breakthrough

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Establishment of ME/CFS biobank in the UK

ME RESEARCH UK
ISSUE 14
AUTUMN 2011
www.meresearch.org.uk

Breakthrough

Breakthrough magazine is published twice a year and is available free of charge.

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ME Research UK is a registered charity, number SC036942 (from 1st November 2011, SCIO number SC036942).

Chair of Editorial Board: Dr Neil Abbot
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Publisher: ME Research UK

ME Research UK funds research into Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (also known as ME/CFS). We have an international remit, and our principal aim is to commission and fund high-quality scientific (biomedical) investigation into the causes, consequences and treatment of ME/CFS. We also aim 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.

First published by ME Research UK, 2011

editorial

Winds of change are sweeping through the charity world, and we have to be ready for them. The days when people supported charities simply through a sense of civic or personal duty are ending. The new generation of donors is just as passionate about its worthy causes, but more informed, more questioning and more open to different ways of giving.

Standing orders have been the mainstay of charity giving for almost fifty years, and people have become familiar with donating cash through collecting boxes in shops and cafes, as well as by cheque. But the incredible growth in new technologies means there are now numerous alternative methods of making a charitable donation; in fact, it has never been easier, while continued support has never been more vital.

A recent report by the Media Trust (2009) pointed out that the ability of charities to respond to these new developments depends upon their size and resources. Of the 161,960 registered charities in England and Wales and 23,345 in Scotland, the vast majority (85%) are classed as small or micro, and around half have an annual income of less than £10,000. Only a very few gigantic charities have the "dream teams" of multi-skilled marketing and communications professionals ready to take full advantage of the Internet.

My communications role over the past nine years has involved trying to bridge the divide between the old and new charity worlds. ME Research UK is classed as medium sized, and is dwarfed by research funding giants such as Arthritis Research and the Wellcome Trust. We have already seen our operations revolutionised by new technologies. Justgiving allows money to be raised quickly and easily from events, while we now find supporters selling items for us on eBay, raising money via Everyclick (which gives us a donation every time they use a search engine) and by purchasing items on Amazon. What's more, the introduction of credit card processing facilities and the ability to accept donations via our website have also been a great benefit.

Yet, these changes are only the beginning of the communications revolution taking place. Many believe that Facebook will shortly replace e-mail as the main communication medium, as its adoption by multi-channel retailers indicates. Then, there is the mushrooming of charity-specific apps for mobile phones and tablet devices, which might dramatically change the landscape. Donation by texting has also caught on in a big way (see page 19 for our new text donation service). Who knows what will happen if the Big Society really takes off, bringing the resources of big business into charitable giving, as in the recent partnership between Cancer Research UK and Tesco in the Race for Life campaign.

Dramatic changes are coming to the ways in which charities such as ME Research UK raise funds and promote their causes, and innovation is the only survival strategy.

David Newton
Communications Officer
ME Research UK

this issue

Bioenergetics in ME/CFS

Muscle recovery after exercise is slower

Bioenergetics concerns the flow of energy through living things, and its research involves the exploration of cellular processes, including cell respiration and the plethora of other metabolic events that result in the production and use of energy. In the past two years, researchers at the School of Clinical Medical Sciences, University of Newcastle have identified a distinctive muscle bioenergetic abnormality in people with ME/CFS. This abnormality is associated with the autonomic dysfunction found in the majority of ME/CFS patients and with a characteristic cardiac bioenergetic impairment (see *Breakthrough* Spring 2011).

The research interests of the group – which receives funding from ME Research UK, the John Richardson Research Foundation and the Irish ME Trust – also include the chronic disease primary biliary cirrhosis which shares some symptoms with ME/CFS, notably a difficulty sustaining repeat exercise. Since the researchers recently found evidence of abnormalities in the regulation of muscle acid in PBC patients during a programme of repeat exercise, they wondered whether similar bioenergetic abnormalities might also occur in ME/CFS.

To explore the issue, 18 consecutive new patients recruited from the local CFS/ME Clinical Service, and 12 matched healthy control participants attended the exercise laboratory for a range of assessments of cardiopulmonary fitness, maximum voluntary contraction (MVC), and muscle bioenergetic function using magnetic resonance spectroscopy (MRS) during repeat exercise.

To assess maximal exercise capacity, the patients undertook five 5-second maximal isometric contractions of the foot (plantar flexion) while lying down. Force generation was assessed using a calibrated strain gauge and the peak force was regarded as the MVC. For MRS measurements, subjects performed controlled plantar flexion using a purpose-built exercise apparatus within the MRI scanner. Subjects performed three 180-second bouts of plantar flexion contractions at 35% of MVC (to standardise "work done" between patients and controls). Immediately after the MRI exercise protocol subjects were asked to assess their degree of effort, and were asked to grade any discomfort that they were feeling, and they were telephoned 24 hours later and then again five days later with the same questions.

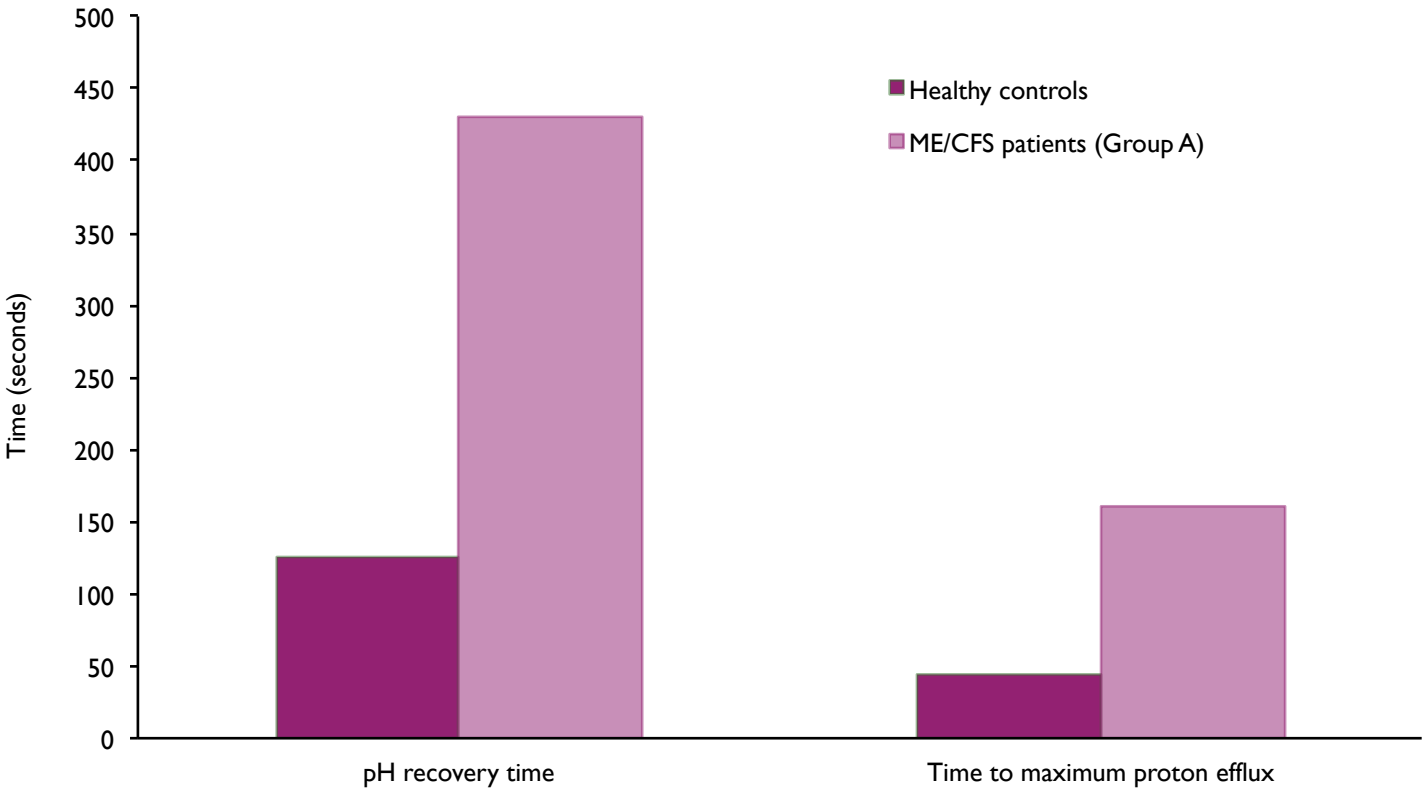
The key findings, published in the European Journal of Clinical Investigation (2011) are shown in the box below, but the major observation was that the peripheral muscles of ME/CFS patients took four times longer to recover (reduce acid levels and restore baseline pH) than those in matched control subjects, and that furthermore there was a significant slowing of the proton excretion response needed to normalise acid levels (see the graph opposite). The net effect was a sustained and significant accumulation of acid (acidosis) in muscle during and following exercise, which could affect muscle function and contribute to the experience of muscle fatigue.

