Documented evidence of inflammation in ME/CFS

Margaret Williams **30th November 2010**

Note: although most of the following information is included in "Magical Medicine: how to make a disease disappear" (http://www.meactionuk.org.uk/magical-medicine.htm), it is presented here as a short 5 page article for ease of access.

It may be instructive to consider how the information below has been so consistently ignored by the Wessely School during the 25 years of Professor Peter White's celebrated "Fatigue Service" and what impact – if any – this information will have on the PACE Trial results and on the Principal Investigators' consequent recommendations for cognitive restructuring interventions.

Some illustrations of published evidence of inflammation in ME/CFS patients include the following:

1955

In this outbreak of ME in Adelaide, Australia, an agent was repeatedly transmitted to monkeys; when the monkeys were killed, microscopically, infiltration of nerve roots with lymphocytes and mononuclear cells was seen and some of the nerve fibres showed patchy damage in the myelin sheaths and axon swellings consistent with neurological involvement. In these monkeys, there were widespread changes involving the **dorsal root ganglia**, cervical and lumbar nerve roots and peripheral nerves. Perivascular collars of lymphocytes and plasma cells were in the cerebral cortex, brainstem and cerebellum, spinal cord and around blood vessels to nerve roots (Pellew RAA, Miles JAR; Med J Aust:1955:2:13:480-482, cited by J Gordon Parish; Postgraduate Medical Journal 1978:54:711-717).

This is particularly significant, given the autopsy evidence presented at the Royal Society of Medicine meeting in the series "Medicine and me" on 11th July 2009 by Dr Abhijit Chaudhuri, where he showed slides of inflammation of the dorsal root ganglia in three ME/CFS patients.

1970

Innes reported isolation of Coxsackie B2 virus from the cerebrospinal fluid: *"The isolation of an enterovirus from the cerebrospinal fluid in the fourth month is in itself remarkable"* (Innes SGB; Lancet:1970:969-971).

1992

"Neurologic symptoms, MRI findings, and lymphocyte phenotyping studies suggest that the patients may have been experiencing ***a chronic, immunologically mediated inflammatory process of the central nervous system****" (*Buchwald, Cheney, Peterson D, Komaroff, Gallo et al; Ann Int Med: 1992:116:103-113).

1994

*"****As with any chronic inflammatory condition affecting the central nervous system****, the T2-bright foci on MRI in (ME)CFS may represent a perivascular cellular infiltrate and/or reactive demyelination of the surrounding white matter. Alternatively, these abnormalities may reflect the results of a vasculopathy specifically involving the small vessels of the cerebral white matter. Specifically, on the basis of our observations, the white matter abnormalities seen on MRI images may represent foci of gliosis or chronic demyelination, which appear to be irreversible"* (Schwartz RE et al; Am J Roentgenology:1994:162:935-941).

1997

"It is now evident that this illness is not simply an imaginary one, nor the result of anxiously amplifying normal bodily sensations. Substantial objective evidence of abnormalities in the central nervous system is now available. Magnetic resonance imaging has revealed punctate areas of high signal in the white matter more often in patients with (ME)CFS than in healthy controls. They may represent areas of ***inflammation*** *or demyelination"* (Komaroff AL. JAMA:1997:278:14:1179-1184).

2004

"These findings are consistent with an activated inflammatory response*. Shockingly, the mean QOL (quality of life) scores as regards limitations on physical functioning were very, very low, similar to those found in people with AIDS and multiple sclerosis*" (Advances in biomedical understanding of ME. Neil Abbot. Vance Spence. InterAction May 2004).

