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ME RESEARCH UK

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AUTUMN 2020

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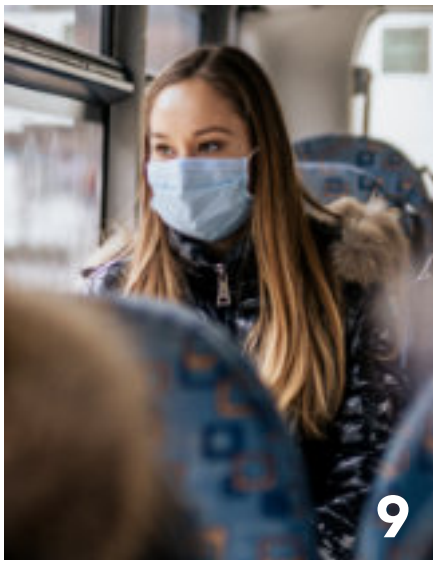

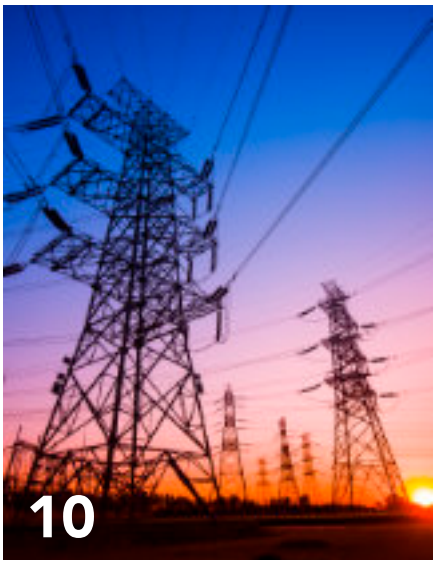

Breakthrough magazine is published by ME Research UK, a Scottish Charitable Incorporated Organisation with the principal aim of commissioning and funding high-quality scientific (biomedical) investigation into the causes, consequences and treatment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS). The charity also aims to energise ME research by identifying potentially important areas for future biomedical research, and producing high quality professional reviews and reports. *Breakthrough* is an open access publication and, apart from images and illustrations, the content may be reproduced free of charge, subject to the terms and conditions found at meres.uk/bt-terms.

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In this issue

In the spotlight

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

Editorial

Welcome to the twentieth anniversary issue of *Breakthrough*. Along with new articles, we have included some of the content from our previous issue (spring 2020) which, due to COVID-19, was only available online.

We are all still dealing with the impact of that pandemic, but growing attention on "Long COVID" and its parallels with ME/CFS does offer hope that we will see further focus on ME/CFS. We continue to inform, influence and invest in research, and are hopeful that this year will see us pass the £2 million mark of cumulative investment, with both the funding and ambition to continue well beyond this.

Our refreshed strategy is set out on page 21, and we have strengthened our Board and staff with Drs Eleanor Roberts and Louise Crozier joining us this year. You can find out more about them both on page 23.

We are delighted that this issue sees the first in a series of articles by Cort Johnson. In the first piece, he reflects on the development of exercise research over the last twenty years and his hopes for the future. You can read the article from page 24.

As ever, this issue of *Breakthrough* rounds up research across the globe, including a new ME Research UK-funded study to be carried out by Profs Jo Nijs and Lode Godderis in Belgium, exploring epigenetic alterations.

We also celebrate the significant contribution that the Countess of Mar has made to the cause of ME/CFS over nearly forty-five years in the House of Lords, following her official retirement in May. I am glad to report that she continues as our Patron and as Chairwoman of Forward-ME.

Although fundraising and events generally remain curtailed at present, we are grateful to everyone who is still raising funds for biomedical research into ME/CFS. Without your support, we would not be able to fund as many studies as we do.

I also feel duty bound to remind you all that Christmas is just around the corner and our 2020 Christmas card selection is now available for purchase: online, by post or by telephone!

Thank you, and I hope you enjoy this bumper anniversary issue of *Breakthrough*.

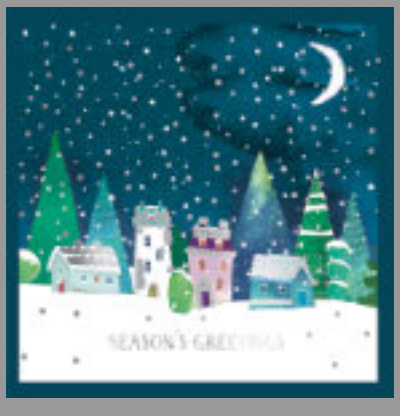
Jonathan Davies
Chair, Board of Trustees

Christmas cards 2020

Our Christmas cards are now available, and you'll find a flyer and order form with this issue.

There's a great selection to choose from, and we are also offering online ordering for residents of the UK, Isle of Man and Channel Islands, at shop.meresearch.org.uk. (Please note, the special offer on notecards is subject to availability.)

All the proceeds go to help support the work of ME Research UK.



Shopping at Amazon

Although lockdown has eased and shops are opening again, many of us are still avoiding the crowds and making full use of online shopping.

We would certainly encourage you to support independent local businesses, many of whom now deliver or who have online ordering. But sometimes it just has to be Amazon.

As a bonus, you can also support ME Research UK every time you shop at amazon.co.uk. And the best thing is that it doesn't cost you a penny more!

The easiest way to sign up is to login to Amazon Smile via meres.uk/smile, and select ME Research UK as your charity.

When you shop – they'll donate!

Dialogues for a Neglected Illness

New series of videos on ME/CFS

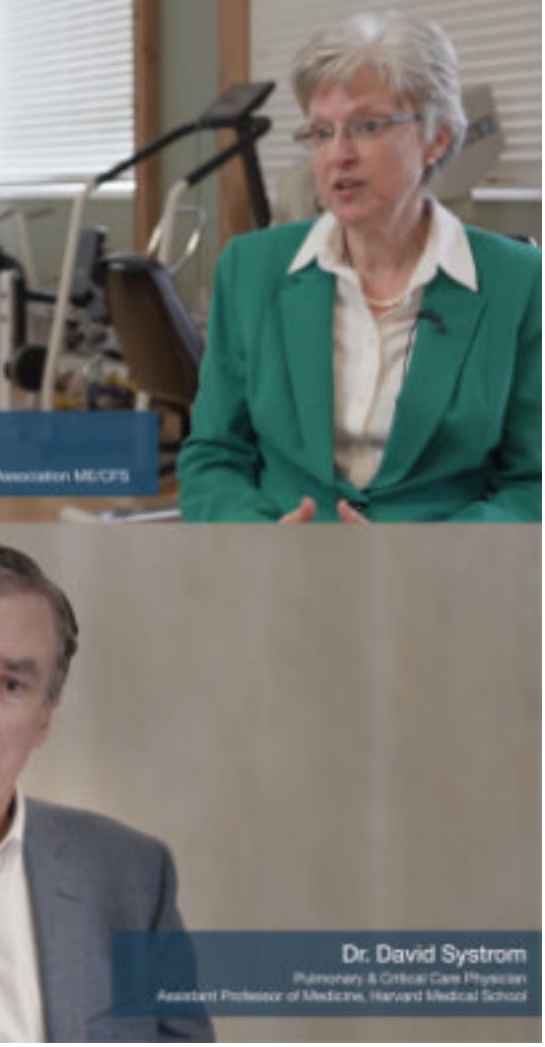
A valuable new resource is currently being developed by filmmakers Natalie Boulton and Josh Biggs, with the help of an award from the Wellcome Public Engagement Fund.

Dialogues for a Neglected Illness is a series of videos addressing different aspects of ME/CFS, including its diagnosis, management, treatment and patient experiences.

The final project will comprise a website containing around a dozen short videos, including interviews with – and input from – doctors, researchers, patients, carers and advocates. All the videos are produced to a very high standard, with contributions from some of the leading lights in ME research. Each is also accompanied by educational materials and references, and the series is available to watch at dialogues-mecfs.co.uk.

There is a wide range of contributors, including such names as Dr Eliana Lacerda, Prof. Jonathan Edwards, Prof. Mark VanNess, Staci Stevens and Dr David Systrom, as well as people with ME/CFS and patient advocates.

The goal is "a resource which patients can use to help their doctors and other health, education and research professionals understand more about this disease and the issues faced".



There are currently eight videos available to watch: an Introduction to ME/CFS, Understanding Post-exertional Malaise, a Quick Guide to Post-Exertional Malaise, two films on Understanding Graded Exercise Therapy, including discussion of the controversial PACE trial, and three videos covering severe and very severe ME.

All are also available on our website (meres.uk/dialogues), as well as being streamed on the project's website and a number of other places.

More videos on other topics will be made available over the course of the year, culminating in a live event with video screening, speaker and Q&A session which is currently scheduled for some time in 2021.

