



# breakthrough

News of the ME research YOU are helping to fund



## New Horizons 2008

### AUTUMN 2008

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Hosted and organised by ME Research UK, and co-sponsored by the Irish ME Trust, the New Horizons 2008 International Conference on ME/CFS Biomedical Research took place on 6th May 2008 at the Wellcome Trust Conference Centre on the Genome Campus at Hinxton near Cambridge, UK.

Building on the success of last year's conference in Edinburgh, the day brought together researchers from around the world, healthcare professionals, representatives from local support groups, and delegates from ME/CFS charities. The full day's programme consisted of invited keynote lectures from scientists from England, Scotland, USA, Canada, Belgium, Sweden and Australia. The full conference was filmed, and a four-DVD set of the day's proceedings can be ordered from ME Research UK at a cost of £5 (including P&P within the UK).

Delegates were welcomed by Sue Waddle, who chaired the conference with Prof. Nancy Klimas and Bob McRae. The conference was then opened formally by Roger Jefcoate CBE, co-founder of ME Research UK and a Patron of the charity. Roger explained that he felt greatly privileged to be welcoming delegates to such a prestigious event.

He continued, "It is a matter of continuing astonishment to me that for so severe an illness, biomedical research is so underfunded... ME Research UK has become a beacon of hope for many patients, some of whom have lived for many years in this sea of darkness and despair. It is heartening to see, therefore, the range of experts who have volunteered to come and share with us their efforts to explore the biomedical basis of the illness."

*Continued on page 2*

## Conference DVD offer

A 4-DVD set of the "New Horizons" conference presentations is available from our headquarters for the special price of £5 (including P&P within the UK).

By popular demand, we have decided to "Energise Biomedical Awareness" by extending this special offer to include patients' GPs, consultants or other healthcare professionals who might benefit from viewing the presentations.

Indeed, we can send one to your local medical or nursing library for its DVD collection. And we'll even include a copy of this Breakthrough magazine, and a covering letter from the charity explaining the importance of "biomedical" investigation of the illness.

To take advantage of this offer, please send us the name of the relevant GP, consultant, other healthcare professional, or medical/nursing library — with the full postal address including postcode — and we'll send the 4-DVD set direct from our charity as a gift.

To simplify matters, we shall not mention the name of the donor, unless you specifically request to be named.

The special price remains £5 (including P&P within the UK), and you can pay by cheque (made payable to "ME Research UK"). Orders can also be made by credit/debit card over the phone (01738 451234) or on the donation form on our website.

# New Horizons 2008

The first keynote lecture was by Prof. Nancy Klimas of the University of Miami School of Medicine and the Miami VA Medical Center. The main emphasis of her presentation "Clinical Aspects of ME/CFS" was on the need to move beyond "case definitional" issues of ME and CFS towards assessing patients on the basis of clinical tests and symptom clusters.

She described a model for the development of the illness involving a genetic predisposition which encounters a triggering event or infection, leading to the production of immune, endocrine or neuroendocrine mediators, resulting in a poor health outcome and persistence of illness.

Dr Jo Nijs, from the Vrije Universiteit Brussel, Belgium, gave an overview of his recent paper on "Intracellular immune dysfunction in ME/CFS: state-of-the-art and therapeutic implications", in which he examined the accumulating evidence in support of intracellular immune dysfunction in the illness.

He and his colleagues concluded that proteolytic cleavage of the native RNase L enzyme is characteristic of dysregulation of intracellular immunity in people with ME/CFS, although the origin of the dysregulation is unexplained at present. It seems plausible that decreased natural killer cell function, the presence of infections and intracellular immune

dysfunctions are interrelated parts of the ME/CFS pathophysiology, but these potential interactions still need to be unravelled.

Dr Byron Hyde from the Nightingale Research Foundation, Ottawa, Canada, outlined some of his conclusions from his years seeing ME and CFS patients. He described myalgic encephalomyelitis not as a syndrome but as a disease process causing a diffuse measurable pathophysiological injury of the brain.

He discussed epidemics during which enterovirus seemed to have an important role, concluding that it would be scientifically inexcusable not to consider that the enterovirus group was responsible for the diffuse brain damage noted in acute onset ME patients.

Dr Derek Enlander (Mount Sinai Medical School, New York) described his treatment of ME/CFS patients with a complex intramuscular injection, oral l-cystine, glutathione, methylcobalamin, folic acid and electrolytes. Based on treatment of approximately 800 patients over 15 years, he explained that he has developed a protocol which has helped 65% of patients, based on SF36 and other test criteria. This protocol seems to be in line with a theory of a methylation cycle defect in ME/CFS.

The role of the ME/CFS Clinic in the UK as regards clinical assessment and service delivery was described in a presentation by Dr Gavin Spickett (Royal Victoria Infirmary, Newcastle upon Tyne). He discussed the care pathways adopted in clinical practice in the North of England, including the key role of medical assessment which aims to undertake a detailed clinical evaluation to identify alternative diagnoses that may present with fatigue to ensure that patients receive appropriate treatment for these.



# Research Conference

With the advent of the NICE Guideline 2007 and its encouragement of earlier diagnosis, the proportion of alternative diagnoses might be expected to rise.

The morning session was brought to a close by Prof. Julia Newton (Institute of Cellular Medicine, Newcastle University) who spoke of her work on the autonomic nervous system and its dysfunction in ME/CFS. She explained how autonomic dysfunction and particularly low blood pressure are a frequent finding in people with the symptom of 'fatigue' generally, and her programme of research is directed towards understanding the role of autonomic dysfunction and developing interventions that target autonomic nervous system abnormalities.

The afternoon session began with an overview of the Whittemore Peterson Institute for NeuroImmune Disease, University of Nevada, by Dr Dan Peterson one of the co-founders, who also discussed some of the work currently underway or planned.

A subset of patients severely affected with ME/CFS with evidence of viral reactivation has been documented to demonstrate a gamma T-cell clonal rearrangement. Studies are currently underway to determine the monoclonality and antigen specificity of this unusual T-cell rearrangement, as well as intensive studies into the possible role of viruses in development of neoplastic disorders in a subset of chronically affected ME/CFS patients.

