

breakthrough

News of the ME Research YOU are helping to fund



**Cardiovascular responses
to standing in ME/CFS**

Breakthrough

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ME Research UK funds research into Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (also known as ME/CFS). It has an international remit, and its principal aim is to commission and fund high-quality scientific (biomedical) investigation into the causes, consequences and treatment of ME/CFS. It also aims to 'energise ME research' by identifying potentially important areas for future biomedical research, producing high quality professional reviews and reports, presenting research at meetings and conferences, and hosting international conferences.

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editorial



It is not widely realised that the bulk of research funding for many, if not all, illnesses comes from charities. In fact, you could say that the advances in medical research over the past 50 years have been founded on the bedrock of the generosity of the people — the good, stout hearts of British women and men who realise there are people worse off than themselves and want to do something about it. A recent report from the Charities Aid Foundation shows just how extraordinary this generosity is: in 2009 and 2010, 56% of adults in the UK donated to general charitable causes, giving around £10.6 billion in total.

Many of these donations come from on-the-ground fundraising events, like supermarket collections or marathons by individual supporters. But amazingly — and something I had never realised before I became a fundraiser — a large proportion of charitable giving comes in the form of legacies, over £2 billion in fact, or nearly one-fifth of all donations. Legacy funding is especially important in particular types of charities, such as emergency and relief, animal welfare, or social service organisations. But

medical research also benefits considerably, and about 22% of its total overall income comes from legacy funding. This means that charities such as Cancer Research UK bring in approx £50 million every year from legacies alone — makes you think, doesn't it?

Fundraising is difficult for many small research charities, but ME Research UK has a particularly difficult task. Why? Well, the first thing is perception; as I am sure that many of you realise, the illness is not "sexy" in the eyes of the public and the media — partly because of the stigma of disparaging labels like "yuppie flu" and "all in the mind" which sadly still exist, and partly because ME/CFS lacks the high profile of an illness like multiple sclerosis which is far more well-known even though its prevalence is between one third and one half that of ME/CFS.

The second thing is that, because so little is really known about the biomedical causes and consequences of ME/CFS, the fundraising mountain is much harder to climb than with other diseases; we have to start at a lower level and therefore we have much further to go to achieve our goals.

That's why I'm trying to focus on creativity and innovation in our many fundraising methods, and why I've targeted legacies for special consideration in this issue of Breakthrough; you will find a legacy pledge form inside. Although it is a sensitive subject, legacy giving has the potential to enhance our income considerably. Research projects are expensive, but they do deliver scientific results that are so beneficial for changing attitudes and increasing awareness. By leaving a legacy you can make a direct and lasting contribution towards our vital work.

Sara Cornwallis
Head of Fundraising
ME Research UK



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EXERCISE AND ITS AFTER-EFFECTS

Abnormal pain processing may be important

Despite the concerns of patient support groups and charities, the National Institute for Clinical Excellence (NICE) Clinical Guideline currently recommends “cognitive-behavioural” therapies, including graded exercise therapy (GET), for people with ME/CFS. The guideline does, however, make clear that it does not regard these interventions as “curative or directed at the underlying disease process, which remains unknown. Rather, such interventions can help some patients cope with the condition and experience improved functioning, and consequently an improved quality of life.” (NICE Guideline, full version, page 252).

And the results of the largest clinical trial to date (the PACE trial; see page 15 of this issue of *Breakthrough*) have confirmed this view, showing that while cognitive behavioural therapies can modestly improve outcomes compared with standard medical care, they are far from being the panacea that is sometimes claimed.

Yet the reality is that in the consulting room or at the clinic, people with ME/CFS are ‘prescribed’ GET for their condition, and some even report being pressurised into undertaking formal exercise programmes. This is particularly worrying because patient surveys suggest that GET might be harmful in some patients; for instance, the 2002 Chief Medical Officer’s report quoted a survey in which 50% of 1,214 patients said they had been “made worse” by GET, while in a 2010 survey 33.1% of 906 patients reported that it had made them “much worse”.

It is important to understanding why many patients experience a worsening of symptoms after exercise, particularly 24 to 48 hours later. While a range of pathophysiological mechanisms could be involved, one possible element might be a disruption to the pain inhibitory system in ME/CFS. This system normally controls the release of analgesic (pain-relieving) chemicals

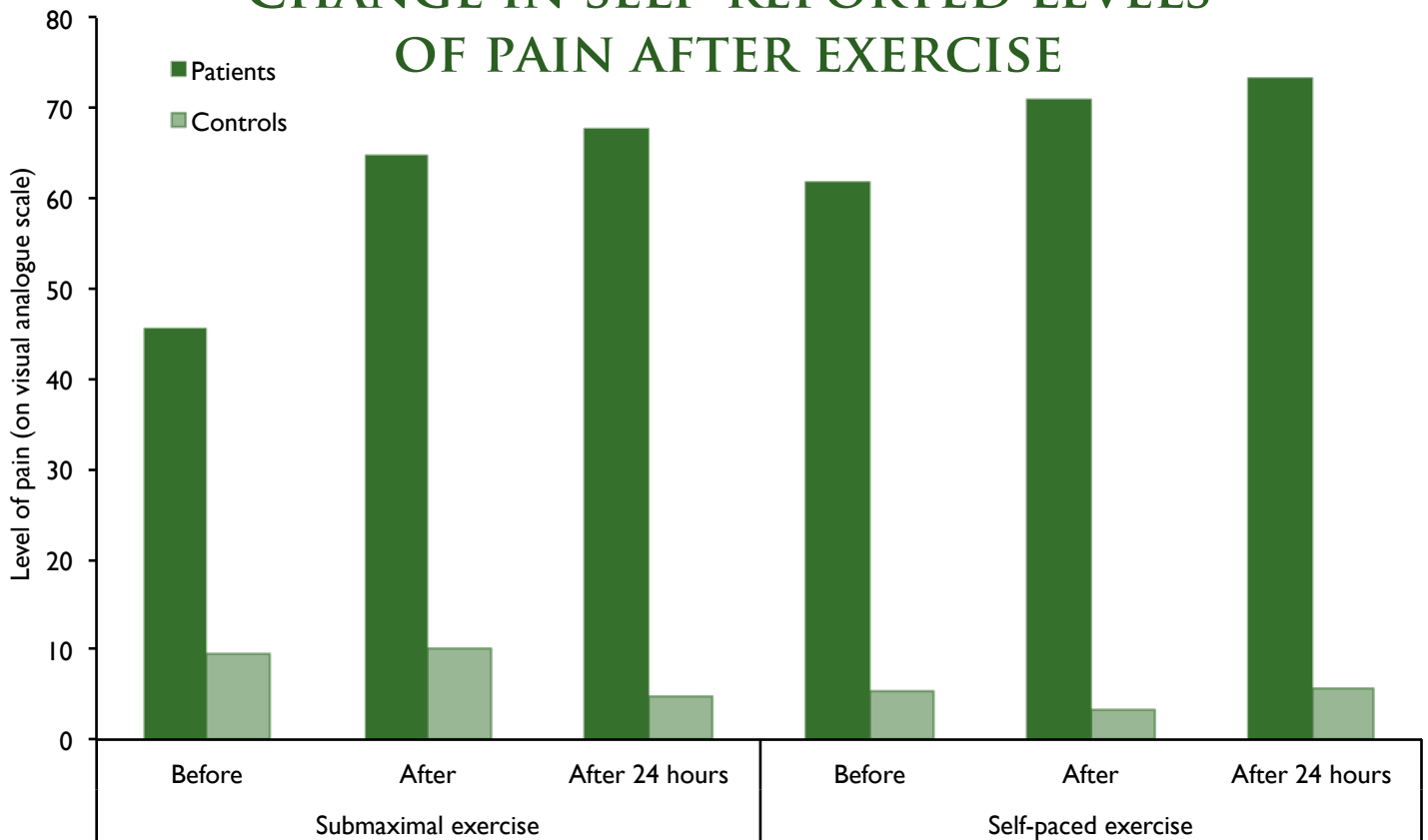
and other factors during exercise, which cause an increase in pain thresholds; put simply, if this system is working properly we do not feel pain so readily when we exercise. There is evidence that this threshold decreases during and after exercise in ME/CFS patients, suggesting that the pain inhibitory system may be impaired.

