

M.E. Research Conference Report: London 1st June 2018

13th Invest in ME Research (IiMER) Conference

Forward

Dr Charles Shepherd summarises key points to emerge from the 2018 conference.



This year's conference was again held at One Great George Street – an impressive Edwardian building, with equally impressive conference facilities, that sits opposite St James's Park in London.

As usual, the audience consisted of people with ME/CFS, carers, charity representatives, health professionals and researchers, from the UK and overseas. The conference was chaired by Dr Ian Gibson with his usual wit and enthusiasm.

Overall, this was an interesting and enjoyable meeting that covered a number of important overseas research initiatives, as well as some clinical presentations that are more relevant to the here and now situation facing people with ME/CFS.

Thank you to everyone who was involved in the organisation of the conference.

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1. Dr Beth Unger, Chief of Chronic Viral Diseases Branch, Centres for Disease Control and Prevention (CDC), Atlanta, GA, USA: Update on what the CDC is doing in relation to ME/CFS

CDC are involved in a number of ME/CFS initiatives and are:

- aiming to properly integrate ME/CFS into mainstream public health.
- collecting epidemiological data on people with ME/CFS – prevalence, age, sex ratio, co-existing medical conditions etc. Preliminary results indicate a much higher prevalence rate (i.e. over 1%) than current epidemiological studies suggest (i.e. up to 0.4%). This is possibly because the surveillance is being done through a self-report telephone survey and a diagnosis of ME/CFS is not then being validated by consulting room clinical assessment.
- looking at the potential role of vaccinations as trigger factors for ME/CFS and absence from school in children with ME/CFS.
- producing educational material, including a new video on clinical assessment and diagnosis, for health professionals.
- updating the CDC website information on ME/CFS for both health professionals (June 2018) and for people with ME/CFS (May 2018) to reflect the content of the Institute of Medicine report



Dr Unger spoke about three research studies – on cardiopulmonary testing, cognitive function and NK cell function – that are in progress and the use of what is called the NASA lean test.

This clinical test measures changes in heart rate and blood pressure when someone stands and leans towards a wall and can be used in the consulting room to assess orthostatic intolerance.

- More info on the NASA lean test [from the Bateman Horne Centre](#)
- CDC [website information](#) on ME/CFS

2. Dr Vicky Whittemore, Programme Director at National Institute of Neurological Disorders and Stroke, National Institutes of Health (NIH), Bethesda, MD, USA: Update on NIH research initiatives

NIH are involved in a number of ME/CFS initiatives, and these include:

- providing a significant increase in research funding for ME/CFS.



- setting up three collaborative research centres and one data collection centre. The collaborative centres are at:
 - Cornell University (identifying biological mechanisms and baseline and post exercise studies: Prof Maureen Hanson),
 - Columbia University (microbiology and comprehensive genetic analysis: Dr Ian Lipkin),
 - Jackson Laboratories, Connecticut (immunology, microbiome and metabolomic studies).
- collaborating with the Canadian Institute of Health Resources.
- establishing a working group at NIH, headed by Steve Roberts, to provide scientific guidance on how to advance ME/CFS research.
- organising a research conference – Accelerating Research on ME/CFS – at NIH on April 4th to 5th 2019. This is in partnership with Solve ME/CFS.

3. Dr Avindra Nath, Head of Infections of the Nervous System at the National Institute of Neurological Diseases and Stroke, National Institutes of Health (NIH), Bethesda, MD, USA: Challenges in study design and identification of patients with post-infectious ME/CFS

Dr Nath is leading an internal research study at the NIH – where they have hospital facilities purely for research purpose use.

This research is looking in great detail at a group of people with ME/CFS who have a clear infectious onset to their illness and are in the very early stages of the illness.

Patients are admitted to the research hospital at NIH for detailed clinical assessment and investigations over a period of 10 days.

Investigations include pre- and post-exercise testing, skin biopsy (to look at nerve fibres in the skin) and a muscle biopsy (as muscle is the best place to look for mitochondrial DNA).

The muscle biopsy also helps to exclude people with primary muscle/mitochondrial disease – which can occasionally be misdiagnosed as ME/CFS, as has previously been discussed at research meetings here in the UK.

