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CFS/ME Research Collaborative Conference report

1-2 September 2014

Introduction

The inaugural conference of the UK CFS/ME Research Collaborative (CMRC) brought together more than 70 researchers and clinicians with an interest in CFS/ME.

Some have worked in this area for many years, while others are entirely new to the field. This is hugely encouraging, as one of the key aims of the CMRC is supporting professionals not currently involved in CFS/ME research to help them develop those skills, connections and collaborations.

In addition, 56 patients, carers and ME advocates took part in a workshop focused on moving research forward. They were joined by 22 conference delegates from a wide range of disciplines for a very productive debate, feedback from which has been sent to the CMRC Executive Board for discussion and, crucially, action.

This report contains an overview of all the presentations and workshops on the programme. What is harder to capture, however, is the infectious atmosphere at the event, and the enthusiasm and collaborative spirit of everyone who attended.

There was a genuine buzz in the air, not just during the question and answer sessions and workshops, but also in the break times, over dinner and at the patient/researcher session: everywhere I heard people discussing how we can work together to move things forward.

On behalf of the CMRC, I would like to thank Clare Ogden, Head of Communications and Policy, Action for M.E. (clare@actionforme.org.uk) for contributing to, and coordinating, the production of this report. I would also like to thank the following people for their contributions to this report:

- Prof Jonathan Edwards, Emeritus Prof of Connective Tissue Medicine, University College London
- Simon McGrath (@smjnotes on Twitter)
- Karen Hainsworth
- Russell Fleming
- Dr Charles Shepherd, Honorary Medical Adviser, ME Association
- Sally Crowe, Crowe Associates
- Sonya Chowdhury, CEO, Action for M.E.

And finally, I want to extend a huge thank you not only to everyone who attended the conference, but to all the patients, carers and professionals who support the work of the CMRC. Thank you for demonstrating that by coming together we can turn the CFS/ME field around for patient benefit.

Stephen Holgate
CMRC Chair

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Welcome

Prof Stephen Holgate, CMRC Chair

Prof Holgate began by setting out the need for a CFS/ME research collaborative in the UK, citing:

- difficulties in getting the condition recognised by the medical profession
- the likelihood of CFS/ME being more than one disease with multiple causative pathways and levels of severity
- disagreement over mechanisms, what we should be capturing, and how we measure it
- the need for careful phenotyping and different scientific methods
- paucity of new treatments
- the very variable quality of research, with much speculation and conjecture based on poor evidence
- the breakdown in trust between patients, clinicians, researchers and funders.
- fragmented, low-level funding
- lack of research industry interest.

“We are dealing with a very complicated interaction between genetic and environmental factors, with a number of different manifestations,” he said.

Prof Holgate highlighted the need for collaborative working between scientists, medical charities and patients and carers. “The future lies in these different components coming together in a single agenda,” he said.

He acknowledged with thanks the efforts of all the individuals who had contributed to the genesis of the conference, in particular:

- Sonya Chowdhury, Action for M.E.
- Esther Crawley, University of Bristol
- Joe McNamara and Neha Issar-Brown, Medical Research Council
- Hugh Perry, University of Southampton
- Christine Vincent, University of Southampton
- international colleagues who had been so willing to travel
- all those who attended

Prof Holgate finished by saying, “I hope the next two days are enjoyable, exciting and open up some opportunities. This isn’t about finishing something, it’s about starting something, and if we can do this right, I see no reason why we can’t go onto much greater things in the future.”

Anne Faulkner Lecture: The neuroimmune basis of fatigue
Prof Robert Dantzer, University of Texas Anderson Cancer Centre

In his presentation, Prof Robert Dantzer explained how sickness behaviour, which includes fatigue, is part of the normal, 'healthy', response to infection and usually subsides after the infection. It is triggered by cytokines released by immune cells when they detect a pathogen. Chronic fatigue may be linked to long-term activation of sickness behaviour. Prof Dantzer finishes by describing the 'orexin' system in the brain, which may play a critical role in fatigue and could be a target for drug therapies.

"Remember that last time we had the flu — the sleepiness, depressed mood, decreased activity, fatigue, reduced appetite, etcetera? All of this is triggered by cytokines released by white blood cells". Prof Robert Dantzer is describing 'sickness behaviour', the characteristic response of all mammals to an infection. It is a biological process that exists to promote recovery and healing.

Prof Dantzer's pioneering research helped reveal the biology of sickness behaviour. He now works on cancer-related fatigue, which he believes could be a result of sickness behaviour gone wrong — and which might be related to chronic fatigue syndrome, both in symptoms and underlying mechanisms.

In his model, cancer-related fatigue is driven by white blood cells releasing tiny molecules called cytokines that act on the brain. This process is modified by risk factors, including the version of immune genes you have, neuroendocrine factors and psychosocial factors.

"Previous work on communication pathways between the immune system and the brain needs to guide us", said Prof Dantzer, as he reviewed the long-running saga of how researchers discovered the relationship between sickness, fatigue and inflammation.

The brain's "immunostat"

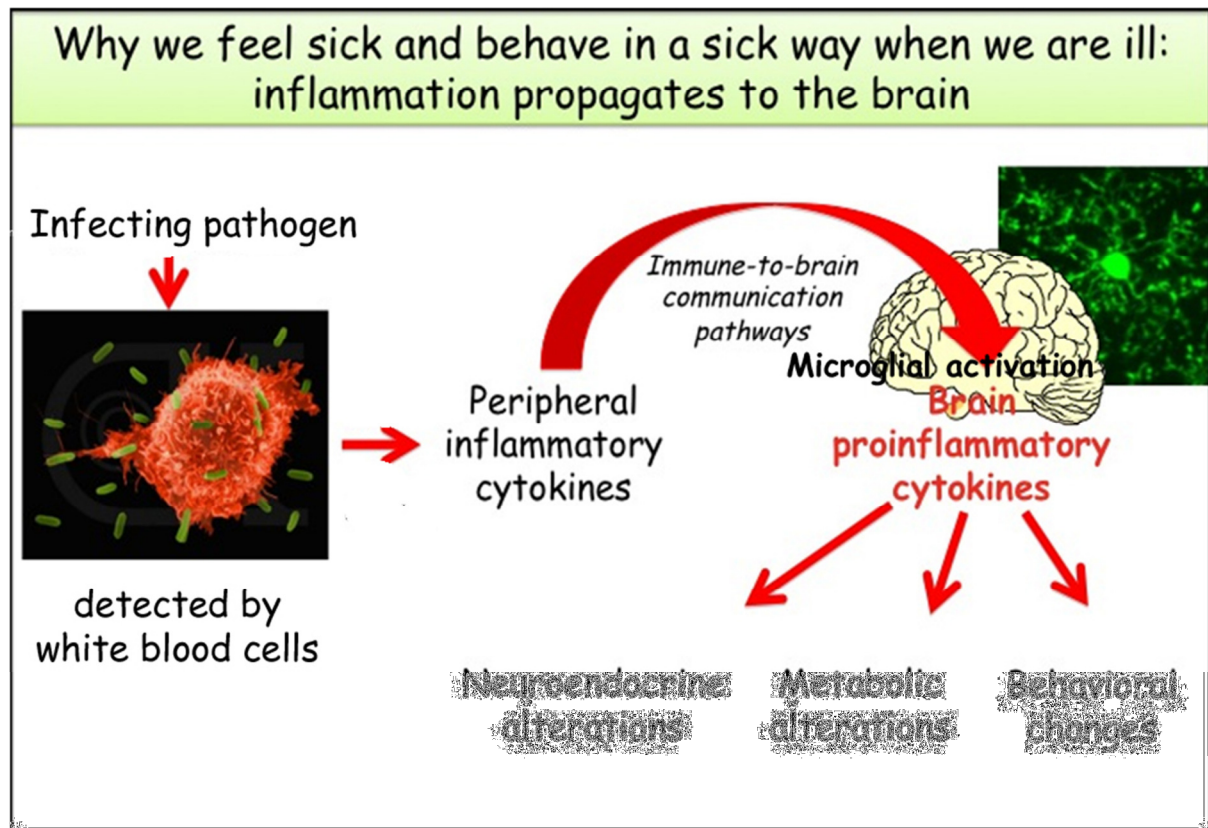
Researchers began to realise that, just like any other organ, the immune system is regulated by the brain. There must be what Prof Dantzer calls an 'immunostat' in the brain, and much like a thermostat in a central heating system, senses and regulates the temperature, the immunostat senses the state of the immune system and regulates it accordingly. But this requires communication between the immune system and the brain.

Work in the 1980s found evidence of two-way communication between the brain and the immune system. When they detect infection, immune cells produce molecules called cytokines (Interleukin 1, IL-1, is a key cytokine here). These molecules signal to the brain, alerting it to inflammation in the body. Back then, it was a radical idea that the immune system could produce molecules that affect the brain and physiology. It took a bit longer to discover that these same molecules also lead to changes in behaviour.

More research showed that the communication is a two-way street: the brain controls the release of molecules that regulate the immune cells, including glucocorticoids via

the Hypothalamus-Pituitary-Adrenal (HPA) axis. (Glucocorticoids are widely used in medicine to damp down inflammation.)

These and other discoveries on the immune mechanisms of fever were brought together in 1988 by Benjamin Hart with his proposal that sickness behaviour is a normal and important process, part of the animals' deliberate response to infection driven by biology (www.ncbi.nlm.nih.gov/pubmed/3050629). A key part of the model is that it is a temporary situation to deal with infection: inflammation → sickness behaviour → removal of pathogen → restoration of normal behaviour.



Slide reproduced from Prof Dantzer's presentation, modified slightly for simplicity

The key steps leading to sickness behaviour are:

1. White blood cells recognise invading pathogens. (At this point, the cells use receptors that identify generic 'foreign' markers, such as bacterial cells walls, rather than recognising specific bugs such as the flu virus.)
2. The white blood cells release cytokines in the body.
3. Immune-to-brain communication takes signal to the brain (either via the blood, or the nerves innervating the site of the body in which the inflammatory response takes place).
4. This activates microglia - the brain's innate immune cells - which release more cytokines into the brain. So activation of immune cells in the body leads to activation of immune cells in the brain.
5. This leads to more biological changes and, ultimately, to sickness behaviour, including fatigue.

The first evidence that microglia played a critical role came in 1992, when a study showed that microglia produced IL-1 in the brain in response to inflammation in the

rest of the body. Subsequent work using fMRI brain imaging shows that inflammation leads to microglia being activated throughout the brain within a few hours.

LPS – used in experiments to trigger inflammation

Many experiments that probe the role of inflammation in sickness behaviour use a molecule called 'LPS' to trigger inflammation. LPS, or lipopolysaccharide, is a component of the cell wall of many types of bacteria and acts as an alarm signal to the body. Many immune cells have receptors that bind LPS, and this binding acts as a trigger that launches the immune response, including the release of cytokines. It's a convenient way for researchers to generate a 'clean' signal of inflammation, and zero in on the body's immune response, without the complications of an ongoing infection.

Sickness behaviour is flexible

Prof Dantzer made the point that while sickness behaviour is normally a standard set of responses driven by infection, it is affected by the environment too. This is the "motivational state" view of sickness behaviour. Normally, when we are sick the world no longer matters to us, what matters is taking care of the injured body – that's exactly what the brain wants us to do – but in extreme situations this can be overridden, as the following experiment showed.

Female mice with young pups, if injected with LPS at room temperature, show lethargy typical of sickness behaviour, and won't respond if the pups' nest is removed. However, if pups are dispersed in the cage, the female mice will overcome their sickness and bring back their pups to the stack of cotton wool they normally use to build the nest. But if the experiment is repeated with the temperature reduced to a chilly 6 degrees centigrade, then the mother mouse will react to the harsher circumstances threatening her pups and not only bring back her dispersed pups to the stack of cotton wool but make use of the material to rebuild the nest. So behaviour depends not just on inflammation, but the environment too. Or, as Prof Dantzer said "Inflammation-induced sickness is a motivational state that reorganizes the priorities of the sick individual". And those priorities are flexible according to the environment.

Prof Dantzer said that up to this point he'd described normal, 'healthy' sickness behaviour. It's normal to feel sick in response to an infection in the same way it's normal to feel afraid in response to a threat. Essentially:

- The brain has an 'immunostat' that recognises the immune response in the body – this is the origin of sickness behaviour.
- This reorganises sick animal's priorities.
- Crucially, sickness behaviour is normally fully reversible.

"To be healthy is to be able to become ill and recover from it..."

(Georges Canguilhem: "être en bonne santé, c'est pouvoir tomber malade et s'en relever")

Prof Dantzer moved on to what might go wrong when we don't recover normally, asking, "Is chronic fatigue or depression a form of sickness disorder?"

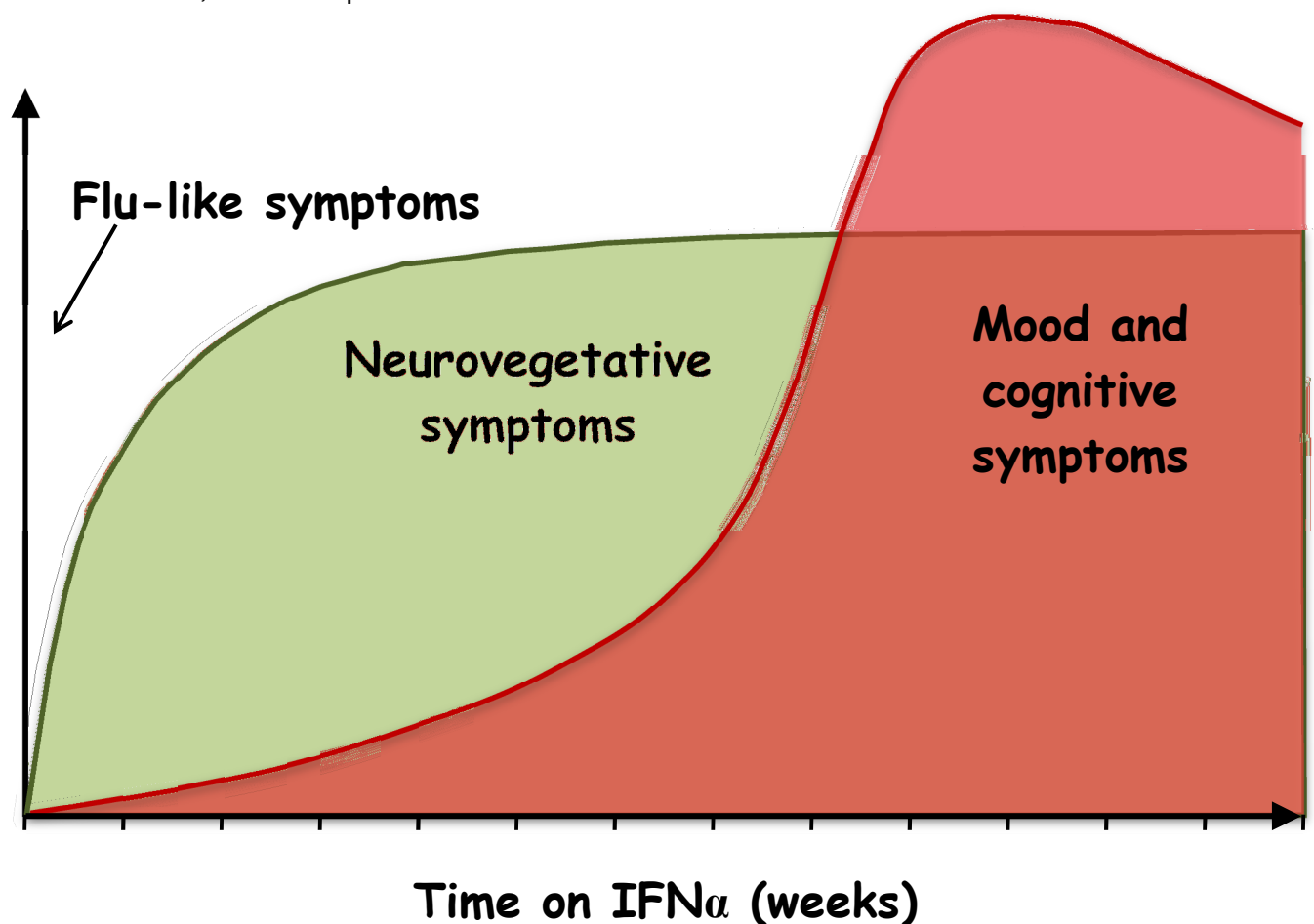
Inflammation: unpicking its roles in fatigue, sickness and depression

Historically, much sickness behaviour research has focused on inflammation causing depression rather than fatigue.

