breakthrough

News of the ME Research YOU have funded

£1 million of biomedical research

An overview of the projects you have helped us to fund

ME RESEARCH UK
SPECIAL ISSUE
SPRING 2014
www.meresearch.org.uk

welcome

It is incredible to think that ME Research UK has awarded £1 million in grants to scientific researchers since it was founded 14 years ago by Robert McRae, Roger Jefcoate CBE DL and myself. So when it was suggested that we produce a special edition of *Breakthrough* magazine to mark the occasion, I jumped at the chance.

And here it is – a booklet describing some of the projects we've helped to fund, classified into subject areas (circulation, muscle, diagnosis etc.) so you can see the breadth and range of the scientific work.

You can also read about some of the less well-known aspects of research funding, such as the need for programmes of research that continue year-on-year, and about some of our other achievements too.

We can be proud of this record, and we know that none of it would have happened without the hard work and generosity of the supporters who share our belief that only biomedical research can defeat ME/CFS.

I am so grateful to you all, for your continued support over the years – none of this could have happened without you. I hope you enjoy reading this special edition, *Breakthrough – £1 million of biomedical research*.

Dr Vance Spence
Chairman
ME Research UK

This is a special edition of *Breakthrough* magazine. The author is Dr Neil Abbot; the editor and designer Dr David Newton; and the publisher ME Research UK.

contents

"[ME/CFS] is a genuine illness and imposes a substantial burden on the health of the UK population. Improvement of health and social care for people affected by the condition is an urgent challenge." Chief Medical Officer Report, 2002

a significant achievement

The first £1 million of funding awarded by ME Research UK represents 35 specific biomedical projects, the results of which have now been published as 58 research papers in peer-reviewed scientific journals.

In fact, we have been able to fund more specific research projects on ME/CFS than any other single organisation in the world outside the American continent – and this is thanks to generous donations from patients, their families and friends, and other ME organisations (such as the Irish ME Trust and the John Richardson Research Foundation).

Our research has taken place at institutions in the UK and overseas (see pages 6 and 7), and has involved many of the systems of the body.

To date, the most important findings have centred around the autonomic nervous system, which controls some core body functions such as heart rate, digestion and breathing; the immune system, which protects us from infection; the circulatory system, particularly the heart and blood vessels which supply oxygen to tissues; and the musculoskeletal system, which is a source of pain and fatigue for many people with ME/CFS.

As the body works as a single functioning unit, however, the research findings on one system of the body can also apply to another (immune cells are carried in the blood circulation, for instance). This is why different aspects of a particular study are sometimes mentioned under different headings in this booklet.
It is worth remembering that without our involvement, impetus or funding (alone or with partners), most of the studies described in this booklet would never have taken place.

For instance, Prof. Julia Newton's research on autonomic dysfunction at the University of Newcastle would not have begun and flourished into the much larger programme we see today; and the Vascular and Inflammatory Diseases Research Group at the University of Dundee would not have uncovered the range of abnormalities in blood and blood vessels.

Similarly, Prof. Jo Nijs' programme in Belgium that is focused on exercise, immunology and its consequences, as well as single investigations such as the exploration of retrovirus in Swedish patients or the experience of pain in Scottish patients, would not have been instigated or completed.

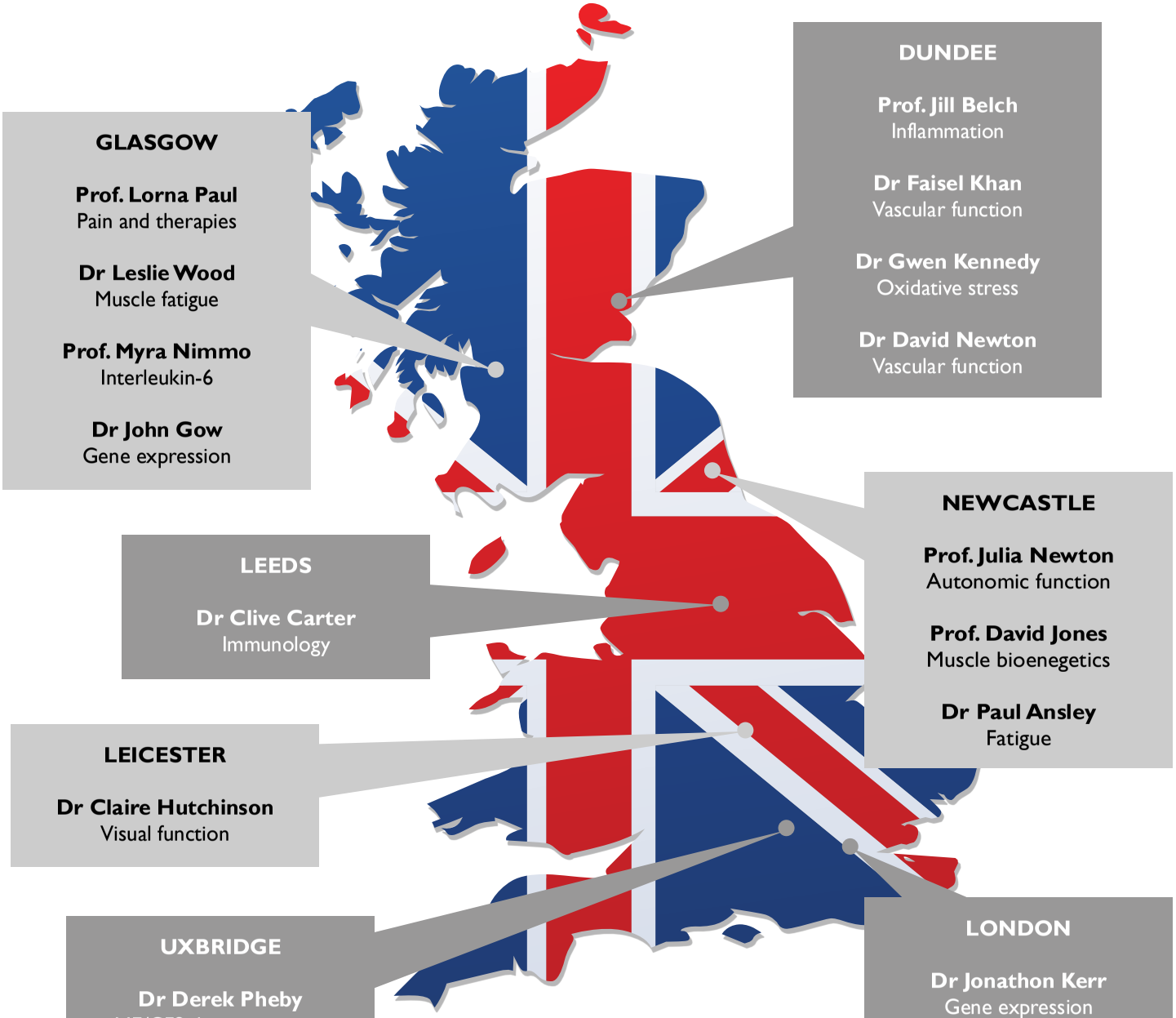
Of course, we've done much more than simply fund research projects; after all, our mission is to 'energise research'.

We act as an information resource for researchers, healthcare professionals and serious journalists.

We also try to raise awareness of the plight of people with ME/CFS, bringing the illness to the attention of a wide range of audiences, including media and government, though public talks, conferences, articles and social media.

However, we never lose sight of the fact that research is our core function, and, with your help, building on the projects we have funded to date, we intend to continue commissioning and funding biomedical research projects across the world.

