12th IACFSME CONFERENCE

OCTOBER 27-30, 2016 - Fort Lauderdale, USA

The conference, opened by the president **Fred Friedberg** (NY, USA), was a day for patients, while the medical and research professionals could attend a series of workshops.

The keynote speaker for the opening address at the patient conference was given by **Vicky Whittemore** from the NIH, where she heads the National Institute of Neurological Disorders and Stroke, (USA). She explained how the NIH is set up with 27 institutes and centres. She has been there for 5 years, and is a programme director in the extramural division.

A current study is recruiting 40 ME/CFS patients who are within 5 years of diagnosis. There will be an extensive analysis with bio-specimen collection. (www.mecfs.ctss.nih.gov/). There will be seminars for education of staff. The whole programme was revitalised in October 2015. They are developing goals involving: collaboration, research, awards, fostering international collaboration etc.

If applying for funding, there would be a request for information – short term, intermediate term and long-term. (www.nih.gov/mecfs). There is a power point presentation on the NIH website. The top 14% of applicants get accepted and then the next 14-24% are good quality applications, but are usually turned down.

The following day the main conference was again opened by **Fred Friedberg**, the theme being**:**

Emerging Science and Clinical care.

The Plenary Session was given by **Øystein Fluge** (Bergen, Norway), on B-lymphocyte depletion and disease mechanisms in ME/CFS. He described how the drug rituximab was a safe way to target B-cells, leading to B-cell depletion. Their first study involved 30 patients (15 CFS and 15 controls), and after 6-10 months a positive response was evident in 67% of those on rituximab. 2/15 of the controls had a positive outcome. No adverse effects were reported. To get a sustained response, ongoing infusions were needed (500mg/m2).

In a further study, 18/29 had a clinical response, while 11/29 had no benefit. Of the 18 positive responders, 11 were in remission at 3 years and 5 were in remission at 5 years. Maintenance gives a prolonged response. Response takes time (8-66 weeks). 2 patients had allergic reactions and 2 had late onset neutropenia. 8/28 had a temporary worsening of their ME/CFS symptoms. 1/28 had a sustained worsening.

They do not support treatment outside clinical trials at this stage, until more evidence is available. They are now doing a multicentre trial on 152 patients. 2 infusions are given 2 weeks apart, followed by maintenance infusions at 3, 6, 9, and 12 months. Symptoms are scored every 2nd week. The SF36 is administered 3 monthly. “Sensewear” armbands are used for 7 day spells.

In discussion he posed the question that an auto-immune basis could be suggested for overlapping syndromes such as POTS, CRPS etc. He questioned whether ME/CFS symptoms are caused by energetic effects such as endothelial dysfunction. i.e. Is there inadequate auto-regulation of blood flow? The anaerobic threshold is reached at low workload in these patients. Cause of fatigue may be depletion of intracellular energy metabolism, increased lactate production, insufficient supply of oxygen.

The team are doing: autoantibody screen, peptide array, immune-phenotyping, cytokine analysis, immune-genetic analyses, exome sequencing and metabolic profiling. There is also a focus on amino acid metabolism as shown in previous studies, and abnormalities were discussed. They are working with the hypothesis that there is a defect in

central energy metabolism leading to changes in the serum amino acid profile. A particular abnormality found in some women was impairment in the pyruvate dehydrogenase (PDH) complex. This was not seen in men. But there was increased 3-methylhistadine likely due to increased endogenous protein catabolism. They are also looking at gene expression in PBMCs – the hypothesis being that there may be obstruction in the central energetic pathway, at the PDH complex level.

Session 1: The latest research in immunology and the microbiome.

Jose Montoya (Stanford, USA) showed that exercise testing highlighted the differences in cytokine profile and network between patients with ME/CFS and healthy sedentary controls. Exercise was shown to highlight abnormal cytokines and growth factor profiles in CFS, compared to resting values. The most discriminatory cytokines at 24 hours post-exercise included interleukin 1β, platelet activator inhibitor, CD40 ligand, MIP1α and INFγ. 24 hours post-exercise was found to be the best discrimination between ME/CFS and controls.