However, what doctors call 'depression' has different elements, and fatigue counts as a big part of it:

- Mood symptoms including feelings of sadness, irritability and crying
- Affective/cognitive symptoms including self-dislike, guilt and worthlessness
- Neurovegetative symptoms, which include the CFS/ME symptoms of fatigue, problems with sleep and concentration.

Prof Dantzer showed this fascinating slide based on the work carried out by his former student, Lucile Capuron:



This slide broke down how different types of symptoms appeared at different times in cancer patients given the cytokine interferon-alpha as therapy. The fastest response comes from flu-like symptoms (malaise) that appear rapidly with each repeated dose (but fade fast due to anti-fever drugs).

But within a few days the neurovegetative symptoms start, including of fatigue, sleep problems and difficulty concentrating. After a week or so both mood and cognitive symptoms cut in.

So a problem is that when researchers said they found 'depression' in response to inflammation, sometimes they only meant fatigue and other CFS/ME-like symptoms. A study (www.ncbi.nlm.nih.gov/pmc/articles/PMC2621309) on an inflammation-linked disorder called Metabolic Syndrome found that there was a link of inflammation with depression overall, but that while there was a significant link for the neurovegetative symptoms, the link with mood and affective symptoms was not statistically significant.

Deconstructing fatigue – what exactly does inflammation affect?

Prof Dantzer argues if we really want to understand the biology we need to go further and 'deconstruct' even fatigue. The idea is to break it into the 'neurobehavioural units' corresponding to the way the brains works. Fatigue, said Prof Dantzer, could be seen as having two elements:

- The physical ability to do things .
- Motivation: willingness or wanting desire to do things.

He said that patients they see at his cancer centre have more problems with motivation, but he also believes biological systems underpin both elements of fatigue.

Prof Dantzer gave the example of motivated behaviour and how it is affected in different ways by different aspects of inflammation. Motivated behaviour can be broken into two steps. In the case of feeding, there is

- a 'seeking' phase of accessing the food, then
- a 'taking' (or consummatory phase of eating it.

So in predators, like cats, this would be hunting and eating. It turns out that different parts of the brain are involved in theses *seeking* vs *taking* steps.

An experiment (www.ncbi.nlm.nih.gov/pubmed/24136220) helped show the difference and how inflammation can affect both steps but at different times. If rats pressed a lever five times (*seeking* behaviour) they were rewarded with tasty food (the rat equivalent of "very nice wine from Bordeaux" said Prof Dantzer, who is French). The rats had free access to normal rather bland laboratory food ("like wine from Bristol", suggested Prof Dantzer, who was speaking in a lecture hall in Bristol).

Healthy rats press the lever to get the "Rat Bordeaux". When rats were injected with a cytokine to cause inflammation and tested ninety minutes later during the peak of sickness, they ate less 'Rat Bordeaux' (the food that required more energy-requiring *seeking* behaviour of lever-pressing), but still ate easy-access boring food (simple *taking* behaviour). This fits with physical exhaustion.

However, the results were different when they did a similar study on mice at a later stage (one day on) where depression would have cut in for mice. This study used grain (unexciting food) or chocolate (which mice apparently love). A single lever press was needed for grain, but ten presses were needed for chocolate. This time the LPS-injected mice injected worked less than healthy mice overall, but more of what they ate was chocolate, even though it was more work. It was if the problem was motivation – they were less likely to respond overall but if they opted for engaging in an effort, then this effort needed to be for a big incentive rather than a small one.

Similar studies have been done in humans, though they used money instead of chocolate as the incentive. Prof Dantzer said the beauty of this approach was they could study motivation both in animals and humans (and run experiments in animals that wouldn't be possible in humans).

Orexin – the key to inflammation-related fatigue

Prof Dantzer finished his presentation by describing a recently-discovered system in the hypothalamus of the brain that plays a key role in regulating energy levels - and could be a target for drugs to treat fatigue. The orexin system senses metabolic status and the balance between feeding and energy expenditure. It responds to glucose as well as leptin, a key molecule signalling energy levels that has been implicated in CFS/ME).

The orexin system also plays a role in sleep versus wakefulness. Unlike healthy rats, those given LPS fail to become more active at night. What's really interesting is that the reduction in activity correlates with reduced levels of orexin. However, rats given orexin as well as LPS don't show any reduction in activity (www.ncbi.nlm.nih.gov/pmc/articles/PMC3155688), suggesting that orexin plays a key role in activity levels.

Orexin as a treatment for fatigue?

Researchers suspected that orexin may play a similar role in the cancer-related fatigue resulting from chemotherapy. They found that giving mice chemotherapy did indeed lead to lower levels of activity, indicating fatigue and a reduction in their orexin levels. Crucially, giving mice orexin alongside the chemo restored their activity levels, again suggesting reduced orexin played a central role in fatigue. He said that there are now drugs for narcolepsy targeting the orexin system, and perhaps they could one day be used for fatigue too.

Prof Dantzer said his group are working on a test of orexin as a treatment for cancer-related fatigue.

Conclusion

Prof Dantzer summed up by saying how hard it was to study a disorder characterised by symptoms, and urged a more detailed approach, probing what is really happening in the brain:

“It’s time now to deconstruct fatigue. We cannot continue to label patients; we have to find out how their brain is working, what is behind chronic fatigue. We are doing that now in cancer patients. There is no reason not to do it in CFS/ME.”

Finally he pointed out the challenge ahead: “We know what causes fatigue, we still do not know what is responsible for the chronification of fatigue”.

This article covers most of the points in the presentation, but does not aim to be a comprehensive summary.

The Anne Faulkner lecture was given in honour of the founder of the CFS Research Foundation, who recently died after raising more than £1 million for CFS/ME research.

Interferon-alpha rapidly changes brain microstructure

Dr Neil Harrison, University of Sussex

Interferon-alpha (IFN-alpha) is an immune system chemical, a pro-inflammatory cytokine that's a useful treatment for Hepatitis-C virus. However, most treated patients rapidly develop debilitating fatigue that can continue even after treatment has finished. This phenomenon of persistent fatigue is strikingly similar to CFS/ME.

Dr Harrison explained preliminary results from his study of how IFN-alpha changes brain microstructure. He and his team have recruited 18 (of a planned 52) patients starting IFN-alpha-based treatment for Hepatitis-C, and scanned them twice using an advanced structural magnetic resonance imaging (MRI) technique called quantitative magnetisation transfer: once before and once four-to-five hours after their first dose of IFN-alpha.

The team also took blood samples to measure cytokine levels, and followed patients up for six months to monitor changes in their fatigue levels. Their aim was to investigate whether changes induced by IFN-alpha in brain microstructure and/or cytokine expression could predict which individuals were most susceptible to developing chronic fatigue.

What they found was that the basal ganglia in the left-side of the brains of patients appeared to be affected, four-to-five hours after treatment. This results in 'hot spots' appearing in a part of the brain called the basal ganglia – on the left hand side of the brain in particular. And this hyperactivity in the basal ganglia seems to predict who is most likely to develop fatigue.

Dr Harrison admitted that they were perplexed by this finding – it is not related to the location of the injections – but that they expected to see a bi-lateral affect as the number of subjects increased.

Prof Jonathan Edwards says: "Quantitative magnetisation transfer assesses the extent to which protons (hydrogen atoms) are present in the randomly behaving form present in water and how much in a more regularised form in larger molecules.

"It is not clear what the changes he found would mean biochemically but it is interesting that other researchers have found changes on the left side in basal ganglia in a related experiment using a different type of analysis. What I like about this is that it does not seem to be just 'cytokines causing inflammation' but something much more specific."

Dr Charles Shepherd comments: "This is a potentially very important new finding because other researchers, including neurologists Prof Peter Behan and Dr Abhijit Chaudhuri, have proposed that the basal ganglia have a role in the causation of the central brain fatigue that occurs in many neurological disorders".

Interferon-alpha induced persistent fatigue

Alice Russell, Kings College London

Alice Russell's team have recently studied Hepatitis-C patients being treated with Interferon-alpha (IFN-alpha), to examine some of the possible biological mechanisms underlying the development of persistent fatigue.

This is one of the CFS/ME research studies being funded by the MRC and by looking at differences (including gene expression markers) between people who develop CFS/ME symptoms and those who do not, and those where symptoms persist after treatment is over and those who do not we may find some important clues as to what may be happening in CFS/ME during the very early post infection phase.

"We recruited 25 patients receiving IFN-alpha," Alice explained. "Blood was collected using PAXgene tubes at baseline and at four, 12 and 24 weeks. We assessed their fatigue levels using the Chalder Fatigue Questionnaire at the beginning of the treatment, and at follow-up, six months post-treatment. Patients were stratified according to whether their fatigue levels at follow-up had improved/returned to baseline levels, or worsened."

"Our data shows that patients who had persistent fatigue had an increased inflammatory immune response as early as week four and that continued throughout the treatment."

"This means that IFN- α treated patients provide a potential basis on which to model the pathogenesis of CFS."

Prof Jonathan Edwards commented: "Dr Neil Harrison's and Alice Russell's papers on IFN-alpha highlighted for me the possibility that fatigue in CFS/ME may not necessarily be mediated by the typical 'inflammatory' cytokines such as TNF [a type of cytokine that can cause cell death].

"Instead, it may involve something specific, such as an interferon, that is not necessarily in itself inflammatory, or it may be that the site of production and action of the cytokine may be very localised.

"The key message from these studies for me was that you can get severe fatigue with just one cytokine that is not directly involved in cell migration or tissue swelling. IFN-alpha may not be the right one for CFS/ME but it illustrates the fact that there are several options."

Blood cytokine concentrations in CFS: a systematic review
Dr Lisa Blundell, Barts and the London School of Medicine and Dentistry

Dr Blundell gave an overview of her literature review of the hypothesis that blood cytokines play a role in the pathophysiology of CFS.

Having found 1,637 papers possibly relevant papers through database searches, and excluding duplicates and those that did not fit the review criteria, Dr Blundell was left with 29 papers to review.

She found little or no support for the role of circulating cytokines in CFS/ME, except a slight increase in TNFbeta in the blood in five out of seven studies, which requires further investigation. Nor was there evidence that stimulus (such as exercise) leads to greater concentrations of these cytokines in comparison to controls.

During the discussion that followed, it may also be that we may not be measuring the right cytokines and looking at free levels of cytokines in the blood is not going to tell you much about localized cytokine activity/activation in specific tissues such as the brain – which could be far more important in symptom production in CFS/ME.

Prof Jonathan Edwards comments: “This might seem to dampen down enthusiasm for cytokines causing fatigue. However, as Prof Maria Fitzgerald pointed out, almost certainly nobody should have expected to find cytokines free in the blood.

“I know from rheumatoid arthritis, which is perhaps the grossest inflammatory disease of all, that finding cytokines in blood is far from easy, even when the cytokine responsive CRP protein is showing sky high. The reason may be that in rheumatoid arthritis the cytokines raising the CRP are made inside the liver in Kupffer cells, right next to where the CRP is made. The important lesson was learnt when rheumatoid arthritis patients were given anti-TNF and it worked – the cytokine is there but acting locally. As the meeting progressed this became a consistent theme.”

“And maybe TGFbeta is more important than we thought. TGFbeta does not get talked about much but five out of seven studies got a result for TGFbeta. This might actually make sense because this is a cytokine that gets involved in response threshold setting. If there is a stimulatory pathway acting locally that we cannot find in the blood there might still be a general feedback response through TGFbeta that did show up in blood.”

Resveratrol treatment on TNF- α -induced cytokine release

Kate Earl, University of Liverpool

Looking at reduced muscle function, a complex disorder affecting a wide spectrum of individuals, Kate Earl has undertaken a study to establish a tumour necrosis factor alpha (TNF-alpha)-induced model of increased cytokine release from muscle cells, grown and differentiated into myotubes in culture.

She also looked at nutritional interventions that might attenuate the release of cytokines. Resveratrol is a naturally occurring dietary compound derived from cocoa, peanuts and red grapes. This study is looking at the effect of Resveratrol on cultured muscle cells. It was found that the Resveratrol reduced the ability of TNF alpha to stimulate the release of other cytokines in muscle cells.

Prof Jonathan Edwards comments: "TNF-alpha seems to be important for muscle cells in that not only does it affect them but it may stimulate them to make their own 'inflammatory' cytokines in a vicious cycle. The effect acts on basic respiratory mechanisms involving reactive oxygen species. Resveratrol was found to reduce the ability of TNF-alpha to stimulate release of other cytokines from the muscle cells.

"It was intriguing to see a compound found in normal diet having an effect on cell cytokine handling in this way. Together with the presentation from Prof Anne McArdle, these were the only data looking specifically at muscle."

"One might ask the question whether muscle is really the target in CFS/ME, since a lot of other groups seem to place the problem more centrally in the brain. However, taking Prof Holgate's multiple (and multisystem) disease idea to heart, I think it is good to see all these potential targets under study. Muscle may be targeted directly in some cases and brain in others, or the problem may be a general one that affects cell metabolism across the board. Anything non-toxic that alters cytokine production is going to be of interest wherever it can act, I think."

Working together for more and better research that benefits people with CFS/ME
Facilitated by Sally Crowe

NB. For an overview of the four workshops attended by researchers, see p 53.