£1 million of funding
35 ME/CFS biomedical projects



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Pain and therapies

Dr Leslie Wood
Muscle fatigue

Prof. Myra Nimmo
Interleukin-6

Dr John Gow
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DUNDEE

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genes and systems analysis

The completion of the Human Genome Project in 2003 was the spur for the investigation of genes in a range of diseases. Since then, there has been an explosion of techniques available to researchers – raising the possibility of identifying the genetic factors involved in ME/CFS, and of exploring complex link-patterns between different findings, including genes, lifestyle and the environment.

The hunt for a gene signature

At the moment, there are no reliable laboratory markers to back up the clinical diagnosis of ME/CFS. Genetic analysis is one area of scientific investigation with the potential to reveal a laboratory 'signature' for the illness.

We helped Dr John Gow at Glasgow Caledonian University to measure the expression (activity) of 39,000 genes across the whole human genome using DNA chip microarray technology.

In comparison with healthy individuals, the activity of 366 genes was altered in post-infectious ME/CFS patients. These were genes involved mainly in the functioning of the immune system.

Genes at a snip

Dr Jonathan Kerr's group at St George's Hospital, University of London was one of the most active in defining the genetic basis of ME/CFS, and we supported it to undertake an analysis of single nucleotide polymorphisms (SNPs, pronounced 'snips').

SNPs are small genetic changes in DNA that vary between individuals, and they account for around 1% of the human genome. If a signature for ME/CFS can be found in these SNP-containing regions, it would allow patients to be quickly and simply 'diagnosed' from a sample of tissue.

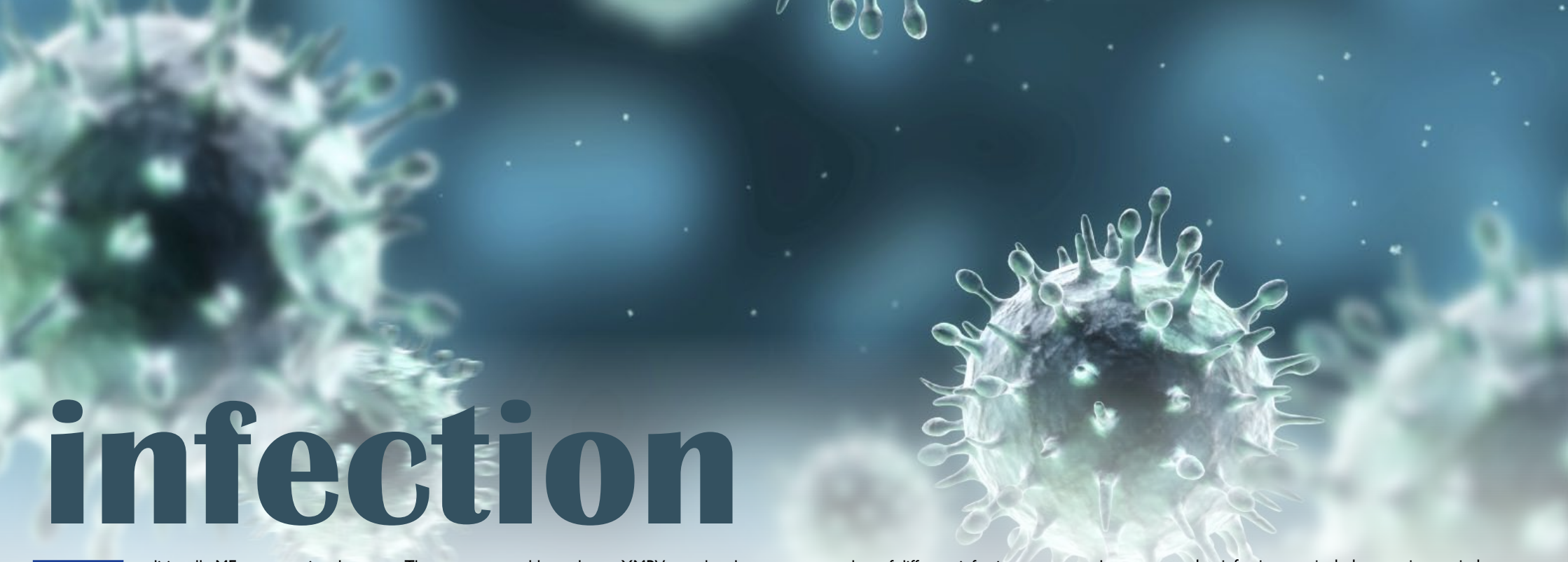
Dr Kerr's team found 21 SNPs that were significantly associated with ME/CFS (compared with healthy people and those with depression), and 148 SNP variants significantly associated with the symptoms experienced by patients, raising the possibility of SNP analysis as a clinically useful tool.

Adopting a systems approach

Modern computing has powered the explosion in 'Systems Biology' – a sophisticated method involving complex computational and mathematical tools to analyse vast amounts of related data. Systems approaches can help scientists get to grips with processes causing disease, and assess how changes in one or more symptoms might impact on disease overall.

Since 2006, we've supported a range of studies at Newcastle University (see page 30), and these have resulted in a very rich dataset of clinical and experimental information.

Currently, we are funding the researchers to undertaking a cross-discipline collaboration, applying complex systems analyses to this dataset. This approach may yield novel insights, and lead to new clinical or biomarker studies.



infection

Traditionally, ME was associated with epidemic 'outbreaks', and even today around half of all ME/CFS patients say that their illness started with an acute, infectious-like episode.

So, it's no surprise that there has been interest in researching infectious agents that might be involved in causing or maintaining the illness.

Testing for retrovirus

In 2009, the most prestigious scientific journal in the world, *Science*, published dramatic findings suggesting a link between xenotropic murine leukaemia virus-related virus (XMRV) and ME/CFS.

In association with the Irish ME Trust, we were delighted to help Profs Blomberg and Goffries in Sweden to conduct a thorough 18-month investigation in Swedish patients.

The team was unable to detect XMRV or related viruses using several different methods (virus isolation, PCR or serology) in white blood cells or plasma from people with ME/CFS or from healthy Swedish blood donors. Similar negative findings have been reported by many researchers across the world, and XMRV is now believed to be a contaminant of some laboratory procedures.

Hunting for infection

In addition, we gave further funding to Prof. Jonas Blomberg's team at the University of Uppsala to exhaustively 'interrogate' ME/CFS patients for evidence of a specific persistent or past infection.

In particular, the group intend to hunt for evidence of the presence of specific microbes previously reported to occur in people with the illness. Importantly, the researchers are using novel multiplex technology which allows one blood sample to be tested for a large number of different infectious agents at the same time, reducing laboratory time and costs.

To date, the team has published a paper reporting antibodies to one specific bacteria (*Chlamydia* HSP60) in about 24% of patients, compared with fewer than 1% of healthy blood donors.

Persistent infection?

Apoptosis is the method by which the body destroys its unwanted cells. This important process helps to control infections, as well as removing cells that have reached the end of their natural life. Neutrophils are white blood cells which fight infection, and they also undergo apoptosis.

Dr Kennedy (University of Dundee) found abnormally high rates of apoptosis in the neutrophils of both adults and children with ME/CFS. Her findings support the view that infection, particularly a persistent viral infection, may underlie the immune changes seen in many people with ME/CFS.

Main infectious agents associated with ME/CFS

Viruses

Enteroviruses, including coxsackievirus
Epstein-Barr virus (EBV)
Cytomegalovirus
Human herpes virus 6
Parvovirus B19

Bacteria

Chlamydia pneumoniae
Coxiella burnetii (Q-fever)
Mycoplasma spp.
Brucella spp.
Borrelia burgdorferi (Lyme disease)

definitions and diagnosis

One of the most animated debates surrounding ME/CFS concerns the name of the illness and how it is diagnosed. At present, a range of possible definitions exist (at least 11), but each is different, and today the terms ME, CFS and their various combinations mean different things to different people.

