# Essential investigations for people with ME/CFS?

**by Margaret Williams**

On 14th January 2008 Fred Springfield drew attention on Co-Cure to a Review Article associated with inflammation in medically ill patients –

"**Identification and treatment of symptoms associated with inflammation in medically ill patients**";
Robert Dantzer et al; Psychoneuroendocrinology 2008:33:18-29.

The Review was the result of a meeting on 28th and 29th May 2007 in Bordeaux, France, on inflammation, psychiatry, neurosciences and psychoneuroimmunology, attended by experts from the US, France, the UK and Israel.

As noted by Fred Springfield, whilst not relating specifically to ME/CFS, the Review may nevertheless be of interest to the ME/CFS community, whose members may be aware that there is evidence of low-grade (but still important) inflammation in ME/CFS -- see, for example,

"*Low grade inflammation and arterial wave reflection in patients with CFS*"; VA Spence et al, Clin Sci 2007, Epub ahead of print: doi:10.1042/CS20070274

which contains 54 references and demonstrates that, despite the recent reporting that markers of post-infective fatigue syndromes are not sustained into the chronic phase of the illness and play no role in persisting symptoms, hsCRP levels in (ME)CFS are indeed indicative of chronic, low-grade, sub-clinical inflammation. (Within the last ten years, researchers have developed a high sensitivity immunoassay known as hsCRP, which is a much better assay and a more sensitive marker than CRP, as it can measure levels below 10mg/L. Whilst some clinicians may still regard low levels as unimportant, nevertheless at these levels, measurement of conditions indicative of chronic, low-grade inflammation are now possible).

The Review recommends testing for a standardised set of inflammatory biomarkers, but the NICE Guideline on "CFS/ME" issued in August 2007 **specifically proscribes** such tests.

The following are quotations that might be relevant for people with ME/CFS:

- "The most harmful and costly health problems in the Western World are originating from a few diseases (and) in addition to the specific symptoms that are characteristic of each of these conditions, most patients experience non-specific symptoms that are similar in all these conditions and include depressed mood, altered cognition, fatigue, and sleep disorders".

- "The possibility that immune-to-brain communication pathways represent the main biological mechanism for symptom burden experienced by medically ill patients has now gained credibility in the medical community".

- "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".

- "Among the myriad of questionnaires that are available to categorise or assess fatigue, sleep disorders, altered cognition and pain, none specifically refers to inflammation-associated neurobehavioural alterations".

- **"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 hatoglobin; 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".

- "There have been significant advances in imaging techniques during the past ten years (and) a variety of imaging techniques have enabled inflammation in the brain to be viewed in real time. However, except in conditions of severe systemic inflammation, signalling of systemic inflammation to the healthy brain does not involve structural damage".

- "It is important to highlight the distinction between signalling by molecules typically associated with inflammation and an inflammatory response *per se*. During systemic inflammation there is induction of IL-1β and other proinflammatory cytokines, but there is no inflammatory response in the brain. It is of interest that microinjection of IL-1β into the brain at concentrations that would typically give rise to inflammation in peripheral tissues does not lead to typical inflammation within the brain parenchyma. This indicates that the biological significance of IL-1β in the brain parenchyma is different from that in other tissues".

- "Although we have the necessary tools to image inflammation in the brain, it seems we do not have sufficiently sensitive tools to image signalling in the brain consequent to a systemic inflammatory response".

- "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. Targeting cell trafficking into the central nervous system is unlikely to be a very useful approach since symptoms of sickness are dependent on the activation of brain cytokine signalling independently of any blood cell recruitment".

- "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 Review notes that despite major advances in the understanding of the immune-to-brain communication pathways that underlie the pathophysiology of symptoms in inflammatory conditions, little has been done to translate this knowledge to the clinics.

## Essential investigations for people with ME/CFS?

***16th January 2008***

As NICE is now in the process of contacting selected people asking for their input on the advisability of it producing guidance on the use of Ampligen in "CFS/ME", might NICE also be persuaded to seek the input of experienced vascular biologists on the advisability of it recommending specific testing for inflammation in ME/CFS?