Researchers from Belgium have been investigating this aspect in a study funded by ME Research UK, and recently published their findings in the *Journal of Internal Medicine*. Their objective was to determine whether a worsening in symptoms after exercise in ME/CFS patients is indeed related to dysfunction of the pain inhibitory system.

They used a device called an algometer (or algometer) to measure pain thresholds before and after exercise in 22 women with ME/CFS as well as 22 healthy women matched for age and body mass index. An algometer consists of a pressure gauge attached to



CHANGE IN SELF-REPORTED LEVELS OF PAIN AFTER EXERCISE



a narrow rod, the end of which is pushed against the subject's skin until he or she reports feeling pain. The pressure at which this occurs can be read from the gauge and indicates the pain pressure threshold. This was measured between the thumb and forefinger on both hands, at both calves, and on the back.

Alometry was performed before and after two different types of exercise test on a cycle ergometer. In the first test, subjects cycled continuously at about 60 to 70 revolutions per minute while the resistance (and hence the workload)

was increased until the subject's heart rate reached 75% of the predicted

maximum, or until they were unable to continue.

This was the 'submaximal' exercise test.

In the second test (conducted a week later), subjects were asked to estimate how long they thought they could cycle before their symptoms got worse, and they then cycled for a period that was 50 to 75% shorter than their estimate. In addition, heart rate and workload limits were chosen to keep the exercise intensity well below the subject's anaerobic threshold (i.e. the point at which lactic acid starts to accumulate in the muscles). This was the 'self-paced' and physiologically limited exercise test.

The participants also filled in questionnaires to assess the severity of their symptoms, their functional status and wellbeing, and the severity of their fatigue.

The differences between ME/CFS patients and healthy subjects were clear. In the patients, pain pressure thresholds decreased by up to 10% at most measurement sites following both types of exercise, meaning individuals were more sensitive to pain after exercise than they were before. In the healthy subjects the opposite was true: their pain pressure

thresholds consistently increased after exercise by an average of 10%, meaning they had become less sensitive to pain.

Furthermore, ME/

CFS patients also experienced a worsening of their symptoms after exercise; as the graph above shows, pain was dramatically higher in the patients than in the control subjects, increasing even further 24 hours after both types of exercise. Levels of fatigue were also increased, and directly correlated with the drop in pain thresholds in the patients.

The researchers conclude that these results suggest the pain inhibitory system is indeed impaired in ME/CFS, because it did not respond to exercise in the patient group as it did in the control group. And also that

this dysfunction may be at least partially responsible for the increase in symptoms that patients regularly experience after exercise (a number of other mechanisms may also potentially be involved).

Given that self-paced exercise is to be preferred routinely to the rigours of a full-blown exercise programme, an accompanying expert editorial in the same issue of the *Journal of Internal Medicine* suggests that "the time may have come to replace the concept of 'graded exercise therapy' with 'paced exercise therapy' in CFS, using flexible and individually tailored exercise programmes that not only augment patients' physical condition but also help them to better recognize 'bodily signals' and connect these to realistic goals and aspirations."



DR JO NIJS

XMRV: the endgame begins

In Autumn 2009, the prestigious scientific journal *Science* published findings from the University of Nevada, USA, suggesting a link between xenotropic murine leukaemia virus-related virus (XMRV) and ME/CFS. Remarkably, the retrovirus could be detected in the peripheral blood mononuclear cells of 67% of the patients but in only 3.7% of control subjects.

The researchers also reported data suggesting that infected white blood cells could pass the virus on to uninfected cells — an appealing suggestion at first glance, since the presence of infectious XMRV in the white blood cells of ME/CFS patients could account for some of the known neurological and immune features of the chronic illness.

In the 20 months since the initial *Science* report, twelve distinct studies have been published by other researchers across the world keen to test their own populations of patients. As the table below shows, these studies have not been able to find significant levels of the retrovirus in their

patient groups, although one investigation (Lo *et al*, 2010), instead of finding XMRV itself, detected a more diverse group of closely related MLV viruses in 86.5% of patients compared with 6.8% of controls.

Anecdotally, there have been suggestions that XMRV positivity can be found in other populations, but these data have been presented in poster form only (*International Workshop on XMRV* at Bethesda, Maryland, September 2010) and remain unpublished and so beyond assessment.

As the list of negative published studies has grown, attention has turned to the possible reasons for the inability of independent researchers to confirm the original positive findings.

For instance, geographical differences in the distribution of XMRV might exist, as is the case with another human retrovirus, HTLV-1, although this explanation becomes increasingly unlikely as studies increase.

Or differences in laboratory methodologies might be to blame, hence the

recent attempts of the NIH's Blood XMRV Scientific Research Working Group to arrive at an agreed protocol for laboratory testing.

Finally, four recent reports in the journal *Retrovirology* suggest that laboratory contamination might underlie XMRV-positive findings; in this schema, XMRV originates from the chance recombination of mouse viruses during laboratory experiments, with positive findings reflecting cell-line contamination rather than true infection in humans.

Fortunately, as of May 2011, we await the results of several important investigations. In one, a \$1.3 million investigation funded by the US government, three labs have each been given 150 patient and 150 control samples for testing in a blinded manner; the results will be known only when the codes are broken later this year.

Collectively, these more definitive studies should at least tell us whether or not XMRV is associated with ME/CFS. If XMRV is not the culprit, we must continue researching to find out what is.

Publications on XMRV in ME/CFS cohorts: October 2009 to May 2011

First author, Country	Journal, Date	Patients positive for XMRV?
Lombardi, USA	<i>Science</i> , October 2009	Yes (67%)
Erlwein, UK	<i>PloS One</i> , January 2010 & March 2011 (re-analysis)	No
van Kuppewald, the Netherlands	<i>BMJ</i> , February 2010	No
Groom, UK	<i>Retrovirology</i> , February 2010	No
Switzer, USA	<i>Retrovirology</i> , July 2010	No
Lo, USA	<i>Proc Natl Acad Sci</i> , August 2010	No (but 86.5% MLV)
Hong, China	<i>Virology Journal</i> , September 2010	No
Henrich, USA	<i>J Infect Dis</i> , November 2010	No
Hohn, Germany	<i>PloS One</i> , December 2010	No
Satterfeld, USA	<i>Retrovirology</i> , February 2011	No
Furuta, Japan	<i>Retrovirology</i> , March 2011	No
Schutzer, USA	<i>Ann Neurol</i> , April 2011	No
Shin, USA	<i>Journal of Virology</i> , May 2011	No



Donating solid organs for transplant

The decision by the National Blood Service in the UK to permanently defer ME/CFS patients from donating blood, raises the question of how safe solid-organ transplants are from people with this illness. The question is important because transmission of viruses by solid organ transplantation is well recognised in cases of hepatitis B, hepatitis C and HIV.

