The 2017 Invest in ME Research conference – held on Friday 2nd June

This year's conference was 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 expected, there was an excellent mixture of people with ME/CFS, carers and parents, charity representatives, health professionals and researchers from all over the world, and the conference was once again chaired – with usual good humour – by Dr Ian Gibson.

Overall, there was an emphasis on immunology and new approaches to research that are aimed at increasing our understanding of the underlying disease process in ME/CFS, how abnormalities that are being identified might link-in with each other, and how these findings could then lead to more effective forms of treatment.

Presentations covering treatment were largely focused on the clinical trials taking place in Norway into the use of Rituximab and cyclophosphamide.

My report follows the order of events on the day. As some presentations contained information on research or clinical trials that may be submitted for publication, this has been omitted so as not to prejudice future publication of the results. I have concentrated on reporting information that can be easily understood rather than complex scientific information that formed part of some presentations.

1. Dr Ian Gibson

Dr Ian Gibson opened the meeting with some quotes from a letter written by Sir Bruce Keogh, National Medical Director at NHS England, relating to discussions that are currently taking place at NICE.

The letter stated that NICE are considering the results from 3 US trials and the 2011 PACE trial as part of their decision-making process as to whether the 2007 NICE guideline on ME/CFS needs to be properly reviewed and updated.

Not surprising, the current NICE guideline recommendations relating to CBT and GET were also referred to in this letter.

2. Professor Ian Charles – Quadram Institute of Food Health, University of Norwich

Professor Charles spoke about the important overlap between food and health, the role of the microbiome (i.e. the various bacteria and viruses that inhabit various locations in the human body) in helping to regulate the body's immune system, and signalling systems that link the brain and gut – where they appear to play a role in normal mental/cognitive functioning. He explained how microbiome research is starting to provide important new insights about possible causal mechanisms in diseases such as diabetes and obesity.

Professor Charles updated the meeting on the new Quadram Institute Building in Norwich – where building work is nearing completion. They expect to be fully established there during the summer of 2018. This research site for food, health and environmental sciences in Norwich will become the largest single site for this type of research in Europe containing 3,000 scientists and 14,000 students. It will bring together the Norfolk and Norwich University Hospital (including the regional endoscopy service), the University of East Anglia and the pharmaceutical industry.

The presentation finished with a 'guided tour' video of the new Quadram building.

3. Dr Vicky Whittemore – Programme Director, National Institutes of Neurological Disorders and Stroke at NIH, USA

Dr Whittemore started off by explaining how the NIH (National Institutes of Health), which is an American equivalent of the UK Medical Research Council, operates and funds research.

There are 27 separate Institutes and Centres at NIH – each with a defined research agenda focused on specific diseases or body systems. The NIH funds both intramural (i.e. in house) research and extramural research at centres all over the world (including a £1.5 million grant to the ME Biobank here in the UK).

As ME/CFS is an illness that covers a wide range of symptoms and body systems (i.e. genetics, infection, brain, muscle, immune and endocrine systems) it now has 24 different homes at NIH!

Dr Whittemore emphasised that there had been a very welcome and significant shift in the NIH approach to ME/CFS and Dr Francis Collins, NIH Director, was very committed to ME/CFS research.

The most important initiative has been the re-establishment of the Trans-NIH ME/CFS working group in 2015. This group is chaired by Dr Walter Koroshtz and coordinated by Dr Whittemore. It has representatives from the 24 institutes and meets at monthly intervals.

Achievements so far include obtaining increased funding for ME/CFS research (now at $8 million per annum) and in January 2017 funding was announced to set up three collaborative research centres for ME/CFS in America.

Discussions are also underway with overseas research groups, including those in Canada and UK, who may want to link in to this NIH initiative. Some high-quality applications have been received and these will be reviewed in July. NIH aims to reach a decision and make a funding announcement in September.

Dr Avi Nath at NIH is leading some important internal research involving 40 people with ME/CFS; 20 healthy controls and 20 people who have recovered from Lyme disease. They will all have very careful assessments including detailed blood testing; exercise testing to study post-exertional malaise and tilt table testing to assess autonomic nervous system dysfunction.