2006

"(ME)CFS is a poorly defined medical condition which involves inflammatory and immune activation*. The Type I interferon antiviral pathway has been repeatedly shown to be activated in the most afflicted patients. An abnormal truncated form of ribonuclease L (37-kDa RNase L) is also found in (ME)CFS patients and this protein has been proposed as a biological marker for (ME)CFS****. The levels of this abnormal protein have been significantly correlated to the extent of inflammatory symptoms displayed by (ME)CFS patients. (Our) results suggest that chronic inflammation due to excess nitric oxide plays a role in (ME)CFS and that the normal resolution of the inflammatory process is impaired****"* (M Fremont, K De Meirleir et al. JCFS 2006:13(4):17-28).

2007

*"****A number of symptoms of CFS are linked to inflammatory processes….CFS has been found to be associated with increased immune activation and inflammatory cytokine levels****….Our expanded understanding of the genomics of (ME)CFS has reinforced the evidence that the illness is rooted in a biologic pathogenesis that involves cellular dysfunction and interactions between the physiologic stress response and* ***inflammation****"* (Nancy G Klimas and Anne O'Brien Koneru ; Curr Rheumatol Rep 2007:9:6:482-487).

2008

In a personal communication, Nancy Klimas, Professor of Medicine at the University of Miami, world-renowned immunologist and expert on ME/CFS, said that 80% of all ME/CFS patients (both severely and not so severely ill) do have evidence of inflammation if the correct scans are employed, and she believes that 100% of ME/CFS patients actually have inflammation.

2008

On 17th December 2008 Emory University School of Medicine issued a press release by Kathi Baker: "*A new study conducted by researchers from Emory University and the Centres for Disease Control and Prevention (CDC) shows that* ***individuals with (ME)CFS have increased blood levels of the inflammatory chemicals*** *known to increase risk for developing illnesses ranging from cardiovascular disease and dementia to diabetes and cancer. 'We don't know where the increased inflammation is coming from in patients with (ME)CFS symptoms in our study, and although depression has been associated with increased inflammation, in our study it did not account for the increased inflammation in individuals with (ME)CFS' (explained Dr Charles L Raison).* ***The researchers found that subjects with (ME)CFS had higher levels of CRP (c-reactive protein) than did well individuals and also had higher scores on an inflammatory factor that included both CRP and white blood cell levels****".*

2009

In the study to which the above press release relates, the authors stated: "*The current study examined plasma concentrations of high-sensitivity c-reactive protein (hs-CRP), white blood cell count (WBC) and a combined inflammation factor in a large (457) population-based sample. Log-transformed mean plasma concentrations of hs-CRP were increased in subjects with (ME)CFS when compared to subjects who were well"* (Charles L Raison et al; Brain, Behaviour and Immunity 2009:23:3:327-337).

2009

Professor M Maes from Belgium reviewed recent findings on inflammatory and oxidative and nitrosative stress pathways and reported: "***The 'psychosomatic' symptoms experienced by (ME/CFS patients are caused by intracellular inflammation.*** *Symptoms occurring in (ME)CFS have a genuine organic cause, that is activation of peripheral and central IO and NS pathways and gut-derived inflammation"* (Curr Opin Psychiatry 2009:22(1):75-83).

2009

Professors Mary Ann Fletcher and Nancy Klimas published yet more confirmatory evidence of immune dysfunction and inflammation in the maintenance of ME/CFS:

*"In this study, 10 of 16 cytokines examined showed good to fair promise as biomarkers. However, the cytokine changes observed are likely to be more indicative of immune activation and inflammation…**Many of the symptoms are inflammatory in nature**….*

"Pro-inflammatory cytokines: A significant elevation in the relative amounts of 4 of 5 pro-inflammatory cytokines in peripheral blood plasma of patients with (ME)CFS was found when compared with the controls. In cases, lymphotoxin (LT)α was elevated by 257% and IL-6 by 100% over the controls.

"Anti-inflammatory cytokines: IL-3 was significantly lower in (ME)CFS patients.

"The probability of chronic inflammation in (ME)CFS patients is supported by the elevation of four members of the pro-inflammatory cytokine cascade , LTα, IL-1α, IL-1β and IL-6, in the (ME)CFS samples compared to controls.