Dr Faisal Khan (The Institute of Cardiovascular Research, University of Dundee) described his specific work on vascular function, and discussed recent results showing that arterial stiffness is significantly elevated in CFS patients compared with control subjects. The



degree of "stiffness" is associated with levels of serum C-reactive protein, pointing to a role of low grade inflammation and oxidative stress.

Dr Jonathan Kerr (Department of Cellular and Molecular Medicine, St George's University of London) described the background to the molecular studies that he has been conducting over the past four years. In his most recent study, the group determined for each CFS subtype the fold difference of each of the 88 CFS-associated genes compared with normal persons. Genomic analysis reveals some common and distinct disease associations among the genetic subtypes.

Prof. Birgitta Evengård (Clinic Infectious Diseases, Umeå University, Sweden) gave the penultimate lecture of the day on the role of the Swedish twin registry in searching for a biomarker for the illness. She described the ongoing work on characterising the epidemiological patterns and the role of genes and environment in the most severe phenotype of fatigue illnesses, the chronic fatigue syndrome, in a representative sample of the Swedish population.

The population-based design enables the possibility of evaluating the validity of the CFS definition and, through molecular epidemiology, identify biological determinants of potential value for diagnosis. (Continued in sidebar) ●

## Q Fever

In the final presentation, Dr Stephen Graves (Director, Australian Rickettsial Reference Laboratory, Australia) shared his wide experience of "Q Fever" and "Flinders Island Spotted Fever", and their possible relationship to CFS. He explained that a period of fatigue after an infectious disease is well recognised, which when it lasts for months is referred to as "post-infectious chronic fatigue".

The Q-fever research group hypothesise that many cases of CFS are really "post-infectious chronic fatigue", and that a proportion of these cases are sequelae of Q Fever (infection with *Coxiella burnetii*) or Flinders Island Spotted Fever (infection with *Rickettsia honei*, strain marmionii). These bacteria have an intracellular lifestyle, passing between vertebrates and invertebrates.

Post-Q Fever chronic fatigue was first reported in Australia in 1996 and antigen from *C. burnetii* is known to persist in patients' bone marrow and white blood cells, leading (in a genetically predisposed subpopulation) to immune dysregulation and ongoing fatigue. Dr Graves presented data showing that post-Q fever Fatigue Syndrome (QFS) follows 10 to 20% of clinically overt cases of acute primary Q fever, and its symptoms match standard CFS definitions. Patients with QFS also show significant variant patterns of cytokine responses compared with controls.

If correct, public health measures to reduce rickettsial infections could have a positive impact on the incidence of CFS.

## WHAT IS Vitamin D?

Vitamin D is a group of fat-soluble “pro-hormones” which have no hormonal activity in themselves but can be converted into active hormones by the body. The two major forms are vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol).

People get vitamin D from two sources. The first is ultraviolet B radiation from sunlight, which penetrates the skin stimulating the production of vitamin D3. The other source is diet, particularly fatty fish such as salmon and herring which are naturally rich in vitamin D. However, much of our vitamin D intake today comes from fortified products like milk or breakfast cereals, or from dietary supplements. An adequate intake for adults is 400 to 600 IU per day.

Once in the body, vitamin D is converted in the liver and kidney to form calcidiol (25-hydroxy-vitamin D), the physiologically active form, and is released into the circulation. Vitamin D nutritional status is determined from the blood calcidiol level, which is optimally 35 to 55 ng/mL, while vitamin D deficiency is defined as a level less than 20 ng/mL.

Vitamin D is important for the maintenance of organ function: for instance, it regulates blood calcium by assisting its absorption from food and re-absorption in the kidneys; it is essential for a strong skeleton; and it has a significant influence on the immune system.

# Vitamin D status and



Rickets is commonly thought of as the classic disease of vitamin D deficiency, but science is recognising that it is merely the extreme end of a spectrum of possible disorders; in effect, the tip of the vitamin D deficiency iceberg. The reality is that vitamin D deficiency remains common in the population. In young people, at both the foetal stage and during childhood, vitamin D deficiency can cause skeletal deformities and growth retardation, and increase the risk of hip fracture in later life. In adults, it can result in osteopenia and osteoporosis, and muscle weakness (see sidebar on the opposite page).

Recent scientific work, centering on the discovery that vitamin D receptors are widely distributed in the body and can be found in most cells and tissues, has thrown new light on this vitamin and its role in a variety of key functions. Most interest, however, concerns the part played by vitamin D or its deficiency on the risk of chronic illnesses, including autoimmune and infectious diseases, the common malignancies, and cardiovascular disease.

Why might this be important in ME/CFS? Well, as a chronic illness with immune, infectious and cardiovascular aspects, there is at least a possibility that vitamin D deficiency/insufficiency could be involved in the development or maintenance of the condition or its specific symptoms. For example, vitamin D is known to affect vascular smooth muscle cell proliferation, inflammation, vascular calcification and blood pressure, all of which are involved in cardiovascular risk, while there is evidence that ME/CFS patients have associated cardiovascular symptoms, including attenuated heart rate and blood pressure regulation and — as a recent report from the University of Dundee showed — increased arterial stiffness. Again, vitamin D inadequacy has been linked with impaired neuromuscular functioning and chronic pain, two important facets of the day-to-day experience of ME/CFS patients.

These considerations, including the fact that Vitamin D is known to influence inflammatory processes — whether as an

# cardiovascular function

inhibitory influence on TNF- $\alpha$  and interleukin-1 production, or by reducing the activation of macrophages — intrigued researchers at the Institute of Cardiovascular Research, University Dundee. And their interest was further stimulated by a 2007 report of improvement in endothelial vascular function in vitamin D-deficient patients with type 2 diabetes after a single large dose of oral vitamin D2 — suggesting, albeit tentatively, that there might even be a therapeutic role for vitamin D in ME/CFS patients, whose endothelial vascular function has been found to be dysregulated by previous work in the unit.