Clarification is an urgent challenge if patients are to get the clinical help they deserve, which is why we've targeted resources at the problem.

Comparing diagnoses

With our support, Prof. Nijs in Brussels is presently comparing the three most commonly used definitions of CFS, ME and ME/CFS. He will examine whether there are clinical differences between groups of patients meeting different definitions.

Key features of ME/CFS, such as the ability of muscles to recover after exercise, and memory or reaction times (cognitive performance) will be investigated. Comparisons will be made with multiple sclerosis and fibromyalgia patients, as they also experience high levels of fatigue and pain.

Diagnosing by questionnaire

The DePaul Symptom Questionnaire, developed by Prof. Leonard Jason and colleagues at De Paul University, Chicago, aims to capture core symptoms of ME and CFS in a structured manner. Importantly, it produces a 'diagnosis' based on several of the more common definitions of ME, CFS and ME/CFS.

Prof. Newton at Newcastle University has collected a large volume of clinical, autonomic and symptom data from several hundred patients, who together make up the so-called 'ME Research UK cohort'.

We have funded Prof. Newton's team to test the DePaul Symptom Questionnaire in this large group of patients. If sufficiently sensitive, the instrument could greatly improve confidence in the diagnosis and save valuable clinical time.

Diagnosis lacks sensitivity

The most widely used definition of chronic fatigue syndrome was proposed by the Centers for Disease Control (CDC) in 1994. But there are concerns that it is too broad and includes patients with illnesses other than ME/CFS.

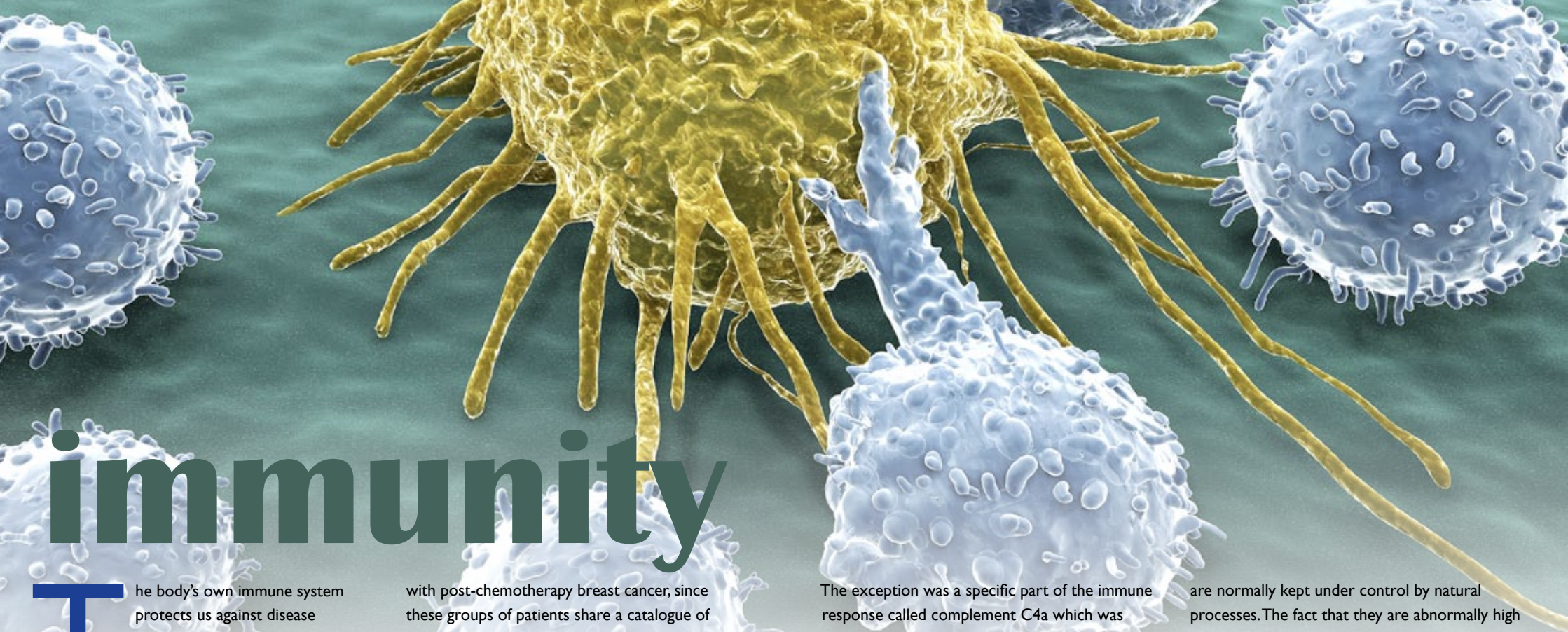
As part of one of our research programmes, Prof. Belch's team at the University of Dundee compared the symptoms of three different groups of patients, all fitting the CDC-1994 definition of chronic fatigue syndrome, but reporting different causes of their illness: Gulf War veterans, agricultural workers exposed to insecticides, and ME/CFS patients.

Clear differences in patterns of symptoms were found between the groups, highlighting the shortcomings of the standard CDC-1994 definition.

Misdiagnosis is widespread

The Newcastle CFS/ME Clinical Service takes referrals from local GPs, and researchers at Newcastle examined the records of every patient referred in 2008/9. The key discovery was that around 40% of these patients were eventually diagnosed with illnesses other than ME/CFS. The main alternative diagnoses were fatigue associated with a chronic disease (47% of all alternative diagnoses); a primary sleep disorder; psychological/psychiatric illnesses; and cardiovascular diseases.

These findings – which have now been confirmed by other researchers – reveal a high rate of misdiagnosis of ME/CFS in primary care.



immunity

The body's own immune system protects us against disease by detecting and destroying a wide variety of organisms – viruses, bacteria and fungi.

Immune abnormalities found in ME/CFS patients include reduced natural killer cells, and increases in various types of 'cytokines' (which regulate the immune system). The causes of these abnormalities remain unknown, however, making further immunological research particularly important.

Comparison with cancer

A lot can be learned by comparing immune function in different chronic illnesses. That's why in 2013 we funded a team at St James's University Hospital, Leeds to perform a range of complex immune tests in ME/CFS patients and in people with post-chemotherapy breast cancer, since these groups of patients share a catalogue of symptoms including debilitating fatigue and pain.

Dr Carter and colleagues will examine white blood cells (lymphocytes) and their 'surface proteins' before and after treatment. The investigators hope to shed light on any major common immunological mechanisms that might be responsible for the shared symptoms.

Immunity and exercise

The response of the immune system to exercise could well explain some of the symptoms ME/CFS patients experience after they do too much. Prof. Jo Nijs and colleagues at Vrije Universiteit Brussel showed that different types of exercise triggered symptoms, such as pain, but did not produce corresponding changes in key immune system constituents circulating in the bloodstream. The exception was a specific part of the immune response called complement C4a which was identified as a possible biomarker for the development of post-exercise symptoms.

Interleukins and radicals: two studies

Interleukin-6 (IL6) is a key component of the body's immune response to illness. Its metabolic and anti-inflammatory effects are vital for health, including the capacity to sustain physical work. We funded Prof. Myra Nimmo (University of Loughborough) to look at levels of IL6 and some of its byproducts during bicycle exercise in ME/CFS patients.

Exercise did not alter levels of IL6 or its byproducts in the blood, but levels of oxygen free radicals in the bloodstream were high in patients at rest, and very high after exercise. Free radicals can damage tissues, so they are normally kept under control by natural processes. The fact that they are abnormally high in ME/CFS patients, particularly after exercise, suggests that they may be involved in the post-exercise symptoms that patients experience.

