healthy and unhealthy lifestyles as regards fatigue severity or impairment of function? No, although a definitive answer would require a full population-based epidemiological study.

AUSTRALIA

Infections and their consequences

ME/CFS cases are commonly triggered by a viral infection, and the burning question is why, in some people, an initial infection persists — with serious consequences that can last a lifetime — while other people swiftly recover their health.

The Dubbo Infection Outcomes Study Group in Australia has followed 300 people with acute infection with Epstein-Barr virus, Q fever or Ross River virus, from the time of symptom onset until their recovery.

The Group's most recent report (published in *Clinical Infectious Diseases* 2008) shows that individual differences in genes that have critical roles in the immune response to infection — cytokine genes — have a key role in subsequent differences in the severity of illness, as well as its outcome over the longer term. Specifically, the type of interferon-gamma and interleukin-10 genes carried by the infected person were important.

As the authors explain, the challenge faced by the immune system of an infected person is to respond with sufficient intensity and duration to control or eliminate the infecting pathogen, while minimising immune injuries. People whose genetic makeup favours a more intense inflammatory reaction (at the start) are likely to experience more severe symptoms of infectious disease and a more protracted illness. The challenge for medical science is to identify these individuals early, and have a treatment plan prepared.

HISTORY CORNER

Enteroviruses

Time marches on, they say, but sometimes it can seem to move very slowly, at least where research into ME/CFS is concerned! In 1994, a scientific letter (McGarry et al, *Annals of Internal Medicine*) reported the postmortem findings on a 30-year-old woman with ME/CFS who died of other causes. Because a flu-like illness was sometimes involved in ME/CFS and because circumstantial evidence implicated enteroviruses, the authors from the Southern General Hospital, Glasgow, had examined her central nervous system for the presence of enterovirus using polymerase chain reaction (PCR) analysis. Control samples were obtained from four patients who died of cerebrovascular diseases and from four deceased age and sex-matched patients.

While no enteroviral sequences were detected in any of the control tissues, positive PCR sequences were detected in muscle, heart and brain samples from the hypothalamus and brain stem region of the patient. Sequence analyses revealed an enterovirus with an 83% similarity to Coxsackievirus B3.

From this, the authors concluded that enterovirus infection (and hypothalamic dysfunction) could be involved in the development of ME/CFS, and that the persistent symptoms might be a result of the persistence of enterovirus in particular parts of the central nervous system.

The same authors subsequently published a larger study in which muscle biopsy samples were positive for

enterovirus in approximately 25% of 121 ME/CFS patients, and in approximately 20% of those with other neuromuscular disorders.

Postmortem investigations have a medico-scientific role, particularly if their isolated results can be conjoined with subsequent findings such as the high prevalence of stomach enterovirus in ME/CFS patients reported by Dr Chia in California in 2008.

For that reason, the current plans to establish a tissue bank for ME/CFS patient samples, acting as a central repository for specific neuromuscular tissues after death, should be supported and expedited.

BELGIUM

A load of baloney?

Since around 1990, when the term 'Chronic Fatigue Syndrome' came into vogue, there have been a goodly number of investigations on the role of 'personality' in the development and maintenance of the illness, with some reports claiming rates of personality disorders as high as 40% among patients. Some of these claimed personality disorders go under exotic names such as alexithymia (emotional deficiency), action proneness, learned helplessness and histrionic states. However, it turns out that these claims may have been a load of baloney all along.

Belgian investigators (*Journal of Psychosomatic Research*, 2009) have now evaluated the prevalence of 'DSM-IV-TR personality disorders' in a sample of 50 women with ME/CFS and, importantly, in two control samples (closely matched to the patients for gender, age, educational level, family structure and marital state) of 50 healthy Flemish civilians and 50 psychiatric patients.

The results showed a striking similarity between the ME/CFS sample and the Flemish healthy control group on various measures, including the prevalence rates of personality disorder diagnoses. In fact, the prevalence of an Axis II disorder (defined as 'underlying pervasive or personality conditions, as well as mental retardation') was 12% in both the healthy Flemish and ME/CFS groups, compared with 54% in the

psychiatric sample, leading the researchers to conclude that 'personality pathology' has no major role to play in ME/CFS.

To the healthcare professionals who see ME/CFS as an illness existing within an 'extended multifactorial framework in which personality disorders play an essential role', these results must come as a profound shock. Still, facts must be faced and, as the Belgian authors themselves say, 'The results of the present study are unambiguous and straightforward.'

UK

Nursing mirror

The NICE Guideline of 2007 accepted that most patients with ME/CFS would be managed in primary care, a setting in which Practice Nurses are acquiring a greater role. A recent investigation from the School of Community-Based Medicine, University of Manchester (*BMC Nursing*, 2009) aimed to discover the current level of knowledge and understanding of the condition of 29 Practice Nurses using semi-structured interviews.