The authors point out that total post-exercise acid exposure was approximately 50-fold higher in ME/CFS patients when exercising to the same degree as normal controls, with none of the apparent reduction in acidosis with repeat exercise observed in healthy subjects. Why this should be remains unknown, but – since acid is actively transported from the muscle by Na-H antiporters which are in turn regulated by the autonomic nervous system – it is possible that the acid transporters are impaired (a phenomenon that might be related to the autonomic dysfunction found frequently in ME/CFS patients), although a reduction in vascular run-off may also be a possibility.

What did the results show?

- The study used magnetic resonance spectroscopy (MRS) to explore the recovery of lower leg muscles during three bouts of exercise.
- In the ME/CFS group as a whole, there were significant reductions in anaerobic threshold, heart rate, oxygen consumption and peak work (power in watts) compared with controls.
- The peak force that the patients could exert (their maximum voluntary contraction) was lower on average than for healthy controls, although it varied greatly between individual patients. Thus, only a subset of patients (those achieving normal phosphocreatine depletion values, greater than 33%; group A) could be directly compared with controls, since only in these patients was the level of "muscle work" equivalent to that of the healthy controls.
- Compared with healthy people, an increase in acidosis (decreased pH) within the muscle was seen in Group A ME/CFS patients after similar muscle work at each of the three exercise periods. In addition, these patients had a significant, almost fourfold prolongation of the time taken for pH to recover to baseline; i.e., for the level of muscle acid to fall back to normal (see the graph).
- The key message was that some ME/CFS patients have a profound abnormality in bioenergetic function when exercising at comparable levels to healthy people.

Time taken to recover pH levels and to achieve maximum proton efflux



Post-exercise symptoms in ME and CFS

In the historical literature, the hallmark of myalgic encephalomyelitis (ME) was marked loss of muscle power (fatigability), often in response to minor degrees of exercise. Muscle cramps, twitching and extreme muscle tenderness were also common findings.

In Dr Melvin Ramsay's words from 1978: "*This was sometimes obvious as the patients winced even on light palpitation of the affected muscle; but much more frequently it took the form of minute foci* [points] *of muscle tenderness which had to be carefully sought and for no ostensible reason were generally found in the trapezii and gastrocnemii* [neck and calf area]."

Even in modern times, within the diagnostic umbrella called ME/CFS, "post-exercise" symptoms are central; 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 the very presence of post-exercise symptoms greatly helps to distinguish ME/CFS from, say, major depressive disorder.

Much of the current thinking about the role of exercise in CFS and ME is driven by simple models of "deconditioning", and the notion that regular exercise will be beneficial. But we already know that too vigorous exercise or activity can trigger post-exertional symptoms in most people with ME/CFS. We also know from research that patients respond to an exercise challenge with an enhanced complement activation, increased oxidative stress, and an exaggeration of resting differences in gene expression profile in peripheral blood mononuclear cells.

So, it is entirely possible – perhaps even likely – that over-exercising causes harm, possibly because something is organically wrong with muscle metabolism, as this study in the *European Journal of Clinical Investigation* suggests. What value exercise programmes in these circumstances?

Fifty-two years after Sir Donald Acheson reviewed a clinical syndrome called ME for the *American Journal of Medicine*, the characteristic delay in muscle recovery after exercise is a phenomenon that few researchers have studied and few healthcare professionals take into consideration when examining patients.

XMRV: the blows rain down

Twenty-four months ago, the most prestigious scientific journal in the world, *Science*, published findings suggesting a link between xenotropic murine leukaemia virus-related virus (XMRV) and ME/CFS. The researchers, Lombardi *et al* from the Whittemore Peterson Institute (WPI) in Nevada, had found the retrovirus in two-thirds of ME/CFS patients' blood samples, but in only 4% of control samples – an amazing find if it were true and could be confirmed by others.

Since then, 17 distinct studies have been published by other researchers in the UK, USA, China, Germany, the Netherlands, Japan and Canada; none has been able to find significant levels of the virus, let alone see such a dramatic difference in infection between ME/CFS patients and healthy controls. While each "negative" study has been a set-back to the hypothesis that XMRV has a role in the illness, the theory has received blows from other quarters too.

First, in December 2010, four studies appeared in the journal *Retrovirology*. Collectively, these suggested that XMRV might have originated from the chance recombination of mouse viruses during laboratory experiments, with positive findings reflecting cell-line contamination rather than true infection in humans. One of these studies by Hue *et al* from University College London had compared XMRV gene sequences from the cell line 22Rv1 with sequences found in XMRV-positive patients; virus genetic diversity was found to be greater between cell lines than between patients, suggesting contamination of patient samples by cell line virus in the lab.

Second, in May 2011, a report from Paprotka *et al* at the National Cancer Institute in Maryland had examined the origins of previously used human prostate cancer cell lines. The early versions of the cell line, which were still in storage, harboured no XMRV, but DNA matching one half of the virus was found in two different strains of mice that had been studied subsequently. The researchers concluded that XMRV was generated from a unique recombination of pieces of two mouse viruses "*that took place around 1993–1996 in a nude mouse*", and spread in reagents used by other labs.

Then came the third blow – the inability of other groups to find XMRV positivity in some of the *same* patients examined in the original study. One group tested 100 ME/CFS samples, 14 from the cohort testing positive at the WPI; the researchers failed to "*find XMRV or related MLVs either as viral sequences or infectious viruses*" or antibodies to these viruses in any of the patient samples. Another study conducted by Prof. Jay Levy of the University of California examined samples from 43 patients who had tested XMRV-positive at WPI: all samples tested negative.

