Response to Jo Edwards

Professor Emeritus Jonathan Edwards states in his Qeios Review Article: *"The absence of structural or biochemical pathology in ME/CFS has meant that definition is based entirely on symptoms and their dynamics over time"* (A Proposed Mechanism for ME/CFS Invoking Macrophage FcγRI and Interferon Gamma. 27th May 2025: Preprint Vl. CC-BY 4.0 doi.org/10.32388/8GI3CT).

With no disrespect to Professor Edwards, structural and biochemical abnormalities and impaired muscle recovery after exercise are well-documented in ME/CFS: given the sheer extent of published and "grey" evidence (eg. evidence presented at conferences) that disproves such an assertion, it is difficult to understand why Professor Edwards does not recognise this.

Does this mean that Professor Edwards rejects, for instance, the evidence of structural degradation of muscle found in ME by the late Professor Wilhelmina Behan, a recognised and renowned international authority on muscle pathology? Her findings are unambiguous: *"Evidence of mitochondrial abnormalities was present in 80% of the cases with the commonest change (seen in 70%) being branching and fusion of cristae, producing 'compartmentalisation'. Mitochondrial pleomorphism, size variation and occasional focal vacuolation were detectable in 64%…Vacuolation of mitochondria was frequent…In some cases there was swelling of the whole mitochondrion with rupture of the outer membranes…prominent secondary lysosomes were common in some of the worst affected cases…The pleomorphism of the mitochondria in the patients' muscle biopsies was in clear contrast to the findings in 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"* (WMH Behan et al. Acta Neuropathologica 1991:83:61-65).

In respect of Professor Edwards' denial of biochemical pathology, there is clear evidence of reduced blood volume in most ME patients. A frequent clinical presentation of this is postural intolerance and persistent thirst. Professor Edwards may not be familiar with this as he does not see patients with ME. The cause is invariably impairment of the hypothalamic-pituitary-adrenal axis. Demitrack et al were the first to describe this in 1991 (Journal of Clinical Endocrinology and Metabolism 1991:73:6:1224-1234), since when there have been many papers confirming this finding. A consultant physician recently informed me that most patients he sees arrive at the consultation with a bottle of water. They then proceed to drink from this throughout the consultation. Some also have to empty their bladder half way through the consultation because of excessive urinary output secondary to the HPA axis deficiency.

A few examples of documented muscle abnormalities in ME/CFS

1. **1984**: Arnold et al demonstrated excessive intracellular acidosis of skeletal muscle on exercise in ME/CFS patients, with a significant abnormality in oxidative muscle metabolism and a resultant acceleration in glycolysis (Proceedings of the Third Annual Meeting of the Society for Magnetic Resonance in Medicine, New York: 1984: 12-13).

2. **1985**: "*The most important findings were type II fibre predominance, subtle and scattered fibre necrosis and bizarre tubular structures and mitochondrial abnormalities. About 75% of the patients had definitely abnormal single fibre electromyography results"* (Goran A Jamal Stig Hansen JNNP 1985:48:691-694).

3. **1987**: Leonard Archer demonstrated *"Muscle biopsies showed necrosis and type II fibre predominance*" (JRCGP: 1987:37:212-216).

4. **1988:** "*What is certain is that it becomes plain that this is an organic illness in which muscle metabolism is severely affected*" (Crit Rev Neurobiol: 1988:4:2:157-178).

5. **1988**: Archard and Bowles et al published the results of their research into muscle abnormalities in ME/CFS: "*These data show that enterovirus RNA is present in skeletal muscle of some patients with postviral fatigue syndrome up to 20 years after onset of disease and suggest that persistent viral infection has an aetiological role. These results provide further evidence that Coxsackie B virus plays a major role in ME, either directly or by triggering immunological responses which result in abnormal muscle metabolism"* (JRSM 1988:81:325-331).

6. **1988**: Teahon et al published a study of skeletal muscle function in ME/CFS; it showed significantly lower levels of intracellular RNA, suggesting that ME/CFS patients have an impaired capacity to synthesise muscle protein, a finding which cannot be explained by disuse (Clinical Science 1988: 75: Suppl 18:45).