Fortunately, the issue has been the subject of an informative letter in the journal *Transplantation* (April 2011) by clinicians from the NHS Blood and Transplant Service in Bristol.

The researchers undertook a retrospective survey of people who

had received solid organ transplants from patients with ME/CFS, to find out whether the recipients developed any symptoms of the illness in the months and years following transplant.

After searching the UK Transplant Registry Donor Database, between January 2005 and December 2009, it was possible to identify 10 deceased solid organ donors who were recorded as having ME/CFS, and who had donated 27 solid organs (including 17 kidneys, 6 livers, 2 lungs, one heart and one pancreas) to 25 recipients. The centres where these recipients were being followed were contacted to establish whether any of

them had developed symptoms of ME/CFS.

Of the 18 solid organ recipients with available data, none had developed fatigue to the chronic level that would be required for diagnosis, one recipient had unexplained myalgia (muscle pain), and no other recipients had reported any other symptoms of ME/CFS.

On the basis of these findings, the authors conclude that there is no justification at present for excluding those with ME/CFS from organ donation. This is perhaps good news for those awaiting organ transplants, given the shortage of organs in the UK, and the significant mortality of those patients on the waiting list for an organ.

Donating blood

The possibility that people with ME/CFS might be infected with a novel retrovirus has galvanised regulatory and public health authorities around the world.

- In April 2010, Canada, Australia and New Zealand banned patients with a history of ME/CFS from donating blood.
- In June 2010, the task force set up by the American Association of Blood Banks (whose members collect most of the US blood supply) to examine the presence of XMRV in blood products recommended that people with ME/CFS should be actively discouraged from donating blood until more is known about the potential risks.
- On 1st November 2010, the UK's National Blood Service banned ME/CFS patients from donating blood, ostensibly to protect the health of the donors.
- In December 2010, an FDA advisory committee recommended that potential blood donors in the USA be excluded from donating if they have a diagnosis of ME/CFS, while acknowledging divergent results of studies.
- In December 2010, the American Red Cross halted blood donations from ME/CFS patients.
- In March 2011, the HHS Blood XMRV Scientific Research Working Group reported that there was no convincing evidence that transfusion is associated with either ME/CFS or prostate cancer, but recommended additional epidemiological studies.



In Search of Pain Relief

Alternative options for the treatment of pain in ME/CFS

Benjamin Franklin believed that “*The best of all medicines is resting and fasting.*” Or at least he said he did, since he didn’t do much of either in his long and fascinating life. But what would he have done if he’d been offered a pill to relieve the symptoms of a serious chronic illness? Like all of us, he’d have happily gobbled down the pill.

However, patients with ME/CFS do not have the benefit of a magic tablet. The best they can hope for at present is some strategy to manage their symptoms, the most debilitating of which for many is pain. In one survey 79% of patients said they have severe pain at least some of the time, and this figure is higher in formal research studies with between 84 and 94% of patients reporting some degree of muscle or joint pain.

When conventional therapies fail, many people become disillusioned with mainstream medicine and look around in desperation for something that works. So they turn to treatments that remain unproven and controversial, and which belong to the world of complementary and alternative medicine. These include therapies such as homeopathy, acupuncture and hypnosis, and many ME/CFS patients have given these options a try. Other interventions include cognitive behavioural therapy and graded exercise therapy which are used in a conventional medical setting, but are associated with

their own controversies, particularly among ME/CFS patients and charities.

In the last issue of *Breakthrough* (Autumn 2010), we reported the results of a study investigating the specific characteristics of the pain experienced by ME/CFS patients. This work was conducted by Dr Rebecca Marshall, Prof. Lorna Paul and Dr Les Wood at Glasgow Caledonian University, and was part-funded by ME Research UK. They looked at the types of pain described by patients, how severe they are, and what parts of the body are affected.

The group has now published a follow-up scientific paper in the journal *Physiotherapy Pain and Practice*, investigating what kinds of complementary and alternative medicine, physiotherapy, and management strategies have been tried by ME/CFS patients to ease their pain, and which of them they have found to be successful.

The researchers interviewed 50 adult patients with ME/CFS (defined by the CDC criteria, which requires there to be a least four of eight symptoms, including muscle pain and headache), including ten individuals severely disabled by their condition. No participants had any other long-standing diseases, or any history of depression or psychiatric illness.

The questionnaires used in the interviews collected information about the pain associated with their illness (and in fact these are the results reported in their previous paper), as well as the treatments they had tried in an attempt to manage their pain, and how successful these had been.

Forty-five patients said they had tried a complementary or alternative treatment for pain relief at some time throughout their illness, while 18 were using one at the time of the survey. It is important to note here that this survey is not evaluating the effectiveness of the treatment, but rather how successful patients have perceived it to be.

The most common therapy was acupuncture, used by 23 patients (including 5 of the most severely disabled). This option also appeared to have had the most success, with 14 participants (around 60%) reporting that it had helped relieve their pain. However, 8 patients had stopped the treatment because it was too expensive, and

6 because of difficulties in getting to the clinic.

A number of clinical trials of acupuncture have been conducted in ME/CFS patients; most have been based in China, and all have reported success rates

60% of patients reported that acupuncture helped relieve their pain

of more than 78%. However, the quality of these studies has generally been poor, different kinds of acupuncture have been used, not all included a dummy control treatment, and not all specifically measured pain as an outcome. Despite this, studies of acupuncture in other medical conditions such as low back pain suggest that it can be useful as a supplement to conventional treatments. New, high-quality trials of acupuncture for specific symptoms of ME/CFS might even be worthwhile, possibly combined with existing drugs. For instance, one recent trial found acupuncture plus diclofenac to be more effective than placebo acupuncture plus diclofenac for osteoarthritis of the knee.

In the Glasgow study, the next most popular therapy after acupuncture was massage, which had been tried by 18 patients. Only 5 individuals experienced any pain relief, and the majority said their pain actually increased during treatment and was worse the next day. The patients





Dr Les Wood and Prof. Lorna Paul

Twenty-seven patients had received some form of treatment from a physiotherapist. The most successful therapies appeared to be those that involved gentle exercise, although only a handful of individuals had tried each one, meaning it's impossible

their pain? Unfortunately, it still seems largely a matter of pot luck. A few therapies appear to help some people, but they do not work for everyone, and the scientific evidence in their support is hardly conclusive. Unfortunately, this survey can provide only a snapshot of the alternative options for pain relief used by ME/CFS patients, and cannot supply any evidence for the effectiveness of any particular treatment or therapy.

However, the findings do perhaps point to those complementary and alternative therapies that may provide the best likelihood of success, and which are worth researching further: namely, acupuncture, soft tissue massage and gentle exercise.

In fact, the most frequently reported simple methods of easing pain in the survey were warm baths (partly offset by the fatigue of trying to get dried afterwards), application of heat (using hot water bottles, heat pads or electric blankets), lying down and drinking water.

Conventional medicine has so far largely failed to provide effective pain treatments for ME/CFS patients, and, as the authors of this report point out, "At the moment there is an extremely poor evidence base for any pain management strategies." For this reason, people with the illness will continue to look for alternative methods to relieve the pain they experience, hopefully without spending large sums on the more outlandish therapies that have little chance of working.

