

# UK CFS/M.E. Research Collaborative

Report of the fifth Annual Science Conference  
19 and 20 September 2019, Bristol



Pictures on the cover, from top left:

- Dr Luis Nacul and Professor Alain Moreau
- Sonya Chowdhury, chief Executive of Action for M.E., Prof Chris Ponting, Deputy Chair of the CMRC and David Tuller
- Prof Stephen Holgate, Chair of the CMRC
- Delegates on day one of the conference

This report was written thanks to contributions from Action for M.E., ME Association, Charlotte Stevens, Emily Beardall and Katrina Pears.

## Foreword

The aim of the CFS/M.E. Research Collaborative (CMRC) is to promote the discovery of the biological mechanisms that underpin M.E./CFS, which will drive the development of targeted new treatments for this highly underserved patient population.

There was a high turnout of researchers, health professionals, students and people with M.E./CFS at the fifth annual CMRC conference, which was held in Bristol on 19 - 20 September. It was organised by Action for M.E., who were also on hand during the day to assist and film the speakers.

The feedback from delegates at the conference stated that there was a much greater sense of focus and direction. There seemed to be a tacit agreement among researchers that there exist multiple subgroups within the M.E./CFS cohort, each with different pathologies, and a need for them to be identified and separated – in order to create more targeted diagnosis and treatments.

There was a wonderful metaphor used, referring to the subgroups as “different types of elephants” – M.E./CFS being the elephant in the room – and that what works for one group will not necessarily work for another.

Another point that all speakers seemed to agree on is the lack of funding available for M.E./CFS research. This situation has not enabled the large studies that are required to create reproducible results and make real progress in the field. However, Professor Moreau commented, things are looking more positive, with the National Institutes of Health (NIH) in America recently seen to be setting the standard.

## Contents

Foreword .....	3
Welcome and Introduction – Prof Stephen Holgate, University of Southampton, CMRC Chair .....	6
The views of a Doctor with M.E. on educating medical students about M.E./CFS - Dr Nina Muirhead, Buckinghamshire Healthcare NHS Trust .....	7
Identification of post-exertional dysregulated circulating microRNAs in M.E./CFS pathogenesis - Prof Alain Moreau, University of Montreal .....	8
European collaboration in M.E./CFS: The EUROMENE network - Dr Eliana Lacerda, London School of Hygiene & Tropical Medicine; CureME .....	9
What will it take for the pharmaceutical industry to engage in M.E./CFS drug discovery? - Dr Mark Jones, UCB Pharma .....	10
The economic impact of CFS/M.E. - Dr Rachel Hunter, University College London.....	11
M.E./CFS, IBS and Fibromyalgia: Chance association or common pathway? - Rachel French, Colorectal Registrar, County Durham & Darlington NHS Foundation Trust.....	12
Twins-UK and the study of chronic pain genetics - Prof Frances Williams, Kings College London.....	13
The UK M.E./CFS Biobank: Accelerating global research in M.E./CFS - Dr Luis Nacul, London School of Hygiene & Tropical Medicine; CureME .....	14
Investigating the possibility of a role of mtDNA variation in M.E./CFS - Jo Elson (Newcastle University).....	15
Alterations of cellular metabolism observed in muscle cells, indicating possible factors present in plasma of patients with M.E./CFS capable of modifying cell function – Dr Tiffany Lodge, University of Oxford .....	16
Effects of whole-body cryotherapy among CFS patients- preliminary results - Pawel Zalewski (Nicolaus Copernicus University, Poland).....	17

MRC-funded update: Imaging exercise-induced Post-Exertional Malaise in M.E./CFS - Dr Neil Harrison, University of Sussex .....	18
Anne Faulkner Memorial Lecture: Big data and open science: a powerful combination to generate new understanding of disease - Prof Cathie Sudlow, Chief Scientist, UK Biobank, University of Edinburgh.....	19
Differential microRNA profiles in PBMC's and plasma EVs of severely affected M.E./CFS - Dr Elisa Oltra, Universidad Católica de Valencia, Spain.....	20
MRC-funded update: Persistent fatigue induced by interferon-alpha: a novel, inflammation-based, proxy model of chronic fatigue syndrome - Prof Carmine Pariante, Kings College London.....	21
Working together versus the pain, isolation and fatigue of arthritis - Stephen Simpson, Director of Research, Versus Arthritis .....	22
Cellular immune function in M.E./CFS - Jackie Cliff, London School of Hygiene and Tropical Medicine .....	23
Is inflammation the link between the body and the brain? - Prof Carmine Pariante, Kings College London .....	24
Cellular bioenergetics in M.E./CFS - Dr Cara Tomas, Newcastle University .....	25
Delegate Feedback .....	26

## Welcome and Introduction – Prof Stephen Holgate, University of Southampton, CMRC Chair

Professor Holgate is the chair of the CMRC and is Medical Research Council Clinical Physician within Medicine at the University of Southampton.

He started by expressing the need for a single international voice, emphasising that collaboration is key. He also commented on the valuable contributions of the Patient Advisory Group.

This being the fifth annual conference, Prof Holgate reflected on what the CMRC has achieved so far, and highlighted where efforts need to be concentrated going forward, including what needs to be done politically and scientifically, with a focus on evidence for causative factors.

He talked about a new initiative with the James LIND Alliance, in which patients and clinicians get together and help determine research priorities for a given illness, which are then published. Working with this group is now a priority for the CMRC.

Professor Holgate commented that biological research is moving forwards at a tremendous rate and that real progress is being made. It's good news, he said, that other organisations are taking an interest in 'chronic fatigue' as a potentially common symptom (such as Arthritis UK and The Kennedy Trust), which is important in moving the agenda forward nationally.