Prof. Paula Robson-Ansley (Northumbria University) also received our support to look at the effect of physical and mental challenges on circulating IL6 concentrations. The challenges involved contractions of the forearm muscles, and a combination of physical and mental tasks that are commonly encountered in daily living.

People with ME/CFS had significant impairments in both physical and cognitive function. However, their IL6 levels were not altered by the challenges, indicating that a specific immune dysfunction involving IL6 is unlikely to be involved in the illness.

circulation and the blood

Thanks to your support, our scientists are continuing to increase understanding of the circulation, particularly the heart and blood vessels which pump blood around the body to support the vital organs and functions, and its importance in ME/CFS.

Some of the abnormalities uncovered by researchers have been associated with a future risk of cardiovascular problems, such as heart disease and stroke, in other diseases.

Free radicals in the blood

Circulating in the bloodstream are highly reactive molecules called free radicals, which can cause damage to cells. This damage, called oxidative stress, is implicated in cardiovascular disease, most neurological diseases and ageing.

Dr Gwen Kennedy and colleagues at the Institute of Cardiovascular Research in Dundee have found abnormally high levels of oxidative stress in people with ME/CFS. This was the case in both high-risk patients (with high blood pressure and/or obesity) and low-risk patients, suggesting that ME/CFS is yet another condition associated with the production of free radicals which can damage cells.

Are platelets sticky?

Platelets are small cells in the blood which are important in wound healing; they stick together (coagulate) around an injury forming a clot. Some studies had suggested that people with ME/CFS might have a problem with coagulation, requiring anti-coagulant therapy.

However, Prof. Belch's group (University of Dundee) found that patients with ME/CFS actually tended to have fewer platelets than healthy controls, and that these were no more prone to coagulation than normal, questioning the need for anti-platelet therapy.

Acetylcholine dysfunction

Acetylcholine is an important chemical in the nervous system. It helps to transmit signals to and from the brain, and it is also involved in widening blood vessels.

In several experiments, Dr Faisel Khan and colleagues (Vascular and Inflammatory Diseases Research Unit, University of Dundee) have shown that blood vessels of people with ME/CFS are abnormally sensitive to acetylcholine. Such sensitivity is highly unusual, and may indicate a problem with the way blood vessels are controlled by the nervous system.

Blood vessel lining and stiffness

As ME/CFS is associated with cardiovascular symptoms, Dr David Newton (University of Dundee) performed experiments on the inner lining of blood vessels in the body (the endothelium). He found that the capacity of both larger (brachial artery) and smaller (skin) vessels to widen was reduced, suggesting an abnormality of blood vessels generally.

In the same unit, Dr Faisel Khan found arteries of ME/CFS patients to be stiffer than those of healthy individuals of the same age, and that the arterial stiffness was related to inflammation.

Impaired cardiac function

It's one thing to look at blood, blood vessels and chemical messengers, but what about the heart itself? Dr Kieran Hollingsworth and colleagues at the Newcastle Magnetic Resonance Centre used magnetic resonance tagging to do just that.

They found an increase in 'residual torsion' – a measure of the 'twist' of the heart during a beat – in patients compared with controls, indicating that the patients' heart muscles were taking longer to relax. Furthermore, cardiac output (which is the output of blood by the heart per minute) was significantly lower in ME/CFS patients than in controls.

In a separate study, the same research group found bioenergetic abnormalities in both cardiac and skeletal muscle, suggesting there is an underlying defect in the way that cells make energy.

clinical trials and therapies

Patients and their families just want to get well, and clinical trials of treatments are where the rubber meets the road. We are always ready to hear from researchers with ideas for trials of potentially useful therapies, and here are some of the studies we have funded to date.

Clinical trials of vitamin D

There is considerable evidence that vitamin D is important for health, particularly for the cardiovascular system. We funded Dr Faisel Khan at the University of Dundee to conduct a pilot study which found vitamin D levels to be associated with cardiovascular risk factors such as arterial stiffness and endothelial function in ME/CFS patients.

Subsequently, we provided funding for a full-scale clinical trial of high-dose oral vitamin D supplementation. The aims are to test whether vitamin D can reduce arterial stiffness and improve other outcomes, such as endothelial function and quality of life, in people with ME/CFS. The results of this study will be published in 2014.

What therapies do patients use?

People with ME/CFS do not have the benefit of a magic pill to relieve their symptoms. The best they can hope for at present is some relief using a variety of therapies, but which? Dr Rebecca Marshall at Glasgow Caledonian University asked patients what kinds of therapies they had tried and which had been successful. Around 90% of patients said they had tried a complementary treatment for pain relief, the most common, and apparently successful, being acupuncture.

The other most popular interventions were massage, reflexology and physiotherapy. The most frequently reported 'therapies' used were warm baths, application of heat (hot water bottles, heat pads or electric blankets), and drinking water (which can help people with autonomic nervous system symptoms, such as dizziness).

Clinical trials of pain inhibition

When healthy people exercise, there is a natural mechanism which inhibits pain. This does not work properly in some chronic pain conditions, so we funded Dr Mira Meeus, the ME Research UK Fellow in Brussels, and colleagues to perform a trial to see if the inhibition of pain during exercise could be improved by drug therapy.

The agent supplied in this trial was intravenous citalopram, but the study had to be stopped early due to quite severe side-effects in the patients, an unusual and interesting finding which the researchers reported in the scientific literature. To complete the investigations, another trial was designed using the drug acetaminophen in rheumatoid arthritis and ME/CFS patients, and also in healthy people.

Overall, ME/CFS patients had more abnormalities in the way the body deals with pain signals than rheumatoid arthritis patients, but acetaminophen had only a limited positive effect on pain inhibition.

the brain and nervous system

The neurological problems associated with ME/CFS can result in some of the most disabling symptoms experienced by patients in their everyday lives. For this reason, we're always happy to hear from established researchers wishing to undertake studies designed to understand the impact of the illness on the brain and nervous system.

Problems with eyes and vision

Vision-related problems are common in people with ME/CFS – yet their presence is virtually ignored by science. We were delighted to fund the Vision and Language Research Group at University of Leicester to identify and quantify some of these problems.

In three excellent scientific papers, Dr Claire Hutchinson has reported that people with ME/CFS have significant impairments in processing visual information and in moving their visual attention. She also found eye movement dysfunction to be a prominent feature – almost all patients had some degree of sensitivity to bright lights; and most experienced eye pain and were unable to focus vision and/or attention. Each of these symptoms was severe or very severe in almost one-third of her patients.

Brain metabolism

In ME/CFS patients, cognitive problems including loss of memory or slower reaction times might be related to impaired processes in the brain, such as reduced brain blood flow or abnormalities of brain biochemistry. Glutathione is produced by the body to prevent damage to cells, and one theory is that its levels are lower in the brains of people with ME/CFS.

With our help, Prof. Puri (MRC Clinical Sciences Centre, Hammersmith) used magnetic resonance spectroscopic imaging to measure glutathione levels. These were no lower in ME/CFS patients than in healthy people, raising doubts about the usefulness of glutathione supplements.

Autonomic nervous system symptoms

The inability to stand still for long without suffering ill effects is characteristic of ME/CFS, suggesting that the autonomic nervous system, which controls some core body functions, such as heart rate, may be functioning abnormally.

Prof. Julia Newton and Prof. David Jones of Newcastle University have access to one of the largest autonomic testing labs in Europe. In a series of important scientific reports, they have found dysfunction of the autonomic nervous system in three-quarters of ME/CFS patients, and have identified a range of other autonomic-related problems (see page 30).

Brain blood flow and pain

Blood flow to the brain may be lower in ME/CFS patients than in healthy people, raising the possibility that flow is insufficient to activate the brain's natural pain inhibition during and after exercise.

