



**International Science Symposium on ME/CFS
3-4 December 2010 Bond University, Queensland, Australia**

Programma en achtergrondinformatie:

http://www.bond.edu.au/research/research-at-bond/events/BD3_014159

[Verslag [Rosamund Vallungs/IACFS](#), aanvullingen/hyperlinks etc.:/ FT]

This invitational meeting was a rather unique gathering of 30 internationally recognized neuroscientists and clinicians including those with and without expertise in ME/CFS.

The purpose of the meeting was to share ideas from different scientific and clinical perspectives with the goal of encouraging international collaborations to advance science and practice. The symposium was funded by the Alison Hunter Memorial Foundation.

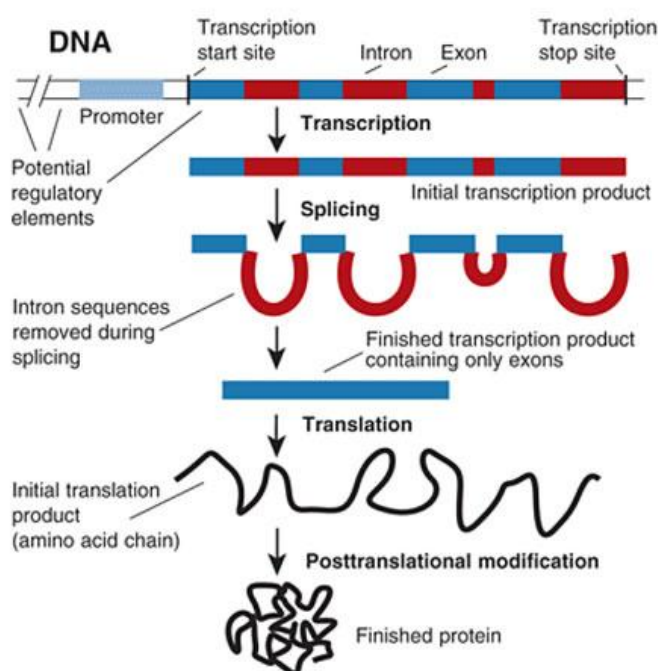
The first paper was by [Nancy Klimas](#) (Miami, Florida, USA), and she presented a systems biology approach to ME/CFS.



dr. Nancy Klimas, foto: www.cfs-aktuell.de

She described CFS as a disorder of homeostatic imbalance. She briefly outlined her 25 year history of involvement with this illness, when initially she worked on the theory of a chronic immune activation syndrome, with an immunological focus. It was next recognised as a neuro-inflammatory disorder, and now genomics have become involved. She listed and described some of her current research work.

One study involved an exercise challenge to induce relapse, looking at the [gene expression](#) and immune changes before, immediately after and 4 hours later. 3 matched groups were studied: Gulf War illness, CFS and controls. The exercise challenge was 8 minutes on an exercycle with measurement of VO2 max.



The gene expression showed significant differences in those with GWI and CFS. (By case definition GWI and CFS meet the same criteria). Immunological pathways were similarly affected these were mainly inflammatory, and the immune cascade led to many symptoms 4 hours later. Symptoms involved the endocrine, immune, autonomic and neurological systems. The genes regulating NK function which included abnormal perforin and granzyme levels were affected.

She then went on to describe Broderick's 3 basic elements of analysis of immune signals, and related this to the states after the 8 minute exercise challenge:

1. Those that looked different
2. Those that hang out with a different crowd
3. Those that behave differently (altered response dynamics)

In this study there was persistent inflammation, a surge in immune interaction and an IL-1 splash effect. There was a huge cascade effect in 8 minutes and persisting 4 hours later. Homeostasis is messed up and needs to remodel.

There is a need to focus on autonomic and immune therapies which do interface with each other. This study confirms that graded exercise is not good for those with CFS, and patients must stop exercise well short of the aerobic threshold. Breaks between exercise need to be twice as long as the duration of the exercise.

[Hugh Perry](#) (Southampton, UK) discussed the adaptive and maladaptive components of what he describes as sickness behaviour. He then focussed on the language of sickness in relation to the way the systems behave during inflammation, for example feeling ill with pain and fever. He described sickness behaviour as an organised strategy which is not bad. An example of sickness behaviour would be an infection which leads to an inflammatory response with release of cytokines, which then communicate with the brain and cause symptoms such as malaise, fever and depression. Systemic inflammation activates selective brain regions, with different challenges activating different regions. This mechanism works through the macrophages in the brain via the blood-brain-barrier. Endothelial cells communicate with the macrophages via the microglia. This is an important part of homeostasis, and is usually transient.

