Hosted and organised by ME Research UK, and co-sponsored by the Irish ME Trust, the New Horizons 2008: International Conference on ME/CFS Biomedical Research took place on 6th May 2008 at the Wellcome Trust Conference Centre near Cambridge, UK.

Building on the success of the 2007 conference at Heriot-Watt University, Edinburgh, the day brought together researchers from around the world, healthcare professionals, representatives from local support groups, and delegates from ME/CFS charities. The full day's programme consisted of invited keynote lectures from scientists from Scotland, England, USA, Canada, Belgium, Sweden and Australia.

Morning session

Roger Jefcoate CBE

Delegates were welcomed by Sue Waddle who was chairing the conference with Prof. Nancy Klimas and Bob McRae. The conference proper was opened formally by Roger Jefcoate CBE, co-founder of ME Research UK with Dr Vance Spence and Bob McRae.

Nancy Klimas and Sue Waddle

The first keynote lecture was by Prof. Nancy Klimas (pictured left, with Sue Waddle) of the University of Miami School of Medicine and the Miami VA Medical Center, who directs the UM/VAMC Gulf War and Chronic Fatigue Syndrome Research Center, which focuses on better understanding of the neuro-immune-endocrine interactions in both these complex disorders. Her presentation was entitled "Clinical Aspects of ME/CFS", and her key initial emphasis was on the need to move beyond "case definitional" issues of ME and CFS towards

assessing patients (sub-grouping) on the basis of clinical tests and symptom clusters as outlined in the Canadian Consensus Definition of 2003, of which she was a co-author. In her view, the post-exertional nature of symptoms are key, but it is also important to identify sleep anomalies, pain and autonomic dysfunctions which can be prevalent.

The next keynote lecture was given by Dr Jo Nijs, an academic physiotherapist with special interest in chronic pain and ME/CFS who works at the Vrije Universiteit Brussel, Belgium, and the University College of Antwerp where he is Head of the Division of Musculoskeletal Physiotherapy.

Dr Jo Nijs

Dr Nijs gave an overview of his recent paper on "Intracellular immune dysfunction in ME/CFS: state-of-the-art and therapeutic implications", in which he examined the accumulating evidence in support of intracellular immune dysfunction in the illness. From an in-depth review of the scientific literature, he and his colleagues concluded that proteolytic cleavage of the native RNase L enzyme is characteristic of dysregulation of intracellular immunity in people with ME/CFS, although the origin of the dysregulation is unexplained at present.

In the final presentation of the first session, Dr Gregor Purdie, a general practitioner and GP Adviser to NHS Dumfries and Galloway, described service development and patient pathways from the perspective of the practising clinician. Dr Purdie has been actively involved in moves towards setting up a Scottish Clinical Network on ME/CFS, the outcome being "responsive, empathetic, patient-centred care of high quality delivered by clinicians who have kept abreast of the latest research, with seamless working between primary, secondary and tertiary care".

In the following session, Dr Byron Hyde, from Nightingale Research Foundation, Canada, outlined some of his conclusions from his years seeing ME and CFS patients. He explained that unlike physicians in other countries, he operates inside the Canadian healthcare system within which he can order any blood, urine or tissue test free of charge for any Canadian citizen, including MRI and SPECT imaging.

Dr Byron Hyde

His talk began by outlining myalgic encephalomyelitis which he described not as a syndrome but a disease process causing a diffuse measurable pathophysiological injury of the brain

(CNS). He showed SPECT scans from his practice, and observed that they showed evidence of brain injuries. As regards the question of the triggers or causes of ME, he discussed epidemics, particularly the 1984-1992 Ontario ME epidemic period during which enterovirus seemed to have an important role, concluding that it would be scientifically inexcusable not to consider that the enterovirus group was responsible for the diffuse brain damage noted in acute onset ME patients. As regards ME patients across the board, Dr Hyde's view is that the cause of the illness could be anything (virus, immunisation, physical trauma) that can cause a chronic diffuse injury of the CNS, hence the need for brain SPECT and brain PET imaging in evaluation.

Dr Derek Enlander and
Dr Jonathan Kerr

Dr Derek Enlander (Mount Sinai Medical School, New York; and New York ME/CFS Center, New York, USA) gave the next presentation which described his treatment of ME/CFS patients with a complex intramuscular injection, oral l-cystine, glutathione, methylcobalalmin, follinic acid and electrolytes.