7. **1989**: Professor Tim Peters spoke at a meeting of microbiologists held at the University of Cambridge: "*Other muscle abnormalities have been reported, with decreased levels inside the cell of a key enzyme called succinate dehydrogenase, which plays an important role in energy production inside the mitochondria (the power house of the cell)".* A report of this conference was published in the ME Association Newsletter, Autumn 1989, page 16.

8. **1990**: ***"Previous studies have shown biochemical and structural abnormalities of muscle in patients with the chronic fatigue syndrome"*** (Aerobic work capacity in patients with chronic fatigue syndrome. MS Riley DR McClusky et al BMJ:1990:301:953-956).

9. **1991:** *"The features of this disorder suggest that the fatigue is caused by involvement of both muscle and the central nervous system…We used the polymerase chain reaction to search for the presence of enteroviral RNA sequences in a well-characterised group of patients with the postviral fatigue syndrome…53% were positive for enteroviral RNA sequences in muscle…Statistical analysis shows that these results are highly significant…On the basis of this study…there is persistent enteroviral infection in the muscle of some patients with the postviral fatigue syndrome and this interferes with cell metabolism and is causally related to the fatigue" (*JW Gow et al. BMJ 1991:302:696-696).

10. **1992**: US researchers (including Robert Gallo, the co-discoverer of the HIV virus) found that *"57% of patients were bed-ridden, shut in or unable to work. Immunologic (lymphocyte phenotyping) studies revealed a significantly increased CD4 / CD8 ratio. Magnetic resonance scans of the brain showed punctate, subcortical areas of high signal intensity consistent with oedema or demyelination in 78% of patients. 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"* (A chronic illness characterized by fatigue, neurologic and immunologic disorders, and active human herpes Type 6 infection. Dedra Buchwald, Paul Cheney, Robert Gallo, Anthony L Komaroff et al Ann Intern Med 1992:116:2:103-113).

11. **1992:** A Press Release for the Albany, New York, International Clinical and Research Conference on ME/CFS (held on 2nd-4th October 1992) from the Department of Neurology, Institute of Neurological Science, University of Glasgow said: "*We will report…our new findings relating particularly to enteroviral infection. We have now extended our PCR data to cover hundreds of patients together with controls and have continued to find a very significant proportion of the patients' muscle biopsies to contain enterovirus on PCR. In addition we have used several different types of enteroviral primers and have obtained identical results in the patients with these primers, the control muscle biopsies from healthy subjects and patients with other muscle diseases being entirely negative. We furthermore have isolated RNA from patients and probed this with large enterovirus probes which demonstrated that full length 7.4 kilobase virus was present in these patients. Indeed, detailed studies including Northern Blot analysis showed that the material was true virus….Furthermore, this virus was shown to be replicating normally at the level of transcription. Sequence analysis of this isolated material showed that it had 80% homology with coxsackie B viruses and 76% homology with poliomyelitis virus, demonstrating beyond doubt that the material was enterovirus. We were able to extend these studies…by being able to study post-mortem material from a definite case of chronic fatigue syndrome….This showed that enterovirus was present in skeletal muscle, in heart muscle, but particularly was abundant in brain. Detailed studies of the brain enterovirus revealed that it was most prevalent in diencephalic, particularly hypothalamic, regions".*

12. **1993:** UK researchers Barnes et al demonstrated that there is a significant abnormality in oxidative muscle metabolism with a resultant acceleration in glycolysis in ME/CFS patients (JNNP:1993:56:679-683).

13. **1995**: "*We examined venous blood lactate responses to exercise at a work rate below the anaerobic threshold in relation to psychiatric disorder. Our results suggest that some patients with ME/CFS have impaired muscle metabolism that is not readily explained by physical inactivity or psychiatric disorder"* (Lane & Archard: BMJ 1995:311:544-545).