IACFS/ME conference

Annual meeting moves online

The 13th scientific conference of the International Association for CFS/ME was held online on 21 August, and was attended by our new Science and Engagement Director, Dr Louise Crozier. Seventeen oral presentations were given over five sessions, kicking off with a discussion of several projects related to COVID-19 and tracking the development of ME/CFS after infection. Other sessions were dedicated to immunology, metabolism, heart rate variability, research/clinical networks and treatments. Among more than 270 attendees, 20% were early-stage researchers.

The most promising data were related to immunology and metabolism, with evidence for B-cell receptor disruption, presented by Dr Sato from the National Institute of Neuroscience, and a defect in a key enzyme for energy production in ME/CFS cells, presented by Dr Petterson from the University of Norway. A database tool was also presented, to enable researchers to search large datasets easily and effectively to find key genes and pathways, which should help focus efforts in future research.

US Congress

In May, a Bill was introduced into the US Congress by Representative Jamie Raskin calling for "the expansion, intensification, and coordination of the programs and activities of the National Institutes of Health with respect to post-viral chronic neuroimmune diseases, specifically myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), to support the COVID–19 response, and for other purposes".

If passed, an additional $60 million would be allocated to existing ME/CFS research projects and into researching connections between ME/CFS and COVID-19 survivors over a four-year period to 2024.

ME Research UK heartily welcomes the possibility of additional funding and the recognition of the reality of ME/CFS, but Congress must pass the Bill before words become action.

The Countess takes centre stage at the

The Countess of Mar

An appreciation

In May, when the Countess of Mar retired officially from the House of Lords after almost forty-five years of service, the ME community lost a champion of the first rank and a redoubtable campaigner for acceptance of the illness, for research, and for the proper treatment from government and the NHS of those affected by ME.

Her departure was marked by an article in *The Telegraph* in which, with typical good humoured directness, she said, "I don't want to be there past my best-before date." One of the privileges of membership of the House is access to ministers, politicians and decision-makers, which she utilised to the utmost and to the benefit of those affected by ME.

Her zeal for a revolution in the perception and treatment of ME/CFS stemmed from her own experience of organophosphate poisoning which led to autonomic dysfunction. Concern turned to action and she was a member of several European Community Select Committees – on the environment, agriculture and consumer protection – as well as being secretary of the All-Party Parliamentary Group on Pesticides and Organophosphates, and a leading light and vice-chair of the All-Party Parliamentary Group on ME.

10th anniversary of Forward-ME in 2018

In 2008 and under her chairmanship, she created the Forward-ME group, which consists of a broad spectrum of charities and voluntary organisations (including ME Research UK). The group's aim is to promote effective joint working by organisations to maximise impact on behalf of all people with ME and CFS in the UK.

Hansard records thirty-six instances of the Countess speaking to the Chamber specifically about ME/CFS since 2006. This does not include contributions to debates regarding neurological conditions or concerning those affected by long-term chronic illnesses in general. The contributions run the full gamut of issues which affect the ME community – social security, personal independence payments, work capability assessments, children and young persons, as well as research. Her comments on the PACE trial, cognitive behavioural therapy and neurological conditions are especially noteworthy and informed.

In their Lordships' debate on ME in 2008 – over a decade before the historic 2019 House of Commons debate – the Countess elicited the following confirmation from the Government: "My Lords, the Government accept the World Health Organisation's classification of CFS/ME as a neurological condition of an unknown cause." This acceptance has been used to remind the Department of Work and Pension of the nature of the illness ever since.

The Countess's activities have not been confined to the red benches either. She has been a vociferous letter-writer in defence of those affected by the illness and in challenging misconceptions about the illness. Her role has also led to invitations to speak at various events, such as the launch of the CMRC, and a lecture on "ME/CFS: Frontiers" at the Royal Society of Medicine in 2015. The aim was to give delegates "a rare opportunity to learn about ME/CFS from a clinical, scientific and political perspective". Her speech included a quote from Frantz Fanon and was addressed to the medics present.

"Ladies and gentlemen, I know how very difficult it is to say 'Sorry, I got it wrong', especially when your whole career has been based on a particular belief. I have been told that, in medicine, nothing will change until the old guard moves on. The history of medicine is littered with instances of this phenomenon. It is my very sincere wish that the situation will change radically long before the changing of the guard."

"There is still some way to go before we know causes and cure, but we are well on the way"

Through her work, Margaret has spoken truth unto power and pointed out the injustices that surround ME/CFS and the treatment of those with the condition. Although she has now retired from the House of Lords, we know that she will not be withdrawing from the fight, and we are truly grateful for all that she has done thus far.

"I believe that between us we have managed to change the perception of ME by the medical profession and the public. There is still some way to go before we know causes and cure, but we are well on the way to finding them."

DecodeME

The world largest ME/CFS DNA study

In June this year, a collaboration of researchers, patients and advocates announced £3.2 million in funding for what will be the largest ever study looking at DNA changes in people with ME/CFS.

The DecodeME study is led by Prof. Chris Ponting of the MRC Human Genetics Unit at the University of Edinburgh, and funded by the Medical Research Council and the National Institute for Health Research.

The researchers aim to look at saliva samples from 20,000 people with ME/CFS, to see whether the disease is partly genetic, and to investigate the underlying causes of the condition.

Prof. Ponting says: "Our focus will be on DNA differences that increase a person's risk of becoming ill with ME/CFS. We chose to study DNA because significant differences between people with, and without, ME/CFS must reflect a biological cause of the illness. It is our hope that this study will transform ME/CFS research by injecting much-needed robust evidence into the field."

The participation of people with ME/CFS across the UK will be essential to the study's success. Anyone with ME/CFS who wants to take part can register their interest right away at www.decodeme.org.uk. Participants need to be aged 16 years or over.

The long haul

Parallels between Long COVID and ME

It is becoming clear that many survivors of an initial COVID-19 infection are now reporting longer-term post-viral complications including fatigue, muscle pain and brain fog – symptoms that will be very familiar to people with ME.

These parallels between so-called "Long COVID" and ME have not gone unnoticed by sufferers, and have been highlighted in the media as well as in the scientific literature.

In an interview for ITV News, London GP Dr Sarah Jarvis highlighted the striking similarities in symptoms between Long COVID and ME. Another worthwhile listen is the interview with Prof. Paul Garner of the Liverpool School of Tropical Medicine (himself a Long COVID sufferer) on The Bunker Daily podcast: "This is very similar to ME and long-term fatigue… And patients are not being believed by employers and health professionals."

In the search for a way to manage their continued symptoms, many COVID-19 long-haulers have been drawn to resources prepared for those with ME, including NICE's guideline on ME/CFS. NICE has consequently been prompted to issue clarification on the use of graded exercise therapy (GET) for those recovering from COVID-19.

"It should not be assumed that the recommendations [on GET] apply to people with fatigue following COVID-19. [They] only apply to people with a diagnosis of ME/CFS as part of specialist care, and CG53 is clear that this should be part of an individualised, person-centred programme of care, with GET only recommended for people with mild to moderate symptoms. As the guideline is currently being updated, it is possible that these recommendations may change. The evidence for and against graded exercise therapy is one of the important issues the guideline committee is considering."

This last statement is encouraging as we wait for publication of the updated guidelines. These have been delayed by the pandemic, but are now expected to be published in April 2021.

Power moves

Newcastle researchers have been looking at **abnormalities in muscle energy production**

In a series of studies conducted over the last few years, researchers at Newcastle University have been trying to determine the cause of the severe fatigue and post-exertional malaise that are experienced by patients with ME/CFS.

Post-exertional malaise can be defined as the worsening of symptoms after even minor physical or mental exertion, and it is considered to be one of the hallmark symptoms of the illness.

Muscle abnormalities

ME Research UK has funded several of the team's projects exploring the mechanisms underlying abnormal muscle fatigue in ME/CFS.

Notable findings from these projects include a reduction in the levels of cellular ATP (which transports energy around the body) in ME/CFS patients, as well as abnormalities in AMPK signalling (which is responsible for regulating cellular energy levels in cells).

The latest study was conducted by Dr Cara Tomas, Prof. Mark Walker and colleagues, who reanalysed findings from their previous work, comparing them between two groups of patients: those who are moderately affected (housebound) and those who are severely affected by ME/CFS (bedbound).

The researchers measured respiration rates in blood cells from both groups of ME/CFS patients and from healthy control subjects, to determine if there

"highlights the importance of conducting research into the most severely affected patients"

Prof. Mark Walker, Dr Audrey Brown, Prof. Julia Newton and Dr Cara Tomas

was a difference in mitochondrial function and in metabolic pathways such as glycolysis.

Mitochondria are responsible for the majority of energy production in cells, while glycolysis is the process by which glucose is broken down to release energy.

The investigators found that mitochondrial function was reduced by a similar extent in both the moderately and severely affected ME/CFS patients (compared with the healthy control subjects). Hence, it was not associated with disease severity, and therefore likely to be a result of ME/CFS itself, and not just deconditioning in response to severe symptoms.

