For the attention of Professor Sir Simon Wessely, Professors Peter White OBE and Michael Sharpe

Margaret Williams 23rd February 2013

Your attention is drawn to two recently published papers, one on fibromyalgia (FM) and the other on myalgic encephalomyelitis (ME).

You will doubtless recall that in 1999, Professors Wessely and Sharpe published their conviction that FM and ME (referred to as CFS/ME), together with irritable bowel syndrome and pre-menstrual syndrome, constitute but one single functional somatic syndrome (Functional somatic syndromes: one or many? S. Wessely, C Nimnuan, M Sharpe. Lancet 1999:354:936-939) and that in 2004, Professor White published his belief that CFS/ME is an individual functional somatic syndrome (In Debate: there is only one functional somatic syndrome. Peter D White. British Journal of Psychiatry 2004:185:95-96). In the latter paper, two of you said you still stood by your thesis that FM and ME are components of a single functional somatic syndrome.

Furthermore, when NICE was compiling its Clinical Guideline 53 on CFS/ME, Professor White advised NICE against prescribing anything for bowel problems, stating authoritatively that such interventions: "*are not treatments of CFS/ME since bowel symptoms are not part of CFS/ME"* (85 FULL 229.6.4.55).

It seems that those who disagreed with such views may have been correct.

On 17th December 2012 a paper on fibromyalgia from the University of Illinois, Chicago, was published in BMC Clinical Pathology which seriously undermines your own beliefs (Unique immunologic patterns in fibromyalgia. Frederick Behm et al: http://www.biomedcentral.com/1472-6890/12/25). Here are some extracts:

"*Recent data highlight the role of the immune system in FM. Aberrant expressions of immune mediators, such as cytokines, have been linked to the pathogenesis and traits of FM. We therefore determined whether cytokine production by immune cells is altered in FM patients by comparing the cellular responses …of a large number of patients with FM to those of healthy matched controls".*

"FM is common in patients with autoimmune disorders, such as systemic lupus erythematosus, Sjogren's Syndrome and rheumatoid arthritis".

"We utilised multiple immunologic methods to develop an objective test….This test is based on specific abnormalities in the cytokine levels of stimulated peripheral blood mononuclear cells".

"In the past, FM was claimed to be a rheumatologic, neurologic or psychiatric disease despite the fact that there were no objective links to any of these pathways".

"Our findings uncovered evidence that FM is instead an immunologic disorder. They prove that the immunologic basis of FM occurs independently of any subjective features".

The second paper is about ME (Plasmacytoid Dendritic Cells in the Duodenum of Individuals Diagnosed with Myalgic Encephalomyelitis are Uniquely Immunoreactive to Antibodies to Human Endogenous Retroviral Proteins. Kenny L de Meirleir; Marc Fremont, Vincent Lombardi et al. In vivo 2013:12:177-188). Here are some extracts from it:

"*Myalgic encephalomyelitis (ME) is a debilitating illness…characterised by neurocognitive dysfunction, inflammation, immune abnormalities and gastrointestinal distress. An increasing body of evidence suggests that disruptions in the gut may contribute to the induction of neuroinflammation. Therefore, reports of human endogenous retroviral (HERV) expression in association with neuroinflammatory diseases prompted us to investigate the gut of individuals with ME for the presence of HERV proteins".*

"Autoimmune diseases such as multiple sclerosis (MS) and systemic lupus erythematosus (SLE) have many symptoms that overlap with those of ME".

"Neurological manifestations often associated with ME are analogous to the neuroinflammation and cognitive abnormalities associated with MS and SLE".

"Additionally, gastrointestinal aberrations, which are common to individuals with MS and SLE, are among the most frequent symptoms reported by those with ME".

"HERV proteins and serum antibodies against HERVs have been associated with a number of autoimmune diseases, including MS and SLE".

"Individuals with ME have a significant number of symptoms that are similar to those described in autoimmune diseases such as MS and SLE. Additionally, the expression of HERV proteins has been observed in the lymphoid tissue of individuals with autoimmune disease….the gut represents the largest lymphoid compartment and is a significant site of ME-related pathology".

"In this study we have shown that gut biopsies from 8 out of 12 individuals with ME displayed immunoreactivity consistent with the presence of HERV proteins. However, the same immunoreactivity was not observed in the biopsies of the controls".

"Additionally, we have shown that the immunoreactivity was observed in cells with a phenotype that is consistent with pDCs (plasmacytoid dendritic cells). *These observations suggest that the presence of the HERV protein in pDCs may be associated with a pathological manifestation in at least a subset of individuals with ME*".

"*While the expression of endogenous retroviral proteins in the pDCs of ME cases does not intrinsically explain pathology, the observation that the immunoreactive proteins are only observed in pDCs is supportive of this concept. This supposition is further supported by our previous report of the dysregulation of inflammatory cytokines in a cohort of ME cases".*

"These data suggest that our observations in subjects with ME may not be unique to this disease but may, in fact, be common to diseases characterised by chronic inflammation".

"Although the Canadian consensus criteria for ME and the Fukuda criteria for CFS do not include symptoms of autoimmunity, the recent study by Fluge et al supports the notion that at least a subset of individuals with ME may have an autoimmune element to their disease. Autoimmune diseases such as SLE, MS and rheumatoid arthritis have several common symptoms that overlap with those of ME and all have been associated with the pDC dysfunction. Moreover, the same autoimmune diseases are also reported to be associated with the expression of HERVs".

"Inflammation is known to increase HERV expression; therefore if pDC-associated inflammation drives the expression of endogenous retroviruses, it is also conceivable that dysregulated expression of other proteins in pDCs may occur. Consequently, the antigen-presenting abilities of pDCs may contribute to the production of auto-reactive antibodies, as is observed in ME".

"The presence of these proteins in the pDCs of individuals with ME but not in controls does support an involvement of pDCs in ME".

Clearly the role of the immune system in both FM and ME is important.

You will recall that, in his evidence given on 10th August 2004 before Lord Lloyd of Berwick at the Independent Inquiry into Gulf War Illnesses, Sir Simon is on record as affirming: "*A man has got to know his limitations and my limitations are immunology"* (Professor Simon Wessely; Minutes of Proceedings).

Can it now be understood why so many people find it inexplicable that Sir Simon was awarded the inaugural John Maddox Prize for being *"an inspiration"* for *"standing up for science";* for working with *"courage and dignity to uphold the standards of science and evidence against the forces of prejudice"*; for battling "*to ensure that sense, reason and evidence base play a role in the most contentious debates"* and for his "*sustained resilience and determination to promote good science"*, whilst Professor White was awarded an OBE for services to medical education on CFS?