Kenny de Meirlier (Brussels, Belgium) found a panel of biomarkers which accurately identifies CFS/ME patients, contributing to the understanding of this disease. High sensitivity and specificity was noted. A panel of 4 parameters were measured: Il-8, CD14, prostaglandin E2 and absolute CD3/CD57+lymphocytes. Each of these markers relates to the disorder. It is probable that lipopolysaccharide likely from gut bacteria, plays an important role in pathophysiology of ME/CFS. This all represents a step towards identifying biomarkers.

Jose Montoya (Stanford, USA) gave a further presentation profiling circulating cytokines associated with disease severity. 17 cytokines correlated with severity, of which 13 were pro-inflammatory, likely substantiating symptoms experienced by patients.

Ludovic Giloteaux (NY, USA) discussed alterations in the enteric bacterial and viral microbiome. He related his presentation to the many gastrointestinal symptoms experienced by patients with ME/CFS. He concluded that results of the study indicate dysbiosis of the gut microbiota. This suggests an increased incidence of microbial translocation, which may play a role in inflammatory symptoms. His group hypothesise that changes in the virome may contribute to intestinal inflammation and bacterial dysbiosis. There was less richness of bacteria in patients than controls – there were more beneficial bacteria in the controls. Looking at this, 83% of patients could be correctly classified.

Session 2: Treatment Studies and Clinical Practice

Olav Mella (Bergen, Norway) gave an overview of reflections on the rituximab studies. Efforts are directed at understanding the disease mechanisms and attempting to find a drug treatment. They feel it is an advantage to be able to correlate laboratory findings with clinical manifestations and response to interventional treatment. It is probable that symptoms will have a molecular counterpart, as well as patients having a genetic susceptibility. Results of immune manipulation with the drugs rituximab and cyclophosphamide make an immunological malfunction plausible.

They are now in a phase 3 trial using rituximab, and results will be available in October 2017. He warned that we must not take results for granted. He asked the question “Is the immune system the common factor?” in patients being studied. There is NOT an immune deficiency. Allergies do change, and it is likely there is hyper-immunity. Not all immune therapies work.

The drug cyclophosphamide is an old drug used for immune suppression. It is being used in breast cancer for high dose chemotherapy with stem cell transplantation. In low doses it can enhance immune response in advanced cancers. There is now an ongoing Phase 2 trial for patients with ME/CFS. One infusion is given every 4 weeks, six times. The endpoints are as in the rituximab trials. There is then to be a 12 month observation period, looking at toxicity, symptom level etc. Already symptoms are seen to be improving. In the short term, toxicity is worse than in the cancer patients. 1-2 weeks after infusion, ME/CFS symptoms are worse. This is a broader acting drug than rituximab. Patients are all very similar in responses, with multiple body symptoms. It is likely that there is an inhibition of energy metabolism. A biproduct is lactate and its consequences. This blocks production of energy. New ATP is not produced. There is also flow-mediated dilatation of blood vessels, and a lack of NO is seen. The immune dysfunction may cause a mitochondrial defect.

He noted that the reaction to rituximab gives relief of all symptoms, indicating mitochondrial involvement.

Lucinda Bateman (Salt Lake City,USA) reported on the Synergy Trial for CFS – The phase 2 study uses low-dose methylphenindate plus mitochondrial support. (A previous trial reported by Blockmans had been positive). In the phase 1 trial there was 20% improvement in 32% of patients. In the Phase 2 trial there was a strong placebo response noted, and although symptoms were decreased in the majority of ME/CFS patients, statistical significance was not achieved. 2 subgroups had the greatest response: the severe group and those with both fatigue and pain. There were no obvious ill effects. There was a long list of nutrients in the support formula.

D.C. Shungu (New York, USA) used N-acetyl-cysteine (NAC) to alleviate cortical glutathione (GSH) deficit with a view to improving symptoms in ME/CFS. Previous studies had shown 36% deficit in occipital cortex glutathione – the primary tissue anti-oxidant. The latest study reported provided evidence that NAC crosses the blood-brain barrier to spur the in situ synthesis and elevation of cortical GSH. Symptoms were ameliorated. Further studies will be needed to look at clinical efficacy, dosage and treatment duration of NAC.

