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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

Around 190,000 people have a diagnosis of ME/CFS in the UK, and there are approximately 9,300 newly diagnosed cases each year. Yet, how valid a diagnosis of ME/CFS really is depends crucially on the rigour of the initial clinical assessment, and the efforts made to exclude other treatable conditions that might be causing the collection of symptoms. If the examination is cursory – and if the clinician is sceptical, alienated or just plain disinterested – the 'diagnosis' can easily become a convenient lay-by for clinically complex cases that don't fit into any other category.

Every year ME Research UK gets about 400 calls or e-mails from patients. A small number of these – not a flood, but a regular trickle – are from patients reporting that they have improved after being re-diagnosed with and treated for another condition. These conditions have included Addison's disease, multiple sclerosis, sleep apnoea, primary mitochondrial disease, primary liver disease and paranoid schizophrenia – and in every case the caller has been content with the re-diagnosis and/or the new treatments it has brought.

So, there is certainly anecdotal evidence that something is amiss with the diagnosis of ME/CFS at the GP surgery. Thanks to two good scientific papers from reputable clinical research groups in the UK, we now have formal research evidence to back up these patients' anecdotes.

In the first, researchers examined the records of every patient referred by local GPs to the Newcastle CFS/ME Clinical Service in 2008 and 2009. The key finding was that 103 (40%) of referrals were eventually diagnosed with other conditions which could explain the concatenation of symptoms. The main alternative diagnoses in these patients were fatigue associated with a chronic disease (47% of all alternative diagnoses); a primary sleep disorder (20%); psychological/psychiatric illnesses (15%, most commonly, depression, anxiety and post-traumatic stress disorder); and cardiovascular disorders (4%).

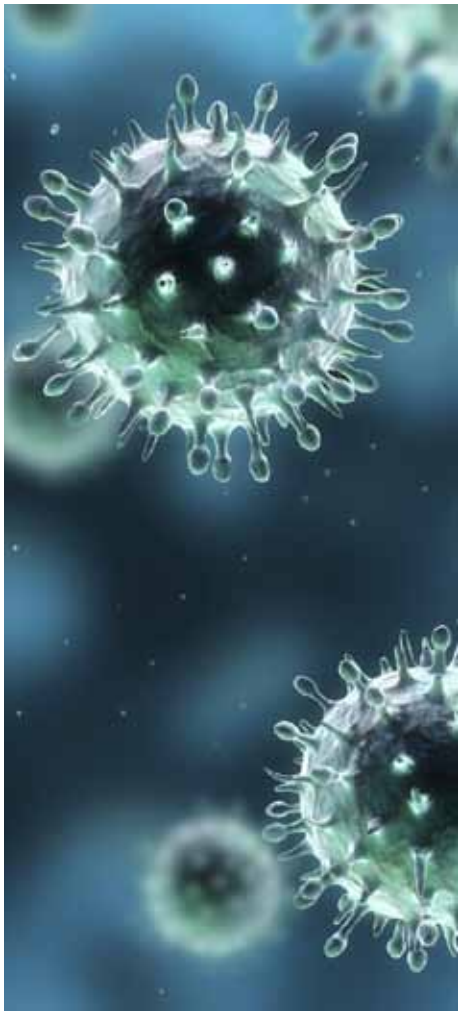
The second report (see page 12 of this issue of *Breakthrough*) examined the prevalence of alternative diagnoses in patients referred by GPs to the specialist clinic at St Bartholomew's Hospital, London in 2007 and 2008. Its major finding was that a diagnosis of 'CFS' was eventually confirmed in only 54% of patients, the rest being given alternative, treatable medical (21%) or psychiatric diagnoses (22%).

These reports provide clear, formal evidence that almost half of patients referred from primary care with a diagnosis of ME/CFS actually have something else wrong with them – a fact that is not discovered until they are lucky enough to be seen at a specialist clinic. This is misdiagnosis on a grand scale.

Something has to change. In the short term, continuing education for GPs should be beefed up – ideally with input from ME/CFS charities and experts. In the longer term, the problem could be resolved by the creation of ME/CFS Centres of Excellence at key points throughout the UK, offering biomedical assessment, proper diagnosis, treatment and onward referrals, all under one roof.

As well as improving patient care, these centres would become validated 'research resources' of properly diagnosed patients for biomedical studies of the future.

Dr Neil Abbot
Research & Operations Director
ME Research UK



this issue

Searching for microbiological biomarkers

Traditionally, myalgic encephalomyelitis has been associated with outbreaks of an epidemic character, such as the famous example in 1955 at the Royal Free Hospital, London. Even today, around half of all ME/CFS patients – non-epidemic cases seen in clinics throughout the developed world – report that their illness started with an acute, infectious-like episode. So, it's no surprise there has been some research into which infectious agents might be involved, either in causing the illness or in maintaining its severity.

The table below lists some of the main viruses or bacteria that have been implicated in ME/CFS at some time, though to date no single agent has been proved to be the 'smoking gun' in a majority of cases.

It is most likely that various different infectious agents can trigger the disease, and that the characteristics and development of the subsequent illness will depend on the genetic make-up and immune competence of the person infected. Also, the type of infection might be an important factor; as the scientific review by Devanur and Kerr (*Journal of Clinical Virology*, 2006) pointed out, viruses can trigger ME/CFS either by a hit-and-run mechanism (in which the virus is present at the beginning of the illness but cannot be detected later) or through a persistent infection (in which the virus is present both at the beginning of the illness and after months or years, and is detectable in patients with ME/CFS presenting to the clinic).

Given the potential importance of the role of infection in the illness, ME Research UK has awarded a grant to Swedish researchers to interrogate a group of ME/CFS patients exhaustively for evidence of a specific persistent or past infection. The team, headed by Prof. Jonas Blomberg (pictured right) at the University of Uppsala, Sweden, will hunt for nucleic acids from microbes reported to occur in elevated amounts or increased frequency in ME/CFS patients. They will also look for antibodies against these same microbes.

Importantly, the researchers will use novel multiplex technology (see box) which allows one blood sample to be tested for a large number of different infectious agents at the same time. The technique means that multiple pathogens are tested for simultaneously, which diminishes variation between assays and tests, and reduces assay time and costs.

This is the second grant that we have awarded to Prof. Jonas Blomberg's team. The first, funded in conjunction with the Irish ME Trust, was a thorough investigation of the possible presence of XMRV in Swedish patients. The results of this 18-month project (Elfaitouri et al, *PLoS ONE*, 2011) were that XMRV and related virus could not be detected by several different methods (virus isolation, PCR and serology) in white blood cells or plasma from Swedish patients with ME/CFS or fibromyalgia, or in blood sera from Swedish blood donors, using the sensitive PCR techniques specifically developed.