> 17 studies have been unable to find significant levels of the virus in ME/CFS

Then, dramatically, on 31st May, *Science* published an "Editorial Expression of Concern" by its editor-in chief, Bruce Alberts, and asked the authors of the Lombardi *et al* study to retract voluntarily the entire paper, a very unusual request which the authors have declined (see opposite page).

Finally, *Science* published a $500,000 study from the Blood XMRV Scientific Research Working Group (BWG) in which none of nine labs could reproducibly detect XMRV or its relatives in the samples (see opposite page). The same issue of the journal in September 2011 contained a "partial retraction" of the original paper, after two coauthors, Silverman and Das Gupta, reported finding contamination in their original samples.

Does this mean that XMRV can be ruled out as an important factor in ME/CFS? Not entirely, since there remains the possibility that the levels of markers in blood may be at or below the limit of detection of all assays and/or fluctuate over time as recently described in studies on experimentally infected macaque monkeys. And we still await the results of a $2.3 million investigation funded by the US government and led by Prof. Ian Lipkin of Columbia University, in which six labs will test 150 patient and 150 control samples in a blinded manner. Only when the blind-codes are cracked early in 2012 will the results be revealed to a scientific world watching with uneasy suspense.

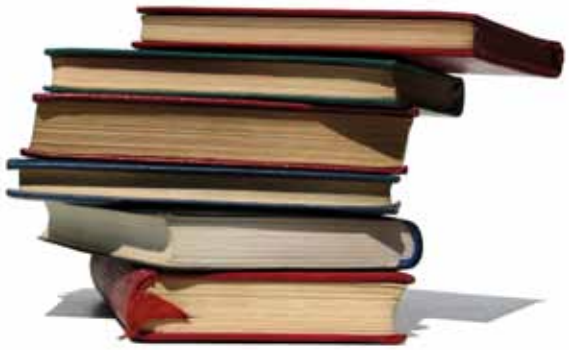
Retractions in the scientific literature

The voluntary or involuntary "retraction" of results published in the scientific literature is rarely discussed. The assumption of working scientists is that data published by others are *bona fide*; i.e., that no fraud is involved and that the findings are not the result of relatively basic errors or laboratory contamination. It generally takes a major drama – such as the informal request by *Science* for the authors of the Lombardi *et al* study on XMRV to voluntarily withdraw their 2009 report – for the issue of retraction to come to the fore. But, are there many retractions, and does it matter if there are?

A recent review article by Dr Grant Steen in the *Journal of Medical Ethics* has attempted to assess the risk to patients of misleading information that was later retracted. He found that 788 English-language papers had been retracted between 2000 and 2010, and he focussed on the 180 of these which described new research with humans or freshly derived human material.

The group of 180 retracted papers had been cited by other researchers over 5,000 times, suggesting that ideas promulgated in retracted papers can influence subsequent research. Overall, 9,189 patients had been treated in the 180 studies, and a further 70,501 patients were treated in 851 secondary studies which had cited a retracted paper. Overall, 6,573 patients were treated in studies later invalidated by fraud, while 2,616 patients were treated in studies invalidated by error.

So, while retractions for error or fraud are relatively rare (given the 7 million studies published in 10 years), flawed reports do have serious consequences. For patients, risks include enrollment in an experimental therapy for a condition which might already have an accepted therapy; for researchers, time, energy and money can be wasted in the pursuit of red herrings. But perhaps the most serious consequence is the undermining of the scientific literature, an international resource we should all be able to trust.



The most serious consequence is the undermining of the scientific literature we should all be able to trust

The BWG's multi-laboratory study

- Scientists at nine different laboratories, including two that had previously found an association between XMRV and ME/CFS, tested blood samples from two groups: 14 ME/CFS patients (and one patient contact), all previously reported to be infected with XMRV or a related virus; and 15 healthy controls who had been established as negative for XMRV and MLVs by polymerase chain reaction, serology and culture by multiple laboratories.
- Each laboratory independently tested the samples, which were "blind-coded" (so that none of the labs knew to which group each of the samples belonged), using assays of their own choosing.
- Only two laboratories (those associated with the original 2009 report) reported evidence of XMRV/MLVs. But they found the virus in healthy controls as often as in the patients – and there was no agreement between the two labs on which patient samples tested positive.
- As the authors said, "*The inconsistent reactive results from the two laboratories that previously reported detection of XMRV… and the negative results from all other laboratories… strongly suggest that the positive reactivity in this study represents false positive results due to assay non-specificity or cross-reactivity.*" Based on this, the authors concluded that screening of blood donors for XMRV was not warranted.
- BWG member Michael Busch, head of the Blood Systems Research Institute in San Francisco, said, "*I commend* [the authors of the 2009 paper] *on their scientific integrity and commitment to the scientific process… This has been a difficult and disappointing process for them and for CFS patients, but hopefully we have all learned lessons that will guide future research and lead to discovery of the cause and cure of this disease.*"

The correct diagnosis

Are we getting better at diagnosing ME/CFS?

At present, there are many ways of diagnosing ME, CFS, CFIDS, CFS/ME and ME/CFS – and just listing these acronyms illustrates the confusion that besets the field. Yet each new definition delivers only a "diagnosis of exclusion" of other conditions, based on clusters of vaguely defined symptoms shared with other illnesses. How valid a diagnosis of ME/CFS really is depends critically on the rigour of the initial clinical assessment, and the efforts expended to exclude other treatable conditions that might be causing the collection of symptoms.

The clinical guideline produced by the UK's National Institute for Health and Clinical Excellence (NICE) in 2007 came up with its own variant of diagnostic criteria for "CFS/ME" – new, unexplained, persistent/recurrent fatigue with a post-exercise component plus one or more of a range of common symptoms such as difficulty with sleeping, muscle and/or joint pain and headaches. It is also recommended that patients be referred to specialist ME/CFS clinical services. Such broad-brush criteria, combined with the lack of GP education about ME/CFS, have led to concerns about the application of the guideline in the surgery or clinic.

Fortunately, a recently published study (appearing in the *Journal of the Royal College of Physicians of Edinburgh*) has opened a window into the appropriateness of referrals to one ME/CFS service. With funding from ME Research UK, the John Richardson Research Group and the Irish ME Trust, Prof. Julia Newton and colleagues at Newcastle University examined the records of every patient referred to the Newcastle CFS/ME Clinical Service between November 2008 and December 2009. Each patient had complete data on the UK national minimum dataset, a standard ME/CFS assessment tool, from which the diagnosis could be checked.