Madison Sunnquist (Chicago, USA) presented a re-examination of the CBT theory of CFS. Her study concluded that those with ME/CFS do not reduce activity level due to illness beliefs. Exercise-based interventions also lack empirical justification and may not be appropriate.

David Patrick (Vancouver, Canada) discussed the potential for immunosignature assay to aid in classification and prediction of rituximab response in ME/CFS. 200 peptides were selected. 77.8% of blinded samples were correctly identified. Looking at the Norwegian rituximab trials, 200 peptides differentiated treatment responders from non-responders 92% of the time. This could help towards identifying patients likely to respond to treatment using B-cell depletion.

Session 3 – Gulf War Illness

Nancy Klimas (Miami FL, USA) gave an excellent overview of the problems associated with Gulf War Illness (GWI) which first came to light following the war in 1990.The unexplained illness with multiple symptoms has many similarities and some differences when compared to ME/CFS.

This was a short war, but there was tremendous exposure to a number of issues: sand, heat, bugs, pesticides, oil fires, the wearing of chemical protection suits, pyridostigmine, sarin gas etc. Pesticide exposure was highly likely, and neurotoxins were predominant. One third of returning veterans were ill, and many remained ill. There are complex scientific and clinical challenges, with similar controversies to ME/CFS. There are many overlaps. The prognosis is not well defined and the illness can last years. There is more post-exertional malaise in ME/CFS, but a lot can be learnt from GWI.

There are now many ongoing clinical trials, examples being coenzyme Q10, low dose naltrexone, acupuncture etc.

Kirsty Sullivan (Boston, USA) discussed brain-immune interactions in GWI, with reference to cytokines and cognition. She explained how cytokines release pain modulatory substances. 14% of participants were female. Fatigue, pain and cognition were compared to evaluations of 16 cytokines. There were significant plasma cytokine biomarker differences correlating with reduced performance on tasks of information processing and sustained attention.

Lubov Nathanson (Florida, USA) and his team had used a genomic approach to find the mechanisms of GWI pathobiology. They found an increased abundance of hypomethylated promoters of genes participating in signal transduction in the cells of those with GWI. There was enrichment in hypermethylated promoters of genes involved in apoptosis and cell differentiation. It is probable that DNA methylation is one of the factors regulating gene expression in GWI.

Travis Craddock (Florida, USA) has been using gene expression signatures to identify novel treatment strategies in GWI. There was correlation of gene expression patterns in 18 illnesses overlapping considerably with GWI. These were mainly brain, muscular and auto-immune disorders. Of the associated drugs, immunosuppressants currently used in rheumatoid arthritis, and hormone based therapies were identified as the best available candidates for treating GWI symptoms.

Session 4: Diagnosing ME/CFS difficult clinical cases

This session was chaired by **Nancy Klimas** (Florida, USA), and involved a panel of expert ME/CFS clinicians. Each participant presented a case for the panel to discuss. There was also considerable audience participation. The cases were many and varied, and the most frequently reported symptoms related to post-exertional malaise (PEM) and orthostatic intolerance (OI).

Session 5: CFS, SEID, ME case definitions: Clinical versus research

This session was presented by **Leonard Jason** (Chicago, USA), with discussion by **Lucinda Bateman** (Salt Lake City, USA) and **John Kaiser** (San Francisco, USA).Fatigue is evident in 15-25% of the population at any one time, prolonged fatigue occurs in about 8% and chronic fatigue in 4-5%. This 4-5% is embraced by the Oxford criteria. The Fukuda criteria have much variability and not all the core symptoms are included. The Empiric criteria (2005) include psychiatric patients – eg depression fits these criteria. 2.2% of the population at any one time have a depressive disorder. The Canadian criteria require the inclusion of core symptoms, and are more accurate. The International criteria include the core symptoms of PEM, cognitive problems and non-refreshing sleep. The IOM criteria include SEID, but exclusionary illnesses are required for completeness.

