



The ME Association

Informing and supporting those affected by ME / CFS

Invest in ME conference, 24 May 2010 - first full length report of all the presentations

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- **This is a personal summary of the 2010 Invest in ME conference that has been prepared for ME Association members. A further summary, with additional background information, will appear in the July issue of ME Essential magazine. This summary was prepared by Dr Charles Shepherd, Hon Medical Adviser, The ME Association, to whom any comments or corrections should be sent via meconnect@meassociation.org.uk**

Outside in the bright spring sunshine, the temperature was soaring and the roads around St James's Park were being prepared for the State Opening of Parliament the following day. In the impressive conference venue at One Birdcage Walk - home to the Institute of Mechanical Engineers - the hall was almost full by 9am for the fifth Invest in ME conference.

Attending was the usual mix of predominantly patients and patient group representatives, many of whom came from abroad, as well as a much smaller number of health professionals and researchers. Among the doctors present were Dr Dan Peterson (USA), Dr Sarah Myhill, and my colleague from the ANZMES support group in New Zealand, Dr Ros Vallings. And it was good to meet former MP Dr Ian Gibson again, who is maintaining his interest in ME/CFS research. I also understand that the Editor of the British Medical Journal had accepted an invitation to attend.

The theme this year was research with all of the speakers - the exception being Jonathan Kerr - coming from America.

The conference was chaired by Professor Malcolm Hooper. With a very tight schedule to keep to, and most presentations filling the time available, written questions were largely left to the Plenary Session at the end.

It was long day for people with ME/CFS, especially those who were unwell and had not been able to stay in London the night before. Fortunately, the hall remained cool given the almost 30 degree heat outside.

The main talking point in the follow up to this meeting is the announcement from Professor Brigitte Huber about not finding any evidence of XMRV infection in the three different cohorts of CFS patients that were investigated by her group in Boston.

CONFERENCE PRESENTATIONS

Professor Leonard Jason PhD

Professor of Clinical and Community Psychology, DePaul University, Chicago, USA

How Case Definitions Can Stigmatize: Implications for Epidemiology, Aetiology and Pathology.

Professor Jason opened the conference with an excellent presentation that traced the development of the various ways in which chronic fatigue syndrome (CFS) has been defined by the international medical community for both clinical and research purposes. One of his early slides used a stack of cards to illustrate just how important it is to get the case definition correct - because this forms the foundation for everything else that follows in the way of research into epidemiology, causation and treatment. So where the basic definition of an illness lacks reliability, accuracy and specificity the quality of research and treatment based on that definition is likely to be flawed.

Starting with epidemiology (= how many people have a disease) Professor Jason went over some very familiar ground:

- Fatigue as a symptom is very common in the general population with studies suggesting that around 25% of people will report some degree of fatigue when asked.
- Around 4% of the population will report more severe and persistent fatigue - which may involve a combination of medical, psychological (stress, depression etc) and social factors.
- A much smaller number will have CFS - where there is a more specific form of exercise-induced fatigue along with a number of other very characteristic symptoms.

Professor Jason then reviewed the way in which doctors had developed various ways of deciding how people with CFS could be defined and separated out from those who just have more generalised chronic fatigue disorders. Dissatisfaction with the original (1988) Holmes et al definition for CFS resulted in the 1994 Fukuda et al definition. This was followed by the most recent development - the Centre for Disease Control (CDC) empirical CFS criteria.

The overall effect has been to progressively broaden the patient entry criteria into what constitutes CFS. This, in turn, has produced a very significant increase in the number of people who have CFS using these criteria. So the prevalence of CFS in the USA, when based on these changes, has jumped from around 4 per 100,000 of the population back in 1997 (= around 800,000 people in the USA) to 25.4 per 100,000 of the population today.

While underestimating the prevalence of a condition clearly has important implications for financial resources and service development, over-estimating the prevalence can easily lead to seriously flawed research into causation, possible biomarkers and inaccurate results from clinical trials into possible new forms of treatment.