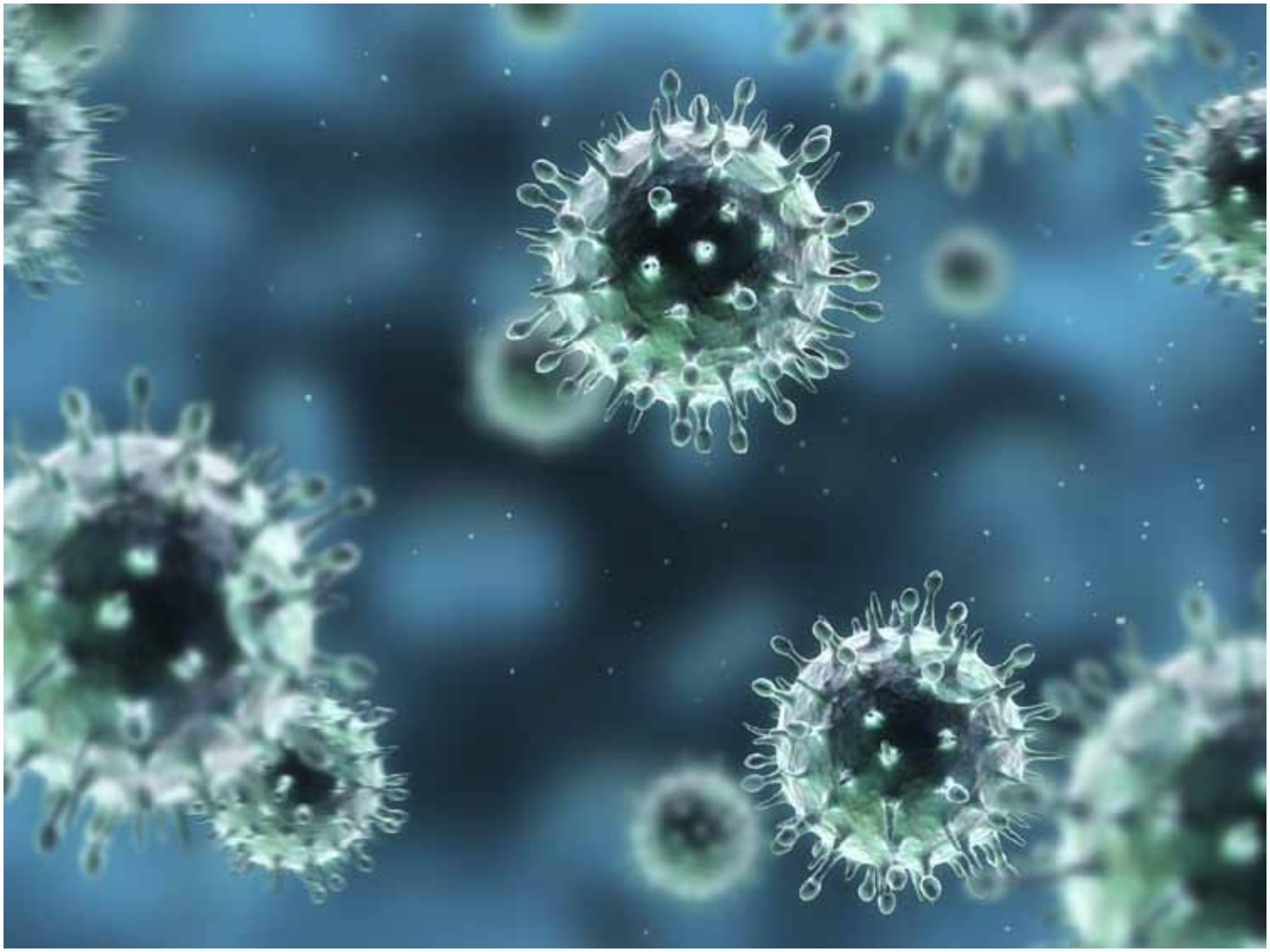
Despite these negative findings, which accorded with results from other research groups around the world, Prof. Blomberg is determined to continue the hunt for viruses and bacteria which might be involved in this serious illness.

Part of the new project consists of a development phase, involving the refinement of a 'variation tolerant capture multiplex assay' or VOCMA capable of probing for a large number of potentially relevant infectious agents. The major phase, however, involves deploying this multiplex technology to probe for nucleic acids (the identifying signatures of microbes) to around 15 infectious agents previously reported to be connected with ME/CFS.

The method is flexible: it can be adapted to include new microbes, and if some microbes do not yield useful information, they can be excluded. The agents investigated will include RNA viruses (such as enteroviruses), small DNA viruses (such

Main infectious agents associated with ME/CFS in research studies

Viruses	Enteroviruses, including coxsackievirus
	Epstein-Barr virus (EBV)
	Cytomegalovirus
	Human herpes virus 6
	Parvovirus B19
Bacteria	*Chlamydia pneumoniae*
	Coxiella burnetii (Q-fever)
	Mycoplasma spp.
	Brucella spp.
	Borrelia burgdorferi (Lyme disease)



as parvovirus), large DNA viruses (such as EBV and herpes virus 6), and bacteria including *Staphylocci*, *Borrelia*, *Chlamydiae* and *Mycoplasma*. In addition, sensitive antibody tests will establish whether patients have ever been in contact with infectious agents.

The aim of ME Research UK's support was to 'pump-prime' the project, which is part of a larger investigation by the Swedish group on the development of biomarkers in ME/CFS. No clear consensus on a laboratory diagnostic set of markers has yet emerged in the illness. However, as Professor Blomberg says, "*Given the range and scope of intriguing findings by separate research groups, the situation is ripe for the creation of a set of biomarkers. Some might be proteins in cerebrospinal fluid or blood, some might be immunological, and some might be microbiological (nucleic acid and antimicrobial antibody) as our investigation using multiplex technology hopes to reveal. Together with good clinical data (including neuroimaging), I think we have a chance of creating a robust set of criteria which can aid diagnosis and perhaps also reveal more about the origins of ME/CFS.*"

What is multiplex?

Traditional laboratory techniques have involved scientists testing one sample for one thing at a time, making research a slow, costly and painstaking business. Mulitplex is an assay technique that performs multiple sets of reactions in parallel, allowing a large number of different tests to be made on the same sample simultaneously – a dramatic technological advance.

As well as providing more information on biological processes, the technique increases the number of tests that can be done in a given period, and delivers results faster with analysis in real-time.

The technique has played an important role in functional genomics. In particular, it can detect the functioning of all the biomolecules in a biological sample simultaneously, for example during various stages of an experimental treatment.

Multiplex systems can be customized to the user's specific bioassay needs (nucleic acids, antigen-antibody binding, enzymes and receptor-ligand) so they have great potential. In the Swedish study, they are being applied to the detection of infection, allowing a large number of different infectious agents to be probed for at the same time using only one sample from each patient.

Prof. Blomberg's team has been developing a new multiplex method – variation-tolerant capture multiplex analysis (VOCMA) – for the simultaneous detection of nucleic acid from viruses, bacteria and fungi.

In a recent technical report (20th European Congress of Clinical Microbiology and Infectious Diseases), Prof. Blomberg says, "*A multiplex method like VOCMA saves time, reduces the cost per microbe analysed, as well as the consumption of sample, and increases the possibility of discovering co-infections.*"

Are ME/CFS patients more sensitive to pain?

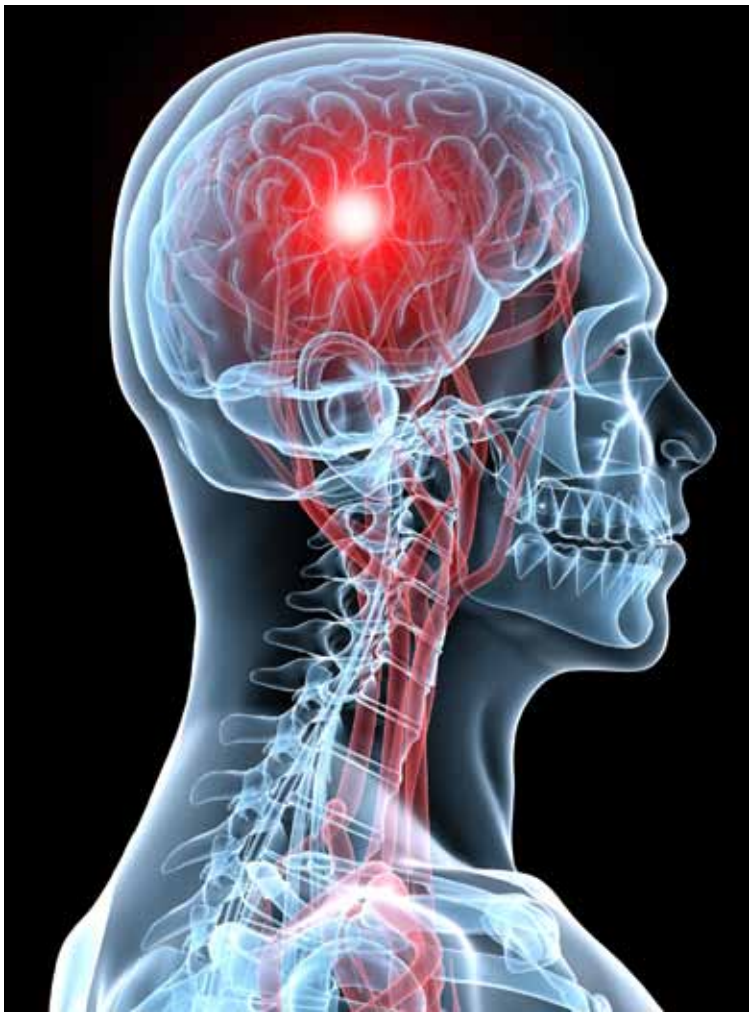
Widespread and persistent pain is common in people with ME/CFS. In surveys, around 80% of patients say that they have severe pain sometimes, much or all of the time, while 84 to 94% of patients in formal research studies report some degree of muscle or joint pain. Also, around one-third of patients say that chronic pain limits or restricts their everyday activities, and that pain is a more disabling day-to-day symptom than fatigue.