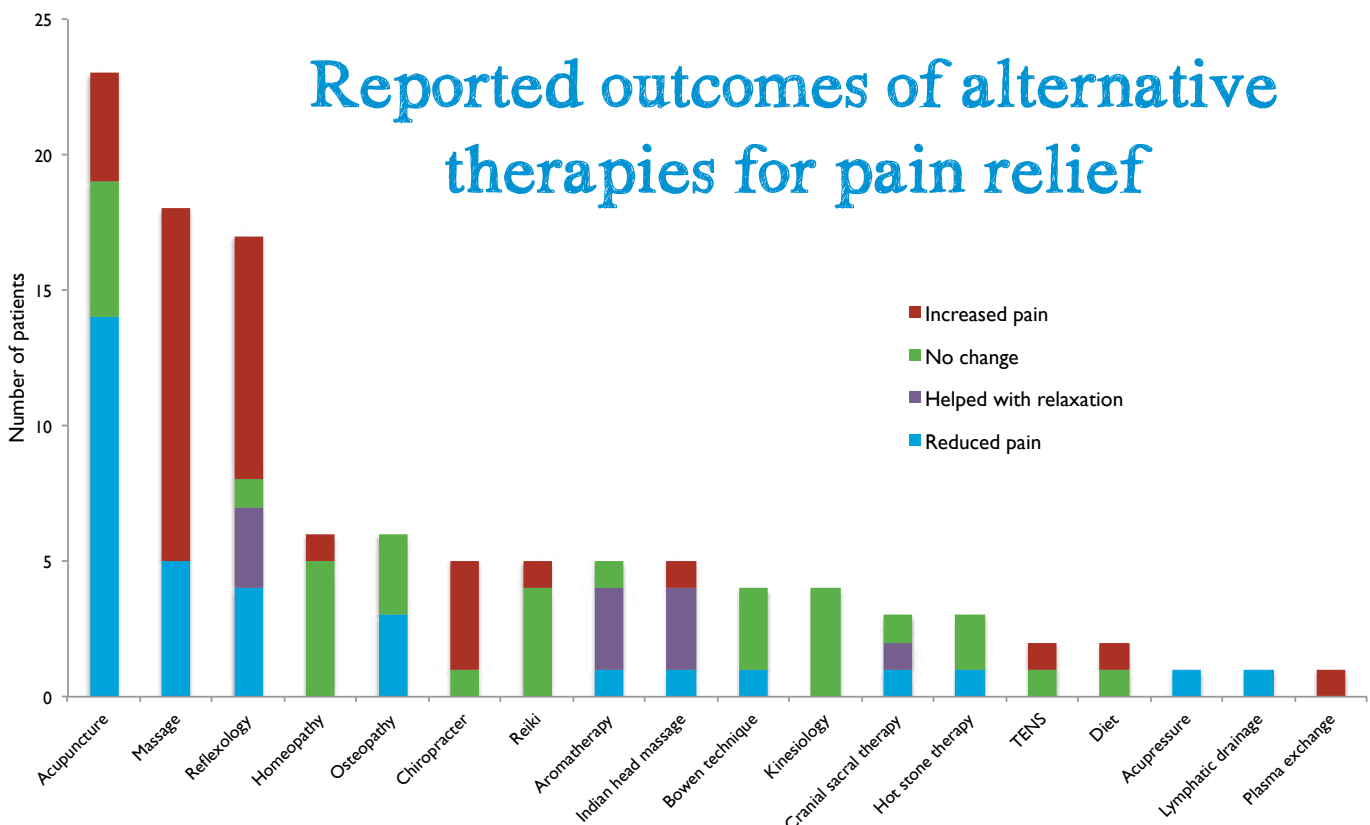
reported that deep and firm pressure was used in their treatments, but, as the researchers point out, there are more than eighty different styles of massage, and gentle pressure may actually be more effective in ME/CFS. There is evidence for this from one other study, suggesting that gentle soft tissue treatments may warrant further research.

The graph below summarises these results, as well as those for the other complementary therapies. Reflexology had been tried by 17 patients, but only 4 reported any benefit, and 9 said it increased their pain. Each of the other complementary therapies was tried by only 6 or fewer patients, with varying degrees of success, which makes it very difficult to generalise these results.

to draw any firm conclusions about their effects. However, most patients had tried to manage their pain themselves by undertaking physical activity of some kind, and pacing and stretching were reported to be the most successful of these techniques.

Graded exercise was the intervention that was most commonly prescribed by physiotherapists, and was generally the most painful; indeed, 11 of the 12 patients who had tried it said that it increased their pain. Eleven patients said that cognitive behavioural therapy had been beneficial, while 13 said that it was no help, and 22 had refused to have the therapy.

So, which of these treatments should the ME/CFS patient pick to help alleviate



Cardiovascular responses to standing

Time to recommend vascular testing for all ME/CFS patients?

The University of Newcastle houses the most active ME/CFS biomedical research group in Europe, and one of the most active in the world. Since 2006, with funding from ME Research UK and partners, the group has come up with a range of fascinating findings (see opposite page), and continues to push at the boundaries.

In the past, the group has found a worsening of symptoms with orthostatic stresses (such as standing) and an impairment of “skeletal muscle bioenergetics” in many patients. Because of these findings, Prof. Newton, Prof. Jones and their colleagues began to hypothesise that the impaired muscle function they had observed previously was not confined only to skeletal muscle, but in fact represented a larger, systemic abnormality.

If this were the case, then the muscle of the heart could also be affected, and this might explain the impaired cardiovascular function seen in many patients on standing, as well as the symptoms experienced by many. In addition, it would provide pointers towards potential treatments.