He then went on to talk about chronic neurological disease when microglia increase in number and activation and become primed. Exaggerated sickness behaviour then occurs in those with chronic brain disease, in response to infection. The microglia release cytokines very readily if already primed. A maladaptive pathway develops.



foto: <http://www.wellcomecollection.org/whats-on/events/balloon-debate-ageing/hugh-perry.aspx>

One study involved the follow up of 300 Alzheimer's disease (AD) patients 2 monthly for 6 months. Those who had an infection had a more rapid mental decline, while those who had suffered no infection showed no change. Other behaviours also changed greatly as a result of infection. He described obesity, smoking, age and gray hair as all contributing to earlier AD as all these have inflammatory effects.

He concluded by saying that systemic infections lead to distortion and maladaptation exhibited by sickness behaviour, because of the primed microglia. This in turn leads to accelerated progression of brain disease. He said that a vaccination can be used as a challenge to demonstrate changes. Functional MRI has more use at detecting these changes.



[Mary Ann Fletcher](#) (Miami, Florida) presented her work on biomarkers for CFS. The goal in CFS research has been to find a biomarker or combination of biomarkers. This will enhance the ability to diagnose and demonstrate severity of the illness, define subsets and help to manage trials.

Natural killer (NK) cells were studied initially looking at function and the diminution of perforin and granzyme. 176 CFS patients showed significantly lower function in NK cells compared to controls. She then went on to describe how [neuropeptide-Y](#) (NPY) is involved in the stress reaction with increase in norepinephrine and NPY from the sympathetic nerve endings. In a controlled study, NPY was considerably higher in CFS compared to controls.

Use of receiver operating curve (ROC) analysis was described, and this showed discrimination between CFS patients and controls. Using ROC, NPY was found to be 80% sensitive in CFS, (which is better than the PSA test we use to help diagnose cancer of the prostate). NPY also correlates with markers of disease severity. Other potential biomarkers using this technique included 10 of 16 cytokines measured, NK cell function and dipeptidyl peptidase/[CD26](#) which is indicative of immune activation. This is all part of a complex integrated system.

In the future, exercise challenge will be included in testing this paradigm, and computer analysis will be developed to stimulate research in further clinical trials. These abnormalities may have applications in other diseases.



[Voor artikelen van Mary Ann Fletcher, klik op nevenstaand logo]

[Dominic O'Donovan](#) (Cambridge, UK) a neuropathologist presented the results of autopsy on 4 patients who had a specialist diagnosis of CFS:

- A 32 year old male with a 20 year history of CFS, who died of a suicide overdose of medication. Spinal cord and brain at autopsy showed excess [corpora amylacea](#), which was in excess of normal ageing. There were intermediate filaments closely related to glial cells, and maybe within the glia rather than the axons. No evidence of [ganglionitis](#). (EBV negative)
- A female of 32 with a 5 year history. She had refused any medical help and been bedridden and refused food and water. She finally died of renal failure. The pathology showed a focal chronic inflammatory infiltrate (T8 lymphocytes) in the [dorsal root ganglia](#). (EBV negative).
- A female of 43 an assisted suicide in Switzerland with a barbiturate overdose. The brain showed global [ischaemia](#), but this was likely due to the drugs used. Dorsal root ganglia showed mild excess of lymphocytic nodules of nageotte but with no obvious inflammation, but this could represent a subtle chronic inflammatory state.
- A female of 31 whose death may have been due to opiate ingestion. There was some toxic demyelination with spinal [subarachnoid haemorrhage](#), but she was on warfarin. There was some mild possible chronic ganglionitis.

Differential diagnosis here was discussed and would have included AIDs, [Sjogren's syndrome](#), [varicella zoster](#) and [paraneoplastic disease](#).

These results have raised the possibility that some cases of CFS may have sensory or autonomic ganglionitis. A specific brain and tissue bank in the UK is proposed.