Despite this, there has been very little scientific investigation of the pain characteristics of ME/CFS patients. One of the very few studies done – part of a PhD studentship at Glasgow Caledonian University – was funded by ME Research UK and published in the *Journal of Musculoskeletal Pain*. As the results of this investigation showed (see Figure), the patients used words such as 'throbbing', 'aching', 'tender', 'gnawing' and 'burning' to describe their pain experience, while those with more severe illness also used 'exhausting' and 'nagging'.

These descriptions may give clues as to the mechanisms causing pain in ME/CFS; in particular, 'burning' pain is often associated with neuropathic conditions in which the nerves have been damaged. Significantly, ME/CFS patients reported more pain than did patients with rheumatoid arthritis or multiple sclerosis in previous studies, both conditions in which pain is recognised as a major symptom.

Fibromyalgia is an illness with overlapping symptoms to ME/CFS, and one concept which has been extensively explored in fibromyalgia research in recent years concerns central sensitization – an increased sensitivity of cells in the spinal cord and the brain to various stimuli, including touch, heat, cold and chemicals. Central sensitization is believed to underlie many chronic pain conditions (see Box), leading to an increased sensitivity to pain, but could it also be a factor in the pain felt by ME/CFS patients?

One of the most active ME/CFS and fibromyalgia research groups in the world is headed by Prof. Jo Nijs at Vrije Universiteit and Artesis University College Antwerp in Belgium. With funding from ME Research UK, he and his colleagues have been investigating immunological responses to exercise, and have been undertaking a comparison of the different criteria for myalgic encephalomyelitis and CFS currently in use. The group also has a long-standing interest in central sensitization, and has just published a narrative review of its potential relevance in ME/CFS (in the *European Journal of Clinical Investigation*, February 2012).



After searching the scientific literature, they found a range of experimental studies that had tested patients' responses to stimuli including mechanical pressure, heat, aerosol inhalation of histamine, and electrical stimulation. Taking the studies as a whole, there was good evidence that ME/CFS patients had a generalised hyperalgesia (an increased sensitivity to pain throughout the body). Furthermore, patients' pain sensitivity increased after stressors, such as harmful heat pain, and following exercise – an unusual observation since sensitivity to pain normally decreases in people during physical activity.

These findings came as no surprise to the researchers, who say that the presence of central sensitization accords with many of the symptoms of ME/CFS, as well as simply increasing sensitivity to pain. For example, infections are associated with the illness (see page 4), and immune dysfunctions are characteristic features. Infection is known to trigger the release of the substances promoting inflammation, such as interleukin-1b, which play a role in sensitising peripheral nerves, and infections themselves can activate cells in the spinal cord which enhance the pain response.

Also, the activity of the hypothalamus–pituitary–adrenal (HPA) axis – a major player in the neuroendocrine system that controls reactions to stress and regulates many body processes – is known to be blunted in ME/CFS, and some crucial factors in the HPA axis are involved in pain sensitivity. In particular, low cortisol levels might contribute to (pain) hypersensitivity since cortisol levels are involved in pain inhibition.

Finally, the neurocognitive symptoms seen in patients – principally memory and attention span and associated emotional processes – could inhibit central nervous system pathways from the brain downwards, resulting in sensitization of nerve cells in the spinal cord. Indeed, this could explain why psychological

therapies designed to help patients manage symptoms and cope better with illness can be helpful in a minority of cases, as some patient surveys and clinical trials have shown.

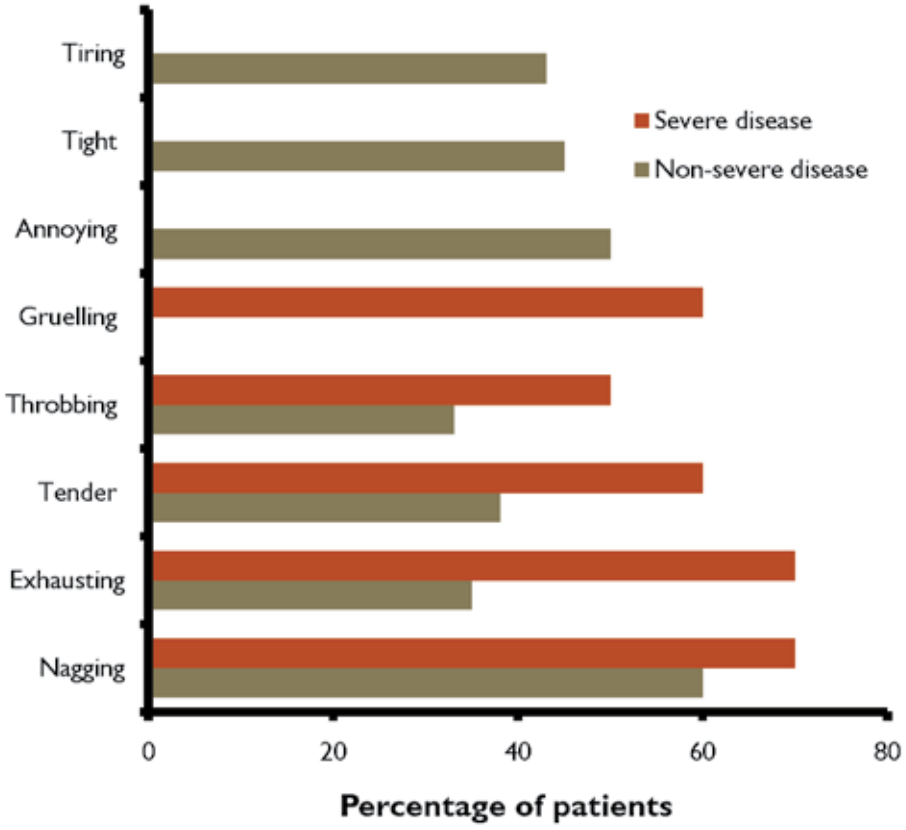
The fact that central sensitization can be found in ME/CFS patients raises the question of treatment strategies to desensitize the central nervous system, making it less sensitive to painful stimuli. Fortunately, over the past few years there has been ongoing scientific work to develop targets specifically designed to block or reduce central sensitization. Various centrally acting drugs that have shown promise in animal models include analgesics, serotonin reuptake inhibitor drugs, the serotonin precursor tryptophan, opioids, and NMDA receptor antagonists (a class of anaesthetic). However, some of these agents may not be appropriate for ME/CFS patients.

Likewise, various non-invasive treatment options have been proposed, based on the premise that nerve pathways from the brain downwards could be activated to help inhibit pain. These therapies include transcranial magnetic stimulation and transcutaneous electric nerve stimulation, and may also include cognitive techniques or biofeedback to address the emotional aspects of increased pain.

Of course, it is widely recognised that the 'black box' diagnosis of ME/CFS probably contains a variety of different types of patients, and it will be important to identify patients with a clinical picture dominated by central sensitization. The researchers say that these patients could be identified clinically by questioning them regarding hypersensitivity to bright light, sound, smell, hot or cold sensations, pressure, touch, and mechanical loading, whereas widespread sensitivity to pain can be recognised by testing muscle tone at various anatomical locations. Interestingly, the new International Consensus Criteria for ME (*Journal of Internal Medicine*, 2011) includes several characteristics related to central sensitization.

