New Horizons: International Conference on ME/CFS Biomedical Research

Hosted and organised by ME Research UK, and co-sponsored by the Irish ME Trust, the New Horizons International Conference on ME/CFS Biomedical Research took place on Friday 25th May 2007, at the Edinburgh Conference Centre, a purpose-built and disability-friendly venue in an attractive campus setting at Heriot-Watt University, Edinburgh.

This event was the first International Conference on ME/CFS biomedical research ever to be held in the UK. Many of the 130 attendees were biomedical researchers, but there were also representatives from a variety of healthcare professions, and delegates from local ME/CFS support groups in the UK, Norway, Canada and Egypt. In addition, there were representatives from most ME charities, including Invest in ME and the 25% ME Group. The aim of the day was to bring together researchers working towards understanding the biomedical basis of ME/CFS, and to raise awareness of the need for biomedical investigation of the illness. The full day's programme consisted of invited keynote lectures and shorter research presentations from scientists from Scotland, England, USA, Canada, Belgium, Spain and Japan.

Alex Fergusson MSP

The conference was opened by Alex Fergusson MSP, Presiding Officer (Speaker) of the Scottish Parliament, and former Chair of the Cross-Party Group on ME at the Parliament. Alex spoke of his own family's experience of ME/CFS, stressing the need for research to move beyond psychosocial aspects and towards the elucidation of the pathophysiology of the physical illness.

Dr Vance Spence of ME Research UK chaired all the sessions, and his first task was to acknowledge the support given by various groups, most notably the 25% ME Group which supports bedbound and housebound people with the illness, and which had contributed financially towards speakers' travel costs and Invest in ME, the energetic organisation which had worked in conference partnership with ME Research UK during 2007.

The first keynote lecture was by Dr Jonathan Kerr, the Sir Joseph Hotung Senior Lecturer in Inflammation and Honorary Consultant in Microbiology in the Department of Cellular and Molecular Medicine, St George's University of London. His interest in the illness began during a study of parvovirus B19 infection, which showed that a percentage of infected cases developed ME/CFS persisting for several years, and he is now principal investigator of a research group on gene expression in ME/CFS, which could lead to a diagnostic test for the genes were abnormally expressed in CFS/ME patients, but remained normal in a control group of healthy people matched by age, gender and geographical location.

Dr Jonathan Kerr

Because the genes that were abnormal showed problems in several systems of the body including the immune system, in neurological function and mitochondrial metabolism, it was decided that a multidisciplinary team should be formed so that all the different facets of the illness could be addressed. These results have now been reproduced using a combination of microarray analysis (47,000 human genes and their variants), massive parallel signature sequencing and confirmation of the involvement of individual genes using taqman PCR.

Dr Estibaliz Olano, a senior scientist with Progenika (a biotech company based in Bilbao, Spain), gave the next keynote lecture, 'Genetic Profiles in Severe Forms of Fibromyalgia and Chronic Fatigue Syndrome'. She described the investigations of the Bilbao group, centering around efforts to distinguish FM and ME/CFS, two illnesses with somewhat overlapping symptoms, difficult to distinguish and diagnose properly. The group used single nucleotide polymorphism analysis (SNP) to investigate differences in the genetic profiles, using 186 FM patients and 217 CFS patients. For each sample, one

Dr Estibaliz Olano

hundred and seven SNPs were genotyped, and an independent second association study with 126 FM and 156 ME/CFS patients was used to validate the results. The group identified 15 SNPs able to discriminate between FM and CFS patients, and the analysis of further SNPs allowed differential genetic profiling between the most aggressive FM phenotype and the mild forms, and between a severe CFS phenotype and a milder one. The study indicated that genetic profiling via SNP analysis might become a very effective tool to discriminate between the more severe FM and ME/CFS cases, and suggest these are two separate illnesses with an important genetic component.

Before the morning break, Dr Akikazu Sakudo, research associate in the Department of Virology, Research Institute for Microbial Diseases, Osaka University, Japan, described his use of spectroscopic methods to develop a diagnostic method of objectively identifying chronic diseases such as ME/CFS. With Prof. Kazuyoshi Ikuta, Professor in the Department of Virology, Dr Sakudo has been using visible and near-infrared (Vis-NIR) spectroscopy to examine blood sera from ME/CFS patients and healthy donors. In their study on 45 patients and 54 donors, they found that it was possible to discriminate between the two groups, correctly identifying 100% healthy donors and 93.3% of the ME/CFS patients from masked serum samples, suggesting that Vis-NIR spectroscopy for sera combined with chemometrics analysis could provide a promising tool for the objective diagnosis of the illness.

After the break, there was a presentation by Dr Gregor Purdie, a general practitioner and GP Adviser to NHS Dumfries and Galloway on service development and patient pathways from the perspective of the practising clinician. Dr Purdie has been actively involved in working with people with ME/CFS since the late 1990s, and he described recent moves towards setting up a Scottish Clinical Network on ME/CFS, the outcome being "responsive, empathetic, patient-centered care of high quality delivered by clinicians who have kept abreast of the latest research, with seamless working between primary, secondary and tertiary care".