The aim is to recruit 40 people with very well defined ME/CFS and 40 healthy controls. The entry criteria appear to be very strict – and involves a committee of 5 physicians to ensure that the subjects do indeed have ME/CFS.

As a result, the recruitment process is moving quite slowly, and they currently only have 13 people with ME/CFS and 16 healthy controls.



Dr Nath added that the team are very keen to work with the ME/CFS patient community and answer any questions that people have about this research.

During the Q & A, he was reluctant to go as far as saying that NIH regarded/classified ME/CFS as a neurological disease but did say that the neurological involvement needs to be investigated.

- There is a [more detailed summary of this research](#) in the report from the 2017 CMRC Research Conference where Dr Nath gave a more detailed presentation.

4. PhD students from the Quadram Institute of Bioscience, Norwich: Role of the gut microbiome in ME/CFS

- a. Katherine Seaton outlined a theory about how the composition of the human microbiome (i.e. the viral and bacterial organisms that inhabit a healthy digestive system) may change to either cause or be involved in non-gastrointestinal disease.

In the case of ME/CFS, this could involve an intestinal infection producing changes in the microbiome and inflammation in the lining of the gut. This then results in a 'leaky gut' and transfer of infectious particles into the blood stream. The final outcome is an immune system reaction – possibly involving the production of autoantibodies (antibodies which can harm normal body tissues).

To test this theory, they are collecting blood and stool samples from 10 people with severe M.E. and 10 household controls that are being recruited from ME/CFS referral centres in Norfolk and Surrey – who would all be sharing the same environment and possibly the same food. Nutrition may, however, differ – so both groups are keeping food diaries of what they are eating.

- b. Fiona Newberry (presenting on behalf of Ernie Hsieh) spoke about other linked research in Norwich, which is aiming to identify disease specific alterations in the microbiome and virome in a severe ME/CFS group.
- c. Professor Simon Carding was unable to attend and give a presentation.

5. Dr Kristian Sommerfelt, Haukeland University Hospital, Bergen, Norway; a clinical presentation on Myoclonic jerks



Myoclonic jerks (or twitches) refer to sudden, involuntary jerking movements in a muscle or group of muscles. They are usually caused by sudden muscle contractions, called positive myoclonus, or by muscle relaxation, called negative myoclonus.

Myoclonic jerks may occur alone or in sequence, in a pattern or without pattern. Although they are not part of the normal diagnostic criteria for ME/CFS, myoclonic jerks are reported by some people with the disease.

In this clinical presentation from Dr Sommerfelt, who sees 20 to 25 ME/CFS patients per year, he described some of the cases that he had dealt with:

- c.80% of the patients he had studied experienced sudden solitary and unilateral (one sided) jerks in the hand and foot,
- c.20% had fast bilateral (on both sides of the body) jerks in the shoulders and arms, and,
- a video was shown of a female patient with far more severe myoclonic jerks where the abnormal movements diminished while she was reading.

Two drug treatment options were described – a benzodiazepine drug called midazolam, and gabapentin – and a successful response had also been reported by a person who was taking part in the Norwegian trial of cyclophosphamide.

- I wrote about myoclonus and myoclonic jerks in ME/CFS in more detail in the Autumn 2016 issue of ME Essential magazine.

6. Dr Peter Johnsen, Internal Medicine, University Hospital of North Norway, Harstad, Norway: Double-blind, single centre, placebo-controlled, randomised clinical trial treating ME/CFS with faecal microbiome transplantation (FMT)

Faecal Microbiota Transplant (FMT) is a procedure in which faecal matter, or stool, is collected from a tested donor, mixed with a saline or other solution, strained, and placed in a patient, by colonoscopy, endoscopy, sigmoidoscopy, or enema.

The normal purpose of FMT is to replace good bacteria that has been killed or suppressed, usually by the use of antibiotics, causing bad bacteria – specifically *Clostridium difficile* – to over-populate the colon.



This infection causes a very serious condition called *C. diff. colitis*, resulting in often debilitating, and sometimes fatal diarrhoea.