Since its first description, central sensitization has become an increasingly important concept in pain research. It is known to underlie many pain conditions (from allodynia caused by nerve injury, to headache), and now the review from the Brussels team has shown that it could be involved in ME/CFS as well. In their view, a change in thinking towards studying and treating ME/CFS as a central sensitization disorder appears warranted, particularly as therapeutic interventions become available.

Descriptions of pain used by ME/CFS patients



What is central sensitization?

- Nerve impulses can be thought of as messages fired along nerve fibres at great speed. Central sensitization involves an abnormal increase in the firing of nerve cells lying deep within the central nervous system (i.e., the brain and the spinal cord). This leads to an increase in the pain experienced by the person.
- The increased firing (excitability) is typically triggered by a burst of activity in nociceptors (pain receptors) which send nerve signals to the spinal cord and brain.
- The mechanisms involved in central sensitization are complicated. Some are top-down (from brain to the periphery), such as when sensory processing is altered in the brain. Others are bottom-up (from periphery to brain), such as when local infections trigger the release of the inflammatory molecules which activate cells in the spinal cord.
- An example of central sensitization is when a very light touch of the skin (from low-threshold sensory fibres) activates nerve cells in the spinal cord or brainstem that normally only respond to harmful stimuli. In this case, the light touch produces pain inappropriately – to the person, the pain feels like it comes from the skin or limb, whereas actually it is a manifestation of abnormal sensory processing in the central nervous system.
- Central sensitization is known to be responsible for tactile allodynia (pain in response to light brushing of the skin) and for the spread of pain hypersensitivity beyond an area of tissue damage so that adjacent non-damaged tissue is tender. The phenomenon can also occur after surgery, contributing to pain on movement or touch; during migraine attacks where brushing hair is often painful; and in some patients with nerve damage where even blowing on the skin produces excruciating burning pain.

ME/CFS and the increased risk of cancer

The fact that ME/CFS has an infectious onset in many cases, and is associated with abnormalities of cellular immunity, raises the question of whether people with the illness are at an increased risk of developing cancer.

There is certainly no definitive evidence that this is the case – principally because the large-scale epidemiological studies needed to establish a link have not been conducted. Yet, over the years, there have been intriguing, if inconclusive, hints that there may be an association between ME/CFS and cancer.

For example, a survey of deaths from a memorial list in the USA found that one-fifth of the ME/CFS patients listed had died of cancer (see the box opposite). And an analysis in 1998 of data from the Nevada Cancer Registry, found the incidence of non-Hodgkin lymphoma and primary brain tumours to be comparatively higher in two northern Nevada counties where well-documented outbreaks of CFS had occurred between 1984 and 1986.

The existence of such fragmentary evidence, plus the biological plausibility that the immune abnormalities or infections found in ME/CFS might increase the cancer risk, led researchers at the National Cancer Institute to undertake a large case–control study (published in *Cancer*, 2012) among elderly adults in the United States, using linked data from cancer registries and Medicare claims files.

The advantage of this experimental design is that very large sample sizes can be obtained – a crucial step if valid conclusions are to be drawn about the connections between highly heterogeneous diseases such as cancer (which contains many different types of tumour at many different stages) and ME/CFS (which is most probably a diagnostic 'black box' containing different clinical groups of patients).

The National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) programme provided the cancer data from registries across the US, with 'cases' defined as people aged 66 to 99 years with first cancers from 1992 to 2005. The occurrence of 'CFS' was assessed from Medicare claims using ICD codings. For analysis, a combined SEER-Medicare data set was created electronically to allow the link between cancer and ME/CFS to be explored.

"CFS was not associated with cancer overall"

Overall, the presence of CFS was similar in cancer cases and controls (0.5% in each). The table below shows that CFS was not associated with cancer overall, but was associated with a significantly increased risk of non-Hodgkin lymphoma (NHL; odds ratio 1.29). Looking at the subtypes of NHL, CFS was associated with diffuse large B cell lymphoma (odds ratio 1.34), marginal zone lymphoma (odds ratio 1.88) and B cell NHL not otherwise specified (odds ratio 1.51).

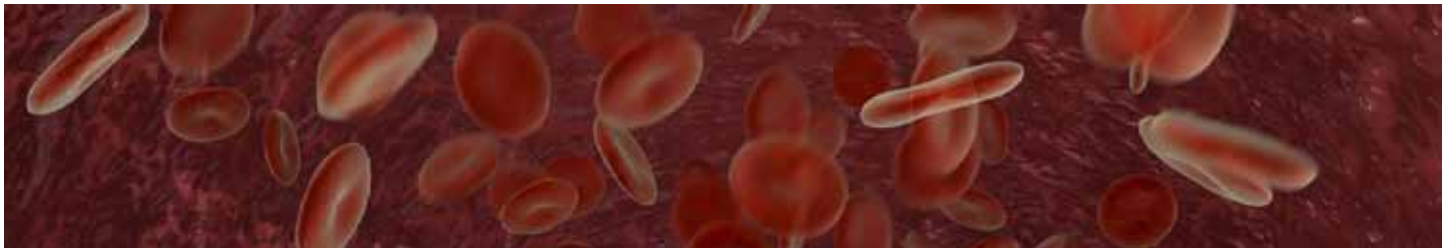
There were also initially significant associations between CFS and a few other cancers, including cancers of the pancreas, kidney and breast, but these became non-significant after correction for multiple comparisons.

Whilst the finding that the overall cancer risk was not increased is encouraging, what might explain the increased risk of NHL in people diagnosed with CFS in the USA between 1992 and 2005?

Well, we can only speculate, but the researchers point to the immune

Associations between ME/CFS and overall cancer or non-Hodgkin lymphoma (NHL) subtypes

Cancer type	Number of people	% with CFS	Odds ratio (risk)	Significance of association
Controls	100,000	0.5	1.0 (reference)	
All cancers	1,176,950	0.5	0.99	Not significant
Overall NHL	57,632	0.7	1.29	p<0.001
NHL subtype				
Diffuse large B cell lymphoma	16,470	0.7	1.34	p<0.002
Marginal zone lymphoma	3,358	1.2	1.88	p<0.001
B cell NHL	2,930	0.9	1.51	p=0.037



Immune links between ME/CFS and cancer

Cancer fatigue is a well-recognised, often intense symptom experienced during and after treatment. Since cancer and ME/CFS share both fatigue and severe disability, researchers in Antwerp speculated that there could be other links between the two pathologies, particularly as regards immune abnormalities.

The key findings of their 2009 review, published in *Anticancer Research*, were that both conditions share abnormalities in the RNase L antiviral pathway and in the major intracellular mechanism NF-κB which regulates inflammatory and oxidative stress (see below).

In addition, natural killer cell malfunction has long been recognised as an important factor in the development and reoccurrence of cancer, and this has also been documented repeatedly in people with ME/CFS. The researchers pointed out that these immunological problems are clearly apparent and quite similar in both diseases.

While there are clear differences between cancer and ME/CFS – most prominently in cause, illness progression and mortality – the researchers were nevertheless intrigued by the shared immune abnormalities. It may be that these overlapping immune dysfunctions are involved in shaping some of the symptoms shared by both illnesses.

Factor	ME/CFS	Cancer
Ribonuclease L (RNaseL)	Increased activity → increased apoptosis	Decreased activity → decreased apoptosis
Nuclear factor kappa beta (NF-κB)	Increased activation	Increased activation
Natural killer cells	Decreased activity	Decreased activity

abnormalities (some shared with cancer – see the box above) that have been observed in ME/CFS patients – including increased immune activation, reduced natural killer cell activity (see page 14), and the presence of autoantibodies – and to some of the viruses and bacteria that have been implicated in the development and maintenance of the illness (see page 4).

Since both immune disturbances and viral infections have been implicated in the development of diffuse large B cell lymphoma and marginal zone lymphoma in other contexts, the authors suggest that similar associations are at least plausible in ME/CFS. However, they caution that the study was limited to people aged 66 years and older, so that the findings may not be generalisable to younger (non-elderly) populations.