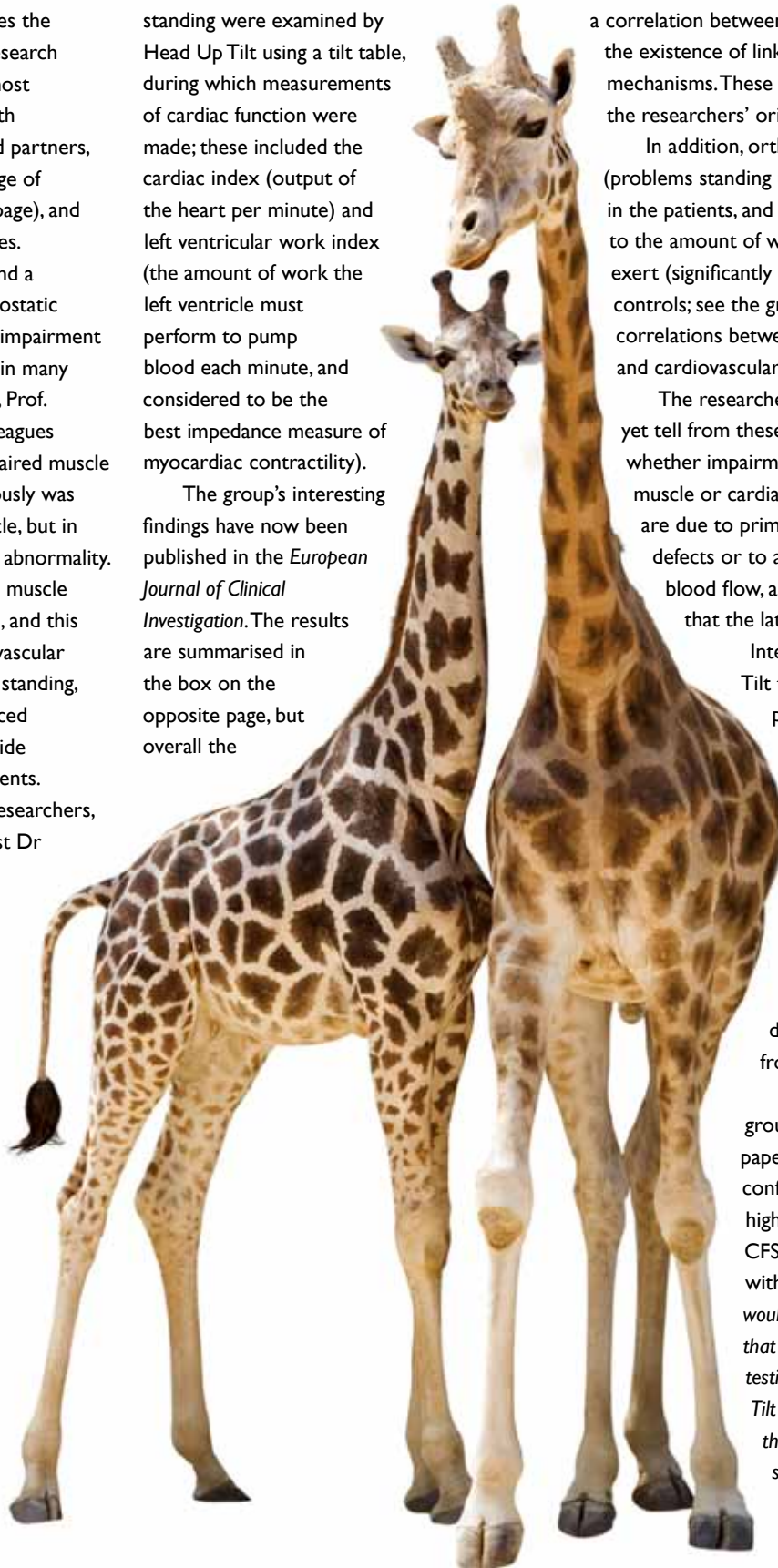
To explore these issues, the researchers, in conjunction with senior physicist Dr Kieren Hollingsworth, examined skeletal (lower leg) and heart muscle using magnetic resonance spectroscopy (MRS), a technique that provides a non-invasive window into cellular metabolism deep within the tissues.

In skeletal muscle, measurements of maximum voluntary contractions were made during exercise, while heart muscle was assessed using MRS imaging of cardiac high-energy phosphate metabolism, including phosphocreatine and ATP. Magnetic resonance imaging of the heart was also carried out.

Another experiment tested the diagnostic usefulness of measuring haemodynamic and cardiac function in a large group of 64 ME/CFS patients and matched controls, who all underwent formal autonomic assessment in the cardiovascular laboratory. The participants' haemodynamic responses to prolonged

standing were examined by Head Up Tilt using a tilt table, during which measurements of cardiac function were made; these included the cardiac index (output of the heart per minute) and left ventricular work index (the amount of work the left ventricle must perform to pump blood each minute, and considered to be the best impedance measure of myocardial contractility).

The group's interesting findings have now been published in the *European Journal of Clinical Investigation*. The results are summarised in the box on the opposite page, but overall the



study demonstrated that “bioenergetic abnormalities” could indeed be found both in skeletal and cardiac muscle, with

a correlation between the two suggesting the existence of linked underpinning mechanisms. These findings accord with the researchers' original hypothesis.

In addition, orthostatic symptoms (problems standing up) were prevalent in the patients, and these were related to the amount of work the heart had to exert (significantly more in patients than controls; see the graph). There were also correlations between cardiac bioenergetics and cardiovascular responses to standing.

The researchers say that they cannot yet tell from these MRS experiments whether impairments of skeletal muscle or cardiac energy metabolism are due to primary mitochondrial defects or to alterations in muscle blood flow, although they suggest that the latter is more likely.

Interestingly, the Head Up Tilt test (which simulates prolonged standing) was again found to be a revealing and sensitive test of abnormalities in ME/CFS patients. Yet, this is the very assessment tool that the NICE clinical guideline of 2007 (section 1.2.2.6) actively discourages clinicians from using to aid diagnosis.

As the research group says in its published paper, given that their study confirms a comparatively high diagnostic rate in ME/CFS, particularly in those with a history of fainting, “we would recommend therefore that referral for cardiovascular testing, including Head Up Tilt testing, is encouraged in those where symptoms on standing are predominant”.

Since most ME/CFS patients have symptoms on standing, particularly problems with standing still, it is surely time for NICE actively to recommend cardiovascular testing.



Prof. Julia Newton

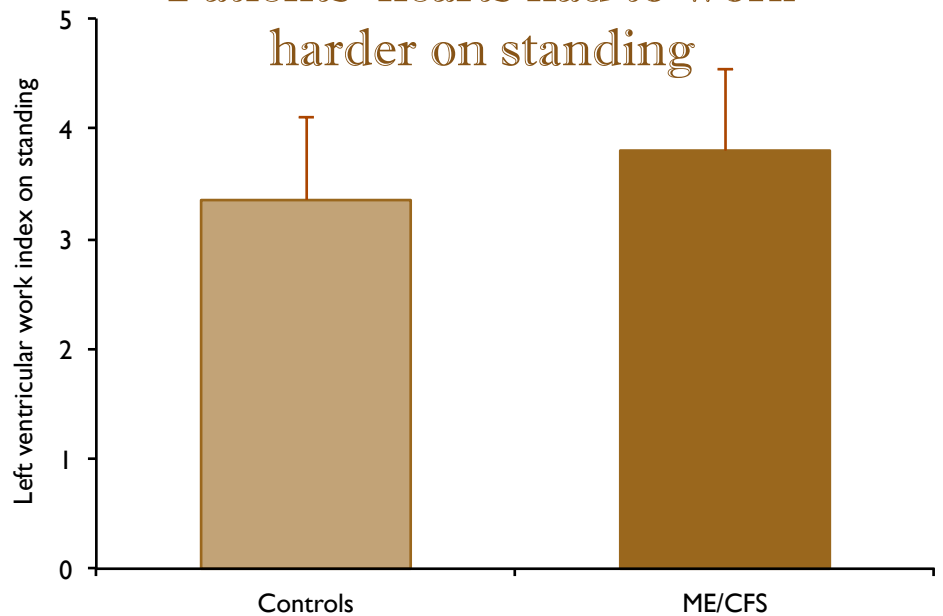
What did the results show?

- Abnormalities of both skeletal muscle and of heart “bioenergetics” can coincide in ME/CFS
- Significantly more patients (40%) than controls (23%) had a history of loss of consciousness
- Clinical symptoms on standing were found in 95% of patients compared with 39% of controls
- Postorthotic tachycardia syndrome (POTS) was found in 31% of patients but only 6% of controls
- There was a subset of ME/CFS patients (one third) in whom an underlying cardiac abnormality may be present (specifically those with a PCr/ATP ratio less than 1.6).
- In response to prolonged standing, the hearts of the ME/CFS patients had to work harder than in the controls (see graph below)
- Patients whose hearts had to work abnormally harder had significantly more orthostatic symptoms



Dr Kieren Hollingsworth

Patients’ hearts had to work harder on standing



Scientific progression at the University of Newcastle

Prof. Julia Newton and Prof. David Jones are based at the School of Clinical Medical Sciences in the University of Newcastle, and they lead one of the very few research programmes anywhere in the world on ME/CFS — a rare example of a consistent, directed, problem-solving approach to tackling the illness.