Nearly 80 people with CFS/ME, carers, clinicians and researchers attended this session which was facilitated by Sally Crowe from Crowe Associates. Sally herself as a personal connection with CFS/ME and has previously worked in the CFS/ME field on other projects. This session was designed with input from Action for M.E.'s patient reference group and CEO Sonya Chowdhury.

This report has been prepared independently by Sally Crowe and will be used by the CMRC to inform future work.

Prior to the workshop, participants received information about the session suggested by the patient reference group and details of the research cycle that would help inform discussion and engagement on the day. On arrival, participants were asked to pick which specific discussions topics they wanted to participate in from a choice of five (outlined later in report).

The workshops began with Sally outlining its objectives. These were:

- consider current opportunities for participation in research, and where patients and carers have made a difference
- identify specific ways that the CFS/ME community can contribute meaningfully to CFS/ME research projects (eg. clinical trials)
- identify what the CFS/ME community can contribute overall to CFS/ME research
- produce a report of comments, ideas and discussion points for the CMRC to consider .

The workshop process

This report is a summary of the large amount of material generated by the workshop participants. The programme is described in **Appendix 1**.

There were eight discussion tables with between five to ten people at each, facilitated by a range of people with research interests in CFS/ME. Sonya Chowdhury (Action for M.E. and CRMC Executive Board) circulated the room, listening and inputting to a variety of discussions.

There were two discussion sessions, one general (with the research cycle as a structure, if needed) and the longer session more focussed on particular topics concerning research. Participants selected the topic that most interested them. All participants were encouraged to write their ideas and contributions ahead of each discussion on post its. More than 300 post-its were collected in all, as well as notes from some of the facilitators. Facilitators were asked to check the content of their topic summary once produced.

The comments and ideas were overwhelmingly constructive and 'on topic'. There was one comment about not being listened to (it was not clear if this was to do with

the workshop or their experience of CFS/ME), and another sceptical about the purpose of the day "purely cosmetic with the real agenda already set". There were two post-its that were unreadable.

The afternoon was typified by several things:

- the cordiality of debate and discussion
- the majority of the input coming from participants, rather than facilitators or presenters
- a willingness to work together differently during the afternoon
- the quality of the contributions.

First discussion round

Using the structure of the clinical research cycle, post-its where possible have been themed into the 10 stages of the cycle, which include:

1. **Identifying research topics/questions** - providing context for research, generating ideas.
2. **Prioritising** - working out what is most important and beneficial to research from multiple perspectives.
3. **Commissioning** - where research funders advertise and select research to support.
4. **Designing research** - incorporating research planning, publicity and advertising for recruitment studies.
5. **Managing research** - recruitment to studies, ethics arrangements, informed consent, gateways to access study participants.
6. **Undertaking research** - helping with data collection, advocacy for study participants.
7. **Analysing and interpreting results** - helping with data collection, advocacy for study participants.
8. **Disseminating** - getting findings and results out within an agreed plan, generating interest, debate in results, changing treatments and care based on new research.
9. **Evaluating** - how can the research team improve and learn from the experience?
10. **Reviewing what we know**
11. **What the gaps are?** - developing consensus, lobbying for new research.

As there were so many similar post-its for some of these stages, a summary has been made for each stage. Stages 5 and 6, and 9 and 10 have been combined as the comments did not fit easily into these individual categories. The full lists of comments are in **Appendix 2**.

Ten stages of the research cycle - themes from first discussion round, some combined because of overlap in comments

1. Identifying research topics/questions	<ul style="list-style-type: none"> • Clarification on diagnosis and sub types of the condition, with subsequent classification and stratification for research • Specific research ideas included causal and onset, pregnancy, a range of biomedical and neurological approaches, biomarkers, links with virus e.g. Epstein Barr, stress, quality of life research, environmental, pain, long term follow up, and much more • How CFS/ME compares to other chronic conditions, making the case for more and good quality research, and having people with CFS/ME at the centre of the research process, using patient experience data.
2. Prioritising	<ul style="list-style-type: none"> • Priorities described included diagnostic, issues for severely affected, strategies for daily living and research into the stigma of CFS/ME • Using patient experience as a basis for ideas • Less emphasis on psychological research • Direction and coordination of research effort.
3. Commissioning	<ul style="list-style-type: none"> • Engaging drug companies and public funders to do more research • Commissioning more multidisciplinary research and connecting different areas of CFS/ME research.
4. Designing research	<ul style="list-style-type: none"> • More 'outreach' in research, and personalised approaches in studies • More integration and consistency across research projects e.g. diagnostic criteria • Multidisciplinary research teams • How to include people with multiple diagnosis/conditions? • Standardized objective outcome measures alongside other measures, such as user generated outcome measures.
5. Managing research and 6. Undertaking research	<ul style="list-style-type: none"> • More linkage with patients to studies they might be interested in, advertising and awareness of studies in patient population • Informed consent and effort to reduce drop out with more understanding of the effort people take to participate in research • Strategies for including people who are house or bed bound.

7. Analysing and interpreting results	<ul style="list-style-type: none"> • Evaluation to include patient comments • Stratify study results based on various demographics and co morbidity.
8. Disseminating	<ul style="list-style-type: none"> • Need for plain language reporting as well as traditional approach • Transparency in reporting • Using results dissemination as a way of showing involvement in research is worthwhile • How to keep specialists up to date, and generalists aware of developments a challenge.
9. Evaluating and 10. Reviewing what we know and what the gaps are	<ul style="list-style-type: none"> • Inter-disciplinary research combined with an open mindedness and a lack of defensiveness about individual disciplines will help the conversation about evaluation, gaps and consensus in research • Acknowledge the diverse patient group and associated challenges.

Second round of discussions on topic areas

This discussion round was more focussed on solutions and ideas, building on the first round, but in 5 key topic areas.

These were:

- recruitment to studies
- getting the right research plan (protocol)
- moving ahead on research priorities
- sharing (dissemination) of research results
- building research collaborations.

Note: There are some overlaps in content.

Topic 1: Recruitment of participants to research studies

Facilitated by Paul Little, Southampton University

Key questions:

- What matters from a ME/CFS experiential point of view?
- What factors help and hinder recruitment to studies?

Comments, views and ideas:

- clarity for research teams and potential study participants if there are sub categories (severity or other classifications) that have a bearing on recruitment to the study
- people with CFS/ME could be involved in developing the criteria for inclusion in a study
- proactive programme of asking people with CFS/ME to get involved in studies, via support groups, charities, online communities
- advertising studies through CFS/ME charities, support groups and social groups, CFS/ME clinics and GP surgeries (where appropriate) for recruitment
- consider incentives for taking part in a study - holistic therapies for example (as long as they don't interfere with the research), feeling part of something important
- develop a register of people with CFS/ME that want to be in research
- develop an online 'place' where people can register their interest in research - and/or find out what studies are going on in their area ([Clinical Trials Gateway](#) – but not very public – or [People in Research](#))
- geographical location of studies is of great importance to potential participants - being clear about where these are, and offers to assist with travel may help recruitment if the distance feels to far
- be open and friendly in the first approach - help potential study participants feel confidence in the team (get the basics right) and then develop trust
- how to instil hope, without making false or untested claims about potential solutions and causes of CFS/ME
- develop a template letter for people with CFS/ME to use to express their desire to get involved in research - for GP? CFS/ME specialist staff?
- be clear about if and how the research clinic environment can be controlled for light and sound sensitivity for example, or if not what else may be provided
- engage with us - there are many of us out there that want to get involved!
- researchers be available for talks and presentations about their work to support groups etc so that their ideas and name are known and relationships can be built - then if and when they are recruiting to a study they might find it easier.

Topic 2: Participating in CFS/ME research studies - getting the right 'research protocol' (plan)
Facilitated by Clare Ogden, Action for M.E.

Key questions:

- What matters from an experiential CFS/ME point of view?
- What do researchers need to plan for to enable people with CFS/ME to participate fully in research, and stay with the study to the end?

Comments, views and ideas:

- Options for severely affected so that they can participate in studies and stay participating e.g. home visits, online or telephone communication, sending in samples by courier
- Multicentre studies so that there is some element of 'local' for participants
- Making sure that the assessment or monitoring criteria, outcomes measures are clear, achievable and some degree of fine tuning/flexibility with study participants
- Initial 'assessment' of study participants to see what will work for them - *what will help you stay with this study?* E.g. do they prefer communication via phone or email, will they transport to get to research clinics, what timing of clinics will make it easier for them to attend?
- Regular follow up (checking in) and communication with study participants to trouble shoot problems and check if they are supported enough to stay in the study
- Stay in listening mode as researchers
- Remember that study participants have to manage their CFS/ME whilst they are in the study
- Are you for real? Will I be accepted and respected as someone with CFS/ME
- Research mentor? Someone who has been through a research study, who can help them anticipate issues?
- Running research clinics from GP surgeries or support groups may increase numbers participating due to 'known' environment
- Help to fill in paperwork for enrolling to a study - and realistic time frame to achieve this step
- Setting clear expectations on both sides of what is required to participate fully in a study - no grey areas!
- At the end of the study reflect on what could have been done better, what worked from a practical point of view and why?
- Ensure that study participants aren't out of pocket financially by participating in a study
- Respect and recognise the effort of study participants in taking part in research
- Exact follow up of people that drop out so that if the intervention or research method makes them feel worse this is captured
- "I am a living set of stats" who has never taken part in any research, how can my experience be tapped into?
- Patient cohorts with Post Exertional Malaise and without.

Topic 3: Moving ahead on research priorities

Two groups facilitated separately by Mary Jane Willows, Association of Young People with ME and Neha Issar-Brown, Medical Research Council

Key question:

- How can the CFS/ME community advocate and lobby for research priorities (where they have been developed) to become funded studies?

Comments, views and ideas:

- Need to 'think big' in terms of funding and resource
- Demonstrating the economic burden of CFS/ME and thus making the argument for more resources
- How does CFS/ME compare to other chronic conditions/syndromes? Has it a different research profile and why? Can the wider research community (including patients and researchers) learn from other fields, e.g. How much are the names associated with the condition (s) holding us back? Could we take the example of the wider MS community (where there a various known sub-sets of the disease) in agreeing on one name/banner that everyone can get behind for the purposes of raising the research profile and funds
- Important to enthuse new and early career researchers with research priorities (and pilot or feasibility studies), how do we make CFS/ME a 'sexy' area of research to develop? Targeting undergraduates
- Important for the patient community to show support for researchers and the wider research endeavour in CFS/ME, not only for attracting new researchers to the field but also retaining the established and experienced researchers
- Achieving research priorities is a complex process, we might not all agree with them - if that is the case then make criticism constructive so that the research community can benefit from and/or utilise the criticism to inform research and take the field forward
- A balanced profile/portfolio of research is needed in CFS/ME, including basic, biomedical, services delivery, treatment focussed (including holistic and alternative therapies). Biopsychosocial as a term may cover all of these
- Using social media as a way of communicating the pressing research issues in CFS/ME, and raising its profile. Using the patient experiential message to reinforce why research is needed - no cure for example, invoking sympathy for the lived experience of having CFS/ME
- Re all above - there needs to be a positive message about research opportunities, and that the CFS/ME community can be resourceful in campaigning for research
- Does the complexity of CFS/ME put researchers off?
- Do we need high profile, (e.g. celebrity, sports person) people that can talk about both recovery, but also living with CFS/ME, and highlight research priorities?
- All of the interested parties (researchers and patients etc) need to believe and agree that their research interests will move our understanding of and treatments for CFS/ME on
- Research portfolio needs to have space for the ideas 'from the ground' of either patient, carer or clinical experience as well as the top flight researchers
- What's important in CFS/ME research from a variety of perspectives?

Topic 4: Disseminating (sharing the results of) CFS/ME research, and research engagement in general

Two groups facilitated separately by Charles Shepherd, ME Association and Alastair Miller, Joint Royal College of Physicians Training Board

Key questions:

- What can individuals and groups do to share results in a co-ordinated and productive way?
- How can the profile of CFS/ME research be increased
- What can the CFS/ME community do to assist this?

Comments, views and ideas:

- Feedback on study to study participants (as distinct from general dissemination of research results)
- Similar point (to Topic 3) about finding consensus for a common term (via an expert panel) so that the messages can be clear and simple to the general public
- Working with intermediaries such as the Science Media Centre, Sense about Science as 'brokers' for sharing research
- Charities have plain language summaries of research
- For health professionals and CFS/ME specialists develop a timely research summary that covers all worthwhile, interesting research with an expert commentary or critical appraisal. This could be a collaborative project across CFS/ME charities, with support from the CMRC
- An accessible and up to date database of the CFS/ME research portfolio (UK/Worldwide) - up and coming studies could be profiled to alert people to the research opportunities and if they want to participate/volunteer?
- Use social media to share important research findings
- Charities to link their public campaigns to research findings
- Need for GP specific awareness activity
- Being creative in sharing research results - in an artistic way to appeal to a wider group?
- What do we do with unpublished (peer review journal) research - is there somewhere it can be made available?
- More Open Access publishing (where authors pay for their article to be published) to get round the problem of paywalls for research
- Consider and expand the diversity of journals that can be approached to consider publishing CFS/ME research?
- Consider having links to resources that address agreed quality criteria for research such as EQUATOR <http://www.equator-network.org/>
- Use the power of a 'real story' to accompany research, ensure that those that can't tell their story do so in another way.

Topic 5: What does a successful research collaboration look and feel like?
Two groups facilitated separately by Sally Crowe, Crowe Associates and Joe McNamara, Medical Research Council

Key question:

- From an experiential CFS/ME perspective, what have we learnt from past positive, and more negative experiences of collaborating for research?

Comments, views and ideas:

- Trust and transparency are issues to address in any collaboration
- Early engagement in the research process and that you are listened to and your views are taken into account
- The researchers are addressing issues that are meaningful to patients including the better targeting of treatments (stratification), building in quality of life measures, and charting the recovery journey so that it can be shared more widely (natural history of the disease)
- Developing a mutual relationship that has respect for each other's views and perspectives - avoiding patronisation of people with CFS/ME and confrontational approaches with researchers
- Keeping in mind who the research is for and why - for patients it is about better treatments, care and prevention. Research professionals are often motivated by the desire to make a difference and help improve the lives of sufferers; however, to be successful in the field they also need to think about their research careers. There was concern that researchers were wary of becoming involved in CFS/ME studies and the issue of building research capacity by attracting new scientists to the field needed to be addressed
- Taking a purely psychosocial view of CFS/ME is a barrier to collaboration – the logistical challenge of involving patient in the research process should not be underestimated
- Making views about psychosocial research in CFS/ME personal, is a barrier to collaboration
- Don't misconstrue my anger and desperation "I want solutions in my lifetime!"
- Collaboration is a human activity and we need to invest in and build relationships
- The best doctors are the ones that have family or friend connections to CFS/ME and understand - how can we replicate this understanding in research?
- Some clear information about the nature and different types of research to help people have a shared understanding
- Good collaborators can act as critical friends
- Professionals accept that for many people with CFS/ME researching it for personal reasons is important and valid
- Develop standard approaches for ethics committees?
- Learn from other successful collaborations - what did they do that worked?
- Develop a 'patient/researcher collaboration questionnaire database' - the idea being that researchers can access a bank of worked up questions that have relevance for patients in words they understand in a format they find acceptable - please find full details of this idea in **Appendix 3**.