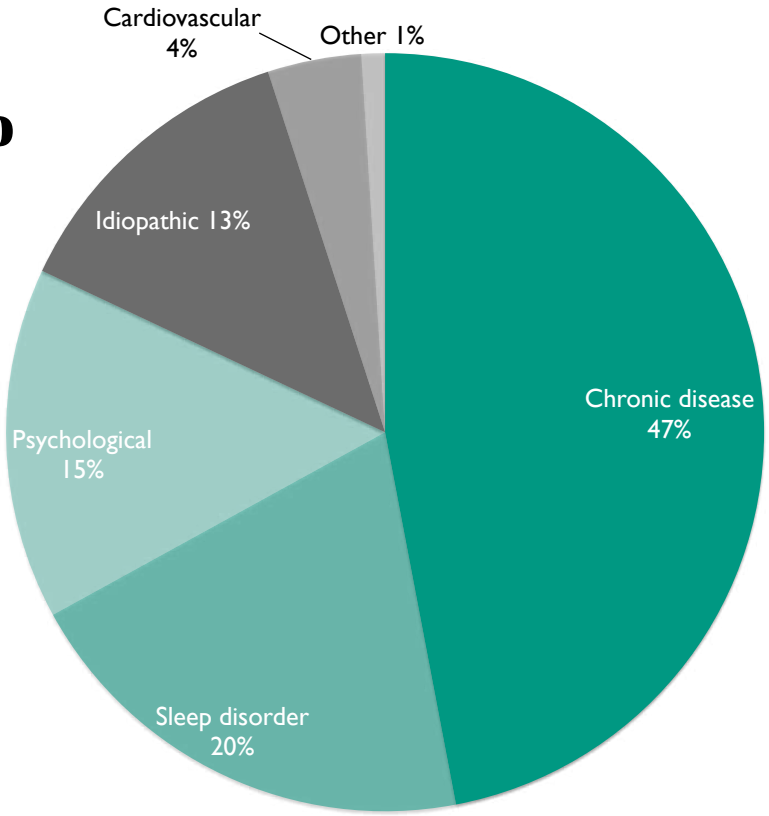
Looking at the results, Prof. Newton (pictured above with nurses Katharine Wilton and Jessie Pairman) found that 260 patients had been referred to the clinical service in 2008 and 2009 (approximately 19 referrals per month). Interestingly, the proportion of patients found to be correctly diagnosed with ME/CFS by the Newcastle service increased significantly compared with the results of a previous service audit in 2007 (60 versus 36%, respectively), a finding which might suggest that the introduction of the NICE clinical guideline in 2007 had somewhat improved the correct identification of these patients by GPs.

ME/CFS can easily become a stopping-off point for complex patients with other illnesses

However, the most important finding was that 103 (40%) of patients seen by the Newcastle Service could in fact be diagnosed with other conditions. As the Figure opposite shows, the most common alternative diagnosis in these patients was fatigue associated with a chronic disease (47% of all alternative diagnoses, listed in the Table). The next common alternative diagnosis was primary sleep disorder (20%), including 8 patients with obstructive sleep apnoea and 12 with another primary sleep disorder – an important finding since sleep disorders form a significant and potentially treatable diagnostic group. Furthermore, 15% of all alternative diagnoses were psychological/psychiatric illnesses (most commonly, depression, anxiety and post-traumatic stress disorder); 13% were "unexplained" but not ME/CFS (5.2% of total referrals); and 4% were cardiovascular disorders (vasovagal syncope in patients with fatigue symptoms, who also had a history of episodes of loss of consciousness, with the diagnosis made after a reproduction of symptoms in head-up tilt testing).

Prof. Newton's results concur with those from two smaller service audits (Dundee 1993; Newcastle 2007), and reiterate that a significant minority of UK patients referred from primary care with a diagnosis of ME/CFS can receive alternative, exclusionary

Other diagnoses in patients found not to have ME/CFS



diagnoses if investigated at a specialist clinic. And they illustrate that in the absence of a full clinical assessment (which most patients in the community have either never undergone, or last had many years ago), the diagnosis of ME/CFS can easily become a stopping-off point for clinically complex patients with a variety of different illnesses.

This problem is encountered not only in the UK. A fascinating commentary in 2008 in *Minnesota Medicine* (available online) described the difficulties experienced at a clinic in the USA for patients with fatigue, exercise intolerance and weakness (i.e., patients very like ME/CFS patients in the UK). After reporting on three paediatric cases (all of whom received serious, new diagnoses), the authors commented that, "*a thoughtful and thorough physical exam can sometimes reveal otherwise hidden diagnoses*". Commentaries like this, and investigations like this one at Newcastle, certainly raise the question of which treatable diagnoses might be uncovered if all patients currently parked in the ME/CFS diagnostic layby were examined intensively at a specialist Centre of Excellence by thoughtful and thorough physicians.

The ideal would be for ME/CFS or the subtypes within to be diagnosed objectively with criteria based on clinical or laboratory measurements. Illnesses are most easily accepted when they have a specific clinical or scientific "signature", such as a biochemical test and/or a cluster of specific signs, which establishes diagnostic validity and confers legitimacy in the eyes of healthcare professionals. The discovery of such a signature specific for ME/CFS would transform the outlook for patients.

Specific chronic diseases found in the 47% of patients who did not meet the criteria for ME/CFS

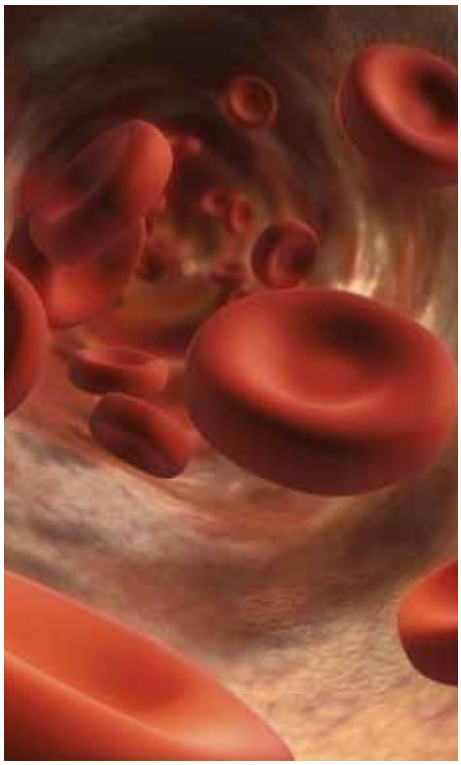
Diseases	Number of patients
Metabolic syndrome	8
Neurological disorder	13
Connective tissue disorder/autoimmune disease	9
Medications	1
Pain	3
Fibromyalgia	5
Coeliac disease	2
Overtraining syndrome	1
Cancer	1
Other conditions	
Lower body mass index	1
Haemochromatosis	1
Microprolactinoma	1
Lyme disease	1
Immunocompromised	1

Taking it to the bank

Establishing an ME/CFS Biobank in the UK

Biobanks are large collections of biological specimens (blood, tissue, cell or DNA samples) obtained from donors – patients or healthy people – who have volunteered their tissues for research. Each sample is linked with comprehensive clinical information about the donor (clinically "well-characterised" in research parlance), a fact that makes biobanks particularly useful for medical research. From the patients' perspective, the information they provide can be used in many research studies over many years, even though samples and information are donated once only. From the perspective of the scientist, there exists a valuable database of well-characterised samples, with individual privacy and confidentiality maintained, which can be accessed for approved research projects.

Over the past decade, a range of national and some multinational population-based biobanks have been established (listed in the box below), and a large number of "disease-specific" biobanks have been formed across the world, for illnesses such as cancer, schizophrenia, heart disease, and demyelinating diseases such as MS. In the same period, two biobanks have been created to house samples from ME/CFS patients: the "SolveCFS BioBank" (part of the Genetic Alliance BioBank) run by the CFIDS Association of America; and the Whittemore Peterson Institute for neuro-immune disease



repository of more than 8,000 samples and clinical information collected between 2006 and 2009. However, both ME/CFS-specific repositories are located in the USA, and their existence highlights the need for similar biobanks in Europe, particularly the UK.