But the first step in determining whether there is an association between vitamin D and vascular function in people with ME/CFS is to find out if the vitamin D levels really are lower than normal (since if not, there is no point in looking further). To investigate this, ME Research UK has given a small “extension funding” award to

Dr Faisal Khan of the Institute of Cardiovascular Research to test vitamin D levels in already-collected samples acquired from two separate studies previously funded by our charity. Dr Khan aims to measure the main circulating form of serum vitamin D (25-hydroxy-vitamin-D3 — see the sidebar on the left) as well as the active hormone 1,25-dihydroxy-vitamin D3. These measures will then be related to previously-assessed vascular function in the two ME/CFS and control populations.

If an association is found, a subsequent intervention trial might show whether vitamin D supplementation could be a relatively simple, effective way of contributing to reducing risk of cardiovascular disease in ME/CFS patients. In other illnesses, small scale intervention studies, aimed at increasing levels of 25-hydroxy-vitamin D in populations at risk of cardiovascular disease, have reported beneficial effects, and the same might be true for ME/CFS. ●



## Vitamin D deficiency

The major cause of Vitamin D deficiency is inadequate sunlight coupled with inadequate dietary intake. However, medical conditions that limit its absorption or impair conversion of vitamin D into active metabolites (e.g., liver or kidney disorders) can also be responsible. Vitamin D deficiency/insufficiency can affect tissues and processes, or influence medical conditions.

The protein or mineral content of bone can be reduced (osteoporosis), or there can be a loss of bone (osteopenia), leading to osteomalacia and weakness.

Skeletal muscles have a vitamin D receptor and may require vitamin D to function optimally since a deficiency is associated with muscle weakness.

Vitamin D deficiency tends to increase the risk of infections, such as TB and influenza.

Vitamin D regulates the expression of genes associated with cancers, but whether its deficiency per se increases the risk of cancer remains unproven despite evidence of an association between low levels of 25-hydroxyvitamin D and increased risks of colon, prostate and breast cancer.

25-hydroxy-vitamin D levels are associated with important cardiovascular risk factors, and low levels are associated with hypertension, increased vascular resistance, increased left ventricular mass index and increased coronary calcification.

## WHAT IS ME/CFS?

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

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

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

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

# Research Challenges

For Socrates, uncertainty was better than certainty because it presented challenges which, when overcome, resulted in the discovery of the real facts of the world. From this lofty viewpoint, then, ME Research UK should be proud to be working in the field of ME/CFS. Aside from the usual challenges of conventional biomedical science, there are particular specific challenges which impact on "making a breakthrough".

### Funding challenge

Money is the platform which supports all biomedical research. But medical research is expensive — one medium-sized clinical trial can cost £300,000 and can possibly have an inconclusive result — so big money will be needed to unravel the causes and find cures for ME/CFS.

The diagram below gives a very basic outline of the origins of medical research funding in the UK. The main elements are the Medical Research Council (MRC) and the NHS Research and Development, which allocate funds to established research groups with a track record of success in a certain area.

It is very difficult, however, for any researchers in any field to obtain funding from these central sources, and in any case the money available (some £1.3 billion in the current year, for *all* types of research across *all* illnesses) does not go far given the expense of the investigations and many

demands made. Even if the biomedical investigation of ME/CFS got its 'fair share' of central funding — something that many of us are still pressing for — that share would fund only a small part of the biomedical activity that is necessary.

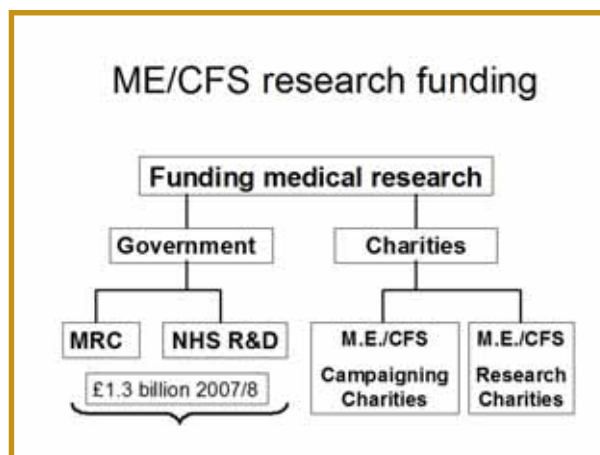
In fact, a significant proportion of research funding comes from charitable sources — the Association of Medical Research Charities estimates that some £791 million was spent overall in 2006/7; for example, Cancer Research UK raised £468 million in 2006/7. We have to do the same for ME/CFS. As most patients are too ill to fundraise themselves, our strategy has to be to raise awareness of the need for biomedical research into the illness, to ensure that our organisations are worthy of public trust, and to get and keep the research community on-side in the struggle.

### The elephant in the room

One issue, ever-present but rarely alluded to in the media or the mainstream scientific literature, concerns the overarching influence of the psychosocial model of the illness, which emphasises "beliefs, coping styles, and behaviours" (summarised in the Chief Medical Officer's report of 2002). This model colours the perception of the illness across the board — take the Medical Research Council for example: the vast bulk of its £3 million ME/CFS grant-spend since 2003 has gone towards research into psychological management strategies, while around 33 other applications, some from established biomedical research groups with a track record in the field, have been rejected (see pages 8 and 9). Moving basic scientific and clinical research centre-stage into the minds of opinion formers and healthcare professionals is one of the greatest challenges.

### Diagnostic challenge

CFS is not a 'clean' diagnosis. In 2007 there were at least three



# in ME/CFS

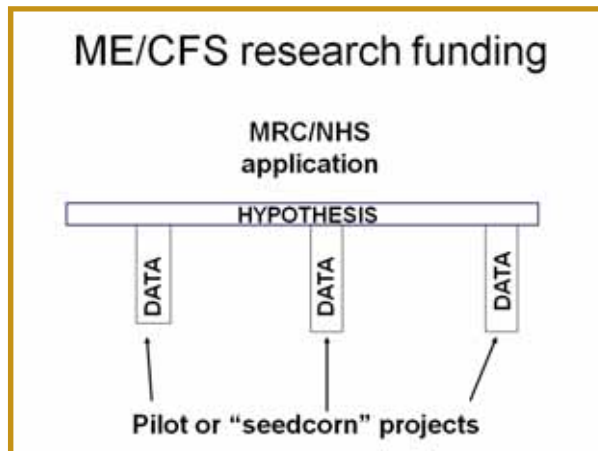
different definitions of CFS in use, all non-validated and all based on vague, non-specific symptoms shared with other common illnesses. While it is likely that they overlap, they do not *necessarily* contain scientifically comparable groups of patients, a fact which tends to increase the costs of research studies, because ideally volunteers need to be screened and categorised by medical examination.