For naming the illness, M.E. (Myalgic Encephalomyelitis) is the term most preferred by patients. Many people still refer to the illness as CFS (Chronic Fatigue Syndrome). The acronym ME/CFS is used widely internationally now.

Lucinda Bateman feels there is a critical lack of firm diagnosis, with a lot of overlap into co-morbid conditions. The purpose of the IOM meeting was to improve diagnosis, with emphasis on objectively measureable features. The core criteria are listed. Other co-morbid illnesses may be present, and must be diagnosed and treated.

John Kaiser would like to see big pharmaceutical companies involved. The lack of consistent name, cause and criteria means a lack of interest from these organisations. The Fukuda criteria are not specific enough (and often include depressive patients). The Canadian criteria seem too complex and are not taken up by clinicians – there is a need to involve GPs. The IOM criteria are more specific and accurate because of inclusion of PEM. He felt CFS as the name of the illness is not appropriate and ME/CFS is now more commonly used.

Co-morbid illnesses tend to muddy the research – they are allowed in clinical practice, but not in research. Ideally the same criteria should be used clinically and in research. An ICD-10 code is needed.

Session 6: Symptom Provocation Studies 1

J.Mark Van Ness and his team (Stockton CA, USA) showed how cardiopulmonary exercise testing demonstrates post-exertional chronotropic incompetence. This is the inability of the heart to increase its rate commensurate with increased functional demands. He concluded that those with ME/CFS appear to display post-exertional reductions in the peak HR response to exercise. This could contribute to exercise intolerance observed reductions in oxygen consumption during PEM. The combination of elevation in resting heart rate and reduction in peak exercise heart rate may contribute to the impaired quality of life. For the test they used the fittest of the patients, so admit the results may not be entirely accurate.

Lily Chu (California, USA) explained how the symptoms of PEM are sometimes delayed and often prolonged. Of 150 subjects studied, 129 (89%) experienced PEM with both physical/cognitive exertion and emotional distress. Fatigue was the most commonly exacerbated symptom, but subjects also experienced many of the characteristic symptoms of ME/CFS. 11% reported a post-trigger delay of at least 24 hours, and 23% endured PEM for 3 or more days. It is important that in the future, researchers need to enquire about the wide range of symptoms experienced associated with PEM, and capture the various time courses of PEM.

Sarah Knight (Melbourne, Australia) had looked at cognitive function in adolescents with ME/CFS. She found that adolescents with ME/CFS are slower to process information, and have less capacity to sustain attention before and following cognitive exertion. Clinicians and schools need to be aware of these difficulties. Schools need to support these young people appropriately in the school environment.

Session 7: Public Health.

Leonard Jason (Chicago, USA) in estimating the rates of paediatric ME/CFS in a community based sample said that children were under-diagnosed or mis-diagnosed. Deciding which case definition to use to estimate prevalence data is imperative. Exclusion of other illnesses will be more restrictive, while the IOM criteria are more general and encompassing clinically.

Peter Rowe (Baltimore, USA) discussed a 2 year follow-up on impaired range of motion (ROM) in adolescent ME/CFS. He found that those with impaired ROM noticed significant improvement in ROM scores over 2 years in association with multi-modal therapy. This was also associated with some functional outcomes. The independent contributions of specific forms of physical therapy v general increases in activity to improvement in ROM scores, warrant further study.

Susan Levine (New York, USA) presented work on allergic disorder phenotypes and patterns of medical co-morbidity and clinical dysfunction. Their object was to determine whether certain allergic disorders are more common in ME/CFS. They

found that a history of sinusitis and hives is predictive of a ME/CFS diagnosis, and appears to define a novel phenotypic subset, with distinct patterns of co-morbidity and exaggerated pain symptoms. Further studies will look at whether there is a Th2 shift and secretion of mast cells which may alter pain pathways. Mast cell associated disorders may include: migraine, CRPS, FM etc. Those with ME/CFS coupled with sinusitis/hives may be a distinct subgroup, with unique patterns of co-morbidity. This could help predict possible therapeutic responses.