Furthermore, they warn against any direct interpretation or application of these results in a clinical setting; as they say, "*We could not estimate the absolute risk of non-Hodgkin lymphoma associated with CFS, but the risk is likely too small to affect the clinical management of patients.*"

Deaths in a memorial list

In 2006, the journal *Health Care for Women International* published an analysis of a memorial list by Prof. Lenny Jason and colleagues at the University of Chicago.

The list, tabulated by the National CFIDS Foundation, contained information on 166 deceased individuals reported to have a diagnosis of CFS and whose list data had been supplied by relatives and friends.

The four most prevalent causes of death were heart failure (20% of the total sample), suicide (20%), cancer (19%) and complications of CFS (11%). The average age at death was 47.8 years in those who died from cancer (significantly younger than the mean age of death for cancer in the USA, 72 years), and 39.3 years for those who had committed suicide.

As Prof. Jason pointed out, it is impossible to generalise from the data on the memorial list to the overall population of patients with ME/CFS. The various methodological limitations – the 'self-report' nature of the data from patients' relatives, the absence of independent confirmation of cause of death, and the incompleteness of the information itself (e.g., the type of cancer or heart disease) – all conspire to limit the scientific conclusions that can be drawn.

Nevertheless, the tabulated information has value, and highlights the tragic consequences of ME/CFS for some patients.

We already know that the prognosis is poor for many people with the illness – one review in 2004 concluded that, "*patients exhibit severe, long-term functional impairment… Substantial improvement is uncommon and is less than 6%*" – and it is well-recognised that the presence of long-term illness impacts significantly on life expectancy.

Impaired cardiac function

Dr Kieren Hollingsworth, Tim Hodgson and Tamsin Gaudie (Senior Research Radiographers)

Some ME/CFS patients experience heart symptoms, most commonly cardiac arrhythmias including tachycardia (racing heart) or palpitations usually associated with autonomic nervous system dysfunction. In fact, for some patients they can be the most frightening aspects of their debilitating illness.

In the scientific literature, a few reports have confirmed the existence of abnormalities of cardiac function in some patients. For instance, a study in 2006 found that ME/CFS patients had relatively short QT intervals (measures of the time of the heart's electrical cycle) compared with healthy people. Also, in 2009, Japanese researchers reported cardiac dysfunction with low cardiac output in some oriental patients, and an echocardiographic study from 2010 found that the ability of the heart to contract was reduced.

Overall, however, little formal research has been conducted on the presence of heart abnormalities in ME/CFS patients, and what these might mean for the individual patient.

Since 2008, ME Research UK, in conjunction with the John Richardson Research Group and the Irish ME Trust, has funded Professor Julia Newton of the Institute for Ageing and Health, University of Newcastle to explore some of the mechanisms behind autonomic nervous system abnormalities in a large cohort of ME/CFS patients. She and her colleagues Prof. David Jones and senior physicist Dr Kieren Hollingsworth of the Institute of Cellular Medicine have been using state of the art magnetic resonance techniques to investigate whether autonomic nervous system symptoms (which can be found in around three-quarters of patients) are associated with abnormalities in other major organ systems, something we know to be the case in other illnesses.

Their investigations of the heart have been throwing up some intriguing findings. For example, in a previous report (discussed in full in *Breakthrough*, Spring 2011) they showed that 'bioenergetic abnormalities' could be found both in the muscles of the skeleton and in heart muscle, with a correlation between the two suggesting the existence of linked underlying mechanisms.

Also, they found that the hearts of the ME/CFS patients had to work harder during prolonged standing than in healthy people. These findings raised the question of whether abnormalities could be detected in the function of the heart, particularly during the heartbeat.

To investigate these aspects, the team have been using cardiac MRI tagging, a complex technique that has been used previously to examine the function of the heart during the ageing process, in which gradual changes might be expected to occur subclinically (before actual symptoms can be observed).

The researchers thought it could be the ideal tool to examine the hearts of ME/CFS patients for defects that are not yet

clinically apparent. The technique allows accurate assessment of myocardial (heart muscle) movement in three dimensions, and gives detailed information about 'myocardial transmural strain' (an indication of the shortening of heart muscle fibres) and torsion (a measure of the 'twist' of the heart during the beat), two events that can be affected by energy deficits before they are obvious clinically.

Their experiment involved 12 women with well-defined ME/CFS and 10 closely matched, sedentary healthy women. Each person underwent cardiac examinations using an MRI scanner for cardiac tagging, and cardiac MRI cine imaging to assess cardiac form and structure, as well as systolic and diastolic function.

The group's findings have now been published in the March 2012 issue of the *Journal of Internal Medicine* (see the box below). The Figure below illustrates one of the main findings – the dramatic increase in residual torsion in patients compared with controls. This is a measure of the efficiency of the release of torsion and strain during the relaxation phase of the heartbeat. ME/CFS patients had 200% more residual torsion than the matched controls, indicating that their heart muscle was taking longer to relax.

To put this in context, healthy people have an increase in residual torsion of around 50% between the ages of 22 and 69 years, possibly because ageing affects the lining of the muscle fibres which permit the heart to relax. Why residual torsion is raised even more in people with ME/CFS is unclear, but – because the level of torsion was found to be related to end-diastolic volume – the researchers speculate that low total blood volume might be involved.

In fact, the research team says that its overall findings strongly suggest a marked reduction in the total (central) blood volume in ME/CFS patients – since a smaller volume flowing into the heart would lead to a lower amount of blood pumped by the ventricle and a lower cardiac output.

This suggestion is not new: low total blood volume and associated autonomic nervous system dysfunction have been proposed as part of the disease process in subgroups of ME/CFS patients in the past. Indeed, one investigation in 2002 found a 9% lower blood volume in ME/CFS patients than in controls. A further study in 2010 showed that the reductions in cardiac output and end-diastolic volume in ME/CFS could be entirely accounted for by a reduction in the total blood volume, and an accompanying editorial pointed out that the results did not imply heart disease, but rather pointed to "circulatory impairment".

So, what can be done – or should be done – about correcting low cardiac blood volume? Well, blood volume is known to be affected by relative inactivity, and so may be a reflection of chronic ill-health rather than ME/CFS per se. If this is so, keeping active, such as by pacing, may improve total blood volume. Also, there is anecdotal evidence that ME/CFS patients have had symptomatic improvements with the administration of intravenous fluid as a treatment intervention (although this is not without its drawbacks and risks), and the researchers say that they intend to explore interventions to restore fluid volume in ME/CFS patients.

They also point out, however, that ME/CFS patients may indeed have primary myocardial deficits that are not associated with low total blood volume, and this possibility needs to be explored too.

What did the results show?

There were no significant differences in resting heart rate or systolic/diastolic blood pressure between patients and controls.

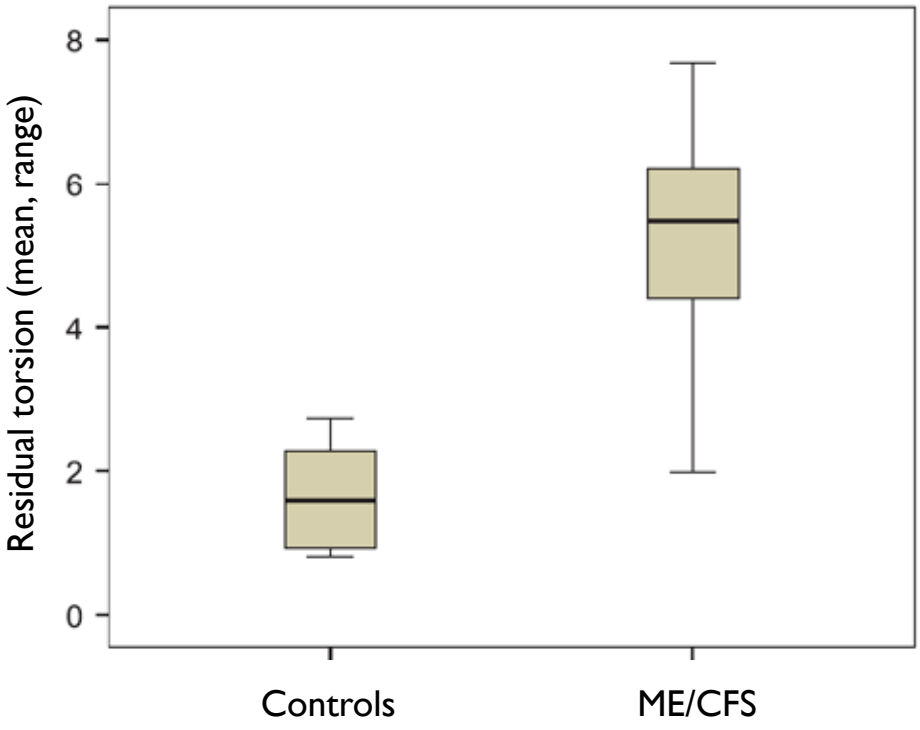
In the ME/CFS patients, left ventricular mass (the thickness of the heart wall at the ventricle) was substantially reduced (by 23%) compared with controls.