[Olga Sukocheva](#) (Adelaide, Australia) presented the immunohistochemical and microbiological post mortem findings in a 20 year old patient with fatal idiopathic encephalopathy. This patient had been diagnosed with CFS following a severe encephalitic like illness aged 10. There was evidence of inflammatory damage with suppression of microglial cells. Down regulation of ankyrin B was detected in the white matter of the [hippocampus](#). There was no significant difference in ankyrin G. Tests for [Coxiella burnetii](#) and Legionella were instituted. C. burnetii antigens were present in [astrocytes](#), and in the [microglial cells](#) in the grey matter of the hippocampus. C. burnetii antigen was also found in spleen and liver macrophages, lymphoid tissue, bone marrow, lung and heart tissues. [Legionella](#) antigen was not found.



foto: Invest in ME

[Dan Peterson](#) (Nevada, USA) started his talk with a brief overview of the incidence and effects of CFS in the USA. He then went on to describe research problems, such as the varied definition, heterogeneity of patients, lack of biomarkers, patient self-selection, researcher bias and lack of funding. He described a number of scientific journeys undertaken in CFS research. He stressed the importance of bringing together the patient, biotechnology, database informatics, genomics and clinical medical guidelines. Diseases can now be defined from a molecular perspective. Networking and collaboration are keys to successful research. There needs to be large-scale clinical data gathering, with international biospecimen collection. He then went on to discuss the importance of looking at viral infections in CFS. Leukotropic herpes viruses particularly [HHV6](#), [HCMV](#) and [EBV](#) are among a number of major candidates in CFS. He reported on large studies in which active HHV6 was detected in 28%, HCMV in 29% and EBV in 51%. 10% were co-infected. Active EBV infection significantly correlates with the presence of auto-antibodies, with antibodies directed at [thyroid peroxidase](#) and parietal cells. Up to 30% of patients may respond to antiviral medication.

Ekua Brenu (Queensland, Australia) had looked at innate and adaptive immunity in CFS. It was postulated that her study could assist in developing biomarkers. The study involved 253 patients and 100 controls. Studies were undertaken at zero and 6 months. Cytotoxic activity of [NK cells](#) and [CD8+T cells](#) was significantly reduced. [Perforin](#) and [granzyme](#) activity was reduced. When looking at NK cell phenotypes, CD56 bright cells were significantly diminished. Cytokine secretion from [CD4+T cells](#) showed significant elevation of [IL-10](#), [IFN- \$\gamma\$](#) and [TNF- \$\alpha\$](#) . FOXP3 expression was also heightened in the CFS group. Vaso-active intestinal peptide (VIP) receptors were also investigated and found to be significantly elevated.

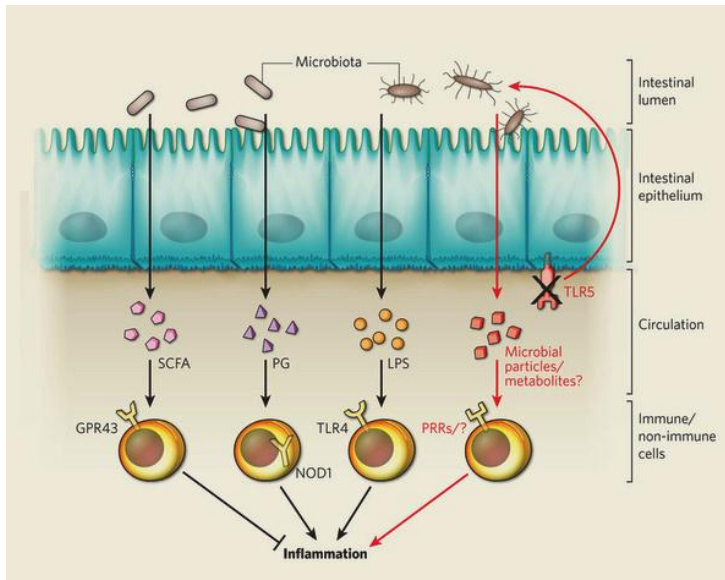
[Voor de theorie/biomarkers van Brenu en kollega's: [klik hier](#) en [hier](#)]



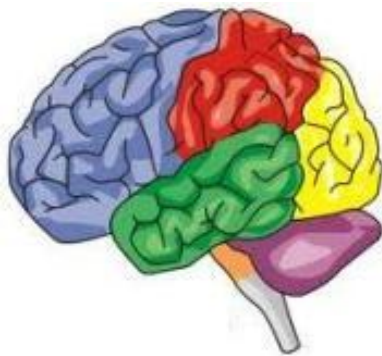
Prof. De Meirleir, foto: Een Vandaag 29 mei 2010