Panel discussion for researchers and Associate Members

Prof Stephen Holgate, CMRC Chair

The following researchers gave a short overview of their work, picking out their key findings and explaining why they were important:

- Prof Robert Dantzer (see p 6)
- Dr Stuart Watson (see p 31)
- Prof Wan-Fai Ng (see p 32)
- Prof Carmine Pariante (see p 33)
- Dr Sue Wilson (see p 34)
- Prof Anne McArdle (see p 35)
- Dr Esther Crawley (see p 36)
- Prof Andrew Lloyd (see p 38)
- Prof Ian Lipkin (see p 44)

The panel then took questions from the audience.

The first question was to Prof Pariante regarding fatigue in his cohort of Hepatitis C patients. Able to observe onset and duration of fatigue once Interferon-alpha treatment starts, he then monitors recovery once treatment stops.

“Data is still being collected,” he said, “but there does not seem to be a direct relationship between the improvement and viral infection.” Some people remained profoundly fatigued despite completely clearing the virus and their general health improving, he said. For others, the opposite was true: their fatigue abated once treatment stopped, even though the infection was still present.

Prof Pariante concluded, “So unfortunately it [fatigue] is not directly related to the virus. I think it’s more about how the body responds to this massive, massive inflammation and obviously some people will be more sensitive to that.”

Next, a patient explained that he had had severe fatigue and brain fog when he first got M.E. “I went from being a programmer and holding everything in my head to not knowing what day of the week it was,” he recalled. “I could barely walk anymore.” He felt that unless someone had these symptoms they didn’t have M.E. and continued, “I feel very strongly that we have to tighten up the criteria on what M.E. is and what it isn’t.”

The bigger picture

“I think you make some excellent points but I would caution you against trying to make the overall umbrella too small,” replied Prof Lipkin, stressing the importance of looking at the bigger picture. “It’s very difficult to get funded to do research in this arena. I think if you talk to my colleagues they will tell you this is a huge challenge, and has been now for decades.”

However, there are organisations that are very successful at pulling in big money. “If you use cancer as an analogy, the American Cancer Society is very useful for all the people who have different types of cancer to come together under one banner and get the resources to support a whole range of cancers.”

There was a problem with that, said the patient. If you applied therapy to a mixed bag of people you got skewed results.

“Absolutely, I agree with you completely,” replied Prof Lipkin. “At the level of investigating pathogenesis, which is how you get ill in the first place, or [if you’re looking at] ways in which people respond to different kinds of therapy, there, it’s very important to parse narrowly.”

Using a whole range of symptoms and biomarkers is useful in describing specific groups of people, he said. “From the vantage point of science and doing research, you should find ways in which you can be more discrete in terms of thinking about mechanism and disease.”

Picking up this theme, Prof Dantzer drew on his experience in cancer research and agreed it was really important to cast the net wide at first. “The symptom such as fatigue never happens by itself, it happens in a cluster of other symptoms and we see that very well in cancer patients.”

There will be common mechanisms, he said, such as inflammation or mitochondrial dysfunction but they may present similarly or differently in a given selection of patients. He suggested the need to study all symptoms, only pulling out the differences at a later stage.

Perceptions of the condition

“Does the panel think that a different perception of ME and CFS would actually help improve the availability of funding?” asked a UK film producer working on a film about CFS/ME, *Canary in a Coal Mine*.

“From the children’s perspective,” said Dr Crawley, “they would say they really need a different public perception to enable them to go back to school, to enable them to talk to their friends, even just to enable them to talk to their siblings. This is a very stigmatising illness, particularly for children and we should take every opportunity to talk about how devastating the illness is.”

Dr Crawley felt taking a drip, drip, drip approach was necessary to change the public perception of CFS/ME, and that events such as this patient-researcher session and working together were really important to achieve this.

Referring to his work on the 2011 film *Contagion*, which generated worldwide exposure for issues related to his own field of emerging infectious diseases, Prof Lipkin suggested that a well-known narrator for the producer’s documentary was critical. “You need to get somebody who is visible and well known who can promote something you are trying to do, otherwise it just gets lost.”

Selecting patients for research

A patient commented to the panel that if the principle selection of patient cohorts is flawed then so are the results. He suggested using the Canadian Consensus Criteria to avoid this problem.

“Your point is that if the wrong people go into the research, then the research becomes pointless,” reflected Dr Watson. “I think you’re both right and wrong all at the same time.”

He explained that in a recent study at Newcastle, they had selected candidates very carefully, excluding anybody who had a current or previous episode of a psychiatric disorder like depression or anxiety. Consequently they had found different results from previous studies regarding childhood adversity.

Agreeing with the rest of the panel, Dr Watson emphasised that looking at a broad range of symptoms was important.

“We wanted to characterise patients very well,” he said, “and so we recorded lots of different things and one of the things that we recorded was pain in the jaw.” It threw up some interesting results.

“We found that those with chronic fatigue and jaw pain were different to people who had chronic fatigue and didn’t have jaw pain.” Primarily, they found a difference in cognitive performance and brain fog.

Though these might be chance findings, Dr Watson said that stratifying within this umbrella allowed them to draw out differences that were potentially markers of separate biological processes. He concluded, “Inclusivity but stratification is the message that is coming through across the panel, I think.

Purpose of criteria

Prof Lloyd, involved in both the Australian criteria and reviewing the Center for Disease Control and Prevention case definition, said there were now a total of 11 different criteria sets for CFS/ME.

“One thing I would advise is to be very clear about the purpose of the criteria,” he added. “From the point of view of making a diagnosis, the criteria broadly matter but actually what really matters is the care that leads from the diagnosis.”

This was a completely different issue for criteria for entry into a clinical trial or a research study, he said, where it was important to understand the similarities and differences within the disorder.

“I have the strong sense that we could generate another thirty criteria and it won’t advance the cause. My sense is we need to get on and do good quality research, characterising our patients by a broad range of characteristics, using various criteria to understand their similarities and differences and then to understand what the biology of the disorder is.”

Prof Holgate summed up this part of the discussion, saying, “The whole idea of stratifying this condition is obviously a major topic, and something we’ll be talking about as we move this whole field forward.”

Referring to his own speciality of bronchial asthma, Prof Holgate explained how classification was by severity because it linked to therapeutic options. But as it was

now known that there are at least six different variants of asthma, he feels that, in fact, this hides ignorance about the illness.

What we call CFS/ME

A patient wondered about the meaning of chronic pain syndrome, asking Dr Crawley, "Isn't it just another term to confuse things?"

"What you call fibromyalgia in adults presents slightly differently in children, so we tend to call it chronic pain syndrome," said Dr Crawley. "I completely agree it's likely to be a fibromyalgia type problem," she added, but that ultimately she didn't choose what to call it.

Prof Holgate acknowledged that there is anger around certain terms, and drew attention to the Multiple Sclerosis Society, which has been very successful in raising funds and its profile.

"They've got one word, but there is likely to be 30 diseases under that one heading with different pathways and different factors," he explained. "I think that is part of the problem. We have this acronym, called chronic fatigue syndrome or ME, or fibromyalgia if you want to blur the edges. It really adds to the confusion and it gives a false security that we understand what we're talking about."

Once the biological pathways become clear, he said, there will be a way of renaming this disease, or range of diseases, based on the driving mechanisms. "And the sooner we get to the mechanistic pathways the better," he concluded. Finally, he asked Prof Lloyd if they have the same problem with naming it in Australia.

"I think we're a bit more laid back, to be honest," replied Prof Lloyd languidly, and the audience burst into laughter.

Integration of services

A carer asked if adult CFS/ME services were going to be integrated in the same way as children's services. Her son had fallen ill at 15 and had lots of people investigating in a joined-up way, she said. But as soon as he turned 16, he was considered an adult and was looked after by a variety of departments who failed to communicate with one another.

"I think that is really, really important, that sense of bringing people together with different skills" said Dr Watson, explaining that they are attempting this at Newcastle by, for example, drawing together immunology and autonomic research, and attempting to coordinate at a clinical level and a research level.

"I think in a way this meeting is about that," said Prof Holgate, "about joining things up, not splitting them apart." Referring to the fragmentation in services, he said the same problem had existed in adult cystic fibrosis and that, "in the end, they had to redesign adult services."

Translational research

A complementary practitioner said he would like more diagnostic tests available, including one for measuring cortisol.

“I think the important point you are trying to make is that there is scientific underpinning of the mechanisms that are involved in this disease,” reflected Prof Holgate. “And these need to be linked to some of the therapeutic outcomes that you actually deliver within your different clinical domains.”

Prof Lloyd felt that new approaches should be underpinned by research evidence. “We don’t yet have that,” he said, “science has to drive the outcomes.” But typically with science, moving from discovery into impact is a slow process.

“We need to make sure that the outcomes that are emerging out of the research are captured by the people who then develop that next phase,” said Prof Holgate. “We need to pick them up and run with them.”

Co-morbidities

An audience member said that gut problems such as IBS were common in people with ME and asked if that linked to recovery.

“Co-morbidities are obviously massive subject,” confirmed Prof Holgate, citing fibromyalgia, allergies and joint pain as just some of the illnesses and symptoms that were linked to ME/CFS.

Dr Crawley agreed co-morbidities should be investigated further. “This goes back to what all of us have been saying, which is that you need really well classified patients. We need to follow them and describe them and their co-morbid disorders. We just finished a study looking at eating disorders and symptoms, which are a really big problem in children. I completely agree we need to look at it in more detail.”

The session ended with Prof Holgate thanking all those who had attended. He kept the door wide open for further collaboration with patients.

“What would be interesting is if you wanted to send in any questions that you have to us, we can reflect on those,” he said. “So if you have issues you want to raise, put them in an email, put them on paper and let us know. We’ll discuss them and think about them.”

Further patient-researcher sessions could also be arranged, if people had liked the way it had been done. The audience applauded enthusiastically.

“Don’t forget, for the Collaborative,” said Prof Holgate, “this isn’t the end of the meeting: this is the beginning of the journey.”

Understanding the pathogenesis of autonomic dysfunction in chronic fatigue syndrome and its relationship with cognitive impairment

Dr Stuart Watson (for Prof Julia Newton), Newcastle University

Prof Newton's team have recruited the same set of patients to take part in a number of studies, which Dr Watson gave an overview of in his presentation, stressing that they had collected only preliminary data for some so far.

"We have recruited to time and to target, largely because of the community of people with CFS/ME," he said. "They have knocked on the door, got in touch on Facebook and come forward to take part in this research, which has been fantastic."

Studies include dexamethasone suppression of cortisol, showing that glucocorticoid receptors in people with CFS/ME are down-regulated, contradicting previous reports.

Another looking at immune function found no evidence for an increase in pro-inflammatory cytokines, again contrasting with previous studies. Considering why this might be, Dr Watson explained that they had taken pains to exclude people who had current or past psychological issues. "Clearly there is a link between the HPA axis and depression," he said.

"Similarly, we also looked at childhood adversity; previously studies have found high levels of this – abuse, neglect – in people with CFS/ME. But we didn't; we found the same levels as with healthy controls, because we were very careful to exclude people with existing or historic psychiatric disorders."

A further study is investigating whether autonomic nervous system (ANS) dysfunction could be a contributing factor to the pathological processes behind CFS/ME, using a standardised test called valsalva manoeuvre.

Another investigates cognitive impairment in people with CFS/ME by looking at the links between fatigue, objective task performance and subjective reports of memory.

Dr Watson also mentioned other relevant studies being undertaken by the team, including mitochondrial genomics, the way muscle cells behave in people with CFS/ME, and subjective experiences of sleep.

"The headline from the sleep study is that sleep disturbances were highly unpredictable and variable over time, but played a key role in symptom maintenance for people with CFS/ME," he said.

Prof Jonathan Edwards comments: "For me the interesting aspect here was the evidence of neuroendocrine imbalance, together with clinical evidence of autonomic disturbance, in the absence of blood cytokine changes. The implication for me is, again, that central nervous signalling pathways can be measurably abnormal without there being any peripheral cytokine evidence.

"Of note, Dr Watson is a psychiatrist working together with Dr Newton on a wide range of aspects of CFS/ME, and their collaboration seems to be doing much to fit everything together in a unified biological model."

Biological fingerprints of fatigue
Prof Wan-Fai Ng, Newcastle University

Prof Ng described his ongoing work on the hypothesis that there are common biological pathways underpinning fatigue.

Identifying this “biological fingerprint” will, he says, improve our understanding of the underpinning biological basis of fatigue, provide an objective measure to assess the effectiveness of treatments for alleviating fatigue, and aid diagnosis of CFS/ME.

To do this, Prof Ng is looking at patients with primary Sjogren’s syndrome, some of whom experience high levels of fatigue, while others do not. The study which is using RNA extraction from white blood samples from patients with Sjogren’s Syndrome (SS) – where fatigue can be a very prominent and disabling clinic feature – to see if they can identify any markers in the blood (biomarkers) that are consistent with people who have SS plus fatigue and are not present in patients with SS who do not have fatigue.

This research is also looking for changes in gene expression analysis that correlate with fatigue. The work will then progress to see if similar markers are present in people with CFS/ME. Although not related to the MRC funded study, there is a clinical trial of Rituximab taking place in people with Sjogren’s Syndrome in Newcastle.

Prof Jonathan Edwards comments: “Interestingly Prof Pariente found a pattern of change in gene expression in Sjogren’s patients but this tended to be more marked in those with less fatigue. Sjogren’s patients were drawn from a cohort within which a trial of rituximab is taking place and it is hoped that response to treatment can be correlated with the serological fingerprint.

“This study emphasised to me the fact that different facets of a single disease may be mediated by different pathways. It rather looks as if fatigue in Sjogren’s syndrome is mediated by pathways that are not involved in the production of other features of the disease.”

Inflammation and fatigue: is it different from depression?

Prof Carmine Pariante, King's College London

Following on from Alice Russell's presentation, Prof Pariante explained in more detail the studies he and his team have been conducting looking at the effect of interferon-alpha treatment on fatigue levels in patients with Hepatitis C.

They have been exploring what happens to various biomarkers when people with chronic hepatitis C infection are treated with interferon alpha (IFN alpha). The aim is to see if there are differences between those who develop fatigue and other CFS/ME like symptoms and those who do not, and what happens when these symptoms persist when treatment has stopped and their viral load is removed. This study is also examining whether there are changes in gene expression between the two groups – which could again provide useful clues as to what may be happening in CFS/ME.