The Dundee Group

The team from the Department of Medicine, University of Dundee gave the next three presentations. The keynote lecture was given by Prof. Jill Belch, Head of the Vascular Diseases Research Unit, University of Dundee. While her main clinical interests are vascular medicine and inflammatory disease, Prof. Belch has been very supportive of ME/CFS research over the past 10 years, and her department has hosted a range of research studies into the illness. Prof. Belch began by describing the problems of diagnosis, and showed the results of a small study done in the 1990s in her department, in which 28/100 consecutive ME/CFS patients, after proper examination, were found to have alternative medical diagnoses, illustrating the importance of a full medical examination of all patients fulfilling the vague CFS criteria. She described subsequent work on three groups of patients all fulfilling the criteria for CFS, but between which very different clinical and biomedical profiles can be identified (Gulf War veterans, organophosphate poisoning patients, and sporadic CFS patients). Prof. Belch described the range of potentially important findings reported by her group in scientific papers from 2003 to 2007. These include increased oxidative stress (findings now confirmed by at least four other research groups worldwide); abnormally sensitive acetylcholine metabolism (an unusual finding since in cardiovascular diseases — such as diabetes, stroke and high cholesterol — blood flow responses to acetylcholine are normally blunted); 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. While these tests are not yet diagnostic markers, they show that if scientific effort and funding are directed towards a problem, researchers can uncover, within a proportion of ME/CFS patients, biological anomalies that might well help to explain many of the clinical features associated with the illness, and might also indicate areas for therapeutic treatment.

This keynote lecture was followed by a presentation from Dr Faisel Khan, a clinical scientist and senior lecturer in the Department of Medicine at the University of Dundee. He is a vascular medicine specialist with a particular interest in blood vessel activity in patients with vascular disease, and in the non-invasive assessment of vascular function using laser Doppler imaging, ultrasound and pulse wave analysis. Dr Khan described a recent study into arterial stiffness in ME/CFS patients, during which 41 patients and 35 healthy volunteers were examined, and arterial stiffness measured by the SphygmoCor pulse waveform analysis system. ME/CFS patients had significantly increased levels of C-reactive protein (CRP), and arterial stiffness was significantly greater in patients than in control subjects, which correlated with CRP. The question remains whether ME/CFS patients have a significantly increased risk of having a future cardiovascular event, and further work is being planned to explore this. A further presentation from the team was given by Dr Gwen Kennedy, a post-doctoral fellow in the department, specialising in research into inflammatory and auto-immune diseases such as systemic sclerosis, diabetes, multiple sclerosis and rheumatoid arthritis. Dr Kennedy has conducted several studies in ME/CFS, and her current work is a study of inflammatory markers in children with the illness. As analysis of the data from this study is still incomplete, Dr Kennedy discussed various aspects of the organisation of the study and demographic results.

The final presentation of the morning was a survey and literature review of 'Attitudes to ME/CFS among healthcare professions' by Joan Crawford who is undertaking a Masters degree at Liverpool Hope University, and completing a dissertation on the attitudes of nurses towards people with ME/CFS, multiple sclerosis and rheumatoid arthritis. The attitudes of healthcare professionals to ME/CFS patients is one of the most contentious areas, and the most painful for patients and carers to have to deal with, and Ms Crawford gave a review of the research literature and showed some of her survey results.

Dr Jo Nijs

The first keynote lecture of the afternoon was from Dr Jo Nijs who is an academic physiotherapist with special interest in chronic pain and ME/CFS. He teaches human physiology at the Vrije Universiteit Brussel in Belgium, and musculoskeletal physiotherapy at the University College of Antwerp where he is head of the Division of Musculoskeletal Physiotherapy. Dr Nijs gave an overview of chronic widespread pain in people with ME/CFS, recent developments and therapeutic implications. He described how people with ME/CFS experience chronic musculoskeletal pain which is even more debilitating than the 'fatiguing' aspect of their illness. There is scientific research data from around the world which enables clinicians to understand, at least in part, chronic musculoskeletal pain in this illness. His overview of these research studies showed that generalised joint hypermobility and benign joint hypermobility syndrome appear to be highly prevalent, though their clinical importance is unknown.

The physiological response to exercise is an important issue for ME/CFS patients, and Mark Robinson of the Department of Applied Physiology, University of Strathclyde, Glasgow presented

data from a pilot study on interleukin-6 and exercise. Interleukin-6 is a cytokine, and there is evidence that it has a significant metabolic role and increases dramatically in response to exercise, so it could be a key candidate for investigation in ME/CFS patients whose observed illness might be associated with limitations in fuel utilisation and/or replenishment. The pilot study described involved six ME/CFS patients and six healthy control subjects matched for age and physical activity levels. The exercise was undertaken at 90% lactate threshold, allowing a 'matching' of the metabolic load between controls and patients. All subjects visited the laboratory on 2 occasions, the first being for identification of the lactate threshold. On the second occasion, subjects exercised at their identified exercise load in the morning after having taken a standardised liquid meal, and blood samples were taken for pre and post-exercise and 24 hour measurements. The results, which have yet to be published, show that power output was lower in the CFS group, and there were indications of lower receptor levels at baseline, so there is justification in investigating a larger sample.