Based on treatment of approximately 800 patients over 15 years, he explained that he has developed a protocol which has helped 65% of patients, based on SF36 and other test criteria. Although the protocol originally started with weekly intramuscular kutapressin, results indicated that only approx 30% of patients were helped, so Dr Enlander has persisted over the past decade to better these results, adding (in stages) intramuscular magnesium sulphate, calphosan, methylcobalamin, folic acid, glutathione, trace zinc and molybdenum. This protocol seemed to be in line with a theory of a methylation cycle defect in ME/CFS. Although glutathione is poorly absorbed, Dr Enlander surmised that if glutathione was given by intramuscular and oral routes, a certain percentage will enter the circulation, so the protocol was extended to include daily oral capsules of glutathione and l-cystine, and daily oral capsules containing a range of vitamins. The addition of a potassium, sodium, magnesium and calcium combination seems to help muscle weakness and pain.

Gavin Spickett and Malcolm Hooper

The role of the ME/CFS Clinic in the UK as regards clinical assessment and service delivery was described in a presentation by Dr Gavin Spickett (Consultant Clinical Immunologist, Royal Victoria Infirmary, Newcastle upon Tyne).

His presentation discussed the care pathways adopted in clinical practice in the North of England — recently described in the Nice Guideline 2007 — including the key role of medical assessment which aims to undertake a detailed clinical evaluation (after GPs have already performed routine tests, including pre-screening bloods) to identify alternative diagnoses that may present with fatigue to ensure that patients receive appropriate treatment for these. Evidence from studies in the clinics has shown that experienced clinicians are able to make alternative diagnoses in a significant percentage of patients referred from primary care with suspected ME/CFS, and that education programmes directed at primary care, as well as strict referral guidelines, do not seem to have reduced the prevalence of alternative diagnoses. For example, an audit of the Newcastle clinic in 1998 showed that 17% of patients referred could be given alternative diagnoses, and a recent re-audit in 2007 showed that in the first three years of the new service ME/CFS was confirmed in only 56% of referrals, with the remainder consisting of alternative diagnoses (28%), sleep apnoea (9%), and depression and anxiety (7%).

Julia Newton and Bob McRae

The morning session was brought to a close by Prof. Julia Newton (Senior Lecturer, Institute of Cellular Medicine, Newcastle University) who spoke of her work on the autonomic nervous system and its dysfunction in ME/CFS. Prof. Newton explained how the autonomic nervous system is responsible for subconscious activities that occur in the human body, such as respiration, bladder and bowel function.

It is also integral to the maintenance of cardiovascular functions such as maintenance of heart rate and blood pressure. Autonomic dysfunction and particularly low blood pressure (hypotension) are a frequent finding in people with the symptom of ‘fatigue’ generally, and her programme of research is directed towards understanding the role of autonomic dysfunction and developing interventions that target autonomic nervous system abnormalities.

She explained to a rapt audience that her research group has recently shown that 89% of those with ME/CFS experience symptoms on standing (orthostatic intolerance) and autonomic nervous system symptoms are frequently present in those with ME/CFS, the degree of which correlates with fatigue severity and is comparable to the symptom burden seen in a range of fatigue-associated chronic diseases. Again, her studies examining haemodynamic responses to standing have shown that 27% (n=63) of ME/CFS patients have Positional Orthostatic Tachycardia Syndrome, and that cardiovascular parameters correlate with increasing fatigue.

The afternoon session began with an overview of the Whittemore Peterson Institute for NeuroImmune Disease, University of Nevada, by Dr Dan Peterson one of the co-founders, who also discussed some of the work currently underway or planned.

Dan Peterson

The aim of the Institute is to be a comprehensive medical research facility devoted to patients with neuro-immune diseases such as ME/CFS, atypical multiple sclerosis, fibromyalgia, and other similarly presenting illnesses which account for billions in lost wages and increased healthcare costs yet receive relatively little attention or funding at the National Institutes of Health or the CDC. At present, the institute is under construction within the Center for Molecular Medicine on the campus of the University of Nevada, Reno, School of Medicine, and is scheduled to open formally in late summer 2010. This $70 million project brings basic researchers, clinical doctors and patients together to facilitate the exchange of new ideas and better communication.

Since its inception, the Institute has focused on research into the pathogenesis and aetiology of a subset of ME/CFS patients manifesting primarily neurological symptoms and concomitant laboratory abnormalities of the innate immune system. Additionally, translational studies have been instituted with respect to techniques to determine functionality and to explore promising therapeutic agents. In addition, as ME/CFS is a significant contributor to the financial burden, as well as functional disability, of the society at large, new approaches with respect to patient management are being encouraged and a structure to implement these patient-centred cost-effective approaches are being designed and implemented.