Dr Jo Nijs at Vrije Universiteit Brussel has just started a series of experiments using complex techniques including brain imaging and laser-evoked potentials to investigate these aspects.

Bedside diagnostic tool?

At present, testing for autonomic nervous system dysfunction can only be done in a clinical setting, so there is a need for a simple assessment method that can be used at the bedside or in the patient's home.

With our support, Dr James Frith of the UK NIHR Biomedical Research Centre in Newcastle has been assessing the usefulness of objective measures of blood pressure variability (which is controlled by the nervous system) as easy-to-use diagnostic tools.

exercise and muscle

Historically, the main symptom of ME was a profound loss of muscle power after exercise, along with muscle pain, tenderness and swelling. And still today, symptoms after exercise are central to a diagnosis made by GPs using the UK NICE Clinical Guideline.

It's no surprise, then, that we've put resources into understanding the workings of muscles and patients' responses to exercise.

Muscle strength is lower

As muscle fatigue with abnormally slow recovery is frequently reported by patients, our Research Fellow in Brussels, Dr Kelly Ickmans, decided to look at changes in the upper arm muscles during and after exercise with a hand-held instrument which measures force and strength.

She found that upper limb muscle function returned much more slowly in ME/CFS patients than healthy people, but, intriguingly, only if they could also be diagnosed with fibromyalgia; i.e. only if they also had widespread pain as a major symptom.

Magnetic resonance spectroscopy of muscle

Prof. David Jones of Newcastle Biomedicine used magnetic resonance spectroscopy to explore the recovery of lower leg muscles during three bouts of exercise. Compared with healthy people, an increase in muscle acid levels was seen in ME/CFS patients at each exercise bout. These patients also had a significant, almost fourfold prolongation of the time taken for muscle acid levels to recover to normal.

Abnormalities on repeat exercise?

Clinical tests for diagnosing ME/CFS are urgently needed, and repeat exercise testing (after 24 hours) has been suggested as a way of detecting a delayed loss of muscle power.

With our support, Prof. Brian Macintosh and Dr Ellie Stein at the University of Calgary, Canada tested patients on an electronically braked cycle while taking measurements of blood, metabolism (oxygen consumption) and muscle function. Surprisingly, neither patients nor controls showed decreased performance after 24 hours, making repeat exercise testing in this way an unlikely candidate as a diagnostic test.

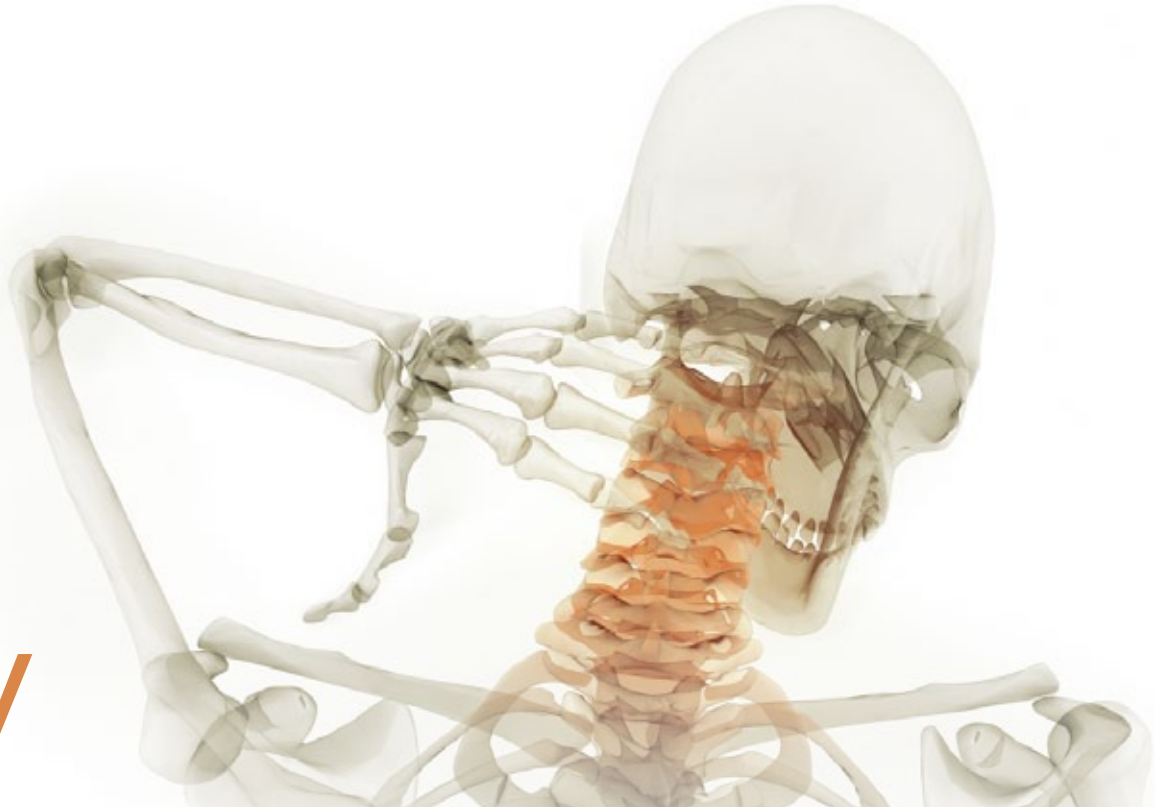
Cost of walking is greater

Prof. Lorna Paul (Nursing and Health Care, University of Glasgow) has a particular interest in the effect of chronic illness on the energy needed to walk, since this is where illness impacts most on patients' everyday lives.

She found that walking speed was slower and oxygen uptake lower in people with ME/CFS than healthy people. However, after taking differences in walking speed into account, the net 'cost' of walking was significantly greater for people with ME/CFS.

Why walking should make higher energy demands on ME/CFS patients remains unknown, but this may be due to physiological or metabolic factors involved in the illness.

pain and sensitivity



Pain is a very common symptom in ME/CFS – between 84 and 94% of patients in studies report some degree of muscle or joint pain.

Despite this, there has been very little scientific study of the experience of pain in the illness, something which your funding has helped us to remedy.

Experiences of pain

Dr Rebecca Marshall at Glasgow Caledonian University was funded to look at the specific pain characteristics of ME/CFS patients – the kind of pain experienced, its severity, and its location. She visited moderately and severely ill patients in their own homes to conduct her interviews.

Significantly, ME/CFS patients had worse pain than that reported by people with rheumatoid arthritis or multiple sclerosis. Patients used words such as 'throbbing', 'aching', and 'burning' to describe their pain, while those with more severe illness also used 'exhausting' and 'nagging' or 'gruelling'.

These descriptions may give clues about the causes of pain in ME/CFS; in particular, 'burning' pain is often associated with conditions where the nerves have been damaged.

This was the first major study to document pain and provide objective scientific back-up to patients' own experiences.

Increased sensitivity to pain?

People with ME/CFS may have an increase in the activity of nerve cells lying in the brain and spinal cord. This 'central sensitisation' can increase the pain experienced in response to various stimuli, including touch, heat, cold and chemicals.

Prof. Jo Nijs' team in Antwerp published a narrative review of its potential relevance in ME/CFS, based on studies funded by ME Research UK and others.

They found good evidence that ME/CFS patients had an increased sensitivity to pain throughout the body and that sensitivity to pain increased after stress events, such as harmful heat pain and (unusually) following exercise.

Fortunately, there is ongoing scientific work to develop treatments to 'desensitise' the central nervous system; these include centrally acting drugs, and non-invasive methods such as transcranial magnetic stimulation.

Pain across the board

Over the years, we have funded a number of investigations which have assessed pain alongside other measures, and so have been able to gather useful additional information on this important symptom.