What can be done about this? We could return to diagnosing 'classic' myalgic encephalomyelitis (ME), involving an infectious onset, a variety of neuromuscular symptoms and signs and a post-exercise component. But there are several different definitions — none recognised by modern medicine or science today. One strategy which has a lot of support is to 'subgroup' patients on the basis of symptom clusters — the Canadian definition of 2003 could be the basis for such an attempt — or on severity of existing symptoms (which might result in the identification of 'classic' ME patients at one end of the spectrum, as suggested in one scientific paper in 2003).

## Need for consistency

There is also a need for consistent directed work over a broad front. Funding a smallish pilot study is one thing, but real breakthroughs come at the end of a programme of painstaking work by a specialist group of researchers.

One of the few examples in ME/CFS in the world is the work at the Vascular and Inflammatory Diseases Research Unit, University of Dundee, which has received several grants from ME Research UK since 2001. In a step-by-step progression involving both adults and young people with the illness, the group has uncovered unusual sensitivity of blood flow responses to acetylcholine, increased oxidative stress



in the bloodstream, an unexpected increase in dying (apoptotic) white blood cells, and increased cardiovascular risk factors with arterial stiffness in patients.

Such a progression — whether towards positive findings or away from negative ones — is the norm for scientific investigation. The burning need in this illness is for there to be *many* groups undertaking programmes of research across a range of basic and clinical science fields so that a 'critical mass' of investigators can produce a 'critical mass' of biomedical data.

## Targeting scarce resources

Research charities such as Cancer Research UK, which raise millions of pounds per annum, have the luxury of providing core funding for dedicated research units year-on-year. As this is impossible in ME/CFS at present, our short-term strategy has been to provide essentially pilot funding to 'pump prime' work of potential importance (see the diagram above). The resulting publications help to build critical mass in the scientific literature, and the data obtained can form the basis of researchers' subsequent applications for central funding. The challenge here is to make best use of scarce resources. ●

*An expanded version of this article appears on our website*

## WHAT IS ME Research UK?

ME Research UK is a medical research charity which commissions and funds scientific (biomedical) investigation into the causes and treatment of ME/CFS. We also have a mission to "Energise ME Research", and our in-house team identifies potentially important biomedical research projects, maintains a database of information on ME/CFS, produces high quality professional reports, and hosts scientific conferences.

Recognising that much of the existing research into ME/CFS has concentrated on psychological interventions designed to "manage" the illness, ME Research UK believes that biomedical research is urgently required and is what most patients and carers want to see. For this, researchers with fresh, novel ideas have to be recruited and encouraged to undertake research in this field. This is the most difficult task of all, and ME Research UK sees its role at this leading edge: to give help to biomedical scientists for novel research projects that would otherwise not be funded, and to support research groups to the stage where they can apply to major funding agencies for further support based on their initial data.

With your help — and building on our close working relationships with researchers and other ME/CFS organisations — ME Research UK can be a force for change, and a source of real hope for thousands of people.

## ME Research UK currently funded ME/CFS projects

At present, we fund the work of a growing number of scientists, some listed below (our website lists others).

### Autonomic dysfunction and its consequences — a clinical cohort study (clinical fellowship)

Prof. Julia Newton, University of Newcastle

### Vitamin D Status and its association with cardiovascular function

Dr Faisal Khan, University of Dundee

### SNPs within CFS-associated human genes

Dr J Kerr, St George's University of London

### Non-invasive structural and functional neuroimaging

Prof. BK Puri, MRC Clinical Sciences Centre, Imperial College London

### An investigation into biochemical and blood flow aspects of ME/CFS in children

Dr Gwen Kennedy, University of Dundee

### Focal and global endothelial function and their association with arterial stiffness

Dr Faisal Khan, University of Dundee

### Post-exertional malaise in ME/CFS: the role of intracellular immunity and sensory processing

Dr Jo Nijs, University College Antwerp

# Medical Research Council:

In May 2003, the Medical Research Council (MRC) announced its “research strategy for CFS/ME”, widely welcomed as the first formal research strategy for the illness. It listed a number of strategic themes of particular importance (case definition, epidemiology, pathophysiology, interventions, health service research, research capacity and the value of lay participation). Subsequent initiatives by the MRC included the issue of a notice highlighting CFS/ME as a current strategic priority (2003), a CFS/ME workshop (2003), and a “Joint Action for ME” workshop (2006).

So, what research has since been funded? Well, at least five separate studies (see the sidebar on the opposite page) costing at least £3,180,900 have been supported. From the bald titles, it is impossible to determine what each involves, but it seems that three fall far short of being definitive (one is for “indirect support”, one is for a “CFS-like illness”, and one is simply a feasibility study, albeit an expensive one), while the remaining two are randomised clinical trials (RCTs) of psychosocial strategies.

From details published in the National Research Register (before it ceased publication in October 2007), we know that the largest (PACE) trial is a four-arm RCT comparing cognitive-behavioural therapy (CBT), graded exercise therapy (GET), adaptive pacing and “usual medical care” alone. As its blurb explained, “CBT will be based on the illness model of fear avoidance... GET... on the illness model of deconditioning and exercise avoidance”.

The FINE trial, by contrast, offers severely affected patients supportive listening, GP “treatment as usual”, or a

nurse-led self-help approach which includes elements of CBT and GET delivered in the patient’s home (four 90-minute sessions, with six 30-minute phone conversations over 18 weeks), with a qualitative interview to explore “patient views on illness causation, beliefs about chronic fatigue... and previous experience of treatment and doctor-patient relationships”.

