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ME RESEARCH UK

Welcome

Breakthrough magazine is published by ME Research UK, a Scottish Charitable Incorporated Organisation that funds research into Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (also known as ME/CFS). The charity has an international remit, and its principal aim is to commission and fund high-quality scientific (biomedical) investigation into the causes, consequences, and treatment of ME/CFS. It also aims to energise ME research by identifying potentially important areas for future biomedical research, and producing high quality professional reviews and reports.

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In the spotlight

What's happening in the world of ME research and funding

Editorial

Welcome to the spring 2019 edition of *Breakthrough*. Our team has been working hard, as always, to bring you some of the latest news from the world of ME.

In this issue, you can read a summary of the parliamentary debate about ME that took place in January. I watched the debate live—as I'm sure did many of you—and I would like to add my own thanks to Carol Monaghan and other MPs who worked so hard to secure this debate in the main chamber. It was a shame to see the time given to each MP shortened as the debate progressed, as I am sure there were many important points left unspoken.

However, it was pleasing to see the amount of support there was for more biomedical research. As well as continuing to fund our researchers directly using our own funds, ME Research UK will continue to work with others to try to ensure that research into ME receives the central funding it needs.

This issue also brings you updates on research completed over the past few months, and lets you know about exciting new research—funded by your generous donations—that is starting. As always, we have also included reports on other research into ME taking place around the world.

Also included in this issue is news about our annual Spring Prize Draw (we hope you are able to support us by buying tickets), along with ideas about how you can support us by raising funds to support our work.

Readers of the last issue will be aware that I joined ME Research UK in

September. It has certainly been a busy few months so far! Much of the focus has been on understanding more about the condition and the organisation, while starting to develop strategic plans for the next few years.

Our five-year strategy is nearly complete, and we will soon be able to send out updates to you via our website and on social media. We will also include some more details about our strategy in the autumn issue of *Breakthrough*.

I hope you enjoy the magazine. As always, please get in contact with comments and questions. If you are on social media, please like or follow us on Facebook (MEResearchUK) and Twitter (@MEResearchUK). And you can also find me on Twitter (@MERUKCEO).

Best wishes,
Simon
CEO, ME Research UK

AmazonSmile

AmazonSmile is a simple way for you to support ME Research UK every time you shop, at no additional cost to you.

You'll find the exact same low prices, vast selection, and convenient shopping experience as amazon.co.uk, with the added bonus that Amazon will donate a portion of the purchase price to your selected charity.

To shop at AmazonSmile, simply go to smile.amazon.co.uk from the web browser on your computer or mobile device. You may also want to add a bookmark to smile.amazon.co.uk to make it even easier to return.

On your first visit, you need to select ME Research UK as your chosen charity before you begin shopping.

Amazon will donate 0.5% of the net purchase price (excluding VAT, returns, and shipping fees) of your eligible AmazonSmile purchases to ME Research UK.

Spring Prize Draw

With the profits going directly to fund biomedical research into ME/CFS, our Spring Prize Draw is a great way to support our work, make a difference, and perhaps win one of our three cash prizes.

Entrants must be over 16 years old and live in Great Britain. Each ticket costs £1, and you have the chance to win £300, £150, or £50. Enclosed with this issue of *Breakthrough* is a book of ten £1 tickets, but, if you would like more, just call or email us and we will be happy to send out more books.

Completed stubs and cheques (made payable to "ME Research UK") must be returned to us by 16 July 2019, with the Draw taking place on 18 July 2019. We will be in contact with the lucky winners as soon as possible thereafter. More details can be found on the tickets, and the full Terms and Conditions are on our website: meres.uk/PrizeDraw.

Selling tickets can help raise awareness of ME/CFS, and helps us invest in the kind of biomedical research highlighted in this magazine.

Forward motion

Parliament debates ME research funding

Carol Monaghan and other MPs are to be commended for securing parliamentary time for a debate titled "Appropriate ME Treatment" on 24 January 2019 in the chamber of the House of Commons. This followed two Westminster Hall debates on 20 February and 21 June 2018, and a successful petition to the Backbench Business Committee for a wide-ranging debate on ME.

Regrettably, pressure of time on the day meant that MPs were asked to limit their speeches progressively from 4 to 3, and then to 2 minutes apiece, and much useful comment was probably left unsaid, and the opportunity to make specific points lost. Nevertheless, 27 backbench MPs had the opportunity to contribute and 57 speeches were delivered.

From these, a number of themes emerged, one of which was a recognition of the lack of research investment into ME, and a demand that far more biomedical research be funded, given the prevalence and severity of the illness.

In the 21 June 2018 Westminster Hall debate, Steve Brine, Parliamentary Under Secretary of State for Health and Social Care, commented that, "Since 2011, the MRC has funded seven projects on CFS/ME, totalling £2.62 million, and it is ready to support further applications of the highest scientific quality, which is required to make those scientific breakthroughs… The MRC has had an open

cross-board highlight notice on ME since 2003. It was updated in 2011 alongside a bespoke funding call in that year.