After correction for individual body size, the various measures of 'blood pool volume' in the heart were significantly lower in patients than controls:

- stroke volume (the amount of blood pumped by the left ventricle in one contraction) was lower by 26%;
- cardiac output (the output of blood by the heart per minute) was lower by 21%;
- end diastolic volume (the volume of blood in each ventricle at the end of diastole) was lower by 25%.

Intriguingly, residual torsion (at 150% of the end-systolic time) was significantly higher in the patients (see Figure), indicating a delay in the release of torsion ('twist') at the end of the beat.

The higher residual torsion in patients indicates a delay in the release of 'twist' at the end of the heart beat



Research bites from around the world

AUSTRALIA

Do patients fake it?

Problems with memory, concentration, attention and information processing are frequent and disabling symptoms associated with ME/CFS. In fact, around 90% of 2,073 patients in one large study reported cognitive symptoms, which can be made worse by physical or mental exertion. However, there is a view that ME/CFS patients are actually fine – it's just that they put in less effort than other people during neurocognitive testing at clinics and research labs, possibly to obtain state benefits. It's an insulting suggestion, but can it be true?

Earlier this year, researchers at the University of Adelaide in Australia examined whether suboptimal effort was associated with cognitive deficits, using an instrument called the Validity Indicator Profile (VIP) which, intriguingly, can distinguish between intentional and unintentional poor performance. However, in the 54 ME/CFS patients examined (44% of whom were on benefits), VIP performance was classified as 'valid', indicating high levels of effort and an intention to perform well – findings very similar to those seen in healthy people from the community. Importantly, the receipt of benefits or a disability pension was not associated with the effort put in by patients, undermining the suggestion that patients fake cognitive deficits for financial gain.

Source: *Cockshell & Mathias, J Clin Exper Neuropsych, 2012*

LONDON

Who the heck has ME/CFS?

As the Editorial on page 2 points out, there is both anecdotal and research evidence that some GPs are diagnosing ME/CFS inaccurately, and a recent study has added to the mounting concern. The investigation, conducted by clinicians at the London School of Medicine, examined the prevalence of alternative diagnoses in patients referred by GPs to a hospital clinic with a definite or provisional diagnosis of 'CFS' between March 2007 and September 2008.

The major finding was that a diagnosis of 'CFS' was eventually confirmed in only 137 of 250 patients (54%) assessed at the clinic. Of the rest, 53 patients (21%) were given alternative medical diagnoses (most commonly primary sleep disorders, endocrine disorders, nutritional disorders and pain disorders), while 54 patients (22%) received alternative psychiatric diagnoses (most commonly a depressive illness or anxiety disorder). As around 9,300 people are newly diagnosed with ME/CFS every year in the UK, mostly by GPs, it makes you wonder how many of them actually have another, treatable condition, doesn't it?

Source: *Devasahayam et al., J R Soc Med Sh Rep, 2012*

MARYLAND

Rintatolimod trial

Clinical trials of non-psychological treatments are quite rare in ME/CFS, so it can be exciting when one comes along, particularly if the most severely affected patients are included. One recent example was a phase III randomised trial in which the TLR-3 agonist rintatolimod was compared with placebo in 234 people suffering with long-standing, debilitating ME/CFS at 12 different centres across the USA.

After 40 weeks, exercise tolerance (total achievable exercise time on a treadmill) was significantly improved in the patients on intravenous rintatolimod therapy (400 mg twice weekly) compared with those on placebo. The size of the improvement was around 20%, equating to approximately 68 seconds of additional treadmill activity. Indeed, the authors say that this level of improvement represents approximately twice the minimum considered medically significant by regulatory agencies. Rintatolimod also reduced dependence on symptom-relieving drugs compared with placebo, and it seems to have been well-tolerated with no serious adverse effects definitely related to the drug.

Under its more common name, Ampligen, rintatolimod has been well-known to ME/CFS patients since the first preliminary report of its potential usefulness in 1994. Ampligen has known antiviral and immunomodulatory properties, and these positive results suggest that it may become part of the therapeutic armoury of treatments for ME/CFS, providing FDA approval is finally granted.

Source: *Strayer et al., PLoS ONE, 2012*

NORWAY

Hope for youngsters

Young people with ME/CFS are thought to have better rates of improvement or recovery than adults, and a report from Oslo University Hospital, Norway has provided further support for this belief. Clinicians in the Paediatric Outpatient Clinic, who had completed a study of adolescents with ME/CFS in 2009, followed up 38 of their cases, focusing on any changes in clinical symptoms and autonomic cardiovascular control at a second visit about 8 months after the first.

At the second visit, patients reported significant improvements in fatigue severity, muscular pain, concentration and post-exertional malaise. Furthermore, their baseline heart rate, blood pressure and a variety of cardiovascular measurements had significantly improved. Thus, the majority of adolescents with ME/CFS experienced improvements during a relatively short follow-up, a finding that gives some hope to families coping with a youngster with the illness.

Source: *Sulheim et al. BioPsychoSocial Medicine, 2012*

SPAIN

Antipsychotic not useful for fibromyalgia pain

Apparently, some antipsychotics can be effective treatments for a variety of painful conditions, lessening pain as well as the anxiety or depression associated with pain. One of these is amisulpride which has been shown to be effective for pain in animal models, and in patients with burning mouth syndrome. At the Universidad de Granada, Madrid, researchers undertook an exploratory 12-week study of the usefulness of amisulpride for pain in fibromyalgia, an illness which has a diagnostic and symptom overlap with ME/CFS. Amisulpride was given to 40 patients alongside their current drugs, at an initial dose of 25 mg per day rising according to the clinical response and tolerability (the mean final dose was 87.5 mg per day).

There was no significant change in the fibromyalgia score over the 12 weeks, and no change in the patients' pain severity, although there was a mild improvement in sleep overall. Importantly, 26 of the 40 patients either withdrew from the study, mainly due to adverse reactions, or were lost to follow-up. So, despite its promising results in some chronic painful conditions, amisulpride did not seem to benefit these patients, and was poorly tolerated by them. Science does not always throw up positive results, but the negative ones can be just as useful for excluding ineffective or even harmful therapies.

Source: *Rico-Villademoros et al., Clin Rheumatol, 2012*

BELGIUM

Post-exertional symptoms for diagnosis

There is much discussion about particular criteria for the diagnosis of ME, CFS, PVFS, CFS/ME or ME/CFS – just listing these acronyms makes the head spin. But, in the absence of hard data from real patients, much of the speculation generates more heat than light, and produces more angst than understanding. That's why the results of a recent investigation on patients from the Maes Clinic in Belgium are so valuable.

The investigators raised the question of whether clinical differences could be observed between CFS patients with post-exertional symptoms and those without such symptoms. Using statistical models, they found that a combination of fatigue, a subjective feeling of infection, and post-exertional malaise defined groups of patients in which distinct differences in clinical symptoms (and inflammatory biomarkers) could be found.

The researchers' conclusion was that whilst the traditional (Fukuda) definition of CFS can adequately distinguish between CFS and uncomplicated 'chronic fatigue', patients fulfilling the Fukuda definition should be subdivided into those with post-exertional malaise and those without. Interestingly, the UK's NICE Clinical Guideline of 2007 insists that post-exertional symptoms should be present for a diagnosis of 'CFS/ME' to be made, so the importance of post-exercise symptoms is already recognised formally. The challenge remains to get GPs and healthcare professionals to apply the criteria in practice when diagnosing patients in the clinic.