Drs Les Wood and Lorna Paul

Rebecca Marshall, who is undertaking a PhD at Glasgow Caledonian University with Dr Lorna Paul in the School of Health and Social Care, gave the next presentation which was derived from her doctoral studies on the pain experience in people with ME/CFS. This is a experiencing volunteers from support groups across Scotland. For this descriptive, cross-sectional study, 50 people (38 women, 12 men) were recruited, including ten people who represented the housebound or bedbound. A variety of conclusions were presented, including the fact that 66% of participants reported they were in a stable (chronic) condition, with 24% reporting that their condition was worsening; 79% of participants reported muscle pain as their 'worst pain' on the day of the interview; and that pain-questionnaire information suggested that the most common 'descriptors' of pain, included aching, throbbing and exhausting.

The next presentation was from Dr Les Wood, a senior lecturer in the Department of Physiology, Glasgow Caledonian University. His research interests include cutaneous influences on motoneuronal excitability, and nutritional analysis of dietary intake, and he discussed his recent pilot data on motoneurone excitability after fatiguing exercise in patients with ME/CFS. Dr Wood was looking at the Hoffmann reflex (H-reflex), a neurophysiological tool which allows investigations of factors which may influence the excitability of motoneurones in the spinal cord. In his experiments, H-reflex excitability was monitored before and after fatiguing contractions of the triceps surae muscle group in subjects with CFS/ME and in matched control subjects. Fatiguing contractions were made by subjects producing 40 maximum voluntary plantar flexion contractions against a foot plate connected to a force transducer which recorded changes in the force of contraction. The purpose of this was to investigate if the excitability of motoneurones controlling muscle contraction was differently affected by fatigue in subjects with CFS/ME.

Prof. Nancy Klimas

Prof. Nancy Klimas is Professor of Medicine, Psychology, Microbiology and Immunology, University of Miami School of Medicine and the Miami VA Medical Center. She directs the UM/VAMC Gulf War and Chronic Fatigue Syndrome Research Center which focuses on better understanding of the neuro-immune-endocrine interactions in CFS and Gulf War syndrome, and their role role in the pathogenesis of these complex disorders. She continues to work nationally and internationally to bring a better understanding of ME/CFS and Gulf War syndrome to clinicians and policy makers. Her presentation was entitled 'The Immunology of ME/CFS', and she shared with the audience her reflections from her many years as a clinician and researcher. Prof. Klimas described a model for the development of the illness; the model postulates a genetic predisposition which encounters a triggering event or infection, leading to the production of immune, endocrine or neuroendocrine mediators, resulting in a poor health outcome and persistence of illness. The role of a possible genetic predisposition is supported by past work on HLA DR haplotypes, and possibly by studies discussed earlier in the day. She pointed out that there is a clear association between ME/CFS and a viral-like infection in research studies, and referred to the 2006 paper in the British Medical Journal on 253 patients with acute infection in 11% of an ME/CFS-like illness developed that was predicted largely by the severity of the acute illness rather than by demographic or psychological factors. Prof. Klimas explained that the key is for the subgroups currently within the umbrella diagnosis 'CFS' to be teased apart, so that each can be researched and treated separately. Her conclusion was that there has been significant progress in our understanding of ME/CFS, that the neuroendocrine, immune and central nervous systems are linked, and cannot be considered separately. More effective therapies, based on this new understanding, will become available.

Dr Eleanor Stein

The final keynote lecture of the day was by Dr Eleanor Stein, a psychiatrist in private practice in Calgary, Canada. She graduated from the University of Alberta Medical School, completing her residency at the University of London in 1992. She is author of the excellent overview 'Assessment and Treatment of Patients with ME/CFS: Clinical Guidelines for Psychiatrists' which concludes that "the medical literature is clear that ME/CFS is not the same as depression or any other psychiatric disorder", and this was one of the insights she explored with the conference. Dr Stein discussed the history of behavioural intervention generally, and the results of behavioural interventions in ME/CFS, and gave suggestions for future directions. She described how, early in the 'modern era' of ME/CFS, it was assumed that it was an infectious epidemic disorder, but that later in the absence of finding a single physical cause, psychological causes were hypothesised. While correlations have been found between activity avoidance, illness attribution and illness severity, the direction of causality has not been proven. Her review of the literature showed that there are 7 randomised controlled trials using UK-style cognitive behavioural therapy for 'CFS', but that two of these selected patients as defined by the Oxford/UK Criteria so that the

results are not necessarily generalisable to patients with ME/CFS, and that two have had negative results. Of the positive studies, one used the 1994 Fukuda criteria "with the exception of the criterion requiring four of eight additional symptoms to be present" (which effectively meant that the study was not examining ME/CFS), and another was in adolescents. A recent study using cognitive behavioural therapy (the first to measure cognitive function) found no objective benefit to cognitive function pre/post intervention.

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