"ME research remains an area of high strategic importance for the MRC. Applications that focus on the underpinning mechanisms of ME are encouraged, with priority areas including immune dysregulation…, pain, improved sub-phenotyping and stratification of ME, and mechanisms of ME in children and young people…"

Carol Monaghan countered this assertion: "The Medical Research Council is putting £2.6 million into ME research. Unfortunately, that is not for biomedical research—or little of it is."

Responding to the Motion before the House of Commons, the Minister elaborated further on why central funding has been lacking for biomedical research. "The truth is—sometimes it is a hard and inconvenient truth to hear—there have not been good enough research proposals in the ME space, partly because of the stigma… and partly because of the division in the medical community. We need people to come forward with good research proposals in this space; that can only be advantageous."

ME Research UK has an unrivalled reputation for funding ME research. After all, data from an ME Research UK-funded study were used as the basis of the successful bid by Prof. Julia Newton for the very funding from the MRC to which the Minister referred.

The Minister's comment vindicates the need to build a strong and diverse research base, populated by a flow of new entrants to the field, to work collaboratively, and to be supported to the point where they can apply successfully for central funding. That is how ME Research UK operates: seedcorn funding for scientifically sound research projects, and supporting scientists to build a greater research base. Yet, relying solely on charity funding derived mostly from those affected by the illness cannot be the only solution.

What cannot be accepted is for researchers to bear any portion of blame for the lack of central funding for studies into ME. The Minister acknowledged barriers to research input created by stigma surrounding the illness and divisions within the medical community, but announced no plan to tackle or evaluate these—at any level, or in any particular organisation, group, or profession.

There was also no commitment to incentivise sub-MRC funded biomedical research (either alone or in partnership with charities) to the point where the MRC felt able to make a full grant. Such a stepped approach—and acceptance of biomedical research as the key to understanding ME—could also unlock corporate, trust, and other funding, which would lead to a transformed research landscape.

As Carol Monaghan made clear in her closing remarks, "On the question of medical research, I am sure that many researchers will have heard what he said. However, it is notable that, although there is some excellent biomedical research going on just now, it is being funded by charities, and not by the Government. The Government need to take this seriously."

MPs passed the parliamentary Motion—which included a call on the Government "to provide increased funding for biomedical research into the diagnosis and treatment of ME"—without a Division. In fulfilment of this direction, ME Research UK further calls on the Government to identify and implement positive actions that will support researchers to develop the high-quality applications that the MRC says it craves. Given the track record ME Research UK has in this area, we would welcome the opportunity to discuss with the Government concrete steps to advance the research agenda as swiftly as possible.

Treatment avenues

Can pharmacogenomics help identify new therapies for ME?

Elsewhere in this issue of *Breakthrough*, you can read about a newly funded research project in Vermont looking for anti-citrullinated autoantibodies in blood samples from patients with ME/CFS (see page 8). If these antibodies are found, they might indicate the presence of specific immunological abnormalities that could be targeted for intervention.

And then, on page 11, we also detail the other ongoing projects currently supported by ME Research UK, including investigations into AMPK abnormalities, the functions of other autoantibodies, and low Nrf2 activity. If there is a common theme among many of these studies, it is a search for pathological changes in ME/CFS that might serve as targets for treatment.

The development of new drugs is hugely expensive and can take many years. An alternative strategy, however, is to identify existing, approved treatments for other conditions that may also have potential in ME/CFS. And this is the approach taken in a new study from Florida, USA.

"immunological dysfunction is at the heart of ME/CFS"

This pharmacogenomic study is due to be published in the journal, *Clinical Therapeutics*, and its nine authors include Prof. Nancy Klimas, Director of the Institute for Neuro Immune Medicine, who has enjoyed a distinguished career uncovering some of the immune abnormalities present in ME/CFS.

In this new study, gene expression data were obtained from 33 patients with ME/CFS (including 23 women and 10 men) and 21 healthy control subjects (15 women and 6 men), and the investigators were specifically interested in predefined gene modules. A gene module is a group of genes that have similar expression profiles (i.e. similar activity), and that

are also likely to be related in function. Detection of these modules is commonly used to help interpret the biological consequences of gene expression data.

A total of 4,620 gene modules were analysed, and those modules that showed the greatest differences in expression between patients and controls were singled out for further analysis. Importantly, these analyses were carried out separately for men and women.

In men, the gene modules with the greatest ME/CFS-associated differences included those related to immune regulation and mitochondrial dysfunction, while, in women, the most significant modules were those related to immune factors and cardiac function. The effect sizes were small in men, and very small to intermediate in women.

The gene modules related to immune regulation and inflammation, and metabolic and cardiac function were strongly associated with a number of measures of fatigue in the patients. More specifically, the mechanisms of immune regulation that were identified involve B-cell receptor, T-cell receptor, tumour necrosis factor alpha, and transforming growth factor beta pathways.

Cross-referencing these results with pharmacogenomics data (i.e. information on how genes will affect treatment responses), the investigators identified several drug classes that target these specific pathways. For example, some immunosuppressants target tumour necrosis factor alpha, transforming growth factor beta, and T-cell receptor pathways. But there are a number of other drug categories that may also have potential.

So these results lend further support to the idea that immunological dysfunction is at the heart of ME/CFS, and this evidence is being built on by projects that ME Research UK is currently funding. The findings also suggest a number of potential targets for approved drugs, and we can only hope that this work progresses to the point that these treatments can be tested clinically.