He reported that the National Institutes of Health (NIH) is making significant progress in America and that they have now funded four M.E./CFS research centres. The CMRC is currently trying to link with them in the UK to form an international alliance and to collaborate and share data.

Prof Holgate ended his speech by saying that it had been a slow start for the CMRC, and it has taken a long time to get to where they are today. But the pace of progress is certainly picking up and the CMRC is now in a position to apply pressure on UK funding bodies for high-quality research to “uncover the mysteries of this devastating disease.”

You can watch the presentation here: <https://www.youtube.com/watch?v=AK5UONg0diM&t=346s>



## The views of a Doctor with M.E. on educating medical students about M.E./CFS - Dr Nina Muirhead, Buckinghamshire Healthcare NHS Trust

Dr Muirhead shared her personal M.E./CFS story and used her insight as a doctor and academic to discuss ways of educating medical students, doctors and other health professionals about the illness. She specialises in dermatology in oncology surgery but also has a Masters in Education, has written medical textbooks and is a tutor at Cardiff University.

Dr Muirhead's M.E./CFS began two years ago and she gave details of the numerous diverse symptoms she had. She carried on working and looking after her young children but her symptoms worsened until she had difficulty climbing stairs, walking, and carrying out normal activities of daily living.

She saw 13 different doctors before finally receiving an M.E./CFS diagnosis. Most doctors are not taught about M.E./CFS at medical school and may not even believe in the condition. The current guidelines do not fit with the patient experience, adding to the problem. Doctors are starting to realise they do not know enough though, and a *British Medical Journal* article in July 2018 reported that 90% of cases are thought to go undiagnosed and that people with M.E./CFS are substantially undercounted, underdiagnosed and undertreated. HIV and multiple sclerosis are examples of how knowledge can advance and perceptions can change, resulting in better outcomes for people with illnesses that were previously poorly understood.

The UK Medical Schools Council has given permission for Dr Muirhead to send questionnaires to every medical school to find out whether they cover M.E./CFS, what is taught, what specialism the academics are from (e.g. neurology, immunology, psychiatry) and whether it is included in exams. It also asks whether they would be interested in incorporating centrally provided teaching on the illness into their curriculum, for example lectures, e-learning, interactive tutorials involving patients. Dr Muirhead is piloting these teaching methods for M.E./CFS at Cardiff University for the current academic year with a view to rolling it out across all UK medical schools through the UK Medical Schools Council.

Dr Muirhead would also like to see the creation of post-graduate certificates and diplomas in the biological science of M.E./CFS for health professionals so that patients UK-wide can request to see a "M.E./CFS-qualified" practitioner. A professional body could be established to offer these courses and issue members with regular updates, as the science of the illness is at last moving along quickly now. Dr Muirhead finished by inviting any suggestions for working collaboratively to make these ideas happen.

You can watch the presentation here: <https://www.youtube.com/watch?v=19ehJpZ4g9M&t=769s>



## Identification of post-exertional dysregulated circulating microRNAs in M.E./CFS pathogenesis - Prof Alain Moreau, University of Montreal

Prof Moreau presented a dynamic model of M.E./CFS, stressing that genetic and environmental interactions are important. He said that there is probably some genetic predisposition to the disease which is then triggered by environmental factors such as infections or chemicals.

His hypothesis is that M.E./CFS is caused by a disturbance in the expression of microRNA's, which modulate the immune function, energy metabolism and physiological stress response. The purpose of his study was to identify circulating miRNAs linked to the disease, in order to better understand the cause.

*Note: miRNAs are small molecules that can affect the expression of certain genes and therefore the production of certain proteins. miRNA's can be used as biomarkers for diagnosis and therapeutic drugs can modulate their effects.*

Professor Moreau's team developed a 'stress test' to reproduce post-exertional malaise (PEM) in patients, without the need for exercise. This involved wearing a cuff (similar to a blood pressure cuff) that massaged the arm. They took blood samples from the participants (including mostly bed-bound M.E. patients, and healthy controls) before and after the "stress test" and then analysed the levels of circulating miRNAs in the blood. This stimulation was so gentle that it failed to produce a response (a change in miRNA levels) in healthy controls, but it did in those with M.E./CFS.

They found that in M.E./CFS there was a distinctive molecular footprint (an expression of different levels of miRNAs) at baseline and after stimulation (with the stress test), compared to controls. They also found that the differences in the stress-activated levels of miRNAs (representing PEM) were more specific than the ones at baseline; some levels increased after stimulation and some decreased, compared to controls.

The results were very preliminary and still undergoing analysis and so are not conclusive, but they seem promising and appear to agree with the findings from other studies in this area. Perhaps more interesting than the individual miRNA differences themselves was what Professor Moreau said was the most important finding from this study: that there are subgroups of patients.

Using molecular profiling of the miRNA levels in the M.E./CFS samples, he was able to separate them into four distinct subgroups, shown by differences in the levels of circulating miRNAs that also correlated with symptoms and differences in response to fatigue questionnaires taken from the patients. This means that we cannot "lump" all M.E./CFS patients together in studies as it is going to 'blur' the results; we must first separate them out into their distinct subgroups and then study the causes and potential treatments for each group as what works for one may not work for another. The team are currently carrying out a replication study in the same cohort two years later, to see if the test is robust and if they get the same results. Then they will validate these selected miRNAs in a larger cohort and try to replicate the findings. If validated, these could be used to develop specific diagnostic tests, as well as potential drug targets.