Both patient groups also had lower rates of ATP-linked respiration, pointing to a possible defect in metabolic pathways such as glycolysis and/or the OXPHOS pathways (both key pathways for ATP production and, hence, energy levels). This reduced respiration rate was linked to disease severity, with a greater reduction seen in the severely affected group.

Glycolysis levels

In their previous study, the researchers had found no difference in glycolysis between control subjects and ME/CFS patients. However, by separating out the patients into two groups by disease severity, we can now see that the most severely affected patients do actually appear to have reduced glycolysis levels, while moderately affected patients do not.

In summary, this study has shown that moderately affected (housebound) patients have a mitochondrial impairment, while those who are severely affected (bedbound) have both mitochondrial and glycolytic impairments. But what does this all mean?

Firstly, the mitochondrial defect in both ME/CFS groups suggests that the post-exertional malaise and fatigue may be caused by a defect in one of the metabolic pathways such as glycolysis or OXPHOS.

Secondly, the study highlights the importance of conducting research into the most severely affected ME/CFS patients, where possible. However, there are multiple challenges in involving this group in research, as the Newcastle team is exploring in another branch of their work (see pages 28 to 29 of this issue).

Potential next steps would be to test these methods in other diseases with symptoms of severe fatigue, to determine if the findings are a result of the symptoms (fatigue) or the underlying disease (ME/CFS).

Some of our current projects

The role of inflammation and nitric oxide production in ME/CFS

Dr Francisco Westermeier, FH Joanneum University of Applied Sciences, Austria

One consequence of an activated immune system is inflammation, which can cause tissue damage if it persists. Dr Westermeier is looking at whether ME/CFS is associated with alterations in the production of a chemical called nitric oxide, too much of which can cause prolonged inflammation.

Investigating sensory processing and cognitive function in ME/CFS

Dr Sanjay Kumar, Oxford Brookes University, UK

Hypersensitivity is a common problem in people with ME/CFS, the resulting physical and mental overload leading to a number of symptoms. Dr Kumar is investigating patterns of sensory processing in ME/CFS, and how they affect functional performance, including cognitive processes.

Exploring an anti-citrullinated antibody signature in ME/CFS

Prof. Mercedes Rincon, University of Vermont, USA

Citrullination is a change in a protein whereby it becomes identified as foreign by the immune system, sometimes in response to infection. Prof. Rincon is investigating whether this might be happening in ME/CFS, by looking for antibodies in the blood that are targeted on these citrullinated proteins.

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 study, Prof. Younger is investigating whether this is caused by activated peripheral immune cells crossing into the brain, as found in multiple sclerosis.

Sea change

New study explores **epigenetic alterations and pain in ME/CFS**

Epigenetics is a fascinating field looking at genetic changes that can be passed from one generation to the next, not as a result of alterations in the DNA sequence, but instead caused by changes in gene activity and expression (how information from the gene is used to make proteins).

One consequence of epigenetics is the possibility that the behaviour and experiences of an individual can affect the health of their children and grandchildren, perhaps putting them at a higher risk of disease. Science fiction writers have also explored how epigenetics might allow knowledge and experience to be passed down generations.

As far as we know, there are not yet any indications that the risk of developing ME/CFS can be inherited via epigenetics. However, there is evidence that epigenetic changes may play a role in the pathophysiology of the illness, including the post-exertional malaise experienced by many patients with ME/CFS.

This is the area that Prof. Jo Nijs from Vrije Univeristeit Brussel, Prof. Lode Godderis from the University of Leuven and their colleagues are exploring in a new research study recently awarded funding by ME Research UK.

Prof. Jo Nijs

Prof. Lode Godderis

These investigators' previous research uncovered the role of central sensitisation in the chronic pain experienced by many people with ME/CFS at rest and/or after exercise. This is the idea that the central nervous system is hypersensitive in these individuals, leading to an increased sensitivity to pain.

The mechanisms involved in central sensitisation are complicated, but two factors – and how they are altered by epigenetic changes – may be particularly important.

Brain-derived neurotrophic factor (BDNF) is a protein involved in a number of neurological functions. It is released during exercise and physical activity, but can also increase the sensitivity of pain pathways. In the researchers' previous study funded by ME Research UK, people with ME/CFS had in-

creased BDNF levels, but the methylation of DNA within the *BDNF* gene (an epigenetic mechanism) was lower than normal.

Histone de-acetylases (HDACs) are a group of enzymes known to be increased during neural sensitisation and pain, although their activity is decreased during exercise (in contrast to BDNF), and they have not yet been studied in ME/CFS.

This is some of the background of evidence behind the new project being conducted by Profs Nijs and Godderis, in which they plan to investigate further the role of BDNF and HDACs in the central sensitisation and post-exertional malaise experienced by people with ME/CFS, and the epigenetic changes occurring in these genes.

Eighty patients with ME/CFS will be enrolled and split into two groups. The first group will undergo a session of aerobic exercise, while, as a control, the other will undergo a test designed to trigger emotional stress. Various clinical and laboratory assessments will be performed before and after these sessions, including measuring the expression of BDNF and HDACs in the blood, as well as DNA methylation in the *BDNF* gene and in the genes regulating HDAC expression.

Epigenetic changes have been shown to contribute to the pathogenesis of a number of disorders – including Alzheimer's disease and some cancers – leading to the development of potential new treatments. The investigators hope that the same will be true in ME/CFS, and their results might ultimately lead to new diagnostic markers and treatment strategies.

Message received?

New research from Germany looking at the effects of **immunoglobulin on adrenergic receptor activation**

The immune system is a fertile area for research in ME/CFS, and a number of recent and ongoing studies funded by ME Research UK have been exploring various aspects of abnormal immune function in the illness.

This includes work carried out by Prof. Carmen Scheibenbogen and her team at the Institute for Medical Immunology in Berlin, and the first results from their research were recently published in the journal, *Brain, Behavior, & Immunity – Health*.

Immunoglobulins

Immunoglobulins (also known as antibodies) play a key role in the immune system. They are proteins produced by the white blood cells which recognise and attack harmful invaders such as bacteria and viruses.

Some immunoglobulins (autoantibodies) are directed against the body's own proteins, cells or tissues, which can lead to the development of a so-called autoimmune disease such as multiple sclerosis or lupus.

Some recent research suggests that these immunoglobulins may also have a role in ME/CFS, at least in some patients.

In 2016, Prof. Scheibenbogen's team found that nearly a third of ME/CFS patients they studied had increased levels of autoantibodies directed against adrenergic receptors. These receptors are involved in the sympathetic nervous system, and are

"Targeting of the adrenergic system has potential as a treatment"

Prof. Carmen Scheibenbogen (second right) and her team

found in many cells of the body, including immune cells.

In their current study, the group wanted to look in detail at the effects of immunoglobulins on adrenergic receptors and on immune function in ME/CFS.

The researchers obtained blood samples from five ME/CFS patients with increased levels of autoantibodies against adrenergic receptors, from five ME/CFS patients with normal autoantibody levels, and from six healthy control subjects.

In the first part of the experiments, immunoglobulin isolated from these samples was added to cells containing adrenergic receptors, in order to assess whether or not the receptors became activated as a result.

In the second part, the immunoglobulin was added to immune cells (specifically, white blood cells called monocytes) to see if this altered their function.

Receptor activation

Firstly, immunoglobulin from healthy control subjects activated the adrenergic receptors (as demonstrated by a change in signalling), and there was a similar result with immunoglobulin from ME/CFS patients with normal autoantibody levels.

In contrast, there were no such effects when using immunoglobulin taken from patients with increased autoantibody levels.

Secondly, immunoglobulin from healthy controls also had an effect on immune cell function, by inhibiting the production of cytokines and T-cells.

Immunoglobulin from patients with increased autoantibodies had no such effect, while there was a modest effect using immunoglobulin from those with normal levels.