"Interleukin-13, associated with inhibitory effects on inflammatory cytokine production, was lower in cases compared to controls.

*"**The results from this study support a T_H2 shift, pro-inflammatory cytokine up-regulation and down-regulation of important mediators of cytotoxic cell function**".* (Journal of Translational Medicine 2009:7:96: doi:10.1186/1479-5876-7-96)

2009

In her lecture in November 2009 at the University of Miami, Professor Nancy Klimas said about viruses and ME/CFS that much of the research at Miami and internationally found that the viruses studied all have several things in common: they infect cells of the immune system and the neurological system; they are capable of causing latent infections and they can reactivate under certain conditions.

She also said that their early work at Miami in the late 1980s (published in the Journal of Clinical Microbiology in 1989) showed that ME/CFS patients had immune activation and poor anti-viral cell function. She then went on to discuss the importance of the findings of the retrovirus XMRV (evidence of which was published in Science on 8th October 2009), saying that it was *"very impressive work"*. She continued: "*This Science paper was amazing for a number of reasons. First, this team had put together such strong science that they could go for a Science paper. Science is like the Mecca of*

publication. If you get your stuff in Science, that's the best place you could possibly (get it published). And they don't take just anything and they sure, sure, sure don't take anything unless it's extremely well done, validated and tested out. So they took this paper – they not only took it, they put it in Science Express. They thought it was so important, they published on a very fast track…The way (the researchers at the Whittemore Peterson Institute) looked is very sophisticated…They then tried to find (the virus) in all these other ways…they looked from a whole different angle. Still found it. Backed up and looked from another angle. Still found it…they had five different kinds of ways they looked for this virus. And they were able to find the virus. That's why Science was so impressed…It is a virus that can infect tissues that aren't white blood cells… ***We've always thought something like that has to go on in (ME)CFS because you all have some neuro-inflammation. Your brain has a low grade level of inflammation. And you have some inflammation in the tissues that make hormones, particularly in the hypothalamic-pituitary-axis. And this is a virus that infects that type of tissue****…It's pretty impressive that out of 101 (ME)CFS cases defined by clinical case definition or a research case definition that they found 99 with the virus…And, oh, by the way, we have a biomarker. Not a small deal. A biomarker – the virus itself. No better biomarker than something that's clearly, tightly associated with an illness…So the conclusion, it really is a big thing. It's a big thing…That work we were already doing plays right into this. All the genomics work and all the immunology work. This is all critical to the better understanding of this illness and how this virus plays into it"* (with grateful acknowledgement to PANDORA and http://aboutmecfs.org/Rsrch/XMRVKlimas.aspx and http://aboutmecfs.org/Rsrch/XMRVKlimasII.aspx).

2010

On 19th September 2010 in a radio interview (South Florida Spotlite, interviewed by Ron St John), world expert in ME/CFS Professor Nancy Klimas (principal investigator of the National Institute for Health's Centre for Multidisciplinary Studies of (ME)CFS Pathophysiology at the University of Miami) was clear: *"…****there is a chronic inflammation, neuro-inflammation****, and it upsets the whole balance of your systems…the patients become terribly ill…. The immune system is really cranked up;* ***it's a tremendous amount of inflammation. I think that if doctors could get this in their heads that it's sort of like lupus or one of these really inflammatory disorders…it is that level of inflammation. There's a tremendous amount of inflammatory stuff going on, and there's a lot of inflammation in the brain itself****"* (http://www.litemiami.com/spotlite/index.aspx)

Note on inflammation

Following an international meeting on inflammation held in Bordeaux, France, Robert Dantzer et al published a Review entitled "Identification and treatment of symptoms associated with inflammation in medically ill patients" (Psychoneuroendocrinology 2008:33:18-29). Given the documented evidence of inflammation in ME/CFS, this Review has important implications for people with the disorder. It recommends testing with a standard battery of inflammatory markers in medically ill patients. Quotations that might be relevant for people with ME/CFS include the following:

"This meeting brought together clinicians and basic scientists with a common interest in understanding inflammation and associated symptoms in medically ill patients (and it) focused on: (a) predominant symptoms associated with inflammation, (b) markers of inflammation at the periphery, (c) possible markers of brain inflammation associated with low-grade peripheral inflammation in humans, (d) animal models of inflammation-associated symptoms, and (e) domains of intervention for controlling inflammation-associated symptoms".