You can watch the presentation here: <https://www.youtube.com/watch?v=eKbVBcxwt88>

## European collaboration in M.E./CFS: The EUROMENE network - Dr Eliana Lacerda, London School of Hygiene & Tropical Medicine; CureME

The aim of EUROMENE network is: “to establish a sustainable network of researchers from diverse fields, to work in M.E./CFS with multidisciplinary approach”, fundamentally to achieve collaboration across Europe. Numerous challenges are faced when studying M.E./CFS which are both contextual and scientific, for example; efforts have previously been concentrated in a few countries, and by only small groups of people.

The proposal of the EUROMENE project is to:

- collect population-based data on M.E./CFS
- establish a synchronised European database
- access potential biomarkers, by harmonising infrastructure efforts
- agree on M.E./CFS case definition(s) for clinical and research purposes
- assess the socio-economic impact of M.E./CFS in Europe.

Through this the EUROMENE networks has set up several working groups, looking at:

- epidemiology
- biomarkers
- socio-economics
- clinical research/ diagnostic criteria
- conference, seminars, training and schools
- dissemination and patient involvement.

The EUROMENE network has submitted its proposal to the European Cooperation in Science and Technology (COST).

Progress is being made, with increased participation across countries (it started with 10, now there are 21) with increased numbers of meetings between working groups. Other progress within the workings groups has included: reporting on existing M.E./CFS biobanks of sample collections in the EU, publishing a protocol for a systematic review on the prevalence of M.E./CFS in Europe, guidelines for infection-associated clinical and biomedical research, and the establishment of two summer schools in Pavia and Berlin.

Despite the progress which is being made, EUROMENE still faces several challenges, such as imbalance of participation among the working groups, lack of involvement of some participating countries, distinct ethical requirements across EU, lack of funding for research and the uncertainty of Brexit.

You can watch the presentation here: <https://www.youtube.com/watch?v=0aTQD-eMfQo>



## What will it take for the pharmaceutical industry to engage in M.E./CFS drug discovery? - Dr Mark Jones, UCB Pharma

Dr Jones came to the field after his daughter fell ill with M.E./CFS.

After delivering a heart-felt story of her illness experience, he showed a video about personalised medicine, which included his daughter.

Dr Jones then went on to highlight the key barriers that are in the way of drug development and delivery.

These include, regulatory bodies, who weigh up the benefits of the drug against the risk of side effects, and the National Institute for Clinical Excellence, who assess the cost-effectiveness of a drug.

Looking at what current drugs we could be using to help alleviate M.E./CFS symptoms and improve quality of life, instead of trying to develop new ones, could also be a valuable approach. The need for patient feedback from advisory groups is also important.

Emphasis for the need to move towards precision medicine (or personalised medicine) was conveyed. This involves looking at particular biomarkers that will allow more precise targeting of drugs, in order to determine who will respond best based on their genes, rather than through the process of trial and error.

He stressed the need to identify the subgroups within M.E./CFS with a clear phenotype in order to identify specific drug targets.

You can watch the presentation here: <https://www.youtube.com/watch?v=VZ421O605j0&t=1381s>



## The economic impact of CFS/M.E. - Dr Rachel Hunter, University College London

Dr Hunter is a health economist and looks at healthcare costs, social care costs, admissions costs and loss of productivity. She uses this data in presentations to the Government to highlight the costs that would be “wiped away” if a treatment was available.

She started by detailing that only six studies have been completed worldwide, compared with 29 for Multiple Sclerosis, and that these studies were very small and of poor quality.

Dr Hunter has collected data from the UK M.E./CFS Biobank (see page 12 for more details on the Biobank) in order to calculate further estimates on costs and the preliminary results are shown in the table below.

Employment and benefits statistics		
	CFS/ME	Healthy Controls
Hours of work/study per week (mean (sd))	16 (16)*	47 (19)*
Occupational status % (n)		
In full-time paid work	12% (30)	60% (78)
In part-time paid work	14% (36)	17% (22)
Self-employed full-time	1% (2)	5% (6)
Self-employed part-time	8% (21)	4% (5)
Looking after home or family full-time	6% (15)	6% (8)
In full-time education	3% (7)	5% (7)
In education less than full-time	1% (2)	1% (1)
Unemployed	1% (3)	1% (1)
Retired	6% (16)	2% (3)
Sick or disabled	48% (123)	0
Unpaid or voluntary work	1% (3)	1 (1%)
Benefits – Yes % (n)	65% (161)	28% (35)

Following this, she stated that the average annual income for someone with M.E./CFS is £10,844 less than a healthy person and has estimated further costs at over £1 billion per year.

Dr Hunter then went on the detail similar findings at an international level, *Brenna and Gitto 2018*, whose findings are in line with the preliminary results analysed by her team.

In conclusion, she found that there is a significant loss to individuals and the economy from loss of earnings due to M.E./CFS. She also stated that health care spending may be hard to judge as reduced access to appropriate treatment may reduce costs.

You can watch the presentation here: <https://www.youtube.com/watch?v=QN1eUCPmFZw>

## M.E./CFS, IBS and Fibromyalgia: Chance association or common pathway? - Rachel French, Colorectal Registrar, County Durham & Darlington NHS Foundation Trust

Miss French, who is a surgeon specialising in gastroenterology, has been looking into the possible link between M.E./CFS, Irritable Bowel Syndrome and Fibromyalgia.

All three conditions are diagnosed based on reported history and symptoms, with no 'formal' diagnostic tests. There is strong anecdotal evidence for a link as they are often diagnosed together.

She carried out a database search and the reported prevalence of each condition shows that they are all co-morbidities of each other and there are many studies on the association between M.E./CFS and Fibromyalgia.

It was also demonstrated that people with M.E./CFS and Fibromyalgia are more likely to have bowel disorders.

Miss French suggested there may be a common pathophysiological pathway for all three of the conditions, either linked by infection, genetics, microbiome or autonomic dysfunction. She is currently carrying out a questionnaire-based data collection to try and determine if these conditions pre-dispose each other.