In one study, researchers at the University of Dundee undertook clinical examinations of ME/CFS patients, Gulf War veterans and people exposed to organophosphate insecticides. Muscle pain and multi-joint pain were high in all of these patient groups (and affected between 80 and 96% of individuals), but they were found to be highest in the Gulf War veterans.

In another study on exercise and immunology, researchers in Brussels found that pain was triggered by exercising just below maximum levels and also by self-paced exercise, even after 24 hours. These findings showed that people with ME/CFS need to be cautious when they are exercising.

children and young people

The most important single cause of long term absence from school in Britain is ME/CFS, yet you wouldn't know it from the newspapers – nor the scientific literature!

So, with co-funders the Young ME Sufferers Trust and Search ME, we awarded a grant to the Vascular and Inflammatory Diseases Research Unit in Dundee to undertake some biomedical research investigations in children.

Quality of life is very low

Dr Gwen Kennedy decided to investigate the quality of life of young people with ME/CFS using standard measures to quantify the impact on their lives. She collected information from children, and their parents, about their physical abilities, social limitations, general health, pain or discomfort, and interactions with family and peers. Importantly, the illness had started with an infection in 88% of the children, while only one of the 25 children was currently attending school full-time.

The main finding was that children with ME/CFS scored significantly lower than healthy children in 10 out of 14 key areas of life, including overall health and social limitations due to physical health.

Self-esteem, body pain and discomfort, and the effect of the child's health on family activities were also significantly worse for children with ME/CFS. In fact, the quality of life reported by these youngsters was worse than that of children with type 1 diabetes or asthma. This work, now published in the high-ranking journal *Pediatics* in the USA, crystallises the seriousness of the impact of ME/CFS in the young, and provides a signpost for future action.

Biochemical abnormalities can be found

The researchers at the University of Dundee had previously reported a whole raft of abnormalities in adults with ME/CFS, mainly involving the immune and cardiovascular systems (see page 30).

Some of these abnormalities are associated with a future risk of cardiovascular problems, such as heart disease and stroke. Could such abnormalities also occur in young people with the illness?

The answer was yes. Compared with healthy children, the youngsters with ME/CFS had higher levels of oxidative stress, reduced levels of antioxidant vitamins, and a greater percentage of white blood cells undergoing apoptosis, the method by which the body destroys its unwanted cells.

Increased apoptosis can be a sign of abnormalities in the immune system, possibly related to a persistent viral infection or quicker-than-normal turnover of the most common white blood cells, neutrophils.

This is supported by the fact that illness started with a viral infection in most of the young people investigated.

research infrastructure

The infrastructure of research – the buildings, the labs, database management and the human expertise – is just as important as the particular studies conducted. And that's why we've put resources into establishing the hard wiring of two key resources for the future – the UK ME/CFS Biobank and the UK ME/CFS Disease Register.

UK ME/CFS Biobank

Biobanks are large collections of biological specimens (tissue, blood, DNA samples etc.) from people who have volunteered their tissues for research. Crucially, every sample is linked with comprehensive clinical information about the donor, making biobanks particularly useful for medical research. Many biobanks exist to cater for other illnesses, so it was time to have one specifically for ME/CFS.

A consortium of charities – ME Research UK, Action for ME and the ME Association – joined forces to make this happen. The project is led by Dr Eliana Lacerda and Dr Luis Nacul from the London School of Hygiene and Tropical Medicine. At present, the biobank contains stored samples from over 200 ME/CFS patients (and healthy people for comparison), representing around 9200 aliquots of blood sub-products available to medical researchers for specific research studies.

Major funding award from the USA

The dramatic news in July 2013 was that the National Institutes of Health in the USA had given a large award – £1,029,411 over three years – to the UK ME/CFS Biobank project. The grant will enable important research on the immunology and genetics of ME/CFS, and help to expand the Biobank to store samples from over 500 participants, which will be made available to medical researchers internationally.

UK ME/CFS Disease Register

Disease registers hold key information on patients with a particular illness, and, unlike biobanks, generally contain clinical information alone. The ME/CFS Disease Register is the first systematic attempt to develop a central database in the UK containing information volunteered by people with ME/CFS.

Led by Prof. Derek Pheby of Buckinghamshire New University, it presently contains the details of over 300 ME/CFS patients; most were originally identified from GP practices, while others were from a specialist database of severely affected patients. Each patient has been properly diagnosed, and has completed a range of assessments, including health status and quality of life, and visual analogue scales for pain and fatigue.

By sponsoring its relocation to Buckinghamshire New University, the hope of the consortium of charities is that the Disease Register will develop into a repository of high-quality information on many thousands of patients. It may, in fact, come to be linked with the UK ME/CFS Biobank, or with a specific tissue bank, in the longer term.

programmes of research

Unravelling the scientific basis of ME/CFS is no simple matter. Funding one-off investigations is important, but real breakthroughs in modern science come at the end of programmes of painstaking work by a specialist group of researchers. That's why we've tried to give continuing support to key groups early in their investigations when it can be particularly tough to get funding.

VIDR, University of Dundee

The Vascular and Inflammatory Diseases Research Unit in Dundee has received a range of grants from ME Research UK in the past 12 years. In a step-by-step progression involving both adults and young people with ME/CFS, the group has reported a number of abnormalities:

- Unusual sensitivity of blood flow to acetylcholine.
- Increased levels of free radicals in the blood.
- An unexpected increase in apoptotic white blood cells.
- Increased cardiovascular risk factors with arterial stiffness.
- Biochemical anomalies in children mirroring those found in adults.
- An association between vitamin D and cardiovascular risk.

Newcastle Biomedicine, Newcastle University

Prof. Julia Newton, Prof. David Jones and colleagues have been funded by ME Research UK and partners since 2006, and they lead one of the very few research programmes anywhere in the world on ME/CFS.

Their programme is a rare example of a consistent, directed, problem-solving approach to tackling the illness, which has uncovered:

- Dysfunction of the autonomic nervous system in three-quarters of patients.
- An abnormal heart rate and impaired cardiovascular responses to standing.
- Lower blood pressure, and abnormal blood pressure regulation.
- Substantially slower recovery from exercise of skeletal muscles.
- Impaired cardiac function, including reduced cardiac mass and blood volume.
- A high level of misdiagnosis of ME/CFS in primary care.
- Distinct physiological and clinical differences between older and younger people with ME/CFS.

Medical Research Council award

The 2012 award by the Medical Research Council of almost £1 million to Prof. Julia Newton, Dr Fai Ng and colleagues at Newcastle Biomedicine, Newcastle University for two biomedical projects was a great boost for research into ME/CFS in the UK. We were proud to have funded the essential biomedical research which has led to this prestigious award.