Professor Jason also compared some of the key differences between the way in which CFS is defined by the Fukuda criteria and the Canadian Criteria - in particular the way in which critical ME/CFS symptoms such as post-exertional malaise, cognitive dysfunction and unrefreshing sleep are not necessarily required by Fukuda and how people with a major depressive illness could also be diagnosed as having CFS using the new CDC empirical criteria.

The results of having an unsatisfactory case definition are wide ranging and serious - over-estimating the number of people who have this illness, bringing people into research studies that should not even be there, not being able to identify biomarkers for the disease, and failing to identify beneficial forms of treatment based on that research.

Professor Jason has written a very helpful review of the main problems he sees with the new CDC empirical CFS criteria and the resulting increase in CFS prevalence estimates. This was written for the benefit of Board members of the IACFS/ME. Professor Jason's review can be accessed via the [IACFS/ME website](#).

Professor Jason has just had a very interesting paper published which looks at how ME/CFS is covered in medical textbooks. Reference: Frequency and content analysis of chronic fatigue syndrome in medical textbooks. *Australian Journal of Primary Health*, 2010, 16, 174 - 178.

Professor Nora Chapman PhD**Associate Professor of Pathology and Microbiology, University of Nebraska Medical Centre, USA**
Persistent Enteroviral Infections

Professor Chapman is a research scientist who studies persistent coxsackie virus infections (part of the enteroviral group) in murine (= mouse) models of chronic myocarditis (= viral inflammation of the heart muscle) and dilated cardiomyopathy (= the resulting dilation and failure of heart muscle). Mice have the same cellular enteroviral receptors (= sites where a virus can enter the cell) so can develop the same enteroviral diseases as humans. Her research in this area has demonstrated that the production of defective forms of enteroviral infection in the heart and other tissues can lead to persisting enteroviral infection, which is very hard to then clear. This is despite active antiviral immune responses taking place in the acute stages of the illness.

Although Professor Chapman is not currently carrying out any ME/CFS research, we know that enteroviral infections can infect a wide variety of tissues - including muscle and brain - and sometimes trigger ME/CFS. However, there is conflicting evidence from the research so far as to whether these triggering enteroviral infections then persist and play an on-going role in disease causation in ME/CFS.

The presentation therefore concentrated on her work in inflammatory heart conditions and the effects of persisting enteroviral (coxsackie B infection) and replication of these viruses, on infected cell function. Professor Chapman is also working with Dr John Chia in relation to his finding of enteroviral infection in stomach biopsies.

More information, along with relevant references, on the possible role of persisting enteroviral infection in ME/CFS can be found in section 5:1 of *ME/CFS/PVFS - An Exploration of the Key Clinical Issues*

Dr John Chia**Infectious Disease Specialist, Torrance, California, USA**
Enterovirus in ME/CFS - Diagnosis and Treatment

Dr John Chia first became interested in ME/CFS research as a result of his son developing the illness several years ago. Having investigated all the various theories regarding what may be the cause of ME/CFS, and the work already carried out in the UK in relation to enteroviral infection, Dr Chia concluded that it was time to revisit the possible role of persisting enteroviral infection.

Dr Chia started off by summarising the wide range of tissues - cardiovascular, central nervous system and muscle, gastro-intestinal, respiratory, skin (where a chickenpox like rash can sometimes appear) - that over 70 different enteroviral infections can infect along with the equally wide variety of clinical presentations and symptoms that occur. In some cases, acute enteroviral infections can cause a CD8+ T lymphopenia (= lowering of a specific sub-group of white blood cells) which predisposes to the reactivation of endogenous herpes viruses.

Given the wide variety of clinical presentations related to enteroviral infections, Dr Chia stressed the need for physicians to take a comprehensive clinical history regarding the onset of ME/CFS and to be alert to the possibility of an enteroviral trigger. He illustrated this point by referring to the case of enteroviral shellfish poisoning, which may be misdiagnosed as an allergic reaction, and then treated with steroids - which could be a factor in increasing the risk of ME/CFS developing in these patients.