Support for CMRC proposal

The CFS ME Research Collaborative (CMRC) recently submitted a request to the MRC and NIHR to support the expansion of existing ME/CFS research infrastructure. If this is received positively, then full grant applications will need to be written for funds to build on the existing ME/CFS Biobank and create a full ME/CFS Bio-resource, including samples of blood/plasma and urine.

It is hoped that this resource will include 20,000 samples from participants and control subjects. This compares to the current UK ME/CFS Biobank which holds samples from approximately 600 donors, including those with ME/CFS. The creation of this resource will allow for significantly larger and more explanatory studies to take place, in particular those requiring DNA samples.

ME Research UK is not a member of the CMRC. However, we were asked to give our views on the proposal. After a review, we are supportive of this initiative, and believe that, if funded, it will hopefully lead to an increase in the amount of rigorous biomedical research taking place throughout the research sector.

We also hope that the development of such a large UK ME/CFS Bio-resource would lead to further research proposals being generated, allowing us to support many more projects in the future. In order to get 20,000 samples, there would need to be a fully co-ordinated campaign involving all of the main ME charities in the UK.

We have therefore written a letter to the CMRC indicating our support for the proposal, and also confirming that we would be willing to support the campaign for samples to be sent to the newly established Bio-resource, should the application be successful. This has been submitted along with the proposal.

We wish the CMRC well with the application, and we hope to be able to update you with developments in future issues.

right on target

A Vermont research group is using UK ME/CFS Biobank samples to look for **anti-citrullinated autoantibodies** in patients with ME/CFS

The UK ME/CFS Biobank was established at the London School of Hygiene and Tropical Medicine in 2016, since when it has provided biological samples from ME/CFS patients to researchers worldwide. As one of its original co-funders, ME Research UK is always encouraged to see scientists making good use of the Biobank's resources, and we recently awarded a research grant to a team in Burlington, Vermont, to do just that.

Prof. Mercedes Rincon is Professor of Medicine at the University of Vermont, and the research group she heads is interested in the molecular mechanisms underlying autoimmune diseases. Prof. Rincon also has an interest in ME/CFS, and her co-investigators include Prof. David Maughan, whose wife, Cathleen, has had the illness for the last twenty years.

Targeted autoantibodies

Spurred on by this personal involvement, the group has conducted previous research looking at the immunological basis of ME/CFS, including the detection of specific autoantibodies that target citrullinated proteins. Their new study, funded by ME Research UK, aims to confirm these preliminary findings in a larger group of patients.

For a more complete description of autoimmunity, see our article in the Autumn 2017 issue of *Breakthrough* (available on our website). However, briefly, autoantibodies occur when the immune system wrongly identifies the body's own healthy cells as harmful, and produces antibodies against them. This can lead to the development of a so-called autoimmune disease such as multiple sclerosis or lupus. Recent findings suggest that autoantibodies may also have a role in ME/CFS, at least in some patients.

Prof. Rincon explains, "Citrullination is a protein modification that can happen sometimes in response to some

Prof. David Maughan, **Dr Cathleen Gleeson** (ME/CFS patient), and **Prof. Mercedes Rincon** from the University of Vermont

"The outcomes could provide insight into the involvement of autoimmunity in ME/CFS"

infectious agents. Citrullination makes a 'self protein' become a 'foreign protein', and therefore recognised by the immune system. This leads to the generation of antibodies against those citrullinated changes."

Such anti-citrullinated antibodies have been detected in rheumatoid arthritis—itself an autoimmune disease—where they have a pathological role and are used in diagnosis. The characteristics of ME/CFS suggest the involvement of autoantibodies in that illness, and ME Research UK is currently supporting Dr Madlen Löbel and Prof. Carmen Scheibenbogen, at the Institute of Medical Immunology in Berlin, to look at the function of β2 adrenergic receptor autoantibodies in ME/CFS.

Biobank samples

Prof. Rincon's team, on the other hand, plans to look specifically for autoantibodies targeted on citrullinated proteins. Using blood samples obtained from the UK ME/CFS Biobank, the researchers will compare autoantibody levels between ME/CFS patients and a group of healthy control subjects.

These results will also be compared with those from patients with multiple sclerosis—another known autoimmune disease—and compared with previous findings in patients with rheumatoid arthritis.

The outcomes of this study could provide valuable insight into the pathophysiology of ME/CFS, and the potential involvement of autoimmunity in the illness. They may also help to identify effective treatments, and to provide the basis for further research looking at specific sites of citrullination and targets for intervention. We will report the findings in a future issue of *Breakthrough*, so watch this space!

Other current ongoing projects

Tracking peripheral immune cell infiltration of the brain in ME

Prof. Jarred Younger, University of Alabama, USA

Considerable evidence indicates the presence of neuroinflammation and an activated immune system in the brains of people with ME/CFS. In this newly funded study, Prof. Younger is investigating whether this is caused by activated peripheral immune cells crossing into the brain, as found in multiple sclerosis.