NIH is also setting up an ME/CFS Data Management Co-ordinating Centre and arranging educational seminars on ME/CFS.

Website: www.nih.gov/mecfs Email: Vicky.Whitttemore@nih.gov

4. Professor Donald Staines – National Centre for Neuroimmunology and Emerging Diseases, Griffiths University, Australia

This presentation focused on the work that Professor Staines (pictured with Professor Sonya Marshall-Gradisnik) and his team in Queensland have been doing at a molecular level on cellular signalling mechanisms that involve calcium ions.

This is a process that could link in with some of the immune system disturbances found in ME/CFS.

As this is complex scientific material, and some of it has not yet been published, I will not go into any detail – apart from mentioning that it is possible that disturbances in the way that calcium ions are behaving in ME/CFS could form part of the underlying disease process.

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(2): 284–293. Published online 2016 Nov 23.
doi: 10.1111/cei.12882 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5217865/

CS note: One important question that was asked related to how these findings could be translated into treatment, especially using drugs that affect calcium ion channels in the body. At present this approach is very speculative.

However, it is interesting to note 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 ME Association's Explanation of the Key Clinical Issues.

5. Professor Nancy Klimas – Director, Institute for Neuroimmiune Medicine, Nova Southeastern University, USA

Although Professor Klimas is best known for her research on the immunology of ME/CFS, this presentation concentrated on the genetic component. She explained how genetic studies are very costly to perform and large numbers of patients – in the region of 30,000 – are required to get meaningful results.

Professor Klimas has assembled a large multidisciplinary team, which will be led by two 'Blue Ribbon Fellowship' medical students. The research will aim to understand the genetic risk in ME/CFS and the possible role of gene mutations (= permanent alterations in the DNA sequence that makes up a gene, such that the sequence differs from what is found in most people). This sort of information could help to provide a 'genetic signature' for ME/CFS and explain why some people recover from ME/CFS and others do not.

This is going to be a global study whereby people with a diagnosis of ME/CFS will be asked to donate clinical data using social media. 600 people have signed up so far.

Participation in the study requires participants to have a computer, an email account and agreement to map their genes using a genetic testing website. People who agree to participate will be asked to provide the research group with their raw genetic data to help compile an ME/CFS Genetic Database.

Besides providing genetic data, participants will be completing online surveys at their own pace. All communication is done via secure email server – so no travel is necessary and participation can be done from home.

More information, including a video, here: http://www.nova.edu/nim/research/mecfs-genes.html

CS note: After the presentation, I spoke to Professor Klimas about the UK MEGA research study and the overlap that this has with the one she is now doing.

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6. Dr Jakob Theorell – Karolinska Institute, Sweden

Dr Theorell's research is focused on people who have what are called immunodeficiency syndromes (i.e. their immune systems are not functioning effectively). In relation to ME/CFS, he has been looking at a specific part of the immune system orchestra called cytotoxic lymphocytes. These are cells that combat intracellular infections with dysfunctional abnormalities being reported in previous research studies.

He started off by describing the way in which NK (natural killer) cells act by recognising infected target cells, locking onto these target cells, and then releasing what are called pro-inflammatory cytokines. Several research studies have looked at the function and phenotype of cytotoxic lymphocytes in ME/CFS, but their role remains uncertain.

This study involved 48 people with ME/CFS (meeting Fukuda and Canadian criteria) in two independent cohorts from Oslo and Stockholm plus matched controls. The phenotype and function of lymphocytes in frozen and thawed PBMCs (peripheral blood mononuclear cells) was evaluated using flow cytometry and compared to cells from age and sex matched controls.

There were no consistent differences found between people with ME/CFS and healthy controls in the wide range of functional tests involving cytotoxic lymphocytes – e.g. cell numbers, activation status, target cell killing capacity and cytokine release. In addition, no clear subgroups were identified.

These results do not therefore point to a role for defects in lymphocyte cytotoxicity in ME/CFS. Neither do they support the use of NK cell function as a biomarker for ME/CFS.