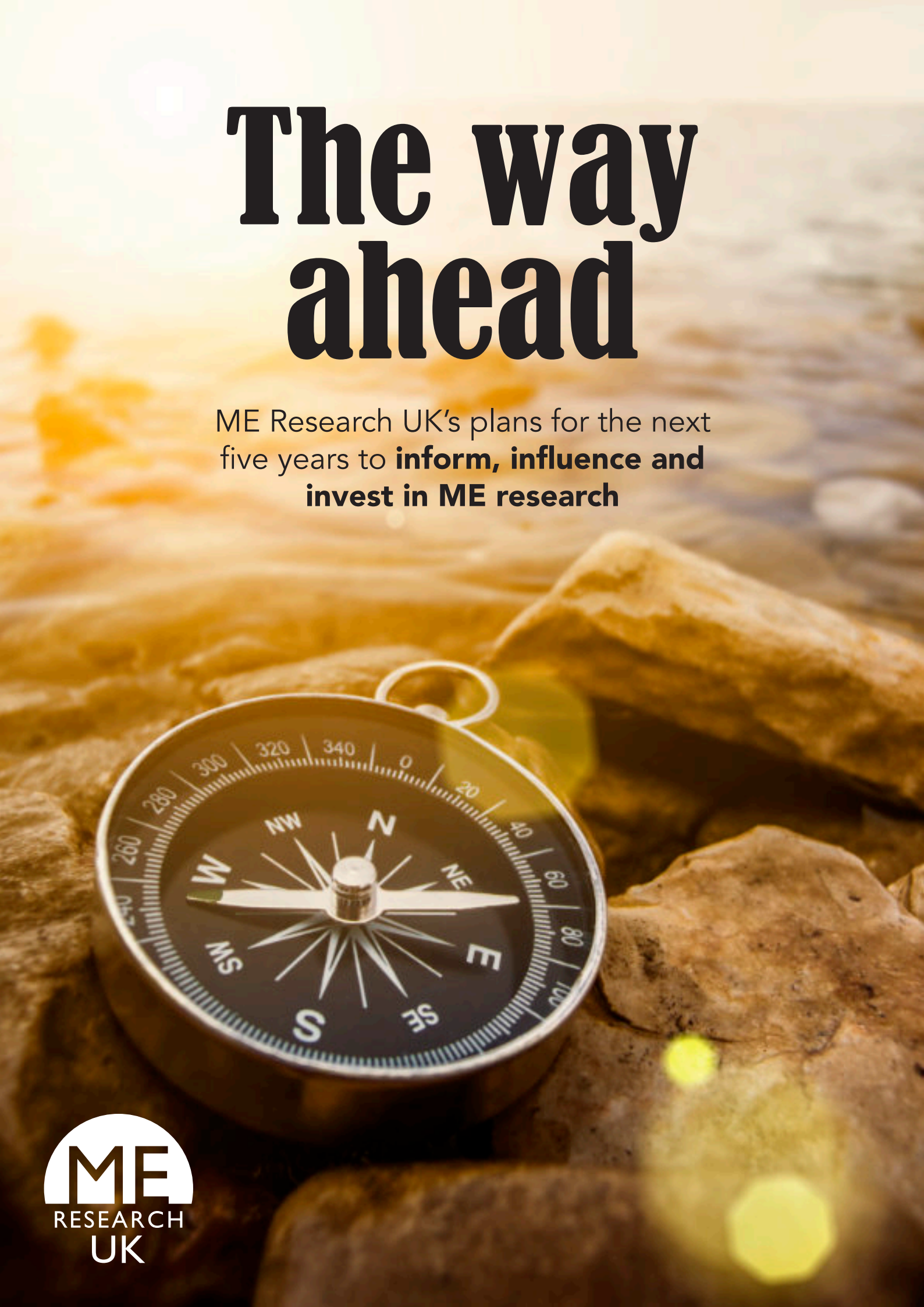
How can we summarise these fairly complex results, and what do they mean for patients with ME/CFS?

The key finding of this study is that, in a subgroup of ME/CFS patients with increased autoantibody levels, the activation of adrenergic receptors by immunoglobulin is lower than normal. This suggests that many of the symptoms of the illness – such as immune activation and autonomic abnormalities – may be mediated or made worse by dysfunction of these receptors.

The authors suggest that targeting of the adrenergic system may therefore have potential as a treatment for ME/CFS. However, this goal could be a long way off. In the meantime, we look forward to the continuation of this research by Prof. Scheibenbogen and her team as they explore the area further.

The way ahead

ME Research UK's plans for the next five years to **inform, influence and invest in ME research**



Bob and Vance at our tenth anniversary celebration in 2010

How it all began

ME Research UK – or the ME Research Group for Education and Support (MERGE), as it was originally called – was established by Dr Vance Spence and Robert McRae in 2000, thanks to the impetus and financial backing of Founding Patron, Roger Jefcoate DL CBE.

The charity's mission was to fund high-quality scientific (biomedical) research into ME/CFS, and to provide information about research which was accessible to as diverse an audience as possible. They realised that only through high-quality research would the illness be understood and, eventually, a cure found.

Vance and Bob were diagnosed with ME/CFS in the 1980s and 1990s, respectively, and they shared a vision and a desire to ensure that more research into the illness, which so affected their lives, could be carried out and the results better understood.

From the outset, each brought their own professionalism to the fledgling charity and their legacy imbues our work today. Vance, as a leading research scientist at the University of Dundee, ensured that rigorous science was at the core of the charity. Bob, a senior banker with Clydesdale Bank, created the structures that allowed ME Research UK to operate with utmost probity and financial security.

Both Bob and Vance knew that only solid research would change the prevailing attitude of scientists and the medical community to the illness. This research had to be sound, and researchers and supporters had to trust the charity financially. Scientific rigour and financial probity are therefore the twin strands that thread through our organisation, and could be said to be the DNA that made us the charity we are today.

Of course, Vance, Bob and Roger are not alone in being pivotal to the growth of the charity – Betty McRae was a long serving and highly valued Trustee and also our Founding Ambassador, while Dr Neil Abbot, our Research & Operations Director, was the core of the charity for many years, writing *Breakthrough* magazine and establishing close ties with researchers worldwide.

However, what we achieved and how we will continue to deliver on our mission is due to our supporters. It is thanks to your generosity that we have funded all our work so far, and how – with your continued support – we intend growing into the future.

Our plans for the future

Over the past months, we have reviewed our previous work and looked closely at the wider ME/CFS research environment. This has enabled us to shape our priorities for the coming years and form our strategic plan.

This plan is designed to maximise our available funding, and help us deliver our mission of informing, influencing and investing in ME/CFS research worldwide, ultimately to end the suffering caused by ME/CFS.

We want to achieve ambitious goals that we believe are key to understanding the causes and consequences of the condition, as well as identifying potential treatments. There are four areas of focus:

Science

We will establish ME Research UK as a leading expert on ME/CFS biomedical research by:

- Proactively funding biomedical research;
- Working collaboratively with other institutions and organisations to influence the biomedical research agenda;
- Taking a leading role in interpreting, analysing and commenting on published biomedical research in a way that can be understood by a range of audiences; and
- Developing key criteria that can provide funding at all levels, including students, research teams and fellows.

Awareness

We will ensure that ME Research UK has a growing base of engaged supporters covering various communities by:

- Ensuring our brand is recognised by a range of audiences; and
- Undertaking activities that raise awareness of ME/CFS and our work across all relevant audiences.

People

We will ensure that employees and volunteers are the best available and are supported to give of their best by:

- Recruiting volunteers throughout the UK; and
- Reviewing our current structure, and investing in the best people to achieve our goals.

Funding

We will maximise the funding available to ME Research UK for biomedical research by:

- Increasing the amount of money we spend on research;
- Securing funding from a wider range of sources; and
- Controlling non-research costs and maintaining financial discipline.

Our five-year plan is ambitious, but we believe that robust biomedical research is the only way to understand ME/CFS. We will continue to work to achieve our vision.

We believe that our strategy will build on the work of the past twenty years, maintaining our focus on funding the best biomedical research, while committing resources to informing as many people as we can about the condition and the need for more research, and influencing others to join us in investing far more funding into ME/CFS research.

Since embarking on our strategic plan, we have already undertaken a number of activities to help us to achieve our goals. We have:

- Recruited a Science & Engagement Director to help us fund researchers and encourage collaboration between institutions and others;
- Published a global call for applications encouraging researchers to submit research proposals to us;
- Published a global call for PhD studentships to encourage universities to apply to us for funding for ME/CFS PhD placements;
- Promoted volunteering opportunities to seek new ambassadors and community fundraising champions throughout the UK; and
- Started a review of our marketing and branding to ensure we are communicating in the most appropriate way to our supporters, while also looking at how we can reach a much wider audience.

How to help build our future

ME Research UK's exciting plans for the next few years have been made possible largely through the generosity of funds from bequests and family trusts.

By remembering ME Research UK in your Will, you can give a gift that costs nothing to make now, but could transform the ME/CFS research landscape and help play a vital part in changing the understanding of ME/CFS far into the future.

When the time is right for you – and you have made provisions for those closest to you – leaving a gift in your Will to us will ensure that your hopes and wishes will live on through ME Research UK.

Every gift in every Will makes a difference to us, whatever its size. You can simply make your bequest to ME Research UK or choose to specify that your gift be used for research specifically. Gifts with no restrictions help us invest in our work where we know the need is the greatest, whereas a bequest specified for research will only be used to fund biomedical research.

Our website has information on how to leave a gift to us in your Will, and can also help with wording.

Through *Breakthrough* magazine we reach out to supporters to mobilise their contacts to assist us. There are many companies and individuals who can help make research happen but do not know about the work we do or how to help. This can range from ME Research UK being nominated and chosen as a company's featured charity, matched sponsorship for employee fundraising activities, or even being a Pledger in the 2020 Christmas Big Give.

The Big Give runs the UK's biggest match-funding campaign, the Christmas Challenge, and offers supporters of participating charities the opportunity to have their donation doubled or even quadrupled. You can read more about The Big Give on page 7 of this issue.

