

breakthrough

News of the ME research YOU are helping to fund

**Quality of life
of children
with ME/CFS**



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Breakthrough

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

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Editorial



ME/CFS affects youngsters as well as adults. According to the 2002 report to the Chief Medical Officer, approximately 9,000 (0.07%) of the 13 million people under the age of 16 in the UK have this diagnosis, which means that 9,000 families are supporting a child with the illness.

My daughter developed ME when she was 12, after having glandular fever. Like many parents, we thought that it would resolve quickly, but when it didn't we realised that we were dealing with a serious illness. Initially, the GP was supportive if baffled, as was the paediatrician to whom we were referred. Things began to change, however, when the paediatrician intimated that a lack of recovery after 6 months must be because of "problems at either school or home". Once we realised that the initial interest from the medical profession had turned to scepticism, we became very scared.

We then sought more help and were lucky to get a referral to Dr Nigel Speight, a paediatrician (now retired) who specialised in ME. His two key pieces of advice were to only let our daughter do half of what she thinks she can do; and to

keep a low profile as a family in case Care Proceedings were brought against us. Given the first paediatrician's threat to place our daughter on a psychological ward for assessment if she failed to recover soon, we could well believe that this might happen — so we heeded this wise advice.

At her worst, our daughter was fed by hand, bed-bound, unable to bathe and dress herself, and in lots of pain. Today, 12 years later, the situation has improved slightly; she can feed herself and sometimes goes out in a wheelchair, but now has other serious ME-related conditions and remains a very ill young lady. Without Dr Speight's support, I believe that she would have been removed from our care, and could have been given the label Munchausen's Syndrome by Proxy.

My child was badly let down by almost every professional she came into contact with, but our family's story is not unique. While tragedies such as the deaths of Sophia Mirza and Lynn Gilderdale are fortunately rare, there remain many families doubly scarred — by the severe, chronic illness of a child, and by the severe, chronic scepticism of professionals who should know better.

The reality and seriousness of ME/CFS has been described in three official reports over the past 8 years, yet their conclusions have barely reached the clinic or surgery. Recognition is still a pressing issue, but there is diagnosis too: healthcare professionals need to be able to distinguish post-viral ME and related neuropathies from vaguely defined 'fatigue states' within the ME/CFS diagnostic basket, and be compassionate in their responses. They also need to work more closely with biomedical scientists in promoting the fact that ME is a serious biomedical problem deserving of research and appropriate treatment.

Sue Waddle
Spokesperson
ME Research UK



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The quality of life of children with ME/CFS

In Western societies, ME/CFS is thought to affect 50 to 70 children per 100,000. Most eventually improve in health, but some remain ill or even get worse over time. A report to the Chief

Medical Officer of England concluded that ME/CFS represents “a substantial problem in the young”, while the Royal College of Paediatrics and Child Health has produced evidence-based guidelines on how best to diagnose and manage the illness in children.

Dr Gwen Kennedy and her colleagues in the Vascular and Inflammatory Diseases Research Unit, in the University of Dundee, have recently completed one of the first ever biomedical research projects in children with ME/CFS. Her work was supported by ME Research UK, Tenovus Scotland, The Young ME Sufferers (Tymes) Trust (see the box opposite for more information) and Search ME.

Dr Kennedy’s group has previously reported a whole raft of abnormalities in adults with ME/CFS, mainly involving the immune and cardiovascular systems. These findings have included an increase in the programmed death (apoptosis) of white blood cells, raised levels of oxidative stress which can damage blood vessels and other organs, increased markers of inflammation, and abnormalities in blood vessel function. All of these are potentially associated with a future risk for cardiovascular problems such as heart disease and stroke.

These studies have all been in adults with ME/CFS, but for her latest work Dr Kennedy decided to focus on children with the disease. One aspect was to investigate whether the abnormalities found in adult patients are also present in children with ME/CFS. These results have yet to be published, but another important aim of the research was to investigate objectively the quality of life of children with ME/CFS, and these results were published recently in *Pediatrics*.



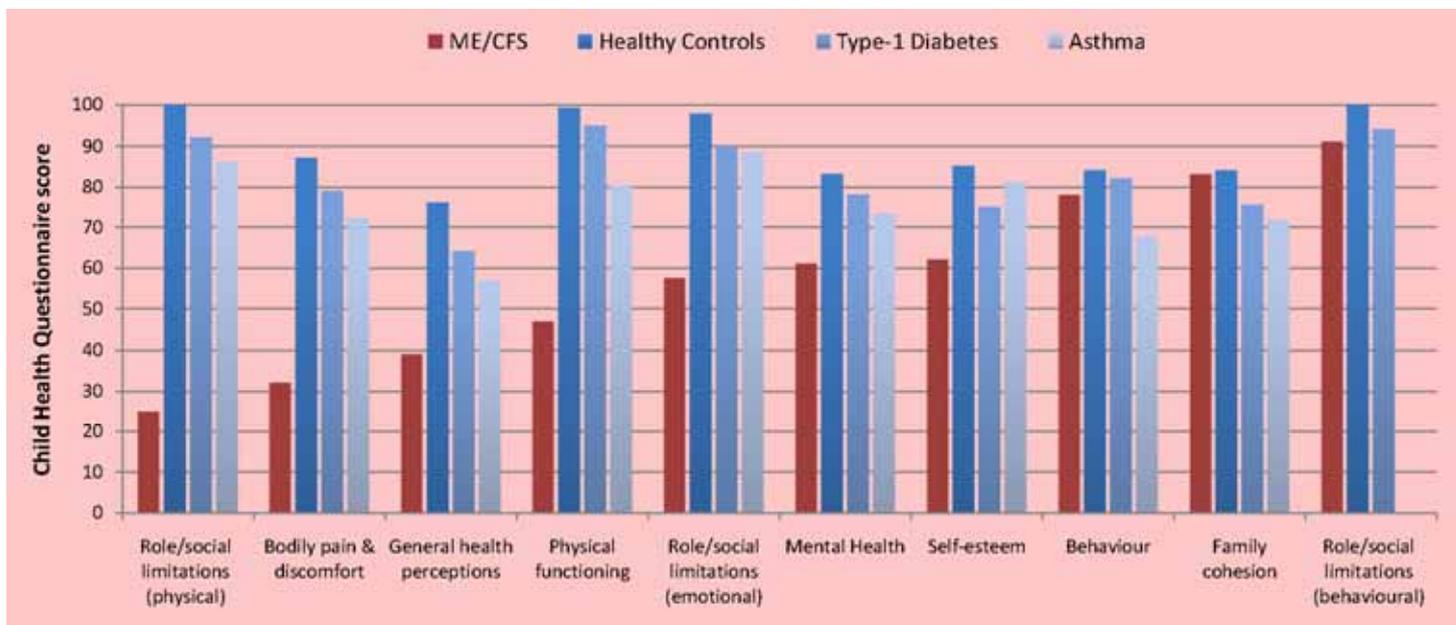
Dr Gwen Kennedy

Twenty-five children with ME/CFS and 23 healthy children were recruited from throughout the UK. All were between the ages of 10 and 18 years, and the healthy children were matched to the patients for age, gender and stage of puberty. This meant that a comparison between the two groups was as valid as possible.