"Since 2006, [ME Research UK] has provided the pilot funding for many distinct projects, which have allowed us to accumulate the data on which the successful applications to the MRC were based. [Their success] shows what can be achieved by biomedical researchers working closely with medical research charities in a supportive and collaborative way." Prof. Julia Newton

£1 million of funding
35 ME/CFS biomedical projects

Year	Principal grant-holder	Project title
2013	Dr Clive Carter *Leeds Teaching Hospital NHS Trust*	Lymphocyte phenotype and cytokine production – common pathways of immunomodulation?
	Dr Derek Pheby *Buckinghamshire New University*	ME Disease Register: transfer and implementation *(co-funded with the ME Association and Action for ME)*
2012	Dr Luis Nacul & Dr Eliana Lacerda *London School of Hygiene and Tropical Medicine*	Phase 2: UK ME/CFS Biobank – establishment of an international resource *(co-funded with the ME Association & Action for ME)*
	Prof. Jo Nijs *Vrije Universiteit Brussels, Belgium*	The sensitized brain: experiments using laser-evoked potentials and cerebral blood flow
	Prof. Julia Newton *University of Newcastle*	DePaul Symptom Questionnaire: evaluation in the ME Research UK cohort
2011	Prof. Jonas Blomberg *Uppsala University Hospital, Sweden*	Development of a rational diagnostic system based on microbiological biomarkers
	Dr Luis Nacul & Dr Eliana Lacerda *London School of Hygiene and Tropical Medicine*	UK ME/CFS Biobank – establishment of an international resource *(co-funded with the ME Association & Action for ME)*
	Dr Claire Hutchinson *University of Leicester*	Visual function in ME/CFS *(co-funded with the Irish ME Trust)*
2010	Prof. Julia Newton *University of Newcastle*	A systems approach to modelling symptom data
	Dr Gwen Kennedy *University of Dundee*	Physical and Functional Impact of ME/CFS: 4-year follow up
	Prof. Jo Nijs *Vrije Universiteit Brussels, Belgium*	Comparing definitions of ME, CFS and ME/CFS: neurocognitive and autonomic manifestations
	Prof. David Jones *University of Newcastle*	Does muscle bioenergetic abnormality cause peripheral fatigue?
	Prof. Jonas Blomberg *Uppsala University Hospital, Sweden*	XMRV in ME/CFS in Sweden: an independent confirmation *(co-funded with the Irish ME Trust)*
2009	Prof. Jo Nijs *Vrije Universiteit Brussels, Belgium*	Impaired pain inhibition during exercise: a clinical experiment targeting brain neurotransmission
	Dr Faisel Khan *University of Dundee*	Oral vitamin D supplementation and cardiovascular disease risk in ME/CFS: a clinical trial
2008	Prof. Julia Newton *University of Newcastle*	Autonomic dysfunction and its consequences in ME/CFS: a clinical cohort study *(co-funded with the Irish ME Trust & the John Richardson Research Group)*
	Dr Paula Ansley *Northumbria University*	Novel mechanisms of fatigue: the effect of a non-infective inflammatory stimulus
	Dr Faisel Khan *University of Dundee*	Vitamin D status and its association with cardiovascular function
2007	Dr David Newton *University of Dundee*	Peripheral microvascular endothelial function in ME/CFS
	Prof. Jo Nijs *University College Antwerp, Belgium*	Aetiology of post-exertional malaise: the role of intracellular immunity and sensory processing
	Dr Jonathan Kerr *St George's, University of London*	Gene expression in peripheral blood of patients with Gulf War Syndrome *(co-funded with the Irish ME Trust)*
	Dr Faisel Khan *University of Dundee*	Focal and global endothelial function and their association with arterial stiffness
	Dr MacIntosh & Dr Stein *University of Calgary, Alberta, Canada*	Exercise tolerance in patients diagnosed with ME/CFS
	Dr Jonathan Kerr *St George's, University of London*	Single nucleotide polymorphisms (SNPs) within 53 CFS-associated human genes
	Prof. Myra Nimmo *University of Strathclyde*	Resting levels of interleukin-6 and its cognate receptors: extension funding
2006	Dr Gwen Kennedy *University of Dundee*	Biochemical and blood flow aspects of ME/CFS in children *(co-funded with The Young ME Sufferers Trust & Search ME)*
	Prof. Lorna Paul *Glasgow Caledonian University*	Physiological cost of walking at self-selected and matched speeds: a pilot study

Year	Principal grant-holder	Project title
2006	Prof. Julia Newton *University of Newcastle*	Autonomic dysfunction in ME/CFS: longitudinal cohort study
Pre-2006	Dr Faisel Khan *University of Dundee*	Acetylcholine-mediated vasodilatation: the role of nitric oxide, prostacyclin and EDHF
	Prof. Lorna Paul *Glasgow Caledonian University*	Pain and therapeutic intervention (programme)
	Dr Gwen Kennedy *University of Dundee*	Vascular biology of ME/CFS: further investigations
	Prof. Myra Nimmo *University of Strathclyde*	Interleukin-6 and its receptors: response to a standardised exercise challenge
	Dr Leslie Wood *Glasgow Caledonian University*	Muscle fatigue and effects on H-reflex excitability
	Dr John Gow *University of Glasgow*	Differential gene expression in ME/CFS patients
	Prof. Jill Belch *University of Dundee*	Chronic inflammation and apoptosis (research programme)

Publications from ME Research UK-funded projects

First author	Short title	Reference
Hutchinson CV	Vision-related symptoms as a clinical feature of CFS/ME? Evidence from the DePaul Symptom Questionnaire	*British Journal of Ophthalmology 2014; 98(1): 144–5*
Jason LA	Are ME and CFS different illnesses? A preliminary analysis	*Journal of Health Psychology 2014 Feb 7*
Ickmans K	Can recovery of peripheral muscle function predict cognitive task performance in CFS with and without fibromyalgia?	*Physical Therapy 2014 Apr; 94(4): 511–22*
Meeus M	Endogenous pain modulation in response to exercise in patients with rheumatoid arthritis, CFS and comorbid fibromyalgia	*Pain Practice 2014 Feb 17*
Ickmans K	Recovery of upper limb muscle function in CFS with and without fibromyalgia	*European Journal of Clinical Investigation 2013 Nov 11*
Badham SP	Characterising eye movement dysfunction in ME/CFS	*Graefes Arch Clin Exp Ophthalmol 2013; 251(12): 2769–76*
Elfaitouri A	Epitopes of microbial and human heat shock protein 60 and their recognition in ME	*PLoS One 2013; 8(11): e81155*
Jason LA	Contrasting CFS versus ME/CFS	*Fatigue: Biomedicine, Health & Behavior 2013; 1(3): 168–183*
He J	Cerebral vascular control is associated with skeletal muscle pH in CFS patients both at rest and during dynamic stimulation	*Neuroimage Clinical 2013; 2: 168–73*
Ickmans K	Association between cognitive performance, physical fitness, and physical activity level in women with CFS	*Journal of Rehabilitation Research & Development 2013; 50(6): 795–810*
Hutchinson CV	Patterns of abnormal visual attention in ME	*Optometry & Vision Science 2013; 90(6): 607–14*
Lewis I	Is CFS in older patients a different disease? A clinical cohort study	*European Journal of Clinical Investigation 2013; 43(3): 302–8*
Lewis I	Clinical characteristics of a novel subgroup of CFS patients with postural orthostatic tachycardia syndrome	*Journal of Internal Medicine 2013; 273(5): 501–10*
Meeus M	Does acetaminophen activate endogenous pain inhibition in CFS/fibromyalgia and rheumatoid arthritis?	*Pain Physician 2013; 16(2): E61–70*
Frith J	Impaired blood pressure variability in CFS: a potential biomarker	*Quarterly Journal of Medicine 2012; 105(9): 831–8*
Blomberg J	No evidence for XML-RV infection in Sweden using internally controlled multiepitope suspension array serology	*Clinical & Vaccine Immunology 2012; 19(9): 1399–410*
Puri BK	Regional grey and white matter volumetric changes in ME (CFS): a voxel-based morphometry 3 T MRI study	*British Journal of Radiology 2012; 85(1015): e270–3*
Hollingsworth KG	Impaired cardiac function in CFS measured using magnetic resonance cardiac tagging	*Journal of Internal Medicine 2012; 271(3): 264–70*
Newton DJ	Large and small artery endothelial dysfunction in CFS	*International Journal of Cardiology 2012; 154(3): 335–6*
Nijs J	In the mind or in the brain? Scientific evidence for central sensitisation in CFS	*European Journal of Clinical Investigation 2012; 42(2): 203–12*
Jones DE	Loss of capacity to recover from acidosis on repeat exercise in CFS: a case-control study	*European Journal of Clinical Investigation 2012; 42(2): 186–94*
Elfaitouri A	Murine gammaretrovirus group G3 was not found in Swedish patients with ME/CFS and fibromyalgia	*PLoS One 2011; 6(10): e24602*
Blomberg J	Phylogeny-directed search for murine leukemia virus-like retroviruses in vertebrate genomes and in ME/CFS and prostate cancer	*Advances in Virology 2011; Published Special Issue: Article ID 341294*
Meeus M	Symptom fluctuations and daily physical activity in patients with CFS: a case-control study	*Archives of Physical & Medical Rehabilitation 2011 Nov; 92(11): 1820–6*