Kenny de Meirlier (Brussels, Belgium): Because chronic activation of the immune system is present in progressive HIV and is a better predictor of disease outcome than viral load, it is important to test the hypothesis that a similar pattern may be observed in XMRV positive CFS patients. 16 XMRV positive patients (using culture assay) had a large number of tests performed. These patients were found to have reduced lymphocyte numbers and CD-57+lymphocytes reduced, as observed in HIV. There was evidence of an activated innate immune system (increased elastase activity and C4a). sCD14 was significantly higher than expected, and this correlated with plasma [lipo-polysaccharide](#) (LPS) a proinflammatory component of the gram-negative bacterial envelope. Low stool IgA indicated dysfunctional mucosa-associated lymphal tissue in XMRV positive patients. Serum IL-8, IL-10, MCP-1 and MIP-1 β are increased and might constitute a biological signature for viral infection.

This all provides supportive evidence for microbial translocation being part of the pathology of XMRV +ve patients. He described a Norwegian study of severely disabled CFS patients in which the plasma LPS was elevated in those with a low [Karnofsky score](#). This suggests a leaky gut syndrome. Stool analysis in CFS patients has indicated overgrowth of enterococci, streptococci and fungi with diminished E.Coli count. This can lead to overproduction of [hydrogen sulphide](#) which is toxic to mitochondria and affects ATP.



Richard Kwiatek (Adelaide, Australia) is a rheumatologist with a particular interest in neuro-imaging.



[MRI](#) was performed to look for brainstem dysfunction in CFS. Whole-brain optimised voxel-based volumetry and novel quantification of T1-weighted and T-2 weighted signal levels in structural MRI were used. Voxels build a 3-D map of the brain. In the CFS patients seated pulse pressure was reduced, and seated heart rate and asleep heart rate were increased, compared to controls. This was then correlated with brain change, other symptoms and fatigue. [Prefrontal white matter](#) volume reduced with increasing sleeping heart rate in CFS with the opposite in controls. Midbrain white matter volume reduced with increasing fatigue. There was a strong correlation between total brainstem grey matter volume and seated pulse pressure in the CFS patients. Brainstem grey matter changes suggest a failure of cerebrovascular auto-regulation, potentially mediated by astrocytes. Astrocyte dysfunction may therefore be central to CFS pathogenesis. There seems to be disrupted autonomic nervous system homeostasis. He does not feel it is reduced blood volume that will be causing this.



Barrie Marmion (Adelaide, Australia) has [studied Q-fever](#) and its aftermath for many years. There were 11 suffering from post Q-fever fatigue syndrome out of 39 who had had the acute illness in one study cited. The *C. burnetii* antigen persists, and causes immune modulation with gene expression and symptoms. Usually it is continuous from the initial onset, but episodic relapses may occur due to re-infection or inadvertent Q-fever vaccination. IL-6 is elevated and IL-2 is down. The symptoms fit the criteria for a diagnosis of CFS. 3 Q-fever groups were studied and there were differences in the frequency of carriage of [HLA-DR B1*11](#) and of [IFN- \$\gamma\$](#) 35% were positive in the post-Q-fever syndrome group, and the levels were low in the controls and Q-fever recovered group and the Q-fever endocarditis group.. These differences support the concept of different immune states in chronic Q fever, determined by genetic variations in host immune responses, rather than by the properties of *C. burnetii*.

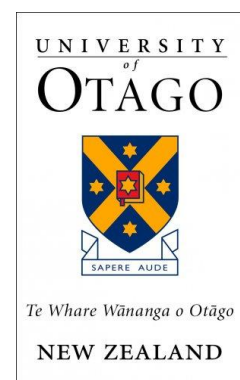
[Anne Boullerne](#) (Illinois, USA) discussed the issue of chronic fatigue in relation to CFS and MS.



Bron: University of Illinois at Chicago

She described MS as a characteristic auto-immune disorder. She outlined the differences in incidence, symptoms, duration of illness etc. She emphasised that while MS is a neuro-immune disease, CFS is an acquired severe complex system dysfunction. In MS there is oligoclonal IgG in the [CSF](#) in 95% of cases, and brain lesions with T and B cells are seen on MRI.