The initial diagnosis of ME/CFS had been made by the children’s local consultant paediatrician or general practitioner according to a revised version of the CDC-1994 case definition, but it was also confirmed by the researchers from a clinical examination.

Each child was asked to complete the Child Form of the Child Health Questionnaire, while their parents were asked to





complete the Parent Form. This questionnaire collects information on a number of different areas related to the quality of life of an individual. These include their physical abilities, their social limitations, how they perceive their general health, whether they experience any pain or discomfort, and how they are able to interact with their family. The questionnaire also covers emotional and mental health, including self-esteem, behaviour and their effect on the parents. The responses were converted into scores for each area, which were then summed to produce a total score out of 100, with higher scores indicating a better health status.

The children were asked about their situation when they became unwell, factors which may have contributed to the illness, and whether they thought they were currently improving, worsening or unchanged. They were also asked what impact the CDC-1994 minor criteria symptoms (short term memory loss, sore throat, tender lymph nodes, muscle pain, multi-joint pain, headaches, un-refreshing sleep and post exertional malaise) had on their lives.

The main finding of the study was that children with ME/CFS scored significantly lower than the healthy children in 10 out of 14 areas covered by the Child Health Questionnaire (illustrated in the chart above). They had particularly low scores for global health (21.4 compared with 84.1 in the healthy children) and for social limitations due to physical health (24.9 compared with 100). Self-esteem, mental health, body pain and discomfort, and the

effect of the child's health on family activities were also significantly worse for children with ME/CFS. However, there were no differences between children with ME/CFS and healthy children in how well the family got along, or in the children's perception of their own behaviour.

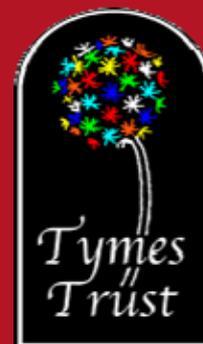
It is important to note that the quality of life reported by these children with ME/CFS was not only worse than that of healthy children of a similar age, but also worse than that of children with type 1 diabetes or those with asthma (as reported in previous studies, and illustrated in the chart above). Furthermore, the physical symptoms of ME/CFS can be at least as disabling as those of multiple sclerosis and other chronic conditions.

Importantly, the illness had started with an infection in 88% of the children, while only one child (out of 25) was able to attend school full-time. Fortunately, just over half of the children who participated felt that their symptoms were improving, and the prognosis for children with ME/CFS is generally better than for adults, although no long-term studies have been conducted. However, Dr Kennedy's findings confirm that ME/CFS does have a serious impact on children's quality of life, and she comments:

"This experience of illness occurs at a particularly vulnerable time of life when disruption to education and family has the severest consequences... it is important that the condition be recognised and diagnosed so that the consequences on quality of life can be attenuated." ●

The Tymes Trust

The Young ME Sufferers (Tymes) Trust, one of the major co-founders of the study at the University of Dundee, is the longest established national UK service for children and young people with ME and their families.



A well-respected national charity, its entire professional team give their time free of charge. It runs an Advice Line, provides access to ME experts for doctors, teachers and social workers, and produces a magazine for children, families and professionals. The Trust played a major role in producing the children's section of the Department of Health Report on CFS/ME (2002). It promotes interactive virtual education for children with ME, and provides the Tymes Trustcard — a pass card for children in school, endorsed by the Association of School and College Leaders.

More information can be obtained from 08450 039002 or at its website www.tymestrust.org.

Exercise, immunology and pain

Traditionally, the cardinal symptom of ME was profound, post-exertional loss of muscle power (fatigability) associated with muscle pain, tenderness and swelling. And still today, “post-exertional” symptoms are key; the NICE Clinical Guideline of 2007 informs GPs that, for a diagnosis of ME/CFS to be made, fatigue characterised by post-exertional malaise “typically delayed, for example by at least 24 hours, with slow recovery over several days” has to be present. It is worth emphasising that post-exercise symptoms are not present in other fatigue-related disorders, and that their very presence greatly helps to distinguish ME/CFS from, say, major depressive disorder.

Given this, it is surprising that so little is known about muscle physiology, the role of exercise, or indeed about patients’ responses to exercise in a laboratory setting. One research group, however, has a long-standing interest in this aspect: Prof. Jo Nijs and his colleagues at Vrije Universiteit Brussel and University College Antwerp in Belgium. With funding from ME Research UK, these researchers have been investigating immunological responses to exercise, and the effect of different kinds of exercise on these responses, and their latest scientific report has just been published in the *Journal of Internal Medicine* (April 2010).

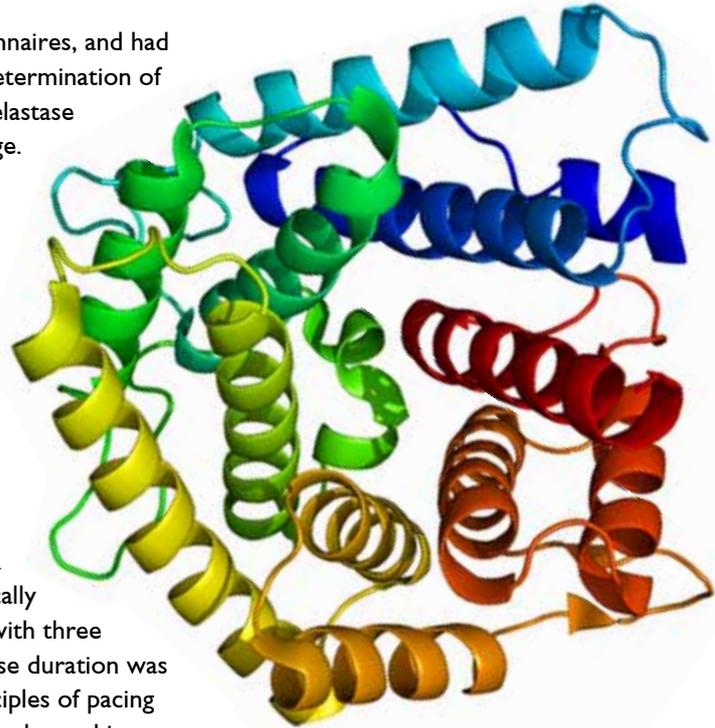
Prof. Nijs and his team were looking at whether different exercise regimes trigger increases in elastase activity, IL-1b and complement C4a levels, and whether changes in these parameters might be associated with exacerbations of symptoms following exercise in people with ME/CFS. The experimental group consisted of women with ME/CFS plus ACR-defined chronic widespread pain (a group the researchers believed would more closely represent ME/CFS patients in the community in whom pain is a major symptom), and 22 non-athletic female controls.