Peter Johnsen and colleagues have already completed the first clinical trial to assess the use of FMT in people with irritable bowel syndrome. Results indicate that FMT can have a significant effect on both IBS symptoms and on fatigue, which is an important symptom in IBS.

- **Research paper:**
[Johnsen P et al.](#) *Faecal microbiota transplantation versus placebo for moderate-to-severe irritable bowel syndrome: a double-blind, randomised, placebo-controlled, parallel-group, single-centre trial.* *Lancet Gastroenterology Hepatology*, 2018, 3, 17-24.

They are now going to carry out a similar type of trial to see if FMT can be helpful in people with ME/CFS. Eighty ME/CFS patients will receive either a donor transplant or placebo FMT, with a 12 month follow up period.

The primary end point will be the efficacy of FMT at 3 months. The trial will be launched in August 2018 with final results expected in August 2020. The study will also involve biobanking of faeces, blood and urine samples to look at immune and metabolomics responses.

FMT has to be used with caution – so the screening regime for the FMT donors is just as extensive as the donors for any other tissue. This is not a ‘do it yourself’ method of treatment.

- I wrote about FMT, including some of the potential dangers of this approach if not done under proper medical supervision, in the Autumn 2017 issue of ME Essential magazine.
- More information on [Faecal Microbiota Transplant](#) from the Fecal Transplant Foundation in America

7. Professor Karl Tronstad, Cellular Energetics, Department of Biomedicine, Haukeland University Hospital, Bergen, Norway: Cellular energetics



Karl Tronstad and his group have already reported on changes in amino acids and gene regulation that are consistent with altered regulation of the central enzyme pyruvate dehydrogenase in people with ME/CFS compared to healthy controls.

They have also reported how serum from people with ME/CFS changed energy metabolism in healthy muscle cells in culture.

These changes suggest that there is an important immunological-metabolic defect in ME/CFS.

He then summarised how some of these existing research findings relate to abnormalities in the way that glucose is broken down through a process called glycolysis – so that energy in the form of ATP is being produced at a cellular level.

And went on to describe a research study being funded by the Norwegian Research Council that will further investigate the role of defective energy metabolism in ME/CFS, where the primary defect may be an abnormal immune system response to a triggering infection.

- **Research paper:**
Fluge O et al. *Metabolic profiling indicates impaired pyruvate dehydrogenase function in myalgic encephalopathy/chronic fatigue syndrome*. [JCI Insight](#). 2016 Dec 22; 1(21): e89376. Published online 2016 Dec 22. doi: [10.1172/jci.insight.89376](https://doi.org/10.1172/jci.insight.89376)

8. Professor Don Staines, National Centre for Neuroimmunology and Emerging Diseases, Griffiths University, Queensland, Australia: Emerging TRP pathology: the way forward in pharmacotherapeutics and treatment

Don Staines summarised the current findings relating to what is called TRP pathology, the possible role of abnormalities in calcium ion channels in ME/CFS, and some of the immune system research on natural killer (NK) cell function that is being carried out by the researchers at Griffiths University in Australia.



The presentation covered a lot of very complex scientific information – most of which occurs at a cellular or intracellular level – and some of which has not yet been published.

The important practical point is that calcium ion channels are involved in transporting calcium ions into all kinds of cells and that calcium is a very important molecule for all kinds of cellular functions.

Other researchers have already suggested that ME/CFS could involve what is called a calcium ion channelopathy, where this mechanism is not functioning properly. If this turns out to be true, it could be something that will respond to drugs that affect calcium transportation.

- **CS note:** It is interesting that there has been a report in the medical literature about a drug called verapamil being helpful in relieving unexplained exertional muscle pain. There are also some people with ME/CFS who have been treated with a calcium channel blocking drug called nimodipine – but without any evidence on efficacy or safety from a proper clinical trial.
More information on these two drugs can be found in the Treatment section of the 2018 ME Association 'An Exploration of the Key Clinical Issues'.
- **Research paper:**
[Nguyen et al.](#) *Impaired calcium mobilization in natural killer cells from chronic fatigue syndrome/myalgic encephalomyelitis patients is associated with transient receptor potential melastatin 3 ion channels.* [Clin Exp Immunol](#). 2017 Feb; 187: 284–293.