In total, approximately 91% of the total grant-spend on ME/CFS in five years has gone on trials of non-specific management and coping strategies. It is important to point out, however, that neither of these trials is actually worthless; in an ideal world in which £100 million had been invested over five years in ME/CFS research, a 3% spend on assessing the usefulness of various coping strategies, such as CBT, relaxation or meditation, might have been acceptable. The point at issue is that most of the MRC’s inadequate grant-spend has gone on this aspect at the expense of truly biomedical research, the reverse of the situation in other illnesses such as multiple sclerosis or rheumatoid arthritis. Even the dogs in the street would think this record dismal.

Thanks to the Freedom of Information Act, and the stalwart patients who have repeatedly requested information, we have a (fuzzy) picture of the research projects which the MRC has NOT funded to June



Cartoon by Trish Campbell

# a case to answer?

2008. They seem to total at least 33 (see the table below), some biomedical and targeted at pathophysiology. It is unlikely that these 33 applications were so badly written that they could be rejected (since some were from established researchers with a track record in this and other fields, as our personal communications have established). So, was their scientific basis less sound than, say, the “pragmatic rehabilitation” of the FINE trial, supported by RCT data on ambulant patients but only a case report on the non-ambulatory patients of particular interest?

There are three main schools of thought about what has gone on. First, that within the MRC the biopsychosocial model of ME/CFS is the current paradigm, leading referees and committee members to be chosen, probably unwittingly, to deliver a

particular outcome (since psychosocial aspects colour the perception of the illness across the board, this would be no surprise). Second, that the MRC is simply a large stolid bureaucracy for which ME/CFS biomedical research has very low priority indeed given the other demand on its resources (£1.3 billion in 2008 for all types of research on all illnesses). Third, that something even more fishy is going on.

In the summer of 2008, an answer to a parliamentary written question revealed that the MRC is to constitute a CFS/ME multi-disciplinary panel. If this is a genuine attempt to kick-start biomedical investigation rather than a public relations exercise, the mystery panel's first act could be to discover whether or not the MRC has a case to answer over the non-funding of biomedical research since 2003. ●

*Table. Unfunded applications to the MRC between 2002 and 2008*

<i>Time-frame</i>	<i>“CFS/ME” Subject area</i>
<i>2002 to 2005 (11 total)</i>	<i>Neurophysiology of fatigue; Population-based/epidemiological studies (4 applications); Neurotransmitters and stress; Neuroimaging; Clinical and laboratory characterisation (physiology/diagnosis); Dietary intervention — RCT; Facilitated self-help — RCT; Psychosocial and genetic factors in young people</i>
<i>2005 to 2006 (12 total)</i>	<i>Pathophysiology, including studies regarding genetics/biomarkers, immunology and neuroimaging (7 applications); Population-based/epidemiological studies (3); Primary care study; Experimental medicine study</i>
<i>2006 to April 2007 (7 total)</i>	<i>Cognitive outcomes in children — pathophysiology; Epidemiological studies — epidemiology; Biomarkers; Pathophysiology (2 applications); Molecular pathogenesis — pathophysiology; Molecular and genetic characterisation — pathophysiology; Neuroimaging — pathophysiology</i>
<i>May 2007 to June 2008 (3 total)</i>	<i>Biomarkers — pathophysiology; Management and treatment — intervention; Management and treatment — observational study</i>

## MRC currently funded “CFS/ME” projects

*(Sources: MRC website; Hansard, written answers)*

Two large clinical trials of new approaches to treating CFS/ME:  
 a) PACE (Pacing, Activity and Cognitive Behaviour Therapy: a Randomised Evaluation, £2,076,363) [Prof. PD White, Psychological Medicine, Queen Mary and Westfield College]  
 b) FINE (Fatigue Intervention by Nurses Evaluation, £824,129) [Dr AJ Wearden, Psychological Science, Uni. of Manchester]

A preliminary epidemiological project to test the feasibility of identifying the risk factors for persistent symptoms of fatigue and abdominal and widespread pain (£118,263) [Prof. F Creed, Psychological Medicine, University of Manchester]

An epidemiological study to assess ethnic variations of the prevalence of a CFS-like illness, associations with potential risk factors, and coping behaviours (£162,145) [Prof. K Bhui, Cultural Psychiatry and Epidemiology, Queen Mary and Westfield College]

Indirect support through a trial exploring the management of patients with persistent unexplained symptoms [Specifics unknown]

One project was mentioned in Hansard (12th June 2008) but is not on the MRC website: General and specific risk markers and preventive factors for chronic fatigue and irritable bowel syndromes (£367,000) [Dr C Clark, Centre for Psychiatry, Barts and The London School of Medicine]

## Obsession and compulsions

Some of you reading this page have obsessive-compulsive disorder (OCD), which is a chronic anxiety condition most often characterised by obsessive, distressing and intrusive thoughts, and related compulsions — at least, so it says in a scientific study in the *Journal of Chronic Fatigue Syndrome*.

There is a problem, however — the report shows no such thing.

The researchers from Kuwait University gave questionnaires (the Arabic Scale of CFS and the Arabic Scale of Obsession Compulsion) to 427 healthy volunteer Kuwaiti male and female college students with an average age of 19.7 years. As the report says itself, “It is worth noting that those undergraduates were neither disturbed clinical cases... and that none stated that they suffered from CFS.”

Given that none of the participants had the symptom clusters of ME/CFS, or had undergone a clinical assessment on any CFS or ME definition, the conclusion of the study that “there is an obsessive compulsive element in CFS” seems bizarre indeed.

Does this matter? Well, yes, actually. Most people read only the titles or abstracts of scientific papers (ME Research UK’s geeks are an exception), so this report now gives a most misleading impression as it sticks its head up in the scientific literature.

The *Journal of Chronic Fatigue Syndrome* is to cease publication shortly. ●

# Recent Research from



## Genes and diagnosis

Across the world, several groups have been working on gene expression profiling, and efforts are underway to find expression patterns that might have diagnostic value. While Dr Jonathan Kerr is already at the forefront of this drive in the UK, another team from Nagoya University Hospital, Japan has recently reported its preliminary results in *Molecular Medicine*.