Gordon Broderick (Alberta, Canada) explored the role of sex hormones in driving symptom severity. Women are more often affected with this illness, often with disruption in menstrual cycles and immune function. Results of their study indicate that, particularly the effects of testosterone and oestradiol on fatigue severity in ME/CFS, vary according to progesterone levels, when controlling the menstrual cycle and menopause.

K.Sagherian (Baltimore, USA) reported on fatigue in nurses and absence from the workplace. This is particularly relevant in shift workers. Insomnia (27.5%) and sleep apnoea (17.5%) were found to be associated with fatigue, and were often associated with ongoing chronic fatigue, leading to work absence. Nursing management needs to monitor for fatigue, including screening of nurses for sleep apnoea.

Raymond Perrin (Manchester, UK) – discussed the accuracy of a physical screening tool for ME/CFS, using his osteopathic background. 5 specific physical signs were used. The most accurate signs used to achieve a ME/CFS diagnosis were thoracic spine dysfunction, coeliac plexus tenderness and chest tenderness. These signs can be an effective aid to diagnosis.

Katherine Rowe (Melbourne, Australia) discussed the demographics of young people diagnosed with ME/CFS in Victoria, Australia. M:F ratio was 1:3, and mean age of onset was 14.6 years. The rural/urban mix was proportionate to the population, but the ethnic mix was not representative of the population of the state or of the hospital clientale. 80% had an Anglo/Celtic background (approx. 25% of the population), predominantly of Scottish/Irish descent. Another 11% had a N European background. No Middle Eastern or African patients were seen. 3 of 5 of Asian descent had a Caucasian parent.

90% reported a defined onset following infection, (commonly EBV), and gradual onset was more commonly associated with OI and hyperextensible joints. There was occasional association with endocrine disorders, overtraining in athletes or after neurological insult. Depression and anxiety was reported at only marginally higher rate than in the adolescent population.

Session 8: Research on Autonomic Functioning and Co-morbidities

Madison Keefe (Washington DC, USA) – her study was to determine if those with ME/CFS developed postural tachycardia after exercise, and to look at the contributions of heart rate variability, sympathetic and parasympathetic dysfunction. 2 groups were studied: START (Stress test activated reversible tachycardia) and STOPP (Stress test originated phantom perception). There was a significant increase in ΔLFa (sympathetic modulation) after exercise in the START group, suggesting the postural tachycardia was due to sympathetic activity. The postural tachycardia was dependant on exercise which differentiates this finding from OI identified by tilt table testing. This may relate to brain stem atrophy as reported in the START groups, and this may relate to autonomic dysfunction.

James Baraniuk (Washington DC,USA) – Dolorimetry is used for pain measurement. The objective of the study was to determine the distribution of pressure-induced tenderness using dolorimetry for 18 tender points in ME/CFS, FM, GWI and SC women, and to see if this could discriminate between the groups. GWI was distinct from ME/CFS and the other groups both by their history, symptoms and systemic hyperalgesia.

Kunihisa Miwa (Miwa Naika, Japan) focussed on truncal ataxia in ME/CFS. He found that those with ME/CFS and a positive Romberg test had not only OI, but also experienced sitting intolerance. Truncal ataxia or disequilibrium appears to play an important role in the genesis of postural intolerance and is a useful sign of advanced disease.

Session 9: Advances in Brain research and Neurological Studies.

Benjamin Natelson (New York, USA) reviewed the assessment of neurobiological dysfunction in ME/CFS. There were no differences in neurobiological abnormalities between ME/CFS patients with or without psychiatric diagnosis. However, significant differences in the number of abnormal spinal fluids, ventricular lactate, cortical glutathione and cerebral blood flow between ME/CFS and control groups were found. Future research may show these to be potential biomarkers in ME/CFS.

James Baraniuk (Washington DC,USA) found disruptional connectivity in GWI and concluded that the simple 0-back test (see a letter, push a button) was sufficient to identify significant differences in brain function between controls and GWI phenotypes These patterns offer models for potential pathological differences that may discriminate between ME/CFS phenotypes.

