UK CFS/ME Research Collaborative

Report of the fourth Annual Science Conference

13 and 14 September 2017, Bristol

Sponsored by the Medical Research Council and Arthritis Research UK

UK CFS/ME RESEARCH COLLABORATIVE

MRC Medical Research Council

action for m·e

me

wellcome trust

NHS National Institute for Health Research

ARTHRITIS RESEARCH UK

#CMRC2017

Pictured on the cover, from top left:

- Physiotherapist Emily Tims and Occupational Therapist Beverly Knops, with some of the poster presentations
- Prof José Montoya, Stanford ME/CFS Initiative, presenting the Anne Faulkner Memorial Lecture, on day two of the conference
- Prof Stephen Holgate, CMRC Chair
- Prof Julia Newton discussing opportunities for collaboration with other delegates.

Uniting behind a common goal

Now in its fourth year, the UK CFS/ME Research Collaborative (CMRC)'s annual conference, held in Bristol in September 2017, brought together scientists, clinicians, industry professionals and people affected by M.E.

The buzz this year was palpable. For me, it really feels like the mood has changed, and that everyone there felt able to unite behind a common goal – to unlock the biology of M.E.

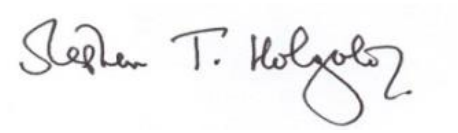
It's a feeling echoed elsewhere. Since the conference, the US National Institutes of Health has announced four grants for CFS/ME research totalling more than $7 million, with the aim of establishing a coordinated scientific research network, with three research centres and a data management site working as a consortium to further the understanding of CFS/ME. I look forward to exploring how the CMRC can contribute to, and build on, such powerful foundations.

On behalf of the CMRC Executive Board I extend a sincere thank you to all those whose energy and enthusiasm made the conference possible, including our sponsors the Medical Research Council and Arthritis UK, and to delegates and speakers who travelled from America, Australia and Europe.

My particular thanks go to volunteers Karen Hainsworth, Emily Beardall, Katrina Pears, Rachel Ephgrave and Charlotte Stephens, who dedicated considerable time and energy to write this report, with contributions from Dr Charles Shepherd, Honorary Medical Advisor, ME Association, and Clare Ogden, Head of Communications and Policy, Action for M.E.

I am also hugely grateful to the Action for M.E. staff team, led by Sonya Chowdhury, for organising the conference, and for filming the presentations – which have been viewed more than 7,400 times since at www.tinyurl.com/actionformeyoutube

With input from patients and professionals at the conference, we are already thinking about next year's event (see p 49), and what needs to happen to make it truly patient-centred. As someone with a keen interest in M.E. research, your input will be invaluable. Please, join us – I hope to see you there.



Stephen Holgate
CMRC Chair

A note on terminology
The terms ME and CFS were both used throughout the conference, with some speakers using one or the other, and some using them interchangeably. This report uses the term CFS/ME throughout, except when it is quoting a speaker directly.

Conference reflections

Dr Charles Shepherd, Honorary Medical Adviser, ME Association says:

"Overall, it was a busy, stimulating, and very enjoyable event. It has also been the most impressive open international biomedical research conference to take place this year and the only one where the public are provided with almost instant access to videos covering most of the presentations and to this summary. I would like to add my congratulations to the CMRC and the event organisers. Well done CMRC!

"We were fully booked with both UK and overseas researchers – a good proportion being students or established researchers who are new to ME/CFS research. This year the ME Association (with the help of a private donor) sponsored five students to attend the conference. There was no particular emphasis to the conference, with presentations, posters and workshops covering a wide range of research topics. However, a theme running through many of the key presentations was the need for meaningful collaboration among researchers, and involvement from the patient community when research is being planned and protocols developed. It was also stressed that while fatigue is an important part of ME/CFS, this is a multisystem disease with a range of other core symptoms.

"What I found particularly helpful was to have the world's two leading experts on autonomic nervous system dysfunction in ME/CFS – Profs Julia Newton and Peter Rowe – together to talk about orthostatic intolerance, neurally mediated hypotension and postural tachycardia syndrome in ME/CFS. And, having several presentations on how different types of neuroimaging are helping us to understand the neuropathology of ME/CFS, were very welcome."

Katrina Pears, volunteer, Action for M.E. says:

"I was very fortunate to attend this year's CMRC conference and help Action for M.E. out in some of the organisation. Although this was not the first research conference I have been to, it was the first CMRC conference, which completely exceeded my expectations.

"The two days were very tiring, but I also found it a very rewarding and worthwhile experience, knowing that slowly we are starting to understand some of the biology behind this horrible illness, and that there is a reason why we feel this way. The talks themselves covered a wide range of topics, with something for everyone, with some more heavy on the biology than others, such as brain imaging, orthostatic intolerance, and chemical compositions of the blood. I found all the speakers very engaging and passionate about their research, and the talks were interesting to listen to.

"On the second day, I had the opportunity to attend one of the workshops on orthostatic intolerance, and found this a very useful experience with tips for managing my own condition. Outside of the talks, there were plenty of opportunities to engage with the speakers about their research, and ask questions. I found everyone very approachable with a lot of common ground to talk about. For the talks I found too much to take in at the time, it's great to know that I can go back and watch them on YouTube."

Contents

Plenary Session: Catalysing Collaboration

Welcome
Prof Stephen Holgate, CMRC Chair, University of Southampton

Welcoming participants to the conference, Prof Stephen Holgate, Professor of Immunopharmacology and Chair of the CFS/ME Research Collaborative (CMRC), said he was impressed by the research carried out over the past 12 months, both in the UK and abroad.

Of great importance, he felt, was that the National Institutes of Health (NIH) was now taking this illness seriously, with activities "not least of which is the phenotyping of patients with post-infectious CFS/ME." He also highlighted an NIH biomarker study looking at the severely affected. This vulnerable group are clearly a high priority in the US with the Open Medicine Foundation already fundraising for phase two of a project searching for biomarkers in the severely ill.

Turning his focus to the UK, Prof Holgate moved on to the recent work of the CMRC and reiterated his original aims for the collaboration that he started four years ago. Having recognised there were tremendously challenging questions to be answered, he'd decided upon two goals. The first was to improve the quality of research in CFS/ME.

The second was "to try to persuade people to come out of different fields of medical science to engage with us and bring in new methodology and technology." And things are on track.

Over the past 12 months, the CRC has experienced some "extraordinary interactions" and there were some exciting changes to come, he explained. But there had been some losses too with Profs Hugh Perry and Julia Newton stepping down from the CMRC Executive Board to focus on other roles, though both still continue to actively support the work of the CMRC.

"I'm delighted to say that Prof Patrick Chinnery who works at the Mitochondrial Unit at Cambridge – a brilliant scientist working in Multiple Sclerosis and mitochondrial metabolism – is joining in place of Hugh Perry," continued Prof Holgate. "So we will have that neuroscience connection which is very important to the executive."

Engaging with industry

He went on to thank several people who were now working with the CMRC, including Mark Edwards (see p 45), Executive Board member, who was helping the CMRC interface with the biotechnology sector; Mark Dalrympol from Life Arc, a new biotech charity spun out of a Medical Research Council (MRC) team which will support CFS/ME translational research; Mark Jones from UCB, a biopharmaceutical company focusing on neurology and immunology; and James Brodie from pharmaceutical giant Glaxo-Smith Klein, who has an interest in the neuroscience of CFS/ME.

"Though these are all starting points," Prof Holgate said, "it does indicate that industry is interested and wants to engage with us even though we don't have any simple targets to be able to present to them now. The fact they've joined us is terrific."

Co-sponsors of the CMRC conference, Arthritis UK, are also keen to work collaboratively. Having recently created a new pain road map with the charity, Prof Holgate was inspired by its patient-centered view. Joint projects are on the cards.

Not everyone wanted to jump aboard however. The Academy of Medical Sciences had declined to commission a hard-hitting report on CFS/ME – the equivalent of work undertaken in the US by the Institute of Medicine – after being approached by Pro Holgate. "I felt that we needed some high-level politics in medicine to start to pull some levers to get this dreadful condition recognised more sincerely," he explained. But the Academy weren't interested. There is a chance however they could support a pain and fatigue report led by Arthritis UK.

As usual, money for research was in short supply. Even so, the MRC were now funding 17% of CFS/ME proposals submitted to them compared with 0% two years ago. Prof Holgate acknowledged this may sound disappointing but explained it was a very important change of direction.

"As we start to ramp up the quality of research you won't just see a switch and suddenly money pouring in. You'll see people almost getting there but not quite, reconfiguring their applications and then coming back in a different way. So this is the right direction of travel and I think it's wonderful that we are seeing this happening now."

Neha Issar Brown, Programme Manager at the MRC was, "very keen indeed that this connectivity with the MRC remains," he said, "and we are very keen to ensure it does as well."

Commenting on the recent funding application to the MRC by the MEGA bioresource, Prof Holgate explained that the MEGA team, led by Prof Esther Crawley, had seen off more than 50 other applicants to reach the final interview stage, but was unfortunately not successful.

"But I can tell you this is not the end by any means," he said. And having learned from the MRC feedback, the MEGA team will be looking for funding elsewhere.

Encouraging developments

Returning to international collaborations, Prof Holgate was encouraged by an upcoming meeting with a key player in the US. UK scientists will attend a meeting with the NIH's Vicky Whitmore, "who has taken a great interest in what this collaborative is doing," he said. He hoped joint NIH/UK initiatives would emerge.

Prof Holgate concluded by saying that the CMRC was in a much stronger place than four years ago with a tremendous group of people on board. "But the strength of the organisation depends on you all," he said looking into the audience of patients and scientists. The plan now is to revisit the vision of the collaborative and consider the focus for the next two or three years. And he confirmed later that the CMRC would be launching patient-led initiatives as an important part of that picture.

You can watch a film of this presentation at www.tinyurl.com/actionformeyoutube

Plenary Session: Biology of CFS/ME

Post-infectious CFS/ME study at National Institutes of Health
Dr Avindra Nath, National Institutes of Health

An expert in how infections affect the central nervous system, Dr Avindra Nath is relatively new to CFS/ME research. He presented a new National Institutes of Health (NIH) program to investigate if immune dysregulation may contribute to the pathophysiology of CFS/ME and if immune therapy can alter the course of the illness. The studies will be focused on a defined subset of patients who have an infection like illness at onset, as these patients are most likely to have similarities in immune profiles.

The NIH has tried hard to collaborate with and gain the confidence of the CFS/ME community, said Dr Nath, through regular seminars and meeting with advocates. It has tried to take any comments on board and understand the main concerns of the community, such as their illness not being taken seriously or being branded as psychological.

Post-infectious hypothesis

The overall hypothesis is that post-infectious CFS/ME is triggered by a viral illness that results in immune-mediated brain dysfunction. The NIH has proposed a three-phase study; the first phase is a cross sectional study to define the post-infectious CFS/ME phenotype and its pathophysiology. Phase two will validate the biomarkers found in phase 1 in a longitudinal study and phase three will be an early phase intervention trial that will target the biomarkers validated in phase two.

The presentation focused on phase one, the cross-sectional study, currently being carried out. Recruitment will include 40 post-infectious CFS/ME patients and 40 controls, 20 of which are healthy; the other 20 will be recovered Lyme disease patients without fatigue. Selection criteria for the CFS/ME cohort includes documentation of onset following infection, meeting accepted criteria for CFS/ME and having a symptoms for a duration of over six months but less than five years.

The first aim of this study is to define the clinical phenotype using in-depth assessments for all domains of the illness. Extensive testing of subjects is carried out for phenotyping, including medical history, physical exams, an extensive panel of blood work, neurological assessment, psychiatric evaluation, neuropsychological assessment, autonomic testing, rheumatologic evaluation structural MRI scans of the brain and exercise capacity testing. After the extensive phenotyping process, each patients' data is reviewed by a board of five experts, for a unanimous agreement on whether the patient is considered a suitable post-infectious CFS/ME patient to participate in the study.