Comparing ME/CFS and IBS: gut immune and microbiome changes

Prof. Yan Yiannakou, Newcastle upon Tyne Hospitals NHS Foundation Trust, UK

ME/CFS is more common among patients with IBS than in the general population, and similarities between the two conditions suggest a shared pathophysiology. Prof. Yiannakou is looking at this potential association by assessing immune activation and the gut microbiome in samples from patients with ME/CFS, those with IBS, and those with both conditions.

Investigating abnormalities in AMPK activation

Prof. Mark Walker, Newcastle University, UK

AMPK is important in regulating energy in the cell. It is normally activated during muscle contraction, but this is impaired in muscle cells from ME/CFS patients. This project, led by Prof. Walker, is looking at the mechanism by which AMPK is activated pharmacologically, but not by muscle contraction, and may help identify potential new targets for treatment.

The role of autoantibodies in ME/CFS

Prof. Carmen Scheibenbogen & Dr Madlen Löbel, Charité University Medicine Berlin, Germany

Autoantibodies may have a role in ME/CFS. Prof. Scheibenbogen and Dr Löbel previously found that nearly a third of their ME/CFS patients had increased levels of autoantibodies against adrenergic receptors, and they are now expanding these findings by looking at the function of β2 adrenergic receptor autoantibodies in the illness.

Two dimensional sequencing and machine learning to maximise genetic marker detection

Prof. Brett Lidbury, Australian National University, Canberra, Australia

Prof. Lidbury and his team are engaged in identifying genetic biomarkers for ME/CFS. Genetic sequencing is challenging because it is expensive and requires large patient numbers. One strategy to overcome this is to pool DNA from many different individuals, and that is the aim of this ongoing project, which will then look for ME/CFS-associated genetic changes.

Combatting oxidative stress

Prof. Faisel Khan, University of Dundee, UK

High levels of harmful reactive oxygen molecules have been detected in people with ME/CFS. Nrf2 is a protein involved in the regulation of the body's natural defence against this oxidative stress, and Prof. Khan is testing whether Nrf2 activity is low in ME/CFS, and whether this antioxidant system can be activated by certain foods and therapeutic drugs.

lost in a book

Research from Leicester provides an **objective assessment of the reading problems** experienced by people with ME/CFS

Many people with ME/CFS suffer from problems with their eyes and vision, such as oversensitivity to light, troubles with focusing, and dry eyes. Reading can therefore be challenging, particularly for long periods, and pattern glare, headaches, and difficulty tracking lines of text are commonly reported.

However, before now, the reading performance of ME/CFS patients had not been assessed objectively. Over the last few years, Dr Claire Hutchinson and her colleagues at the University of Leicester have been looking in depth at some of the vision-related problems associated with ME/CFS, and this work has been supported, in part, by grants from ME Research UK.

Visual symptoms

The group has found that most ME/CFS patients experience a degree of eye pain and sensitivity to bright lights. Using sophisticated eye-tracking techniques, they have also showed that patients struggle to focus on one object and ignore irrelevant information, are slow in shifting attention between objects, are slower than normal and less accurate in their eye movements, and are vulnerable to pattern-related visual stress. Pattern-related visual stress causes distortions of print, including text that appears to jump, swirling effects, and letters that can double, fade, or blur.

In their latest ME Research UK-funded study, published in *Frontiers in Psychology*, the Leicester team evaluated what impact ME/CFS has on reading performance. A total of 27 ME/CFS patients and 27 healthy control subjects took part in the research; all had normal or corrected-to-normal vision (i.e. they wore spectacles or contact lenses), and none had any history of eye disease.

Dr Claire Hutchinson, **Rachel Wilson** and **Dr Kevin Paterson** from the University of Leicester

"Treating vision-related symptoms could improve the everyday lives of patients"

Reading measures

Reading acuity – the smallest print size that can be read without significant mistakes

Maximum reading speed – not limited by print size

Average reading speed

Critical print size – the smallest print size that can be read at maximum speed

Uncrowded visual acuity – the ability to identify words or letters on their own

Crowded visual acuity – the ability to identify a target letter surrounded by other letters

Reading performance was assessed using two standardised tests—the Minnesota Reading Acuity Chart and the Radner Rate of Reading Chart—which produce several measures (see box).

Reading performance

As expected, the maximum reading speed was slower in ME/CFS patients than in control subjects, and patients also tended to have a slower average reading speed. However, reading acuity and critical print size were not different between the two groups, indicating that the reading difficulties were not due to an inability to make out smaller print. Furthermore, ME/CFS patients and control subjects performed similarly on a vocabulary test, showing that the differences in reading performance between the two groups were unlikely to be due to cognitive problems.

The researchers also looked at uncrowded and crowded visual acuity (see box) using the logMar Crowded Test. While uncrowded visual acuity appeared to be similar in patients and controls, ME/CFS patients did have greater problems with visual crowding and performed less well on that test. Furthermore, those individuals who were more susceptible to visual crowding were also shown to read more slowly.

These findings build on a considerable body of work from Dr Hutchinson and her team, in which they have detailed and explored the vision-related symptoms associated with ME/CFS. While many people with the illness know how difficult it can be to read comfortably, particularly for long periods, this is the first time these problems have been assessed objectively in a laboratory.