Of course, many supporters wish to make regular donations every month. If you give to us regularly we can plan future projects and work of the charity knowing that we have a secure base. We never agree to fund research until we have the money available, and so having a regular income lets us invest more in our work. You can make a regular donation via the form on the inside back cover of *Breakthrough* or on our website.

Dr Louise Crozier

Meet our new colleague

I am delighted to join ME Research UK as Science and Engagement Director, and excited to take on the challenge of identifying key areas of research that deserve more funding.

My background is in molecular microbiology, where I worked on significant issues facing the world today, such as food waste, foodborne disease and preventing exposure to pathogenic microbes. My PhD was on food poisoning bacteria such as *E. coli* and *Salmonella*, and I studied gene expression changes in these bacteria, and helped identify key changes in metabolism that help them survive on food products and cause disease.

I then worked in industry for several years, helping to trial a new technology for reducing microbes in different environments. During that time, I developed the science programme for the company, and regularly gave presentations communicating complex science for many different audiences. In my spare time, I volunteer as a STEM Ambassador, helping to inspire young people to pursue a career in science.

I am looking forward to getting involved in the world of ME research, engaging with researchers worldwide and helping communicate key findings in the science, as well as promoting the importance of research into ME.

Dr Eleanor Roberts

Our newest Trustee

We were very pleased to welcome Eleanor to the Board of ME Research UK as a Trustee earlier this year.

Eleanor has a strong background in biomedical research, including a PhD in HIV neuropathology, and has built a successful career as a science writer. As someone living with ME, she also brings that insight and understanding of the illness which, when combined with her significant research experience and expertise, further strengthens our scientific capability.

Within days of becoming a Trustee, Eleanor attended the CMRC conference on our behalf, and her knowledge and perspective have already proved invaluable.

Postcards from Nevada

In the first in a series of articles, journalist **Cort Johnson** gives us an overview of exercise research in ME over the last two decades

Twenty years ago, ME Research UK was formed to do one thing – fund biomedical research into ME. At that time, things were not looking good for ME research around the world.

In the USA, Brian Mahy at the CDC had just been removed from his post for spending over half of the $23 million that Congress had specifically allocated for ME on other things – and then lying to Congress about it.

Early controversies

Exercise, then as now, was a big topic, and a major point of controversy. While a few researchers were sure that strenuous exercise was causing ME patients harm, others believed that more exercise not less was the answer.

A Dutch exercise study reported that people with ME were as fit, if not fitter, than healthy control subjects. Peter White's exercise study found that people with ME/CFS were weaker than both depressed patients and healthy control subjects, but concluded that physical deconditioning was helping "to maintain physical disability". White's editorial, "The role of physical inactivity in chronic fatigue syndrome", proposed that bed rest was producing many of the symptoms in ME.

This interpretation of ME/CFS largely held sway with UK funders. Not long afterwards, White would receive funding for the biggest and most expensive study ever done in ME/CFS, to


Cort Johnson

assess the effects of graded exercise therapy and cognitive behavioural therapy – the PACE trial.

Where are we now?

Twenty years later, while we are still far from a consensus regarding ME's origins, we've made real progress understanding exercise's effects on the body. We can now show that short but intense periods of exercise can have dramatic effects on ME/CFS patients' physiology – effects that may be unique to the disease.

No series of studies better highlight how unusual ME is than the two-day exercise studies carried out by Workwell Foundation researchers.

Two-day exercise studies are rarely done in medicine for the simple reason that they've been spectacularly unilluminating. People with heart failure, kidney disease or other serious diseases can jump on a bike, exercise to exhaustion, and then reproduce their energy levels during a second exercise test the next day.

The one exception to that rule thus far has been ME. Something happens during that first exercise bout that damages ME patients' ability to produce energy the next day. Instead of getting stronger, as some healthy people do, or at least maintaining their own, as people with heart disease do, they get weaker.

The deeper exercise physiologists have looked, the more they've found. Early studies focused mostly on the ability to generate maximal amounts of energy, but later studies suggest that just about everything that can go wrong during a maximal exercise test does in some patients. Many people with ME are producing too much lactate; some are not moving enough air in and out of their lungs; many can't get their heart rates high enough; and most don't appear to be utilising oxygen well.

New technologies

Our understanding of what exercise does to ME exploded when Harvard pulmonologist David Systrom entered the field. Systrom brought two much needed ingredients to the ME/CFS field: a stellar reputation and improved technology. Systrom's invasive exercise studies found reduced delivery of blood to the heart (preload) and widespread evidence of poor oxygen extraction.

Systrom concluded that the poor oxygen extraction was likely caused by three things: a mitochondrial defect in the muscles, problems with the microcirculation, and/or physiologically triggered hyperventilation. But his contribution didn't end there. Systrom's introduction of an old drug, Mestinon (pyridostigmine bromide), to the ME/CFS field has, in some cases, produced dramatic results (in fact, the Open Medicine Foundation is currently funding a Mestinon trial).

"it's clear how much richer and deeper this field is than it was before"

Systrom isn't the only scientist to find possible oxygen extraction problems. Dikoma Shungu's finding of increased lactate levels in the ventricles of ME patients' brains suggested problems with oxygen consumption exist there as well. And Jarred Younger used new technology to find widespread brain regions with increased lactate – again possibly indicating oxygen problems.

Julia Newton may have put it

all together when she linked the stagnant hypoxia she found in the brains of ME patients to the hyperventilation and acidic blood caused by the muscles.

As findings from exercise studies potentially merge with findings from brain studies, it's clear how much richer and deeper this field is than it was before. Instead of one-off exercise studies that often revealed little, researchers are using two-day exercise studies to demonstrate biologically that post-exertional malaise exists. And invasive cardiopulmonary exercise studies are producing new insights into the metabolic and pulmonary issues in ME.

New hypotheses

New insights into exercise have coincided with a bevy of new and interesting hypotheses. Damaged small nerve fibres may be preventing blood from reaching the tissues; narrowed blood vessels may be triggering an explosion of fatigue and pain producing vasodilators; inborn errors of metabolism may be knocking some patients' energy-producing engines off loop.

Plus, we have a new, surprising and potentially groundbreaking ally. The $170 million, 2,600-person National Institutes of Health MoTrPAC study that aims to get at the molecular roots of exercise will provide insights we can hardly imagine now – insights ME researchers will surely be able to use to help us get at the core of this perhaps uniquely exertion-intolerant disease.

Twenty years ago, Peter White had a receptive audience as he parlayed his study results into a huge CBT/GET trial designed to fix the deconditioning he was sure played a significant role in ME. In 2018, Dutch researcher Frans Visser proved him wrong. Visser's stroke of genius was to show that everyone with ME/CFS – whether they were bedridden or not, or deconditioned or not – had diminished stroke volumes and a reduced cardiac index on a tilt table test.

Recently, Visser did it again, this time with a two-day exercise study, when he demonstrated that, no matter how severe their disease, people with ME have diminished exercise capacity. It's simply part – perhaps the essential part – of this disease.

Progress

Science has marched on – and done its job. Spurious hypotheses have been weeded out and richer ones have taken their place. Given the pace of progress and the dogged commitment of researchers, it seems likely that we will learn more about what's causing the exertion problems of ME in the next five years than we have in the past twenty.

Twenty years after the charity began, ME Research UK maintains the same kind of commitment in supporting the work of a growing number of scientists around the world – work it is confident will change how ME is viewed and treated.

You can read more from Cort on his website: healthrising.org.

Life lessons

New study investigating the experience of **living with severe ME/CFS**


Victoria Strassheim

Around a quarter of people with ME/CFS can be categorised as having severe or very severe illness, and may need a wheelchair to get around, or be house- or even bed-bound.

The infographic on the opposite page illustrates some of the issues these people have to deal with in their daily lives. In addition, three of the videos from Dialogues for a Neglected Illness (meres.uk/dialogues) cover this topic and are well worth watching.

However, despite the considerable impact of their illness on these individuals' health and wellbeing, their poor quality of life, and the restrictions on their day-to-day activities, very little research has been done on severe and very severe ME/CFS.