The second aim is to determine the underlying physiology of fatigue by collecting and analysing a range of samples, tests and questionnaires. The patients are first taken off any non-essential medication that may affect these results. Samples for collection include saliva, stool, blood and cerebrospinal fluid.

Tests include functional MRI's of the brain, metabolic studies in a metabolic chamber (such as measuring energy expenditure and utilisation of oxygen), transcranial magnetic stimulation and detailed autonomic testing. Many different symptomatic questionnaires are also administered, including the multidimensional fatigue inventory, neuropathic pain scale and Beck depression inventory.

To measure the effects and physiological mechanisms behind post exertional malaise, each of these tests are carried out before and after an exercise stress test (cardiopulmonary exercise test), to induce post-exertional malaise. Blood, cerebrospinal fluid and symptomatic questionnaires are collected one hour before and after CPET and then 24, 48, and 72 hours after.

The third aim of the study is to determine if there are abnormal immune and microbiome profiles, through detailed immunological studies in blood and spinal fluid, including screening for autoantibodies to neural antigens.

Finally, the fourth aim is to determine if these features can be reproduced in a laboratory environment in ex-vivo studies, using pluripotent stem cells and mice models. If a disease model can be made through these methods, it would be very helpful in trying to identify the cause and pathophysiology of the illness, as well as developing treatment approaches.

The study has only just started, but initial experience seems encouraging. Patients have tolerated the procedures well and the team of investigators remain enthusiastic, committed and dedicated to the cause. It will be some time before the study is completed and published but it has the makings of a very extensive, well designed and encouraging research.

You can watch a film of this presentation at www.tinyurl.com/actionformeyoutube

Imaging in research
Dr Matt Wall, Imanova Centre for Imaging Sciences

Dr Wall explained that Imanova is a translational research company that specialises in applying positron emission tomography (PET) and magnetic resonance imaging (MRI) scanning techniques to early drug development and improving our understanding of disease causation.

Established in 2011, Imanova involved an alliance between the MRC, Imperial College London, King's College London and University College London, to act as a centre of excellence for imaging sciences in the UK and as a conduit between academia and industry. Imanova is now part of a USA company called Invicro.

By working with academics and commercial pharmaceutical companies, Dr Wall explained how new types of neuroimaging (including combinations of MRI and PET scanners) could be used in both research aimed at causation of disease such as ME/CFS and in clinical trials of new drug treatments. PET scans, for example, can demonstrate that a drug crosses the blood brain barrier and enters the central nervous system, or give more detailed quantitative information about neurochemistry and brain receptor densities.

MRI can give a number of useful readouts in the brain, including detailed structural, functional, and metabolic data. By combining the two techniques the entire pathway of a drug response, or a pathological disease process, can be investigated. Examples from recent work on Multiple Sclerosis were given, where a combined PET and MRI study had revealed that inflammation in the hippocampus was closely related to both hippocampal function, and the clinical symptomatology of MS (particularly in the depressive symptoms often seen in MS patients).

In conclusion, said Dr Wall, PET and functional MRI are both powerful techniques, but using them together in combination is where they can really deliver, as the strengths of one technique complement the other. By using them to effectively characterise disease states, we have a better chance of designing targeted interventions, which we can then evaluate using similar methods.

You can watch a film of this presentation at www.tinyurl.com/actionformeyoutube

The challenge of chronic pain: how neuroscience can help

Prof Maria Fitzgerald, University College, London

Pain has a biological adaptive purpose as a response to actual or potential tissue damage, explained Prof Fitzgerald. It acts as a warning or to make us escape from a dangerous situation, to rest in order to heal, and to learn to avoid pain in the future. Chronic pain is often maladaptive as it may not be related to an actual injury, as in back pain, fibromyalgia or migraine. Chronic pain can cause suffering, depression, anxiety, and lack of mobility. In turn this causes a huge economic burden due to working days lost.

Changes in neural connections within spinal cord nociceptive circuits following injury can account for many aspects of chronic pain and the characteristics of "difficult to explain" clinical pain syndromes. The pain is too intense, too prolonged, too widespread to be related to injury, and is triggered by non-noxious stimulation, so there is hyperalgesia and allodynia. This is caused by decreased inhibitory neuronal function and dysfunctional descending control systems in the spinal cord.

In chronic pain there is a neuroimmune interaction, as there is microglial activation around nociceptor terminals in the spinal cord after peripheral nerve damage, and this is part of an integrated protection against harm.

There are several risk factors which together increase the risk of developing chronic pain; these include gender, genotype and epigenetic profile; and environmental influences such as acute injury or disease; and the interaction between these.

Measuring chronic pain

Visual analogue scales where the patient is asked to score their pain from zero to 10 are used but they are inadequate as they are subjective and a more objective measure is needed, for example as an end point to evaluate treatment benefit.
Biomarkers involving sensory testing, skin biopsy and functional brain imaging are being explored. Sensory testing measuring the patient's threshold for heat, cold, pain, vibration and pressure found clusters within fibromyalgia for sensory loss, thermal hyperalgesia and mechanical hyperalgesia, and predicted the efficacy of analgesics (Baron R et al. 2017, *Pain*).

Skin biopsies showed that compared with control subjects, patients with fibromyalgia syndrome but not patients with depression had impaired small fibre function with increased cold and warm detection thresholds in quantitative sensory testing (Üçeyler D et al. 2013, *Brain*). Methods of brain imaging for chronic pain include functional magnetic imaging (fMRI) for regions showing increased activity, resting networks showing which regions are closely correlated activity, and structural brain imaging showing where cortical thickness and differences in white matter tracts.

Prof Fitzgerald finished by saying that there is a move away from one-size-fits-all approach towards greater pain subgrouping and phenotypes. Etiology, genotype, and environmental factors lead to individual pathophysiological changes and individual pain profiles. Precise diagnostic tools are a prerequisite to define the pain phenotype so that individualised treatment of pathophysiology can be given.

Transient receptor potential ion channels and impaired calcium signalling in natural killer (NK) cells in CFS/ME patients

Prof Don Staines, National Centre for Neuroimmunology and Emerging Diseases (NCNED), Griffith University, Australia

Prof Staines acknowledged the NCNED team led by Prof Sonya Marshall-Gradisnik and himself and the team's research into the possible role of impaired homeostasis due to defective transient receptor potential (TRP) ion channels. These are crucial players in a complex process of intracellular calcium signalling and have a huge impact on the human organism.

"We know that this illness is characterised by immune dysfunction," he said, and acknowledged the strong history of research into natural killer (NK) cells in CFS/ME. Varying in type, NK cells are responsible for attacking infected or cancerous cells. They stand alone in that they enable researchers to correlate illness impact with cellular dysfunction, he said.

Prof Staines made it very clear, however, that the illness is not solely about NK cells: "I want you to think of this as a metaphor or exemplar of what may be happening in every cell, in every tissue, in every organ in the body that expresses this particular receptor type."

While NK cells have an important role in immune defence, they provide a model that can be measured in the lab. It is the TRP ion channels, which sit mostly on the cell surface allowing calcium into the cell, that are the real focus. Their journey started by looking at whether there was a difference in NK cell function between people with CFS/ME and controls.

"In studies we can very clearly see that the percentage of lysis is impaired compared with unfatigued healthy controls," he explained "and longitudinal research over 12 to 18 months shows a prolonged sustained impairment of NK cell activity in people with CFS/ME."

The role of genetics

Genetics seem to be playing a role. The Griffith team have found Single Nucleotide Polymorphisms (SNPs) within TRP ion channel genes in patients compared with controls. "It's not an all or nothing but you do see significant differences." And there are really quite marked odds ratios.

If you've got that combination of SNPs then the odds are between three and seven fold that you will be associated with the illness, he explained.

The most prevalent polymorphisms appear to be in the TRPM3 ion channel. "That really stood out to us as being significant. The TRPM3 gene has more isoforms than any other TRP type and are widely distributed throughout the body, certainly in areas such as brain and pancreas."

"The intriguing thing is they are also known as threat receptors," said Prof Staines. Their role is to receive and regulate incoming threats and translate them into calcium signalling as a way of managing homeostasis"

"There's an incredible variety of things that are perceived as a threat by the human organism," he said. Triggers include changes in osmotic pressure and stretch induced by exercise, vibration

experienced during travel, or viral, bacterial or parasitic infections. Temperature changes, perfumes, cigarette smoke and petrol vapours are in the list too.

It's not entirely clear how such an event is triggered but essentially it allows calcium as the second messenger to enter into the cell. "This conveys a message to every cell, every tissue, every organ in the body that holds these particular receptors and they pretty much all do with a certain amount of variation," he said.

What's more the signal is likely amplified as it moves through the signalling cascade. "So if there are abnormalities in these receptors then the necessary amplification of calcium signalling required to restore homeostasis and prevent detrimental effects from happening can be exacerbated. And that's a very important point to understand with this illness, we think."

But CFS/ME patients not only have apparently defective TRPM3 receptors. The NCNED team has also found decreased TRPM3 receptor expression on the cell surface in patients with CFS/ME.

The Griffith team are keen to search for therapeutic drugs. Using flow cytometry they can test how much calcium flows into the cell while subjecting it to different interventions. It's fairly tricky, said Prof Staines but by using agents which block the amount of calcium coming into the cell at a molecular level and drugs which deplete the amount of calcium in the endoplasmic reticulum, they can assess the efficacy of drug interventions.

Prof Staines was keen to point out the complexity of the calcium signalling system. Not only does calcium have enormous control over gene expression and various biochemical pathways, but it is also closely integrated with the cyclic AMP internal secondary messenger system. These are arguably two of the most important intracellular systems and very closely related, he said.

"Together they have a very powerful role in long term potentiation in the brain which is about memory formation and concentration," said Prof Staines. "Also these receptors are located in the pancreas where they regulate insulin secretion. And one of the characteristics of ME/CFS is the crash that people have for any number of reasons and it arguably involves the insulin regulation system".

"What we're seeing is a far more complex and integrated mechanism of pathology than we first imagined," said Prof Staines.

Fatigue and arthritis: what are the issues for research?
Prof Alan Silman, University of Oxford

Prof Silman began by explaining that there are three broad groups of musculoskeletal disorders, where the predominant characteristic is:

- inflammation, eg. rheumatoid arthritis (RA), lupus
- musculoskeletal pain, eg. osteoarthritis, chronic back pain
- bone fracture, eg. osteoporosis.

Inflammatory disorders have an overall prevalence of around 1% and degenerative disorders of around 30%. Fractures due to osteoporosis have a lifetime incidence of 33% in women and 20% in men. Inflammatory disorders can affect any age group from children through to the elderly, whereas degenerative disorders, osteoporotic fractures mostly affect the elderly.

The World Bank has investigated the global burden of diseases, producing a figure calculated by severity, proportion affected and duration. Although heart disease and cancer are very severe diseases, their impact on individual sufferers is not necessarily life-long. Musculoskeletal diseases are chronic, with symptoms persisting for several decades of a person's life, so these were found to have the highest global burden.

Why does arthritis cause fatigue?

Fatigue is as important a symptom in arthritis as any of the others but until recently, clinicians and researchers have not focused on this. RA, as an example of inflammatory disease, is characterised by swelling, pain, pain on movement, tenderness, and warmth of the joint.

Sjögren's syndrome is another inflammatory condition, which has become more widely known because the tennis player Venus Williams has this disease. This is an autoimmune condition damaging the lacrimal and salivary glands causing dry eyes and dry mouth. Sjögren's also characteristically causes profound fatigue compared with the other inflammatory conditions. It is still unclear, says Prof Silman, whether fatigue is being caused by a common mechanism across all autoimmune inflammatory conditions. One simple marker for inflammation in the body is C-reactive protein, which is raised in many of these disorders. Other molecules produced include TNF, Interleukin-1 and Interleukin-6 which lead to end-organ destruction.

The systemic effects of Interleukin-6 in RA may cause fatigue via a number of different pathways, including increasing the risk of cardiovascular disease, such as angina and heart failure, which is the major cause of premature death in those with this condition.

Treatments such as methotrexate, which is the first drug of choice in RA, controls the joint inflammation, and more recently the Interleukin-6 receptor blocker tocilizumab and TNF receptor blocker adalimumab are being used. A 2016 Cochrane review of 32 studies found that regardless of which drug and which mechanism of action used to reduce inflammation, there is a reduction in fatigue.