As the researchers conclude, "Identifying and treating vision-related symptoms of ME/CFS could provide a means of improving the everyday lives of patients".

out of sight...

Recent work looking at **how to involve severely ill ME/CFS patients in research**

There is a considerable lack of information about those people with ME/CFS who are severely ill. They are often neglected—even though they have worse prospects of recovery—and under-represented in what little research is done.

A large part of the problem is that their challenging circumstances mean these individuals have difficulty accessing medical care and engaging in medical research. Is there any way of improving this situation?

With funding from ME Research UK, Victoria Strassheim and colleagues at Newcastle University have been conducting a programme of research concentrating on severely affected ME/CFS patients. Over the last couple of years, Victoria has published a review of existing research on severe ME, and an exploration of the effects of deconditioning in these patients. A third paper was recently published in *BMJ Open*, and looks specifically at how to include severely affected ME/CFS patients in research.

The first part of the project was to attempt to contact and evaluate patients with severe ME/CFS within the Northern England Clinical Network. The participants were adults with ME/CFS who were wheelchair-, house-, or bed-bound. A total of 483 questionnaire packs—including the Barthel Functional Outcome Measure and the De Paul fatigue questionnaire—were sent out to those people identified.

Unfortunately, only 63 packs were returned, although 76% to 88% of participants managed to complete the questionnaires successfully. The responses provided a host of information on the burden of symptoms and functional difficulties patients have to live with. The findings of the survey are freely available to download from the *BMJ Open* website: bit.ly/StrassheimSurvey.

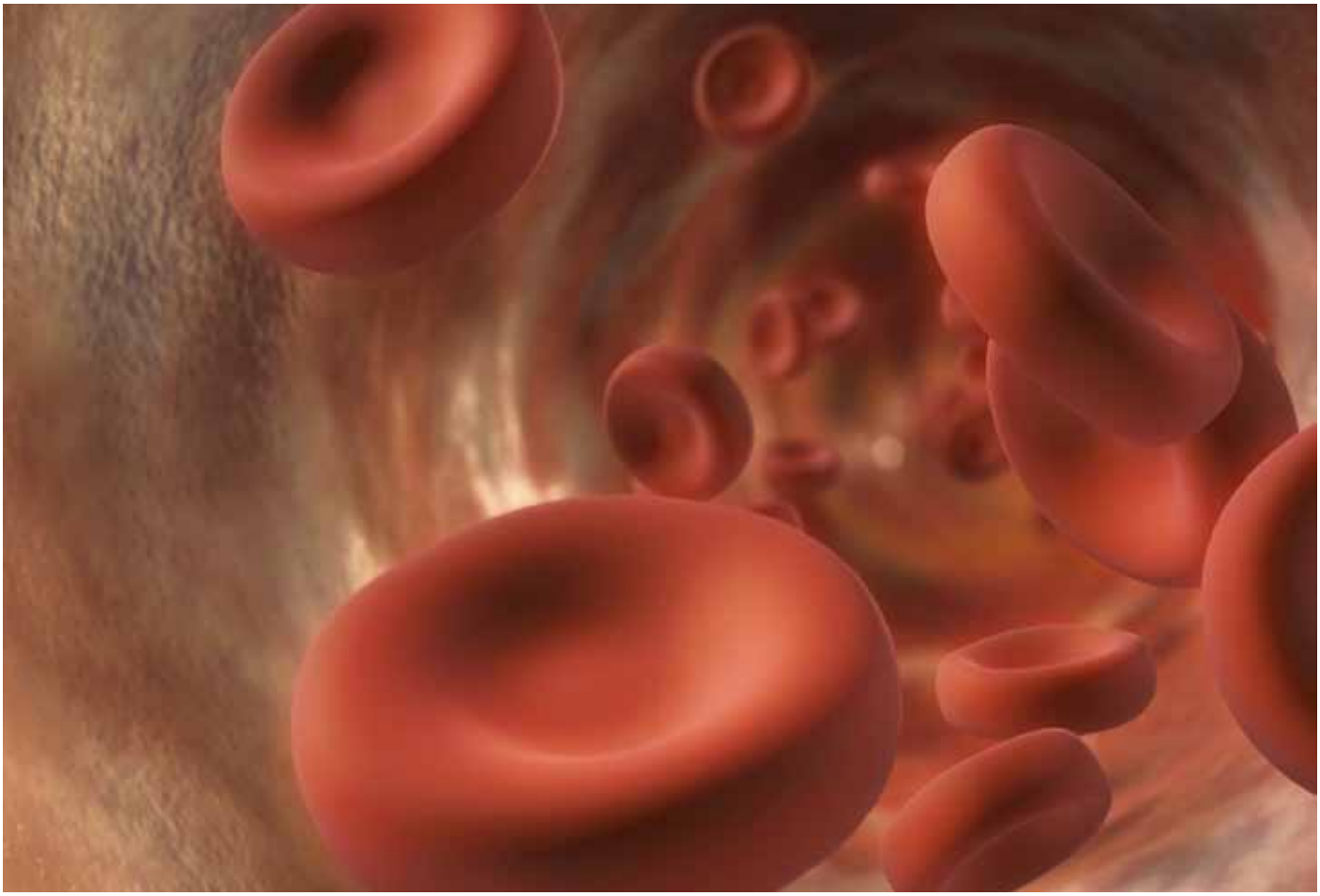
The second part of the project involved making a series of home visits to five severely ill ME/CFS patients, and attempting to complete assessments previously conducted in people with mild or moderate ME/CFS.