Dr Faisel Khan (The Institute of Cardiovascular Research, University of Dundee) described how his keynote lecture represented the work of a very active group which has uncovered a range of findings on ME/CFS patients in scientific papers from 2003 to 2007.

Ken Chan, Neil Abbot and Faisel Khan

These include increased oxidative stress, abnormally sensitive acetylcholine metabolism, and increased neutrophil apoptosis — specifically a larger proportion of dying (apoptotic) cells than in healthy subjects — consistent with an activated inflammatory process which is possibly the consequence of a past or present infection.

In his keynote lecture, Dr Jonathan Kerr (Department of Cellular and Molecular Medicine, St George's University of London) described the background to the molecular studies that he has been conducting over the past four years. In previous work, he characterised gene expression in peripheral blood from 25 patients with ME/CFS, and 50 normal blood donors using the Affymetrix U133+2 microarray.

Dr Jonathan Kerr

Genes showing differential expression were further analysed using quantitative polymerase chain reaction in 55 patients with ME/CFS and 75 normal blood donors. Differential expression was confirmed for 88 genes, 85 of which were upregulated and three downregulated. Highly represented functions were haematological disease and function, immunological disease and function, cancer, cell death, immune response and infection. Clustering of data from patients with ME/CFS revealed seven distinct subtypes with distinct differences in Medical Outcomes Survey Short Form-36 scores, clinical phenotypes and severity.

In the most recent study which he described, the group determined for each CFS subtype the fold difference of each of the 88 CFS-associated genes compared with normal persons. Using a fold-difference cut-off of greater than 1.5, those genes that were differentially expressed in each CFS subtype were determined. As Dr Kerr explained, genomic analysis revealed some common (neurological, haematological, cancer) and some distinct (metabolic, endocrine, cardiovascular, immunological, inflammatory) disease associations among the subtypes. Subtypes 1, 2 and 7 were the most severe, and subtype 3 was the mildest. Clinical features of each subtype were as follows: subtype 1 (cognitive, musculoskeletal, sleep, anxiety/depression); subtype 2 (musculoskeletal, pain, anxiety/depression); subtype 3 (mild); subtype 4 (cognitive); subtype 5 (musculoskeletal, gastrointestinal); subtype 6 (postexertional); subtype 7 (pain, infectious, musculoskeletal, sleep, neurological, gastrointestinal, neurocognitive, anxiety/depression).

Prof. Birgitta Evengård (Clinic Infectious Diseases, Umeå University, Sweden) gave the pentultimate lecture of the day on the role of the Swedish twin registry in searching for a biomarker for the illness.

Birgitta Evengård

She described the ongoing work on characterising the epidemiological patterns and the role of genes and environment in the most severe phenotype of fatigue illnesses, the chronic

fatigue syndrome (CFS), in a representative sample of the Swedish population. In the project, collection of epidemiological data, clinical and biological data, psychological and socio-demographic data are included, all evaluated with a gender perspective. The aim is to describe the prevalence of conditions characterised by chronic fatigue and their risk factors in patients and affected twins, the latter compared to their healthy co-twins. The population-based design enables the possibility of evaluating the validity of the CFS definition and, through molecular epidemiology, identify biological determinants of potential value for diagnosis.

Stephen Graves

In the final presentation of the day, Dr Stephen Graves (Director, Australian Rickettsial Reference Laboratory, New South Wales, Australia) shared with the audience his wide experience of "Q Fever" (Coxiella burnetii), "Flinders Island Spotted Fever" (Rickettsia honei strain marmionii) and their possible relationship to ME/CFS.

He explained that a period of fatigue after an infectious disease is a well-recognised phenomenon, which when it lasts for months and is referred to as "post-infectious chronic fatigue". The Q-fever research group hypothesise that many cases of CFS are really "post-infectious chronic fatigue" and that a proportion of these cases are sequelae arising from Q Fever (infection with Coxiella burnetii) or Flinders Island Spotted Fever (infection with Rickettsia honei, strain marmionii). These two bacteria have an obligate, intracellular life style (as do viruses), passing between eukaryotic cells of vertebrates (bush mammals, reptiles, humans) and invertebrates (ticks). Post-typhus chronic fatigue Flinders Island Spotted Fever was first reported in Australia in 1940 but recent data (2008) shows the persistence of rickettsiae in peripheral blood mononuclear cells of affected patients.

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