Research paper:

Theorelli J et al. Unperturbed cytotoxic lymphocyte phenotype and function in myalgic encephalomyelitis/chronic fatigue syndrome patients
Front. Immunol. 26 June 2017 | doi: 10.3389/fimmu.2017.00723
http://journal.frontiersin.org/article/10.3389/fimmu.2017.00723/full

7. Fane Mensah – PhD student at University College London

This presentation consisted of a summary of key points from a paper which has reviewed the immunology of ME/CFS.

The most consistent abnormality to be reported in ME/CFS is a decrease in number and function of NK cells.

Studies that have looked at cytokines (= immune system chemicals) have produced inconsistent results. However, there is some emerging evidence of changes in the cytokine make up in relation to illness duration. There is no clear relationship between markers of immune system dysfunction and symptoms in ME/CFS at present.

Research paper:

Mensah F et al. Chronic fatigue syndrome and the immune system: Where are we now? Neurophysiol Clin. 2017 Apr; 47(2): 131-138. doi: 10.1016/j.neucli.2017.02.002. https://www.ncbi.nlm.nih.gov/pubmed/28410877

8. Dr Jo Cambridge – Professorial Research Assistant, University College London

Dr Cambridge belongs to a well-established research group at UCL that have a keen interest in drug treatment (i.e. Rituximab) that involves the depletion of an important component of the immune system orchestra called B cells.

This research, where Professor Jonathan Edwards has played a key role, helped to establish that drugs like Rituximab, can be a very effective form of treatment for some people who have a more severe form of rheumatoid arthritis (RA). Successful use in RA has led to Rituximab being used in other autoimmune rheumatic conditions like lupus/SLE.

Her research group have also been exploring how B cell depletion helps to modify the disease process in RA through removing what are called immune complexes and reducing inflammation in the joints and why there can be a marked variation in response between patients. One factor that has been identified is that B cell depletion therapy works best when autoantibodies (= antibodies that the body makes against its own tissues) are present.

As readers will be aware from previous IiMER conference reports, the group at UCL has been involved in looking at B cell status in people with ME/CFS and whether Rituximab could be an effective form of treatment. They are also now looking at whether autoantibodies could be involved in the blockage in energy metabolism (= energy production at a cellular level) that has been described by Drs Fluge and Mella in Norway.

CS note: This presentation did not contain an update on the proposal to carry out a clinical trial of Rituximab here in the UK. My understanding is that this will not now be taking place at UCL and the intention is to carry out the trial in Norwich. The Norwegian phase 3 clinical trial will finish in September 2017 and we expect the results to be published at some point in 2018. Hopefully, the Norwegian trial will confirm that Rituximab is a safe and effective form of treatment for at least a sub-group of people with ME/CFS and that this will then lead to a high-quality UK clinical trial.

9. Professor Simon Carding – Leader in Gut Health and Food Safety Programme, Institute of Food research, Norwich Research Park and University of East Anglia students

Professor Simon Carding introduced four PhD students who are working at the Institute of Food Research and carrying out research projects on components of a research hypothesis that involves the gut.

The hypothesis is looking at the possibility that a viral infection involving the lining of the intestine leads to alterations in the content of the gut microbiome. This then leads to inflammation in the lining of the gut and increased permeability of the intestinal wall (= a 'leaky gut"). Infection can then enter the body via the blood supply to the intestine, which leads to a more generalized inflammatory response.

As the PhD students explained, there is already some evidence of changes in the diversity of the microbiome in ME/CFS (studies by Hanson and Hornig in the USA for example) and this could lead to changes in the level of an immune system component in the gut lining called immunoglobulin A (IgA).

CS Note: This is an interesting hypothesis that is supported by some published evidence but it requires a lot more work to pull it all together. During the Q and A session I referred to the work of the UK post-mortem tissue research group – which collects intestinal tissue in

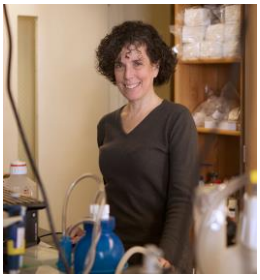
addition to muscle and brain – and offered to try and arrange for the Norwich group to have some intestinal specimens to look for pathological changes that would be consistent with their hypothesis.