Using microarray techniques to probe for 1467 genes in the peripheral blood of 11 ME/CFS patients and controls, followed up by confirmatory PCR, the researchers pinpointed 9 genes with mRNA levels significantly different from the controls. Next, to test whether this gene cluster might be useful for “differential diagnosis” of ME/CFS, additional patients and non-CFS fatigue controls were recruited. It was found that the expression pattern of the 9 genes could distinguish the majority of ME/CFS patients from non-CFS patients; 94% of the ME/CFS patients and 92% of the non-CFS patients could be correctly classified by the expression patterns of the 9-gene cluster.

Crucially, most of the 9 genes could be categorized into distinct groupings — including host defence, energy metabolism or signal transduction — similar though not identical to the functional groupings found by other research groups. Interesting times; and we await the results of the larger clinical study which this group is conducting. ●



## Healing at a distance

No treatments for ME/CFS can be called curative, so it’s unsurprising that unusual therapies are sometimes trialled on patients. The most recent example is “distant healing”, a form of spiritual healing said to be ineffable, mysterious and indefinable. A consortium of European researchers, with a grant from the European Commission, evaluated distant healing in 409 patients with stable, chronic illness. The patients had been recruited from 14 private practices in Germany and Austria, and were randomised to receive immediate healing for 6 months or to have their “treatment” deferred for 6 months.

In total, 462 healers from 21 European countries supplied their services; they were from many different healing traditions and practised distant healing individually or in groups by either prayer or by imagining the transmission of “healing energy”.

The results (published in *Psychotherapy and Psychosomatics*) showed that ME/CFS patients had very low quality of life and symptom scores before the study even began — a result which confirms the high human cost of this illness. Overall, however, there were no differences over 6 months in post-treatment mental or physical health scores between the groups treated or untreated with distant healing. A surprising result? Perhaps not, given that distant healing has yet to be shown to have specific efficacy for any illness. ●

# around the World



## Exploding the depression myth

The idea that depression is at the root of the symptoms of ME/CFS has been exploded in two interesting overviews. The first, aptly titled "Don't Assume It's Depression" (Journal of Clinical Psychiatry), was a systematic review of the scientific literature on ME/CFS and depression conducted by researchers at West Virginia University. Their initial premise was that since "at least 1 million Americans have CFS... yet more than 80% go undiagnosed", it is important for clinicians to clearly identify the condition and differentiate it from other conditions, such as depression, which can cause superficially similar symptoms. From the literature, they found a basket of indicators — from the clinical history, physical and mental examinations, and diagnostic arena — which could be useful. Crucially, they stress that a good history (taken by the examining physician) is more important than any available diagnostic test to diagnose ME/CFS and differentiate it from depression. The Table below shows the

key points of difference, including perhaps the clearest indicator: the fact that ME/CFS patients show frustration at their physical limitations, and generally do not have the usual depressive symptoms of lack of enjoyment of life, guilt and lack of motivation.

The second review (Journal of the American Academy of Physician Assistants) described how biological abnormalities separate ME/CFS from depression, emphasising that while the conditions share certain symptoms, many others, such as sore throat, lymphadenopathy, arthralgias, myalgias and post-exertional fatigue, are not typical of psychiatric illness. In addition, the review outlines some of the evidence for physiological differences, with two of the most important being sleep (reduced REM sleep latency in depression versus reduced slow-wave deep sleep in ME/CFS), and hypothalamus and pituitary function (high circulating cortisol levels in depression versus low in ME/CFS, compared with controls). ●

### ME/CFS

Post-exertional malaise  
Unrefreshing sleep/excessive sleep  
Intense frustration at not functioning well  
Less likely to interpret symptoms in terms of negative emotional states  
Weaker and more pain complaints  
Frequent or recurring sore throat  
Tender cervical or axillary lymph nodes  
More non-REM sleep disturbances

### Depression

Feel better after exercise or activity  
Insomnia/excessive sleep  
Apathy and anhedonia  
More likely to interpret symptoms in terms of negative emotional states  
Stronger and have fewer pain complaints  
Not applicable  
Not applicable  
More REM sleep disturbances

## Neurotherapeutic review

It is rare to find an impressive review in the ME/CFS literature. But one recent article in the journal Expert Review of Neurotherapeutics, from Miguel Servet Universty Hospital in Spain, contains a very good overview of the definitional issues surrounding the illness, and a short exploration of the uses of methylphenidate.

The article reiterates that the cognitive problems reported by ME/CFS patients (and indeed by reports in the early ME literature) are some of the most disabling and disruptive symptoms; these include difficulties with concentration, short-term memory and thinking, as well as impaired attention and slowed processing speed. And it suggests that neurostimulants, such as bupropion and dextro-amphetamine, might have a role in improving these neurocognitive deficits. Indeed, when methylphenidate (a mild psychostimulant that inhibits dopamine and norepinephrine reuptake) was supplied to 60 ME/CFS patients with concentration difficulties during a 4-week trial in 2006, it was found to "significantly" improve fatigue and concentration compared with placebo, though improvement was seen in only a minority.

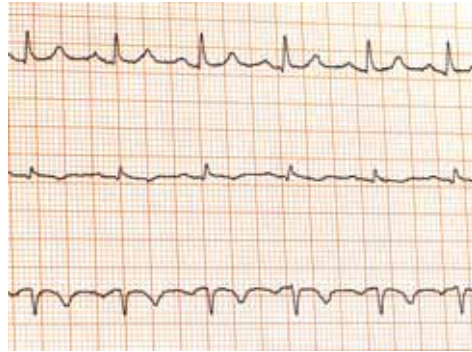
While the authors suggest that neurostimulants such as methylphenidate, might have a role in the therapeutic armamentarium of ME/CFS, it is worth remembering that these are not curative, and that not everyone with the diagnosis will benefit from them. ●

## Non-drug treatments

At our New Horizons conference (see page 3), Prof. Julia Newton spoke about autonomic nervous system dysfunction in ME/CFS patients, a majority of whom experience symptoms on standing (orthostatic intolerance). She discussed tilt-training, but there are other non-pharmacological interventions available, as outlined in a superb overview of orthostatic hypotension published earlier this year in *Cardiology in Review*.