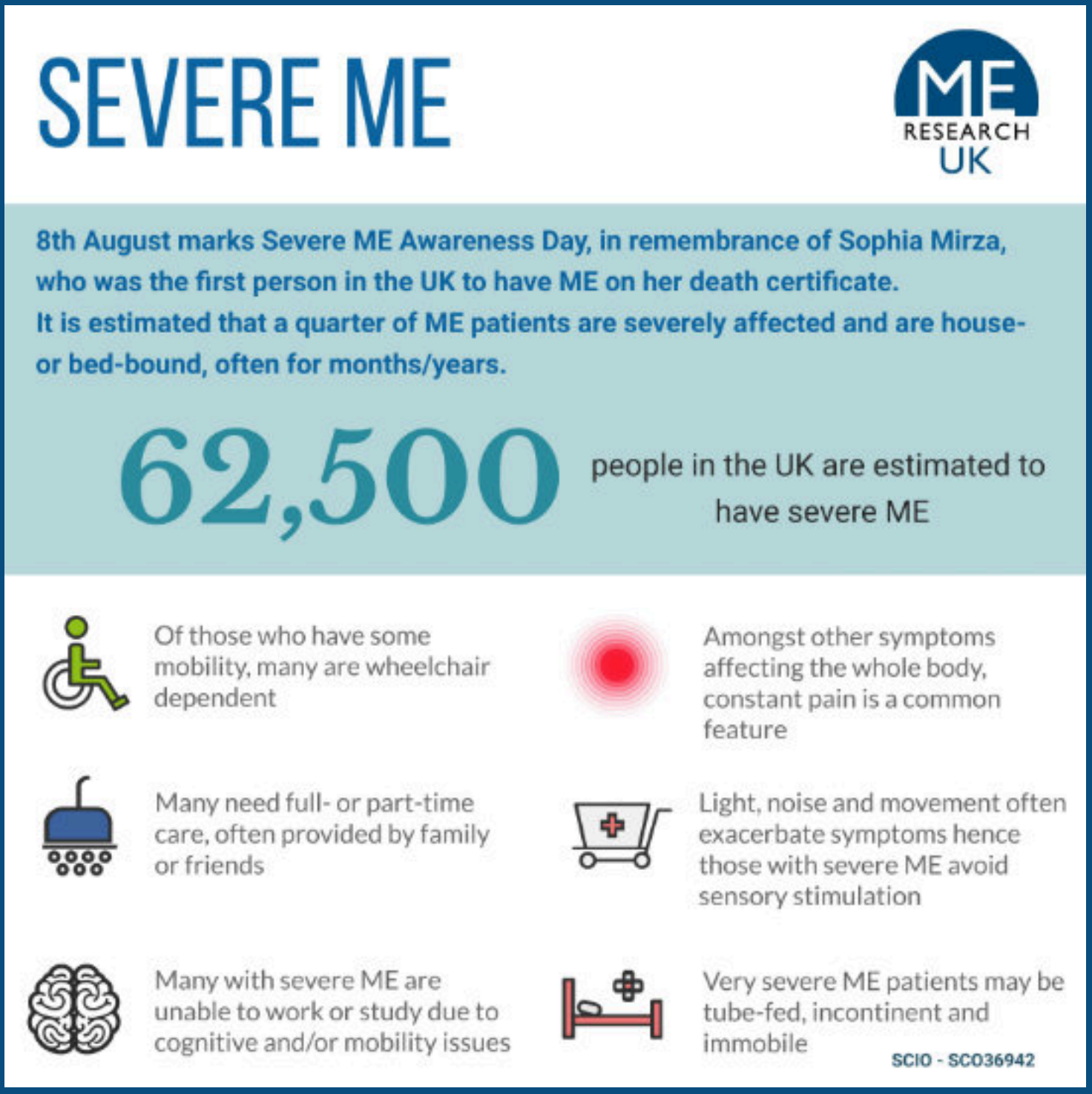
This is largely because the health burdens on these people makes it very difficult for them to engage with research. They are often not able to attend for hospital visits, and the research procedures may be impossible to carry out, or else have a detrimental impact on their symptoms for days afterwards.

The plight of patients with severe ME/CFS has been the subject of a series of studies funded by ME Research UK over the last few years, and carried out by Victoria Strassheim, Prof. Julia Newton and colleagues at Newcastle University.

This work has included a review of existing research on severe ME, an exploration of the effects of deconditioning in these patients and, most recently, an exploration of how to include severely affected ME/CFS patients in research.

This last phase included questionnaire packs sent out to patients with severe ME/CFS within the Northern England Clinical Network, and home visits to five individuals, who underwent a number of assessments and took part in a recorded, semi-structured interview.

Victoria and colleagues now plan to analyse these recordings in more detail, to identify patterns in the participants' responses. So ME Research UK



has provided funds to allow them to do just that, with financial support from the Sophie Miles Bequest and ME North East. The analysis has three goals:

- To explore the personal experience of individuals with severe ME/CFS.
- To find themes that may help identify factors placing people at greater risk of experiencing severe and very severe ME/CFS.
- To provide a better understanding of this population to enable the research and practice community to engage with them more effectively.

This last goal is particularly important. While ME/CFS is already under-researched compared with other chronic conditions, these most severely ill patients are under-represented in what little research is done.

Hopefully, the insights gained in this study will help us understand better how to involve this important group of people in the research process.

Research bites

Our round-up of recent research from around the world

Intra-brainstem connectivity

Barnden et al., NeuroImage: Clinical, 2019

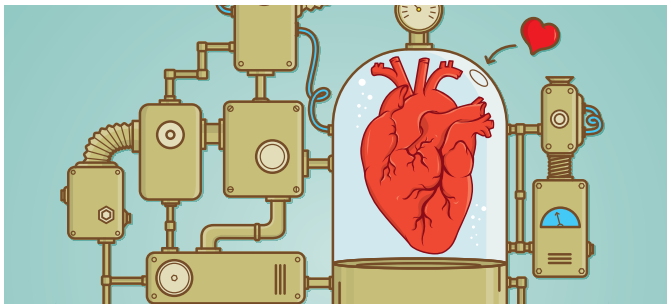
Functional connectivity describes the links that exist between different regions of the brain, and which allow information to be processed. Activity occurring in two regions of the brain at the same time suggests a connection between those regions – either a direct pathway or an indirect cause-and-effect. Last year, researchers in Melbourne, Australia published results from their ME Research UK-funded study looking at functional connectivity in adolescents with ME/CFS. Another Australian group has also recently investigated this area, assessing connectivity in various regions of the brainstem in people with ME/CFS, at rest and while performing tests of attention and concentration.

Deficits in intra-brainstem connectivity were found in the ME/CFS group, but only while performing cognitive tests. Specifically, connectivity was reduced between the medulla (autonomic function) and midbrain (motor function, and auditory and visual processing) within the brainstem, and between the brainstem and other parts of the brain. The authors conclude that deficits in brainstem connectivity may help explain some of the autonomic changes in ME/CFS, as well as impairments in attention, memory, cognitive function and other symptoms. There is a long history of reports of brainstem abnormalities in ME/CFS, so it is good to see research continuing in this area.

Natural born killers

Eaton-Fitch et al., Systematic Reviews, 2019

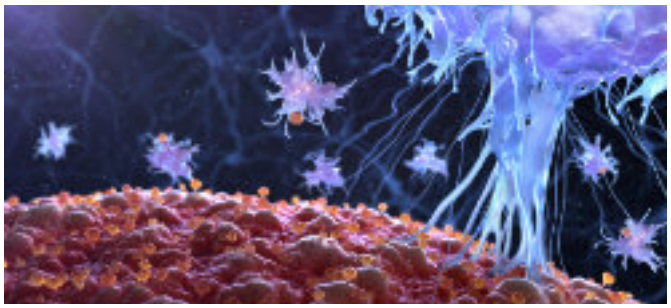
Despite their dramatic name, natural killer (NK) cells are actually an important part of our immune system and help protect us from viruses by killing cells that have been infected. A systematic review of seventeen studies confirmed that NK cytotoxicity (their ability to destroy other cells) is consistently compromised in some ME/CFS patients, compared with control subjects. This suggests they may be less able to fight off infections, but also that NK cytotoxicity may represent a biomarker that could help define a subgroup of ME/CFS patients.



Heart regulation

Nelson et al., Medicine, 2019

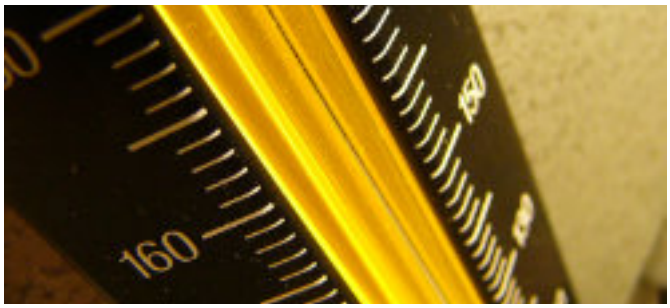
Another recent systematic review has provided "evidence of altered cardiac autonomic regulation in ME/CFS". Cardiac autonomic regulation refers to the body's system that controls the functions of the heart, such as heart rate. Combining the results of multiple studies, various measures of heart rate under different conditions (e.g. at rest and during exercise) were abnormal in ME/CFS patients compared with controls, confirming the altered autonomic cardiac function that has also been reported in previous studies funded by ME Research UK.



T-cell metabolism

Mandarano et al., J Clinical Invest, 2020

Helper and killer T-cells are white blood cells involved in the immune response to infection. Helper T-cells assist other immune cells, while killer T-cells destroy infected cells and tumours. A recently published study has found that there are abnormalities in the metabolism pathways of these types of T cells in patients with ME/CFS. Specifically, glycolysis was reduced in both types of cell while at rest, and also in killer T-cells when activated. These alterations in metabolism are consistent with other findings suggesting that immune function is dysfunctional in ME/CFS patients.