You can watch the presentation here: <https://www.youtube.com/watch?v=i9c6fnCXE88>

## Twins-UK and the study of chronic pain genetics - Prof Frances Williams, Kings College London

Twins-UK is a biosource that collects data in the form of questionnaires and biological samples (blood, saliva, urine) from volunteer adult twins throughout the UK.

This enables the study of genetics and environmental factors involved in the development and progression of various traits and diseases.

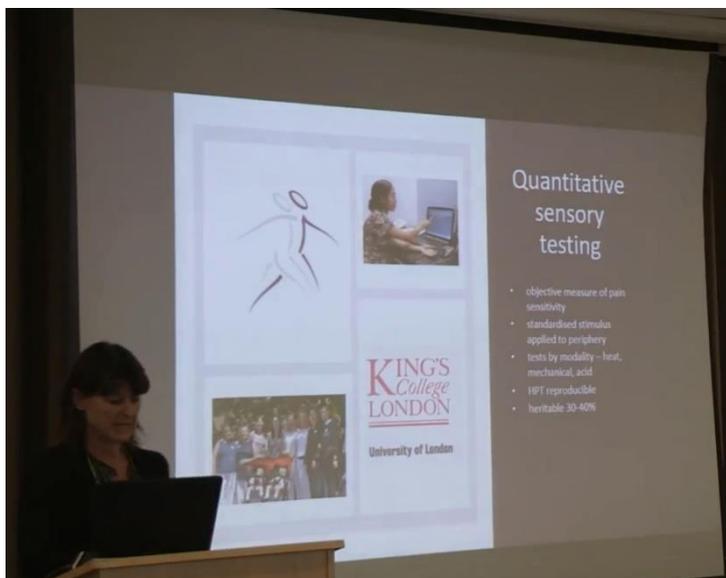
Professor Frances and her team has conducted a study on pain genetics in which twins underwent a pain test using increasing heat, in order to identify variants influencing pain perception.

The results revealed that the more 'insensitive' people to pain had a higher number of rare genetic variants. Also, the risk of experiencing chronic pain increases with increased age and Body Mass Index.

They have also shown that chronic pain syndromes (including irritable bowel syndrome, fibromyalgia and chronic pelvic pain) are heritable conditions and their results suggest that they share an underlying chronic pain genetic disposition which is 68% heritable. Also a form of pain called neuropathic pain is 37% heritable.

Finally, chronic widespread pain and neuropathic pain were shown to have shared genetic factors.

You can watch the presentation here: <https://www.youtube.com/watch?v=407fxoyD-VQ&t=588s>



## The UK M.E./CFS Biobank: Accelerating global research in M.E./CFS - Dr Luis Nacul, London School of Hygiene & Tropical Medicine; CureME

The UK CFS/M.E. biobank is a repository that stores and manages biological samples for use in research, and to facilitate in sharing research. Biobanks provide an excellent resource to use, as they ensure: standardisation and quality assurance, cost and time effectiveness. The biobank can be used to test and formulate hypotheses, understand different disease pathways, investigate different disease subgroups and ultimately for biomarker discovery.



The biobank has now over 600 participants, including confirmed cases of M.E./CFS. Samples are all from people between 18 and 60, covering the different severities of M.E./CFS. The samples stored also contain healthy controls and those with Multiple Sclerosis (MS), and these are matched by age, sex and area of residence. The biobank stores several different blood samples (whole blood, serum, plasma, red blood cells and peripheral blood mononuclear cells) with over 30,000 aliquots stored. Alongside this the biobank holds clinical and questionnaire data for all samples, such as blood pressure, weight, pain and fatigue scales.

The biobank was designed to be comprehensive to cover a wide number of studies and not just for one purpose. Therefore, anyone with a good hypothesis on pathophysiology can apply to use the samples. Using the biobank is a cost-effective approach for M.E./CFS research as the have already been collected and are kept secure using the storage facilities at the Royal Free hospital. The biobank does have a few priority areas for applications, including improving diagnosis. All applications to the biobank are subject to a review process.

The biobank has successfully established a partnership and the sharing of data and samples has started to expand over the world, showing the wider opportunities for collaboration. Setting up the biobank has been a long journey, involving consultation processes with people with M.E. to address any concerns.

The final few slides of Dr Nacul's presentation focused on some examples of data-based research comparing health controls of people with MS and M.E. Generally, results show the lowest scoring for people with M.E. in categories such as: bodily pain, mental health and physical function. Further to this, findings show the strongest symptom predictors of disease severity for MS is neurocognitive; for mild M.E. it is post exertional malaise; and for severe M.E. it is neuroendocrine.

You can watch the presentation here: <https://www.youtube.com/watch?v=5FonUVDyc0I>

## Investigating the possibility of a role of mtDNA variation in M.E./CFS - Jo Elson (Newcastle University)

Ms Elson started investigating the role of mitochondrial DNA (mtDNA) mutations in M.E./CFS after finding that 50% of people with mitochondrial dysfunction reported severe fatigue. However, mitochondrial dysfunction is not found to be higher in the M.E./CFS population.

After completing 270 mtDNA sequences from M.E./CFS patients, her group found no confirmed mutations at a level sufficient to cause a biochemical defect. Therefore, M.E./CFS does not fall into the spectrum of classical inherited mitochondrial disease.

Next, she looked into the possible role of mtDNA variants (or polymorphisms) in the susceptibility to M.E./CFS. She found that the majority of people with M.E./CFS have no deleterious mitochondrial DNA variants.

There was a significant difference between controls and M.E./CFS patients; that more of them have no deleterious variants. This observation has also been replicated, so is not a chance find.