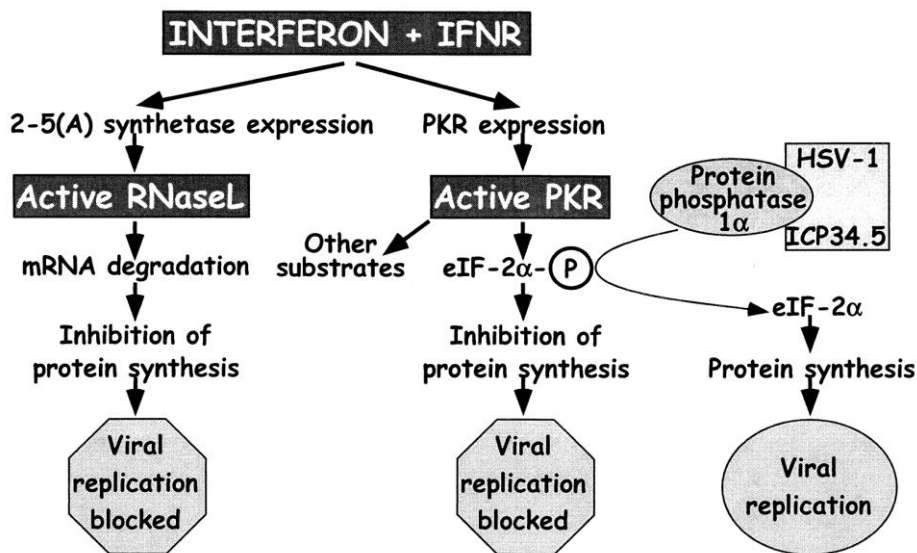
She asks the question Is [gliosis](#) present in CFS? In CFS MRI abnormalities maybe found such as small punctate subcortical white matter intensities in the frontal lobes, small ventricular volume, slow blood flow and some atrophy. She had looked at functional MRI in relation to control imagery and visual imagery. Both were found to be slower in CFS compared to controls. Changes associated with finger tapping and auditory monitoring correlated with subjective fatigue and brain response during challenge involving memory. Using [M.R. Spectroscopy](#), there was an increase in [choline](#) in the [basal ganglia](#), no significant difference in glutathione, and ventricular lactate was elevated. There was no alteration in levels of GABA and glutamate. In a rat model for Gulf War Syndrome, using pyridostigmine, there was no gliosis and no increased permeability of the blood brain barrier. A possible auto-immunity including vasoactive neuropeptides is hypothesised.



Warren Tate, bron: <http://www.stuff.co.nz/national/4332107/Rutherford-winner-left-no-stone-untuned>

Warren Tate (Dunedin, NZ) and his team have just initiated a study to develop tools that can accurately detect molecular changes within cells in response to double-stranded RNA (dsRNA) relevant to CFS. He explained how recent XMRV findings had stimulated research and a need for a bank of genetic material. Biomarkers need to be established as well as less specific markers to reflect changes in global homeostasis. There needs to be targeting of a vulnerable point in the biology of XMRV viral RNA that determines the ratio of its structural and enzyme proteins. He went on to describe types of biomarkers: Specific such as in a cell undergoing apoptosis: RNaseL, PKR, phosphorylation of PKR etc Specific biomarkers of disturbed homeostasis General biomarkers marking global disturbed homeostasis of various organs

He explained the RNaseL activation pathway. RNaseL cleavage may be specific to CFS. He is currently studying the ratio of the RNaseL terminal fragment to uncleaved protein. He will also be looking at abnormal PKR activation. This is cleaved by caspase to form the 37D fragment. This undergoes phosphorylation which can be measured the protein-synthesis factor e1F2. These 2 phosphorylation events will be detected by specific antibodies against the phosphopeptides of the 2 proteins.



Bron: <http://www.pnas.org/content/97/11/6097/F1.large.jpg>

Douglas Feinstein (Chicago, Illinois, USA) presented study of noradrenergic treatments for neuro-degenerative diseases.

nor-ad-ren-er-gic (nôr'ăd-rə-nûr'jĭk)
adj.
 Stimulated by or releasing [norepinephrine](#)