14. **1995**: UK researchers Geoffrey Clements et al reported that: "*Enteroviral sequences were found in significantly more ME/CFS patients than in the two comparison groups. The presence of the enteroviral sequences in a significant number of patients points to some role in ME/CFS. A variety of immunological disturbances have been reported for ME/CFS patients which may relate in some way to the enteroviral persistence. This study provides evidence for the involvement of enteroviruses in just under half of the patients presenting with ME/CFS and it confirms and extends previous studies using muscle biopsies. We provide evidence for the presence of viral sequences in serum in over 40% of ME/CFS patients*" (J Med Virol 1995:45:156-161).

15: **1996**: Pizzigallo E et al reported: *"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-oxidase 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 mitochondrial origin (which) could explain the drop in functional capability of the muscle"* (JCFS 1996:2:(2/3):76-77)

16. **1998:** UK researchers Russell Lane and Leonard Archard published their findings of muscle abnormalities in response to exercise in ME/CFS patients: "*The object of this study was to examine the proportions of types I and II muscle fibres and the degree of muscle fibre atrophy and hypertrophy in patients with ME/CFS in relation to lactate responses to exercise, and to determine to what extent any abnormalities found might be due to inactivity. Muscle fibre histometry in patients with ME/CFS did not show changes expected as a result of inactivity. The authors note that one of these patients had an inflammatory infiltrate, and it would seem that inflammation and class I MHC expression may occur in biopsies from patients with ME/CFS. The authors note that this is of some interest, as they have argued previously that some forms of ME/CFS may follow a previous virally-mediated inflammatory myopathy".* In general, following exercise, patients with ME/CFS showed more type I muscle fibre predominance and infrequent muscle fibre atrophy, unlike that which would be expected in healthy sedentary people. (JNNP 1998:64:362-367).

17. **1999**: Paul et al provided irrefutable evidence of delayed muscle recovery after exercise: "*The use of 31 P-nuclear magnetic resonance (31 P-NMR) has now provided positive evidence of defective oxidative capacity in ME/CFS. Patients with ME/CFS reach exhaustion more rapidly than normal subjects, in keeping with an abnormality in oxidative metabolism and a resultant acceleration of glycolysis in the working skeletal muscles. When the rate of resynthesis of phosphocreatine (PCr) following exercise is measured, this abnormality is confirmed. (This) provides a conclusive demonstration that recovery is significantly delayed in patients with ME/CFS. The results demonstrate that patients with ME/CFS fail to recover properly from fatiguing exercise and that this failure is more pronounced 24 hours after exercise*" (European Journal of Neurology 1999:6:63-69).

18. **2025:** It is notable that a newly-released Dutch study found that the changes seen in ME/CFS patients differed from those of healthy but inactive people, with patients showing change in muscle fibres, problems with energy production in the muscles due to poorly functioning mitochrondria and fewer capillaries in the muscles of ME/CFS patients (Amsterdam UMC & the Vrijie Universiteit Amsterdam website MedRxiv).

I mention just one more illustration: in 2001 evidence was presented by SCM Richards et al (including psychiatrist Anthony Cleare, who works with and co-authors papers on ME/CFS with Simon Wessely) at the British Rheumatologists' Conference in Edinburgh showing that 53% of ME/CFS patients were excreting in their urine significant levels of creatine and other muscle-related metabolites including choline and glycine, indicating on-going muscle damage, as creatine has been shown to be a sensitive marker of muscle inflammation and this is objective evidence of muscle pathology.

Finally, it would be helpful if Professor Edwards would be kind enough to explain for non-immunologists if his postulation disproves or substantiates the view of Professor Nancy Klimas, then Clinical Professor of Medicine in Microbiology/Immunology/Allergy and Psychology, University of Miami School of Medicine and undoubtedly one of the world's foremost researcher-clinicians into the aberrant immunology seen in ME/CFS patients. She maintains that 80% of all ME/CFS patients – both severely and not so severely ill – have evidence of

inflammation if the correct scans are used. She further maintains that in fact, 100% of ME/CFS patients have chronic inflammation (2008: personal communication). Does Professor Edwards agree?

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