She concluded that classical mitochondrial dysfunction, relating to adenosine triphosphate (ATP) production, is most likely not the problem in people with M.E./CFS.

However, she proposed that there may be a problem with the cells utilising the ATP that is produced. Also, she pointed out that she was only focusing on mitochondrial defects in relation to the production of ATP.

Mitochondria are involved in many other processes, such as immunity and cell signalling, which may be where the fault hat is causing the disease pathology lies.

Alterations of cellular metabolism observed in muscle cells, indicating possible factors present in plasma of patients with M.E./CFS capable of modifying cell function  
– Dr Tiffany Lodge, University of Oxford

Dr Lodge presented some hot-off-the-press initial results coming from one of the studies being carried out by Dr Karl Morten's research team at Oxford University.

This relatively small pilot study, funded by the ME Association's Research Ramsey Fund, was investigating the effects of factors present in the plasma of M.E./CFS patients on metabolic function.

They used a fluorescence intracellular oxygen sensing probe to detect changes in oxygen levels of muscle cells in response to plasma treatments.

They took muscle cells from healthy controls and applied plasma from healthy controls to one sample and plasma from M.E./CFS patients to another.

Unfortunately, we cannot share the results until they are published.

## Effects of whole-body cryotherapy among CFS patients- preliminary results - Pawel Zalewski (Nicolaus Copernicus University, Poland)

Mr. Zalewski began by highlighting how poorly recognised and understood M.E./CFS is in Poland, and that it is gravely underdiagnosed.

In Poland, cryotherapy has been recognised as a safe and effective therapy option for a range of different conditions.

He commented, to polite amusement from the audience, that:

“In Poland, cryochambers are commonly used but M.E./CFS does not exist. In the UK, M.E./CFS exists but people are afraid to use cryochambers!”

Cryostimulation is the most extreme stimulation you can apply to organs. However, cryotherapy is different to cold water immersion therapy as there is no water involved, it produces no pain and is less of a sudden shock to the body.

It produces acute and delayed strong modulatory effects on the cardiovascular system, as well as on the sympathetic and parasympathetic nervous systems and the immune system.

This presents as a safe alternative to exercise for those that are exercise intolerant, as it produces the same effects on the body.

Recruitment of patients for the study was very thorough, with a lot of exclusion criteria and assessments. However, half of the recruited patients dropped out as they did not like the therapy (could not tolerate the cold).

The therapy involves patients sitting in a cryochamber at  $-120^{\circ}\text{C}$  for three minutes (built up in increments of 30 seconds), followed by some gentle stretching for 30 minutes after.

The preliminary results showed that cryotherapy improved autonomic symptoms and the patients reported significant improvements. However, it is too early to determine how long-lasting these results will be.

## MRC-funded update: Imaging exercise-induced Post-Exertional Malaise in M.E./CFS - Dr Neil Harrison, University of Sussex

Dr Harrison's hypothesis is that people with M.E./CFS show a heightened and more persistent inflammatory response to stressors (e.g. exercise) that disrupts healthy brain function. His research team are conducting several studies (using the same set of data) looking at a cardinal symptom of M.E./CFS, post-exertional malaise (PEM), through the use of cardiopulmonary exercise testing (CPET).

The study is still ongoing, and they hope to recruit 20 patients and 20 controls altogether, but the preliminary findings from the ten patients and five controls that have taken part in the study so far were presented.

The aims of the study are:

- To investigate how physiological and perceptual markers of exercise performance change during a standard incremental CPET in M.E./CFS patients.
- To investigate whether awareness of changes in internal physiological state (called interoceptive awareness) is altered in M.E./CFS and how this relates to exercise performance and exercise-induced PEM.
- To compare the stability of physiological and perceptual exercise parameters during repeated CPET testing (24 hours apart) between individuals with M.E./CFS and healthy controls.

The preliminary results show that at peak exercise, patients showed decreases in oxygen intake (VO<sub>2</sub>) and total exercise time between day one and day two; an effect that was not observed in controls. Power was also reduced between the days, but this was also observed, to a lesser extent, in controls. Additionally, patients reached a higher RER and heart rate on the second day compared to controls.

The M.E./CFS group reported higher rates of fatigue (ROF) on both days compared with controls, but the scores were higher on day two compared to day one, at rest and during exercise. These results show a decline in both physiological and perceptual exercise parameters in people with M.E./CFS that was not observed in controls. This suggests a potential physiological basis for perceptual experience of fatigue and PEM.

Dr Harrison's team will also be using advanced brain imaging in order to understand more about the neuronal networks that underlie the neurobiological basis of PEM in M.E./CFS. They will compare advanced brain imaging data in concert with changes in blood markers and behavioural data before and after exercise.

Recruitment and data collection for all parts of this dynamic study is still ongoing, and so a larger data set will be presented next year, from which more conclusive results can be drawn. They hope to complete the study by early 2019 and the initial data analysis by mid-2019.

You can watch the presentation here: <https://www.youtube.com/watch?v=sfEYNNrvY5w&t=90s>

## Anne Faulkner Memorial Lecture: Big data and open science: a powerful combination to generate new understanding of disease - Professor Cathie Sudlow, Chief Scientist, UK Biobank, University of Edinburgh

Professor Sudlow's talk focused on the value of using large volumes of data for research, such as the UK Biobank, and how this resource could be used to reveal more about M.E./CFS.

The term "big data" refers to large volumes of data from a variety of sources being pooled together, and it can be of substantial value if it is used appropriately. Big data studies about the health of a large population over a period of time, known as prospective population-based studies, can be used to find risk factors long before a disease develops. The effects of a potential risk factor (e.g. smoking, high blood pressure) on many different diseases (e.g. lung disease, cancer, vascular disease, dementia) have been assessed using data about 500,000 participants. The sample sizes need to be very large as only a proportion of the participants develop any particular disease during prolonged follow-up.