One of the several interesting findings from the studies on hepatitis C patients being treated with IFN alpha is that the various CFS/ME-like symptoms start to appear at different time intervals. Flu-like feelings occur very quickly; fatigue gradually builds up over a period of several weeks and plateaus. Whereas changes in mood and depression, along with cognitive dysfunction start to appear rather later and again gradually increase in severity before reaching a steady state.

He went on to look at how depression relates to fatigue, and how our understanding of the former can help us map the latter. He also considered how abnormal inflammation affects brain function, and how we can use it to understand fatigue. One other interesting finding from work being done on hepatitis C infection and interferon alpha is a clinical trial that has found that by giving a polyunsaturated fatty acid supplement in the form of EPA (eicosapentaenoic acid) this can reduce the incidence of depression during interferon treatment. This may be relevant to CFS/ME because a small clinical trial has reported benefits from using EPA supplementation in CFS/ME.

Prof Jonathan Edwards comments: "It is clear that there is overlap in some cases but also that there are different determinants of the two problems. In Hepatitis C, patients' depression and fatigue were both problems but they occur at completely different times. Fatigue is almost immediate. Depression comes later.

"Moreover, some patients have one without the other. And it is not just that depression takes a bit longer to kick in. Fatigue can continue for months or years after treatment in the absence of any depression. This presentation showed dissociation between depression and fatigue and clear evidence for the need to refine our approach to 'sickness behaviour'."

Sleep and CFS/ME

Dr Sue Wilson (for Prof David Nutt), Imperial College London

Prof David Nutt and his team are conducting a study looking at slow-wave sleep and daytime functioning in people with CFS/ME. This is a placebo controlled randomized cross-over clinical trial to assess the use of a drug called sodium oxybate, to increase the amount of slow wave sleep and to investigate whether this has an impact on next day function.

“It’s very robustly shown that people with CFS/ME are sleepy in the day, and they have unrefreshing sleep,” explained Dr Wilson. “It’s possible that some of the fundamental mechanisms controlling sleep might be impaired. We also know that patients tell us that when they have better sleep, they feel better the next day. “So what if we give them something that will improve that slow-wave sleep? Would it make any difference the following day?”

The team needs to recruit 12 patients, and use sodium oxybate [a proven treatment for excessive daytime sleepiness (EDS) and cataplexy associated with narcolepsy] to increase their slow wave sleep, which they measure using electrodes stuck to their heads over the course of eight nights in total. “It’s quite full-on for the patients to have this,” said Dr Wilson. “It’s tough for us as researchers, so it must be even tougher for them.”

Several tests are conducted the following day, including multiple sleep latency test (a subjective test measuring how quickly you fall asleep in a quiet environment during the day), grip strength and cognitive tests.

She ended by outlining the progress of the study so far, with four people having already taken part.

Prof Jonathan Edwards comments: “I thought this was fascinating evidence for the need to look at very specific central nervous system pathways if we want to understand fatigue both on a broad basis and broken down into subgroups.”

Mitochondrial function and cytokine production in skeletal muscle of patients with CFS/ME

Prof Anne McArdle, University of Liverpool

Prof McArdle began by saying that this project is almost completed in terms of sample gathering. “But what I can’t do today is show you any data because the project is blinded,” she continued. “We are finalising the collection of our blood samples in particular and we don’t want to compromise the analysis.

“Hopefully what I can do instead is convince you that we are on the right track. I am going to show you some comparative data, particularly from our aging studies, to show you why we are taking this approach.”

The study is exploring muscle abnormalities in CFS/ME through the use of new techniques which can more accurately assess the way in which the mitochondria – organelles responsible for energy production – are behaving in muscle in CFS/ME. This new research in Liverpool has made use of various experimental systems they have developed using both in vitro (studies on tissues removed from a living organism under artificial conditions in a laboratory) and in vivo (studies on tissues not removed from a living organism) experiments to look at the way in which mitochondrial function can be linked to cytokine changes.

Prof Jonathan Edwards comments: “Prof McArdle gave us an account of how mitochondrial function, generation of reactive oxygen species and Adenosine triphosphate [how muscle cells biochemically store and use energy] handling in muscle are all tied in to signalling through cytokines like TNF. Muscle mitochondria are different from those in other cells in their position and density.

“She described a range of experimental systems used in Liverpool both in vivo and in vitro to study the ways in which mitochondrial function might be linked in to cytokine changes. She indicated the importance of feedback loops that could potentially set up long-term abnormalities of regulation of muscle metabolism.”

The epidemiology of CFS/ME in adolescence

Dr Esther Crawley, University of Bristol

Dr Crawley began by highlighting the clear need for investigating CFS/ME in children. “We are prevented from setting up adequate clinical services or conducting research because we don’t know the basics such as how common it is, what the natural history is, what the patterns of CFS/ME in children and adolescents are, and what causes it,” she said.

This project’s objectives are to study prevalence and persistence of CFS/ME, its heterogeneity, and risk factors at different ages.

Key findings so far include:

- girls and boys are affected in equal numbers when younger, but by age 18 the incidence is twice as high in girls
- each family adversity factor (eg. housing, education, financial pressure relationships, substance abuse and crime) in pregnancy increases the risk of developing CFS/ME
- Children report much higher levels of disabling fatigue at age 16 than their parents say they have
- a relatively high proportion of children improve as compared to adults, although not all
- symptom patterns differ with age, with less sleep disturbance and cognitive dysfunction in the younger groups
- overlap with chronic widespread pain (the name given to fibromyalgia in children) seemed less than previously reported, with evidence for different determinants.

This study will also look more at heterogeneity in more detail; and investigate risk factors using directed acyclic graphs, a method that allows researchers to examine causal relationships.

PACE: A trial & tribulations

Prof Peter White, Barts and the London School of Medicine and Dentistry

Prof White gave us what he termed the 'good news' and the 'bad news' regarding to PACE trial. He started with an overview of the trial, which investigated using graded exercise therapy (GET), cognitive behaviour therapy (CBT), and adaptive pacing therapy (APT), all added to specialist medical care (SMC), and SMC alone, showing the results in terms of fatigue, cost effectiveness and serious adverse reactions.

"Both CBT and GET were moderately effective, cost-effective, and safe if delivered individually by appropriately qualified therapists who are properly trained and supervised," he said. APT was no more effective than SMC alone.

Prof White continued by outlining the reactions to the PACE trial from some M.E. patient activists and organisations, which have to date included formal complaints (none upheld), petitions, and a total of 168 Freedom of Information (FOI) Act individual data requests (he had to count them all because he received an FOI Act request asking for the number.)

"Criticism is fine, whereas vexatious complaints and harassment are not," he said. "There are three reasons why this is important for the field.

"Firstly, it's not just the PACE trial that has had these problems – the scientists who wrote the first paper that failed to replicate XMRV findings encountered something similar. It happens whenever researchers find something that isn't popular.

"Secondly, it's important because we are trying to encourage young scientists into the field, and we need to protect them and stop this happening to them.

"Thirdly, it's important because it damages science. We have some reasonable evidence that the campaign against the PACE trial affected our recruitment. We had to apply for an extension from the MRC in order to finish the trial.

"The PACE trial has also played a small role in helping to amend the FOI Act for the better. From 1 October, current research will be exempt from the FOI Act so long as it can be shown that release of that data will be prejudicial to the conduct of the research.

"I think it's really important that we don't just stay biological, or indeed behavioural, but integrate them, as you can see from this slide [CBT normalises cortisol response to wakening in CFS]: a so-called psychological treatment has changed the physiology for the better.

"Perhaps most importantly, we need to stop being dualistic; believing that illnesses are either biological or psychological. They are both; a psychological event cannot happen without a biological event. In the future I hope that neurological and mental health conditions can be classified together as conditions of the nervous system."

Acute infection & post-infective fatigue as a model for CFS

Prof Andrew Lloyd, University of New South Wales

An innovative study that tracked the development of CFS/ME after several different initial infections has revealed surprising findings about the role of the immune system and role of genetic variations in the susceptibility to post-infective fatigue.

The sheep and cattle-farming outpost of Dubbo, four hundred miles inland from Sydney, Australia, was the surprising setting for a key CFS/ME study that put the development of the illness under the microscope. Prof Andrew Lloyd, an infectious diseases physician and immunology researcher from the University of New South Wales in Sydney, has documented the onset of CFS /ME in a tightly-defined subset of patients, and in the process has begun to unravel how CFS/ME develops after an infection.

One of the main difficulties in CFS/ME research, Prof Lloyd argued, is 'heterogeneity.' All the evidence points to CFS/ME being a mixed bag of patients with potentially differing disease processes giving rise to a reasonably similar set of symptoms.

This diversity scrambles research findings, making it difficult to find a consistent set of abnormalities when comparing patients with CFS/ME and healthy individuals. In the 1990s, he tried to explore this problem by systematically analysing patient symptoms to identify subsets of the patient group with closely comparable illness characteristics.

And indeed, he found two broad groups — but even there, the bigger group was a mixed bag. Lloyd concluded that the only way to make progress in the field was to zero in on a tightly-defined group of patients to see what went wrong *as they fell ill*. Cue the “Dubbo” studies of post-infective fatigue.

Tracking patients

The basic idea was simple: track patients from the start of an infection and then compare those that develop post-infective fatigue with those that have exactly the same infection at onset but recover promptly. The goal was to see what was different about those who became fatigued and those who did not.

The team deliberately selected three very different infections which has something of a reputation as triggering prolonged illness:

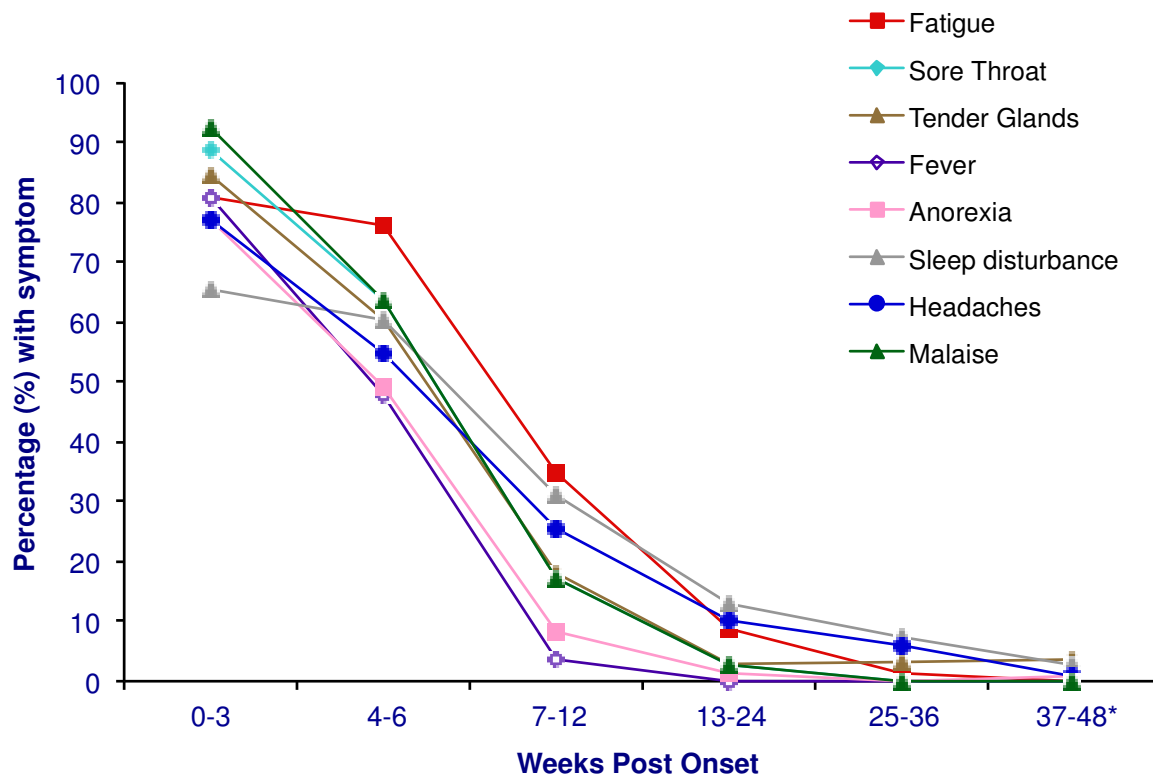
- Epstein-Barr Virus, EBV, a 'great big DNA monster' virus that causes the fever, sore throat and tender lymph nodes typical of glandular fever.
- Ross River Virus, a tiny RNA virus spread by mosquito bites, which causes fever, rash and joint pain.
- *Coxiella burnetii*, a bacterium that causes Q fever, usually picked up from sheep and cattle, which causes a nasty illness with high fever, and drenching sweats as well as inflammation of the liver.

Prof Lloyd had two working hypotheses: the chronic fatigue would be either due to an infection that doesn't go away, or to an immune system that remains stuck on after the infection is gone. He said that at the time he thought: "It's going to be one or

the other – or just possibly a combination. I'll sort it out quicktime, don't you worry!", a comment that drew much laughter. He also suspected genes played a role.

The key to the study was catching people early. They established good relationships with the local doctors so they were notified as soon as there was a new case of glandular Fever, Ross River virus infection, or Q fever. Self-report questionnaires and blood samples were collected regularly and those who remained unwell at 6 months were formally evaluated for CFS (Fukuda criteria) using medical and psychiatric exams as well as laboratory tests.

Results



All three infections led to a similar 'natural history', where the proportion of subjects with ongoing symptoms started high in the acute phase and gradually reduced over time, with fatigue being particularly persistent.

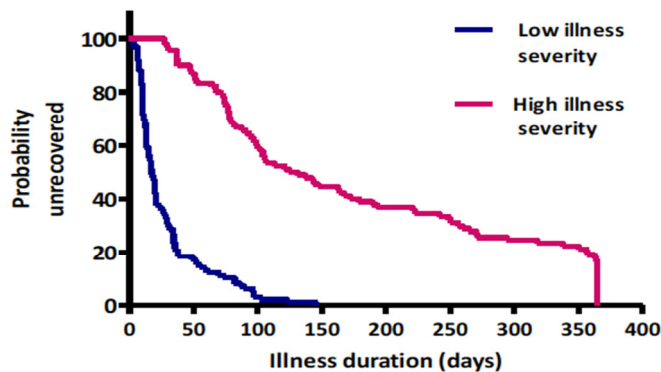
Regardless of the specific infection, around 10-15% formally met CFS criteria at 6 months, with approximately 6% still fatigued at twelve months and around 2% remaining fatigued for many years. Overall, this looked like a good model for studying CFS/ME.

Severity of the acute infection is key

Prof Lloyd and his team then started trying to identify factors that played a role in the development of long-term fatigue. It turned out that neither age, demographics, nor the presence of a psychiatric disorder prior to getting sick predicted fatigue. Nor, surprisingly, did the type of infection, with similar illness duration seen for all three.