Qualitative studies like this do not rate highly in the hierarchy of research evidence, yet they can be very revealing indeed, as the results show. There was considerable ignorance about and limited experience of the clinical features of the illness, its aetiology and appropriate management strategies. And some of the nurses' comments would make a crow blush. For instance, 'I know so little you could write it on a postage stamp'; 'no time paid to it whatsoever, brushed over'; 'I think the money could be better spent'. So the authors correctly recognise that training must begin by addressing some current negative attitudes to patients with ME/CFS.

However, in most there was an openness to training, and a willingness to get to grips with issues, particularly in order to help patients. Interestingly, the Practice Nurses who were most informed had gained their understanding about ME/CFS through contact with patients, friends and personal experiences, rather than any formal training. This is something we all recognise: that understanding and sympathy are kindled (and the desire to help awakened) when there is a personal connection, such as the severe illness of family member.



Friends of ME Research UK

Events coming up



Northern Ireland Campaign

Derek and Grainne Peters (pictured above), who have been great friends of the drive for ME/CFS biomedical research for many years, have kindly given us a personal donation of £3,000, in addition to the recent £2,000 contribution from the Northern Ireland Campaign for ME/CFS Healthcare, the very active campaigning organisation of which Derek is the director and founder.

As Derek says, 'As I have suffered from ME for 25 years, and we've been active campaigners for improved diagnosis, treatment and medical/social support for much of that time, Grainne and I feel it vital to contribute towards ME Research UK's work.'

Wedding Bells

Sally Mason is marrying Owen Magrath on 27th June 2009, and is asking friends and guests to donate to our research programme so we can benefit from their celebration.

Sally has had ME for over three years. Her illness came on suddenly over two days with flu-like symptoms, and from

being a 100% fit 26-year-old, full of energy and working hard, within two days she could hardly walk.

Despite having severe symptoms such as extreme exhaustion and headaches, Sally considers herself one of the lucky ones, and has improved slowly since 2005 through a combination of good medical advice, luck and determination.

Sally and Owen's Justgiving pages are still open to receive online wedding donations, and we all hope they have a wonderful day on 27th June.



Recent events

Lands End to John O'Groats

Rachel Bennett cycled from Lands End to John O'Groats — a distance of 874 miles, the greatest distance between any two points in mainland UK — to raise money for our charity in 2008.

Rachel (pictured below) was part of a larger group of cyclists, all raising money for their favourite charities, and when her online donations via the Justgiving website were included, the total had amassed almost £3,300!



It was quite a trip, and the mid-way point was reached at Windermere where a sign marks the mid-point (437 miles to go either way). At her final destination, there was a mound near the John O'Groats Hotel which marked the site where Dutchman John De Groot constructed his eight-door octagonal house in the early 16th century, running a ferry to Orkney charging 4d, a sum that became known as a Groat.

Congratulations, Rachel, for reaching that spot, and thank you for doing it on our behalf.



Anniversary Festival

The annual Aberdour Festival is ten days of celebrations, with arts, crafts, song, dance, puppetry, sports and so much more, and the 25th Anniversary Festival was a landmark event. The organisers had created a broadly appealing programme of events, including the popular ceilidh band Callanish.

For classical music lovers, they ran a series of three concerts by young musicians from 'Live Music Now'. Favourite events such as the arts weekend were still included, along with many new acts in the halls and hotels in Aberdour, including John Cairney returning to his favourite Fife village for 'My Scotland Story'.

The week-long, action-packed series of events for all ages included the Raft Race, Donkey Brae 7 and 2-mile runs, and the village market.

The photo above shows Moira Robb and her husband Mike, who hosted one of the arts and crafts venues, presenting a cheque for £300 raised at the event to our Chairman Dr Vance Spence at our headquarters in the autumn of 2008.



Charity Bike Ride

Chris Wilkinson took part in the annual charity bike ride from Manchester to Blackpool (and home to Skelmersdale, a total of 100 miles), the second bike ride he has done for our charity. The ride started at Albert Square in Manchester and continued along country lanes through Leigh, Haigh Hall, Preston, Inskip, ending at the Mirror Ball at the South Promenade in Blackpool where riders and friends could enjoy a barbecue, beer-tent and live music. Indeed, some even partook of a well-earned massage thoughtfully provided by volunteers!

The photograph below shows Chris, resplendent in ME Research UK t-shirt, and many thanks to Chris and the family for again taking on this challenge!



Marathon Heroes

As a fundraising event, there is no marathon in the world that comes close to the Flora London Marathon. One of the dominant images of the race is that of thousands clad in fancy dress, tramping the cobbles in support of charitable causes, dressed as rhinos, football team mascots, giant trees and the like.

In 2008, 34,420 runners had crossed the finish in The Mall, and three of them were running for ME Research UK. Our warmest congratulations go to Robert Ogden and Madhi Choudhury, and Ian Bottomley who coursed home within 13 minutes of each other, around the 4-hour mark — a tremendous achievement — jointly raising almost £4,000.

We already have two London Marathon runners supporting us in the 2009 event — Harvey Gurry and Matthew Fielding (pictured below) — whose online Justgiving pages are already filling up.

The lads are in training for the big day, and Matthew is up to 14 miles per session (including a broken thumb). Good luck, gentlemen.





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 PH1 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 PH1 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