[Glial cells](#) are activated producing neurotoxins, which induce neuronal damage and leukocyte infiltration into the CNS. Noradrenaline regulates glial inflammatory responses, exerts neuroprotective effects and helps maintain the integrity of the [blood brain barrier](#) (BBB). Dysregulation of noradrenaline signalling could exacerbate disease. The supposed reductions of noradrenaline increase inflammatory responses, the amyloid burden and neurotropic factors. [Noradrenaline](#) is mainly produced in the locus coeruleus (LC). This part of the brain is damaged in Alzheimer's and Parkinsonism. LC loss correlates with plaque and tangle numbers. The question was asked does increasing noradrenaline in the [CNS](#) improve things? The drug Droxidopa is a precursor of noradrenaline. This drug is in phase 3 trials for neurogenic orthostatic hypotension. In mice the drug leads to improvement in plaques and learning. This drug used in MS and experimental auto-immune encephalomyelitis (EAE) showed stabilisation compared to controls. This trial indicates that the LC is significantly damaged in MS and EAE. Noradrenaline directed therapies need to be considered if there is perhaps also LC disturbance in CFS.



[Voor artikelen van Douglas Feinstein, klik op nevenstaand logo]

[Interview met dr. Feinstein:

<http://www.chicagoflame.com/2.9140/an-interview-with-dr-douglas-feinstein-recipient-of-the-research-career-scientist-award-1.1294572>]



[Doina Ganea](#) (Philadelphia, USA) spoke about [Vasoactive Intestinal Peptide](#) (VIP) an endogenous and exogenous immunomodulator. VIP downregulates the innate immune response by inhibiting the release of pro-inflammatory cytokines, chemokines and nitric oxide by activated macrophages, microglia and dendritic cells. It also affects the adaptive immune response by reducing the co-stimulatory capacity of antigen-presenting cells, and by inducing Th2 type responses. She had looked at several diseases, such as collagen-induced arthritis and autoimmune encephalomyelitis. She had used dendritic cells generated in the presence of VIP/PACAP as immunomodulatory agents, with positive results.



[Monica Carson](#) (California, USA) had studied the CNS expression of the classic chemokine CCL21. This is a predisposing factor for auto-immunity due to the proliferation induced pre-activation. It thus contributes to chronic inflammatory disease and auto-immunity. Experimental work was done using mice. Resulting data indicated that [CCL21 expression within the CNS has the potential to contribute to T-cell mediated CNS pathology](#). This could occur via homeostatic priming of CD4+T cell lymphocytes outside the CNS, and CD4+T cell migration into parenchymal site after infection with organisms such as toxoplasma.

Donald Staines (Gold Coast, Australia) rounded off the formal papers with a presentation looking at novel treatments in CFS. He considered whether [auto-immunity affecting vaso-active neuropeptides suggest a pathomechanism.](#)

ME/CFS may be associated with auto-immunity affecting the function of vaso-active neuropeptides, such as VIP and PACAP (pituitary adenylate cyclase activating peptide). Upsets in adenylate cyclase (AC) signalling and cAMP functioning possibly involving ATP toxicity may be a feature of VN auto-immunity. Purinergic receptors such as ATP negatively regulate AC. He outlined some basic biochemical principles to clarify things; AC amplifies incoming intracellular signals; PACAP is an acetylcholine cotransmitter; AC is involved in long term potentiation and enhanced maintenance of neuronal activity. VIP/PACAP synergism is involved with potentiation of cardiac firing, anti-apoptosis function, cAMP and insulin control, hypoxia regulation and glutamate metabolism. Purinergic signalling is involved in centrally mediated pain (neuropathic pain). He then went on to describe some likely treatment possibilities based on these principles. These included purinergic signalling modulators, VIP/PACAP mimics/analogues, phosphodiesterase inhibitors: eg Rolipram (toxic), Ibudilast, Roflumilast; B cell depletors (Rituximab); chondroitinase; VIP liposomes and lentivirus agents. Some of these could be considered for clinical trials.



[Voor artikelen van Douglas Feinstein, klik op nevenstaand logo]

Interviews met Donald Staines:

<http://www.mygc.com.au/article/news/local-newsroom/10225-bond-looking-to-crack-cfs.php> en <http://blogs.abc.net.au/files/dr-don-staines-online-1.mp3>]

DAY 2 was involved in general discussion with various panels looking at clinical matters, case definition, guidelines and research collaboration. Possible name change was also discussed. There was plenty of open discussion, and being a small group meant an interactive forum with everyone participating.

Some of the salient points:

Name change:

Most people acknowledged that patients do not find the name CFS describes the severity of the illness tends to trivialise it. It was agreed that the name ME was more appropriate in many ways, although still not entirely accurate for this illness. There was some discussion as to whether gut symptoms and possible auto-immune activity could be incorporated.

