Medication and ME/CFS?

Margaret Williams **27th August 2008**

Mitochdondria are the powerhouses of the cells. They are responsible for generating energy as adenosine triphosphate (ATP) and are involved in the apoptosis signalling pathway (apoptosis being programmed cell death).

There is a significant literature suggestive of mitochondrial defects (both structural and functional) in ME/CFS from 1984 to date and it is accepted by informed ME/CFS clinicians and researchers that there is actual biopsy evidence of mitochondrial damage in ME/CFS, for example:

- Behan WM et al, Acta Neuropathol 1991:83(1):61-65 ("*Mitochondrial degeneration was obvious in 40 of the biopsies, with swelling, vacuolation, myelin figures and secondary lysosomes. The pleomorphism of the mitochondria in the patients' muscle biopsies was in clear contrast to the findings in the normal control biopsies. Diffuse or focal atrophy of type II fibres has been reported, and this does indicate muscle damage and not just muscle disuse"*)

- Pizzigallo E et al, JCFS 1996:2 (2/3):76-77 (*"We performed histochemical and quantitative analysis of enzymatic activities and studies of mitochondrial DNA deletions. All specimens showed hypotrophy, fibres fragmentation, red ragged fibres, and fatty and fibrous degeneration. Electron microscopy confirmed these alterations, showing degenerative changes, and allowed us to detect poly/pleomorphism and cristae thickening of the mitochondria. The histochemical and quantitative determination of the enzymatic activity showed important reduction, in particular of the cytochrome-oxydase and citrate-synthetase. The 'common deletion' of 4977 bp of the mitochondrial DNA was increased as high as 3,000 times the normal values in three patients. Our results agree with those of Behan et al 1991 and Gow et al 1994. The alterations are compatible with a myopathy of probable mitochochondrial origin (which) could explain the drop in functional capability of the muscle")*

- Cheney P, Orlando Workshop, International Congress of Bioenergetic Medicine 1999, audio tape #2 ("*The most important thing about exercise is not to have them do aerobic exercise. If you have a defect in the mitochondrial function and you push the mitochondria by exercise, you kill the DNA").* Cheney's findings were supported by Benjamin Natelson, Professor of Neurology at New Jersey Medical School – in his 1999 lecture at the Fatigue 2000 Conference in London, Natelson discussed his work on muscle metabolism using NMR testing the muscle of patients with ME/CFS after exercise, in which his team demonstrated a problem with mitochondrial recovery; this Conference was reported in the ME Association Newsletter Perspectives, Summer 1999:18

- Klimas NG et al, Curr Rheumatol Rep 2007:9(6):482-487 (*"Gene microarray data have led to better understanding of pathogenesis. Research has evaluated genetic signatures (and) described biologic subgroups. Genomic studies demonstrate abnormalities of mitochondrial function"*).

- Nestadt P: http://www.cfids.org/cfidslink/2007/neurobiological.asp (*"These results show that a significant proportion of patients diagnosed with (ME)CFS have elevated ventricular lactate levels, suggesting anaerobic energy conversion in the brain and / or mitochondrial dysfunction").* (Elevated blood lactate levels after mild exercise are considered to be a sign of mitochondrial damage)

- Bell DS: http://dfwcfids.net/index.php?option=com_content&task=view&id=2007&Itemid=754 ("*I agree that ME/CFS is a mitochondrial disease (but) ME/CFS is a mitochondrial disease like no other. There are lots of studies that implicate mitochondrial problems: Dr Hirohiko Kuratsune and carnitine; Dr Suzanne Vernon and genomics; Dr Kenny DeMeirlier (Brussels); Dr Martin Pall (New York); Dr Paul Cheney and many others").*

That there is evidence of disrupted apoptosis in ME/CFS cannot be disputed (Increased neutrophil apoptosis in Chronic Fatigue Syndrome. Kennedy G et al. J Clin Pathol 2004:57(8):891-893)

Attention is therefore drawn to a paper by Neustadt and Pieczenik which reviews the evidence that medications have now emerged as a major cause of mitochondrial damage (Medication-induced mitochondrial damage and disease. Mol Nutr Food Res 2008:52:780-788).

In addition to medication-induced systemic dysfunction, systems most affected are listed as being the muscles, brain, nerves, kidneys, heart, liver, eyes and pancreas.

Acquired conditions in which mitochondrial dysfunction has been implicated include (ME)/chronic fatigue syndrome and fibromyalgia.

The mechanisms of mitochondrial-induced injury and the damage caused by medication-induced production of free radicals are explained in detail by the authors.

Medications documented to induce mitochrondial damage include analgesics; anti-inflammatories; anaesthetics; angina medications; antibiotics; antidepressants; anxiolytics; barbiturates; cholesterol-lowering medications (statins); chemotherapy; and the mood-stabiliser lithium, amongst others, including medications for Parkinson's Disease, diabetes, cancer and HIV/AIDS.

It is a matter of record that psychiatrist Professor Simon Wessely advises the prescription of lithium for patients with ME/CFS: "*There is no doubt that at least half of CFS patients have a disorder of mood. The management of affective disorders is an essential part of the treatment of CFS/ME. Numerous trials attest to the efficacy of tricyclic antidepressants in the treatment of fatigue states.* ***Patients who fail to respond should be treated along similar lines to those proposed for treatment-resistant depression. Adding a second antidepressant agent, especially lithium, may be beneficial****"* (The chronic fatigue syndrome – myalgic encephalomyelitis or postviral fatigue. S Wessely PK Thomas. In: Recent Advances in Clinical Neurology (ed): Christopher Kennard. Churchill Livingstone 1990: pp 85-131).