Over the course of four visits, a number of activities were attempted, including various physical and respiratory tests, cognitive assessments, and several questionnaires. Two patients were able to complete all of the assessments, while the other three achieved around 50%, and were unable or refused to perform the other tests, or could not attend due to ill health.

The investigators conclude that people severely affected by ME/CFS can engage with research, but they have a considerable burden of symptoms and a poor quality of life, and they need more support during the research process. The use of "research advocates" is suggested, to help engage and recruit these individuals into clinical studies.

Research bites

Our round-up of recent research from around the world



Red blood cell deformability

Saha et al., Clinical Hemorheology and Microcirculation, 2018

Red blood cells are responsible for carrying oxygen around the body, and their shape and flexibility allow them to squeeze through the smallest blood vessels, and deliver their oxygen to other tissue cells efficiently. But these properties can be altered by the presence of inflammation and oxidative stress—both of which have been reported in ME/CFS—and this is likely to have an impact on blood flow and oxygenation. Indeed, red blood cell deformability has been investigated as a potential biomarker for conditions including sickle cell disease, malaria, and Gulf War Illness. Perhaps red blood cells also have a role in ME/CFS.

Accordingly, researchers in California decided to look at the characteristics of red blood cells taken from 16 patients with ME/CFS and from 16 age-matched, healthy control subjects. They found that the cells from ME/CFS patients were significantly less deformable than those from healthy controls. The patients' red blood cells were around 10% bigger, and they were less able to deform when entering narrow channels in the investigators' test system. The cells also travelled around 18% slower than control cells. These changes are likely to have consequences for blood flow and oxygen exchange in organs such as the muscles, and may help to explain the pain and fatigue experienced by patients. The investigators suggest that red blood cell deformability may have a role as a diagnostic biomarker for ME/CFS, although this characteristic may well be affected by other inflammatory conditions, so it is by no means the ultimate key to diagnosis.

Cognitive problems

Robinson et al., PLOS One, 2019

A considerable amount of research implicates abnormalities of the autonomic nervous system in ME/CFS; this system regulates core body functions such as heart rate and breathing. Much of this work was conducted by Prof. Julia Newton and her team at Newcastle University (some funded by ME Research UK), and the group recently explored the link between these abnormalities and the cognitive problems that many patients experience. Several measures of cognitive performance were impaired in ME/CFS patients—particularly those relating to basic processing speed—and these correlated with an increase in heart rate variability (indicating autonomic dysfunction). However, it remains to be seen exactly how the two are linked.

Losing your grip

Nacul et al., Frontiers in Neurology, 2018

Apparently, "You can tell more about a man from his shoes than his handshake." That may or may not be true, but researchers from the London School of Hygiene and Tropical Diseases do believe that the strength of a person's handshake could provide informaton on whether or not they have ME/CFS. The team used a hydraulic hand dynamometer to measure hand grip strength in a range of patients, and found that it was lower in those with ME/CFS than in healthy control subjects, and even more so in patients with severe ME/CFS. The investigators suggest that hand grip strength has potential as a diagnostic tool, and perhaps also to measure disease severity and assess responses to treatment.

New frontiers

Chu et al., Frontiers in Pediatrics, 2019

This and the two articles below were part of a Research Topic on ME/CFS collected by the open-access academic publisher, Frontiers. In the first, a group from Stanford University School of Medicine describe the onset and course of disease in 150 US patients fulfilling the 1994 Fukuda criteria for CFS (which potentially includes a number of conditions). Nearly two-thirds of individuals believed their illness started following an infection, while other triggering factors cited included stressful incidents (39%) and exposure to environmental toxins (20%). One of the most interesting findings was that, while symptoms such as muscle pain and post-exertional malaise could improve by up to 25% over time, cognitive symptoms tended to persist.

School's out

Knight et al., Frontiers in Pediatrics, 2018

ME/CFS can have a particularly devastating impact on the lives of young people, and one of the biggest effects is on their schooling, with high rates of school absenteeism reported in children with the illness. A team from Melbourne, Australia, set out to look at other important aspects of school functioning that may ultimately affect individuals' education and career plans. A group of 39 adolescents with ME/CFS were assessed using a number of questionnaires designed to measure aspects of school functioning. Worryingly, in addition to greater school absence, these children reported a poorer quality of school life than unaffected individuals, as well as reduced school connectedness and worse academic performance.

Brain inflammation

Mueller et al., Brain Imaging and Behavior, 2019

In the last issue of *Breakthrough*, we reported on a newly funded study by Prof. Jarred Younger and his team at the University of Alabama, investigating whether immune cells are infiltrating the brain in people with ME/CFS, leading to an inflammatory state. That study has only just started, but Prof. Younger's group has recently published other research providing evidence of neuroinflammation in ME/CFS. They measured levels of four inflammatory metabolites (substances formed as a result of inflammation) in the brains of 15 women with ME/CFS and 15 healthy control subjects, and measured brain temperature, which can also indicate neuroinflammation.