What *did* predict long-term fatigue (and CFS/ME status) was the severity of the initial illness. For example, the 10% or so, who were ill enough initially to be hospitalised

had a 200-fold higher risk of CFS at six months. This graph shows the huge difference in recovery rates between the third of patients who were severely affected in the acute illness (not just the hospitalised) and those who were least affected:



Cytokines can drive symptoms

To begin tracking down the differences in what was happening in the bodies of those who developed CFS/ME, Prof Lloyd started thinking about the ‘acute sickness response’, just as Prof Dantzer had spoken about earlier in the day.

What Prof Lloyd calls the ‘sickness *response*’, and Prof Dantzer calls ‘sickness *behaviour*’ is the same – a biologically-driven process that is evolutionarily conserved across species because it gives survival value, helping the animal or human to focus on recovery from infection. Symptoms include fever, loss of appetite, muscle and joint pain, general malaise (feeling unwell), concentration problems and, of course, fatigue.

Prof Lloyd began to wonder if sickness response had gone wrong could be a factor in post-infective fatigue, much as Prof Dantzer had wondered if it was a factor in cancer-related fatigue.

Lloyd’s group wanted to revisit the early work on sickness response in animal studies “in the flesh – in humans”, using Dubbo patients. They examined the link between two key pro-inflammatory cytokines, IL-1 beta and IL-6, and symptoms during the early *acute* illness phase of Q fever patients. And they found the expected correlation between these cytokines and symptoms such as fatigue, muscle pain, poor concentration and malaise.

Looking for chronic immune activation

So then they tracked cytokine levels over time in the blood samples of their post-infective CFS/ME patients and matched individuals who recovered promptly from the same infection (without fatigue), in order to test the idea of chronic immune activation. They focused on the three key pro-inflammatory cytokines, IL-1b, IL-6 and TNF alpha.

Unfortunately, this hypothesis didn’t pan out either: at three six and twelve months after the initial infection, levels of all three were no different (<http://cid.oxfordjournals.org/content/45/6/732.full>) between fatigued cases and

recovered controls. 'The chronic immune activation hypothesis was looking wobbly,' said Prof Lloyd.

Prof Lloyd pointed out that pro-inflammatory cytokine levels that his group had found in patients during the acute phase were present in *nanograms* per millilitre, which is the level at which they are biologically active.

While some other studies have found elevated pro-inflammatory cytokine levels in CFS/ME patients (unlike his own study), those levels have been in *picograms* per millilitre, that is a thousand times lower, adding "it is not clear at all that that has biological meaning".

Looking for chronic infection

To test the idea of chronic infection, they simply tracked evidence of persistence of the micro-organisms in the blood over time. They found that EBV, which causes glandular fever, did persist at measurable levels in the blood — but that's normal for EBV, and crucially there was no difference between fatigued cases and recovered controls.

For Ross River virus and *Coxiella burnettii* (Q fever), the pathogen was cleared rapidly, and again there was no difference between cases and controls. So that was it for the chronic infection hypothesis.

Cytokine genes play a key role

If it wasn't chronic infection, and wasn't persistently high cytokine levels, maybe there was something else that was driving the development of post-infective fatigue — and they focused in on the effect of inherited variations in genes which encode the immunological and neurological proteins likely to be involved in the sickness response.

They suspected that some people might be genetically programmed to respond more to an infectious insult and so become more severely affected in the acute phase of infection and a greater likelihood of post-infective fatigue.

Specifically, they looked at the genes for five cytokines: the three they'd studied before, plus interleukin (IL)-10 (which inhibits inflammation) and Interferon (IFN)-gamma (which promotes inflammation). There are high- and low-producing variants of each of these genes — could this be behind the different responses of patients?

The results were striking. Patients with the high-producing version of IFN-gamma or the low-producing variant of IL-10 were much more likely to have severe symptoms. The effect was even more prominent in those with the combination of these 'risky' genes, showing that:

- those with one copy of the high-producing IFN-gamma gene were more likely to develop severe symptoms than those with only the low-producing IFN-gamma gene, with an odds ratio of 2.6 (where an odds ratio of 1 means no difference between two groups)
- those who had both copies as the high-producing version were even more likely to have severe symptoms: the odds ratio was 2.9

- those with a double whammy of both high-producing IFN-gamma genes and low-producing IL-10 genes had an odds ratio of 6.8, which is a *really* big effect.

The team also showed that those with the ‘high-producing’ gene version really did produce more cytokine during the acute phase of the illness. Overall, the type of IFN-gamma and IL-10 genes significantly affected illness severity, cytokine protein levels, and the duration of illness—independent of age, gender and even the specific infection type.

“How long you are going to be remain unwell after these acute infections is at least partly determined by your genetic makeup,” Prof Lloyd said, “in particular those two genes.”

However, these genes only explained some of the difference in illness severity between patients, so while they were part of the story, there must be other factors at play too. The team also looked at neuro-behavioural genes (for example, those that affect levels of neurotransmitters) and reported promising results on one, snappily called P2X7.

P2X7 is a neuro-immune gene that has been linked with psychiatric and neurological disorders. It’s also very important immunologically, affecting, for example, recovery prospects from tuberculosis. And Lloyd’s groups has now found that it may play a role in fatigue.

A cell-surface receptor that appears on both white blood cells and on microglia, the brain’s immune cells, P2X7 helps regulate inflammation, playing a specific role in the release of pro-inflammatory cytokines, including our old friend IL-1 along with IL-18, which stimulates release of IFN-gamma from T-cells. When it’s activated, P2X7 acts as a pore, allowing transport of the energy molecule, ATP, across the cell membrane.

In short

Prof Lloyd summed up by returning to his original hypotheses that post-infective fatigue was driven by chronic infection or chronic immune activation. This didn’t pan out: there was no difference between fatigued cases and recovered controls in either pathogen levels or cytokine levels.

The new hypothesis is that “stuff happens” in the acute infection, he said to laughter, though exactly how it happens isn’t clear. Severity of the acute infection predicts post-infective fatigue and our genetic make-up plays a role in both. He said if he had to choose a site where those genes play out, it might be in the body in the acute phase, but in the prolonged phase it’s going to be in the brain. Prof Lloyd added “we need to get over blood” – the answer probably lies “upstairs”.

Future plans

There is a new post-infective fatigue study underway (more conveniently located in Sydney) that will be looking at autonomic factors and circadian rhythms. And, said Prof Lloyd, they wanted “to really get to the money” - by imaging activated microglia in the brain. (In answer to a later question from Prof Ian Lipkin, Prof Lloyd pointed to

evidence in mice that an initial acute inflammation in the body can lead to long-term activation of microglia in the brain. Perhaps something similar is happening in CFS/ME cases that develop after infection.)

He also stressed the importance of using challenge testing. “If we are to continue to look at the blood, we need to use studies in which we carefully make the fatigue worse – transiently, to look at post-exertional exacerbation”, which he described as being “tough for the patients but good for the scientists!”

They are using a cycling exercise as a physical challenge and, intriguingly, they are also using a driving simulation as a cognitive challenge. Both trigger an exacerbation which comes on over hours and lasts a day or two and then resolves – this offers real opportunities to look for biological factors which correlate with the changes in fatigue.

It looks like Prof Lloyd’s group is well set up to reveal yet more about how CFS/ME develops after an infection.

Microbiology & immunology of CFS/ME and other challenging disorders

Prof Ian Lipkin, Columbia University

Prof Ian Lipkin outlined the extraordinary lengths he and his team are prepared to go to in order to track down the source of an illness, with examples ranging from autism to the strange case of Kawasaki Disease. His presentation emphasised the use of high-tech methods and following the evidence wherever it leads, before outlining his CFS/ME research programme that takes a similar approach.

Prof Lipkin is a renowned virus hunter who heads up the Center for Infection and Immunity at Columbia University. He has discovered more than 400 viruses, pioneered new molecular techniques for identifying pathogens and helped the World Health Organisation and Chinese Ministry of Health deal with the SARS outbreak.

Prof Lipkin first studied CFS/ME in the 1990s, when he was asked to investigate a link between Borna disease virus (which he discovered) and the illness. He and Birgitta Evengard did a large study but found no link with the virus. However, the research highlighted that CFS/ME patients did have immune abnormalities. But there was no funding then to pursue further research in the field.

Still, he retained his interest, and when he was asked a few years ago to look at a link between the disease and another virus, this time XMRV/PMLV, he jumped at it. Again the link was disproved for that specific virus, though he added they had “not ruled out viruses at all.” In fact, he’s continuing to hunt for them as part of his new programme of CFS/M.E. research.

Where new human viruses come from

Having devoted much of his life to hunting down viruses, Lipkin knows just how far the task is from being done, and he is acutely aware of “all the infectious agents that are yet to be discovered.”

Just how many unknown viruses are out there was highlighted by work Prof Lipkin did as part of the US Agency for International Development’s Predict programme, an ambitious effort to find the next Ebola lurking in nature before it spreads out of control. Most new human viruses start off life in wild mammals, and they often jump to humans via domesticated animals. New forms of flu, for example, often travel into humans from chickens that caught the virus from wild ducks. So one of Predict’s efforts was to estimate how many viruses there were in mammals – and they found a lot.

Taking a single bat species as an example, Prof Lipkin and colleagues found 55 viruses, 50 of which were new discoveries. They found them by detecting their DNA or RNA in the blood using high-throughput sequencing techniques that Prof Lipkin helped pioneer.

Extrapolating from this work and more on other mammals, he and his collaborators conservatively estimated that there are 320,000 different viruses in mammals, most of them unknown.

That’s a pretty big pool of viruses that could produce the next human disease.

Linking wild viruses to human disease

The next step is to show that a particular virus causes a given disease. That requires detecting an immune response to the virus, particularly by finding the antibodies that help us fight off an active infection.

Looking for antibodies has another huge advantage over looking for DNA or RNA, because they stick around long after the body has defeated the infection and the virus has vanished. The body retains a few 'memory' antibody-producing cells that allow us rapidly produce more antibodies if the microbe shows up again. Prof Lipkin has previously called this approach of focusing on antibodies as looking for "shadows of infection," something he'd like to use in CFS/ME too.

Just as there are microarray chips for detecting DNA or RNA of specific viruses, there are now 'peptide microarrays' that effectively allow researchers to check for antibodies against any virus. Peptides (ie. short protein chains) can mimic every possible viral protein that antibodies might bind to.

"You can cover all vertebrate viruses in a single chip, which is amazing," said Prof Lipkin. When blood is run across the peptide-studded chip, the antibodies in the blood glom onto the peptides they're associated with. And since each antibody was created in response to a particular virus, this reveals all the viruses that have ever infected the individual.

Prof Lipkin used this method to great effect to study an outbreak of the MERS virus in the Middle East. He tested camel blood in Saudi Arabia with peptide microarray chips and found that the vast majority had at some point been infected with MERS. Added to other studies, this work showed that camels were the likely cause of the human MERS outbreak in the region.

Some outbreaks are bug-free

"It's not all about infectious diseases: sometimes it's toxicology."

In late 2007 a slaughterhouse processing thirty thousand pigs a day reported an outbreak of a neurological disease and researchers began looking for a pathogen that caused it.

Prof Lipkin and his colleagues realised that the patients worked at or near the section where workers blew brain tissue out of the pig skulls with a high pressure hose, a new technique that had been introduced when plant owners realized they could sell the brain matter.

The result was a huge mess, including aerosolized bits of myelin, the fatty insulating sheath around nerve fibres. The workers' immune systems, it turns out, were reacting hugely to this, triggering the paralysis or weak limbs and other neurological symptoms. The solution was simple: face masks, along with other protective devices. There was an outbreak of disease, but, it turned out, pathogens had nothing to do with it.

Hunting down microbes with planes

Kawasaki disease occurs in outbreaks, affects mainly children and is sometimes fatal. It's named after the Japanese physician who described it in the 1960s.

Inflammation of blood vessels causes symptoms including rashes, swollen hands and feet and 'strawberry tongue.' Sometimes it affects the heart too, a problem that kills in around 1% of all cases. People have been trying to figure out what causes Kawasaki disease for years, Prof Lipkin's group included: they detected Bornaviruses and other microbes, but none proved to be the cause of Kawasaki disease.

Then a few years ago, a researcher noticed a remarkable association: the outbreaks coincided with changes in wind direction several kilometres up in the atmosphere. Planes with filters flew high into the atmosphere to collect samples. They found very little, and most of what they did find was, apparently, methyl bacteria.

It turned out that tiny amounts of these bacteria were contaminating the commercial kits they were using to test for microbes – which became a big problem when they had so little 'real' sample – and the contaminating bacteria dominated results.

Researchers had to develop tools to remove the contaminants to see what was really going on: "We went from 73% methyl bacteria to 4%," said Prof Lipkin. "And suddenly we began finding things we had never seen before."

Above all they found the fungus *Candida*, which might yet prove to be the trigger of Kawasaki disease. Intriguingly, a forgotten study from the 1970s showed *Candida* can cause a Kawasaki-like disease in mice.

Autism: from viruses to gene defects and bacteria

A new focus of Prof Lipkin's work is the microbiome, the ecosystems of microbes that colonise our body from gut to mouth to skin.

The work began when the CDC asked his laboratory to investigate the possible link between measles RNA from vaccines and children with Autism Spectrum Disorder (ASD) plus gastrointestinal (GI) problems. In blinded studies they found no link, but Prof Lipkin was intrigued by those gut problems. "Some of these kids may have an infection, some may have a genetic defect," he says.

They compared these ASD/GI children with non-autistic children who had similar gut problems. This work revealed that the ASD children had dramatic reductions in the gene expression of enzymes needed to break down carbohydrates in the gut, as well as of the transport proteins that carry digested carbohydrate across the gut wall.

Prof Lipkin's team went on to look at the microbiome in the gut and found a relatively obscure bacterium, *Sutterella*, in the microbiome of around half of patients – but not in controls. What's more, these patients also produced antibodies against the bacterium *Sutterella*, suggesting it had penetrated the gut wall and was provoking an immune response. It's possible too, said Prof Lipkin, that the bacterium produces something that ultimately goes into the brain and causes disease.

So a study investigating a link with a vaccine found none, but researchers kept looking and instead discovered defects in key gut enzymes as well as unusual bacteria in the microbiome that may have resulted in an infection. These findings might explain why some ASD children respond to antibiotics or changes in diet and probiotics.

Prof Lipkin briefly mentioned another study, where they found that a particularly aggressive form of colon cancer was linked to a microbiome that produced low levels of a chemical called butyrate. Butyrate, produced by some gut bacteria, can have a tumour-suppressing effect.

Microbiome medicine

While HIV infection rates are falling in most parts of the world, they continue to rise in Southern Africa, and one of Prof Lipkin's studies revealed a surprising role of the vaginal microbiome in the spread of HIV.