For this reason, a consortium of charities – ME Research UK, Action for ME and the ME Association, with the help of a private donor – have now provided funds for a project to create the infrastructure for a UK ME/CFS biobank. Starting in August 2011 and lasting for 15 months, the primary aim of the project is to set up a disease-specific biobank consisting initially of blood samples from a cohort of well-characterised cases of ME/CFS and healthy controls.

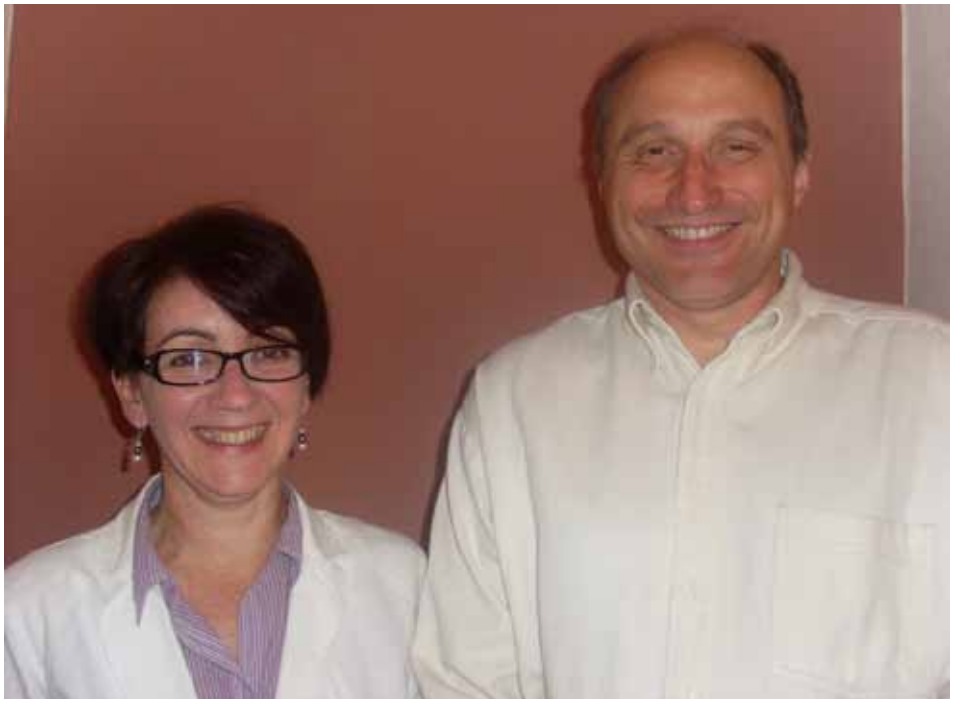
The principal researchers on the project are Dr Eliana Lacerda and Dr Luis Nacul (pictured right) from the London School of Hygiene and Tropical Medicine. The biobank will be situated at London's Royal Free Hospital where it will be able to link in with the extensive research facilities at University College London.

Initially, blood samples will be collected from a group of patients currently enrolled in the ME/CFS Disease Register, including the Case History Research on ME (CHROME) database of severely affected patients. The ME/CFS Disease Register is one of six subprojects within the National ME/CFS Observatory; it established a pilot for a national disease register of confirmed cases of people with the illness, recruiting from 29 general practices in East Yorkshire, East Anglia and London.

All selected donors will have received a diagnosis of ME/CFS at some time in the past. However, since there are inconsistencies in how the diagnosis is made in primary, secondary or tertiary care (see the story

Some population-based biobanks

UK Biobank	An archive of the genetic material from more than 500,000 people. Aims to study genetic and non-genetic risk factors in the development of complex diseases such as cancer and heart disease
Iceland – deCODE Genetics	Biobank of 100,000 genetic samples linked to Icelandic Health Sector Database. It has already mapped genes involved in some common diseases, including stroke and schizophrenia
Swedish National Biobanking Program	An initiative to bring together and utilise information from the 50 to 100 million human samples that are presently stored within the Swedish Health Care system
Generation Scotland	A predominantly family-based biobank drawn from the Scottish population. Aims to identify the inherited factors influencing the risk of illnesses such as heart disease, mental illness, and diseases of the bones and joints



Dr Eliana Lacerda and Dr Luis Nacul

on page 8 of this issue), it will be essential to have all cases newly assessed by a health professional trained in the diagnosis of ME/CFS. Patients will be assessed on whether they fulfill the CDC-1994 (Fukuda) criteria and the Canadian 2003 criteria. Since cases meeting the Canadian criteria have been shown in most cases to also meet the Fukuda criteria, this will enable the subgrouping of cases, throwing light on the appropriateness of the different classifications. In due course, comprehensive phenotyping (categorising patients based on their clinical information – see the box) may enable assessment of enrolled patients according to other clinical criteria.

Confidentiality is a key element of biobanking. Data will be anonymised and confidentiality preserved, and none of the funders of the project will have access to patient data. Furthermore, applications to use the biobank for research will be subject to a formal approval process before anonymised blood products and clinical information about donors are issued.

In the longer term, other people who have been diagnosed with ME/CFS, but not enrolled in the ME/CFS Disease Register, will be able to register an interest in donating blood samples, and precise details of the registration scheme will be announced in due course.

What information will be collected about each donor?

Full history and clinical examination
Confirmation of an ME/CFS diagnosis according to study criteria
Clinical data (phenotype), including disease severity
Demographic (age, gender, etc.), socio-economic and other exposure variables

Medical Outcomes Survey Short Form-36 (SF-36) – functional capacity and quality of life
Pain Analogue Scale – pain severity
Fatigue Severity Scale, and Energy Fatigue Scale
Mini International Neuropsychiatric Interview (MINI)
Epworth Sleepiness Score

Laboratory tests including full blood count, blood chemistry, liver function tests, erythrocyte sedimentation rate, C-reactive protein, rheumatoid factor, thyroid function tests, tissue transglutaminase antibodies, serum vitamin B12, red cell folate, and urine analysis

To begin with, the study has been funded to run until November 2012. After this time, one of the major medical research funding organisations (e.g. the Medical Research Council, the National Institute for Health Research or the Wellcome Trust) may decide to provide funding for this vital piece of research infrastructure on a long-term basis. If such core support does not materialise, then ME Research UK , Action for ME and the ME Association and will work together to maintain the biobank at whatever level of activity can be achieved with available charitable funds until a major source of long term finance can be found.

As the 2009 House of Lords Report on Genomic Medicine made clear, biobanks in general have the potential to contribute significantly to our understanding of the complex interplay of genetic and environmental factors that lead to the development of common diseases. So the establishment of the UK's first ME/CFS biobank, linking bio-specimens with clinical and disease data over the long term, would be an important advance, and a step towards the long-term destination: a repository for blood and tissues from thousands of patients, linked with a post-mortem tissue bank.