First author	Short title	Reference
Meeus M	Serotonergic descending inhibition in chronic pain: design, preliminary results and early cessation of a randomized controlled trial	*In Vivo 2011; 25(6): 1019–25*
Sheikholvaezin A	Rational recombinant XMRV antigen preparation and bead coupling for multiplex serology in a suspension array	*Protein Expression & Purification 2011; 80(2): 176–84*
Newton JL	Physical activity intensity but not sedentary activity is reduced in CFS and is associated with autonomic regulation	*Quarterly Journal of Medicine 2011 Aug; 104(8): 681–7*
Jones DE	Fatigue severity remains stable over time and independently associated with orthostatic symptoms in CFS	*Journal of Internal Medicine 2011 Feb; 269(2): 182–8*
Marshall R	The search for pain relief in people with CFS: A descriptive study	*Physiotherapy in Theory & Practice 2011 Jul; 27(5): 373–83*
Newton JL	The Newcastle NHS CFS Service: not all fatigue is the same	*Journal of the Royal College of Physicians Edinburgh 2010; 40(4): 304–7*
Hollingsworth KG	Impaired cardiovascular response to standing in CFS	*European Journal of Clinical Investigation 2010; 40(7): 608–15*
Van Oosterwijck J	Pain inhibition and post-exertional malaise in ME/CFS: an experimental study	*Journal of Internal Medicine 2010; 268(3): 265–78*
Marshall R	Pain characteristics of people with CFS	*Journal of Musculoskeletal Pain 2010; 18: 127–37*
Costigan A	Orthostatic symptoms predict functional capacity in CFS: implications for management	*Journal of Internal Medicine 2010; 103(8): 589–95*
Nijs J	Unravelling the nature of post-exertional malaise in ME/CFS: The role of elastase, complement C4a and interleukin-1β	*Journal of Internal Medicine 2010; 267(4): 418–35*
Jones DJ	Abnormalities in pH Handling by Peripheral Muscle on 31P MRS and Potential Regulation by Sympathetic Autonomic Function in CFS	*Journal of Internal Medicine 2010; 267(4): 394–401*

First author	Short title	Reference
Kennedy G	Biochemical and vascular aspects of pediatric CFS	*Archives of Pediatric & Adolescent Medicine 2010; 164(9): 817–23*
Kennedy G	Physical and functional impact of CFS/ME in childhood	*Pediatrics 2010;125(6): e1324–30*
Paul L	Physiological cost of walking in those with CFS (CFS): a case-control study	*Disability & Rehabilitation 2009; 31(19): 1598–604*
Robinson M1	Response of plasma IL–6, its soluble receptors and F2–isoprostanes to exercise in CFS	*Scandinavian Journal of Medicine & Science in Sports 2009; 13: 1–9*
Jones DEJ	Perceived fatigue is comparable between different disease groups	*Quarterly Journal of Medicine 2009;102:617–24*
Newton JI	Lower Ambulatory Blood Pressure in CFS	*Psychosomatic Medicine 2009;71(3):361–5*
Hoad A	Postural orthostatic tachycardia syndrome is an under–recognized condition in CFS	*Quarterly Journal of Medicine 2008;101(12):961–5*
Spence VA	Low grade inflammation and arterial wave reflection in patients with CFS	*Clinical Science (Lond) 2008; 114(8): 561–6*
Newton JL	Symptoms of autonomic dysfunction in CFS	*Quarterly Journal of Medicine 2007; 100(8): 519–26*
Spence VA	Inflammation and Arterial Stiffness in Patients with CFS	*Scottish Society for Experimental Medicine, 2007 (Poster)*
Kennedy G	Is CFS a hypercoaguable state associated with platelet activation?	*Blood Coagulation and Fibrinolysis 2006;17: 89–92*
Abbot NC	Chronic fatigue syndrome	*The Lancet 2006; 367: 1574–75*
Kennedy G	Oxidative stress levels are raised in CFS and are associated with clinical symptoms	*Free Radical Biology & Medicine 2005; 39: 584–589*
Spence VA	Standing up for ME: Cardiovascular mechanisms of orthostatic intolerance	*The Biologist 2004; 51(2): 65–70*
Spence VA	Acetylcholine mediated vasodilatation in the microcirculation of patients with CFS	*Prostaglandins, Leukotrienes and Essential Fatty Acids 2004; 70: 403–407*

First author	Short title	Reference
Khan F	Peripheral cholinergic function in humans with CFS, Gulf war syndrome, and with illness following organophosphate exposure	*Clinical Science 2004; 106, 183–89*
Kennedy G	Increased neutrophil apoptosis in CFS	*Journal of Clinical Pathology 2004; 57: 891–893*
Kennedy G	Plasma endothelin–1 levels in CFS	*Rheumatology 2004; 43: 252–253*
Kennedy G	The specificity of the CDC–1994 criteria for CFS: comparison of health status in three groups of patients who fulfil the criteria	*Annals of Epidemiology 2004; 14: 95–100*
Spence VA	Neurophysiologic analysis of neuromuscular symptoms in UK Gulf War veterans	*Neurology 2003; 61: 1827*
Khan F	Prolonged acetylcholine–induced vasodilatation in the peripheral microcirculation of patients with CFS	*Clinical Physiology & Functional Imaging 2003; 23: 282–285*
Spence VA	Enhanced sensitivity of the peripheral cholinergic vascular response in patients with CFS	*American Journal of Medicine 2000; 108: 736–739*

thank you

Thank you for reading *Breakthrough – £1 million of biomedical research*. Further information on the studies described, including references to the published scientific papers, can be found in the Research Section of our website www.meresearch.org.uk.

And thank you for supporting our drive to investigate the biomedical basis of ME/CFS. Scientific research is expensive to fund, and we receive no government assistance. Our website has information about the various ways you can help – from a single donation to a regular gift – and lots of fundraising ideas.

Please help us – together we can make a difference. We are particularly grateful to these organisations, which have given larger donations towards our research programme:

ME Organisations

Irish ME Trust
John Richardson Research Foundation
Irish ME/CFS Association
The Young ME Sufferers Trust
Search ME
N Ireland Campaign for ME/CFS Healthcare
Newry & Mourne ME/FMS Support
ME Support Northern Ireland
Network MESH West London

Other Organisations

Albert Edward Pash Charitable Trust
Alexander Moncur Trust
Armourers' and Brasiers' Gauntlet Trust
Arnold Burton 1998 Charitable Trust
Bothwell Charitable Trust
Chandris Foundation
Chapman Charitable Trust
Christopher HR Reeves Charitable Trust
Clydesdale Bank Charitable Foundation
Edwin George Robinson Charitable Trust
Felicity Wilde Charitable Trust
Fishmongers Company
Garfield Weston Foundation
Gerald Micklem Charitable Trust
Grocers' Charity
Hospital Saturday Fund
Hugh Fraser Foundation
John Lewis Foundation
Kenneth Barge Memorial Trust
MacRobert Trust
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Roger and Jean Jefcoate Trust
Serve All Trust
Souter Charitable Trust
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Trefoil Trust
Wilkinson Charitable Foundation
Yorkshire Building Society Charitable Foundation