Since 2006, the group has received three separate grants from ME Research UK to look at the autonomic nervous system (2006), muscle bioenergetics (2009) and systems analysis (2010), plus another large grant from ME Research UK, the John Richardson Research Group and the Irish ME Trust to investigate muscle, liver and heart function in a large patient cohort (2007).

In a series of novel scientific papers, they have reported that, compared with healthy people, many ME/CFS patients have:

- Dysfunction of the autonomic nervous system (three-quarters of patients).
- Fatigue that is directly related to autonomic nervous system symptoms.
- An abnormal heart rate response to standing.
- Lower blood pressure and abnormal blood pressure regulation.
- Substantially slower recovery from standardised exercise of the skeletal muscles.

Fascinatingly, they have also reported that 40% of patients diagnosed with ME/CFS by GPs actually have alternative

diagnoses, such as a variety of other chronic diseases, primary sleep disorders, and psychological or cardiovascular illnesses.

Such a progression, whether towards positive findings or away from negative ones, is the norm for scientific investigation. In all diseases, real breakthroughs come at the end of programmes of painstaking work by specialist groups of researchers across the world.

The burning need in this illness is for there to be many such groups undertaking programmes of research across a range of basic and clinical sciences fields; a “critical mass” of investigators producing the “critical mass” of biomedical data required to solve the scientific enigma of ME/CFS.

Recent research from around the world



HULL

Montezuma's suggestion

Chocolate is rich in flavonoids, and evidence from observational studies suggests that dietary flavonoids may reduce the risk of death from coronary heart disease, cancer and stroke. Apparently, it was the Aztec Emperor Montezuma II who first noted the effect of chocolate on various symptoms, including fatigue: "A cup of this precious drink [cocoa] permits man to walk for a whole day without food." So, might high-dose chocolate improve the symptoms of ME/CFS?

In a recent study published in *Nutrition Journal* (2010), researchers from Hull York Medical School gave high cocoa liquor/polyphenol-rich (HCL/PR) chocolate or a sham preparation consisting of cocoa liquor-free/low polyphenol chocolate to ten people with ME/CFS, to test their effects on severe fatigue and disability. Individual 15-g foil wrapped bars (provided by Nestlé, which also did the analysis) were prepared, and participants were asked to consume one bar three times a day.

Using a crossover design, patients received either HCL/PR or sham for eight weeks, followed by a two-week washout period, and then eight weeks of whichever preparation they had not eaten previously.

There was a significant improvement in fatigue after eight weeks of taking HCL/PR chocolate (the fatigue score decreased from 33 to 21.5), while the fatigue score worsened again after taking sham chocolate (from 28.5 to 34.5). The score on the London Handicap scale also improved significantly after taking HCL/PR chocolate (increasing from 0.49 to 0.64), and deteriorated after sham chocolate (decreasing from 0.44 to 0.36).

A similar pattern was observed for anxiety and depression, and the average weight of the participants remained unchanged throughout the trial.

The researchers say that the improvement they observed was likely to be due to the high polyphenol content within the active chocolate, and they were surprised at the significance of the results given the small number of trial participants. It would be interesting indeed if the results of this proof-of-concept study could be followed up in a larger independent clinical trial.

NEW JERSEY

Cerebrospinal fluid proteins

ME/CFS shares its symptoms with a range of illnesses, a fact which will complicate diagnosis and research of the condition until a specific biological marker is found.

One 'overlapping' diagnosis is Lyme disease (caused by *Borrelia* bacteria transmitted via tick bites), particularly the neurological Lyme disease syndrome which seems to emerge after treatment. In fact, it has long been suspected that a subgroup of people with ME/CFS do, in fact, have undiagnosed Lyme disease, particularly those in areas of the world where tick bites are common.

Researchers at the New Jersey Medical School have been developing what they call a 'proteomics strategy' — a way of using the number and distribution of proteins to answer questions about specific diseases.

To test their latest strategy, they chose to examine proteins in the cerebrospinal fluid (a key body fluid providing information on the central nervous system) of patients with ME/CFS or post-treatment Lyme disease — two 'syndrome' diagnoses that pose particular challenges. For analysis, the researchers used chromatography coupled to mass spectrometry, a new technique that allows examination of complex biological specimens containing thousands of proteins.

The key findings, published in the journal *PLoS ONE* (2011), were that the patients in the Lyme group and ME/CFS group shared significantly more proteins (305) than either group shared with healthy controls (135 and 166, respectively), but that nevertheless there were clear differences between the ME/CFS and Lyme groups regarding specific cerebrospinal fluid proteins.

Using a preliminary pathway analysis to look in greater detail at some proteins found to be specific for ME/CFS, the researchers found the CDK5 signalling pathway (which has been linked to Parkinson's and Alzheimer's disease) to be significantly enriched — illustrating the feasibility of the research strategy to give information about pathogenetic mechanisms behind diseases.

Might the distribution of cerebrospinal fluid proteins become a useful way of separating 'syndrome' illnesses that presently share similar symptoms? Well, it's early days, and Prof. Schutzer, who helped lead the study, says that the next step is to narrow down the list of proteins to find "the best biomarkers for what is going wrong in the central nervous system" of ME/CFS patients.

NEW YORK

Lactate in the brain

A recent overview of neurocognitive research into ME/CFS found that attention span, memory and reaction time were impaired, a finding that is consistent with the memory and concentration problems that patients themselves complain about. Given that some neuropsychiatric disorders also show similar cognitive symptoms, there is a need to identify specific biomarkers to differentiate ME/CFS as a distinct biomedical disease.

Magnetic resonance spectroscopic imaging is a relatively new technique that gives information about metabolic changes in the central nervous system. The patient is placed inside a powerful magnet which magnetises atoms in the body, causing them to line up. A short radio frequency pulse alters this arrangement, and as the atoms spring back into alignment, a magnetic resonance signal is produced. This signal is analysed to determine the concentrations of various chemicals in the body tissue, and the

information across a region can be collected together to form a two-dimensional image.

Researchers in New York (publishing in the journal *NMR in Biomedicine*, 2010) have used this method to measure levels of a metabolite called lactate in the cerebrospinal fluid (the liquid that surrounds the brain and spinal cord) in 19 ME/CFS patients, 31 people with major depressive disorder (who can have impaired concentration, sleep and appetite) and 23 healthy control subjects.

Significantly, they found that mean lactate levels were higher in the ME/CFS group (0.92 units) than in the healthy volunteers (0.04), while the depressive disorder group had an intermediate level (0.40). Moreover, the researchers found a significant correlation between lactate and mental fatigue in ME/CFS patients, but not in depressed patients or healthy controls.

The scientists point out that high brain lactate levels are consistent with reports of areas of low blood flow to the brain in ME/CFS patients, and also with reports of increased oxidative stress in ME/CFS leading to mitochondrial dysfunction, anaerobic glycolysis and lactate production.

MARYLAND

Types of fatigue

Fatigue gets a bad press. The word is either confused with ordinary, everyday tiredness (particularly in the media) or inappropriately used, as in the name Chronic Fatigue Syndrome.

As many patients belonging to ME/CFS support groups point out, fatigue is not their primary problem. Musculoskeletal weakness and post-exertional myalgia, along with other physical signs and symptoms, are far more prominent, and correspond more closely to the original definition of myalgic encephalomyelitis.