As Prof. Stephen Holgate, Chair, MRC Population and Systems Medicine Board, has said, "*The biobank project is an excellent example of how the ME/CFS charities are working together within the national framework, established by the Medical Research Council expert group, for taking forward the UK's research effort into this poorly understood chronic condition.*"

Recent research from around the world

TORONTO

Exploding the depression myth

The hypothesis that depression is at the root of the symptoms of ME/CFS – a myth particularly prevalent in the 1990s – is slowly crumbling. In fact, a review in 2008 described the range of symptoms that the two illnesses do *not* share, and listed biological abnormalities separating ME/CFS from depression, such as sleep problems (reduced REM sleep latency in depression but reduced slow-wave deep sleep in ME/CFS) and hypothalamus and pituitary function (circulating cortisol levels are high in depression but low in ME/CFS, compared with controls).

Further evidence of differences has come in a recent report from Harvard Medical School (Duffy *et al*, *BMC Neurology*, July 2011) which compared electroencephalogram (EEG) data from the brains of different groups of patients. The researchers employed "spectral coherence", a complex computational derivative of EEG spectral data, which estimates connectivity between brain regions.

Their study involved 390 healthy volunteers, 70 people with ME/CFS, 24 people meeting DSM-IV criteria for major depression, and 148 people with unspecified fatigue. Using "principal components analysis" on the EEG results, the team was able to identify and classify correctly approximately 90% of the 47 *unmedicated* ME/CFS patients and 82 to 92% of the healthy controls. Importantly, no person with depression was classified as having ME/CFS. The researchers say that this fundamental finding indicates that ME/CFS patients "*manifest patterns of functional brain coupling that differ from those of normal controls*", something that "*may help explain known differences in cognition, memory, sleep*" that afflict patients.

Furthermore, their finding of bilateral temporal lobe involvement in 9 out of 10 of the most discriminating coherence factors could be clinically highly significant since greater temporal lobe involvement is consistent with the impairment of global memory that is frequently observed in people with ME/CFS.

SWEDEN

XMRV review

Prof. Blomberg, head of the Research Group of Clinical Virology at the University of Uppsala, received grant funding from ME Research UK and the Irish ME Trust to test for XMRV in Swedish patients and controls. Several publications emanating from this grant, including the results of the experimental study, are "in press", and one has been published in a special issue of *Advances in Virology*, 2011.

In this complex review, Prof. Blomberg explores the phylogenetics (evolutionary relatedness) of murine leukaemia virus-like retroviruses (MLLVs), including their relative, XMRV. He explains that the human genetic make-up contains remnants of infections with retroviruses highly related to MLLVs, although these were integrated in the distant past. In contrast, MLLVs have repeatedly infected animals other than mice more recently; for example, Mediterranean and middle Eastern cats, turkeys, gibbon apes and koalas.

In infected animals, exogenous MLLVs (acquired from outside) are associated with significant diseases, such as encephalitis, malignancy (leukaemia and lymphoma), wasting, immunosuppression and autoimmunity. This makes it especially important to establish if the human species is now also "invaded" by murine (mouse) MLLVs, such as XMRV.

Considering the accumulating number of "negative" studies unable to find XMRV/MLLVs in human populations (see page 6), Prof. Blomberg asks why XMRV might be so hard to detect. One possibility is that chronic infection could establish a low-grade infection in a limited number of cell types, with a waning immune response, becoming progressively harder to detect both by nucleic acid, virus isolation and serological methods – a phenomenon seen in experimentally XMRV-infected macaques and, apparently, not unknown in HTLV and HIV infections. Another possibility, however, is that all reports of XMRV in humans have been due to contamination or serological cross-reaction; as he says, if this were the case, "*it would be a sad outcome of a fascinating and important story*".

UTAH

Does ME/CFS run in families?

While there is anecdotal evidence from ME/CFS patients and carers that the illness can run in families – particularly mothers and their daughters or sons – is there any scientific evidence to back this up? Well, surprisingly there is. One survey of 914 students at the Lyndonville Central School in 1991 found symptoms of ME/CFS among other family members to be one of the strong predictors of ME/CFS in the student, with a high relative risk of 35.9 (other predictors included the ingestion of raw milk, and a history of allergy/asthma). Again, one small family history study in 2001 found significantly higher rates of ME/CFS in the first-degree relatives of ME/CFS cases compared with the relatives of control subjects. Finally, studies on twins have shown a higher "concordance" rate for ME/CFS between monozygotic (identical) twins than between dizygotic (non-identical) twins – suggesting that genetic factors might have an important role.

Building upon these reports, researchers at the University of Utah (Albright et al, BMC Neurology 2011) focused on ME/CFS using specialist methods previously used to investigate heritable components of diseases such as prostate cancer, influenza mortality, aneurysm, cancer, and diabetes. From genealogical records of Utah pioneers and their descendants, representing 15 generations of genealogy data, cross referenced against medical diagnosis data from 1993, a sample group of 811 was chosen. The Genealogical Index of Familiality (GIF) statistic was used to test the hypothesis of "excess relatedness" among ME/CFS cases.

The results showed that the "average relatedness" of ME/CFS cases was significantly greater than expected when all relationships were considered ($p<0.001$) – strong evidence for excess clustering of the illness in families.

This could be due to either a shared environmental factor (location, diet, infection) or shared genes, or a combination of the two. However, there was also a significant "relative risk" of ME/CFS amongst first, second and third degree relatives of existing ME/CFS patients compared with "control" individuals.

As the Table below shows, first-degree relatives (parent/offspring) had nearly three-times the risk (relative risk of 2.70) of also having ME/CFS, while second-degree relatives (siblings or grandparent/grandchild) had 2.3 times the risk.

The authors point out that this strongly supports a genetic contribution to a predisposition to ME/CFS as it has been defined and diagnosed by clinicians in Utah since 1993, and that their study is the first population-based analysis to present such evidence.

Risk of ME/CFS in relatives of existing patients

Degree of relative	Relatives of cases / controls	ME/CFS cases in relatives of cases / controls	Significance	Relative risk (95% confidence interval)
First	5,573 / 28,965	19 / 37	p=0.001	2.70 (1.56–4.66)
Second	15,469 / 80,206	16 / 36	p=0.008	2.34 (1.32–4.19)
Third	39,766 / 201,717	24 / 64	p=0.009	1.93 (1.21–3.07)

NETHERLANDS

Low mitochondrial content

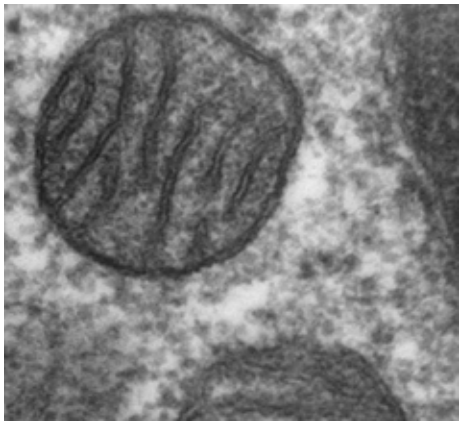
Mitochondria are found in most cells, and their main job is to generate chemical energy. Disorders of mitochondrial function are implicated in a number of diseases, including mental disorders and heart problems, as well as being involved in the ageing process. Since ME/CFS is characterised by a profound, generalised, post-exertional loss of muscle power, it seems reasonable to suggest that mitochondrial dysfunction may be involved.