He then reviewed the various methods of laboratory testing for enteroviral infection: elevated neutralising antibody titres; PCR (polymerase chain reaction) for enteroviral RNA (= genetic material) and immunoperoxidase staining for viral protein. He also reviewed some of the often conflicting research (mainly UK based) that has looked at the role of enteroviral infection in ME./CFS - including the first published report of a UK post-mortem case [1] where enteroviral RNA sequences had been found in the brain (brainstem and hypothalamus), heart and muscle.

Dr Chia then updated the meeting on his own research which has been looking at the presence of persisting enteroviral infection in tissue biopsies (using immunoperoxidase staining) taken from the lining

of the stomach in people with ME/CFS [2].

Dr Chia concluded by summarising the way in which persisting enteroviral infections might be treated. At present, there is no effective antiviral drug treatment available - although the antiviral drug pleconaril has shown some limited benefit. There are no clear benefits from using immunomodulatory treatments such as intravenous immunoglobulin or interferon alpha/gamma. His one recommendation was for a Chinese herbal product known as oxymatrine, which is now available as a commercial product known as Equilibrant. In his own patients this drug has produced beneficial effects in 52% of around 500 cases. However, it does cause a transient exacerbation of pre-existing symptoms in most patients.

Reference 1: McGarry F et al. Enterovirus in Chronic Fatigue Syndrome. *Clinical Science*, 1999, 87, 603 - 608. [Electronic copy.](#)

References to papers published by Dr Chia can be found in section 5:1 (Role of Infection) in *ME/CFS/PVFS - An Exploration of the Key Clinical Issues*.

Reference 2: Chia JKS and Chia AY. Chronic fatigue syndrome is associated with chronic enterovirus infection in the stomach. *Journal of Clinical Pathology*, 2008, 61, 43 - 4. [Electronic copy.](#)

More information on post-mortem studies involving people with ME/CFS, including the post-mortem referred to by Dr Chia, and information regarding the finding of dorsal root ganglionitis in a more recent UK post-mortem, can be found in section 5:4 of the above MEA publication. It should be noted that dorsal root ganglionitis can also be found in people with Sjogren's syndrome who have an autonomic and sensory neuropathy (ref: *Annals of Neurology*, 1990, 27, 304 - 315). Sjogren's syndrome is a rheumatic disorder that has some features that overlap with ME/CFS. The MEA Ramsay Research Fund is currently raising funds and funding a feasibility study with the aim of setting up a UK based tissue and post-mortem brain bank. More info on the Ramsay Research Fund post-mortem initiative can be found at [here](#).

The presentation covered very similar ground to the one given at the conference last year. This is described in more detail in our 2009 conference report in *ME Essential*, issue 111, pages 14 - 17.

Dr Paul Cheney MD PhD

Medical Director, Cheney Clinic, Asheville, North Carolina, USA

Diastolic dysfunction in ME/CFS - A Cardiac Manifestation of Cellular Energy Deficits in ME/CFS

Dr Paul Cheney has a longstanding clinical and research association with ME/CFS. Along with Dr Dan Peterson, he looked after the patients who were involved with the famous Lake Tahoe outbreak during 1984 - 1987. Since 1990 Dr Cheney has led a private clinic in North Carolina where he sees ME/CFS patients from all over the world.

The main theme of Dr Cheney's presentation was the work he has been doing on what he terms 'the oxygen response deficit with exercise in CFS' and the detailed investigation of cardiac (= heart) function in people with ME/CFS. Dr Cheney's presentation contained a great deal of very complex information relating to investigations used to assess cardiac function and it should be noted that these very interesting findings have not yet been independently replicated and published in mainstream peer-reviewed medical journals. Consequently, the observations and conclusions about cardiac function in ME/CFS are not always accepted by international medical opinion.

Among the key points and conclusions made by Dr Cheney were:

- People with ME/CFS seen at this clinic have a much higher incidence of diastolic dysfunction than controls. Diastolic dysfunction refers to the way in which the chambers of the heart develop a defect in the way they fill up with blood during the relaxation phase.
- Diastolic dysfunction is a factor in the development of symptoms related to orthostatic intolerance.
- A high incidence of the patients seen at this clinic have a patent foramen ovale (PFO).
- Relevant investigations include echocardiography and IVRT (isovolumetric relaxation time) responses to oxygen administration.
- CFS is an oxygen toxic state and oxygen toxicity status appears to determine outcome in

therapeutic trials.