This suggests that there is not a single mechanism causing fatigue but that these processes are intertwined. Although there is an initial reduction in fatigue in the first few months after

treatment of the inflammation, there is a levelling off. There is a worthwhile reduction in fatigue but the effect is not sustained.

Prof Silman set out a number of reasons why arthritic pain might cause fatigue, as follows.

- A central mechanism: Touching an inflamed joint is painful but we also know that there is a central component to pain, so when an arthritic knee joint is replaced the pain continues long afterwards. The molecules causing inflammatory pain also cause fatigue, so there may be a common underlying central mechanism between chronic pain and fatigue which could account for the residual fatigue after reduction of inflammatory molecules such as C-reactive protein.
- Sleep disturbance: Pain delays the onset of sleep because it is uncomfortable, patients wake early and concomitant depression may also cause sleep disturbance. There is discussion about the directionality as it has been suggested that disturbed sleep may cause the immune disturbance leading to inflammatory arthritis.
- Struggling through everyday tasks with the functional impairment caused by the arthritis.
- Co-morbidities such as anaemia, heart disease, other autoimmune diseases such as underactive thyroid, and depression may also contribute to fatigue in inflammatory arthritis.
- Medication side effects: Corticosteroids used in inflammatory disorders can make some feel elated but others may feel fatigued. Glucosamine and chondroitin supplements often bought by patients with arthritis can also contribute to fatigue.

He ended his presentation by setting out some research priorities, which included better phenotyping of fatigue, in order to stratify, and enhanced data collection about fatigue in clinical practice. Are there disease-specific issues or lessons learnt, he asked, and why does fatigue persist when all causes seem to have been reversed?

You can watch a film of this presentation at www.tinyurl.com/actionformeyoutube

Examining joint hypermobility syndrome in a London fatigue clinic
Gina Wall, Physiotherapist, Royal Free Hospital Fatigue Service

Joint hypermobility syndrome (JHS) is a heritable disorder of connective tissue thought to be due to problems with the genetic coding for collagen synthesis, regulation and organisation. Symptoms include pain and laxity in multiple joints, which can in some instances be involved in joint subluxations and dislocations or recurrent sprains or strains. Other symptoms can overlap with those of CFS/ME and related disorders.

Other conditions under this umbrella (now known as hypermobility spectrum disorders) include Marfans' syndrome, Ehlers Danlos syndrome and Osteogenesis Imperfecta. JHS has an autosomal dominant pattern of heritability and first-degree relatives with JHS can be identified in 50% of cases. JHS is related to age, sex and race, with women and Asian and Afro-Caribbean ethnic groups being more prone, while diminishing with age.

People with JHS have a stretchiness to their skin and soft tissues which results in a greater degree of flexibility in some or all areas of their body, commonly referred to as being double-jointed.

The study presented was an audit of new patients referred to the Royal Free Hospital Fatigue Service, and who were questioned for symptoms of JHS; the audit was undertaken by Ms Wall, Dr Gabrielle Murphy and Dr Kelly Morris

Ms Wall and Dr Murphy, Clinical Lead at the service, had noticed a high number of patients reporting that they, and also members of their family, are double-jointed. So an audit was carried out to establish the prevalence of JHS in newly-referred patients throughout one year to improve patient care.

There are many neuromusculoskeletal symptoms that may also overlap with JHS, including back pain, fibromyalgia, temporomandibular joint dysfunction, Raynaud's syndrome, osteoarthritis and gastrointestinal dysfunction.

All collagen has a triple helix structure of amino acids, with different collagen types having different properties based on the interlinking segments. This is where mutations in amino acid encoding may influence collagen function.

Ms Wall said that biopsychosocial assessment of persistent symptoms (fatigue, widespread pain, autonomic dysregulation) is becoming more in-depth. Recognising traits and symptoms of JHS enables more detailed patient education and empowerment for the sub-group of fatigue patients with this condition. This also may lead to further evolution of how specialist clinics interact, and the MRC has highlighted sub-phenotyping as a key priority for research in CFS/ME.

Audit method and results

All new patients (GP referrals) seen at the Royal Free fatigue service for fatigue symptoms were audited and assessed for JHS over a 10-month period. All new patients assessed by Dr Murphy were given a five-point questionnaire to identify JHS (Hakim and Grahame, 2003). This tool is quick and easy to complete as the questionnaires have yes/no answers, and it has 84%

sensitivity and 89% specificity for JHS. A proportion of these patients were further physically assessed by Gina using the Beighton Score, which tests whether the patient can carry out nine joint manoeuvres. Someone has hypermobility if they score four or more. A more thorough tool is the Brighton Score, which differentiates JHS from other connective tissue disorders.

Of the 184 new patients came through the clinic, 142 of these completed the questionnaire (76% response rate). Two of these were excluded for incomplete questionnaires. Of the 140 patients, 47 (33.6%) fulfilled criteria for JHS and 93 did not. Eight patients were assessed by Ms Wall using the Beighton score, with confirmed JHS seen in all patients. In a conservative analysis, it was assumed that all patients who did not complete the questionnaire did not meet the screening criteria for JHS. In this case, 47 of 184 (25.5%) is the minimum prevalence of JHS in this cohort.

Future implications

Further investigation is needed, said Ms Wall, with replication of results in other areas and services in the UK, although similar findings from the USA have been published??. The audit raises questions such as: what is really the primary diagnosis for these patients, CFS/ME or JHS? In a musculoskeletal clinical setting, JHS is approached with muscle strengthening and balance work, so the service will be exploring the need for changes to the exercise prescription for the patients with JHS, as it is known that JHS affects proprioception and balance. These exercises may be of benefit in increasing tolerance for physical exertion in those with both fatigue and JHS.

Screening for JHS will now be carried out for all new patients that come to the Royal Free's fatigue service. There is potential for adding the Beighton score to the initial medical assessment as it can be completed in 45-60 seconds. There is also the potential to explore options for clinical study of comparisons of effectiveness of different treatment arms of graded exercise therapy. The team's hypothesis is that exercise therapy might be more effective and tolerable in these patients, but it must be modified.

You can watch a film of this presentation at www.tinyurl.com/actionformeyoutube

Online therapy for adolescents with CFS/ME: An internal pilot within a trial comparing online CBT (FITNET-NHS) with Skype-delivered activity management
Dr Emma Anderson, University of Bristol

As trial manager, Emma explained that she would be presenting initial results from the internal pilot phase of much larger NIHR-funded trial, comparing two treatments for adolescents with CFS/ME; online CBT using the FITNET NHS package, and Skype-delivered activity management. Emma explained that 1% of secondary school children are missing a fifth of school because of CFS/ME. While most recover at six months with specialist treatment, less than 10% will recover without it.

So it's very troubling that the majority of secondary school children with CFS/ME – estimated to be up to 90% – have no access to local specialist treatment at all. "One possible solution is to bring treatment to those children via the internet," said Emma, and referred to a trial undertaken by a Dutch team, published in the Lancet in 2012, on which this trial is based. Delivering online modular CBT programme to children with CFS/ME, primary outcomes showed that they improved much more than those recovering usual care.

The trial (www.bristol.ac.uk/fitnet-nhs) is large and long-running, she explained, and this is just the first phase, now coming up to the one-year point.

The objective of the first year was to assess feasibility of recruitment and trial processes, and get early indications of the acceptability of the two trial treatments. If found to be feasible, the full trial will carry on for the next two and a half years, to assess the effectiveness, and cost-effectiveness of FITNET-NHS, and to undertake subgroup analysis on co-morbid mood disorders.

Remote recruitment

The key feature of the trial is remote recruitment: everything is done online, including consent and eligibility assessment, supported by phone calls. All treatment is delivered by the specialist paediatric CFS/ME team at Bath Royal United Hospital.

Participants are followed up for a year, with the primary outcome for the trial at six months. Follow-ups are by email survey, which both children and parents complete. Adolescents are eligible for the trial if they are aged between 11 and 17 years, have been diagnosed with CFS/ME using NICE guideline criteria, and if they do not have access to a local specialist CFS/ME service

The trail aims ultimately to recruit 734 children, who will be randomised to one of the two trial treatments on a roughly 50/50 basis. The CBT treatment arm includes up to 19 interactive online chapters for adolescents to work through, on subjects such as sleep, thinking patterns, and building up activities, supported by email consultations with a therapist. The Skype-delivered activity management approach involves up to four calls supported by app and paper diaries.

All recruitment consultations are recorded and analysed, as are the interactions with the adolescents and their families, and data from this is used to ensure the process is as effective

as possible. The focus of interviews in the pilot phase is to check the feasibility of the recruitment, using the feedback to improve those processes.

Initial results

Qualitative feedback from the recruitment phone calls indicates that there has been a largely positive response to taking part in the trial, particularly in the context of having no access to treatment. Comments from adolescents and their parents include:

> "*Well the GP has been absolutely awful, basically saying 'Oh nobody knows what chronic fatigue is' and sending him away all the time*."

> "*Either way I know I'm gonna get some sort of treatment out of it, some benefit. So, like, although would've preferred it, at least I'm getting some sort of treatment which is better than nothing and obviously I can't get the physical sessions anymore. So at least I'm getting some sort of benefit and coping strategies...*"

Emma explained that her team was really interested in pre-conceptions about the delivery of treatment, given its unique aspect, ie. being delivered online. Responses were mixed; comments include:

> "*He were just a bit like just like feeling he might feel a bit embarrassed being on Skype that's all*."

> "*I liked the idea of it all being online, I think going to the appointments of different things can be difficult. Whereas this I can just do whenever I fancy*."

While it's too early to share qualitative analysis of the treatment experiences, the team is getting positive feedback from those taking part. Nearly 500 referrals into the service in the first 10 months of the trial have resulted in:

- 179 potentially eligible to take part
- 122 having an initial phone call with a research nurse
- 92 having the eligibility assessment and
- 74 being randomised to treatment.

Retention figures, which are a great indicator of acceptability of the trial and its treatments, show 100% completion of the baseline survey; Only 9% lost at three-month survey follow up; and only 7% lost at six-month follow-up. There has been only one withdrawal from the trial to date.

"We feel positive about the trial and can say confidently at this stage that delivering specialist treatment at home via the internet seems feasible and acceptable for children disabled by fatigue, and their parents," Emma concluded.

The FITNET-NHS trial is sponsored by the University of Bristol. Professor Esther Crawley is the Principal Investigator. This project is funded by the National Institute for Health Research HTA 14/192/109. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the HTA, NIHR, NHS or the Department of Health.

Orthostatic intolerance in CFS/ME: lessons from the last two decades
Dr Peter Rowe, John Hopkins Children's Centre for CFS

Dr Rowe expressed his intention to explore why a proportion of the scientific community has discounted evidence of the link between orthostatic intolerance and CFS/ME and why they have ignored the value in treating this condition.

Orthostatic intolerance is defined as a group of clinical conditions in which symptoms worsen with quiet upright posture and are ameliorated, although not necessarily abolished, by recumbency. Orthostatic intolerance symptoms due to inadequate cerebral blood flow have huge overlap with the symptoms of CFS/ME.

There are two common forms of orthostatic intolerance:

- postural tachycardia syndrome (POTS) is defined as, within 10 minutes of head up tilt, a 30 beat increase in heart rate (40 for children) alongside orthostatic symptoms, in the absence of orthostatic hypotension.
- neurally mediated hypotension (NMH) is associated with a profound drop in blood pressure of 25mm of mercury and a corresponding drop in heart rate on tilt table testing.

Dr Rowe talked about the Institute of Medicine report *Beyond ME/CFS* published in 2015. Written by an expert committee tasked with looking at the diagnostic criteria for CFS/ME, it found that "sufficient evidence indicates a high prevalence of orthostatic intolerance in CFS/ME."

He then reported the contrasting view, expressed by Prof Peter White, who stated that "good epidemiological studies find that objective evidence for orthostatic intolerance occurs in a relatively small minority of patients" and that "some would question whether orthostatic intolerance is a key feature."