An anti-retroviral gel helps prevent HIV infection in many women, but some women remain susceptible, and these women have high levels of cytokines in vaginal tissue. Many of them also had high levels of a bacterium called *Prevotella* in their microbiomes, which was probably driving the high cytokine levels and susceptibility to HIV infection. Treating these women with antibiotics could reduce their level of *Prevotella* and cytokines and, in conjunction with the anti-retroviral gel, help protect them from HIV infection.

So in these three studies Prof Lipkin and collaborators have found evidence that the microbiome might play a role in autism, colon cancer and HIV infections.

CFS/ME research programme

Prof Lipkin outlined his extensive CFS/ME research programme which, because of his expertise, inevitably started with a pathogen hunt: he called it "Bugs R Us." So far they have drawn a blank.

They used a technique he developed called Mass Tag PCR to search for specific pathogens in blood plasma including enteroviruses, influenza A virus, herpes virus and *Borrelia* bacteria, but found no significant differences between patients and controls.

Then, working with Dr Jose Montoya, Prof Lipkin moved on to high-throughput sequencing that can detect any pathogen, but again they found no specific microbes linked to CFS/ME. They did find that a large but poorly-understood group of viruses – torque viruses – were less common in patients than controls, but the significance of this is unclear.

Prof Lipkin explained they had profiled cytokines in CFS/ME patients, as had several other groups. They found differences between those patients who had only been ill for a short time (under three years) and patients who had been ill for longer. Prof Lipkin also reported some intriguing findings from Dan Peterson's Cerebrospinal fluid samples. Cerebrospinal fluid bathes the brain and spinal column, giving a window on what's happening in the brain, which emerged as a key area of interest in this

conference. Cytokine patterns were different in patients and controls, and Prof Lipkin hopes this research will be published fairly soon, but the unpublished results can't be shared here.

Metabolomics: chemical clues in the blood

Prof Lipkin, like many other researchers, believes the emerging field of metabolomics has the potential to reveal a great deal about diseases. Metabolomics is the study of the complete set of small chemicals in any tissue or the blood. These chemicals (or 'metabolites' as they are all the result of metabolic processes) include molecules such as amino acids and hormones like testosterone.

Diseases may have particular chemical fingerprints that will give clues about what's gone wrong in the body, which is why Prof Lipkin is keen to develop his work on this in CFS/ME.

He pointed out that the blood metabolome includes many molecules made by the gut microbiome, as a lot of small molecules cross the gut wall to the blood. For example, some gut bacteria can convert chemical found in beans and fish into tryptophan which is actively transported across the gut into the blood. The body needs tryptophan to make the neurotransmitter serotonin.

The gastrointestinal microbiome's potential to send chemicals into the body is a big reason Prof Lipkin wants to focus on it: "I think it produces compounds which traffic through the body or into the brain and cause all sorts of curious diseases". He added that infection can lead to changes in the microbiome, which could influence the illness. And the microbiome also has the capacity to turn on and turn off the immune system. So the microbiome could be playing a role in CFS/ME in several different ways.

Prof Lipkin is crowdfunding (www.microbediscovery.org) for his microbiome work after twice being turned down by the National Institutes for Health for strange reasons (reviewers of his application said the illness was either psychosomatic or down to a herpes virus infection in white blood cells).

Prof Lipkin wrapped up by outlining the key ways in which he's trying to understand CFS/ME. As well as the microbiome and metabolomic work, he's planning:

- further pathogens searches, this time in white blood cells (where herpes viruses, for instance, can hide out)
- gene expression studies to see if patients have different genes active to healthy controls, which could help show what's going wrong
- proteomics, which is the 'protein fingerprint' of the blood much like metabolomics is the chemical fingerprint; again, differences between patients and controls might reveal clues about what's going wrong in the illness
- functional immunology with the National Institute of Allergies and Infectious Diseases.

Add these to the completed cytokine study and earlier pathogen hunts and you have a comprehensive programme of research into the possible causes of CFS/ME.

Understanding pain mechanism in children and adolescents

Prof Maria Fitzgerald, University College London

“I think it’s very striking there are few studies of pain in CFS/ME patients,” began Prof Fitzgerald. “The field of chronic pain is huge and well-funded, with many people working in it – cancer pain, chronic back pain – but apparently nothing in this area.”

She outlined the concept of central sensitisation, the idea that the central nervous system amplifies the input that comes directly from the peripheral nerves in muscles and joints.

She refuted what she called the Cartesian idea that pain is caused solely by stimulating nociceptors (nerve endings) communicating with the brain, that more stimulation equals greater pain, and that if the pain continues, there must be a biopsychosocial reason. “This is simply not the case,” she said.

“Instead, there is very good evidence for circuits at low levels of the central nervous system, particularly in the dorsal horn of the spinal cord, that are able to modify this input as it comes in, before it even gets to the brain.

“Everybody has in them the mechanism needed to amplify pain. Most of the time, we don’t – but it can happen to everyone.”

Prof Fitzgerald then described how, in chronic pain patients, the state of central sensitisation becomes fixed. This may be because there is a continued source of pain – eg. in chronic back pain – but it may also continue even with no injury present.

There is still debate that this is the mechanism underlying the chronic widespread pain of CFS/ME. It’s possible that descending controls from the brain may set up central sensitisation, says Prof Fitzgerald, but we simply do not know if that is true.

There is very strong evidence that the brain can influence pain processing at spinal cord level.

Expectations of pain

Prof Fitzgerald outlined a study which tested healthy subjects’ expectations of pain. It found that, compared to controls, the same stimulus produced less activity at spinal cord level in those who believed they were using a pain-reducing cream (which was in fact a placebo).

“If this can happen in healthy people, why could it not be manipulated in people who are ill for whatever reason?” asked Prof Fitzgerald.

Another very well-established way that central sensitisation might be maintained is by neuroimmune activation, with microglia releasing cytokines.

However, Prof Fitzgerald stressed that, in the pain field, nobody is looking at cytokine levels in the blood.

“Instead, we are interested in what’s happening to the nociceptive pain circuits in the central nervous system. They don’t really expect a chronic pain patient to have masses of circulating cytokines – what they know to be true is that, with stimulation, these microglia release tiny amounts of cytokines in the area of the circuit, which excites them and, in other words, they hurt.”

But why is it that some people have terrible pain, even when there is apparently no original injury it can be traced back to? Prof Fitzgerald outlined very new research that points to us all being in a state of latent central sensitisation, which healthy individuals are able to suppress all the time.

One explanation might be that infants suppress neuropathic pain following nerve injury by ‘blocking’ anti-inflammatory activity, so a constant state of central sensitisation may be due to a very early life event that we may not even remember. “This may account for why neuropathic pain is rare in young children and also why it can emerge, for no observable reason, in adolescent patients,” says Prof Fitzgerald.

Latent sensitisation

Finally, explaining that this is an idea based on experimental evidence, she referenced a recent paper (*Corder et al, Science, 2013*) which suggests that every time adults are injured, a natural endogenous analgesia kicks in to suppress the pain – but that the pain continues for a considerable time after, even though we can’t feel it.

“This makes us think a bit differently about pain,” says Prof Fitzgerald. “A lot of it is happening a long time after an injury, but if we are healthy and well we are actively suppressing it.

“How is going to help people with CFS/ME? This way of thinking about pain, in terms of its time course, location, spatial distribution, intensity and so on, has been driven by basic research, not clinical observations. It informs and stimulates better treatments.

“How do I know that? For the first time, just published – this morning, in fact – there has been a randomised, controlled, double blind, stratified trial of carbamazepine in neuropathic pain, based on precise sensory profiling (Demant et al, *Pain*, 2014). They found that one group responded amazingly well, and the other two groups did not.

“If you understand the basis of pain, it improves treatment.”

Dr Esther Crawley comments: “Pain is a strong predictor of poor outcomes in our CFS/ME patients, and I think the idea of improving stratification with pain is really important.”

Prof Jonathan Edwards comments: “What I thought was brought out particularly clearly by Prof Fitzgerald and Prof Pariente, in different ways, was the fact that discrepancies in a broad brush view are emerging that might lead us to a specific answer for CFS/ME.”

The epidemiology of adolescent CFS and chronic widespread pain

Prof Jon Tobias, University of Bristol

Data from the UK CFS/ME National Outcomes Database found that 28% of adults with CFS/ME also have fibromyalgia.

Prof Tobias was presenting on behalf of his colleague, Kevin Deere, who has looked at the relationship between this and CFS/ME in 17 year olds, which no previous studies have done from an epidemiological perspective.

The research aims were to see if CFS/ME and chronic widespread pain (which is related to fibromyalgia and more easy to evaluate based on questionnaires) tended to co-exist in adolescence, and to see if these conditions share common risk factors. The analyses were performed in a large population based cohort of adolescents (using the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort) in whom they assessed the presence of both CFS/ME and CWP by questionnaire (CWP was derived from questions asking about pain duration and location

“We went on to use logistic regression to determine if CFS/ME was a determinant for chronic widespread pain, and vice versa,” explained Prof Tobias. “We also looked at other risk factors including gender, maternal education, obesity, depression and anxiety.

“We found that CWP was associated with an increased risk of CFS/ME at a ratio of 3.5% in our initial analysis, but this was attenuated quite markedly when we adjusted for our other risk factors.”

“Similarly, we found that CFS/ME predicted CWP, again at 3.5%, again largely attenuated by these other confounders.”

In addition:

- there was only weak evidence for an increased risk of CWP in CFS
- being female was associated with an increased risk of CWP but not CFS
- depression was associated with an increased risk of CFS but not CWP
- anxiety was associated with an increased risk of both conditions.

Prof Tobias explained the limitations of the study, in that the CWP phenotype is only a proxy measure for fibromyalgia, which is a clinical definition; and also that using even a large population for such a study may not be sufficient, with alternatives including case controlled studies.

“The overlap we found does seem to be somewhat less than in adults. What was also interesting is that the associations between depression and gender were distinct, suggesting different aetio-pathological mechanisms.”

Recovery and persistence from CFS/ME in adolescents

Dr Roberto Nuevo, University of Bristol

There is little evidence about persistence or recovery of CFS/ME in adolescents, says Dr Nuevo, whose study aimed to describe the epidemiology and natural course of CFS/ME in patients between the ages 13 and 18.

This study also used the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort, and investigated the presence of CFS/ME at three time points using parental reports (13 years), parental and child report (16 years) and child reports (18 years).

Dr Nuevo described the prevalence of CFS/ME at ages 13, 15 and 18 years, the natural history and the chance of recovery. As these are unpublished results, more information cannot be shared in this report.

Workshop feedback
Prof Stephen Holgate, CMRC Chair

Prof Holgate asked participants from each of the previous day's workshops to share some of the key points that had emerged.

Workshop one: Working together for more and better research that benefits people with CFS/ME
Facilitated by Sally Crowe

A detailed overview of this session can be found on p 17.

Workshop two: Pain
Facilitated by Prof Maria Fitzgerald

"We had an excellent mix of people in this workshop, including a rheumatologist, a physiotherapist, and the parent of a child with M.E.," reported Prof Fitzgerald. "We began by thinking what a typical patient question would be if they had pain, and agreed that it would be: why do I have pain, what is it for, when will it go away, and what are going to do to make it better?"

The group discussed that it was necessary to move away from current answers to this – ie. you will just have to get used to it – towards measures that can be taken to increase function. The current situation is not helped by NHS constraints which send patients in particular directions.

"We need to use our money in two directions," concluded Prof Fitzgerald. "One is to usefully find out a lot more about pain and CFS/ME, looking for particular types of pain, and the relationship between fatigue and pain. We need to develop new clinical tools, because we can't have outcomes for clinical trials unless we are confident in what we are measuring.

"The second strand, but just as important, is to spend our money on patients who are severely affected. We would start with a small number across the UK, more qualitative but with an attempt at quantitative data, and investigate their pain. We'd have to work with carers and families, and we would use such a study as indicators for the future, to help us create hypotheses."

Workshop three: Sleep and fatigue
Facilitated by Dr Sue Wilson

This group agreed that sleep problems cause a lot of distress in CFS/ME, and that an intervention to improve sleep would be beneficial.

Recent reports of the high incidence of co-morbidity of CFS/ME and sleep disorders were also discussed. "We would like more clinicians to know about this and look for it," said Dr Wilson.

"The third key point was that other research councils have repositories for data, and we felt that all our data about people with CFS/ME should be held in something

similar, to be accessed by other researchers. We didn't know if the MRC would be able to do something about that."

Workshop four: What should we measure? Core outcome sets and PROMs ***Facilitated by Sarah Brookes***

Everyone in this workshop agreed that what we use to capture the impact of CFS/ME on patients, the heterogeneity of the condition, and particularly the degrees of severity, are inadequate.

They explored the process that would needed to be develop some new core outcome sets, an agreed standardised set of measurable, recordable outcomes to be used in all clinical trials in a specific area.

There are already tools to help with this process, for example the COMET initiative (www.comet-initiative.org).

The group hoped that some of the mechanisms that had been elucidated in CFS/ME, and presented over the course of the conference, would eventually lead to therapeutic trials, hopefully using a set of core outcome measures and patient-reported outcome measures that can be used.

Workshop five: Inflammation and infection ***Facilitated by Prof Hugh Perry***

This workshop discussed post-mortem tissue – what could be done with patients brains, for example – and how clinical phenotyping was essential if brains were to be examined.

It was felt that there was a need for in vivo scanning of patients to try and understand what brain areas should be targeted.

They also talked about:

- characterising, rather than categorising, patients
- the need to still recruit as many patients as possible, but more carefully
- inflammation post-vaccination, and whether it would be possible to see what CFS/ME patients' response would be to that sort of stimulation.

Taking collaboration forward: next steps

Prof Stephen Holgate, CMRC Chair

“Yes,” was the resounding answer from delegates when Prof Holgate began his closing address by asking if they would like the Collaborative to continue.

Referencing William Osler, the father of modern medicine, Cofounder of the John Hopkins Medical School in Baltimore and later Regius Professor of Medicine at Oxford, and the author of *The Principles and Practice of Medicine* first published in 1892, Prof Holgate commented that we had practiced medicine in this way ever since.

“But, as I’ve said repeatedly, we are now the threshold of something completely different, and this is what’s exciting,” he continued. “It has two components to it, both beautifully brought out in this meeting.

“The first is that we put the individual patient at the centre of our science; the second is that we use new technology to identify new pathways relating to, in this case, CFS/ME using integrated scientific approaches.”

He then drew out highlights from the conference, the first being the importance of viewing CFS/ME as a multisystem disease(s), and looking at the disease more holistically thereby avoiding a dualistic understanding of the illness as being either physical or mental, when the research literature finds associations with biological, psychological and social abnormalities.

Clear biological basis

The second thing was the clear biological bases to this disorder. “I think there has been a mismatch between what patients think we think, and what we think they think,” he said, to considerable murmurs of agreement

“And that’s a massive issue. I think we need to do something about this, and shouting about the fact that we believe that CFS/ME has a biological basis. We have heard about important gene by environmental interactions (eg. microglia in the central nervous system, skeletal muscle, sensory neurones) which help reinforce this.”