A cause of blood pressure problems?

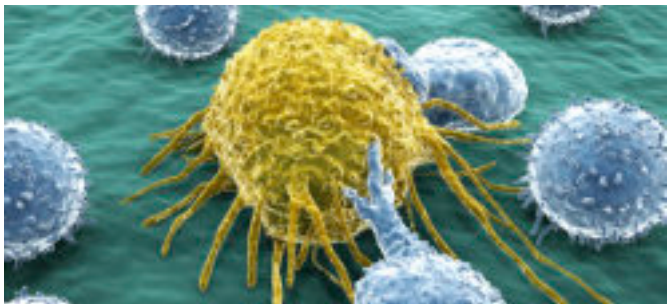
Germain et al., Metabolites, 2020

Plasma is the fluid component of blood which contains many important substances. Researchers from Cornell University analysed plasma from 52 women, equally split between ME/CFS patients and control subjects, and found that a group of compounds linked to blood pressure, called acyl cholines, were decreased in the patients. The authors suggest that a decrease in these acyl cholines – and downstream pathways – could help explain some common ME/CFS symptoms associated with the regulation of blood pressure, such as dizziness, blurred vision and fainting.

Factors in the blood

ME/CFS Research Review, 2019, bit.ly/2UbydyI

The central hypothesis of Stanford researcher, Dr Ron Davis, is that some factor in the blood plasma of ME/CFS patients is driving their illness. In previous experiments, the electrical impedance of a sample of white cells in plasma from ME/CFS patients increased when stimulated with salt, while there were no electrical changes in samples from healthy volunteers. But these changes in impedance disappeared when the ME/CFS cells were placed in plasma from healthy people, suggesting that something in the ME/CFS plasma is making the cells act abnormally. The dramatic difference between ME/CFS and healthy plasma suggests this test might be useful as a biomarker, but the results may also lead to discoveries about the pathology of the illness. Dr Davis has seen that red-blood-cell deformability is reduced in samples from ME/CFS patients, but only when the cells are tested in patients' own plasma, and he has also found that the rise in impedance in ME/CFS white cells seen in the salt tests can be prevented by adding the mitochondrial antioxidant SS-31 or the multiple sclerosis drug copaxone. Ongoing experiments are looking at whether the offending factor is some form of virus, bacteria, fungus or parasite.



Promising new biomarkers

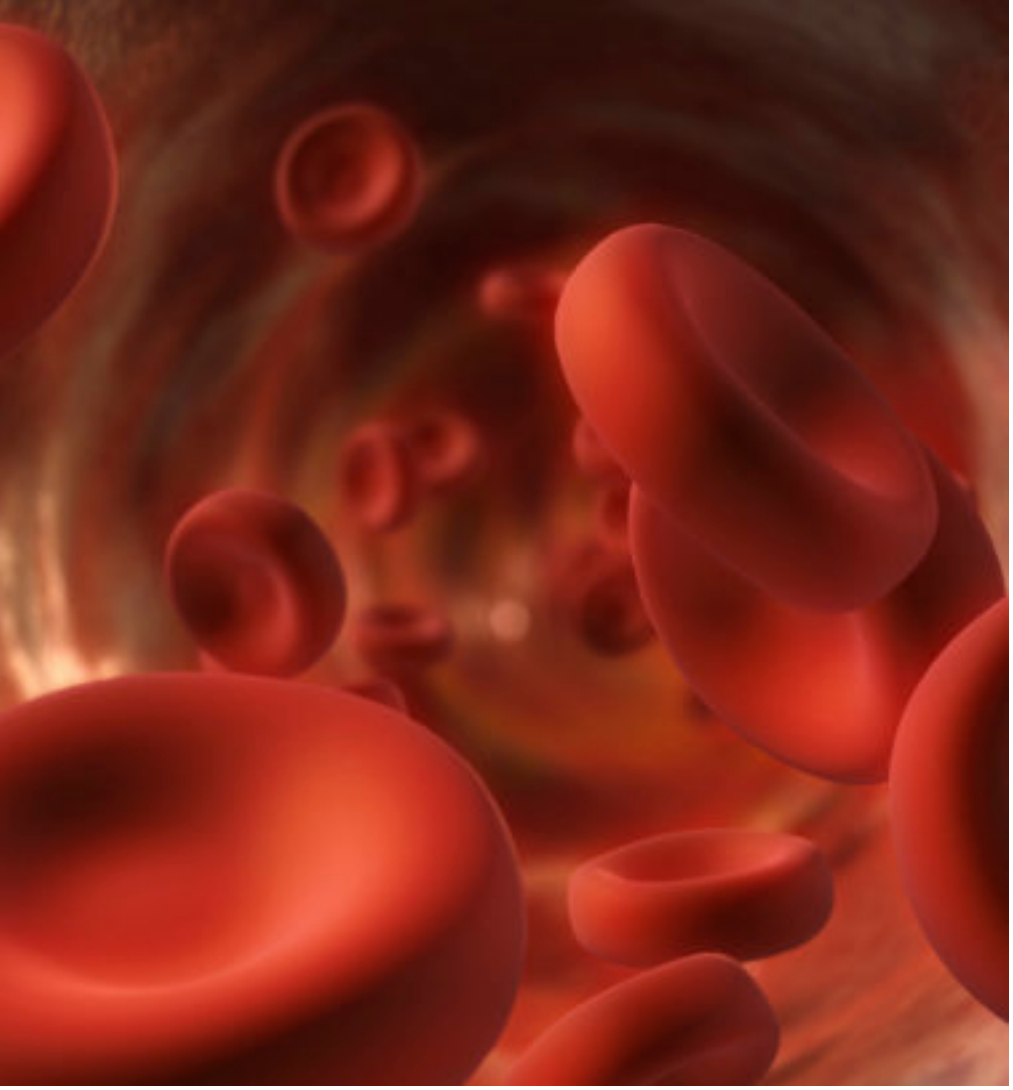
Missailidis et al., Int J of Molecular Sci, 2020

Scientists from Melbourne previously reported that white blood cells (lymphocytes) extracted from ME/CFS patients died faster than normal after having been frozen. They also found abnormalities in mitochondrial respiratory function and a protein called TORC1. The authors now suggest a two-step protocol using these tests as a biomarker: a blood test for lymphocyte death rate 48 hours after freezing, followed by confirmatory tests of TORC1 and respiratory function, if needed. Together, these tests showed promise in distinguishing cells from ME/CFS patients and healthy controls.

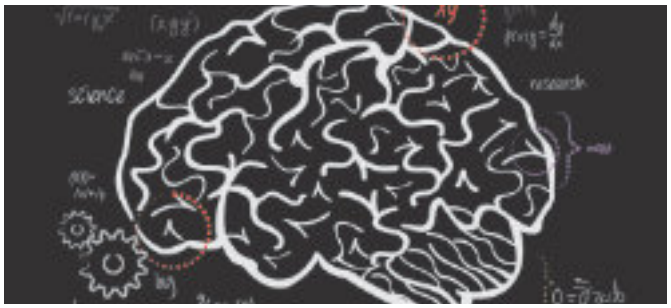
POTS and autoimmunity

Gunningill et al., JAHA, 2019

Many people with ME/CFS have postural orthostatic tachycardia syndrome (POTS), which is characterised by large changes in heart rate on standing, leading to a number of symptoms. New research suggests that POTS is an autoimmune disorder – that is, it stems from the body being mistakenly attacked by its own immune system. Among 55 patients with POTS, the majority had raised levels of autoantibodies targeted on autonomic receptors. This suggests that existing medications targeting the immune system could therefore be an effective treatment for some patients.



"Some factor in the blood plasma of patients [may be] driving their illness"



Brain blood flow

Van Campen et al., Clin Neurophys Pract, 2019

The head-tilt test is used to measure changes in heart rate and blood pressure while patients are gradually tilted into an upright position. By combining this approach with Doppler imaging to measure blood flow to the brain, researchers from the Netherlands found that most ME/CFS patients they studied (including those without blood pressure problems such as POTS or delayed orthostatic hypertension) had reduced cerebral blood flow during this test. These results suggest that the protocol may be an option for use as a tool in the diagnosis of ME/CFS.

Endothelial dysfunction

Scherbakov et al., ESC Heart Failure, 2020

The endothelium – the inner lining of the blood vessels – has been the focus of some of the research we have supported over the years. Endothelial dysfunction is a serious cardiovascular risk factor, but is also common in many autoimmune diseases. In a recent study, researchers from Berlin found that ME/CFS patients with endothelial dysfunction also had higher disease severity, with severe immune symptoms recorded. The authors suggest that endothelial dysfunction may be a marker to assess the potential risk of cardiovascular issues in ME/CFS patients in future clinical trials.