Case Definition:

The [Fukuda definition](#) is still useful for research and one must bear in mind that many previous studies have used this definition so it should not be entirely abandoned, although all agreed that the [Canadian consensus definition](#) is more suitable for clinical diagnosis, and should generally be adopted. It is hoped that this definition will be adopted internationally and renamed accordingly. All agreed that the CDC empirical definition should not be used. The issue brought up earlier at this symposium of sickness behaviour as terminology was thought to be a backward step, and would be unpopular with patients, although Hugh Perry explained his reasoning very clearly.



Diagnosis:

The importance of biomarkers was reiterated. These need to be user friendly and readily available. There should be opportunity to sub-group according to type of onset, symptoms and gene expression. Clinicians new to this illness need to be aware of the range of long-term diagnoses that may emerge in those with CFS, so that regular ongoing surveillance is important. Uniform assessment tools should be encouraged, although it is acknowledged that not all types of testing will be available everywhere.

Management/guidelines:

Guidelines need to be unified, and there should be collaboration among those working on guidelines. Nancy Klimas stressed that financial assistance should be available for a face to face meeting among experts to work on this. There was some discussion about the importance of off-label prescribing, as many clinicians feel uncomfortable if they do not stick to evidence based medicine. A recommendation should go out in support of being able to use medication in this illness, where there is some useful research backup, even if not formally trialled, so that practitioners do not need to fear litigation. A longitudinal n of one trial of a treatment approach on one patient should be deemed useful, and clinicians should be encouraged to do this and write up their results.

Clinical overview:

5 clinicians presented their views on management, and there was much discussion contributed from those on the floor also.

[Mieke van Driel](#) (Queensland, Australia) presented an overview of drugs used in CFS. Few trials have been done, and those that have showed little benefit. She recommended that we should let patients guide the research agenda by teaching us what works for them.

[Don Lewis](#) (Melbourne, Australia) discussed the importance of food intolerances, and emphasised that although gut symptoms maybe prominent, they may not always occur. A strong family history of intolerances is relevant. He firmly believes that intestinal dysbiosis occurs in almost all his patients and the hydrogen sulphide test was positive in 85% of patients. IgG antibodies were found to many different foods. He now proposes formal laboratory based clinical trials.

Bill Cassimatis (Queensland, Australia) has a number of CFS patients in his general practice and he outlined his general approach. He mentioned that a number of women with this illness seemed to be worse cyclically, confirming that in some women, hormones are involved.

This was discussed further by [Rosamund Vallings](#) (Auckland, NZ) who uses oestrogen and progesterone often in women with CFS with cyclical or post menopausal symptoms. Nicole Phillips (Melbourne, Australia) who is a psychiatrist pointed out that some women can become depressed on Depo-Provera.

Norman Hohl (Southport, Australia) Is relatively new to dealing with this illness, but as a travel medicine consultant and qualifications in infectious diseases, he has a strong interest in preventative strategies.

Research directions:

All agreed that this symposium will lead to collaboration internationally. International concurrent trials are needed, and more funding is essential. Larger worldwide studies are likely to increase funding availability. Collection of observational data can be of value. The idea of establishing a CFS registry was considered a valuable approach although this could be often difficult and time consuming for medical practitioners. Using internet self-report will not necessarily generate patients fitting diagnostic criteria. Diagnosis needs to be made with face to face encounter by physicians familiar with the illness. More medical education is thus a very important issue to be addressed.

Immediate plan:

A formal press statement was produced for distribution after the symposium outlining the salient points raised. A list of future directions was also formulated. Some further e-mail discussion and collaboration between the scientists and clinicians is envisaged, and this was a very positive outcome from this symposium. Many of these people were new to CFS and had never met before, and it seems a whole new set of directions for future research will ensue. Those who had presented papers were encouraged to make the full paper available for the website which will be set up and meanwhile the abstracts will be available.

Christine Hunter and her AHMF team were formally thanked, together with the team from Bond University. Without all the dedication and hard work by all of these people, this symposium would never have been possible, and everyone agreed it was an enormous success. The event had been ably chaired by Prof Ken Donald and Prof Mel Miller. I would like to thank the [Alison Hunter Memorial Foundation](#) and [ANZMES](#) for enabling me to attend.



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