The goal of treating orthostatic hypotension is to improve quality of life, and useful non-pharmacological strategies which GPs can advise on include the following. Tilt training — after initial training, patients at home (with another person there for safety) lean against a wall with their feet 15 cm away, increasing the length of time to 30 minutes over days to weeks (evidence suggests that such once-daily orthostatic self training can be effective in preventing the recurrence of fainting). Diet regulation — activity should be planned before meals, which should be larger at night when blood pressure (BP) is usually higher, and post-meal hypotension can be minimised by low cholesterol diets and smaller meals. Other interventions — physical manoeuvres (such as leg crossing and squatting) can help increase BP, wearing waist-high or knee-length elastic stockings can help minimise orthostatic reductions in BP, and drinking water helps increase BP by significantly increasing sympathetic activity. ●

# Recent Research from



## Differences between ME/CFS and fibromyalgia

Fibromyalgia is a condition characterised by widespread pain and tenderness. It also shares many of the same symptoms as ME/CFS, which has led some authorities to consider them manifestations of the same disease. However, while abnormalities of the autonomic nervous system (which controls activities such as heart rate, digestion and breathing) are common in both conditions, they may not be the same, and an Israeli study (published in the *European Journal of Internal Medicine*) has recently explored the differences in autonomic function between fibromyalgia and ME/CFS.

They assessed 30 women with fibromyalgia and 28 with ME/CFS using a head-up tilt test. The volunteers were strapped to a moveable table and rotated from a lying to an upright position for 30 minutes, while the electrical activity of their heart was monitored using an ECG. The QT interval — the distance between two specific points for a single heartbeat on the ECG trace — was measured.

The investigators found that patients with ME/CFS had a shorter QT interval than those with fibromyalgia, when lying and when upright, and also had differences in their cardiovascular response to the test. While the results suggest that fibromyalgia and ME/CFS are different, they also confirm previous reports that autonomic dysfunction can be measured relatively simply in ME/CFS patients. ●



## The economic impact of ME/CFS

It is well recognised that people with ME/CFS are functionally impaired and can be as disabled as patients with multiple sclerosis, heart disease and similar chronic conditions. However, the economic impact of the illness is also likely to be considerable, both to affected individuals and their families, and to society as a whole. Many patients have to leave their jobs and survive on disability income, while health care costs escalate in the search for a definitive diagnosis and treatment.

A recent American study (published in *Dynamic Medicine*) has sought to estimate the direct costs of ME/CFS using archived data from patients in the USA. A community-based sample of 21 ME/CFS patients and 15 control subjects, and a tertiary sample of 114 ME/CFS patients were asked to complete questionnaires on their current and past medical history, tests and medications, as well as sociodemographic characteristics such as current work status and socioeconomic status. Information was also taken from medical records.

From the community-based sample, the direct total cost per ME/CFS patient per year was estimated to be \$2,342, with a total annual direct cost to society of approximately \$2 billion. From the tertiary sample, these figures were \$8,675 and approximately \$7 billion, respectively — substantial economic costs which have been ignored for too long. ●

# around the World



## Similarities between ME/CFS and ciguatera

The symptoms of patients with ME/CFS are remarkably similar to those experienced by people with chronic ciguatera poisoning which is caused by eating fish contaminated with ciguatoxin, a potent neurotoxin (nerve poison). A comparison of these patient groups might be instructive, therefore, particularly as regards the structure of fats in the blood (lipids).

An epitope is the part of a molecule recognised by the immune system, and lipids from ME/CFS patients have epitopes with a similar structure to ciguatoxin. These "acute phase lipids" appear to be associated with mitochondrial phospholipids found in several other diseases, including viral infections, parasitic diseases and other microbial infectious diseases. Researchers from Hawaii-Manoa University in Hawaii have investigated this association in more detail by analysing the blood of 328 ME/CFS patients, 17 patients with chronic ciguatera, 8 Gulf War veterans, 24 patients with prostate cancer and 52 healthy individuals (Journal of Clinical Laboratory Analysis).

Acute phase lipids were found in a large proportion of all the patient groups, though not in the controls, and were part of the phospholipids of the mitochondrial membrane associated with cardiolipin. These phospholipids occur in many diseases, and may be involved in the immune dysfunction seen in ME/CFS. ●



## A review of immune dysfunction in ME/CFS

The immune system is a vital part of the human body's defence against disease. Its various cells and processes identify and kill invading bacteria, viruses and parasites, and when immunity is compromised the effects can be disastrous, as seen in the consequences of AIDS (acquired immune deficiency syndrome).

There is growing evidence that the immune system is impaired to some extent in people with ME/CFS, but little work has been done to develop therapies targeting this area which may improve symptoms. A recent review of the scientific literature on this topic by Belgian researchers (published in the journal Expert Opinion on Therapeutic Targets) sought to summarise current understanding on immune dysfunction in ME/CFS, and identify potential targets for immune therapy in the illness, if possible.

They concluded that proteolytic cleavage of the native RNase L enzyme appears to be characteristic of dysregulation of intracellular immunity in people with ME/CFS, being rare in healthy people and those with depression or fibromyalgia, though the precise cause is unknown. Coupled with increased apoptosis (early death) of immune cells, and the reduced number and activity (cytotoxicity) of natural killer cells seen in the illness, this evidence points to the need for increased efforts to identify and trial effective therapeutic drugs. ●

## Pregnancy and ME/CFS

Very little is known about pregnancy in ME/CFS. Whether or not the course of illness changes, or whether experience of pregnancy and childbirth is different remains largely unexplored — and no-one has a definite idea of the risks that might be involved. Women of childbearing age with ME/CFS are often concerned about the potential consequences of pregnancy on their own and their child's health, and so Peggy Rosati Allen of BirthCare HealthCare at the University of Utah College of Nursing decided to review what was known (Journal of Midwifery and Womens Health).

