

Advances in the biomedical investigation of M.E.

By Dr Neil Abbot and Dr Vance Spence

*Now all the youth of England are on fire,
And silken dalliance in the wardrobe lies;
Now thrive the armourers, and honour's thought
Reigns solely in the breast of every man:
.....For now sits Expectation in the air (Henry V, II, chor. 1, 2)*



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Expectation in the air?! For thousands of people with M.E., living day-to-day with debilitating malaise and pain, the future must sometimes seem bleak indeed. Studies tell us that around 50% are employed but struggling to maintain their lives, with another 40% existing on benefits. While putative treatments come and go in the newspapers and the internet, on the ground people remain unwell with a physical illness. Despite the sterling efforts of support groups many still struggle to get appropriate recognition and help from healthcare professionals.

Yet, for the first time in many years, we both feel optimistic about potential biomedical advances in M.E. research. Although there are several reasons for optimism, this short article will concentrate on just two – the discovery that physiological abnormalities can be detected in many patients with M.E., and the growing realisation by researchers that problems with the case definition of Chronic Fatigue Syndrome (CFS) perplex and confound research into the illness.

Importance of reproducing key findings

First, it is becoming clear from a range of studies that altered biochemical processes can be *reproducibly* observed in groups of M.E. patients, as seen from investigations of anti-viral pathways and oxidative stress. The ability to reproduce a finding is crucial and at the core of scientific investigation. Indeed, it is the basis of modern evidence-based medicine.

The table on page 15 is based on our report of the 2003 Royal Society of Edinburgh/Wellcome Trust workshop on M.E. and lists some recent areas of progress that may prove to be important. A discussion of just one of these developing areas will illustrate what can be achieved if scientific effort and funding are targeted towards a specific research concept, which might well be the stimulus for therapeutic intervention once the processes involved are clarified.

A closer look at free radical damage

Let's consider, for instance, the role of increased oxidative stress. Circulating in the bloodstream are highly reactive molecules, known as free radicals, which can cause damage to the cells of the body; a process called oxidative stress. In healthy people, increases in oxidative free radicals are neutralised by antioxidant defences, and it is only when these defences are overwhelmed that oxidative stress and consequently cell injury results. Such damage is implicated in a number of conditions, including cardiovascular disease, most neurological diseases (including Alzheimer's), and the ageing process.

The chemistry of free radicals is outside the scope of this article, but research papers (from at least five separate research groups) have shown excessive free radical generation in blood, urine and muscle tissues of CFS patients. Indeed, one research group has reported that oxidative by-products were raised by as much as 40% in

these patients compared with healthy control subjects.

It is important to discover the source(s) of these molecules, whether from excessive immune activity, chronic infections or from abnormalities within muscle tissue. There is sufficient evidence to implicate all three of these pathways.

Dedicated funding yields results!

One of the cardinal facts about research work generally is that breakthroughs follow funding (since without it there is no possibility of starting the exploration!). A case in point is the work at the Vascular Diseases Unit in the University of Dundee which, given consistent funding for the past three years, has reported several interesting findings in CFS patients.

For example, our group within this unit has found that vascular (blood vessel) responses to acetylcholine are increased compared with matched control subjects. (Acetylcholine is a substance produced by the layer of endothelial cells lining all blood vessels and which causes them to open). This finding is in contrast to research into a wide variety of cardiovascular diseases – such as diabetes, stroke and high cholesterol – where blood flow responses to acetylcholine are normally blunted. *Why should CFS patients have this seemingly unique thumbprint of increased blood vessel sensitivity to acetylcholine?*

Physiological and biochemical abnormalities found in groups of patients meeting the broad criteria for 'CFS'

Example references are given in brackets.

BIOCHEMICAL	Oxidative stress – explained on page 14 (Richards 2000 et al.; Manuel 2001 et al.; review by Pall 2001; Kennedy et al. 2003; Vecchiet et al. 2003) Dysregulation of anti-viral pathways – i.e. abnormal activity of the anti-viral immune responses (Suhadolnik RJ et al. 1994; De Meirleir et al. 2000; Tiev et al 2003)
VASCULAR – (relating to the circulation)	Endothelial dysregulation – i.e. abnormal responses of small blood vessels selectively to acetylcholine (Spence et al. 2000; Khan et al. 2003 and 2004) Altered brain perfusion i.e. areas of reduced blood flow in the brain (Ichise et al 1992; Costa et al. 1995; Tirelli et al. 1998) Orthostatic hypotension i.e. physiological changes to blood pressure/cardiovascular mechanisms on standing (Streeten et al. 2001; Naschitz et al. 2002; Stewart et al. 2003)
BRAIN	Metabolic abnormalities e.g. alterations of brain choline (important in brain function). (Tomoda et al. 2000; Puri et al. 2002; Chaudhuri et al. 2003)
MUSCLE	Altered metabolism – e.g. changes in muscle composition or use of fuel. (Fulle et al. 2000; Vecchiet et al. 2003; Fulle et al. 2003) Abnormal response to exercise (Lane et al. 1998; Paul et al. 1999; McCully et al. 2004). Enteroviral sequences in muscle – i.e. evidence of a persisting virus in <i>some</i> CFS patients (Lane et al. 2003; Douche-Aourik F et al. 2003)