- Oxygen toxicity is not so much a cause of ME/CFS but a final common pathway that appears to determine outcome.

Dr Cheney also discussed:

- A study which had demonstrated high lactate levels in the brain of people with ME/CFS.
- RNaseL activity in ME/CFS.
- Fingerprint abnormalities in ME/CFS.
- Stem cell treatment (not covered as intended as time had run out)
- Dr Cheney concluded by mentioning some of the treatments he uses in patients seen at this clinic.

Dr Cheney also referred to XMRV and pointed out that 38/47 of his own patients had tested positive for this retrovirus. There was a high incidence of + XMRV test results in other members of the family where a family member with ME/CFS had tested positive.

More information on Dr Cheney's approach to cardiological assessment and management of ME/CFS can be found on The Cheney Clinic website: www.cheneyclinic.com

Professor Julia Newton and colleagues at the University of Newcastle (UK) have just published the results from a study which examined the relationship between skeletal and cardiac muscle function and symptoms on standing in CFS using magnetic resonance spectroscopy (MRS) and impedance cardiography. The MEA Ramsay Research Fund is helping to fund Professor Newton's research into skeletal muscle abnormalities in ME/CFS. More information on this study, and other muscle research, can be found on the [MEA website](#).

Dr Jonathan Kerr MD PhD

Senior Lecturer in Inflammation and Consultant in Microbiology in the Dept of Cellular Medicine, St George's University of London

Study of SNPs to determine subtype status in CFS patients

Dr Kerr briefly summarised his previously reported work on gene expression (= the way in which genes carry out their key functions at a cellular and tissue level) in ME/CFS and the way in which this has helped to identify 7 different subgroups of ME/CFS with distinct clinical phenotypes (= clinical features).

Due to the difficulties in using a comparative gene expression method as an aid to ME/CFS disease and subgroup diagnosis, Dr Kerr's team have now attempted to achieve this aim using a laboratory method based on what is known as single nucleotide polymorphisms (SNP) alleles.

To try and identify SNP allele associations with ME/CFS and ME/CFS sub-groups, Dr Kerr's group have tested the genomic DNA of 108 ME/CFS patients; 17 people with endogenous depression and 68 healthy blood donors for SNP alleles based within 88 CFS associated human genes.

Conclusion: 21 SNPs were significantly associated with ME/CFS when compared to patients with depression and normal controls. 148 SNP alleles had a significant association with one or more ME/CFS subgroups. The study provides evidence that human SNPs located within ME/CFS associated genes are associated with particular gene expression subtypes of ME/CFS. Further work is required to develop this into a clinically useful aid to subgroup diagnosis in ME/CFS.

Dr Nancy Klimas MD

Professor of Medicine, Psychology, Microbiology and Immunology, University of Miami School of Medicine, USA

Immunological Biomarkers in ME/CFS

Professor Klimas is principal investigator at one of the NIH (National Institute of Health) sponsored CFS research centres where she leads a multidisciplinary team involving immunology, neuroendocrinology, behavioural psychology and exercise physiology. The University of Miami CFS research centre is currently looking at interactions between the immune and neuroendocrine (brain-hormone) systems and autonomic

nervous system function in ME/CFS.

The main theme of her presentation was the search for biomarkers, especially those involving immune system dysfunction - because these markers could obviously play a vital role in helping to more accurately define CFS as well as sub-grouping patients under the ME/CFS umbrella. Identification of specific immunological biomarkers could also be used to monitor symptom severity and define subgroups of ME/CFS patients who could then be used in clinical trials involving specific immunomodulatory drugs aimed at increasing antiviral activity or calming down immune system activation.

Professor Klimas started off by summarising the evidence for both immune system activation (= an overactive immune system response resulting from an infection) and immune system function.