Nevertheless, 'fatigue' as scientists use the term, should not be disparaged, since the symptom is actually a core feature of several chronic neurological diseases, as a review in *Physical Medicine and Rehabilitation* (2010) makes clear. Fatigue can be caused by a primary disease process, but other factors (depression, sleep disturbance, medication, etc.) can contribute to the overall burden of an individual patient.

Multiple sclerosis (MS) is an example of 'central fatigue'. More than 40% of MS patients complain of fatigue, and the symptom is believed to be caused by a primary disease process, although depression and sleep disturbance are often co-existing problems. The actual cause of the fatigue remains unknown, but MRI and PET studies suggest that it is related to disease in the grey matter of the brain, particularly in the cerebral cortex, although destruction of nerves is also likely to be a factor.

Myasthenia gravis, in contrast, is an example of a disease where 'peripheral fatigue' is prominent. In this case, we know far more about the mechanism of weakness and fatigue. There is good evidence that changes in neurotransmitters at the junctions between muscle and nerve are involved, causing the force of muscle contractions to be reduced, and fatigue and weakness to be felt by the patient.

So, MS and myasthenia gravis are examples of two very different types of neurologically based fatigue — one central and one peripheral. ME/CFS, with its range of neurological symptoms and signs, muscle pain, and intense physical or mental exhaustion, will ultimately be found to resemble one more than the other. But which remains a mystery at present.



DETROIT

Sleep disturbances

In narcoleptic sleep disorders, people feel excessively sleepy during the day, and may also fall asleep at inappropriate times. Treatments now consist of trying to improve the quality and depth of their sleep to restore the disrupted sleep pattern. But perhaps these therapies might also be helpful to people with ME/CFS?

The question is pertinent because, while problems with sleep are not the cause of most cases of ME/CFS, they are certainly a major contributor to the pain and suffering experienced. For instance, one investigation of the prevalence and severity of symptoms in 1,578 ME/CFS patients found sleep disturbance reported by 91.9% of the group with a high level of severity.

Researchers from a Neurology department in Michigan (publishing in *Pain Practice*, 2010) reviewed the case records of 118 patients who had been referred to their practice over a 5-year period for a range of conditions, from neuromuscular disorders to complaints of weakness and myalgia. Diagnoses of ME/CFS or fibromyalgia were made retrospectively, after review of their case histories.

All patients had undergone polysomnography (monitoring of body functions during sleep), a multiple sleep latency test (which measures how fast people fall asleep) and measurement of human leukocyte antigen (a protein known to be associated with narcolepsy). Based on these tests, 40% of patients met the criteria for a 'narcoleptiform sleep disorder', while many of the others had features that suggested the condition.

Approximately 70% of patients were subsequently treated with sodium oxybate, which is a general anaesthetic commonly used to treat narcoleptic sleep disorders. Of these, three-quarters experienced significant relief of their fatigue; 60% experienced some degree of pain relief; and over half had relief of both their fatigue and pain.

While sodium oxybate itself is not a long term solution to the sleep problems of ME/CFS patients — it has been associated with adverse effects and addiction — the findings point to the need for treatment aimed at disrupted sleep in a range of chronically ill patients, including those meeting the definition of ME/CFS.



NEW JERSEY

Who gets better?

The outcomes of ME/CFS can vary considerably between people. While some research reports say that recovery is a real possibility for some people, others say that recovery is rare though significant improvements can occur in about 40%. But is there any way of predicting what will happen to a particular patient? Are there any characteristics that can identify who is more likely to improve quicker?

A team from New Jersey Medical School has recently attempted to find factors related to the outcome of the illness. As reported in the *Journal of Nervous and Mental Disease* (2010), the researchers examined 94 women with ME/CFS, assessed the severity of their symptoms and physical impairments, and documented the presence of other illnesses.

Over the next 2½ years, these women were contacted every six months and asked about their quality of life, physical functioning, disability and symptom severity.

Importantly, instead of relying on judgments of improvement, the researchers estimated the perceived change in physical functioning using the standardized SF36 questionnaire.

Interestingly, two-thirds of the women reported significant improvements in their physical functioning over the follow-up period, although none could have been considered to have made a full recovery. These women also reported less work-related disability, less fatigue, lower levels of pain, fewer symptoms of depressed mood, and fewer non-specific physical symptoms.

Unfortunately, there were no defining characteristics that distinguished these patients from the others who did not improve or who got progressively worse — there were no differences between the two groups in baseline physical functioning, severity of symptoms, or rate of concomitant illness.

One finding does seem important, however. The patients who had a diagnosis of fibromyalgia as well as ME/CFS were three times less likely to improve, and it may be that patients with the other source of pain characteristic of fibromyalgia fare worse than those without this extra burden to carry.

LONDON

The psychosocial model in perspective

Since 2003, the UK's Medical Research Council (MRC) has funded two large clinical trials of 'cognitive behavioural' approaches for ME/CFS, at a cost exceeding £3 million. The first of these (the FINE trial) reported last year in the *British Medical Journal* that 'pragmatic rehabilitation' for severely affected patients had some short-term benefits, but only a small, non-significant effect after one year.

Indeed, at the end of 12 months, only 17 out of 81 patients allocated to pragmatic rehabilitation were classified as having improved physical functioning, compared with 10 out of 86 patients receiving GP treatment as usual. A surprise result? Not really, given that pragmatic rehabilitation

with its cognitive behavioural components does not, and was never intended to, address the pathophysiological basis of disease in these severely ill people.

The second MRC-funded study (the PACE trial) has just been published in the *Lancet*, reporting modest improvements in some ME/CFS patients after cognitive behavioural (CBT) or graded exercise therapy (GET), compared with medical care alone.

Despite some media spin surrounding the results ("Brain and body training treats ME, UK study says," trumpeted the BBC), the effects of these cognitive behavioural approaches are modest as the table below shows, benefiting around 10 to 15% of patients over and above the benefit of standard medical care.

Indeed, the PACE trial investigators themselves were far more cautious than the media in their conclusions, stating that the addition of these therapies can "moderately improve outcomes" in some patients, while an accompanying *Lancet* editorial asked a most pertinent question: "...have patients

recovered after treatment? The answer depends on one's definition of recovery..."

The results of these two expensive trials simply confirm what we already know from the most recent Cochrane Collaboration systematic review, and from the most comprehensive meta-analysis to date: that psychosocial interventions can help some moderately affected ME/CFS patients manage or cope with their symptoms, but otherwise have only an adjunctive role in the treatment of the illness.

In fact, the situation is exactly the same as in other chronic illnesses, such as multiple sclerosis, where non-specific psychological approaches can help some patients to manage symptoms, but are no substitute for the whole clinical and therapeutic armoury required to treat and (ultimately) cure the underlying disease.

With the psychosocial model now in perspective, biomedical research into ME/CFS can move centre-stage, into the spotlight where it belongs.

Proportion of patients benefiting from each intervention in the PACE trial

Key PACE trial outcomes	Medical care alone	Pacing	CBT	GET
Physical function improved from baseline (%)	58	49	71	70
Fatigue improved from baseline (%)	65	65	76	80
Significant improvement in fatigue and physical function (%)	45	42	59	61
Number in normal ranges for fatigue and physical function (%)	15	16	30	28
Participant-rated positive change in global health (%)	25	31	41	41

MICHIGAN

Herpesviruses revisited

Herpesviruses, such as Epstein-Barr virus (EBV) or human cytomegalovirus (HCMV), were once thought to have a central role in ME/CFS, but this view now has little support. Why? Because there is not much evidence that people with the illness have high levels of viral DNA, herpesvirus antigens or immunoglobulin antibodies to herpesvirus.