In addition, we have found that levels of high-sensitivity C-reactive protein, recognised as a robust marker of the inflammatory process, are significantly increased in CFS patients. We have also observed that a type of white blood cells (called neutrophils) from these patients had a larger proportion of dying (apoptotic) cells than in healthy subjects. These findings are consistent with an activated inflammatory process, possibly the consequence of a past or present infection. *Might some people with CFS have a chronic inflammatory disorder, albeit an unusual one?*

Importantly, a high proportion of these patients had measurable signs of muscle weakness in the arms and/or legs, indicating that clinical signs (rather than self-reported symptoms) can, in fact, be detected in these patients if physicians take care to do a full physical examination.

Important markers of physical illness

Intriguingly, reports in the older literature (1950s and 1960s) on epidemics of 'classical' M.E. were founded on the presence of clinical signs (e.g., muscle weakness/swelling; sensory nerve changes; observable

recurrences of flu-like illness, etc). If these results can be reproduced by other researchers, the implications for further research and for the management of patients are significant. *Will the presence of clinical signs – believed by many healthcare professionals today to be non-existent in M.E. patients – come to be recognised as important markers of physical illness?*

Our purpose here is not to answer these questions, but to show that dedicated investigators who receive sufficient funding can uncover, within a proportion of 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 intervention.

Why we loathe the 'F' word

The second area for optimism is the growing recognition that the category 'CFS' is unsafe and unsatisfactory. The most widely-used definition of CFS – the Fukuda definition – was developed by the US Centres for Disease Control in 1994 by a consensus conference and was not therefore evidence-based on



Reproducible biological anomalies are now being found in M.E. patients

hard data. Its limitations are many. It relies on 'fatigue' as the major criterion, and for that reason alone many patients who fall under this diagnostic label hate the name and use of the 'F-word'. Why? Because for many patients, 'fatigue' itself is not their major problem and does not best represent their experience of pain, malaise, and cognitive problems.

Furthermore, the category 'CFS' makes no attempt to differentiate patients on the basis of severity of illness or level of functional disability and this too may be problematic. Importantly, its specificity is poor, allowing patients with different illnesses (possibly, those with classical viral-onset M.E., fibromyalgia syndrome, or a chronic-fatigue-psychiatric illness) to have a single, common (some say 'dustbin') diagnosis.

In 1995, an article in the *Medical Journal of Australia* asked the question, 'Is CFS a recognisable disease entity with a unique pathophysiology, or is it a ragbag of common non-specific symptoms with many causes, mistakenly labelled as a syndrome?' There is a growing consensus that the answer is very much the latter.

Subgroups come to the fore

In the past months, the authors of at least seven scientific studies have recommended the extraction of 'research-based subsets' based on their findings on CFS patients. Their views are supported by our own research, reported in the journal *Annals of*

Epidemiology in February 2004 (Kennedy et al). This looked at three groups of patients who reported that they had become ill: a) following suspected organophosphate poisoning; b) following service in the Gulf War of 1991; or c) 'sporadically' (a group representing most cases of CFS in the population).

Shattering of the term CFS might allow many patients to move out of the 'dustbin' and into the specific clinic where they belong

Despite the fact that everyone in the study fulfilled the broad CDC-1994 criteria for CFS, clear measurable differences between the three groups were observed in terms of muscle pain and strength, biological parameters, and depression and mental health, highlighting the extraordinary inclusiveness of the case definition for CFS.

This seemingly obscure point about diagnostic classification is actually very important, because the treatment and resources that patients receive is determined, to a large part, by the diagnosis they are given. We believe

that the shattering of the term CFS might allow many patients to move out of the 'dustbin' and into the specific clinic where they belong.

Where do we go from here?

This article has described two fine breezes contributing to a growing air of expectation. As attention turns from various quasi-alternative therapies, biomedical investigation moves to centre stage. The medium to long-term aim is nothing less than a clinical or scientific thumbprint for each of the specific subgroups of CFS patients. Such an advance would be the single transforming event in the lives of many thousands of people.

Experience has convinced us, however, that if this is to be achieved, the funding strategy for M.E. must mirror that of cancer research which obtains 85-90% of its revenue from private sources and ground-level fundraising. It is a huge task, but much can be achieved by a determined and collaborative M.E. community.

The term 'M.E.' has been used throughout this article (since it is the recognised lay term), except where reference is made to research studies investigating formally-defined 'CFS' patients.



Further information

A full list of references to accompany this article, and/or a copy of the workshop report, 'New developments in the biology of M.E./CFS' (small donation welcome), can be obtained from MERGE, The Gateway, North Methven St, Perth PH1 5PP or e-mail merge@pkavs.org.uk.

Alternatively, you can read parts of the aforementioned report and find out more about MERGE's work by visiting www.meresearch.org.uk.