Participants completed two exercise tests one week apart. At each visit they were required to fill out a range of

outcome measure questionnaires, and had blood samples taken for determination of immune variables such as elastase activity and G-actin cleavage. One hour after exercise testing, patients again provided samples and outcome information, and 24 hours later again reported their symptoms.

The first exercise test involved a well-studied “submaximal exercise protocol” using a bicycle. The second exercise was a “self-paced and physiologically limited bicycle exercise” with three “safety breaks”; the exercise duration was determined using the principles of pacing self-management as commonly used in people with ME/CFS, and the activity duration estimated by the participants was then further reduced to account for typical overestimations.

The results (see the box below and the graph opposite) were interesting on a number of levels. As regards post-exercise symptoms, the submaximal exercise and the self-paced, physiologically limited exercise both triggered symptoms, such as pain, after one and 24 hours — as the graph clearly shows — highlighting



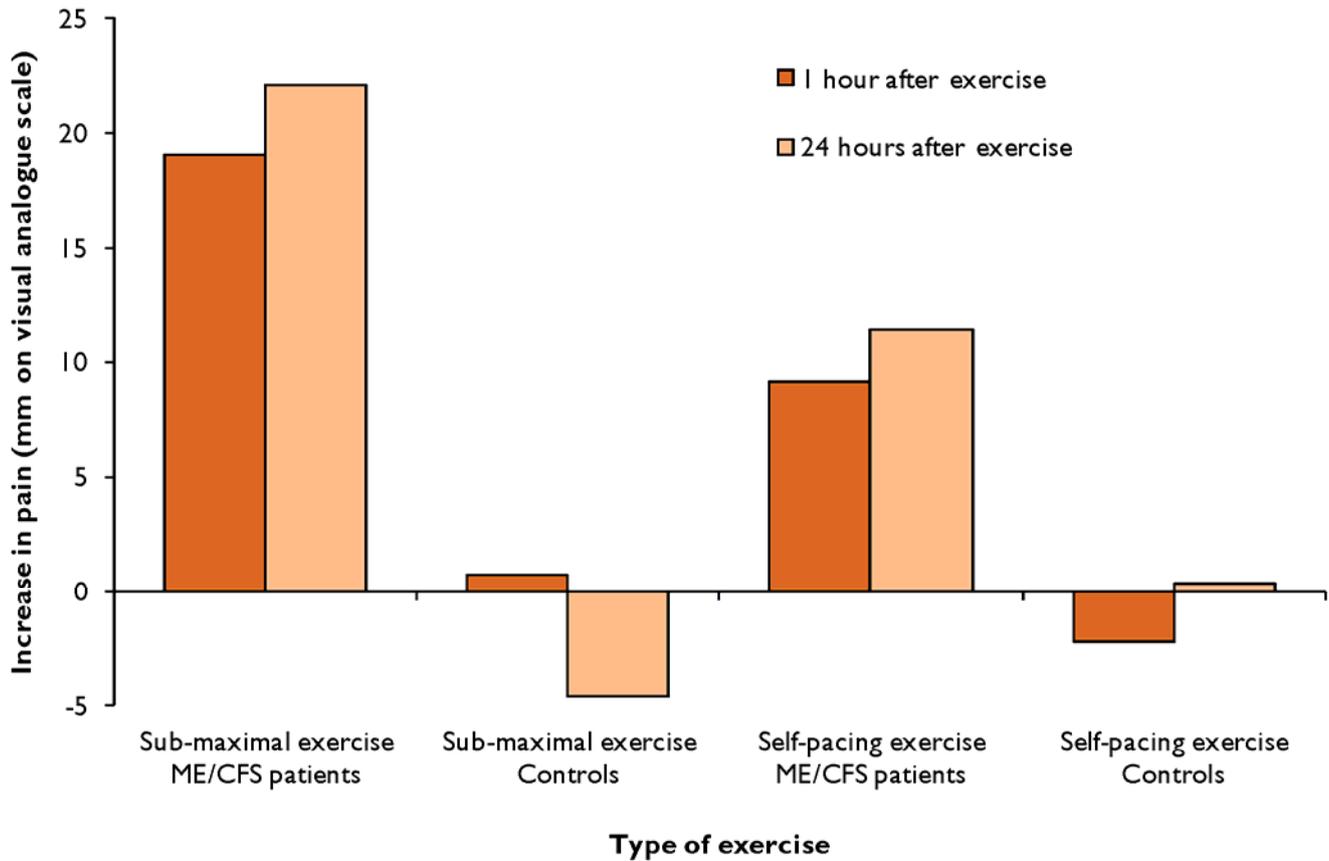
that exercise needs to be employed with caution in ME/CFS patients.

Looking at the immunology, however, neither type of exercise altered circulating levels of IL-1b, complement C4a split product or elastase activity — a most unexpected result. Most fascinatingly, the complement C4a level, measured after exercise, was identified as a possible biomarker for the development of post-exertional symptoms in people with ME/CFS. ●

What did the results show?

- Exercise, even when self-limited, triggered post-exertional symptoms.
- Baseline elastase activity was significantly higher in patients than in controls ($p=0.03$).
- Exercise did not alter elastase activity, IL-1b or complement C4a split product levels ($p>0.05$).
- The change in complement C4a was strongly related to the increase in pain and fatigue 24 hours after self-limited exercise.
- Post-exercise elastase activity, and change in elastase activity, were inversely related to the increase in fatigue one hour after the self-limited exercise.
- There were a number of correlations between post-exercise quality of life subscale scores (e.g., physical activity/function and concentration) and both elastase activity and C4a levels, supporting the clinical importance of both immune markers for these patients.
- The level of complement C4a following submaximal exercise was identified as a clinically important biomarker of post-exercise malaise in people with ME/CFS.

Increase in pain after different types of exercise



Exercise and ME/CFS

Much of the current thinking about the role of exercise in CFS and ME is driven by models of “deconditioning”, and the notion that regular exercise will be beneficial. And overall that is true; regular exercise is good for us all.

However, we already know that too vigorous exercise or activity can trigger post-exertional symptoms in most people with ME/CFS. And we know from research that these patients respond to an exercise challenge with an enhanced complement activation, increased oxidative stress, and an exaggeration of resting differences in the gene expression profile in peripheral blood mononuclear cells. So, it is entirely possible — perhaps even likely — that over-exercising causes harm, simply because something is organically wrong with muscle metabolism. What value do exercise programmes have in these circumstances?

In fact, the characteristic delay in muscle recovery after exercise in ME/CFS (with pain and fatigue occurring for days afterwards) is a phenomenon which few have studied, and which the deconditioning hypothesis does not address. Many questions remain.