Dane Cook (Madison WI, USA) had looked at functional neural consequences of PEM in ME/CFS. Acute exercise was shown to exacerbate symptoms, impaired cognitive performance and affected brain function. This illustrates the potential detrimental effects of PEM for ME/CFS patients.

Session 10: Symptom Provocation Studies 2

Betsy Keller (New York, USA) chaired this session and summarised the important studies described at this conference so far, leading to the current state of our knowledge. These included the work of:
Olav Mella and Øystein Fluge - immunology and treatment,
David Patrick -metagenomics,
Ludivic Giloteaux – microbiome
Peter Rowe – dysautonomia
Susan Levine – allergy profile

Katarina Lien (Oslo, Norway) found that blood lactate increases more rapidly after a previous exercise challenge in those with ME/CFS. She found they had a higher level of lactate at baseline and work rate compared to healthy controls. The first exercise test seems to induce an earlier lactate accumulation in patients when retested the next day. The ME/CFS patients had a decreased physical capacity compared to healthy controls, but the change in peak VO2 after repeated CPET did not discriminate between patients and controls. The lactate increase also occurs in excessive overtraining in athletes, as they begin to produce more lactate. This finding overlaps with ME/CFS.

Betsy Keller (New York, USA) had looked at subsets of ME/CFS patients' responses to a 2-day CPET. She looked for a change of more than 7% in VO2 peak on day 2 and at a decrease in VO2@VAT of more than 13%. Disruption of autonomic and ventilatory responses as indicators of inappropriate recovery (PEM) should be considered. In addition she incidentally reported that of a pair of twins, the microbiome of the affected twin showed less variety of bacteria.

Peter Rowe (Baltimore MD, USA) discussed how their studies have shown that longitudinal neural and soft tissue strain can provoke symptom intensity in ME/CFS, particularly in the limbs and spine, for up to 24 hours. This helps to understand why exercise and other activities of daily living might be capable of provoking symptoms.

Maureen Hanson (Ithaca NY, USA) showed that by mass spectrometry, hundreds of metabolites can be identified in the circulation. 361 metabolites were reviewed. Plasma metabolites differed between patients and controls at baseline, and before and after exercise by a pair of identical twins discordant for ME/CFS. 29 metabolites were lower in the ME/CFS patients, and 4 were higher – this is described as a hypometabolic state. Amino acids, fat metabolism and energy and sugar metabolism are all affected.
It is probable that a diagnostic test can be developed using blood metabolites, but these results need to be replicated in a larger cohort at baseline.

Session 11: Genetics Research

Benjamin Eike (Davie FL, USA) – had looked at 203 Single Nucleotide Polymorphisms (SNPs) in ME/CFS. Review of the genetic data resulted in 3 SNP variants of interest. These 3 SNPs reside within the NDUFS7 gene, which codes for a subunit of NADH dehydrogenase. NADH dehydrogenase is an important complex within the mitochondrial electron transport chain, and takes part in the production of ATP in aerobic respiration. These SNPs did not meet the criteria for a genome-wide association study, but future studies should be performed to determine their significance.

Mary Jeffrey (Miami FL, USA) reported on using gene expression modules to identify gender specific treatments in ME/CFS. The focus was on finding expression patterns related to the immune and inflammatory processes. There was evidence of immune dysregulation. Identification of these gene modules and relevant pathways associated with immune and inflammatory biology can lead to the development of immune-modulating based treatment strategies. Immuno-suppressants and hormone-based therapies were identified as potential candidates for treatment.

Wilfred de Vega (Toronto, Canada) – Epigenetic modifications and glucocorticoid sensitivity in ME/CFS. The objective for this study was to examine the DNA methylome in immune cells in ME/CFS to determine its association with the cellular response to glucocorticoids, and its interaction with symptoms. Results indicate that the epigenetic modifications are a feature of ME/CFS, and there is a potential role for epigenetic modifications in disease manifestation and glucocorticoid hypersensitivity in some patients. The differentially methylated loci could direct work towards biomarkers to improve diagnosis and clinical subtyping.