Microbiota is the scientific name given to the collection of microorganisms that reside in various parts of the human body. Human beings are home to clusters of bacteria including the skin (= skin microbiota), the mouth = (oral microbiota), the vagina (= vaginal microbiota) etc.

The gut microbiota contains tens of trillions of microorganisms, including at least 1000 different species of known bacteria with more than 3 million genes (150 times more than human genes). Microbiota can, in total, weigh up to 2 kg. One third of our gut microbiota is common to most people, while two thirds are specific to each one of us.

In other words, the microbiota in the human intestine is like an individual identity card and when this becomes dysfunctional it has the potential to act as a diagnostic biomarker.

10. Professor Mady Hornig – Associate Professor, Centre for Infection and Immunity, Columbia University Mailman School of Public Health, New York



Professor Hornig is a regular visitor to these conferences. Her research focusses on the role of infective, immune and toxic stimuli in the development of conditions that range from autism to ME/CFS. She has a special interest in establishing how genes and maturational factors can interact with environmental triggers to lead to various brain disorders.

Her ME/CFS research has concentrated on establishing whether there are immune system profiles/signatures that are characteristic of the disease and identifying infections that are linked to ME/CFS.

The first part of her presentation looked at how the brain and the gut communicate and how the composition of the gut microbiome can influence brain development and behaviour. This links in with the observation that gastrointestinal co-morbidity is often present in neurological conditions – the presence of irritable bowel syndrome in ME/CFS being one example.

She also referred to some of the research that her group has carried out on the role of immune system chemicals called cytokines and how distinct 'cytokine signatures' are present during the early stages of ME/CFS. This 'signature' disappears over time as what might be termed 'immune system exhaustion' occurs. They have also looked at cytokines in cerebrospinal fluid in ME/CFS – where there were also some interesting changes in cytokine status.

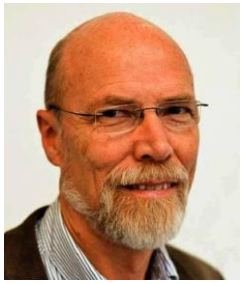
Professor Hornig summarised the results from a recently published study that had looked at microbiome profiles in people with ME/CFS and 50 healthy controls. They concluded that ME/CFS was associated with gut dysbiosis (= a microbe imbalance within the body) and there were interesting differences in profiles between people with ME/CFS who also had irritable bowel syndrome symptoms and those who did not.

Research paper:

Dorottya Nagy-Szakal et al. Fecal metagenomic profiles in subgroups of patients with myalgic encephalomyelitis/chronic fatigue syndrome. *Microbiome*, 2017; 5 (1) DOI: 10.1186/s40168-017-0261-y

https://microbiomejournal.biomedcentral.com/articles/10.1186/s40168-017-0261-y

11. Professor Olav Mella – Department Director, Oncology, Haukeland University Hospital, University of Bergen, Norway



Professor Mella spoke on the current state of two separate clinical trials in Norway involving Rituximab and cyclophosphamide. But he began by looking back at how Rituximab, a drug that is normally used in cancer treatment, especially in a condition called lymphoma where it depletes a key part of the immune system called B cells, became a possible treatment for ME/CFS.

As an oncologist, his interest in the use of this drug in ME/CFS occurred after 3 patients with lymphoma, who also had ME/CFS, noticed that their ME/CFS significantly improved whilst receiving Rituximab.

This led to a small clinical trial involving 30 patients receiving Rituximab and 30 patients receiving a placebo. There was a positive response in 10/15 in the treatment group and 2/15

in the placebo group**.** However, the response was transient and as the B cells returned so did the ME/CFS symptoms.

An open label phase 2 trial, where treatment was maintained over a longer period, also reported benefits. However, improvement was not found in people with more severe ME/CFS.

The Norwegian group are now in the final stages of what is called a double-blind, placebo-controlled phase 3 clinical trial.