The most recent mitochondrial study (Smits *et al*, *Mitochondrion*, 2011) comes from the Neuromuscular Centre in Nijmegen, and has compared skeletal muscle biopsies from 16 people with ME/CFS plus symptoms of muscle pain and/or exercise intolerance to those of 11 healthy controls.

The group also measured mitochondrial respiratory chain complex (RCC) activity – an indication of mitochondrial function – by comparing biopsy data from the ME/CFS patients with two groups of patients with genetically confirmed mitochondrial disorders (22 people with chronic progressive external ophthalmoplegia, and 27 with an A3243G mutation in skeletal muscle).

The researchers found that citrate synthase activity (a marker of mitochondrial content) was decreased in ME/CFS compared to healthy people. However, the activity of the RCC enzymes (and hence energy production) of ME/CFS patients was not at the low levels found in patients with mitochondrial disorders who generally have deficiencies in the RCCs as part of their illness. Furthermore, the energy (ATP) production rate was within the normal range in all ME/CFS patients, whereas it was decreased greatly in three quarters of the patients with mitochondrial disorders.

The fact that mitochondrial function was unaffected in the skeletal muscle of ME/CFS patients, but that mitochondrial content was notably decreased does not support the concept of "primary mitochondrial dysfunction" in ME/CFS, as the authors point out. However, they speculate that "*low mitochondrial content might be a perpetuating factor for complaints such as fatigue, myalgia and exercise intolerance*" in the illness.



AUSTRALIA

Insult to the midbrain

No-one really knows what causes the prominent "cognitive" problems in ME/CFS, such as memory, concentration and attention deficits. However, vascular insufficiency, metabolic dysregulation or an ongoing infectious process have all been postulated as being involved.

A fascinating new case–control study (Barnden *et al*, *NMR in Biomedicine*, 2011) from the University of Adelaide has just reported findings from magnetic resonance imaging of the brain using voxel-based morphometric techniques in 25 ME/CFS subjects (who all fulfilled the Fukuda and Canadian criteria for the condition) and 25 normal control subjects. In addition to brain imaging, clinical and biochemical parameters were all measured in the participants, as well as assessments of haemodynamic (blood flow) aspects, including blood pressure monitoring over 24 hours and autonomic function assessment via blood pressure and heart rate responses.

While there were no differences in the volumes of total brain grey matter, white matter or cerebrospinal fluid between patients and controls, the researchers did find abnormalities in various regions of the brain in ME/CFS patients. For example, there was a highly significant relationship been the patients' duration of fatigue and the reduction in white matter volume at the midbrain. This finding is consistent with midbrain volume loss occurring at a rate of 1% per year of duration of fatigue.

Furthermore, in the brainstem, the caudal basal pons and hypothalamus, relationships were observed between haemodynamic and relative brain volume measurements. In particular, a correlation was observed between grey matter volume at the brainstem and patients' seated pulse blood pressure – a correlation not seen in the healthy controls – suggesting an impaired regulation of brain blood flow.

The authors say that these results are "*consistent with an insult to the midbrain at fatigue onset*" that has a range of effects on other bodily systems. And their conclusion will come as no surprise to the many people with ME/CFS who can report clear triggers for the start of their illness, including physical trauma, surgery and infection.

NETHERLANDS

Disability and school absence

Illness in youngsters has a particular poignancy, and it is sometimes forgotten that around 9,000 people under the age of 16 in the UK have ME/CFS at any one time (on current estimates), and there are likely to be similar numbers in other European countries.

One research group, at Wilhelmina Children's Hospital in Utrecht (Sanne *et al*, *Pediatrics*, 2011) has determined the GP-diagnosed prevalence and pediatrician-diagnosed incidence rates of adolescent ME/CFS in the Netherlands. They collected data (for January to December 2008) from a cross-sectional sample of GPs, and from paediatric hospital departments, with the focus on young people aged 10 to 18 years. Patients received, through their pediatricians, a short survey about their experiences.

The prevalence of ME/CFS (number of cases in the population) was estimated to be 111 per 100,000 adolescents, with an incidence (number of new cases each year) of 12 per 100,000 – figures somewhat lower than those found in other countries by researchers using different

methodologies. But the most interesting devils in this report were in the details.

For instance, the average wait for a diagnosis was 17 months, and illness duration ranged widely from 6 to 110 months. In 22% of patients, the illness started after an acute episode of infectious disease, mostly Epstein Barr virus infection, and 10% of patients had an acute but non-infectious onset. Looking at the consequences of illness, most patients (91%) had severe fatigue and considerably reduced physical functioning compared with their healthy peers. School absence was high, with 90% of young people reporting "considerable", severe or complete school absence in the previous 2 and 26 weeks.

The comments of the authors about extreme disability and high rates of school absence reinforce the points made by the report to the Chief Medical Officer of England in 2002 that this illness "*represents a substantial problem in the young*" and "*can disrupt education and social and family life, at a particularly vulnerable time of life*".

AUSTRALIA

Markers of immune function

Research into the immunological aspects of ME/CFS has been an ongoing quest for the past 25 years. Findings have included low natural killer cell function, dysregulation of the 2'5'A RNase L antiviral pathway, and a predominance of the Th-2 type of cellular immunity that produces certain cytokines to fight infection. Yet the picture remains unclear, possibly because of the range of different kinds of patients coming under this umbrella diagnosis.

Recently, researchers from Bond University, Queensland (Brenu *et al*, *Journal of Translational Medicine*, 2011) have brought newer and more sensitive modern assays to the search for markers of immune function (including new markers) that might be useful diagnostically.

Compared with 50 control samples, a group of 95 ME/CFS patients had significant changes in a plethora of markers, and those that might be useful for further research included natural killer cell phenotypes, natural killer cell activity, CD8+T cell activity, interleukin-10, interferon-γ, TNFα, FoxP3 and vasoactive intestinal peptide receptor 2 (VPACR2). The increased expression of some of these markers suggests the presence of a significant inflammatory response which the immune system has to counter in these patients, possibly a response to viral antigens, adjuvants or autoantibodies in the peripheral circulation.

To the researchers, some of these markers seem to be unique to ME/CFS, and the fact that their levels are changed compared with healthy people reflects "*significant and important immunological dysregulation that could explain some of the clinical symptoms, for example the ongoing sickness experience*" of the ME/CFS population.

Conquering the heights

'Ben Nevis from Loch Eil' by Michael Gordon (mgdesignonline.co.uk)

Three peaks challenge

Everyone who knew Stuart Brown before he got ill described him as an incredibly active man with an enthusiasm for the outdoors, rivalled only by Ray Mears and Bear Grylls! But since Stuart developed ME he has been unable to take part in the activities that he loves, and many aspects of his daily life have been made much more difficult.

To show their support, Stuart's stepsons Chris and Gavin White decided to get together with friends and family to undertake a huge test of stamina and endurance – the famous Three Peaks Challenge, which they did in June 2011. This feat involves climbing the highest mountains in Scotland (Ben Nevis, 4,409 ft), England (Scafell Pike, 3,209 ft) and Wales (Snowdon, 3,560 ft), all within 24 hours.

The team (Chris and Gavin White, Hannah Phillips, Gareth Phillips, Peter Sandford, and Ross Curran, pictured right) completed the challenge successfully, and raised over £2,500 mainly through Justgiving, but also from collecting tins and collection buckets which they took with them to the mountains – how amazing is that?