The national UK Biobank is a collection of baseline questionnaires, physical measures (including from wearable devices) and biological samples for 500,000 UK men and women aged 40-69 years. The data is also linked with healthcare data from the NHS such as death and cause of death, cancers, hospital admissions and primary care data. The addition of genotyping, blood results for lipids, hormone and metabolic substance levels, disease assays, and stool microbiome are underway.

The Biobank allows long-term follow-up for a wide range of health-related outcomes and is open access for approved research. By the end of 2017 the UK Biobank was being used by 6,500 registered researchers for 700 research projects, resulting in 370 publications.

Prof Sudlow concluded with some thoughts on how the UK Biobank could be utilised for M.E./CFS research. The Biobank may be useful for studying the causes of M.E./CFS. Currently, 2,000 of the UK Biobank participants self-report as having the illness, some of whom were in the audience. It is hoped that when primary care data is also linked with the Biobank, more cases will be shown up.

Difficulty in defining and diagnosing M.E./CFS in primary care may affect the number of cases. So far there are some interesting preliminary findings to be followed up as the data accumulates over time.



## Differential microRNA profiles in PBMC and plasma EVs of severely affected M.E./CFS patients - Dr Elisa Oltra, Universidad Católica de Valencia, Spain

MicroRNAs (miRNAs) regulate genes and can modulate the expression of certain proteins. They are attractive candidates for biomarkers of disease.

Dr Oltra's team studied differences in miRNA expression in two types of blood components in 15 people with severe M.E./CFS and 14 healthy controls, and identified potential biomarkers of disease.

These two types of components in blood were peripheral blood mononuclear cells (PBMC) (white blood cells) and plasma extracellular vesicles (EVs).

Biochemical panels taken from blood samples of the M.E./CFS patients revealed significant differences in clinical parameters, which might aid in clinical diagnosis.

Extracellular vesicles (EV) are small 'packages' that are released into the blood from the cells of different organs, as well as from bacteria in the gut. They are involved in long-distance cell communication throughout the body.

Dr Oltra found M.E./CFS patients had an increased number of extracellular vesicles (EVs) when compared to those obtained from healthy individuals.

This feature has been formerly associated with diseases presenting a relevant inflammatory component and agrees with the results published this year by Dr Alegre's group from Hospital Vall d'Hebron, Barcelona, Spain.

miRNA profile analyses revealed over- and under-expression of several specific miRNAs in both cell fractions from the M.E./CFS patients. The top overexpressed miRNAs in EVs found in this study are abundantly expressed in tissues commonly affected in M.E./CFS patients, such as muscle, brain and thyroid gland.

In general, the differences found were more pronounced in the EVs than in the PBMC, suggesting that EVs might be a more sensitive factor for measuring changes in miRNA expression.

Interestingly, Dr Oltra added that many of the miRNAs found to be altered in her study match those found to be altered in previous studies, as well as those reported by Professor Alain Moreau in his study, presented on day one of the conference (see above).

Larger studies need to be carried out to validate these deregulated miRNAs in order to identify a reliable biomarker for M.E./CFS. Evaluation of the cellular pathways linked to deregulated miRNAs might lead to an improved understanding of M.E.'s pathophysiology.

You can watch the presentation here: <https://www.youtube.com/watch?v=henDTetf8Vw&t=4s>

## MRC-funded update: Persistent fatigue induced by interferon-alpha: a novel, inflammation-based, proxy model of chronic fatigue syndrome - Prof Carmine Pariante, Kings College London

Professor Pariante came to give an update on his work. His study involved injecting patients with interferon alpha, a pro-inflammatory cytokine used to treat hepatitis C.

Patients treated with interferon alpha often report experiencing marked and lasting chronic fatigue, which might act as a model of induced M.E./CFS, resulting from immune dysregulation and inflammation. This model allows examination of what happens before, during and after an immune trigger – something that cannot be done in M.E./CFS patients as you cannot pre-empt them developing the illness. This means it may allow a determination of what pre-disposed the development of persistent fatigue; what separated the patients who developed it after treatment from those who didn't. This could in turn help in the understanding of inflammatory triggers – which might also occur in the development of M.E./CFS.

30% of the patients reported persistent fatigue over a six month period after their treatment with interferon alpha ended. Professor Pariante's team measured changes of key inflammatory cytokines: IL-6 and IL-10. They found that IL-6 (a pro-inflammatory cytokine) increased more in the patients that developed persistent fatigue early on in treatment (around four weeks) compared to those who didn't develop this symptom. However, at the end of treatment, these levels had dropped back down to the same between both groups. IL-10 (an anti-inflammatory cytokine) also increased early on (four weeks into treatment) and was much higher in those who developed persistent fatigue; but fell to pre-treatment levels six months after treatment ended.

When comparing the group who developed persistent fatigue six months after treatment ended and the group whose fatigue resolved, no differences were found in the level of reported fatigue before treatment started. There was also no difference in cytokine levels between the groups six months after treatment had ended. This shows that the difference happened early on in the treatment; an over-reaction of the immune system, that led to chronic fatigue. It might mean that we may not be able to see noticeable differences in cytokines in people with M.E./CFS now, as the differences happened early on in the development of the disease. It could be that people who develop M.E./CFS after an illness are more sensitive to immune activation.

Professor Pariante also said that there were no differences in cytokine levels between the control group and M.E./CFS group that they studied. The study found that those who developed depression during treatment did not have the raised cytokine levels seen in those who developed persistent fatigue, showing a clear separation between depression and M.E./CFS.