In addition to lithium, specific medications listed that are known to induce mitochondrial damage include aspirin; acetaminophen (paracetamol / Tylenol); fenoprofen (Nalfon); indomethacin (Indocin, Indocid); naproxen (Naprosyn); lidocaine; amiodarone (Cordarone); tetracycline; amtitriptyline; citalopram (Cipramil); fluoxetine (Prozac); chlorpromazine (Largactil); diazepam (Valium); galantamine (Reminyl) and the statins, amongst others.

The authors state that damage to mitochondria may explain the side effects of many medications: "*Recently it has become known that iatrogenic mitochondrial (damage) explains many adverse reactions from medicines"*.

It was in 1994 at the Dublin International Meeting on ME/CFS (held under the auspices of the World Federation of Neurology) that Charles Poser, Professor of Neurology at Harvard, confirmed that adverse reactions to medication is virtually "*pathognomonic"* of ME/CFS, and that a paradoxical or inappropriate reaction to medications is one of the most important criteria in ME/CFS.

As Neustadt and Pieczenik state that mitochondrial dysfunction has been implicated in fibromyalgia (FM) as well as in (ME)CFS, and as FM has been recognised as an additional burden of suffering in many patients with ME/CFS (Buchwald D et al. Rheum Dis Clin N Am 1996:22:2:219-243), it is of interest that a 2007 paper estimated the prevalence and number of FM patients in ten countries, looking specifically at FM patients' AAT (alpha-1 antitrypsin) phenotypic distribution worldwide. Those countries were Canada, the USA, Denmark, Finland, Germany, Italy, the Netherlands, Spain, Sweden and Pakistan. The authors noted that during the last few years, clinical, epidemiological and pathological evidence suggests that alpha-1 antitrypsin (AAT) deficiency may play a role in the development of FM. Studies on AAT gene frequencies and FM were retrieved from all ten countries. Results showed that a severe deficiency Z allele was found in all these countries, with very high frequencies in Denmark and Sweden; high frequencies in Italy and Spain; intermediate frequencies in Germany, the Netherlands, Canada and the USA, and a low

frequency in Pakistan. The authors conclude that AAT phentotype characterisation should be recommended in all FM patients, and that the possible efficacy of AAT replacement therapy in severely deficient FM patients warrants further study.

This is evidence that argues robustly against the Wessely School belief that, together with "CFS/ME", FM is a single somatoform disorder (S Wessely et al. Lancet 1999:354:936-939).

It also adds to the existing evidence that demonstrates the lack of scientific rigour accepted by the Medical Research Council (MRC) in permitting the Wessely School investigators (who are in charge of the PACE trials on cognitive behaviour therapy and graded exercise therapy in "CFS/ME") intentionally to include people with FM in those trials. Including different patient populations from the outset will inevitably skew the results, and under the WHO taxonomic principles, FM is classified separately from ME/CFS at ICD-10 M79, whereas ME/CFS is classified at G93.3.

Of further concern is the fact --- confirmed by the then Minister of State Dr Stephen Ladyman in July 2004 at the All Party Parliamentary Group of Fibromyalgia (now disbanded) ---that doctors were offered financial inducements to persuade those who do not have ME/CFS (but who have FM) to take part in the MRC trials.

In a separate paper by Professor Julia Newton et al comparing mitochondrial function in patients with primary biliary cirrhosis (PBC), patients with primary sclerosing cholangitis, patients with ME/CFS and normal controls (Pilot Study of Peripheral Muscle Function in Primary Biliary Cirrhosis: Potential Implications for Fatigue Pathogenesis. Hollingsworth KG, Newton JL et al. Clin Gastroenterol Hepatol; in press, September 2008) the authors state that PBC is characterised in 95% of patients by autoantibody responses directed against the mitochondrial antigen pyruvate dehydrogenase complex (PDC). To define mitochondrial function in peripheral muscle during exercise, (31)P magnetic resonance spectroscopy was used.

Whilst the paper is chiefly concerned with mitochondrial dysfunction in patients with primary biliary cirrhosis (and the results clearly indicate mitochondrial dysfunction in patients with PBC, who showed excess muscle acidosis at higher levels of exercise), the authors state about ME/CFS patients: "*Interestingly, prolonged time to maximum proton efflux was also seen in the (ME)CFS control group, indicating that there are aspects of muscle pH handling that are abnormal in this important clinical group".*

Professor Newton is Lead Clinician in the internationally renowned Cardiovascular Investigations Unit at the University of Newcastle, UK, which is the largest autonomic function testing laboratory in Europe; her work focuses on the role of the autonomic nervous system in the development of fatigue, specifically in primary biliary cirrhosis, but also in the pathogenesis of fatigue in ME/CFS. In her Conference pack for the ME Research UK International Research Conference held at the University of Cambridge on 6th May 2008, Professor Newton said: "*Recent results from a series of MR scans have shown impaired proton removal from muscle during exercise in patients with ME/CFS compared to matched controls. This has led us to hypothesise that fatigue arises due to impaired pH run off from muscle during exercise which is influenced by the degree of autonomic dysfunction".*

Despite the irrefutable evidence of mitochondrial dysfunction and damage in patients with ME/CFS, the NICE Guideline on "CFS/ME" proscribes mitochondrial testing and recommends only behavioural modification in the form of cognitive behavioural therapy, together with incremental aerobic exercise, and refers to "***perceived exertion***" (52 page version, page 30). It claims that it *"**offers the best practice advice on the care of people with CFS/ME"*** (52 page version, page 6) and that its advice is "***evidence-based***". It is notable that the alleged evidence-base upon which the Guideline Development Group relied specifically states: "*If patients complained of increased fatigue, they were advised to continue at the same level of exercise"* (Fulcher and White, BMJ 1997:314:1647-1652). Given the evidence of mitochondrial damage, such advice cannot conceivably qualify as "*best practice advice*".