The most comprehensive investigation (Archives of Internal Medicine 2004) had found that 41% of women had experienced no change in ME/CFS symptoms during pregnancy, while 30% reported improvement and 29% worsening, though the specific factors influencing outcome could not be identified. Personal communications with experts such as Dr Nancy Klimas (see page 2) resulted in anecdotal reports on 51 women, most of whom felt an improvement in symptoms during pregnancy, possibly due to immune system and hormonal changes.

Can ME/CFS adversely affect fertility? No-one knows, though the review points out that polycystic ovarian syndrome is reported more often in women with the illness than in controls, and that dysmenorrhoea is almost universal, suggesting that the possibility exists. ●

## FRIENDS SCHEME

Our Friends scheme provides the core support needed for our work to continue. There are three categories: **Individual Friends, Corporate Friends** and **ME Group Friends**, all sharing our aim of a biomedical breakthrough in ME/CFS, and representing many thousands of patients and carers across the globe.

**Individual Friends** can give their support in a variety of ways, such as fundraising, regular donation by standing order, taking a collection box, or by just spreading the word — word-of-mouth is one of the most efficient ways of getting our work known.

The **Group Friends** scheme is for local ME support groups, and there are currently 30 groups informally signed-up. The Groups range from Castleford to Solihull & Birmingham, and from Aberdeen to Warwickshire, and the full list can be found on the Friends of MERUK section of our website.

**Corporate Friends** is designed for larger independent organisations — corporations, larger registered charities, companies, businesses — that share our aims, and the scheme brings collective power to the drive to energise ME research.

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

# Sarah's Marathon



Southend became a popular seaside resort in the Georgian era, and still boasts the world's longest pleasure pier (1.34 miles). And June 2008 saw Sarah Stone continue the fun by

completing the Southend Half Marathon in 124 minutes, an excellent time, raising over £1,800.

Sarah explains, "ME is an illness very close to my heart as my brother, Matthew, is severely affected." Matt was an active young man about to start a postgraduate course in 2002 when he became ill, eventually requiring 24-hour care. The family followed the conventional medical routes to no avail, trying every therapy available, and the expense of private treatment led a large group of Matthew's friends to organise a rolling series of major fundraising events on his behalf. Sarah continues, "All Matt

wishes for now is to carry out some of the basic daily tasks that we all take for granted, and the aim of his family and friends is to rehabilitate him to a stage where he can start his postgraduate studies." ●

## Portrait from a Friend

One of the highlights of our New Horizons conference on 6th May 2008 was the presentation to Dr Vance Spence of a portrait! The watercolour had been painted by Moira Robb, a professional portrait painter before ME left her very severely affected with neurological and brain symptoms.

Prof. Julia Newton presented the portrait to Vance at the end of her own keynote lecture, and as she explained, "It was Vance's 60th birthday very recently, and I've been asked to present him with this portrait to honour this landmark lifetime event, but also in recognition of all his work on behalf of ME patients over the past 25 years. Today seems the perfect time and perfect venue to present the completed work, which Moira says should come from all ME patients."

Moira's aim was to capture the "twinkle in his eye and his sense of humanity, and to say a big thank you for shining a light of truth on this



illness which has taken away so much of our lives". ●

# Mountain Challenge



The Highlander Mountain Marathon is a gruelling, two-day event in the Scottish Highlands, and a major challenge for even the fittest competitors. Yet, Jon Gay (pictured) and Peter Ward not only completed it in April, but came third overall against stiff opposition from more well known teams — an astounding result

compounded by the fact that they finished the event still wearing vests with our logo!

They had been encouraged in their efforts by Simon Overton who has had ME for many years following an initial viral infection which left him with a number of other symptoms that showed central nervous system involvement. After many years of disbelief from doctors, and numerous relapses and hospital admissions, Simon eventually had investigations at the Royal Victoria

Infirmery, Newcastle-upon-Tyne, which confirmed an autonomic nervous system problem. At present, Simon is awaiting surgery to correct some of the damage, and says that “this is one success story that would not have been possible without the work of ME Research UK”. ●

# Corner House Gig

Another night of superb entertainment was provided when Alan and Yvonne Hume held the latest in their series of biannual gigs in May at The Corner House in Newcastle.

One of the organisers, Beverley Thompson, explains, “The gig started off with music played by ‘Folklore’ comprising the two guitarists (Alan and Bob) with Yvonne who sang the harmony (but who couldn’t bash her tambourine as Alan had hidden it for the evening)! Pretty soon we were all clapping and singing.

“There were so many memories for those of us who were flower children in the 1960s, and perhaps are still hippies at heart, though with graying hair and less-than-nimble dancing feet. Magic — all of it.”



Alan compered seamlessly, and complemented the music with fascinating tales of the origins of the songs and their composers. Of course, the serious object of these biannual Guitar Gigs is to raise money for the charity, and it is a tribute to Alan that the gigs have raised over £10,000 in the past year alone. ●

## A MESSAGE FROM OUR PATRONS

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



*The Countess of Mar*

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



*Roger Jefcoate, CBE*

*“Given the recent sea change in the public perception of ME/CFS, and the possibility that patients will now be encouraged and supported rather than derided and scorned, we hope that ME Research UK’s scientific and policy research will lead the way towards a treatment and cure. Please help us to make a real difference to the lives of people with ME/CFS.”*

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.mererearch.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:

## Standing Order Form

**1** Name \_\_\_\_\_  
 Address \_\_\_\_\_  
 \_\_\_\_\_  
 Postcode \_\_\_\_\_  
 Telephone \_\_\_\_\_  
 E-mail address \_\_\_\_\_

**2** To the Manager  
 Bank/Building Society \_\_\_\_\_  
 Branch address \_\_\_\_\_  
 \_\_\_\_\_  
 Postcode \_\_\_\_\_

**3** Name of account holder(s) \_\_\_\_\_  
 Account number \_\_\_\_\_  
 Branch sort code \_\_\_\_\_

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

**5** Pay to: Clydesdale Bank, 23 South Methven Street, Perth PH1 5PQ, UK  
 Account: ME Research UK, Account no: 50419466, Branch code: 82-67-09

**6**  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.

**7** Signature \_\_\_\_\_ Date \_\_\_\_\_

Thank you for your support