9. Professor Theoharis Theoharides, Professor of Pharmacology and Internal Medicine, Tufts University, Boston, USA: The Anne Ortegren Memorial Lecture on mast cell disease and ME/CFS

This lecture was given in memory of Anne Ortegren – an M.E. advocate and patient who sadly died in Sweden earlier this year.



Mast cells are specialised cells that are involved in allergic reactions. Release of chemicals from these cells can cause a wide range of symptoms affecting almost any body system: brain, cardiovascular, gastrointestinal, respiratory, and skin.

Of interest is that mast cell activation increases the permeability of what is called the blood brain barrier – a barrier that helps to prevent harmful substances entering the brain. As a result, mast cells may be involved in activation of nervous tissue called microglia and the development of focal inflammation in key parts of the brain, especially the hypothalamus.

There is growing evidence of an overlap between what is termed mast cell disease and ME/CFS. This may link in with the increased incidence of allergic disease in ME/CFS and research evidence of hypothalamic dysfunction.

Professor Theoharides has an interesting hypothesis that stimulation of the mast cells in the hypothalamus activates microglia leading to the secretion of pro-inflammatory cytokines that disrupt normal physiological mechanisms and have an adverse effect on mitochondrial function.

Treatment of mast cell disease involves avoidance of triggering factors. This includes histamine rich foods (e.g. ripe avocado and tomato, cheese, sardines and spices), deodorants and perfumes, heat, preservatives and stress.

Drug treatment options that were referred to include the use of cyproheptadine, doxepin, hydroxyzine, ibuprofen, propranolol and ranitidine.

- The overlap between mast cell disease and ME/CFS is also covered in the Summer 2017 issue of ME Essential magazine.
- Further information from [Professor Theoharides](#) on mast cell disease.

10. Associate Professor Mady Hornig, Centre for Infection and Immunity, Columbia University Mailman School of Public Health, New York, USA: Parsing heterogeneity in ME/CFS to accelerate discovery of tractable disease phenotypes

Mady Hornig's research concentrates on establishing immune system profiles in ME/CFS and identifying infections that may be linked to the disease.

She reviewed some of the research that has already been published relating to increased levels of some pro-inflammatory cytokines (= immune system chemicals) in the early stage of



ME/CFS and how this could be a marker to differentiate between short and long duration illness.

She also referred to findings that help to differentiate acute viral onset disease from more atypical presentations.

She then covered research into the possible role of the faecal microbiome in ME/CFS and how research into metabolomic profiling (i.e. the pattern of small molecules/metabolites that are left behind in the blood after biological processes) could help to develop clinical phenotypes that can then be used to subgroup people under the ME/CFS umbrella.

- **Research paper:**
[Dorottya Nagy-Szakal et al.](#) *Fecal metagenomic profiles in subgroups of patients with myalgic encephalomyelitis/chronic fatigue syndrome*. *Microbiome*, 2017; 5 (1)

11. Professor Maureen Hanson, Director, Department of Molecular Biology and Genetics, Cornell University, Ithaca, NY, USA: Update on research at Cornell Centre for Energizing Neuroimmune Disease



Maureen Hanson described the NIH Collaborative Research Centre (CRC) studies that are taking place at Cornell.

- An exercise challenge test, where people with ME/CFS will carry out two cardiopulmonary exercise tests (CPETs) using the protocol developed by the Workwell College and Dr Betsy Keller at Ithaca College.
- Professor Dikoma Shungu will lead a neuroimaging project where people with ME/CFS will have magnetic resonance spectroscopy (MRI) scans and positron emission tomography (PET) scans in order to evaluate the role of oxidative stress and neuroinflammation.
The scanning will take place before an initial CPET and before performing a second CPET 24 hours later – to look at the effect of exertion. Blood samples will also be collected before and after each CPET.
- The Cornell labs will also be analysing extracellular vesicle numbers, size and content in the blood plasma. Dr Andrew Grimson's laboratory will be isolating white blood

cells to identify and sequence genes that are being expressed.

By examining patients at baseline and after post-exertional malaise sets in, they hope to gain new insights into this diagnostic and disabling symptom.