For instance, studies show that 20 to 30% of ME/CFS patients have abnormal mitochondrial structure and enzyme function and/or evidence of viral activity in skeletal muscle tissue; are viral particles interfering with the muscles’ ability to carry out specialised functions? Again, post-exercise muscle pain is a widespread symptom — but why is there muscle pain, and could a state of energy depletion during exercise and the development of noxious free radicals be responsible? Furthermore, and most pertinently, how many ME/CFS patients have ever had a comprehensive clinical examination by a GP or consultant, never mind formal muscle testing by a clinical scientist?

Working towards a breakthrough



Dr Gwen Kennedy



Dr Jonathan Kerr



Dr Les Wood and Dr Lorna Paul



Prof. Jonas Blomberg

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

We fund the work of a growing number of scientists in the UK and worldwide, whose research covers several different areas of interest. Our priority is to support innovative clinical and biomedical studies, based in established research institutions, investigating the causes of ME/CFS and

the effectiveness of potential treatments. All our grants are competitive and subject to peer review.

To date, we have invested over £600,000 to support biomedical research, and are particularly grateful to some of the ME organisations that have provided larger donations to help us fund specific projects, some of which are shown below.

Full details of these and other projects, including the resulting scientific papers, can be found on our website: www.mereseearch.org.uk.

Some projects funded by ME Research UK

Pain inhibition during exercise in patients with ME/CFS: targeting neurotransmission

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

Does muscle bioenergetic abnormality cause peripheral fatigue in ME/CFS?

Prof. David Jones, Institute of Cellular Medicine, University of Newcastle

Independent confirmation of the relation between ME/CFS and XMRV in Sweden

Prof. Jonas Blomberg and Prof. Carl-Gerhard Gottfries,

Department of Medical Sciences, Uppsala University Hospital, Sweden

(with co-funding from the Irish ME Trust)

The effects of oral vitamin D supplementation on cardiovascular disease risk in ME/CFS

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

Autonomic nervous system dysfunction — a clinical study

Prof. Julia Newton, School of Clinical Medical Sciences, University of Newcastle

(with co-funding from the Irish ME Trust and the John Richardson Research Group)

The effect of exercise on the immune and sensory systems

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

Interleukin-6 and its receptors

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

Biochemical and blood flow aspects of ME/CFS in children

Dr Gwen Kennedy, Institute of Cardiovascular Research, University of Dundee

(with co-funding from The Young ME Sufferers (TYMES) Trust, and Search ME)

Evaluation of pain and therapeutic interventions

Dr Lorna Paul and Dr Les Wood, Glasgow Caledonian University

Gene expression studies

Dr J Kerr, St George's Hospital, University of London *(co-funded by the Irish ME Trust)*

The funding challenge

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

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

In fact, a significant proportion of research funding for many, if not all, illnesses comes from charitable sources; the Association of Medical Research Charities estimates that £800 million is spent on projects in each year by its members. The annual income of Cancer Research UK alone is between £400 and £500 million — instructive comparison figures for ME Research UK's grant spend of £600,000 in its entire lifetime.

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

Some recent publications from funded projects

Pain inhibition and post-exertional malaise in ME/CFS: an experimental study. *Journal of Internal Medicine* 2010; in press.

Abnormalities in pH handling by peripheral muscle and potential regulation by the autonomic nervous system in chronic fatigue syndrome. *Journal of Internal Medicine* 2010; 267: 394–401.

Unravelling the nature of post-exertional malaise in myalgic encephalomyelitis/chronic fatigue syndrome: the role of elastase, complement C4a and interleukin-1 β . *Journal of Internal Medicine* 2010; in press.

The physical and functional impact of chronic fatigue syndrome/myalgic encephalomyelitis in childhood. *Pediatrics* 2010; in press.

Physiological cost of walking in those with chronic fatigue syndrome (CFS): a case-control study. *Disability and Rehabilitation* 2009; 31: 1598–604.

Response of plasma IL-6, its soluble receptors and F2-isoprostanes to exercise in chronic fatigue syndrome. *Scandinavian Journal of Medicine and Science in Sports* 2009; 13: 1–9.

Perceived fatigue is comparable between different disease groups. *Quarterly Journal of Medicine* 2009; 102: 617–24

Lower ambulatory blood pressure in chronic fatigue syndrome. *Psychosomatic Medicine* 2009; 71: 361–5.

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

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

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

Is chronic fatigue syndrome a hypercoagulable state associated with platelet activation? *Blood Coagulation and Fibrinolysis* 2006; 17: 9–92.

XMRV

An ongoing quest

The discovery of a potential retroviral link to ME/CFS, which is estimated to affect some 17 million people worldwide, certainly caught the world's attention in the autumn of 2009. No bad thing for an under-researched and often-overlooked illness!

The scientific report (which appeared in *Science*, one of the most prestigious scientific journals in the world) described the findings of a consortium of researchers including the Whittemore Peterson Institute (WPI) located at the University of Nevada, USA.

The headline finding was that DNA from a human gammaretrovirus, xenotropic murine leukaemia virus-related virus (XMRV), could be detected in the peripheral blood mononuclear cells of 68 out of 101 ME/CFS patients (67%)

compared with only 8 out of 218 healthy controls (3.7%). In addition, the researchers determined that XMRV proteins were being expressed in blood cells from ME/CFS patients at very high levels compared with controls.

These observations seem to fit neatly, at least at a first glance, with what is already known about ME/CFS as a chronic illness. For example, viruses related to XMRV have been reported to be involved in damage to blood vessels, nerves and natural killer cells (historically low in this illness). As the paper's authors pointed out, some of the most commonly reported features of ME/CFS include neurological symptoms and immune dysfunction with inflammatory cytokine and chemokine upregulation, some of which could be accounted for by infectious XMRV in white blood cells.

As always with scientific discoveries, the unknown wildly exceeds the known

— an exciting place for ME/CFS research to find itself! First and foremost, the finding must be seen to be unequivocal, and the pressing need is for other independent laboratories across the world to test for XMRV infection in their own local populations of ME/CFS patients. For this reason, ME Research UK (with the Irish ME Trust) quickly actioned funding to Swedish researchers to test for the presence of XMRV in Swedish patients (see the opposite page). Their results are eagerly awaited.

Intriguingly, in the five months since the initial discovery was announced, three other studies (see the table below) have been published, all “negative” for the presence of virus in patients. At the time of writing, the results of a further five investigations are awaited, including some on US patients as in the original study. Clearly this ongoing quest is far from over. ●

First author, Country	Title	Journal and date	Result (% positive for XMRV)
Lombardi, USA	Detection of an infectious retrovirus, XMRV, in blood cells of patients with CFS	Science, 23rd October 2009	67%
Erlwein, UK	Failure to detect the novel retrovirus XMRV in CFS	PLoS One, January 2010	0%
van Kuppeveld, Netherlands	Prevalence of XMRV-related virus in patients with CFS in the Netherlands: retrospective analysis of samples from an established cohort	British Medical Journal, February 2010	0%
Groom, UK	Absence of XMRV-related virus in UK patients with CFS	Retrovirology, February 2010	0%



The Swedish Study

For the XMRV discovery to stand the test of time, independent laboratories across the world must attempt to confirm the findings in their own local populations of ME/CFS patients — confirmation and replication are where the rubber meets the road in science.