Source: *Maes et al., Psychiatry Research, 2012*

NETHERLANDS

FatiGo trial

Cognitive behavioural therapy (CBT), a psychotherapeutic approach to all illness, has been given many chances to prove its usefulness in clinical trials on ME/CFS patients. In fact, the therapy and its proponents have enjoyed a good run for their money, in terms of both professional involvement and public funding. Today there is an emerging consensus that CBT can moderately improve outcomes in a minority of people with ME/CFS, benefitting around 10 to 15% of patients over and above the benefit of standard medical care, as shown in the results of the 2011 PACE trial, and in the findings of ME charities' surveys of their members. So, is that the end of an old song?

Er, no. Another large-scale, multicentre, randomised, expensive clinical trial is underway in the Netherlands. Called the FatiGo (Fatigue-Go) trial, it aims to compare CBT with a "multidisciplinary rehabilitation treatment" combining CBT with principles of mindfulness, a gradual increase of activities, body awareness therapy, and pacing. The results are expected in early 2013. Meanwhile, keep calm and carry on.

Source: *Vos-Vromans et al., Trials, 2012*

NORWAY

More chat on ME/CFS Internet forums

Over the last decade, the Internet has become an invaluable resource of health-related information, accessible by healthcare professionals and, crucially, by patients themselves. Also, the number of health-related online support groups and discussion forums has mushroomed, raising the question of whether online activity is greater for some diseases than others, and if so why.

Researchers in psychiatry from Norway, Australia and England – who had a particular interest in this question – have just published their observations of "*disorder-related online discussions*" from 12 Norwegian online forums for illnesses (such as obsessive compulsive disorder, breast cancer, chronic pain), including two forums specifically for ME/CFS issues. They found that ME/CFS forums had much higher numbers of registered users; for example, 'Me-forum' had 50.5 (per 1,000 cases in the population), while the next highest number of registered users (5.4) was for a forum on drug and alcohol dependency. Also, the number of posted messages per 1,000 cases indicated higher online activity on ME/CFS forums compared with others.

As to reasons for this, the authors give a range of possibilities – the most obvious being the particular experiences of ME/CFS patients within traditional healthcare systems (scepticism, hostility, and the possibility of misdiagnosis, etc.) which drive them to seek alternative sources of support and information.

Source: *Knudsen et al., J R Soc Med Sh Rep, 2012*

AUSTRALIA

Low natural killer cells

One of the most consistent abnormalities reported in ME/CFS patients over the past 20 years has been that their natural killer cells are reduced in number and/or have a lower activity than in healthy people. In fact, there was a suggestion at one time that an alternative name for the illness might be 'low natural killer cell' disease.

Natural killer cells have a key role in the targeted killing of tumour cells and virus-infected cells, so it is important that they are present in optimum numbers and that they are as active as they can be. No-one knows, however, whether natural killer cell activity is consistently lower in the illness, or whether it simply changes over time as, for example, patients relapse and recover.

Researchers at Bond University, Australia, decided to look at the activity of natural killer cells and other cytokines over 12 months in 65 ME/CFS patients and 21 non-fatigued healthy controls. The cytotoxic activity of natural killer cells (i.e., their ability to destroy other unwanted cells) was found to vary significantly in patients over the 12 months, but was nevertheless consistently lower throughout the whole year in the patients than in the non-fatigued control group. The authors point out that this decrease in immune function is similar to what is seen in various immunological diseases, and suggests an increased susceptibility to viral and other infections.

Source: *Brenu et al., Journal of Translational Medicine, 2012*

NORWAY

Gut symptoms could be key

On the whole, the gut symptoms that large numbers of people with fibromyalgia and ME/CFS experience are overlooked and under-investigated. They tend to be accepted by healthcare professionals as part of the spectrum of illness, while patients are left to cope with them as best they can. But might the link between gut problems and other symptoms, such as pain and fatigue, be more intimate than we think? A group at Unger-Vetlesen's Institute, Norway have approached this possibility from a novel angle – by examining patients with intestinal problems for the presence of other, more general symptoms. The 84 patients examined all had a main diagnosis of "*gastrointestinal symptoms self-attributed to food hypersensitivity*"; as the article says, patients like these "*often become shuttlecocks between different medical specialists without much help being offered… a psychological explanation model often becomes a diagnostic rescue basket.*" Ring any bells?

Of these patients, all but one were diagnosed with irritable bowel syndrome (IBS), and 58% had severe symptoms of IBS which could not be explained by either immune-mediated food allergy or other organic causes. However, most of these patients with intestinal problems also suffered from severe systemic symptoms, and 71% had the complete triad of IBS, musculoskeletal pain and chronic fatigue often seen in ME/CFS or fibromyalgia. Is it possible, as the authors speculate, that an underlying intestinal dysfunction might be at the root of these two illnesses, at least in some people? It's certainly feasible, and something that needs exploring.

Source: *Berstad et al., Scand J Gastroenterol, 2012*

JAPAN

Diagnosis from a thumb?

We've said for many years that the discovery of a clinical 'thumbprint' for the diagnosis of ME/CFS (or one of its components) would transform the lives of patients and carers. Well, researchers at Osaka University, Japan, have published data suggesting that real thumbs might do the job. They used visible and near-infrared (Vis-NIR) spectroscopy – which derives information from light shone into the skin – to look into the thumbs of 57 ME/CFS patients and 74 healthy volunteers.

Using blinded samples (without knowing which samples were from patients and which from controls), they found that the technique could correctly predict which people were healthy volunteers (in 83.3% of cases) and which were ME/CFS patients (70%). So, is Vis-NIR spectroscopy a shoo-in as an accurate diagnostic tool? Possibly – but this will need to be confirmed by other research groups across the world, and a sensitivity of 70% (which implies that 3 of 10 patients are incorrectly diagnosed) is not particularly impressive as a stand-alone test.

Source: *Sakudo et al., Clin Chim Acta, 2012*

AUSTRALIA

Inflammation of the brain

As you might expect, the journal *Medical Hypotheses* publishes speculative papers about the cause and consequences of diseases. As an 'orphan illness of unknown aetiology', ME/CFS has been the subject of a number of such papers over the years, most recently a contribution on the possible role of brain inflammation. Dr Simon Arnett and colleagues at the Australian National University speculate that the long-term presence of inflammatory substances (mediators) within the central nervous system and brain leads to both neurological dysfunction and patients' symptoms. It may be, for example, that ME/CFS patients have a relative immunodeficiency, such that infections, which are poorly controlled at an early stage, lead to chronic inflammatory responses.

The authors say their theory provides an explanation for the known range and pattern of symptoms seen in ME/CFS, such as the neurological and endocrine changes. Of course, the hypothesis that ME/CFS is a disease of long-term inflammatory processes of the brain raises the question of whether centrally-acting anti-inflammatory treatments might be effective. The authors have particular interest in the use of biological agents against TNF (an inflammatory mediator). These anti-TNF agents have been used with some success for Alzheimer's disease – another condition in which a neuroinflammatory mechanism is increasingly implicated – and could possibly have a role in ME/CFS too.

Source: *Arnett et al., Medical Hypotheses, 2011*

Making music, raising money

Guitar gigs

On May 12th 2012, bang in the middle of ME Awareness week, Alan Hume and friends hosted their 13th gig for ME Research UK in the John Barras Suite at the Corner House pub in Heaton, Newcastle upon Tyne.

Over the years, Alan and friends have raised £10,165 for ME research, an astonishing total since total sales do not exceed 80 tickets, the maximum number of people legally allowed to attend.

As one of Alan's friends Bev Thompson explains, "*It is such an enjoyable night of music and laughter, though there is a serious reason for it all. It must not be forgotten that these devoted parents are supporting ME Research UK in particular because they have been personally affected by ME, as a family member is afflicted. "This has repercussions on every member of the family, not just the victim. Research to help find a cause and a cure is the aim of these gigs. A great deal of money is needed to this end as there is no government funding available.*"

Thank you Alan and friends for another successful fundraiser, and to the manager of the pub who donates the use of the function suite! The all-time donation from these gigs is incredible considering the worldwide recession, and a tremendous achievement indeed.