Paula Waziry (Ft Lauderdale FL, USA) discussed miRNA analysis, in-situ hybridization and STAT1 localization upon stress trigger. The STAT1 pathway is the first line of defence against viral infections. Preliminary studies showed that ME/CFS patients might express higher levels of EBV proteins, and are therefore more prone to viral reactivation from latency. Abnormal nuclear morphology of ME/CFS resembles aging disease. Cells tend to be wrinkled and puckered and show large nucleoli. Further studies should lead to key strategies for therapy.

Jose Montoya (Stanford CA, USA) reported on a very large gene expression study on ME/CFS patients which provides support for an inflammatory or immune-mediated basis for this disease. By understanding the biologic basis of this disease better, development of future diagnostics and therapy will likely be possible.

Medical Education Proposals for ME/CFS

Susan Levine (Ithaca NY, USA) chaired this discussion session where each of the 3 participants presented an overview of what was happening in their areas.

Mady Hornig (Columbia University , USA) discussed their fellowship training programme in the medical schools. They are developing a training programme to create awareness, fill gaps in understanding and pathogenesis. It is hoped to develop a new cohort of clinicians and scientists, who will be knowledgeable about the range of clinical and laboratory findings found in complex immune-mediated disorders such as ME/CFS. What happens at first is often an introduction to research experience, focussed on clinical study design, epidemiology and key strategies for biomarker identification. This covers many disciplines, as well as training in medical ethics.

Anthony Komaroff (Boston, USA) then discussed potential post-graduate programme development. He emphasised that a researcher needs clinical experience. ME/CFS is not taught in their medical schools, so additional training is needed. There are 2 types of research: Laboratory (test tube) and clinical (people). Attention to analysing data must then be included. The curriculum should include the following: clinical epidemiology, biostatistics, analysing outcomes, defining quality of care, health service research and conduct of clinical trials.

Dan Peterson (Nevada, USA) stated that in his area there are no programmes which are accredited for fellowships in ME/CFS. The Simmaron Institute have an established 2 year clinical programme with multisite collaboration. He presented a flow chart showing the building of a 3 year fellowship opportunity. He described a number of obstacles in building the programme, including recruiting and funding.

There were 80 posters displayed demonstrating the enormous amount of research and work now going into solving the many riddles of this complex illness. This certainly shows much hope on the horizon for the many with the illness and for those involved in the clinical aspects.

Summary of conference:

Anthony Komaroff (Boston, USA) gave his usual brilliant overview of the conference with reference to many of the papers and posters presented:

He began by stating that the IOM reports this as a biologically based illness. There have been announcements of expanded research activities by the NIH and educational efforts by the CDC.

Evidence from this meeting covered PEM, immunological findings, microbiome studies, brain research, epigenetics, energy metabolism, diagnostic testing, treatments and the formation of multisite consortia.

Post-exertional malaise (PEM) is triggered physically and cognitively more so than by emotional distress. PEM includes fatigue, cognitive difficulty, sleep disturbances, headache, myalgia and flu-like symptoms. PEM lasts for up to 3 days in 25% of patients.
Studies of PEM show:

1. There are triggers of characteristic gene expression (15 cytokines and growth factors)
2. It is produced by exercise, and 24 hours later there is a decline in peak heart rate.
3. Leads to tachycardia after exercise (as contrasted to altered tilt table test) – this is due to increased sympathetic activity. This also occurs in GWI.

4. Leads to lower oxygen consumption and early conversion to anaerobic metabolism
5. Lactate levels in 2nd test are higher compared to controls, which are lower.

Immunology

1. 15 out of 51 cytokines and growth factors are significantly different.
2. Most cytokines were pro-inflammatory, and levels correlated with symptom severity
3. There are errant B-cells, and early rituximab studies show therapeutic benefit
4. There is reduced diversity and increased clonality of B-cells (Japan)

Microbiome

1. Microbes in gut synthesise hormones and neurotransmitters (eg norepinephrine, serotonin, dopamine, acetylcholine, GABA).
2. There is synthesis of molecules of cytokines and prostaglandins, and elicit production of molecules by the gut immune system.
3. Inflammation leads to leaky gut, allowing bacteria and toxins to enter the bloodstream more often in ME/CFS than controls.
4. Reduced bacterial diversity, with increased number of caudovirals, bacteriophage viruses. All this leads to low inflammation in the gut.