"The diagnostic tools that are favoured by psychiatrists are clearly not the best ones. As pointed out by Joel Dimsdale (San Diego, CA), the concept of somatisation that is used for characterising symptoms in the absence of any detectable disease is of little operational value, if not misleading".

"For instance, the enduring fatigue experienced by the vast majority of breast cancer survivors could easily be labelled as somatisation disorder according to the 4th Edition of the Diagnostic and Statistical Manual of Mental Disorders".

"Making fatigue a somatisation disorder overlooks the fact that fatigue has both mental and physical components, thereby denying a possible organic aetiology to explain such fatigue".

"Furthermore, this emphasis on the lack of an organic basis favours missed diagnoses (e.g. fatigue and thyroid abnormalities, or fatigue and inflammation)".

"Inflammation is not a stable condition. In a given individual it can fluctuate rapidly according to a number of environmental factors (e.g. stressors) and internal variables (e.g. diurnal variation of cortisol)".

"Basic aspects of diagnosis of behavioural disorders remain controversial and lack solid scientific foundations".

"In order to provide consistency, all studies examining the potential impact of inflammatory pathways should include a standard set of inflammatory biomarkers (which should include) the acute phase proteins, CRP, sialic acid and haptoglobin; the inflammatory mediators, prostaglandins E2 and C3A and the innate immune cytokine IL-6 as measured by the high sensitivity (hs)-enzyme-linked immunosorbent assay (ELISA) in plasma. ***These biomarkers, especially hs-CRP and IL-6, have been found to reproducibly identify the presence of an activated immune response in a number of disorders****. Most of these assessments can be run in certified commercial or hospital laboratories".*

"Proinflammatory cytokines induce the production of several downstream inflammatory mediators, such as prostaglandins and nitric oxide. Proinflammatory cytokines and other inflammatory mediators are produced by accessory immune cells, such as macrophages and monocytes in the periphery, and microglia within the central nervous system".

"Peripheral infections can sensitise or exaggerate existing brain inflammatory processes (and) elevated cytokine levels in blood have the potential to reverberate and activate central nervous inflammatory systems".

The Conclusions of the Review note the intense discussion at the meeting that resulted in a series of recommendations for improving understanding of the relationship between inflammation and subjective health complaints.

These recommendations note that because inflammation-associated sickness symptoms are a major impediment to human health, research on the mechanisms and treatment of such symptom burden in physically ill patients should be strongly encouraged; that clinical tools for assessing inflammation-associated symptoms should be standardised; that there should be a minimum set of inflammatory biomarkers; that brain neuroimaging techniques should be used for revealing the brain structures that are influenced by peripheral inflammatory processes and whose ability to process information is impaired by excessive amounts of interoceptive stimuli (**caused, it seems, not – as asserted by Wessely School psychiatrists -- by aberrant focusing on normal bodily sensations or by "remembered illness" but by inflammatory processes),** and that the high presence of inflammation-associated symptoms in physically ill patients provides a background against which it is possible to test alleviating effects of therapies targeting immune-to-brain communication pathways.

The evidence of inflammation in people with ME/CFS is important because the incremental aerobic exercise recommended by the Wessely School and encapsulated in NICE's Clinical Guideline 53 is contra-indicated in cases of inflamed and damaged tissue and inevitably results in post-exertional relapse with malaise, which is the cardinal symptom of ME/CFS.