They also found that the longer patients were treated, the more likely they were to develop persistent fatigue, meaning that perhaps the longer the immune system is over-acting after an illness, the more likely they are to develop chronic fatigue. This presents as an interesting potential model for M.E./CFS and shows something might have happened in the immune system in the initial onset of the disease that is no longer traceable.

You can watch the presentation here: <https://www.youtube.com/watch?v=RBUBumL6wuo&t=5s>

## Working together versus the pain, isolation and fatigue of arthritis - Stephen Simpson, Director of Research, Versus Arthritis

Versus Arthritis (VA) funds musculoskeletal (MSK) conditions research and has similar aims and focus as M.E./CFS research. VA funds around 300 active research projects at a time throughout the UK, from PhD students to Research Centres of Excellence.

VA now focuses on insight-driven research funding, rather than just an open call for all research. This is driven by insight not just from researchers but more importantly from people living with the conditions. Patients also sit on committees, helping to shape VA's research agenda and evaluate grant applications. The charity aims to ensure MSK research is a UK priority, relative to the burden of MSK conditions.

The three key areas for VA-funded research are pain, better treatments and ultimately a cure for MSK conditions, and improving health and health services.

When VA surveys people with MSK conditions such as arthritis, pain is the top priority for research. As a result, VA have increased their investment into pain, including establishing a Pain Centre of Excellence. The following are examples of the research being funded by VA:

- Investigating a protein found on nerves in and around our joints and whether this could be used to reduce pain and inflammation in osteoarthritis
- Whether we can predict the risk of knee pain and painful osteoarthritis following knee joint injury
- The role of exercise and sleep in chronic pain
- Dissecting the tripartite relationship of fatigue, autonomic dysfunction and immune dysregulation
- Behavioural and neural biomarkers of fatigue in inflammatory arthritis
- The *Cloudy with a chance of pain* study with mass participation via wearable technology and apps, correlating the onset of pain with the weather

Although these are worthwhile studies, there needs to be a more structured road map for pain research, so a group of experts in the field have set out 14 key challenges for future pain research.

VA is opening a call at the end of November for multidisciplinary and collaborative research to meet these challenges, along with supporting early career researchers.

Stephen concludes by looking at the joint priorities and intersection between pain and M.E./CFS research. There are shared and distinct mechanisms involving pain and fatigue, the impact across the life course on quality of life, and new interventions and treatments, and these need to be elevated as priorities in the UK research system.

You can watch the presentation here: <https://www.youtube.com/watch?v=CU4IvwZCEXo>

## Cellular immune function in M.E./CFS - Jackie Cliff, London School of Hygiene and Tropical Medicine

Ms Cliff's research team are attempting to create a diagnostic lab test using blood samples.

Their hypothesis is that M.E./CFS is associated with immune dysfunction; specifically, alterations in T cell and/or NK cell phenotype and function.

This may lead to or result from alterations in cytokine production and altered expression of immune cells.

They conducted cytokine analysis and transcriptomics in 251 well-characterised M.E./CFS patients (197 mild/moderate and 54 severe), 46 MS patients and 106 healthy controls. The results cannot be reported at this time as they are unpublished.

They have just finished collecting the last samples and are about to start analyses, which is very exciting and could yield some interesting findings.

The slide below has been taken from their presentation and details their study rationale.

### Study Rationale



- There is no laboratory diagnostic test for ME/CFS
- ME/CFS has unknown aetiology and unclear pathogenesis
- Different body systems/organs involved in ME/CFS
- Blood is an "accessible compartment"
  - for research
  - for lab tests
- Blood contains white blood cells – representing different compartments in the immune system



## Is inflammation the link between the body and the brain? - Prof Carmine Pariante, Kings College London

Professor Pariante returned in the afternoon to give another fascinating talk, this time about inflammation's link to chronic illness.

He spoke of how the immune system communicates to the brain about infection to promote what is termed 'sickness behaviour' (fatigue, lack of concentration, muscle weakness etc.) as a way to conserve energy so that it can be directed towards fighting off the infection and healing the body.

The brain also communicates to the immune system the presence of 'stress' in the environment (which can be physical or emotional), that then activates the immune system in the same way as if it's fighting an infection.

In his studies carried out in patients with depression, he has found IL-6 (an inflammatory cytokine) to be raised, along with cortisol levels. Cortisol has anti-inflammatory effects and acts to keep inflammation caused by IL-6 under control.

In M.E./CFS patients, however, cortisol is often found to be low. This could mean that the IL-6 is then not being kept under control. We also need to find out if low cortisol levels are a cause (if they predispose people to developing M.E./CFS) or are a consequence of the disease.

Professor Pariante also touched on the subject of genetic predisposition and its role in leading to a tendency for immune over-activation. Interestingly, he spoke of how the uterine environment (in the womb during pregnancy) could affect the child's immune response.

Some studies have found that high levels of stress or depression during pregnancy results in high levels of inflammation, which changes the immune system of the child, increasing their inflammation. This can result in the child being more reactive to stress and having an increased risk of inflammatory disorders and depression later on in life.

This biological signature of high immune activation is passed on through generations, which could be due to heritable genetic changes or epigenetic changes in-utero (during pregnancy).

You can watch the presentation here: <https://www.youtube.com/watch?v=Hc1k8GngGJA&t=1s>

## Cellular bioenergetics in M.E./CFS - Dr Cara Tomas, Newcastle University

Dr Tomas, who has had a diagnosis of M.E. for 14 years, detailed previous studies into bioenergetics and the contradictory results produced. Action for M.E. has been pleased to co-fund this study along with other charities.