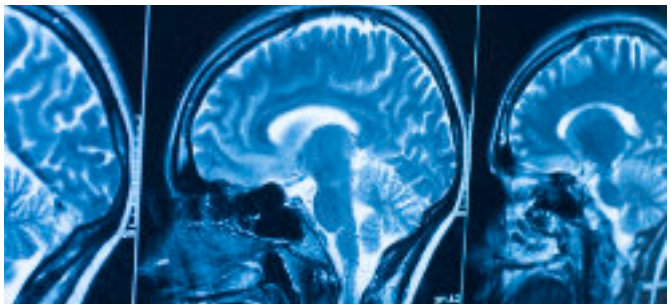
Predicting the severity of PEM

Ghali et al., J Transl Med, 2020

Post-exertional malaise (PEM) – the worsening of symptoms after even minor physical or mental exertion – is one of the hallmark symptoms of ME/CFS. The severity of PEM, and how long it takes to recover, can vary between individuals, and researchers in France recently looked for factors associated with more severe PEM, and which might help to identify patients who would benefit from pacing strategies.

Information – including age and symptoms – was collected from 197 patients with ME/CFS, and the participants' current fatigue levels were assessed using validated questionnaires. A PEM severity score was then calculated based on their experiences over the preceding month. From this analysis, three factors were found to be associated with increased PEM severity. High PEM severity scores were more likely in individuals aged 32 years or older at the onset of ME/CFS, and also more likely in those who reported being susceptible to viral infections over the course of their illness. Suffering from a gastrointestinal infection prior to the onset of ME/CFS was also identified as a risk factor for worse PEM, although this association was less clear.

As there are not yet any treatments for ME/CFS, many patients have to employ pacing techniques to try and manage their symptoms. The researchers hope that these risk factors will help to identify patients at a higher risk of severe PEM, who may therefore particularly benefit from following pacing strategies.



Neurological review

Maksoud et al., PloS ONE, 2020

In this review of 55 neurological studies looking at abnormalities in brain structure and function in ME/CFS, common findings included decreased brain white matter, disrupted autonomic nervous system and impaired cognitive processing. However, most of the studies used the less stringent Fukuda criteria for an ME/CFS diagnosis, leaving the possibility of an overlap with other diseases. This highlights the need for a more rigorous and consistent definition to be used in research to allow effective comparison between studies.

The plasma proteome

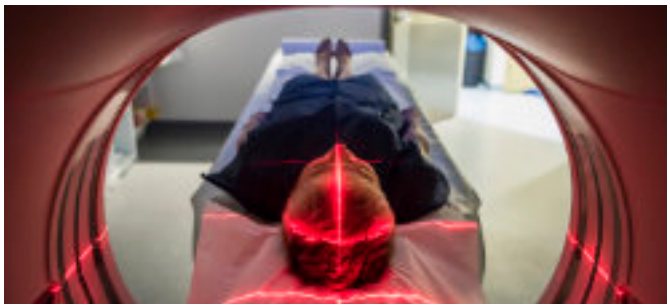
Milivojevic et al., PloS ONE, 2020

Plasma is the fluid component of the blood, containing a wide range of proteins collectively known as the plasma proteome. Researchers recently compared the plasma proteome of ME/CFS patients and healthy control subjects and found some marked differences. In particular, patients had altered levels of immune cells called B cells. Based on these findings, the authors could categorise if an individual had ME/CFS. This could provide a possible biomarker for the disease, although much work is still required to transfer this to the clinic.

What's in a name?

Johnson et al., Death Studies, 2020

Many patients with ME/CFS are unhappy with the label "chronic fatigue syndrome" as they feel it concentrates on only one of their many symptoms, and groups together people with a variety of illnesses. A small survey conducted in the USA suggests that the stigma associated with the label "CFS" may have other consequences. The researchers found that, among people with ME/CFS who had passed away, those who identified as CFS – rather than ME, ME/CFS or CFIDS – were more likely to have died by suicide. Other risk factors were also identified, including being housebound.



Brain activity after exercise

Washington et al., Brain Communications, 2020

As discussed on the opposite page, one of the key symptoms of ME is post-exertional malaise, a feature which is also seen in people with Gulf War Illness. A recent study measured brain activity before and after exercise over the course of two days in patients with Gulf War Illness, those with ME/CFS and a group of healthy control subjects. Significant differences in activity were seen between all three groups after exercise, with three specific regions of the brain activated in only the ME/CFS patients. The authors hope this could lead to a diagnostic tool to distinguish between the conditions.

Friends united

Recent fundraising activities by our supporters. To support ME Research UK and raise funds for ME research, please visit our website for ideas.

Coastal run

While the rest of us resolved to stop smoking, read more or finally get round to painting the garage this year, Tabitha Angle-Smith had grander plans for 2020. Inspired by a friend who was a runner before getting ME, Tabitha challenged herself to make the epic 1,400-km run round the Wales Coast Path, all in aid of ME Research UK. She has already completed the first stage, 126 km from Chester to Bangor, which she ran over three days in January, and had begun the 215-km leg from Bangor to Anglesey before injury meant she had to postpone. You can contribute to this fundraiser by searching for 'Tabitha Angle-Smith' on JustGiving.com. Diolch yn faw, and lwc dda, Tabitha!

Sponsored sew

Alison Whale, who developed ME over 30 years ago, could never have envisaged how successful her sponsored sew would be or the amount she would raise for ME research. Launched during ME Awareness month and in the midst of lockdown, Alison asked people to sponsor her to make as many face masks as she could for however long she could manage, or to donate to ME Research UK in exchange for handmade face masks. The result: beautiful masks and an amazing total for us to invest in further research. Many thanks, Alison. You can still sponsor her via Justgiving: bit.ly/3g1L5QU.

01

02

03

01 Tabitha Angle-Smith well on her way around Wales

02 Some of **Alison Whale**'s more psychedelic mask designs

03 Ava takes the scissors to **Sarah Robinson**'s hair

Welsh duathlon

Continuing our accidental theme, Wales was the location for Mair and Owen Squire's fundraising efforts this March, as they cycled and ran in the Wildflower Duathlon at The National Botanic Gardens of Wales. The duo had also planned to compete in the Mumbles Duathlon, but, regrettably, like many other sporting events this year, the race had to be postponed until a later date. Mair and Owen were competing in aid of ME Research UK, and in support of their friend's fifteen-year-old son who is affected by ME. "At a time when he would be exploring and finding his passions and interests, this high achieving chap struggles to function and is virtually housebound." Many thanks to Mair and Owen and all who supported them in their amazing feat. Thanks also to Melissa Davies whose Cake and Coffee fundraiser at the Tree House, Aberystwyth helped swell the coffers.

Lockdown locks

It had been three years since Sarah Robinson's last haircut, so to raise funds she agreed to let a neighbour – 7-year-old Ava – cut her hair. Four charities benefited, including ME Research UK, and Sarah's locks did not go to waste either, as they were given to Little Princess Trust to make a wig for a child with cancer. Many thanks to Sarah and to her employer, Lane Clark and Peacock LLP, whose Foundation matched-funded many donations.

Priest of Love

Screening of classic British film **in memory of Sophie Miles**

Towards the end of 2019, our CEO, Simon Phillips, attended a special screening of the 1981 film *Priest of Love* at the Rex Cinema in Wareham, Dorset as part of the Purbeck Film Festival. The screening was arranged by the film's director, Prof. Christopher Miles, and his wife Suzy, in memory of their daughter Sophie. Due to her symptoms and health issues, Christopher and Suzy chose ME Research UK as the charity they wished to support.

Priest of Love concentrates on the latter part of the life of novelist D H Lawrence, and the cast includes many familiar actors such as Sir Ian McKellen (in his first film role), Dame Janet Suzman, Sir John Gielguid, Dame Penelope Keith and Ava Gardner. It was directed and produced by Christopher, and filming took place at many of the actual locations where Lawrence had lived, worked and visited.

As part of an enjoyable evening, Simon gave a talk about ME and our work, and this was followed by an extremely entertaining and informative Q&A with Christopher, Dame Janet and Andrea Etherington.

Our CEO, Simon, with **Christopher Miles** before the screening

Sophie's story is sadly all too familiar, as she struggled to get a diagnosis from her GP and was advised that her condition was psychological and given medication. Sophie eventually worked out her own way of managing her symptoms, and was able to live a more active life until she was diagnosed with cancer in 2018. Sadly, Sophie passed away later that year.

We are very grateful to the Miles family, Dame Janet and all those who attended the event. The Sophie Miles Bequest will be used to support ongoing research into ME/CFS.

Christopher, **Sophie** and **Suzy Miles** at the London premiere of *Priest of Love*

Q&A with **Dame Janet Suzman**, **Andrea Etherington** (Purbeck Film Festival) and **Christopher Miles**

Standing Order Form

To support our work, 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**

☐ Please tick this box to indicate you are happy for us to collect and store your personal information, in accordance with our Privacy Policy at meresearch.org.uk.

Name of account holder(s)

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

Address and postcode

Debit amount (£)

Payment date each month

Telephone number

Date of first payment

Name of Bank or Building Society

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

Branch address and postcode

☐ **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