- A collaborative study with Dr Dan Peterson (who was also at the conference) on biomarkers following the use of Ampligen.

12. Professor Markku Partinen, University of Helsinki, Finland: ME/CFS from a sleep medicine perspective



Markku Partinen, a neurologist and sleep medicine expert from Finland.

He gave a very interesting presentation covering both the role of sleep and what we know about sleep abnormalities in ME/CFS.

Key points included:

- a. The two components of the autonomic nervous system (ANS) – sympathetic and parasympathetic nerves – play an important role in sleep regulation. As ANS dysfunction occurs in ME/CFS this could be very relevant.
 - b. Professor Partinen's group have studied the nocturnal cardiac ANS in different sleep stages in patients filling the 2015 Institute of Medicine ME/CFS diagnostic criteria. Results suggest a nocturnal dysfunction of the cardiac ANS presenting as lower parasympathetic tone in deep sleep and higher sympathetic tone asleep.
 - c. The Orexin system, located in the hypothalamus, is also a very important central control mechanism involved in sleep. It is influenced by the circadian rhythms, emotions, energy balance, the endocrine (hormone) system and the autonomic nervous system.
Orexin cells secrete glucose, and this helps to explain why a meal that is high in carbohydrates can make people feel sleepy.
 - d. Regular sound sleep is vital to human health for a number of reasons. It provides energy to and refreshes the brain and also helps to remove toxins and metabolites that have been created during normal waking hours. Professor Partinen described this process very aptly as 'the washing machine of the brain'!
- More [information on the orexin](#) system.
 - **Research paper:**
[Orjatsalo M et al.](#) Autonomic Nervous System Functioning Related to Nocturnal Sleep in Patients With Chronic Fatigue Syndrome Compared to Tired Controls. *Journal of Clinical Sleep Medicine*, 2018, 14, 163 - 171.
 - ME Association [research review covering autonomic nervous system dysfunction](#) in ME/CFS, including sleep related research.

13. Professor James Baraniuk, Professor of Medicine at Georgetown University Medical Centre, Washington DC, USA – Update on NIH funded research



James Baraniuk provided an update on some of the research that he has been doing with a grant from the NIH – in effect it was his report to the NIH!

The study involves:

- exercise testing (sub-maximal to 70% of predicted heart rate),
- neuroimaging (MRI scans) before- and after-exercise, and,
- examining the effect of exercise on both cognitive function and orthostatic intolerance.

It will also consider the lack of evidence for equating ME/CFS with a depressive illness.

His research programme has also been looking at microRNAs and whether they could have a biomarker role.

As the findings from this research have not yet been published I will not reveal them here.

14. Professor Ron Davis, Professor of Biochemistry and Genetics at Stanford School of Medicine, Stanford, CA, USA: Revolutionising biomedical research through technology development

Professor Davis presented an update on all the ME/CFS research taking place at Stanford and as part of the Open Medicine Foundation.

Considerable progress has been made in analysing the data from the severely ill patient study. This has taken some time because the group have only had one bioinformatic scientist analysing the massive amount of data.

There are a considerable number of mutations that are more common in ME/CFS patients than in healthy controls.

This would suggest that these mutations make a patient more susceptible to having ME/CFS.

It could also indicate that some of the mutations are responsible for the severity of the patients that were studied.

They have also found a large number of metabolomic changes that have been previously seen in less severe patients.



These metabolomic differences between healthy controls and other severely ill patients are often much bigger than in studies with less severe patients. A more detailed analysis of this data may help in developing treatments.

One area they are currently studying using the genetic and metabolomic data is the possibility there may be one or more metabolic traps. This is a disruptive metabolic state that a patient can develop, possibly caused by physical stress such as infection. Once a patient is in this state they cannot easily get out by rest.

They are also conducting a system biology and pathway analysis. This shows that a metabolic trap is possible, and that some of the observed mutations make it more likely. If this is the case, Professor Davis believes that it should be possible push the patients out of this state by a specific metabolic intervention. He is very hopeful that this could be a one-time treatment, that takes only a few days, and be relatively inexpensive.

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Thank you.