Despite this, a research group in the USA has reported successful outcomes with long-term antiviral treatment for EBV

or HCMV. These researchers reviewed the records of 142 ME/CFS patients, each of whom originally had raised levels of antibodies to herpesvirus, and who had completed six or more months of herpesvirus subset-directed antiviral therapy. In those who had no other tick-borne infections to complicate the clinical picture, 75% improved with therapy.

But the surprise was that improvements began to be seen at least six weeks into treatment — a fascinating observation causing the researchers to propose a paradigm to explain their findings (*Virus Adaptation and Treatment*, 2011). They speculate that herpesviruses do indeed infect ME/CFS patients, but that the initial infection is contained inside host cells where a variety of cellular disruptions occur, leading ultimately

to symptoms but not the production of infectious new viral particles. This idea is consistent with the death of host cells seen in ME/CFS, and with the suggested effectiveness of antiviral therapies which interrupt the process, though only after a time-lag.

So, should all ME/CFS patients be given antivirals? Well, it is important to note that patients in this study had documented evidence of herpesvirus infection and had been prescribed antivirals for symptoms of infection; whether most ME/CFS patients in the population experience "non-permissive" herpesvirus replication remains to be proven. Furthermore, antiviral drugs are not without side effects, which can include neurotoxicity and reductions in red and white blood cells. So medical advice is essential.

Keep on running!



Passing the Gedächtniskirche

Berlin saw a hairy chest in an orange vest when Alasdair Marshall ran in the full marathon recently, one of 48,744 participants from 122 nations.

Alasdair's cousin, Andrew, was diagnosed with ME aged 27, and has spent the past few years confined to his bed, so the family know the extent of the problem at first hand, and the struggle many patients and their families have to get access to medical care.

The family is very supportive of research, and walked the Great Glen Way for us some years back. Andrew and his family's story forms part of the book *Lost Voices* by Natalie Boulton, exploring the reality of ME/CFS for severely affected patients.

Alasdair got round the course in a very good time, past the Reichstag, by the Kaiser-Wilhelm-Gedächtniskirche, and on to the finish point at the Brandenburg gate in 04:13:58, raising £650 for ME Research UK. All in a distinctive vest of deep orange.



Running South Korea

The Seoul International Marathon 2011 took place on 20th March, and one of the runners crossing the finish line at Jamsil Olympic Main Stadium was Julie Maycock, running her first marathon on behalf of ME Research UK.

Julie (pictured left) is teaching English in South Korea, and trains at the Gwangju Running Club. She was inspired to do something for ME research by the experience of her childhood friend Amy.

Amy developed ME at age 15 and has been housebound for the last 17 years, although she has recently started to improve. Julie says, "I can't begin to imagine what it must be like to have your life on hold, hoping that one day you'll be well enough to lead a 'normal' life."

Julie completed the marathon in a fantastic 4:24:26, raising almost £650; her Justgiving page is still open for donations, and you can read more about her Korean and other adventures at her interesting blog julieamaycock.wordpress.com.

Belfast Marathon 2011

The Deep RiverRock Belfast City Marathon happens on the May bank holiday, when over 18,000 runners hit the streets of the north, south, east and west of the city. Over the years the event has grown tremendously, and now includes national sponsors and celebrities.

In 2011, Antoinette Christie and family, including Paul Christie, Jeanette Marley, Chris Stewart and Sam McIlwaine (all pictured below) made the run for ME Research UK — just the latest in a series of amazing fundraising events the family has undertaken for our charity over the years.

Antoinette's son David has now been ill for eight years (David's story is on our website), but despite the harshness of the situation, Antoinette is determined to look on the bright side and is doing her best to raise awareness of the condition. She says, "There is now a lot of scientific evidence that the illness is a complex physical disorder of the nervous/immune systems, possibly with viral cause, yet very little help is available. Sufferers and their carers are usually left to cope on their own whilst their lives fall apart."

Antoinette and family's Justgiving website for the Belfast marathon will stay open for a few more months; please support them by making a donation if you can.



Double Skydive

In a day of drama, Sam and Joe Hallett descended in a 10,000-foot skydive over in Maidstone, Kent during ME Awareness week.

Their sister Amy, who has had ME for five years, takes up the story: "It was a very long day for them both as, due to cloudy weather, they had to wait until after 4 pm until the jump could begin. But they said it was worth it and loved the experience, although they were both indeed very scared, and Joe actually has a fear of heights but overcame it by thinking of me being so ill."

Sam and Joe (pictured above) managed to raise a whopping £1,588, mainly via their Justgiving page where the messages and donations spurred them on. Also, Amy kept singing, texting and sending them messages via Facebook, with "I Believe I Can Fly", the song by R Kelly. They actually sang this song when they jumped, so it is the family's special song now.

Amy continues, "It was awesome, breathtaking, brilliant — and I am incredibly proud of them and love them very much."



Silver wedding

The German titan, Goethe, wrote that "The sum which two married people owe to one another defies calculation. It is an infinite debt, which can only be discharged through all eternity." All the more reason then to celebrate the silver wedding of Howard and Janine who were married in 1986 (pictured above).

Janine says, "We are excited to be celebrating our anniversary this year. Many of you will know that Howard and our two daughters have had ME/CFS for three years. It is a frustrating condition with little known about its causes and therefore no reliable treatment."

In lieu of anniversary presents, the couple would like their friends and families to make a donation towards research into the illness, hence the Justgiving page which they have created. Thank you, Howard and Janine for thinking of ME Research UK; as the English titan, Shakespeare, wrote of marriage, "Grace and remembrance be to you both."

Quiz night in Northern Ireland

Joan McParland has had ME for many years, and on 19th November 2010, she and husband Thomas hosted a pub quiz fundraiser in The Mountain House, Newry, and sold raffle tickets with fabulous prizes donated by local businesses.

Joan reports, "We had six helpers, my mum aged 80, two Aunties aged 78 and 85, my uncle aged 83, and my son Stephen and his girlfriend. Also, my friends Hugh Boyle and Nicola gave a very generous donation, raffled a food hamper and sold admission tickets. So I had some lovely support on the night."

In addition, the McGorrian family, including son Andrew, aged 10, who suffers from ME, decorated their home and garden for Christmas and invited friends to see the spectacle. They donated the proceedings to the fundraiser, and raised an amazing £330 in six hours.

Andrew was able to attend on the night, and picked out the winning tickets for the raffle. A great night was had by all, and the photo above shows Andrew McGorrian, Thomas and Joan McParland, and Hugh Boyle holding the cheque for over £3,000.



Scientific Steel in Sheffield

The Sheffield ME Group is one of the most active local ME groups in the country, and guest speaker at its AGM in 2010 was our Chairman, Dr Vance Spence, who gave a talk on ME/CFS research, including recent developments on XMRV and some of the result of our recent research projects.

The lecture theatre was full of members, families and friends. Vance was accompanied on his journey by Robert McRae, Trustee and co-founder of ME Research UK, and Ute Elliott presented them with a cheque for £343 raised on the day (all three pictured left).

One of the supportive emails afterwards said, "I attended the excellent and approachable talk on Saturday in Sheffield... Thank you for explaining things so well and making a complex subject approachable."

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.

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Please arrange to debit my/our account with the sum of £ _____ on the _____ day of each month until further notice

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

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