The aim of the new investigation funded by ME Research UK and the Irish ME Trust is to establish whether XMRV nucleic acid can be found in peripheral blood mononuclear cells, plasma and serum of Swedish ME/CFS patients and controls.

Initially, the researchers will retrospectively test previously stored samples from three groups of patients (20 with Fukuda-defined ME/CFS, 20 with fibromyalgia and 20 with irritable bowel) and 20 controls. They will then

prospectively test samples from 120 ME/CFS patients (defined on the Fukuda 1994 and the Canadian 2003 criteria, similar to patients in the original report in *Science*), who will also have functional assessments.

The investigators are well-placed to conduct this investigation. Prof. Blomberg (above left) is head of the Research Group of Clinical Virology at the University of Uppsala, and his research interests include human endogenous retroviruses, and the links between retroviral sequences and diseases such as MS and schizophrenia.

His collaborator Prof. Carl-Gerhard Gottfries (above right) is Professor Emeritus at the Sahlgrenska University Hospital, Mölndal, and founder of the Gottfries Clinic AB in Mölndal, which has conducted clinical research on patients.

Why might confirmatory studies be “negative”?

- Diagnosis or selection of patients might differ between the USA and Europe
- The Nevada ME/CFS patient cohort might have been unique — an “infection cluster”
- Methodological protocols might differ between laboratories, for example, only the Nevada group have performed culture and co-culture of patients’ peripheral blood mononuclear cells
- Unique procedural or other problems might have occurred in the original study

Recent research from around the world

CHICAGO

Kissing disease

Infectious mononucleosis (IM) is a widespread disease caused by the Epstein-Barr virus, and often known as glandular fever or colloquially as kissing disease (because it is spread by mouth). Its symptoms include fever, sore throat and fatigue, but another potential complication is the development of ME/CFS in the longer term. Previous studies have suggested that as many as 12% of adults can develop ME/CFS after suffering from IM, but the equivalent figures for adolescents are unknown.

A research team from Chicago set about filling this knowledge gap by conducting a prospective follow-up study, the results of which have been published in the journal *Pediatrics*. A total of 301 adolescents (aged 12 to 18 years) with IM were telephoned 6 months after their diagnosis to find out about recovery. A

medical evaluation was conducted in those 70 adolescents who had not fully recovered and in 50 who had, and they were then followed up again at 12 and 24 months. A diagnosis of CFS was made if the participant fulfilled the Fukuda criteria, and in the absence of a recognised underlying condition.

Six months after being diagnosed with IM, 13% of the original sample of 301 adolescents were found to meet the criteria for ME/CFS. Most individuals recovered over time, and the figures dropped to 7% by 12 months and 4% by 24 months. All those who still had the illness at 24 months were female and most reported less severe symptoms than they had experienced at 12 months.

IM does therefore appear to be associated with the development of ME/CFS in adolescents, and girls may be at a greater risk. While much more remains to be known, including the various factors that might predict long-term illness, it is certainly encouraging that most children made a full recovery within 2 years.

AUSTRALIA

Bacteria in your guts?

Various gastrointestinal and neurological problems that are common in people with ME/CFS are surprisingly similar to the symptoms of "D-lactic acidosis". This condition arises from bacterial fermentation of carbohydrates in the gastrointestinal tract, leading to increased lactic acid levels in the blood. Could there be an overgrowth of Gram-positive anaerobic lactic acid bacteria in the guts of ME/CFS patients too?

Scientists at the University of Melbourne in Australia examined the faeces of 108 ME/CFS patients and 177 healthy controls for the presence of the most common of the 500 different bacterial species that inhabit the human gut. Their recent paper in the journal *In Vivo* reported significantly increased levels of aerobic Gram-positive intestinal bacteria in the ME/CFS group than the controls, particularly *Enterococcus* and *Streptococcus* species which are the most common aerobic bacteria in humans.

Moreover, the organisms found in the patients produced significantly more lactic acid than those from the healthy subjects ($p < 0.01$), indicating that acidosis was at least a possibility in ME/CFS. The researchers postulate that increased colonisation by *Enterococcus* and *Streptococcus* could heighten intestinal permeability, assisting the absorption of D-lactic acid into the bloodstream. Increased gut permeability might also aid the release of endotoxins from the bacteria themselves, leading to inflammation, immune activation and oxidative stress, which are prominent features in a large subset of ME/CFS patients.

While the cause of the increased colonisation remains unclear, the researchers point out that eradication of all bacteria is not the answer; indigenous bowel microflora have both positive and



negative impacts on health, and the balance of “good” to “bad” bacteria is important. And their next experimental step is to measure D- and L-lactic acid accumulation in the biofluids of ME/CFS patients to confirm whether D-lactic acidosis really is a factor. If so, existing interventions, such as short-course antibiotics, alkalinising agents, a low carbohydrate diet or dietary glucose restriction might prove to be useful.

BELGIUM

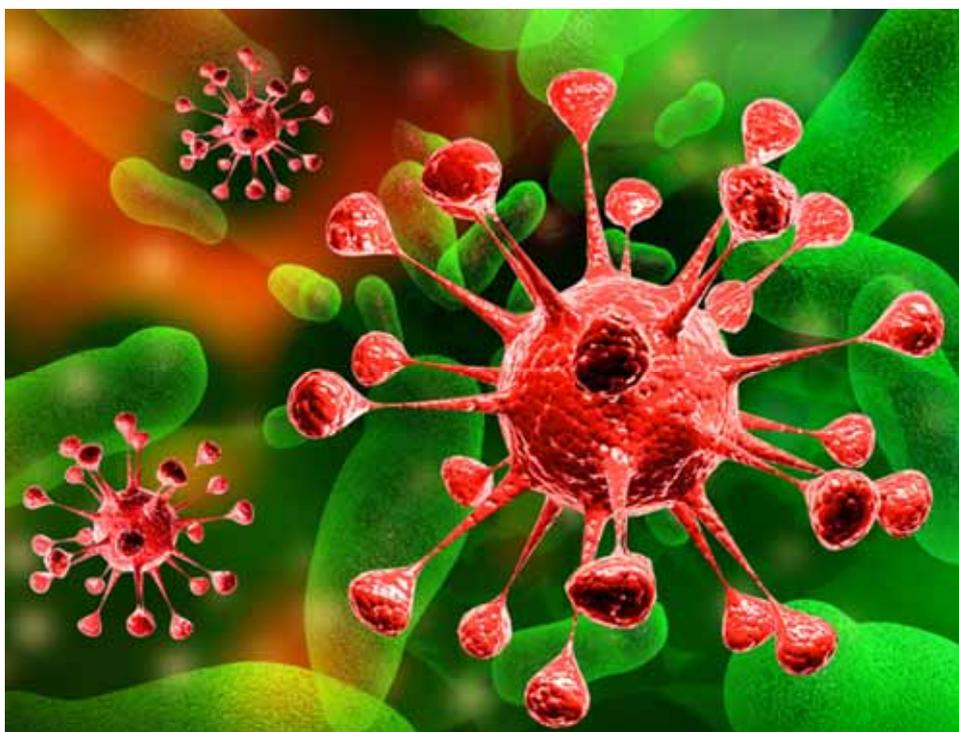
A virus with shoes

While some might dispute the late comedian Bill Hicks’ view of humanity as a virus with shoes, there is no question that the theory of a viral cause for ME/CFS is one that has legs.