He then moved onto heterogeneity, and the fact that CFS/ME is most likely to be “multiple forms of a complicated set of interacting causal pathway, involving disordered immunity and central sensitisation.”

He referenced inflammation, accompanying stress responses, and multiple organ responses. “I was particularly struck today by the re-emphasis on brains, the spinal cord and microglia,” he said.

He talked about triggers, and the possibility that what starts CFS/ME might be different from what maintains it. “We have to think about the biology of those separate process, and identifying endophenotypes; those different causal pathways in the different organs or systemically, that might be causal.”

Connecting biological and behavioural sciences was also important, urged Prof Holgate, if the patient is going to be at the centre. “Without this, we are going to go nowhere, because much of the symptomatology is expressed through the behavioural sciences.”

Prof Holgate described how CFS/ME fits the new medical paradigm of stratified medicine (also called personalised, or P4 medicine), and how this could open new doors to unpick its complexity. This in turn could lead to new diagnostic tests, new treatments and improved clinical care.

Speaking with one voice

By working together and speaking with a single voice, he said, we could increase patient confidence and propagate research in a different way by pooling expertise.

“I think we’re going to have to go back to prioritising, to see what is tractable to make a difference early on” said Prof Holgate. “We also need to focus on early career researchers – I think it was great that we had so many PhD and medical students here, because capacity building is what growing a scientific discipline is all about.”

He moved onto practical steps, setting out what his suggestions for what the CMRC might do next. These were to:

- Penetrate the medical scientific hierarchy to get CFS/ME more recognised: this is an integrated spectrum of disorders with high medical and socio-economic burden. The conference could be a springboard to launch a major report with the Academy of Medical Sciences, the Royal Society, or Academy of Royal Colleges which brings together experts not only from the UK but also overseas.
- Involve patients and carers in helping to set the research agenda, starting with feedback from the Associate Member workshop that took place on the first day of the conference and looking at the possibility of developing a patient register for ease of involvement.
- Work towards a sustainable model to keep the CFS/ME Research Collaborative going: “We can’t go backwards now,” urged Prof Holgate.
- Being more outward-facing and improving international links to further strengthen and validate our approach to CFS/ME research
- Capitalise on the coming together of interdisciplinary researchers to develop national protocols for biobanking, phenotyping and applying the new ‘-omics’ technologies to large numbers of patients across the full disease spectrum.

“Over these past few days, the considerable endorsement of having you all here gives me the energy and enthusiasm to help move this whole field forward and to turn attitudes about the disorder around,” concluded Prof Holgate. “We have to think about what we need as a community to maximise the interactions the Collaborative is trying to promote.”

End of conference summary
Prof Hugh Perry, University of Southampton

Declaring his intention to add only a few things to what Prof Holgate had highlighted in the preceding presentation, Prof Perry said that thought the conference had been hugely successful.

“When I first met Stephen in the context of a CFS/ME meeting, a number of years ago, I remember being appalled at the quality of the science delivered there,” he recalled. “I could not believe the science community could not do a better job. And now here we are, some years later, and it’s abundantly clear that the science community can do something completely different, and really make a significant difference.

He ended by drawing attention to “two things that I think are really important.”

“This cannot fall on the shoulders of a small number of people. I say to the community as a whole: this has to be a shared journey. If we want sustainability, we have to get young researchers to join in, and draw in members of the patient community. This linkage between the science, the charities and so forth, is absolutely essential.

“Some of our scientific peers have been unwilling to engage in a productive conversation about what CFS/ME is. By encouraging more interest, I hope the ripples in the pond will spread out from this meeting, at every different level.”

“I thank everyone who has been involved for their huge amount of work to make this conference happen. I have learnt a lot, and I hope you go away with these words: sustainability is important, and this is a science that needs to be done.

APPENDICES

Appendix 1: Detailed programme for the Associate Member/patient and researcher session

Workshop aim

People with CFS/ME and carers, in collaboration with researchers, to discuss, explore and identify ways they can contribute to the CFS/ME research endeavour

Workshop objectives

1. Consider the current opportunities for participation in research and where patients and carers have made a difference
2. Identify specific ways that the CFS/ME community can contribute meaningfully to CFS/ME research projects, such as clinical trials
3. Identify what the CFS/ME community can contribute to the overall CFS/ME research effort and endeavour
4. To produce a report for the CMRC to consider.

Programme

13.30	Registration and refreshments	
14.00	Welcome and setting the scene for the workshop - the benefits and the challenges of collaborating for research	Stephen Holgate CMRC Chair
14.10	Working together today - so that we get the best out of the afternoon	Sally Crowe Crowe Associates Ltd
14.15	What do we mean by research, and collaboration in research?	Sally Crowe
14.30	What can people with CFS/ME and carers do to help in CFS/ME research?	Table group discussion
15.00	Break	
15.15	Getting to grips with research - focussed table discussions	Table group discussion
16.00	Summing up; reflections on the process	
16.10	Refreshment break	
16.30	Research Panel and discussion	Stephen Holgate
17.30	Networking reception - all workshop and other conference participants invited	
18.30	Depart	

Appendix 2: Full list of comments, views and ideas from first discussion round from the *Working together for more and better research that benefits people with CFS/ME* workshop

Research Cycle 1- Identifying research topics/questions

Theme 1: Ideas and comments on research topics

- we need a better understanding of the cause(s) of various symptoms. Are they really related?
- research into biomedical cause(s) plus possible sub-types of M.E/CFS
- apparently some women with M.E have been much better whilst pregnant but have returned to serious incapacity after the pregnancy - Is this being researched?
- test whether M.E is infectious using transgenic mice (human immune system) & patient saliva
- whatever part of the brain measures fatigue, switches on the fatigue symptoms when we get over tired. Is it responsible for switching the symptoms on by responding to low levels of stress (e.g. picking up a piece of paper from the floor)? Should we not find the part, or parts, of the brain responsible for fatigue symptoms?
- research link between Epstein-Barr virus and CFS/M.E. (Neuro immune studies)
- researchers concentrate on fatigue-but pain/post-exercise symptoms are often important
- how to include research on alternative medicine that may get less funding, but be more useful to patients (including the less conventional areas of mainstream science).
- stratification of disease/patients
- mitochondria and energy generation
- diagnosis is a mess
- biomarkers: link to people who have < 3yrs (M.E/CFS) >3yrs like cancer?
- how do we spot the start of CFS? We should catch it before the downward spiral takes effect with early bio-markers, education and awareness of CFS
- research to lead diagnosis not exclusion diagnosis
- interleukins and B cells
- understanding of depression in CFS/ME
- environmental theories of CFS/ME
- quality of life research
- overactive sympathetic nervous system
- complimentary medicine especially cranial osteopathy
- virology research
- unreasonable stress and Post Traumatic Stress Disorder
- intolerances and allergies
- biobank
- mitochondria assessment
- research into to how best to support people with CFS/ME
- biomarkers.

Theme 2: Comments on the process of generating research topics and CFS/ME research in general

- is there less research into M.E/CFS compared with other chronic illnesses?
- when are we going to get long term follow up of what happens to people with M.E?

- engaging new but relevant scientists into a big ongoing, clinical problem to bring in fresh/alternative ideas
- research should use the patient as the centre and use their case histories. Not just the newly diagnosed patient, but long term patients and even those who have made a recovery
- research should improve patient's quality of life
- an accredited, updated, list of research sources, aims and direction.
- focus on the hallmarks of the condition that patients experience i.e. intolerances to food, drugs, exercise tolerance
- the collaboration between different medical disciplines is key to making progress with M.E/CFS research. This will help encourage interest in more biomedical research. It could also help other illnesses
- Canadian Consensus Criteria as criteria for any study-especially those whose results are in the severe category
- CFS muddies the waters further; many other illnesses may cause CFS. Post Exertional Malaise is the distinction. The "different types" of CFS/ME could be considered confusing. Overlapping conditions of CFS/ME/Fibro
- newly diagnosed, long term patients and even those who have made recovery should take part in research
- in depth case studies of severely affected long term sufferers
- making the case for research in M.E/CFS from a disinterested perspective.

Research Cycle 2 - Prioritising

- diagnostic research must be a priority
- prioritise severely affected patients for studies
- cause - emphasis on showing physical problem. Can we move on?
- very little done on strategies commonly used (what we know now) Care - Nothing?
- too much emphasis on psychological aspects.
- lack of direction and coordination of research efforts. There is a plethora of research, which efforts confuse.
- the most urgent question is to find a clinical test to give a definite diagnosis
- why are there not more studies into graded exercise therapy/different types of exercise?
- research into G.P views and education about CFS/ME
- collect information from patients on what has worked for them, and use as a basis for further research areas
- difficulty working out a balance between wanting a lot of research done, and not making it exhaustive for participants.

Research Cycle 3 - Commissioning

- research is often funded by drug companies. This means that there is a huge gap between medication and the supplements that most of use - which we gather from costly trial and error
- how can we get the pharmaceutical companies to research CFS/M.E on a legitimate therapy
- how do we get MRC to spend more on M.E/CFS research?
- we need multidisciplinary research connecting different areas of CFS/ME (e.g. Gut).

Research Cycle 4 - Designing research

- include severely ill participants (not forget them!) - Its' possible people unable to read letters or emails, and who cannot travel to studies and appointments. Travel to them?
- researchers going to patients, not the other way
- research should listen to participants concerns regarding types of treatment tested - especially when it's obvious to the patient that it could do more harm than good
- diagnostic criteria? Consistency across research projects?
- how to get the severely affected patients (long term) involved in research?
- putting together multidisciplinary research teams (joined up thinking/more complete picture)
- PPI [*patient and public involvement*] focuses research more clearly, and allows for more productive studies
- can data be collected from GP's about their M.E patients?
- which criteria should be used, Fukuda or Oxford. Is there consensus?
- to define subgroups regarding onset and symptoms.
- include or exclude participants with multiple diagnoses?
- integrated holistic approach
- standardized objective outcome measures alongside other measures.
- real time measurement of interleukin levels in M.E patients. Levels vs. symptoms.
- use the Measure Yourself Medical Outcome Profile (MYMOP) - evaluation method?
- how to get more health professionals involved in research into CFS/M.E?
- actigraphy data collection throughout to detect peaks and troughs (mydriasis).
- are ethics committees overzealous?

Research Cycle 5 and 6 - Managing and undertaking research

- NHS job plans make it very difficult to engage with researchers. Fresh people/ideas would help the openness of research
- It would be good to be a part of research and to be offered this at the start of treatment
- How can be patients ask to be linked into studies?
- opportunities to take part in research need to be better advertised/encouraged
- informed consent; patient must be treated like an adult-gives realistic information about the likelihood of treatment being successful, about their data and results
- think about ways in which we can reduce patient drop-outs in studies, particularly in long-term studies. This may involve taking people's opinions in the form of a questionnaire; in order to discover what would help M.E patients to remain in the M.E study e.g. Incentives/location of collecting data etc.
- how are subjects found? How do patients volunteer? Difficulties of a research study-most profoundly affected may not be able to take part. Those less affected may actually be suffering from something else not diagnosed
- it's difficult for researchers to access populations which might be under represented in research e.g. Due to confidentiality issues. Whilst confidentiality is obviously very important, this might hinder our understanding of issues important for hard to reach groups.

Research Cycle 7- Analysing and interpreting results

- evaluation should include patient comments
- how do we help patients to 'track' their improvements (or not) in a consistent way, to guide better help
- stratify study results based on various demographics (e.g. symptoms, severity, age, illness duration, etc.) and co morbidity (e.g. IBS, fibro, MCS).

Research Cycle 8 - Disseminating

- community to increase impact of research findings
- keep out the jargon in reporting to the public and patient audience, research needs to be more lay friendly? Getting results back to patients in a non-medical format
- charities? Get together to employ someone whose sole job it is to review, 'translate' (into lay friendly language) and compress all research into one bulletin. This bulletin could be sent to: charities, newspapers, CFS clinics worldwide, interested GP's, and patient groups
- better communication with the general public-more balanced reporting in the press.
- existing research has been spun as more successful at treating patient that is?
- transparency in research needed. We need to make all information and evidence available to the public. A history of misrepresenting the evidence has led to a lack of trust - we need transparency to restore trust, and ensure good research is done
- think about how to engage non-patient community, the public.
- how does research manage 'not one coat fits all' (being different)
- is it possible to have a dedicated publication only covering the best research?
- disseminating research to clinicians and GP's is essential. At what point should they be involved in the research cycle?
- dissemination of what is already known in plain language
- feedback of research into NICE guidelines (quickly)
- convincing people with M.E that participation in clinical trials is described as worthwhile
- politics and external interests can cause research outcomes to be inappropriate to the patient, whatever input patients may make
- at present there is a tolerance for poor quality research and exaggerated claims of expertise. The focus should be about providing accurate information to patients, in order to allow them to make informed decisions about their own lives.
- PACE-refused to release outcomes laid out in protocol. Spun claims about recovery. There is a need for openness; peer review, minutes of meetings and decisions
- how to get clinicians interested in keeping up to date with research, especially specialist clinicians (most seem shockingly uninterested in keeping up to date).

Research Cycle 9 and 10 - Evaluating and Reviewing what we know/what the gaps are

- ME is complicated. There is a need for personalised approaches in research.
- CFS/ME is not a single condition. How does that challenge research? Is it an opportunity?
- which patients does it work for?
- deciding which criteria of M.E/CFS is used in research and why?
- common top level reporting of symptoms/functions
- recovery stories
- prevention: Who will develop CFS/ME?
- research or even information doesn't reach the wider medical establishment. We all meet blank looks when we ask about side effects
- inter-disciplinary research/open mindedness and a lack of defensiveness about individual disciplines
- putting the illness at the centre of investigation and looking outwards.
- making sense of a diverse patient group (catch 22)
- worth persevering for the research you feel matters.

Appendix 3: Full details of the 'patient/researcher collaboration questionnaire database' idea developed during the *Working together for more and better research that benefits people with CFS/ME* workshop

- a questionnaire must be designed initially by MECFS patients that asks 'the right questions' these will be many and varied but would be simple to achieve a huge and impressive list through the 'action for me' website for example
- a small team would then collate the question data into a structured list
- the list is then passed to a small team of researchers and selected experts to tailor the list of questions into a form that they think will give them maximum information with maximum 'cross check' capability while trying to keep the essence of the question in clear 'non-scientific' language
- at this stage it would be advisable to get a few selected sufferers and researchers in a room with a software engineer to develop the Patient/researcher collaboration questionnaire
- then all we have to do is make sure as many known sufferers and recovered patients as possible have access to and fill in the questionnaire to produce the prime resource material
- this database would update with each ratified entry very much like an accounting spreadsheet
- data from a specific time frame could also be isolated where relevant.
- researchers worldwide would be able to dip in to this resource material, check others research and choose their area to concentrate upon with the aim to build small pieces towards a common goal.