In several regions of the brain, levels of the metabolites were raised in the patients compared with the controls. And some of these changes also correlated with reported levels of fatigue. Particularly significant was an increased choline-to-creatine ratio in the left anterior cingulate. The patients also had raised temperature in several brain regions, not accounted for by changes in body temperature or brain blood flow. The investigators conclude that these changes suggest that ME/CFS is associated with neuroinflammation, and this affects the whole brain rather just specific regions. These findings give us even greater reason to look forward to the results of Prof. Younger's ongoing, ME Research UK-funded study, which we will report here in due course.

Biochemical fingerprints

Xu et al., Analyst, 2019

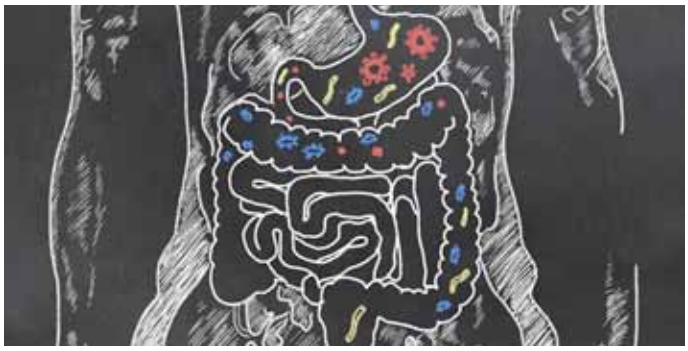
The mitochondria are often referred to as the power stations of the body, and it's no surprise, therefore, that much ME/CFS research has been focussed on these structures, which are found in every cell and are essential for energy production. A research group in Oxford has continued this trend by using Raman micro-spectroscopy to obtain biochemical fingerprints of peripheral blood mononuclear cells from ME/CFS patients. These fingerprints were markedly different from those of cells from healthy subjects, but also showed some similarities to cells that completely lacked any mitochondrial DNA, specifically features relating to an amino acid called phenylalanine. Could this be a potential biomarker for the illness? Time will tell.

Transcriptome analysis

Sweetman et al., Int. J. of Immunopathol. and Pharmacol., 2019

Articles in the last couple of issues of *Breakthrough* alone show how ME/CFS is characterised by widespread abnormalities in the immune and nervous systems, as well as changes in mitochondrial and metabolic function. But what about the genes involved in each of these areas? Researchers in New Zealand analysed the transcriptomes (sets of RNA molecules) of peripheral blood mononuclear cells from ten ME/CFS patients and ten healthy control subjects. They found 27 RNA molecules that were increased or decreased in the patient group, and the genes most significantly altered were in pathways related to mitochondrial function, inflammation, metabolic dysregulation, and circadian clock function.

"ME/CFS is associated with neuro-inflammation affecting the whole brain"



Inflammatory bowel disease

Tsai et al., Journal of Translational Medicine, 2019

Last year, we reported on a newly funded study in Newcastle University investigating the link between ME/CFS and irritable bowel syndrome. In a similar vein is recent research from Taiwan on patients newly diagnosed with inflammatory bowel disease (IBD), a more severe condition which also has similarities with ME/CFS. Using retrospective data from a health insurance database, the investigators found that the risk of developing ME/CFS was more than doubled in patients with IBD—particularly in those with Crohn's disease. Of course, this association does not prove that one condition causes the other, but it does provide further evidence of a link between ME/CFS and bowel conditions.

Hope, disappointment, perseverance

Lacerda et al., Health Expectations, 2019

A team from the London School of Hygiene & Tropical Medicine—which runs the UK ME/CFS Biobank—wanted to find out more about the perspectives of people with ME/CFS who take part in the research they conduct. So they ran a number of focus groups comprised of study participants, and then collated and grouped the results according to theme. The findings are freely available to read online (bit.ly/MEfocus), but are summed up in the paper's title: "hope, disappointment and perseverance". Among many other themes discussed, participants acknowledged the complexity of the illness, and sought coherence in the "jigsaw" of published evidence. They also called for "a more collaborative research culture".

Friends united

Some of our supporters' fundraising activities. If you would like to support ME Research UK and raise funds for ME research, visit our website for a range of ideas.

Sahara trek

When a family member was diagnosed with ME/CFS, Edward Bennett and his father, Roger, decided to raise funds for research into the illness. Edward says, "We were shocked to find that very little funding had been, and continues to be, provided to research a cure for ME. We wish to do something to raise funds to speed up finding a meaningful cure, not only for our family, but for others too." So, in October 2018, they undertook an eight-day, 78-km Action Challenge Sahara Trek in aid of ME Research UK. We thank Edward and Roger (and their four-legged friend) for raising an amazing total which will be used to fund more research into the illness.

Fishermen's friends

Back in October last year, members of the Rotary Club Torpoint Eddystone organised a charity concert at Sclerder Abbey in Cornwall, all in aid of ME Research UK. In these picturesque surroundings, supporters were treated to a wonderful night of singing from the Polperro Fishermen's Choir (who perform traditional Cornish and modern choral music); famed soprano, Nicola Kirsch (who won TV's Stars in their Eyes as Maria Callas in 2000); and talented local girl, Janine Wright. Many thanks to all who supported this event.