Many patients can trace their illness back to some kind of viral infection, and the recent finding that two-thirds of patients in Western USA tested positive for the infectious retrovirus XMRV has given this particular theory a good pair of running shoes as well. However, plenty of other viruses have been implicated in ME/CFS, and a recent study from Belgium, published in the journal *In Vivo*, has turned the spotlight on some of these.

Associations between the illness and a number of viruses (including human herpesvirus-6, Epstein-Barr virus and parvovirus B19) have been reported before. However, the results have been inconsistent because it is very difficult to detect active, pathological viral infections, and to distinguish between active and latent viruses. While active viral infections may not be detectable in the blood, they might persist in other tissues such as the gastrointestinal tract, making this potentially a good site to investigate.

The Belgian group used a technique called real-time polymerase chain reaction to measure viral DNA in gastrointestinal biopsies from 48 ME/CFS patients and from 35 control subjects (who were either healthy or suffering mild gastrointestinal symptoms). Most of the viruses investigated were detected in a similar proportion in both groups, but the exception was parvovirus B19, which was detected in 40% of ME/CFS patients but in



only 15% of control subjects. This virus is known to be linked to a number of diseases and conditions, including “fifth disease” (fever, malaise and a skin rash most commonly seen in children), anaemia and a form of arthritis.

This study provides further evidence of its association with ME/CFS in at least a subgroup of patients, and parvovirus B19 may therefore potentially be a cause of gastrointestinal symptoms in the illness. We wait with interest to see how these investigations develop.

UK

A HOT new therapy?

One symptom commonly reported by patients with ME/CFS is orthostatic intolerance, which is characterised by fainting or a loss in consciousness when standing up, and is caused by abnormalities in the body’s neurological system. An individual with orthostatic intolerance is unable to compensate for the changes in blood pressure that occur on standing, and this leads to a temporary lack of blood flow to the upper body and head.

Home orthostatic (or tilt) training (HOT) is a technique which has proved to be effective for the treatment of orthostatic intolerance in patients with

neurally mediated hypotension, which may share other features with ME/CFS.

Patients are asked to stand and lean with their upper back against a wall and their feet placed 15 cm away from the wall. They do this for up to 30 or 40 minutes, or until they experience symptoms, and then repeat the procedure once or twice a day for several weeks. The idea is that this repetition conditions them over time.

A research team from the National Institute for Health Research in Newcastle wondered whether HOT may be a simple, non-invasive treatment for the symptoms of orthostatic intolerance in patients with ME/CFS. A total of 38 patients completed either a regime of HOT (40 minutes once a day for 6 months), or a sham regime in which they stood for only 10 minutes while exercising their calf muscles.

The results have been published in the *European Journal of Clinical Investigation*, and showed that patients who completed HOT did not experience such a big drop in blood pressure while standing as those who completed the sham treatment. They also tended to show an improvement in their fatigue at the end of six months.

The investigators concluded that a course of HOT may well be an effective strategy for improving the quality of life of patients with ME/CFS, although a large-scale clinical trial is needed to confirm this, and individuals should probably not undertake the therapy by themselves without the advice of their doctors.

BELGIUM

Immune links between ME/CFS and cancer

Cancer fatigue is a well-recognised, often intense symptom experienced both 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 in-depth review, published in *Anticancer Research* in 2009, were that both conditions share abnormalities in the RNase L antiviral pathway and in the major intracellular mechanism NF- κ B which regulates inflammatory and oxidative stress (see the table to the right). 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 point 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 are 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.

HISTORY CORNER

Signs and symptoms in the eyes

In the early 1990s, two reports appeared in the scientific literature reporting ocular (eye) symptoms in ME/CFS. In the first (published in *Optometry and Vision Science* 1992), a research group in Boston, Massachusetts surveyed 190 patients and 198 healthy controls by written questionnaire, and found a range of

Immune abnormalities in ME/CFS and cancer

Factor	ME/CFS	Cancer
Ribonuclease L (RNase L)	Increased activity leading to increased apoptosis	Decreased activity leading to decreased apoptosis
Nuclear factor kappa beta (NF- κ B)	Increased activation	Increased activation
Natural killer cells	Decreased activity	Decreased activity

symptoms to do with dysfunction of the eyes, including sensitivity to light (photophobia) and problems with accommodation probably associated with the ocular muscles. In the study, 24.7% of patients had reduced or stopped driving because of eye problems, compared with only 3% of controls.

In the second study (published in the *Journal of the American Optometry Association* 1994), all of the 25 consecutive CFS patients reported eye symptoms; the most common clinical findings were abnormalities of the pre-ocular tear film and ocular surface (in 19 patients), reduced accommodation for age (18 patients) and dry eyes (9 patients).

Then, in the decade 2000 to 2010, two further reports appeared. The first was a case-control study (in the *Annals of Ophthalmology* 2000) in which the 37 ME/CFS patients had significant eye impairments compared with controls; the

impairments included foggy/shadowed vision and sensitivity to light, and there were associated problems of eyeball movement (oculomotor impairments) or tear deficiency. The second, from Russia (*Vestnik Oftalmologii* 2003), reported “vascular pathology” of the eye in 70.2% of the 218 ME/CFS patients and “dystrophic pathology” in 52.8%.

The astounding thing is that these four smallish studies represent (almost) the sum total of research into eye problems in ME/CFS in the past 30 years, even though such symptoms concern many patients today. Indeed, around 75% of the 2,073 consecutive patients described in the Canadian review of 2003 specifically reported sensitivity to light and dullness of vision to be significant problems.

Astonishing, isn't it? But, as we've said before, time marches on but sometimes it can seem to stand very still indeed where research into ME/CFS is concerned!