However, said Dr Rowe, many global physicians consider orthostatic intolerance to be the most treatable component of CFS/ME and that doing so is an important part of managing symptoms.

The overlap of orthostatic intolerance and CFS/ME

In his clinic in the 1990s, Dr Rowe noted that paediatric patients with CFS/ME and those with fainting spells had similar triggers for their symptoms. Investigations on seven adolescent patients with chronic fatigue, four of whom had CFS/ME diagnoses, showed all had a hypotensive response on tilt table tests and four had very substantial improvements in fatigue and function when treated with medication for NMH.

In 1995, Dr Rowe published a study looking at well characterised CFS/ME patients who reported symptoms compatible with orthostatic intolerance such as light-headedness, diaphoresis, abdominal discomfort, blurred vision and syncope. Conditions exacerbating their fatigue included physical exertion, hot showers, prolonged standing, warm environments and lightheaded episodes.

A three stage tilt table test was carried out, comprising initially of a 70° tilt followed by a second stage where Isoproterenol was administered alongside the tilt to mimic everyday stress. At stage three, increased doses of Isoproterenol were given.

At stage one of the test, 16 out of 23 CFS/ME patients became hypotensive versus none of the controls. At stage two, three more of the CFS/ME patients and one of the controls became hypotensive. The odds ratio for an abnormal tilt for a CFS/ME patient was 55. All the CFS/ME patients had their symptoms exacerbated by the tilt table testing and often remained worse for several days afterwards.

Following these tests nineteen patients were given open treatment in a pilot study for a trial of Florinef. Nine had responses that were quite substantial. Over four months of treatment mean wellness scores increased from 36 to 69, on a scale of 0 to 100. This wellness scale correlates well with the SF-36. These results are similar to what is seen with similar treatments in his clinic to this day.

The Florinef trial demonstrated how common orthostatic intolerance may be in CFS/ME. In two-stage tilt testing to determine eligibility for the treatment trial, 62% of adult patients were found to have NMH, 4% POTS alone and 24% had POTS before their NMH developed.

Since then POTS has been found to be the more common form of orthostatic intolerance. The patients registering normal heart rate and blood pressure response on the tilt testing still had an exacerbation in their CFS/ME symptoms.

Other studies

Every controlled paediatric study looking at CFS and orthostatic intolerance has shown an increased incidence of orthostatic intolerance in paediatric CFS/ME patients. Stewart (1999) found 96% of patients had orthostatic intolerance, Tanaka (2002) found delayed recovery of cerebral oxygenation in 75% of CFS/ME patients versus 10% of controls. Wyller (2007) found that at a tilt of 20° was sufficient for patients with CFS/ME to develop hemodynamic changes.

The data on adults is less consistent. In 14 controlled studies of prolonged orthostatic intolerance testing, the overall prevalence of orthostatic intolerance was found to be 42% in those with CFS/ME versus 15% of controls. However, within these studies there was huge variability ranging from 0% to 79% abnormality in the CFS/ME patients.

Quoting a DH Spodick writing in 1975, Dr Rowe stressed: "We must view published material critically (if not biblically), for too often the ‘Conclusions’ giveth, but the ‘Materials and Methods’ taketh away."

He went on to critically consider the quality of the epidemiological studies, highlighting a study where the exclusion criteria actually removed those with high heart rates (POTS) from the sample and the majority of those deemed eligible refused to take part, leaving only an unrepresentative 14% of the original sample participating.

Methodological problems associated with tilt testing in CFS/ME that could contribute to the heterogeneity in studies include the duration and severity of illness, expectation of treatment

and the proportion of those with co-morbid Ehlers Danlos syndrome (EDS) in the study population (those with EDS have a higher incidence of orthostatic intolerance than average). The practice of cardiologists also varies with respect to the length of the pre-test fast, time of day and duration of tilt.

Five lessons

Dr Rowe set out the five following lessons from the last two decades.

1. Patients with orthostatic intolerance have symptoms that overlap with CFS/ME, but symptom severity is worse in those with both orthostatic intolerance and CFS/ME.

The Vanderbilt Autonomic Group compared those with CFS/ME and POTS to those with POTS alone. POTS patients had many of the CFS/ME symptoms listed in the Fukuda criteria, just not the 4 of the 8 required for a diagnosis of CFS/ME. Prof Julia Newton in Newcastle used the Compass questionnaire to assess a number of autonomic symptoms. The Compass scores were significantly greater in the CFS/ME patients versus controls and correlated well with scores on the Fatigue Impact Scale.

2. Cognitive dysfunction in CFS/ME can be caused by orthostatic stress.

In the orthostatic literature, cognitive dysfunction is talked about as being a direct result of orthostatic hypotension. In the CFS/ME literature, it is considered to have several possible triggers. Insufficient investigation has been done into whether cognitive symptoms in CFS/ME patients are more likely to occur when they are upright. Meadow and Stewart demonstrated in 2012, using an N-back test administered during progressively greater degrees of upright tilt, that increasing orthostatic stress impairs cognitive function in CFS/ME patients with POTS.

3. Inactivity can aggravate orthostatic intolerance in CFS/ME, but it is incorrect to view orthostatic intolerance as due exclusively to deconditioning.

Ideally, when possible, complete bed rest should be avoided by patients as this can aggravate orthostatic intolerance, as demonstrated by research with NASA volunteers, however athletes are seen with POTS when they are clearly not deconditioned. As Mencken stated, "For every complex problem there is a solution that is simple, neat and wrong." Dr Rowe suggests that this is the case for the deconditioning explanation of orthostatic intolerance in CFS/ME.

4. More normal tolerance of exercise is the goal in CFS/ME. Effective management of orthostatic intolerance often enables tolerance of graded increased in exercise.
Dr Rowe gave the example of a patient who had CFS/ME and co-morbidities. She could not exercise at all as it made her too ill. When treated with Ivabradine she became able to hike 10 miles a day, including hiking up hill.

It is important to address orthostatic intolerance so that patients can exercise, he said. If medication is stopped patients get a return of their CFS/ME symptoms even though they are not deconditioned. Some colleagues expect patients to exercise their way out of POTS without medications. Peter Rowe suggested that, just as it would be inappropriate to ask an asthmatic

to start an exercise program without medication to control their symptoms, so it is the case with orthostatic intolerance in CFS/ME.
5. Other factors can influence orthostatic intolerance symptoms in CFS/ME, including adverse neural tension/neural tension dysfunction.

This is not a homogenous problem. Orthostatic intolerance symptoms in CFS/ME can be triggered by other factors. A study was done raising the legs of patients in gradual steps; no active work was done but symptoms were provoked.

Wellness scores for patients with CFS/ME increased from just over 50 to 75 over a period of 24 months when they were treated with multi-modal therapy that included treatment of orthostatic intolerance.

In conclusion, said Dr Rowe, the majority of adult and all paediatric studies show orthostatic intolerance is strongly associated with CFS/ME. Upright posture consistently aggravates CFS/ME symptoms, often long before changes in heart rate and blood pressure, and open treatment of NMH and POTS is associated with improvement in fatigue and other symptoms.

You can watch a film of this presentation at www.tinyurl.com/actionformeyoutube

Orthostatic intolerance in CFS/ME
Prof Dr Frans Visser and Dr Linda van Campen, Cardiac Care Foundation

Prof Visser and Dr van Campen, are cardiologists who have developed a research interest in CFS/ME, especially the role of orthostatic intolerance. They described some of their current research in this area, and the use of pyridostigmine – a drug that is primarily used in myasthenia gravis – as a treatment option.

Prof Visser began by acknowledging that "orthostatic intolerance is a relatively new kid on the block when it comes to CFS/ME criteria."

Discussing the prevalence of orthostatic intolerance in people with CFS/ME, Prof Visser acknowledged that it is very variable between studies, ranging from 30% to 59% prevalence – though in all studies, it occurs more frequently in people with CFS/ME than in healthy volunteers.

In his and Dr van Campen's clinic, based on data from more than 500 patients, there is clinical suspicion of OI in 80% of CFS/ME patients. But in tilt-table testing, they see hemodynamic abnormalities only in around half of patients (44%).

How can we explain this difference in symptomatic complaints versus objective science, asked Prof Visser? The answer lies in the cerebral hypoperfusion, he explained, which is decreased blood flow to key parts of the brain.

Describing the findings of tilt table tests, Prof Visser showed that there is an abnormal decrease in cerebral blood flow when sitting and during standing in CFS/ME patients and that, even in the absence of abnormal hemodynamic findings (eg. POTS) there is abnormal cerebral blood flow decrease.

He concluded by highlighting that, in light on these findings, the still widely-held assumption that CFS/ME is due to deconditioning is in fact emphatically wrong.

Dr van Campen expanded on this, giving overview of research she and Prof Visser had undertaken using CPET testing and actometers.

"In 114 consecutive CFS/ME patients undergoing CPX and Sensewear activity armband we correlated the total number of steps from the Sensewear activity meter with the range of a normal VO2max," she explained, before concluding that their data suggests that cerebral blood flow decline is NOT caused by deconditioning as evidenced by the %VO2max and number of steps, but is part of the disease of CFS/ME.

You can watch a film of this presentation at www.tinyurl.com/actionformeyoutube

Investigating altered metabolism in CFS/ME: Untargeted metabolic profiling of plasma samples by mass spectrometry

Prof James McCullagh, University of Oxford

The aim of the study presented by Prof McCullagh was to use untargeted metabolic profiling of blood plasma to see if there was a difference between CFS/ME patients and controls. Metabolic profiling aims to identify and quantify the complete set of small molecules (metabolites and lipids) in complex biological samples such as cells, tissues, organs and bio-fluids. The metabolome refers to the entirety of metabolites in a biological system. The benefits of this approach are that it is holistic, everything is considered, and can lead to hypothesis generating results.

The study used blood plasma of 59 CFS/ME patient and 24 controls. The blood plasma was diluted in organic solvent before using four separate mass spectrometry coupled with liquid chromatography, methods to analyse the samples**.** This approach is highly sensitive and selective, allowing the identification and quantification of individual metabolites.

An ion map representing all the data acquired provided evidence that over 8,000 individual compounds were measured, of these, 268 metabolites were identified. There was a significant 1.5- fold change between CFS/ME patients in 364 compounds and over a two-fold change for 171 compounds. The study looked at both untargeted (using statistics to identify difference between the two groups) and targeted (identifying compounds and looking at metabolic pathway changes).

The major findings were that amino acids were generally depleted in CFS/ME patients, however, glutamic acid, ATP and AMP were higher in CFS/ME patients, as were a small number of lipids, showing statistically significant changes. The identified compounds were then mapped on to metabolic pathways.

TCA cycle and glycolytic intermediates were slightly increased in CFS/ME patients. Amino acid metabolism showed the most significant depletions with some high fold-change increases for cysteine and cysteate. The urea cycle was found to be quite different between CFS/ME patients and controls; it is unclear how this should be interpreted, some compounds were lower and others higher. For the anaplerotic pathway, where compounds other than glucose are used for energy production by TCA/ Krebs cycle, clear trends were shown where the amino acids were in lower abundance. Results suggested that changes in energy metabolism were taking place in CFS/ME patients.

The study then went on to compare the differences in metabolic profile before and after GET for CFS/ME patients (no controls were used). Several metabolites were found to differ before and after GET. There were no changes in amino acid metabolism; however carnitines (lipids) and phospholipids were depleted after GET. This study had no controls for exercise so it is unclear whether the changes observed were due to a normal exercise profile or CFS/ME. Central energy metabolism metabolites were found to be significantly depleted.

You can watch a film of this presentation at www.tinyurl.com/actionformeyoutube

CFS/ME patients have less mildly deleterious mtDNA population variants: evidence from two population cohorts
Dr Joanna Elson, Newcastle University

Dr Elson is an expert in mitochondrial muscle disease. There is growing interest in the role of mitochondrial function and mitochondrial DNA (mtDNA) variation in ME/CFS. It is now known that fatigue is common and often severe in patients with mitochondrial disease irrespective of their age, gender or mtDNA genotype.

Some cases reports in the literature suggested that ME/CFS patients harbour clinically proven mtDNA mutations.