Kiltwalk 2019

The four Scottish Kiltwalks (in Glasgow, Aberdeen, Dundee, and Edinburgh) are a marvellous way of raising funds for your chosen charity, as all funds raised can be boosted by a further donation of 40% thanks to the generosity of Sir Tom Hunter and the Hunter Foundation. Read more about this year's events on our website: meres.uk/Kiltwalk2019.

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01 You can sign up for the 2019 Kiltwalk right now

02 Edward & Roger Bennett and friend on their Sahara Trek

03 Alicia Masson celebrates completing the Run Norwich 10k

04 Screw ME came up with a novel fundraising idea

Pink or blue?

Members of the Facebook community, Screw ME, last year came up with a novel and fun way to raise funds for ME Research UK and the ME Association. To take part, visitors first had to make a donation and then they could guess whether 3-month pregnant Lynsey was expecting a girl or a boy. Correct guesses will then go into a hat for the chance to win a mystery prize. Amazingly, the fundraiser reached its target within days, and we are very grateful to Screw ME and everyone who took part for their generosity. So, was it a girl or a boy? We're still waiting, but Lynsey must be due around now…

Facebook fundraisers

Facebook has now made it even easier to raise funds for your favourite charities on the popular social media platform. One great idea is to ask family and friends to make a donation to mark your birthday and really make a difference. All you need to do is follow a few simple steps and Facebook can take care of the rest (visit: bit.ly/FbookFund). Many thanks to those supporters who have already taken advantage of the scheme and raised valuable funds for ME Research UK.

Run, Norwich, run!

In August 2018, a record 7,000 runners competed in the annual Run Norwich 10k race. The route passes many of the landmarks of this historic city, including Norwich Castle, the Forum, and Norwich Cathedral, and participants and spectators were entertained with music and entertainment along the way. Running to raise funds for ME research charities was supporter, Alicia Masson. Fortunately, the race took place in the morning, and Alicia managed to avoid the blistering temperatures on the day. So, many thanks to her from all of us at ME Research UK. If you or someone you know is interested in following in Alicia's footsteps and running for ME Research UK, there are a few hints and tips on our website: meres.uk/Running.

Marathon man… and women

The Virgin Money London Marathon is one of the most well-known races in the world, and, this year, fundraising from the event is set to reach one billion pounds. One runner taking part on 28 April is James Everett, who will be raising funds for ME Research UK. James says, "A number of my friends and family have previously suffered, or are currently suffering from ME/CFS, so I'm raising funds for scientific research into this commonly misunderstood condition." We wish James all the best for his training, and if you would like to support him, please visit his Justgiving page: bit.ly/EverettMarathon.

Other supporters running for ME Research UK in the coming months include: Mary MacLellan in the Edinburgh Marathon, Ian and Ruth Britten in the Cheltenham Half Marathon, Tessa Lawlor in the Farnborough Winter Half Marathon, and Tracey Robinson in Color Rush Obstacle Sheffield. Good luck to them all!

What Price Life?

This is the title of a new book of poems and reflections by Yvonne Jupe, and is the latest in a series of books inspired by subjects including the natural world, the art of Monet, and Cornish fisherman. Yvonne has suffered with ME and a variety of other conditions for many years, and says she wrote the pieces in *What Price Life?* in order "to express my feelings and to reach out to other sufferers. It is my sincere hope that this book of poetry will help to unite and strengthen us in our quest for health."

As well as sharing these reflections on the illness with other sufferers and their carers, Yvonne wants to help encourage further research into ME, and is hoping to raise funds for ME Research UK through sales of her book. You can purchase a copy of *What Price Life?* via her website, imagesandreflection.com, and also read extracts from some of her other books.

Standing Order Form

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

Name of account holder(s)

Address

Postcode

Telephone number

Name of Bank or Building Society

Branch address

Branch postcode

Instruction to your Bank or Building Society

To the Manager, Please arrange to debit my/our account with the amount detailed below, once every month until further notice.

Account number

Branch sort code

Debit amount (£)

Payment date each month

Date of first payment

Pay to: Clydesdale Bank, 158/162 High Street, Perth PH1 5PQ, UK, Account: ME Research UK, Account no: 50419466, Branch code: 82-67-09

☐ ***Tick*** *if you would like us to treat this, any future donations to ME Research UK (SC036942), and all payments in the previous 4 years, as Gift Aid donations, meaning your donation can increase in value by a quarter at no extra cost to you. You confirm that you are a UK taxpayer and understand that if you pay less Income Tax and/or Capital Gains Tax than the amount of Gift Aid claimed on all your donations in that tax year it is your responsibility to pay any difference. Please notify us if you wish to cancel this declaration, change your name or home address, or no longer pay sufficient tax on your income and/or capital gains. If you pay Income Tax at the higher or additional rate and want to receive the additional tax relief due to you, you must include all your Gift Aid donations on your Self-Assessment tax return or ask HM Revenue and Customs to adjust your tax code.*

Signature

Date

Thank you for your support