NEW YORK

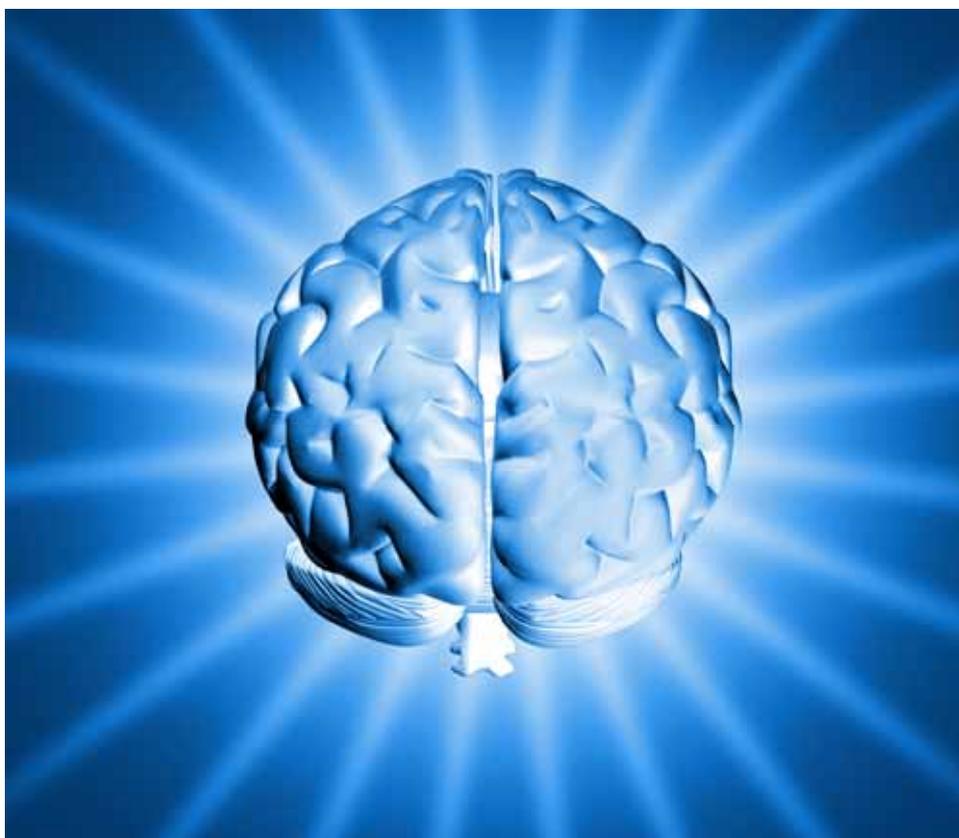
Psychosocial limitations

The cognitive-behavioural model of ME/CFS postulates that fear-based avoidance behaviour and physical deconditioning can explain many of the symptoms and impairments associated with the illness.

However, a thoughtful essay by Dr Fred Friedberg of Stony Brook University, New York (published in the *Bulletin of the IACFS/ME* 2009) has examined the assumptions underlying this model and raised important critical issues. His central thrust is that although cognitive behavioural therapy (CBT) has a role in reducing symptoms and improving functioning, important matters surrounding the clinical trial evidence remain to be resolved.

First, there is considerable doubt about whether avoidance behaviour and physical deconditioning are indeed causal factors in the illness; for example, there is evidence to show that ME/CFS patients are not exercise phobic, and are not more physically deconditioned than comparable healthy people. Again, evidence from a recent systematic review (*Cochrane Collaboration* 2008) has indicated that approximately 40% of patients benefit from CBT, while the placebo response rates in ME/CFS intervention trials have averaged 20%. This indicates that while CBT appears to be superior to placebo, less than a majority of patients actually benefit from it, an important concern that is not commonly addressed.

Another point highlighted by Dr Friedberg concerns the true clinical significance (rather than statistical significance) of self-reported "improvements" measured in trials of CBT; it is not clear in many cases whether these represent illness improvement or simply better coping, or some combination of the two. And, crucially, it is important to know whether real world clinical improvements occurred; for example, whether patients' activity levels actually increased, or whether their employment status changed for the better. As he points out, it is time for an objective, balanced assessment of the effectiveness of CBT.



GERMANY

XMRV: transfusions and transplants

As the possible links between the retrovirus XMRV and ME/CFS or prostate cancer continue to be explored (see page 10 of this issue), the wider implications for populations as a whole are slowly becoming apparent. One recent essay in the journal *Retrovirology* (March 2010) by Prof. Joachim Denner of the Robert Koch Institute in Berlin poses some open questions, and issues a warning.

Reassuringly, he points out that numerous retroviruses have been reported in human tissues and cultured cells in the past, but only a handful (such as HIV-1) have been proven to be linked to human disease. And he reminds us that modern, highly sensitive laboratory methods that detect very small traces of retroviruses can also be prone to contamination, for example by animal viruses which have been found in numerous human cell lines. So it is entirely possible that XMRV might not be a major player in human disease after all; only time will tell. Nevertheless, if future investigations show its importance, then the consequences could be severe. Two

in particular are worth mentioning.

First, the 3 to 4% incidence of XMRV in healthy control samples found in the initial study on ME/CFS patients (*Science* 2009) suggests that several million Americans may be infected. As Prof. Denner says, "If XMRV is indeed widely distributed in the human population and associated with tumours and CFS, should blood donors be tested in order to avoid XMRV transmission?"

Second, if XMRV is indeed circulating widely in the population, there are implications for organ transplants. At the moment, xenotransplantation (from animals, usually pigs, to humans) is being developed to compensate for the increasing shortage of human to human donations, raising the possibility of transmission of pathogens, such as endogenous retroviruses, from pigs to man. Should we therefore start to develop a test to discriminate between XMRV and pig retroviruses, and begin investigating, at this early stage, the potential for recombination between these viruses?

While our primary focus at present has to be on the distribution of XMRV in populations and its impact on human health generally, we should remember that many other unanswered questions stand waiting in the shadows, like ghosts at the feast.

Friends of ME Research UK

INVASION OF THE PENGUINS



This winter past, Liverpool was invaded... by penguins!

As part of the official Go Penguins! campaign, more than 100 penguins were dotted around the city, including 13 at National Museums Liverpool's venues. They were created by artists, schools and community groups, and celebrated Liverpool's unique sense of fun and self expression.

And one of the penguins was raising awareness of ME, and benefiting ME Research UK. Called "Look at ME", the penguin was the creation of Helen Burnley, an experimental young artist who runs a website called "Creative Chaos Art".

The key message of the artwork is: "Look at ME. Do I look like I have an invisible disability? Across the country tens of thousands of people suffer from invisible disabilities. They look well so people assume that they are... but looks can be deceiving. Is it really fair that illness is judged on looks alone? This penguin challenges common perceptions."

Our penguin was living in the Lady Lever Art Gallery, but has now been sold at auction and gone to a good home.



