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Extracts from Medscape Medical News: "Biomarker Research Advances in 'Chronic Fatigue Syndrome' " by Miriam Tucker, 8th November 2016

Comment by Margaret Williams 9th November 2016

According to Professor Anthony Komaroff, Professor of Medicine at Harvard, studies over the last decade point to the biological underpinnings of ME/CFS.

At the biennial International Association for CFS/ME Conference in Fort Lauderdale (27th-30th October 2016), more than 100 papers were presented that further contribute to the existing evidence-base.

In his Summary at the end of the meeting Komaroff said: *"Case control studies comparing patients with ME/CFS to both disease comparison groups and healthy control subjects find robust evidence of an underlying biological process involving the brain and autonomic nervous system, immune system, energy metabolism and oxidative and nitrosative stress"*

He added: *"To those people out there who still question whether there really is anything wrong in this illness, my advice to them would be try consulting the evidence"*.

Jose Montoya, Professor of Medicine at Stanford University, California, presented findings from the largest such study to date (involving 192 patients and 392 healthy but sedentary controls); he found significant elevations for 17 specific cytokines, 13 of them pro-inflammatory, that correlated with symptom severity in the serum of ME/CFS patients compared with controls. Montoya said these findings *"likely substantiate many of the symptoms experienced by patients and the immune nature of the disease"*.

Professor Komaroff commented: "*Many of us for 20 to 30 years have held the hypothesis that symptoms of this illness likely are caused by increased cytokine levels in the brain due to chronic immune activation….This is a very excellent demonstration of it. If those cytokines are the explanation for the symptoms, you would expect there to be a correlation between how high the cytokine was and how severe the symptom was, and that's what they found"*.

Kenny DeMeirleir, Director of the Nevada Centre for Biomedical Research in Reno, Nevada, presented evidence from 70 female and 70 male patients matched with the same number of sedentary controls; it uncovered significant differences for four

specific immune/inflammatory markers in venous blood: (prostaglandin E2, interleukin 8, soluble CD14 – a surrogate marker for bacterial lipopolysaccharide— and CD57+ lymphocytes. The four markers correctly classified 89.5% of the males and 97.1% of the females with ME/CFS as defined by published criteria.

Mady Hornig, Associate Professor of Epidemiology at Columbia University, New York, commented that it was first necessary to use biomarkers "*to parse out the heterogeneity of this disorder before we can know if it is possible to use them for diagnosis*".

This contrasts sharply with the long-held view of the UK psychosocial school: the CMO's Report of 2002 contained an annexe written on 2nd December 2000 by Professor Anthony Pinching, a former Principal Medical Advisor to Action for ME (Annexe 4: General concepts and philosophy of disease**)** on the important issue of sub-groups: *"On present evidence, this question (of sub-groups) may be considered a matter of semantics and personal philosophy…"* and the PACE Investigators stated in their Trial Identifier: *"We chose these broad criteria in older to enhance generalisabiiity and recruitment*". This failure to select as homogenous a cohort as possible has held back medical science in the UK for a generation.

Among several studies demonstrating brain abnormalities in ME/CFS was one involving twenty three adolescents and twenty healthy matched controls; patients displayed significant deficits in information processing speed, sustained attention and poorer performance on tasks of working memory, about which Professor Komaroff commented: "*So, we see many of the same cognitive problems in kids (that are) documented in adults. It's not surprising, but important to document, especially for the sceptical school*".

Genetic differences were also found. In one study, DNA analysis in 53 patients with ME/CFS identified three SNPs (single nucleotide polymorphisms) that involve genes coding for a subunit of the energy molecule nicotinamide adenine dinucleotide hydrate dehydrogenase, about which Professor Komaroff commented: "*That's important, because abundant other evidence of aberrant energy metabolism was presented at this meeting*".

Other studies found dysfunction in genes encoding for hypo - and hypermethylation correlating with clinical symptoms, and significantly altered expression patterns for genes involved in immune regulation.

In addition, in a metabolomics study using mass spectrometry, metabolites that differed most between patients and controls involved pathways harvesting energy from glucose, fatty acids and amino acids. (This finding, suggestive of a hypometabolic state, corresponds to that of Naviaux et al recently published in Proceedings of the National Academy of Sciences 2016:113:7). Komaroff commented that it was consistent: "*It says that some types of metabolic pathway are down-regulated in this illness, whereas others like those involving immunity and inflammation are up-regulated*".

Professor Hornig told Medscape Medical News: *"in addition to accelerating research on causes and treatment, we critically need to find ways to educate medical professionals about the disorder"*.

Attempting to educate the UK medical profession, the DWP and benefits decision-makers, the media and local authorities about ME/CFS has proved impossible for the last 30 years.

Since the psychosocial model is demonstrably wrong, to continue treating ME/CFS as a behavioural disorder is both unethical and harmful, and is wasteful of tax payers' money.

Thirty years of behavioural research and interventions have yielded a null result.

The stranglehold of the psychosocial school in the UK over this disorder must be broken so that actual progress can be made.

How can so much evidence be ignored by so many people for so long?