The next gig is scheduled for 6th October 2012 – but do remember, tickets go quickly!

Jonathan's Half Marathon

Jonathan Handcock initially intended to run a half-marathon in Brighton in 2011, but surgery to repair torn cartilage in his knee meant that the plan had to change. So Jonathan decided to run the 2012 Hastings half-marathon instead!

He was very happy with his time of 2 hours 11 minutes, and the photo on the right shows him during the race, wearing a T-shirt that points out that he is Harry's dad as well as a runner for ME Research UK.

One of the unusual things about Jonathan's run was that he generously offered to match the highest donation made on his Justgiving page, up to £100 max.

He has raised almost £700 to date, exceeding this target. Thank you, Jonathan, for pushing on through injury to make such a successful run for research into ME.

Talk in Gravesham

Joy Birdsey is an ME patient who has been a staunch advocate for other people with the illness for many years – as well as being a great friend of ME Research UK – so it's no surprise that she was asked by Gravesham Council to give a talk on the illness and its consequences to its nurses and social workers on 12th March 2012.

After lots of preparation, Joy managed to put together a talk and information pack for the 25 healthcare professionals who came along, and the topics covered included the history of ME and who gets it.

As Joy continues, "*I arrived to a crowded room of expectant looking people, and essentially told them a story, referring them to their pre-prepared packs which included previous articles from* Breakthrough *Magazine. One article,* The Correct Diagnosis *(Autumn 2011) explained how the diagnosis 'ME/CFS' can easily become a stopping-off point for clinically complex patients with a variety of different illnesses, and this was a great help, as it started a discussion on ME and CFS and the issues that surround these terms.*"

Joy explained that the care and treatment of ME patients is in the hands of people like themselves, working from the bottom up, and the professionals in the audience seemed thrilled to think that they were the ones who would be helping ME patients and their families to go forward!

Thank you to Joy and helpers (including the Isle of Grain group, photo page 18) for putting this 'education day' together, and opening the minds of nurses and social workers to the reality of ME.

Atlantic Rally

Andrea Horne raised funds for ME Research UK by sailing 2,700 miles in the Atlantic Rally for Cruisers (ARC) 2011 race on the yacht 'Maline'. Preparation and training took place in Las Palmas Gran Canaria before the three-week crossing of the Atlantic to St Lucia.

As Andrea said, "*This is a charity very close to my heart as I have had the condition for many years and only now seem to be recovering.*"

What a way to spend your 70th birthday!

Since Alan Nuttall's daughter was diagnosed with mild ME a few years ago, Alan has been fundraising for a local support group in Northallerton, North Yorkshire and also for ME Research UK. Invited to accompany some friends who were cycling from Land's End to John O'Groats, Alan joined them for the second leg in May 2012, and decided to raise funds for ME Research UK.

Their journey began near Carlisle and took them up the west coast of Scotland taking in several islands including Arran and others in the Outer Hebrides.

Alan tells us that they were incredibly lucky with the weather – they had rain on the first day but none thereafter! The fourth day was spent cycling north on Arran in glorious conditions – blue sky and white fluffy clouds. What a marvelous day to celebrate his 70th birthday!

A ferry took them back to the mainland and then to Oban and on to the Outer Hebrides which were stunning in sunshine. Five days later they reached Ullapool, and thence to John O'Groats – a cycling distance of 560 miles.

Alan's donations have reached a whopping £3,250 – mainly through his JustGiving page, which is still open for donations. During his fundraising trip Alan was amazed at the number of people he met who either had ME themselves or had friends or relatives with ME. As he said, "*It really is tragic that so little has been spent on biomedical research.*" Although with help from supporters like Alan, we can change this.

ME Alliance Northern Ireland

1st March 2012 saw a gathering of over 400 people for the launch of the new ME Alliance Northern Ireland. The cornerstone of the launch was a lecture by Dr Derek Enlander, who discussed his long experience with ME/CFS patients.

Other contributors included South Down MLA Jim Wells who will become Minister of Health, Social Services and Public Safety for Northern Ireland in 2013, Michael O'Reilly of the Irish ME Trust, and Horace Reid who introduced the Alliance and explained its purpose. The meeting concluded with a question and answer session, chaired by Dr William Weir, a London-based consultant in infectious diseases.

Joan McParland of the Newry and Mourne ME/FMS Support Group had organised the meeting and was delighted with the turn-out. She and the other colleagues from the Alliance intend to use the new umbrella body to push for improved services for ME/CFS patients across the whole of Northern Ireland.

Enquiries about ME Alliance Northern Ireland can be addressed to Joan at joanmcparland@live.co.uk.

Scottish Parliament reception

As part of ME Awareness Week, 6 to 12th May 2012, the Cross-Party Group on ME at the Scottish Parliament hosted a reception attended by MSPs, ME charities and groups, and their guests. The reception attracted an impressive proportion (22%) of the 129 MSPs, and exhibitors included the larger ME charities with a presence in Scotland, such as the 25% ME Group; EDMESH, Action for ME, the ME Association and ME Research UK.

While attendees were mingling, the documentary '*Voices from the Shadows*' (a moving one-hour feature film in which the hidden voices of severely affected people with ME can be heard) was running on plasma screens around the Garden Lobby, forming a compassionate and moving backdrop to the event.

As Carol Flack, who provides the secretariat to the Cross Party Group on behalf of the 25% ME Group, said afterwards, "*This was an initial step, and the Cross-Party Group will be taking this experience forward to inform our planning of future events and debates. We must keep up the momentum to ensure our MSPs realise their important part in representing the needs of ME sufferers in Scotland through Parliament to the Scottish Government.*"

Dr Neil Abbot (ME Research UK), Joan Kerr (EDMESH) and Justice Secretary Kenny MacAskill MSP

Isle of Grain Disabled and Carers Group (see page 16)

Vegepa for ME – a tremendous achievement

The original Vegepa for ME Scheme, through which every pot of Vegepa sold raised 50p for research into the illness, collected an astonishing £38,642 for ME Research UK's research fund between 2006 and 2012.

The scheme was initiated and organised by Lynne Kersh (right), who cared full-time for her daughter, a long-term ME patient. Lynne says, "*I'm absolutely delighted that during the life of the scheme we have been able to donate to ME Research UK. We've done enormously well, and I'm so proud of all our achievements through the scheme over the past six years.*"

The website still exists – at thevegepaformescheme.com – providing all sorts of information, but is soon to be completely revamped into more of a club meeting place instead of an online shop.

Double walking challenge

Ian Hymers walked 50 miles in two different challenges for ME Research UK this year. The first was the Coastal Challenge with Shepherds Walks (26 miles) on May 7th, and the second was the Haltwhistle Challenge (25 miles) on May 19th.

Ian's wife has had ME for 13 years. Before becoming ill she had a good career and social life. As Ian says, "*This is not the future either of us had envisaged. Imagine having to make the choice between having the energy to wash or get something to eat. The illness is so debilitating it takes away the person's work, friends and social life – in short, their independence.*"

Ian completed his two challenges with great aplomb – and dog Benji (who also supports ME Research UK) was at the finishing line to cheer!

If you would like to sponsor Ian, his Justgiving page is open for donations.

Standing Order Form

To allow us to press ahead with our mission to Energise ME Research, please consider setting up a Standing Order by completing this form and sending it to ME Research UK, The Gateway, North Methven Street, Perth PH1 5PP.

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

giftaid it ○ Tick if you would like us to treat this, any future donations to ME Research UK, and all payments in the previous 4 financial years, as Gift Aid donations until you notify us otherwise. You confirm you have paid or will pay an amount of UK Income Tax and/or Capital Gains Tax for each tax year that is at least equal to the amount of tax that all the charities or CASCs which you donate to will reclaim on your gifts for that particular tax year – 28p of tax on every £1 given up to 5 April 2008 and 25p of tax on every £1 thereafter. Please inform us of changes in your tax status.

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