2010 Belfast City Marathon

Paul Christie Jr (pictured above right) and Sam McIlwaine are in full training mode to run in the Belfast marathon in May 2010. Paul's younger brother David has now been very ill for six years, and the family, including mum Antoinette, have undertaken many events for ME Research UK.

As Antoinette says, "Very little help is available on the NHS, and sufferers and their carers are usually left to cope on their own while their lives fall apart."

On the race day, there is also a relay team consisting of about 15 of Antoinette's family and friends. Paul, Sam and the Relay team have already raised almost £400, and you can show your support by making a donation at their Justgiving page.





Eva Sanders

Eva Sanders was loved and respected by everyone who knew her, so her tragic death in October last year affected the hearts of many.

Eva (pictured left) was a teacher from Greenford and a stalwart member of Network MESH, a long-established ME self-help group covering West London. The Network decided to invite contributions in memory of Eva to further the work of ME Research UK, and within weeks £1,425 in donations towards our biomedical programme had arrived by post and telephone.

Catriona Courtier, a London MESH Trustee, summed up by saying, *“I am delighted with the response in Eva’s memory. This was our way of saying how much Eva meant to her many friends in our group.”*



Nature photocards

Jane Hurst creates some very attractive cards featuring photographs taken by friends and family, all of whom suffer from ME or who care for family members with the illness. The cards are printed on quality card and make excellent birthday cards or thank you notes, but also make ideal gifts in their own right. They include a wonderfully atmospheric photo of Stonehenge, a beautiful close up of Tequila the cat, and a stunning shot of a sunset over Fistral Beach in Cornwall.

As Jane explains, *“People can choose from two packs of five assorted cards (£3.99 plus p&p per pack), and all proceeds are split between ME Research UK and the 25% ME Group for Severe Sufferers.”*

To date, the cards have raised a total of £1,500, and new designs (which can be seen in the Shopping area of ME Research UK’s website) are introduced regularly.

Record donations from VegEPA for ME

VegEPA for ME is a scheme through which every pot of VegEPA sold raises 50p for research into the illness. It now has some 4,500 members in 20 different countries across the world linked by the website at thevegepaformescheme.com. The scheme was initiated in 2006 by Lynne Kersh, who has cared full-time for her daughter Daliany, a long-term ME patient, and over the past 4 years Lynne has been able to donate a whopping £32,000 to ME Research UK.

Dr Vance Spence, our Chairman, said, *“We warmly welcome Lynne’s personal donation from her scheme. The role of the dietary therapies, including EFA supplementation, in relieving the symptoms of ME is an unexplored area of science but one that needs to be investigated; indeed, we welcome applications from academic researchers to carry out experimental work in this field.”*

“£32,000 is an amazing achievement — and we are extremely grateful to Lynne and all her many members across the world.”



CD collection under the hammer

Although severely ill, Simon Overton has great talents as a fundraiser. Most recently, he encouraged his friends to run the Highlander Mountain Marathon for our charity in 2008, and then, astonishingly, undertook a personal skydive 5,000 feet down the North Face of the Eiger in 2009 to raise awareness and help fund further research.

Last year, Simon's father died suddenly. He was a very prolific collector of rare CDs, and the £800 raised from the sale of the collection was donated by Simon to ME Research UK which funds the research being undertaken by Prof. Julia Newton at the Royal Victoria Infirmary in Newcastle-upon-Tyne.

The photo below shows Julia receiving the cheque on our behalf from Simon after one of his clinic appointments.



Priscilla the plastic duck goes north

When Lynda Marney first got ME, one of her greatest regrets was not being able to go cycling which had been a great pleasure. But after fighting back from the illness, she undertook a cycle ride in September 2009, an adventure which took her from Fort William to Inverness together with her brother, Colin Bishop.

As Lynda says, "I just love the feeling of riding my bike — the freedom, the sense of getting around, and the feeling of the cool wind on the face!"

And all the way, Lynda and Colin were accompanied by Priscilla the pink plastic duck sporting her own tiara and very swish ME Research UK t-shirt.

Thank you Lynda and Colin from all of us for going on this great expedition and raising almost £1,200. And three quacks for Pink Plastic Priscilla — tiara, t-shirt and all!



Tony's Great Yorkshire Run

The Great Yorkshire Run is held each year in Sheffield, and in 2009 Tony Sweeney decided to run for our charity because his wife Claire has had ME for a number of years. On the day, Tony romped home in 1 hour 1 minute and 19 seconds, an excellent time considering that it was his first ever run, and that the winner Eliud Kipchoge took a whole 28 minutes 30 seconds to get from start to finish!

Tony raised over £730, and was amazed to receive sponsorship from Hong Kong, Singapore and Ireland, as well as many friends in the UK. And his son was delighted with his Dad's success, as the photo on the left shows.

Just Four Quid

Last push on the campaign. Let's end with a bang!

Visit Zonko's *Just Four Quid* blog at justfourquid.com

The "Just Four Quid" campaign to raise funds for much-needed biomedical research has been running for the best part of a year, and has seen very many generous donations — but we still need more people to join in.

Specially designed for the recession, the appeal invites people with ME and their friends and family to join in a year of cleverly saving money so that they can donate a bit of their saving to research. The idea is simple. Each week, the "Just Four Quid" dedicated daily blog reports on totals raised already, and suggests a new tip for saving cash. If, for example, that tip saves you £10, you might consider donating £5. In this way, you will be better off *and* you will have donated to the campaign.

Examples of Zonko's recent cash-saving tips have been the "week of no chance" in which people who would usually spend £52 per year on lottery tickets were encouraged to give some to research instead; or the "week of the end of the day" in which people were encouraged to shop in the evenings when shops mark down food prices, giving any savings to the campaign.

The key idea of the campaign has been that lots of people donating little and often will raise a huge amount over the year. People can donate to one or both the charities taking part — ME Research UK, and the Ramsay Research Fund of the ME Association — and all of the donation goes directly to the charity chosen since Just Four Quid receives none of the money raised.

We're entering the home straight with this campaign now, so if you've not already been involved over the past few months, you can start helping straight away. Take a look at the Just Four Quid website (justfourquid.com) to get the latest fundraising tip, and if you think it can save you money, give a little back to us. And you can tell other people about the campaign so they can join in. After all, "mony a meikle maks a muckle" as the old saying goes!



Shop at Amazon for ME Research UK

Can there be any easier way to earn money for our charity? If you are buying from Amazon, then just click through the link on the Amazon page on our website, and 5% or more of your purchases could be making its way back to ME Research UK. It really is that easy.

Whether it's books, electronics or toys, Amazon has it all. Provided that you connect to Amazon via one of our links, your shopping will qualify. The amount we get varies according to the type of product and the type of link followed. It won't cost you a penny more, and you won't lose out on other discounts, so please help us by shopping via ME Research UK's Amazon link.

Visit our website for more details.

Read about more Friends' activities and ideas for your own fundraising at our website www.mereseach.org.uk/support