Work conducted by Schoeman et al (2017, Clinically proven mtDNA mutations are not common in those with CFS, *BMC Medical Genetics*) failed to find any clinically proven mtDNA mutations in 93 CFS/ME patients from the UK and South Africa. This observation was also supported by a group working in the US (Billing-Rosset et al, 2016, Mitochondrial DNA variants correlate with symptoms in ME/CFS, Journal of Translational Medicine).

This finding demonstrates that clinically proven mtDNA mutations are not a common element in the aetiology of disease in CFS/ME patients.

An additional study being conducted by Dr Elson's group is underway, looking at the possibility that mtDNA population variation might play a role in either the susceptibility to, or course of ME/CFS. MtDNA variation has been implicated in many common complex diseases.

For over a decade, mtDNA association studies have been conducted using the haplogroup (lineage) association method. This method frequently produces conflicting results.

The CFS/ME study is taking a new approach using a new association method first published earlier this year in the context of Alzheimer's (Elson et al) and cardiovascular disease (Venter et al), and she hopes that data will be published in due course.

Brain health research in an age of platform science: linking cellular and molecular changes to patient response
Dr John Gallacher, University of Oxford

Prof Gallacher introduced himself as the director of Dementias Platform UK (DPUK). He challenged the audience to consider that, "The aim of doing collaborative science is to be ambitious, to answer questions that could not otherwise be answered."

His presentation considered first the nature of the scientific landscape, then the way forward in terms of cohorts, and finally looked at the Dementias Platform specifically. The sorts of collaborative infrastructures used in the latter are not limited to dementia but can be repurposed for different outcomes and uses, hence the relevance to CFS/ME.

A challenge facing science today is that the easy-to-answer problems are mostly solved, said Prof Gallacher. For 'next generation science', emerging problems will be more complex, and require more focused research questions. Answers will be found through applying new technologies alongside greater interdependence between specialties – see figure 1.

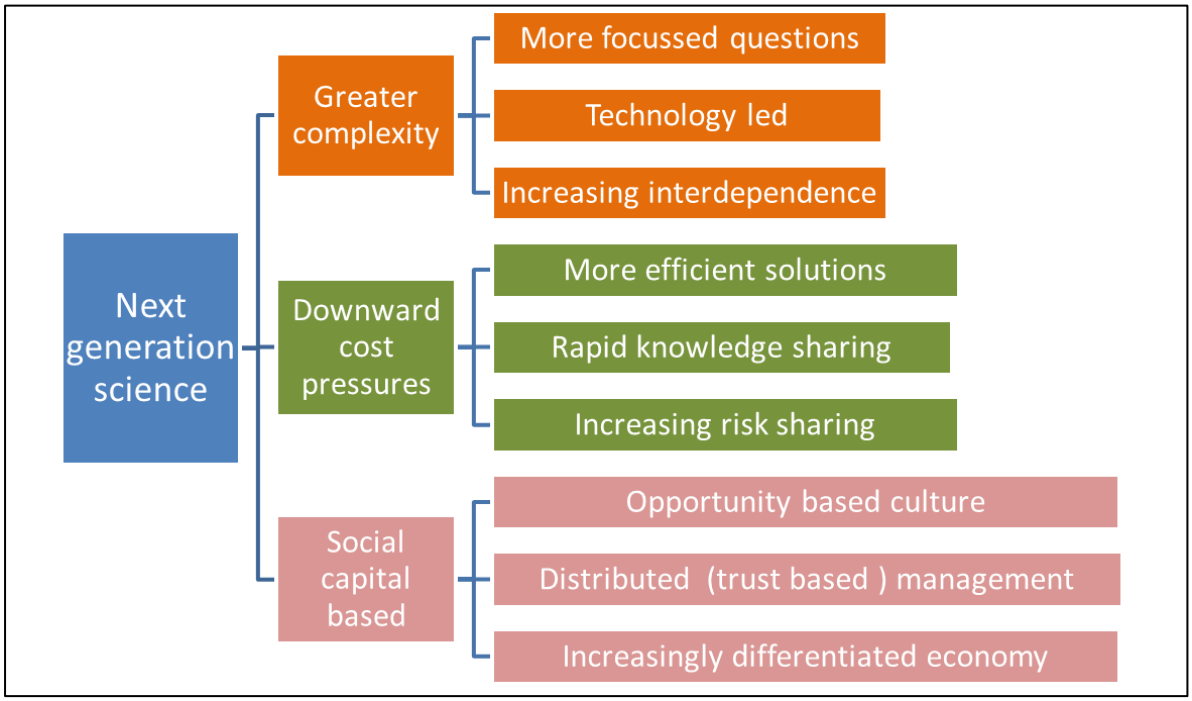


Figure 1: Scientific challenge

Due to downward cost pressures, increasingly efficient solutions will be sought and these will involve greater knowledge and data sharing. For new projects, risk will be shared more widely across stakeholders – with the potential rewards also shared.

Our culture is increasingly social capital based and this needs to be reflected in the science economy if we are to attract the best minds. Increased social capital can be achieved by developing an opportunity-based culture where opportunities are created to empower researchers to do what they enjoy; giving them freedom to operate, and providing an attractive and stimulating research environment. This includes greater differentiation of incentives; one that acknowledges the contribution of the diversity of contributors. For example, where all

those involved in a project obtain academic attribution for their specific contribution, rather than being part of a non-specific list. Getting these aspects right will enable CFS/ME research to attract the best minds.

Prof Gallacher also talked about the need to ask hard questions in order to develop new interventions. Using dementia research as an example, currently, most trials are conducted with patients who are already in an advanced stage of the disease. At this point the brain is already severely damaged, and even if a treatment works, there is limited scope for improvement. Ideally we want to intervene earlier in the disease process, when decline is only just beginning.

At the moment, however, there is no easy way to do studies in early disease dementias as most people won't know they have the disease and may not wish to find out. Although conducting early disease studies is a generic problem, it is a particular challenge for dementia. When prescribing a treatment, ideally, we want one that will work in a particular person, not one that works only in a proportion of people, i.e. it might work in this patient if we are lucky. The precision medicine paradox is that to achieve this level of detail, extremely large cohort studies are required. By way of example, the Prospective Studies Collaboration, linking blood pressure and risk of heart disease shows how using date from 5,000 people, or even 50,000 people, does not clearly show the association. It is not until data from 500,000 people were considered that a very clear relationship becomes apparent. This may be considered as a definitive finding; providing a strong foundation for further work.

Cultural challenge

Prof Gallacher also shared the DPUK experience of data sharing. DPUK holds the view that publicly funded data should be considered as a public good that should be shared with other scientists, within the controls necessary to protect the public interest and protect the identity of participants. We need to encourage greater intellectual generosity, of collaborating for the common good, and of sharing knowledge to accelerate progress and the development of new treatments.

He also highlighted the opportunity within the UK to develop the infrastructure for population studies. The UK has a rich heritage of population studies, each with its own governance, data collection and data management procedures. This works well for the individual studies but is not suitable for comparing data across studies. It's like trying to run a rail network where each line has a different gauge.

This "cottage industry" approach limits sci9entific opportunity and is unnecessary in a digital age. A more coordinated approach where generic solutions to generic problems are operationalised to agreed standards, offer increased data quality, reduced research cycle times and reduced cost. Examples include standard tools for recruitment, data collection and data management, and developing repositories for digital data (as in the MRC DPUK) and for biosamples (as in the NIHR-funded UK biobank).

Cohorts, where people are recruited to be studied over time, provide the best data for identifying disease risk. An example is UK Biobank (www.ukbiobank.ac.uk) which has samples and data from more than 500,000 volunteers. But cohorts are expensive and this limits

exploiting the scientific opportunity they provide. To address this we need to consider how to collect better data at scale more cost-effectively.

Several strategies are available. These include embedding recruitment within existing social infrastructures, automating digital data collection, remote biosampling for routine assays, and selective recall for specialist examinations. The Fahrenheit 451 option (of banning paper-based technologies) should be taken seriously. Identifying the most cost-effective combination of methods to answer specific questions might improve scientific rigour as well as offer substantial cost savings leading to increased UK research capacity.

For example, data collection (exposures and outcomes) would be entirely automated using devices such as smart phones for self-report and specialist devices such as accelerometers for specific objective assessments. Using new technologies frequently provides the opportunity to operate at scale. As an illutrati0on of what becomes possible, UK Biobank captured accelerometry data in 100,000 participants.

The Dementias Platform UK

The DPUK has a mission to use the power of cohort data to accelerate the development of treatments. It acknowledges the need to work as a community, not as individuals, and its core values are explicit. These are to be intellectually generous, creative, and collaborative with all stakeholders. This ethos is intended to earn the trust of the scientific community, in order to encourage collective action in dementia research.

For dementia, where progress has been so limited with no new drugs coming to market for well over a decade, a platform approach makes doing good science easier. It enables cohorts to collect better data by developing data collection tools, analysts to access data more easily by standardising data curation and access, and experimental medicine scientists to recruit the right people for the right study at the right time in the disease process.

DPUK has three core enabling utilities – rapid data access, identification of highly characterised participants, and developing core technologies for experimental medicine. This has been achieved through public private partnership as a model for taking new ideas through to publicly available treatments. The DPUK has a number of research programs, and is building capacity. It is building a community where scientists with common interests can come together to deliver strategic research programs. It facilitates this by paying for groups of scientists focused on dementia to meet regularly in order to prepare and submit a substantial (£1m+) strategic grant. To date, the DPUK has catalysed the winning of over £100M of additional funding for dementia research in the UK.

Dr Gallacher ended his presentation with the question, "Where does CFS/ME go from here?" The challenge is to see the opportunities that can be created, and to identify those that can be addressed and solved. If the Dementias Platform can serve as an encouragement and inspiration to the CFS/ME community, this afternoon would be time well spent.

You can watch a film of this presentation at www.tinyurl.com/actionformeyoutube

Plenary Session: Biology of CFS/ME

Forging international collaborations

Prof Julia Newton, Newcastle University; and Dr Karl Morten, University of Oxford

Prof Newton, Clinical Prof of Aging and Medicine, Newcastle University and Deputy Director of Newcastle NHS Trust, offered her personal view on the importance of collaboration plus her reflections on what is needed for good CFS/ME research.

Prof Newton became committed to solving CFS/ME after hearing "very harrowing stories" from the patients she had seen in her clinic. "But I realised I was not personally knowledgeable enough about the basic science or experienced enough to be able to do this by myself," she said. "So it was really important to form relationships with people." And whether it was immunology or metabolomics, she needed to find experts in the field to work with her.

The key to success has been to forge links not only externally but internally too. Early on, Prof Newton set about building credibility and critical mass in Newcastle University. "What we did was bring together conditions or people with an interest in particular conditions where fatigue was a significant symptom. And we also brought together methodologist who could apply [the same] methodologies across different conditions."

Starting small, she developed what was initially a faculty orientated research group. This has gone from strength to strength, evolving into a university research centre with external recognition and some financial support from the university itself.

Support and scientific rigour

The group meets every month over a free lunch provided by Prof Newton herself. The team discuss new grant applications and listen to invited speakers. "People who might not otherwise have considered working in the field see that there is a structure that they can join and gain support, mentorship and scientific rigour," she explained. "Internally that has been great."

But looking beyond Newcastle University is just as enjoyable: "Externally it's great fun working in this field. There are some fantastic people who are really bright."

Her fatigue unit's biobank, developed from projects funded by the Medical Research Council, Action for M.E., the ME Association and ME Research UK, forms a solid platform for collaboration. It includes tissue samples, as well as sleep and autonomic information, and detailed characteristics of the severely affected and housebound. And it fuels international collaboration.

Newcastle's samples and data have gone to scientists including teams in Dundee (looking at inflammatory markers) and Oxford (researching mitochondria bioenergetics) but also. researchers in South Africa, who have investigated mitochondria DNA; quality of life data has been sent to Prof Lenny Jason in the US. And new partnerships are popping up all the time. "We're starting to work with the Australian group at Griffith [University] with [Profs] Don Staines and Sonya Marshall-Gradisnik," she said.

Giving a specific example of a collaboration that had changed international perspective, Prof Newton described how a Polish connection had proven fruitful.