Retirement for Derek

Derek Peters, pictured below right with his wife Grainne, has had ME for 28 years and been Director of the Northern Ireland Campaign for ME/CFS Healthcare for 14 years. However, on his recent 79th birthday, he decided to retire from active campaigning; as he explains, "*After many years of actively campaigning for improved diagnosis, treatment and medical/social support – including organising 14 scientific conferences – I thought it was time to take things easy. The world has changed enormously since I started, with Facebook, other social media and new forms of campaigning emerging, so it was time to wind up the campaign and make way for fresh ideas.*"

Derek has always been a great friend of the drive for biomedical research into the illness, donating many thousands of pounds to our projects, and his campaign has just given a final donation of £7,000 to our research funds. We wish Derek and Grainne a very happy retirement, and thank him most warmly for all his support through the years.

Clwyd ME Support Group Conference 2011

The Clwyd ME Support Group was founded by committed campaigner Barbara Turnbull, and is now one of the most active local support groups in the country.

Each year, the group hosts an annual conference in Clwyd, and in June 2011 the main speaker was Sue Waddle from ME Research UK, who spoke about the charity, its current research projects and activities, and the many issues surrounding the illness.

Occupational therapist Lynne Williams also gave a short presentation on her role in the specialist ME/CFS team in Herefordshire, and this was followed by a lively question and answer session. The meeting was opened by Alyn and Deeside MP Mark Tami (pictured in the Flintshire Chronicle with Sue, Barbara and Lynne) who takes an active interest in ME and is a strong supporter of the Clwyd group.

As Sue summed up the meeting, "*I received a very warm welcome from everyone I met in Wales. It is inspiring to see such an active local group who persevere despite this illness, and the involvement of the local MP was a particular boon.*"

Courtesy of the Flintshire Chronicle

Dr Judy Mikovits visits Northern Ireland

Earlier this year, on 22nd May, Dr Judy Mikovits arrived in Belfast at the invitation of Joan McParland to give a talk on the work of the Nevada-based Whittemore-Peterson Institute, of which she was Director of Research until very recently. Both are pictured on the left.

To one of the largest audiences ever seen at an ME event in Northern Ireland, Judy gave a presentation entitled "Clinical implications of XMRV/HGRVs in ME/CFS" in which she described XMRV, her findings in ME/CFS patients, and other issues associated with her research.

After the lecture, there was a long question and answer session, in which Basil McCrea, Chairman of the NI Legislative Assembly's University and Higher Education Committee, took an active part.

Joan McParland had baked two celebration cakes to mark the event – one for ME Research UK, and one for the Whittemore Peterson Institute. She summed up the event by saying, "*Judy is an extremely warm human being and willing to do anything she can to help, and it was a delight to be able to have her here to give such a wonderful talk.*"

Bellydance Hafla

Lynne Chapman teaches bellydancing, and organises a Bellydance Hafla every six months, donating the profits to charity. In June this year in Rugby, she hosted the Benn Hall Summer Hafla for ME Research UK, raising £380 during an evening full of dancing and fun. Lynne explains, "*I have had ME since I was twelve, and when I started to learn to bellydance I could rarely make it through a whole class. But my quality of life is so much better since finding this dance. I now have a career, and my body is a lot stronger.*"

Lynne's stage name is Fulya (pictured right), and she is now an aficionado of bellydance, as her website Kookiekaftan explains: "*The wonderful thing about this dance is that you don't need to be of a certain height, weight or age to do it; it looks beautiful and graceful on every size and shape. Many dancers use a coin belt or chain (which represented a dancer's dowry) – the weight of the coins helps you to locate your hips to shimmy and move them better.*"

The photo above shows Dr Neil Abbot receiving cheques for £437 from Ian Steven who organised a fundraising quiz for us

ME Derbyshire

ME Derbyshire is a very active regional group, providing a range of support services, as well as meetings covering ME/CFS related topics. Some members had been at the 2010 talk in Sheffield given by our Chairman Dr Vance Spence, and found it fascinating. So, to mark ME Awareness Week 2011, the Committee decided to make a donation of £1,000 to ME Research UK for biomedical research.

As the Secretary, John Smith, said, "*Our members were particularly keen to support the important work that ME Research UK does, and which has been reported in recent editions of your excellent magazine,* Breakthrough. *We feel we are investing in creating a better future for those people who suffer from ME.*" The photo below, showing Sara, Neil, Vance and Priscilla from our headquarters receiving the cheque, was distributed to local Derbyshire newspapers during ME Awareness Week, with a press release. As Vance said, "*Local groups are the solid backbone of ME support in UK, and we send ME Derbyshire our grateful thanks.*"

Great Ocean Road Half Marathon

The Great Ocean Road Marathon took place at Apollo Bay, south of Melbourne, Australia in Summer 2011, with three runners taking part for ME Research UK: Chris McIntosh, Ben Holdsworth and Ryan Patrick Kelly (pictured below).

The guys' friend Joe Hallett recently did a sky-dive over Kent for our charity, and his sister Amy has had ME for several years. Joe was also due to run the marathon, but had to return home to England early due to tragic circumstances – the death of his best friend James Kourzaris in a shooting incident in Florida, which led to the setting up of a new charity called "Always A Chance" to combat gun crime.

However, Joe's three friends very kindly took up the cudgels on our behalf despite only having two weeks to prepare, raising over £2,200.

So thank you to Chris, Ben and Ryan for overcoming very difficult circumstances to do this event for us on the other side of the globe!

Ways to help us

You can support ME Research UK by fundraising and taking part in sponsored and other events, and we hope the activities on the preceding pages have given you some inspiration. You can also help us by volunteering or simply spreading the word, and there are now several different ways to donate to the charity, either directly or via searching the web or shopping online. Here are a few of the most popular methods, but please visit our website for more ideas. We are very grateful for your invaluable support.

JustTextGiving

Through JustTextGiving, donations can now be sent to ME Research UK from your mobile phone. It is simple, quick and easy, and we receive ALL your donation without any commission being taken off. The maximum that can be donated in a single text is £10, and the money donated is deducted either from your call credit or added to your phone bill.

To donate, text "MEUK01" and the amount to 70070. The donation can be £1, £2, £5 or £10. For example, to donate £2 the message would read: "MEUK01 £2", and should be sent to 70070.

You will receive a thank-you message and an opportunity to add GiftAid to the donation.

Everyclick

You can help us by using search engine Everyclick.com, which gives money to ME Research UK every time you search the web. It's a simple way to raise vital funds, and it won't cost you or ME Research UK a penny – and to date we've raised over £4,200!

Everyclick.com works like any other search engine, allowing users to search for information, news and images, but users also specify a charity to benefit from their clicks.

It's a simple, straightforward way of supporting ME Research UK, so please get started by visiting our dedicated Everyclick search page: www.everyclick.com/meresearchuk.

Shop at Amazon

If you are buying from Amazon, then just click through to Amazon from our website, and 5% or more of your purchase could be making its way back to ME Research UK.

Provided that you connect to Amazon via one of the links on our website, your shopping will qualify. It really is that simple.

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: www.meresearch.org.uk/support/shopping.html.

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