This is a large multicentre trial involving 156 people with (Canadian criteria) ME/CFS (76 receiving Rituximab; 76 receiving a placebo infusion) who have received on-going treatment over a 12-month period followed by follow-up over 24 months.

The trial started in September 2014 and will finish in September 2017. The trial will be unblinded in October 2017.

Progress will be measured by a series of outcome measures – quality of life on the SF36 questionnaire; fatigue scales; total functional level; activity armbands etc – as well as taking careful note of any adverse reactions (but no serious side-effects have been reported so far).

Several sub-group studies, including cardiopulmonary exercise testing, gastrointestinal function and endothelial function/tone of the arterial blood vessel wall – will also be included.

The results will then be analysed and submitted for publication. No announcement will be made until publication of the results in a medical journal - which should occur in 2018.

Professor Mella also spoke about their cyclophosphamide trial. This is again based on a small pilot study where benefits for ME/CFS were reported by 2 out of 3 women with breast cancer who also had ME/CFS. The Norwegian group are now conducting a two-centre phase 2 clinical trial involving 40 people with (Canadian criteria) ME/CFS. The final patient in this trial will finish treatment in July 2017.

CS note: Cyclophosphamide is a drug that acts by suppressing the immune system. As with Rituximab, it is used for some types of cancer – as well as conditions where it is used to dampen down an over active immune system response. As with its use in cancer, some

people with ME/CFS experience nausea and vomiting and some have a transient exacerbation of their ME/CFS symptoms.

12. Dr Ingrid Rekeland, Dept of Oncology, Haukeland University Hospital, University of Bergen, Norway

Dr Rekeland took the place of Dr Oysten Fluge, who was unable to attend due to an accident. Dr Rekeland spoke about another important item of research being carried out by the Norwegian group.

This is looking at whether there is a metabolic obstruction in the pathway that creates glucose into energy inside the mitochondria and whether this could help to explain some of the key symptoms of ME/CFS and the rise in lactic acid production on exertion that is seen in some people with ME/CFS.

This is complex and science involving biochemical reactions that take place at a cellular level which appear to be producing an impairment of a key enzyme called pyruvate dehydrogenase.

The study design hypothesised that changes in serum amino acids may disclose specific defects in energy metabolism in ME/CFS. Analysis in 200 ME/CFS patients and 102 healthy individuals showed a specific reduction of amino acids that fuel oxidative metabolism via the tricarboxylic acetic acid (TCA) cycle, mainly in female ME/CFS patients.

Serum 3-methylhistidine, a marker of endogenous protein catabolism, was significantly increased in male patients. The amino acid pattern suggested functional impairment of pyruvate dehydrogenase (PDH), supported by increased mRNA expression of the inhibitory PDH kinases 1, 2, and 4; sirtuin 4; and PPARδ in peripheral blood mononuclear cells from both sexes.

Myoblasts grown in presence of serum from patients with severe ME/CFS showed metabolic adaptations, including increased mitochondrial respiration and excessive lactate secretion.

The amino acid changes could not be explained by symptom severity, disease duration, age, BMI, or physical activity level among patients.

These findings agree with the clinical disease presentation of ME/CFS: inadequate ATP generation by oxidative phosphorylation and excessive lactate generation upon exertion.

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. doi: 10.1172/jci.insight.89376. https://insight.jci.org/articles/view/89376

13. Professor Warren Tate – Group Leader, Biochemistry Department, School of Biomedical Sciences, University of Otago, New Zealand

Professor Tate opened his presentation by explaining that his research interest in ME/CFS resulted from his daughter developing the illness when she was just 14 years old, following an episode of glandular fever.

He likened the hunt for the cause of ME/CFS to a large jigsaw puzzle where we had some of the pieces in place. But there were still plenty of large pieces missing and a great deal of uncertainty as to how to join the pieces together.

So, he had a long list of questions that need answering – some of which he is now investigating using his expertise as an internationally respected molecular biologist who has revolutionized our understanding of how proteins are synthesized in living cells.