Important markers of immune system activation in ME/CFS include:

- An elevated proportion of CD26 lymphocytes (= a specific type of white blood cell) expressing the activation marker dipeptidyl peptidase IV (DPPIV).
- Polarization of the Th2 (helper type 2) immune response.
- Elevation of pro-inflammatory cytokines (= immune system chemicals) such TNF (tumour necrosis factor) alpha, interleukin 1 and interleukin 6 (a very inflammatory cytokine).
- Important defects in immune system function include natural killer cell (NKC) dysfunction and NKC cytotoxicity (NKCC), CD8 and macrophage abnormalities and antibody production.

Professor Klimas also referred to some new research that has shown that CD26 lymphocyte activation can lead to the production of a substance called neuropeptide Y (NPY), which acts on the adrenaline responses in the sympathetic nervous system. This is a finding that may help to explain some of the symptoms associated with autonomic nervous system dysfunction (= part of the nervous system that controls heart, bladder and bowel function) found in ME/CFS. The observation again opens up the possibility of new forms of treatment.

In relation to NKC dysfunction, Professor Klimas pointed out that this should be considered to be a consistent finding in ME/CFS patients and she believed there was a significant correlation between NKC function and the general state of health/functioning (ie fatigue and cognitive impairment) in ME/CFS patients. However, NKC dysfunction is not unique to ME/CFS - so while NKC dysfunction cannot be used as a diagnostic biomarker, natural killer cell cytotoxicity does appear to be a subgroup marker of disease activity .

Professor Klimas and colleagues working at different academic sites in America and Canada have published a new paper which describes this biomarker work in more detail: Biomarkers in Chronic Fatigue Syndrome: Evaluation of Natural Killer Cell Function and Dipeptidyl Peptidase IV/CD26. An electronic copy of this paper can be accessed via the May news item section of the MEA website or at: <http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0010817>

Professor Brigitte Huber PhD
Professor of Pathology, Tufts University, Boston, USA
Presence of Retrovirus as a Biomarker for ME/CFS

Professor Huber studied immunogenetics at the University of London. She now works in America and has a particular interest in the how cellular and molecular mechanisms are involved in immune system responses.

In relation to ME/CFS, her laboratory has been investigating the role of a human endogenous retrovirus, HERV-K18, as a possible marker or risk factor for people who might develop ME/CFS after an acute viral infection such as Epstein-Barr infection (glandular fever/infectious mononucleosis) or human herpes virus type 6 (HHV-6).

HERV- K18 is a provirus that is inherited into the human genome (in fact around 8% of the human genome is made up of endogenous retrovirus) and transmitted vertically through the germline (= sequence of germ cells containing genetic information). It normally lies dormant within the genome and

cannot produce active retrovirus. When induced it encodes what is called a superantigen (SAg) - a special type of protein that is capable of causing immune system dysregulation.

The researchers at Tufts are pursuing their hypothesis by collecting blood samples from people who develop ME/CFS after an episode of glandular fever. Blood samples are being taken from these patients over a 2 year period in order to check for fluctuations in HERV-K18 expression. The results are being compared to two other patient cohorts - one group with ME/CFS that is not related to glandular fever and another group of healthy controls.

The results so far suggest that the level of HERV-K18 is increased in the CFS patients when compared to healthy controls and that the level fluctuates over the course of time, possibly correlating with disease severity.

XMRV validation study

In a short addition to her presentation Professor Huber presented the results of a study which has attempted to validate the finding of XMRV infection in ME/CFS. This study has involved three independent cohorts of CFS patients - 122 samples from Dr Susan Levine in New York; 105 from Dr Renee Taylor in Chicago; and 11 from the HHV-6 Foundation. Evidence of XMRV infection was assessed using taqman qPCR for XMRV integrase. All of the samples were negative for XMRV integrase. In other words Professor Huber's lab was unable to isolate XMRV in these ME/CFS cohorts.

The important issue of reagent sample contamination, and how this might explain the presence of XMRV in tested samples, was also discussed by Professor Huber.