Brain and Nervous System

1. Impaired speed in information processing, leading to cognitive deficit.
2. Paediatrics: impaired information processing, attention effects worsened by exercise, leading to poor performance.
3. Impaired brain blood flow and effects on cortical glutathione. Not affected by a psychiatric diagnosis.
4. 1/3 patients had a high white cell count and elevated protein in cerebrospinal fluid.
5. Altered heart rate variability due to low cardiac vagal activity.
6. Functional connectivity among different brain regions using: PET, diffusion in MRI in GWI, and EEG in patients at rest (eLORETTA).

Epigenetics

1. Illness caused not by just mutated genes, but may be caused by non-mutated genes which are not expressed appropriately. Gene expression is controlled by many different epigenetic factors.
2. Epigenetic studies being done increasingly.
3. Genes are involved in signal transduction (hypomethylated).
4. Those involved in immune regulation, hormone regulation and mitochondrial dysfunction give significantly different gene expression.
5. In GWI, 19 different groups of genes show significantly altered gene expression. Immuno-suppressant and hormonal therapies might target the dysregulated genes and improve symptoms.
6. 13 different gene loci, involved in glucocorticoid sensitivity that are differently methylated lead to clinical symptoms.
7. Expression of 2 microRNAs in plasma lead to elevated homocysteine in ME/CFS.
8. 3 SNPs are distinguished and involve a code for a subunit of NADH dehydrogenase – an important energy molecule.
9. MicroRNA in spinal fluid predicts orthostatic tachycardia.

Energy Metabolism:

1. Rituximab studies – show a metabolism deficit – key molecule is pyruvate dehydrogenase (PDH). This deficit may be caused by auto-antibodies. This leads to upregulation of PDH inhibitors in white blood cells (WBCs).
2. Peripheral WBCs are less well energised, particularly if exposed to stressors.
3. Citric acid metabolism is depleted
4. Glucose is replaced by fatty acids and amino acids. Different metabolomes involve these.
5. ME/CFS is a hypometabolomic state.

Miscellaneous studies:

1. Symptoms are worsened with true strain. Physical therapy is likely to help.
2. 5 specific osteopathic findings on physical examination aid diagnosis
3. There are higher anti-citrillinated protein antibodies.
4. Mutations in nucleosome transport genes compared to controls, help with diagnosis.
5. A second case was reported of ME/CFS caused by an enterovirus in the brain.
6. Dysregulation in the production of hydrogen sulphide could explain symptoms
7. Subjects with sinusitis and hives have more pain and other symptoms.

Possible diagnostic tests:

1. 4 biomarkers: Interleukin 8, SCD14, PGE2, CD3/CD57 count – give 97% correct diagnosis. This needs replication, and comparison with other fatiguing illnesses. A test needs to be inexpensive and easy to perform and needs low false positives.

Treatments:

1. Low glutathione in the brain – use of N-acetyl-cysteine can improve glutathione levels.
2. Low dose methylphenindate plus a nutritional regime leads to slight improvement in the severely ill.
3. Illness beliefs have not been shown to influence activity levels
4. Multimodal physical therapy causes symptoms in the young
5. Quantitative modelling can be done on available approved drugs – looking for drugs that might target the glucocorticoid receptor.

Finally – collaboration between many clinics and biobanks is happening with sharing of knowledge and expertise.

I would like to thanks ANZMES for their assistance in making it possible for me to attend this conference.
Rosamund Vallings (Auckland, NZ)

An awards ceremony was held on 29th October, 2016. The following awards were presented:

Governor Rudy Pepich Memorial Award
Lucinda Batemen MD

Nelson Gantz Clinician Award
Rosamund Vallings MB BS

Junior Investigator Award
Shari Hardcastle PhD

Special Service Award
David Tuller DrPh
Cort Johnson MS