Among the many questions, are:

- Which physiological 'control centre' in the body is affected to create such a severe and diverse range of symptoms?
- What factors perpetuate the illness?
- What triggers cause the characteristic and frequent relapses that occur during the chronic disease process?
- Why do symptoms often improve during pregnancy?
- Which dysfunctional pathways do we need to examine in more detail?

To help find the missing pieces, he is using the Precision Medicine approach where multiple tests are carried out on small numbers of patients. For example, the Dunedin study is looking at various aspects of the disease in 10 people with ME/CFS and 10 healthy controls.

Other research studies in progress include:

- ✓ Analysis of immune system chemicals called cytokines and plasma microRNAs (= small molecules of RNA that can have profound effects on all aspects of body physiology)
- ✓ An exercise response study in Palmerston North being carried out by Lynette Hodges. This will involves measuring cardiopulmonary function during exercise (as the VanNess studies have done) *
- ✓ A study which is collecting data on what is called immune cell expressed genes (transcriptome) and proteins (proteome)
- ✓ Mitochondrial function and epigenetic changes in the DNA (=genetic material) of cells

In addition to trying to gain a better understanding of the underlying disease process in ME/CFS (where Professor Tate believes that a chronic and fluctuating autoimmune-inflammation involving the paraventricular nucleus in the hypothalamus could be playing a key role) this research is also examining whether a combination of molecular abnormalities could be used to develop a diagnostic test.

*This study has now been published and we will be featuring a lay summary of it on our website in due course: http://onlinelibrary.wiley.com/wol1/doi/10.1111/cpf.12460/abstract

14. Professor Ron Davis - Professor of Biochemistry and Genetics, Stanford School of Medicine, California, USA

Professor Davis also became involved in ME/CFS research because of having a seriously ill family member – his son Whitney. He updated the meeting on the various strands to his research that is looking at the molecular basis to ME/CFS and how this should help to increase both our understanding of the underlying disease process and to provide effective forms of treatment.

This is largely being done through the generous support of his colleagues at the University of Stanford in California, because he has not been successful in obtaining a research grant from the National Institutes of Health.

The first study is focussing on people with severe ME/CFS (20 patients and 10 healthy controls from family members living in the same environment) and involves the collection of

what is called 'big data'. Professor Davis went through a long list of investigations that are being carried out in this group – cell free DNA quantification, viral sequencing, gene expression and whole genome analysis, HLA sequencing, immunology - including cytokine measurements, metabolomics – including defects in the tricarboxylic acid (TCA) or Krebs cycle, and mitochondrial DNA in the severe cases.

The group are also looking for evidence of viral infections (no viruses were detected in most of the patients) and searching for new pathogens/infections in people with ME/CFS (none being found so far).

Professor Davis presented some preliminary results on some of these important new studies and referred to the possible use of drugs that are being used to treat other illnesses – one example being Suramin, which has been used to treat African sleeping sickness and is now being assessed in autism.

- Video explanation of the TCA or Krebs cycle: https://www.khanacademy.org/science/biology/cellular-respiration-and-fermentation/pyruvate-oxidation-and-the-citric-acid-cycle/v/krebs-citric-acid-cycle

Conclusion

The meeting closed with a review of the day from Dr Ian Gibson.

This was an interesting, encouraging and informative conference that covered a number of important new approaches to the way in which the investigation of the underlying disease process in ME/CFS, as well as the development of diagnostic biomarkers, is moving forward.

Hopefully, these developments will also lead to much needed treatments that are aimed at causation rather than symptoms control – as is currently the case.

Thanks to everyone involved in both the organization of this event and the people who gave the presentations.

Dr Charles Shepherd

Hon Medical Adviser, ME Association.

Further information

- A DVD of the conference proceedings can be ordered here:
  http://www.investinme.eu/IIMEC12.shtml#dvd

How you can help the ME Association

If you have found this information useful, then please donate – whatever you can afford – to help us continue with our work of trying to make the UK a better place for people with ME/CFS. Just click the button below:

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Or why not join the ME Association as a member and become part of our community? For a monthly (or annual) payment you will not only be helping to keep us doing what we do best, but you will receive ME Essential magazine – with exclusive content – delivered straight to your door.