It should be noted that while this is the fourth study to be published or reported that has failed to validate the original finding of XMRV in people with ME/CFS this is not a replication study. Validation studies are a very important part of the scientific evaluation process and in the case of XMRV they have used what the investigators believe is the most accurate way that their laboratory can find XMRV. The validation studies have also used patient cohorts that only meet research criteria for CFS. An XMRV replication study would have to use the same laboratory methods as used in the Science study and patients who meet both CFS and Canadian Clinical Criteria. There is no information at present as to when we are likely to see publication of results from the first XMRV replication study but it is rumoured that results from the CDC study may be due for release fairly soon.

Annette Whittemore

Founder and President, Whittemore Peterson Institute for Neuroimmune Diseases, Reno, Nevada, USA

Future Pathways of Research into ME/CFS

Unfortunately, Annette Whittemore was not well on the day of the conference and had to return to her hotel before the afternoon session. So she was unable to deliver her presentation.

Dr Judy Mikovits PhD

Whittemore Peterson Institute, Reno, Nevada, USA

Implications of XMRV Research for ME/CFS

Dr Judy Mikovits went through the key stages of the work that had been carried out in relation to the WPI study into XMRV that had detected this new retrovirus virus in 67% of people with Canadian Criteria CFS and 3.7% of healthy controls. The study was published last year and received widespread media publicity:

Lombardi et al, *Science* 2009, 326, 585-589. [Electronic link.](#)

Dr Mikovits went on to look at some of the key issues relating to XMRV infection and the many unanswered questions: What is the prevalence of XMRV in the human population? Is XMRV a direct cause of ME/CFS or prostate cancer? Does it contribute to their development or progression? And how is XMRV transmitted?

Dr Mikovits also reviewed some of the evidence in relation to XMRV in aggressive prostate cancer.

The WPI is currently carrying out a small UK study which involves XMRV testing but no information on any preliminary results was presented.

Because of the potential risk of blood transfusion transmission from this emerging infection, national blood transfusion services in Canada, Australia and New Zealand have taken the precautionary step to defer donors with ME/CFS from donating blood. The Chief Medical Officer in the UK took a similar decision before the appearance of XMRV. No such restriction currently applies to blood donation in the USA.

The MEA website has a detailed summary covering all aspects of XMRV infection, including a link to the Science paper, and information on XMRV testing here in the UK. The MEA website news archive contains summaries and links to all three of the XMRV validation studies that have so far been published.

Plenary Session

The meeting ended with a 45-minute Question, Answer and Discussion session involving all the speakers. Among the topics raised by members of the audience were the effects of pregnancy and warm climates on ME/CFS; whether the immune system dysregulation increases the risk of miscarriage; follow up studies in people with long term illness; insurance cover; the role of autoimmunity; treatment strategies including the use of hydroxycobalamin/vitamin B12, magnesium, Omega-3 fatty acids, and the energy supplement ribose; and obtaining new/experimental drugs here in the UK.

NB: The NICE guideline on ME/CFS states that the following drugs should not be used for the treatment of ME/CFS: monoamine oxidase inhibitors, glucocorticoids (eg hydrocortisone), mineralocorticoids (eg fludrocortisone), dexamphetamine and methylphenidate (central nervous system stimulants), thyroxine and antiviral agents.

Thanks

Besides all those who travelled a great distance to give their presentations, I would like to thank everyone at Invest in ME who was involved with the administration of this conference for the very smooth organisation on the day and the excellent lunch.

Conference DVD

A DVD of the conference is being prepared - priced at £12 (UK), £13 (Europe) and £14 (Outside Europe). The DVD can be obtained from Invest in ME. More information can be found on the IiME website: <http://www.investinme.org> We will also place an announcement on the MEA website when the DVD is ready.

The IiME website also has more information on the conference. Questions relating to the conference can be sent to IiME at: meconference@investinme.org

- **This summary was prepared by Dr Charles Shepherd, Hon Medical Adviser, The ME Association, to whom any comments or corrections should be sent via meconnect@meassociation.org.uk**