Aims of the study:

- Compare cellular bioenergetics of M.E./CFS patient and healthy control cohorts
- Assess changes in mitochondrial functioning and cellular energy profiles systemically using peripheral blood mononuclear cells (PBMCs)
- Investigate the effect of the following on PBMC bioenergetics:
  - Disease severity
  - Cell freezing
  - Glucose concentration

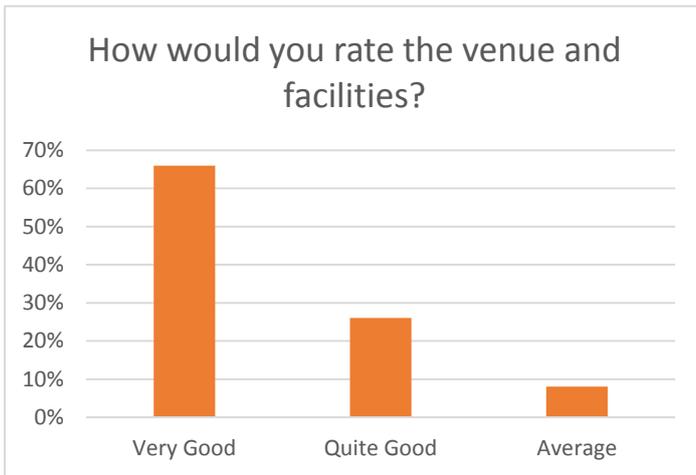
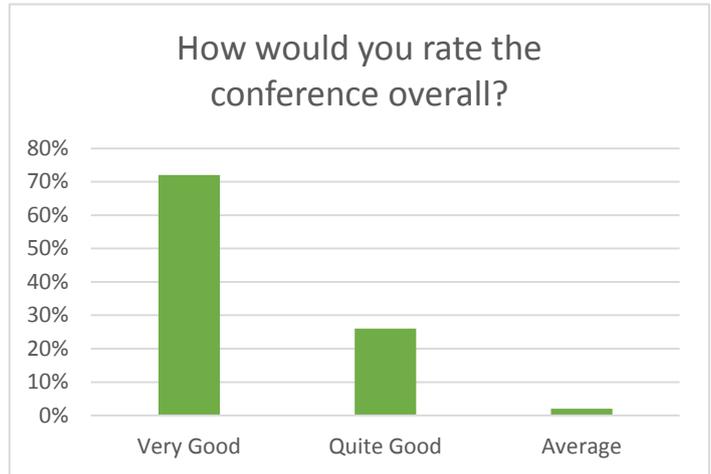
The first experiment was to investigate the effect of disease severity on PBMC mitochondrial functions under the hypothesis, *“Mitochondrial function would be significantly lower in PBMCs from M.E./CFS patients who were severely affected by the disease.”* However they found that this was not the case. She states that they were surprised to find no difference between the cohorts. Next they looked at the effects of cell freezing under the hypothesis, *“freezing PBMCs at -80c would significantly impair mitochondrial function and it would do so to the same extent in PBMCs from M.E./CFS patients and healthy cohorts.”* She found that in all three parameters, M.E./CFS cells have lower mitochondrial respiration, which indicates an impairment, and that clearer differences were observed when using fresh samples rather than ones that had been frozen.

Dr Tomas then detailed an experiment on the effect of glucose concentration under the hypothesis, *“incubation of cells in low-glucose conditions would push the cells to utilise mitochondrial respiration to a greater extent than in high-glucose conditions and Incubation of cells in low-glucose conditions would increase the mitochondrial respiration of M.E./CFS PBMCs and make it comparable to that of healthy controls.”* The results demonstrated a difference in all three patterns, which also confirmed the mitochondrial impairment. They noted that this impairment was present in both low- and high-glucose concentrations and seeing as the lower glucose solution did not improve, it suggested that the mitochondria are already functioning at maximum capacity.

Finally, she presented a study which hypothesised, *“Glycolytic functioning of M.E./CFS PBMCs would be higher than that of healthy controls in order to compensate for the decreased ATP production via oxidative phosphorylation (OXPHOS). Glycolysis would not correlate with disease severity”* Dr Tomas stated that there was no difference between the control and M.E./CFS groups, which suggests that the cells are not compensating for the lack of mitochondrial function in any meaningful way.

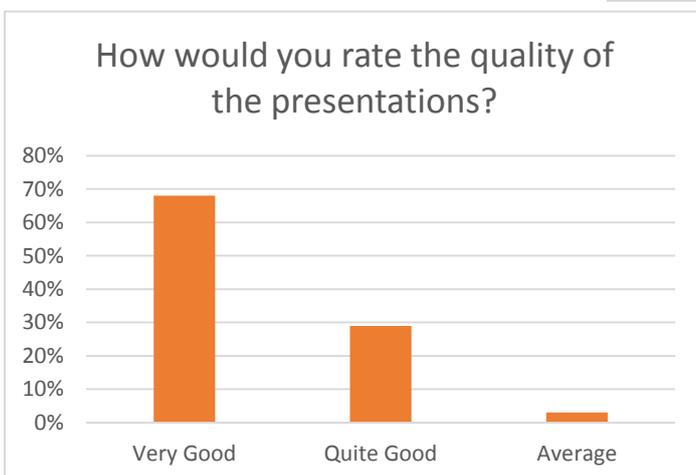
You can watch the presentation here: <https://www.youtube.com/watch?v=cqw0q38eDss&t=18s>

## Delegate Feedback



Our films on Youtube have been watched 4,100 times, with the most popular clip being Dr Nina Muirhead's presentation.

90% of attendees said that they attended a workshop and found it good/very good



Our #CMRC2018 tweets were seen 24,420 times and actively interacted with more than 5,200 times.

This report was written thanks to contributions from Dr Charles Shephard and Charlotte Stephens from the ME Association, Katrina Pears and Emily Beardall.