CFS/ME in Poland

About five years ago, Pawel Zalewski, an autonomic expert with a physiotherapy background at Nicolas Copernicus University, Poland, came over to help sort out system algorithms for autonomic testing. CFS/ME, he said, didn't exist in Poland – but Prof Newton challenged him to take a closer look.

"Pawel went home and started asking questions," said Prof Newton. "He set out to establish whether CFS/ME did exist in Poland. And as an example of his tenacity, he put out a number of TV and radio adverts. He had experts from international groups doing interviews on the television." The result? More than 1,400 people jammed the telephone lines to his research group.

Many did not meet Fukuda criteria but the Polish team drilled down to a very well characterised group of Polish patients. They were subsequently randomised to graded exercise therapy and a control group.

"The results of that will be very interesting and allow us to look at all sorts of things in a society where CFS/ME has not previously been recognised," said Prof Newton. Importantly, this is happening "in a completely research-politics naive cohort."

Other strong collaborations exist closer to home. Prof Newton's team were asked by the ME Association if they could repeat the acumen test (Booth, Myhill and McLaren-Howard , 2015, Mitochondrial dysfunction and the pathophysiology of CFS/ME. *Int J Clin Exp*) which assesses mitochondrial function. If they could reproduce that work in the lab there was the potential to develop an NHS diagnostic test.

But after several attempts to replicate the protocol they were faced with failure. Thinking it might be their lack of expertise, the Newcastle team approached mitochondria expert Prof Karl Morton at Oxford University – see p 34 – to see if he could do any better.

"And that," said Prof Newton, "allowed us to establish a really strong collaboration." They have regular Skype conferences and Prof Morton is advising her PhD students on muscle-cell metabolism, suggesting experiments and advising on novel techniques. This has resulted in a recently published paper on cellular bioenergetics by one of her students (Tomas , Brown , Strassheim, Elson , Newton , Manning, 2017, Cellular bioenergetics is impaired in patients with CFS. *PLoS One*).

Prof Newton felt it was also important to have the right focus. "In my view what we really need to crack CFS/ME is deciding what the really important questions are that we want to answer – and understand how to measure the possible outcomes.

"One of things that I believe has held this field back is that fatigue is quite soft as a measure for endpoints in studies. We need to be able to make sure as a field that we can measure the right thing and we have objective end points that are validated and robust." Characterising patients

properly was also essential, she said, and that "whatever science we do, we take the patient community with us."

As always, there's the additional pressure of sourcing funding and although the charities are very supportive with pump priming, it's really important as an academic to bring in mainstream funding: "If you don't do that then you haven't got a job!"

Julia then handed over to her colleague, Dr Karl Morten, University of Oxford, who described how he first became interested in CFS/ME. "I was invited up to Newcastle to give a talk in 2015, which is sort of the Holy Grail of mitochondrial DNA work. So it was a bit scary going up there to tell them how we do science!"

His take on mitochondrial disease is a little at odds with the mitochondria research community, who insist there must be defects in the individual complexes (embedded in the organelle wall and where respiration takes place). "I work very closely with a big player in this area and she is always saying that ME is not mitochondrial because you don't see abnormal mitochondria on muscle biopsies or impaired mitochondrial enzyme function". Not seeing abnormal mitochondria on muscle biopsies does not necessarily mean mitochondrial function is not compromised," he said.

Understanding mitochondria

Understanding of these little powerhouses is increasing all the time. Years ago they were thought to look like small sausage shape structures but we now know their shape is dependent on the type of cell they're in and can change in response to cellular stress. Mitochondria tend to be elongated in the fibroblasts and more circular in hepatocytes, for example. And far from being just energy producers, their function is more like that of an orchestral conductor. "They do a whole bunch of things," said Dr Morten, "and they sit right in the middle of metabolism."

Previous metabolic profiling of CFS/ME patients has flagged up impaired pyruvate metabolism particularly of pyruvate dehydrogenase (PDH) (Fluge at al, 2015, Metabolic profiling indicates impaired pyruvate dehydrogenase function in ME/CFS. *JCI Insight*). This study is being followed up in our current work by Joe Harvey and James Mccullagh in the Chemistry department at the University of Oxford and suggests that patients have elevated levels of PDH and 2-Oxyglutarate, another compound in the tricarboxylic acid cycle. "It's work in progress and we are quite excited about it," said Dr Morten, as we increase our understanding of CFS/ME we will likely identify potential treatment pathways.

Moving onto his own biological work at Oxford, Dr Morten explained how he uses high throughput platforms which allow the identification of defects in mitochondrial function. Using oxygen sensing probes developed by Luxcel Bioscience we can measure rates of mitochondrial respiration and media acidification (glycolysis) in whole cells. Using the BMG LABTECH Clariostar instrument with an atmospheric control unit (ACU) we are able to control oxygen levels mimicking physiological conditions.

"Glucose concentration is another key parameter to control for with many people still carrying out cell culture experiments in media containing glucose 5 times that found in blood and orders of magnitude above that found in a tissue" he insists. "I am always banging on about this in

Oxford and how we need to model what we do in the laboratory more closely to what happens in patients. How we are doing things in the lab needs to reflect as close as possible to what happens in vivo."
As the cells in the assay use up oxygen in the culture media cell media, the brightness of the fluorescent 0_2 sensing probe rises. In this way, it's possible to determine if a drug or component in the serum either increases or inhibits mitochondrial 0_2 consumption; changes can be monitored in real time. Recent research by Fluge in Norway showed that when CFS/ME serum was added to control muscle cells there was change in the muscle cell mitochondrial function.

But perhaps what's most interesting to people with CFS/ME is his attempts to replicate the Acumen test (Booth, Myhill , McLaren-Howard , 2009, Mitochondrial dysfunction and the pathophysiology of CFS/ME. *Int J Clin Exp*), which produces a mitochondrial energy score derived from a combination of metabolic factors.

The Booth study "showed there was a clear association between the severity of disease and the energy score in neutrophils isolated from ME/CFS patients: the worse the disease, the lower the energy score," explained Dr Morten. So with five months of funding from the ME Association, and relying on colleagues good will in donating blood samples, Dr Morten's team set about trying to replicate the protocol in control samples. They asked two questions: can neutrophils be reliably used to assess mitochondrial function? And can measuring ATP provide a robust assessment of mitochondrial function?

"We found quite a lot of interesting things with this," said Dr Morten. The Acumen protocol measures ATP in granulocytes, a type of white blood cell. But Dr Morten's team struggled to get a pure preparation.

"We tried and tried and we just can't get a decent granulocyte fraction," he said. It seemed to be contaminated with other white and red cell debris. Peripheral Blood Mononuclear Cells (PBMCs) look a better bet where we can reproducibly isolate a pure PBMC fraction. However, PBMC's have a relatively low level of mitochondrial respiration resulting in the requirement of 50,000 cells to run the ATP assays with 500,000 cells required to run mitochondrial respiration assays.

Longitudinal study

Having settled on PBMCs, they carried out a very small longitudinal study three controls giving four blood samples over 10 weeks. The results were pretty consistent with similar ATP levels found at each time point.

"I was one of the controls and at one point had a cold my PBMC ATP levels shot up. This suggest we need to be careful with this type of test and that the natural variation in the control group could be quite large. They could see however, that adding inhibitors or stimulants clearly impacted on 0_2 consumption demonstrating the potential of mimicking the effects of exposure to a pathogen.

Seeking to dig deeper, Dr Morten and his team turned to Prof Wei Huang and Jiabao Xu, Oxford experts in Raman Spectroscopy. This technique excites cells with a laser and visualises signals linked to difference in chemical bond structure.

"Essentially you get a metabolic fingerprint of a single cell, so we can look at very few cells, which is a real bonus," said Dr Morten. "Within the cell we get a fingerprint of the different components: carbohydrates, proteins, amino acids." Using samples from a Newcastle ME/CFS patient and control cohort we have started to observe significant differences in phenylalanine profiles between controls and patients.

Exploring all avenues to examine such complex data, he asked colleagues in the Mathematical Institute, Dr Ning Wang and Prof Hanqing Jin, to do some machine learning (running algorithms) on the data. "And basically the machine learning was quite incredible. We could pick out the controls with 99% accuracy and the patients with 96% accuracy."

Dr Morten plans to run further the tests on samples from Newcastle and the UK CFS/ME biobank around 400 samples, hopefully tying in all the data together. Future studies might include mitochondrial imaging which picks up tiny changes in structure associated with function. Bodywide changes seem important, too. Brain death in rodents, for example, impact massively on kidney mitochondria respiration which suggests "there might be something that the brain/body produces that can stop the mitochondria from working."

But for now Dr Morten aims to build up collaborations with different clinical centres. He's also excited by the UK and international ventures already underway, including research into post-exertional malaise, nutrition, genetics, immunology, brain and muscle metabolism.

"We have got a lot of models feeding in to what we are doing," he says enthusiastically. He ended by thanking CFS/ME patient Jamie, who is working with his time on a part-time basis. "I've spoken to a few people with ME and their knowledge of the illness is phenomenal," he said. "Jamie keeps me on track."

You can watch a film of this presentation at www.tinyurl.com/actionformeyoutube

MRC-funded researchers: updates on MRC-funded research
Prof Carmine Pariante, Kings College London
Prof Esther Crawley, University of Bristol
Dr Neil Harrison, Brighton and Sussex Medical School

Prof Pariante has been examining the effect on markers of immune system activity when patients with hepatitis C infection are given a treatment called interferon alpha.

When this treatment is given, a significant proportion of hepatitis C patients develop side-effects, including fatigue, which might be considered to mimic symptoms relating to CFS/ME.

These are thought to be caused by the production of what are called pro-inflammatory cytokines such as interleukins 6 and 10 (which were measured in this study). Many of those with fatigue continued to experience this symptom for several months after treatment had stopped.

This study is probably the nearest human model we have that creates an CFS/ME-like illness that can be used to examine the effect on immune system regulation during the very early stage of illness, without the use of an infection.

The results, which are being prepared for publication, contain some very interesting observations that could make an important contribution to our understanding of the sequence of events that do follow a triggering viral infection in CFS/ME – if, that is, we are looking at a process that involves an abnormally exaggerated and persisting immune system response, possibly because of a genetic predisposition.

Development of childhood and adolescent CFS/ME

Prof Crawley gave an update on her MRC-funded research which has been looking at the prevalence and possible risk factors that may be involved in the development of childhood and adolescent CFS/ME. This research is making use of the ALSPAC cohort, and several papers have now been published.

“A really big problem within CFS/ME research is bias if you recruit only from clinical centres,” said Prof Crawley, explaining why using the ALSPC cohort is so crucial to this work.
“The reason for that is still only about 10% of children with CFS/ME get a diagnosis from their GP, often despite repeated visits.”

It’s now well-established, said Prof Crawley, that CFS/ME is more common in families that experience adversity, as with most other illnesses.

This is just one of the possible risk factors that the team wanted to explore, along with child abuse/trauma, childhood anxiety and depression, maternal risk factors, physical activity, BMI, blood pressure, sleep and puberty.

Results do not suggest that many of these things are causal. “But we did find very interesting associations with sleep and physical activity,” said Prof Crawley, referring to unpublished data, which she then went onto expand on.

Dr Harrison finished the session by speaking about the role of neuroimaging in CFS/ME and two new research studies that he is involved with – both of which are about to start recruiting in the Brighton and Sussex area.

The first is on the neurobiology of post-exertional fatigue and is being funded by the MRC. This study is using MRI scans to investigate the core symptom of post-exertional malaise in 20 people with CFS/ME and 20 healthy controls. This will involve blood testing for immune system changes and MRI imaging (to see what happens in the brain) before and 24 hours after an exercise challenge.

The second study, which involves Dr Jessica Eccles and the rheumatologist Prof Kevin Davies, is being funded by Arthritis Research UK. This will focus on pain and whether there is an exaggerated response following an inflammatory (i.e. typhoid vaccine) and autonomic nervous system challenge.

Dr Harrison also talked about:

- the role of what is called 'sick behaviour' (the natural physiological response to acute infection that involves fatigue, cognitive impairment, withdrawal, anorexia, and increased pain sensitivity)
- the role of the vagus nerve (during immune system activation)
- what happens when cytokines enter the central nervous system (during an acute episode of virus or vaccine induced immune system activation)
- microglial activation following immune system challenges
- the possible role of specific centres in the brain – like the insula cortex and substantia nigra/ ventral striatum – in symptom development in CFS/ME.

You can watch a film of Prof Carmine and Dr Harrison's presentations at www.tinyurl.com/actionformeyoutube

Inflammation and depression

Prof Carmine Pariante, Kings College London

Prof Carmine Pariante of Kings College in London gave a presentation on the relationship between inflammation and depression.

He showed that some people with depression have raised levels of pro-inflammatory cytokines (interleukin 6) indicating that inflammation could be a key factor in maintaining some cases of depression where treatment with antidepressants has been unsuccessful.

In a study in which infliximab, a tumour necrosis factor antagonist used in inflammatory conditions such as rheumatoid arthritis, was used in patients with treatment-resistant depression and the patients with a higher level of inflammation responded. This shows that patients need personalised treatments in clinical trials depending on which biomarkers are raised in the particular patient, and similarly for research in patients with CFS/ME and raised biomarkers.

When patients with Hepatitis C are treated with Interferon-α, around 30% develop clinically significant depression but this improves when treatment stops. When the biomarkers of inflammation in the blood are measured throughout treatment, interleukin-6 increases with time regardless of whether the patient develops depression.

Transcriptomics, examining mRNA genes, were investigated to discover whether it is the reaction of the body to inflammation that varies when interferon-α is given. In the patients who become depressed, many more genes are activated (n=506) compared with the non-depressed patients (n=70), so the reaction to inflammation is much more intense in the depressed patients.

This can also be applied to CFS/ME patients in that just because there is not a raised level of cytokines does not mean that the body is not reacting to the inflammation but that the body is more sensitive to it. It could be that the body is more sensitive at the beginning of the illness, so this is a lesson which can be learned from research into inflammation and depression.

You can watch a film of this presentation at www.tinyurl.com/actionformeyoutube

Brain MRI studies in CFS/ME: an overview
Dr Jade Thai, University of Bristol

Dr Thai described the results of her PhD student's systematic review of neuroimaging studies in CFS/ME over the past two and a half decades, and looked ahead to future directions for this area of research.

This included structural and functional MRI scans and DTI scans carried out between 1991 and 2016 and published in the scientific journals. An initial search identified 817 potential studies for consideration; of these, 39 were met the inclusion criteria of the systematic review.

Fifteen studies used structural MRI to investigate a number of hypotheses, while 13 studies used functional MRI. All three that used resting state functional MRI scans reported varying degrees of altered resting state functional connectivity in people with CFS/ME, characterised by decrease connectivity in key networks, eg. salient network and fronto-parietal network.

Dr Thai then turned to the neuroimaging studies she conducted with Prof Esther Crawley at the University of Bristol's Clinical Research & Imaging Centre, undertaken with 22 CFS/ME participants and 22 sex- and age-matched healthy controls.

Their voxel-based morphometry study indicates that CFS/ME patient group have greater grey matter volume when compared with the control group. Their fMRI study showed that the CFS/ME group activate more extensive brain network when asked to undertake set tasks, ie. they must exert greater neuronal and metabolic demand.

Although we now have a considerable number of studies in this area, Dr Thai concluded, many of them have used small numbers of patients and produced inconsistent results. What is needed are much larger studies, longitudinal studies (ie. following changes over the course of time) and multi-site studies that make use of multimodal neuroimaging.

"Please contact me, share your data with me, ask me for my data," said Dr Thai, highlighting the need for collaboration. "Other people today have talked about how imaging is expensive… well, guess what: it's cheap! It's not expensive. A resting state scan can give you whole brain connectivity, and that takes six minutes; a structural scan, five minutes.

"I do these scans in babies, in children with autism, in patients with dementia, I can do them in patients with CFS/ME. If you have the right team and protocols, and you can now match your protocols to UK biobank: you don't need to recruit controls! So you don't need to spend that time and money. For paediatric MRI, there's the Cincinnati Paediatric Database of healthy controls, it's already there – and that has been achieved by data sharing."

Patient Advisory Groups: A valuable resource for CFS/ME research

Phil Murray and Rachel E, MEGA Patient Advisory Group, UK

Phil has recovered from CFS/ME and is a member of the Patient Advisory Group (PAG), formed in December 2016 to support the ME/CFS Epidemiology and Genomics Alliance (MEGA). Phil introduced a video by Rachel, who gave her personal account of living with the illness.

Rachel is currently moderately affected by CFS/ME and has been ill for over ten years. She described the impact of the illness, explaining that she has lost her career as a teacher and is now retired on health grounds. She has found it difficult to accept that at her age and after all her training she will not be standing at the front of a Science classroom again and she feels that part of her identity is lost.

Rachel is a wheelchair user, and is often housebound without the help of others. She can feel very ill after simple activities like taking a bath, is often unable to prepare food, suffers with cognitive difficulties (or brain fog), has difficulty sitting or standing upright for long, and has poor mobility. Rachel often experiences considerable discomfort and pain. At times her sleep is disrupted, and at other times she has an overwhelming need to sleep. She relies on others to help care for her children, clean her home and enable her to get out and access the world outside.

The cardinal, defining symptom of post-exertional malaise is the most difficult to cope with and the most disabling to Rachel. Any cognitive, physical, or emotional activity beyond what she can manage to do causes payback in the form exacerbation of all symptoms, delayed by up to 72 hours, and lasting days, weeks or beyond. Pacing helps to maximise what she can do within the boundaries set by CFS/ME, and minimises the risk of payback, but it still happens too often.

Rachel describes herself as one of the lucky ones as she has a supportive GP, and supportive friends and family, and with their help can lead a good, if restricted, life. CFS/ME has impacted on Rachel's family for around 30 years.

The reality of severe CFS/ME

"I have seen how severe ME can leave a person bedbound, unable to reach the bathroom, unable to attend to their own personal care, unable to bear touch on their skin, unable to be hugged, unable to tolerate even the sound of another person's speech, unable to tolerate light even with the darkest sunglasses," she says.

"I have seen how it can rob a person of the ability to speak, of the ability to chew or swallow solid food, and how it can cause seizures and vomiting and ongoing pain, robbing someone of their life for years on end with no hope of a cure."

Rachel is also now seeing the effects of CFS/ME on her teenage daughter who has been ill for three and a half years. She is watching her teenage life, missed experiences, friendships and education pass her by. In Rachel's daughter's words: "You are alive, but it's not living, it is just existing most of the time. It is like you are watching life through a one-way mirror. You can watch everyone else and see what they are doing but you can't participate and they can't see you."

How does the PAG work?

The patients, parents and carers in the PAG represent a cross section of the CFS/ME community and bring experience of CFS/ME but also qualifications and experience in the fields of law, investment management, science, education, college lecturing, management of a university department, journalism, medicine, general practice, biochemistry, immunology, and the pharmaceutical industry.

Phil explained that the PAG uses an online platform, Slack, that allows them to interact with each other to discuss topics, create and share editable documents, and post links to new CFS/ME research.

They also meet via teleconferencing, and communicate by email. They have educated themselves about diagnostic criteria, definitions, research past and present, and the variety of CFS/ME symptoms, as well as keeping up to date with the views and concerns expressed by people with CFS/ME. In total, CFS/ME has affected the 12 patients and carers in the PAG for more than 185 years.

In order to work well together, the PAG needed to build trust and understanding within the group through effective communications, and a shared belief that each point of view counts. Differences of opinion within the group have been a healthy aspect of working together, and they have learned a great deal from one another.

Members encourage one another to prioritise health over PAG work. ME itself causes some challenges of working together as some find phone conversations easier than writing emails or interacting online, whereas others find teleconferences a big drain on their concentration, and members can be ill for days after.

These barriers have been overcome by supporting one another and adapting so that contributions to a teleconference can be emailed in advance, announcements can be made on both Slack and email, and sometimes one-to-one phone conversations are helpful.

The PAG has some suggestions for how to enable those affected by CFS/ME to be members of a Patient Advisory Group, as follows:

- Include both people with CFS/ME and their carers.
- Enable the group to get to know and support one another, making use of several modes of communication (phone, email, online platform).
- Know that ME patients are a valuable resource.
- Give plenty of time for people with CFS/ME to plan the work they need to do for your project, so they can pace themselves.
- Plan meetings and deadlines as much in advance as possible.
- Be sure to hear the voices of the most limited, the most severely ill.

In the case of MEGA, the PAG has contributed to the writing of funding bids, considered research eligibility criteria, trialled patient questionnaires for suitability and relevance, considered acceptable levels of patient burden for sample and data collection, answered questions and stressed the importance of enabling the full range of patients to participate. The

PAG have learnt a lot about the considerable demands and challenges researchers face to secure access to the limited funding available.

Patient input can help ensure research is considering the reality of CFS/ME. For example, questionnaires used to measure disability and symptoms can be very problematic. The PAG has been able to make what they consider are vital recommendations to the research team. For example, that the severely ill, and long-term ill, be included, so that results from studies with only moderately or mildly ill patients are not extrapolated and applied to the severely ill.

Most of the PAG feel that the De Paul Symptom Questionnaire does a fairly good job of capturing ME symptoms, unlike many others commonly in use, although it does take a little time to complete. A PAG can communicate the specifics of why something might work well for one patient taking part in research, and be unworkable for another.

Another area the PAG has discussed is the question of how to distinguish between those suffering from ME, those with ME plus co-morbid depression and anxiety, and patients who have depression and/or anxiety but not ME. The Hospital Anxiety and Depression Scale (HADS) questionnaire often used in research, is very problematic for people with CFS/ME, because you can score high, but for reasons other than mental health problems. For example, you may say that you don't enjoy things that you used to enjoy, because you're physically unable to do them, not because you're depressed and lacking motivation.

A more general difficulty is posed by the word "usually" in a questionnaire. If someone has been ill for years, they may not be able to remember what it was like to be healthy. With effective pacing, people with CFS/ME can learn to minimise their experience of extreme fatigue, but still have very restricted function, therefore the PAG finds that questionnaires measuring function are more relevant than those measuring fatigue.

Another vitally important consideration is that post-exertional malaise be the defining factor for inclusion in a study, however the PAG believes that post-exertional malaise is not defined clearly enough. As Rachel said, when people with CFS/ME overdo it, they don't just get "extra tired", all symptoms worsen: pain, cognitive impairments, sleep disturbances, headaches and migraines, digestive issues, orthostatic intolerance, and others, so it's much more than "malaise".

Why does biomedical research matter?

This brings us, said Phil, to the difference that biomedical research can make to the hundreds of thousands of people with ME who have been left feeling disbelieved and invisible. The still-prevalent idea that CFS/ME is a psychological condition, or psycho-social construct, is terribly damaging to anyone whose body will not work because of CFS/ME.

It is very disheartening that, while science has made such strides in areas such as cancer and AIDS, there is still no treatment and no cure for CFS/ME. The PAG wants to work in a positive, solution-orientated way in partnership with research scientists. In the words of one PAG member: "It can make your day to read research that shows it's real. It really gives you hope. And that difference is being made to people with ME all over the world."

The PAG feels relieved and grateful when eminent scientists and clinicians treat the patient group as friends and as partners, working together with the aim of finding solid knowledge. Because CFS/ME is a "serious, chronic, complex, multisystem disease" (IoM report), we need scientists from different fields to work together. We hope that scientists and funding bodies will focus on the enormous benefit and potential to be gained from collaborative work.

A positive example from last year's CMRC meeting is an encounter one of the PAG members had with a student. He said that speaking to her had encouraged him to pursue his dream of doing ME-related research. He's now undertaking a PhD in the field.

The final message from Phil, Rachel and the PAG was that, on the discouraging days – whether you are a researcher whose grant didn't make it, or a teenager watching her friends through the "one-way mirror of ME" – please don't give up hope: we will crack the conundrum of CFS/ME, together.

You can watch a film of this presentation at www.tinyurl.com/actionformeyoutube

Workshop 1: Managing orthostatic intolerance in CFS/ME: a workshop for practitioners

Dr Peter Rowe, John Hopkins Children's Centre for CFS

This workshop focused on practical tips and treatment for practitioners with only a handful of patients attending. There were lots of opportunities for discussion with a range of case studies where diagnosis was discussed, as well as different treatment options.

Dr Rowe identified orthostatic intolerance and the range of accompanying symptoms. The different types of orthostatic intolerance in CFS/ME (chiefly postural tachycardia syndrome and neutrally mediated hypotension) were discussed along with blood pressure and heart rate charts.

Workshop participants discussed a range of different forms of treatment, from non-pharmacological measures (avoiding factors that precipitate symptoms, compression garments, fluids), treating contributory conditions, and various medications directed at the circulatory problems. Examples and case studies mostly focused on teenagers and young adults. The importance of an individualised approach was highlighted for treatment success.

Participants also discussed the link of other conditions to orthostatic intolerance, such as hypermobility and using the Beighton score to diagnosis.

Workshop 2: How can we work better together to drive scientific breakthrough for people with CFS/ME?
Dr Mark Edwards, independent research physician

Dr Edwards is former clinical research and development director, and Director of Science and Medical Public Affairs at Pfizer. Asking how we can work together better to drive scientific breakthroughs for people with CFS/ME, he led workshop attendees in a lively discussion in the areas of building research and working collaboratively, before drawing on examples in other fields, and suggesting others the CMRC might want to work with to move the field forward.

Workshop attendees agreed that there is a lot of great work going on, but in specific individual areas of interest: we need to pull it all together and refine the questions we are asking. The key is not just to measure things, but to know why we are measuring them: what are our key questions? Clinical trials need a good end-point, but we currently have no consensus on what a primary end point is for CFS/ME research. One delegate commented: "ME is more than just fatigue. Is the CMRC a fatigue collaborative, or an ME collaborative?"

There was agreement that industry, academia, clinicians and patients all have an equal role to play, and that entrenched views are one of the biggest barriers to progress. It was suggested that a CMRC research conference chaired and run by patients would be a very productive next step.

Dr Edwards highlighted that philanthropists are willing to fund research if they know the chance of answers is high, and gave the example of Action on Hearing Loss, who corralled academia to create a completely new area of translational research from scratch, and which now has significant industry involvement. Other suggestions for bodies the CMRC might want to link up with included Picori, set up by the Obama administration; Findacure, who are "great at bringing key players together for patient benefit;" and the James Lind Alliance, who have robust methodology for identifying key research questions.

Workshop 3: Daily fluctuations in fatigue: using technology to identify patterns, predictors, and potential solutions

John McBeth and Katie Druce, University of Manchester

Workshop participants discussed the need for mobile health (mhealth) studies to better understand the mechanisms of fluctuations in fatigue. Overall, participants felt that there was a need for mechanistic studies and agreed that the use of smartphones, wearables and nearables offered substantial advances in the field.

Participants were particularly keen that, in addition to enabling researchers to examine the mechanisms of fatigue fluctuations in people with established fatigue, these methods would enable us to track fatigue volatility and examine symptom onset in children and young people. Participants then discussed and designed their own study, before ideas were condensed into an optimal study design.

Ultimately participants wanted an ecological momentary assessment study, which would ask them to report fatigue at least three times per day. It was important though that the study included the capacity to report fatigue more frequently if study participants wished to. We discussed the need to capture physical and mental fatigue separately and to have some sort of assessment about the qualities of fatigue.

Alongside the traditional variables such as anxiety and mood, participants wanted to collect inflammation, heart rate variability, diet and factors such as menstrual status and stress. A further wish-list of things we were not sure how to measure was drawn up and included brain fog, cognitive function, feeling ‘overwired’ and experiencing sensory overstimulation.

It was clear that to carry out this ideal mhealth study, we would need to draw on the variety of expertise and knowledge of the members of the UK CFS/ME Research Collaborative and other relevant research partners.

Anne Faulkner Memorial Lecture:
Cytokine signature associated with disease severity in CFS/ME/ME patients
Prof José Montoya, Stanford ME/CFS/ME Initiative

Affected by the illness for many years, M.E. advocate Anne Faulkner co-founded the CFS Research Foundation in 1992, and over the next two years the charity awarded grants totalling £2 million for CFS/ME research. The Foundation's Trustees closed the charity following Anne's death in 2014, and the CMRC are honoured to present this lecture each year in recognition of her work.

Offering hope about the progress of CFS/ME research in his Anne Faulkner Memorial Lecture, Prof Montoya touched on some areas of research that Stanford University have been carrying out, including studies on the brain, as well as discussing his recent paper on cytokine signatures.

He also highlighted the role of antiviral drugs in the management of carefully selected patients with CFS/ME, illustrating this with a case study of a 47-year-old man with severe CFS/ME. Human herpes virus (HHV-6A) DNA was found in his blood at the beginning of the illness and later in his cerebrospinal fluid; he also showed an abnormal brain MRI. The man was treated with Valganciclovir, an antiviral medication, which resulted in dramatic improvement. But he relapsed after finishing the six-month and 12-month courses, and so he is set to continue on a five-year regime.

Clinical views of CFS/ME

Prof Montoya also gave an overview of the historical and current status of clinical views of CFS/ME, including the evolution of diagnostic criteria. "One of the biggest mistakes made by modern medicine is to have arrived to the conclusion that diseases such as CFS/ME are a figment of patient's imagination," he commented, adding that the mending of this "historical error in clinical judgment" has finally started to take place.

Study designs at Stanford were outlined, showing that there are randomised, double-blinded, placebo and longitudinal studies, with case controls and detailed statistical analysis. These studies are looking into a whole range of areas within CFS/ME patients; inflammatory gene expression, human leukocyte antigens, brain anatomy and function and cardiac and endothelial function.

Prof Montoya discussed his paper on right arcuate fasciculus abnormalities and reduced white matter volumes seen in CFS/ME patients. He then went on to talk about the results of his recent paper on Cytokine signatures associated with disease severity in CFS/ME in detail.

The presence of two cytokines was found to be significantly different in CFS/ME patients compared with controls; TGFβ was elevated and Resistin was lowered. It was also found that 17 cytokines correlated with disease severity, 13 of which are pro-inflammatory. The use of a new technique called "non-specific binding" when analysing the data was found to increase the specificity of the results and so was shown to be a valuable tool for future research.

He also touched on cerebrospinal fluid leaks, which can often be misdiagnosed as CFS/ME and can be treated with a simple blood patch. Management of CFS/ME through non-pharmacological approaches were covered, such as nutrition (specifically the Mediterranean diet), supplements and pacing.

Prof Montoya then went on to discuss some specific pharmacological approaches that can be used in the management of CFS/ME, such as antiviral medication, anti-inflammatory drugs and immunomodulatory agents. More specifically, he spoke of Stanford University's clinical observations on the feasibility of treating concurrent herpes viruses (EBV and HHV-6) with long term oral antivirals.

He concluded his presentation with a discussion of Stanford's proposed disease model for CFS/ME, that an initial protective immune response is triggered by an infectious agent, which "normal" people would usually recover from. However, in people with CFS/ME, this immune response can evolve into immunopathology. This difference in sustained immune response could be due to differences in genes, or through reactivation of a latent pathogen (such as herpes virus) or by an unknown pathogen.

Prof Montoya concluded by emphasising how we need to switch our narrative from CFS/ME being mysterious and poorly-understood to "an unfolding story of discoveries and excitement."

You can watch a film of this presentation at www.tinyurl.com/actionformeyoutube

Conference reflections
Prof Stephen Holgate, CMRC Chair, University of Southampton

Prof Stephen Holgate closed the conference by thanking everyone who had helped to put this meeting together, noting the way in which several new collaborations had occurred as a result, and indicating that new initiatives, including a research conference for the patient community, would now be followed up.

Reflecting on why the 2017 conference felt different to previous years' events, he said: "It's different because the patients and the clinicians and the researchers are not differentiated. You could hardly tell whether it was a patient or a professional asking a question."

Making specific reference to Prof John Gallacher's Dementias Platform and the opportunities afforded by the technology it employs – and which Prof Gallacher had offered to share – Prof Holgate confirmed that the "big data" approach championed by the MEGA project was the only way forward. Despite being turned down for funding thus far, there was still a huge appetite to meet with other funders to explore how this ambition can be made a reality.

"There is no question that patients must be at that meeting – theirs is the most important voice," said Prof Holgate.

Only by bringing together industry, the charity sector, scientists, clinicians and patients can we achieve our goal, "working from the same hymn sheet."

He ended by saying: "I am going away from this meeting with a great sense of optimism and a tremendous buzz. I want to thank every single person in this room for what you've done: it's your spirit of endeavour that has come out in the last two days, and created this 'can do' atmosphere. Together, we are stronger."

Delegate feedback

The following feedback is presented verbatim from feedback forms completed by delegates.

For professional and student members only: what value do you feel participation in the conference will add / has added to you in your role?

- As a hard pressed full time NHS consultant, I don't have the time to put head over the parapet so this conference very important to feel integrated.
- Illustrates the current research & possible future research
- Great value
- Networking - established contacts & connections
- My role is as a practitioner in clinic and I can bring my current research developments to my patients. I am also a nurse researcher and able to progress my work in light of the conference.
- Linking my research to other areas / ways of looking at CFS/ME.
- Meeting other professionals in the field and making connections. More physiological research evidence to inform clinical & research work.
- Stimulates thought & ideas, but less applicable to direct clinical role.
- Greater awareness of current research areas.
- Good to see more clinicians attending - good networking opportunity & helps to build momentum translating the research into clinical practise (eg managing OI symptoms better). Lots of information & enthusiasm to take back to my CFS team & patients
- Excellent way to update knowledge of a wide range of research
- Knowledge & understanding, promotion & awareness, collaboration & pls see QN5
- Learning from the research & expertise of peers and having an opportunity to become more skilled in assessing & treating patients with CFS/ME but also in conducting research.
- Knowledge of how the collaborative is working, its aims and objectives and current research projects. Very helpful.
- It is an amazing networking opportunity.
- Understanding what research is happening & its direction. Gives me information to add evidence to when I explain to patients

How would you rate the conference overall?

- 90% said very good
- 10% said quite good

Please comment on this further if you wish

- Inspiring, Educational, very good networking, great atmosphere, felt very collaborative, Thanks! Very encouraging to see the collaboration and the interest. At last. Truth & reconciliation.
- Very well organised, brilliant 'introductory' speakers - made transitions smooth. Need more time for questions & general chat.
- Collaborating and networking opportunities have been very helpful.
- Interesting speakers, shame key talk at the end.
- Very informative, well organised. Lots of energy. Thank you.

How would you rate the venue and facilities?

- 63% said very good
- 26% said quite good
- 11% said average

How relevant was the conference for you and your personal/professional interests?

- 67% said very relevant
- 33% said quite relevant

How would you rate the quality of the presentations?

- 84% said very good
- 16% said quite good

How would you rate the workshop you attended?

- 69% said very good
- 23% said quite good
- 8% said average

What plenary sessions, presentations and workshops would you like to see at next year's CMRC conference?

- Would be nice to have had a dedicated session on sleep - biology etc and reference to CFS.
- More of the same; however as above, put the very hard science into one session etc.....
- More on PPI guidelines & application. How practitioners can contribute to research & undertake their own.
- Who might start up and run a 'biobank' or cohort for CFS/ME!
- Immune function in ME. Neurological changes in ME. Translating research to treatment approaches.
- Perhaps events for the recruitment of biomedical post graduate students, try to sell ME/CFS research to students, maybe in a separate event?

Please share any additional comments or feedback you have about the conference

- Fantastic conference, very positive & well run. Need to set up platform / webspace for researchers to recruit study participants & patients to easily find & join studies.
- Very encouraging and relevant.
- Collaboration discussions. Translating research into practice. Difficulty in identifying research groups with interest. Trial interventions and reflections of real practice.
- Congratulations to organisers.
- Thank you.
- nice guideline on autonomic function test & autonomic function test, nice guideline on POT & POTS.

To find out more about the CMRC, including how to become an Associate, Student or Professional Member, visit www.actionforme.org.uk/CMRC