This paper documents a rising tide of research and related policy and guidance pertinent to the diagnosis and care of patients with myalgic encephalomyelitis, commonly referred to as myalgic encephalomyelitis/ chronic fatigue syndrome (ME/CFS), cumulatively representing a sea change occurring over the last ten years.

April 2014

Publications and Initiatives

relevant to the care of patients with myalgic encephalomyelitis/chronic fatigue syndrome

- documenting trajectory of change -

- USA 2014 - *Diagnosis and Treatment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome,* Evidence Report/Technology Assessment for the Agency for Healthcare Research and Quality (AHRQ).[1]

- USA 2014 - National Institutes of Health (NIH) Pathways to Prevention (P2P) Workshop *Advancing the Research on Myalgic Encephalomyelitis/Chronic Fatigue Syndrome,* co-sponsored by the NIH Office of Disease Prevention and the Trans-NIH Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Research Working Group.[2]

- USA 2015 - *Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness,* National Academies of Science, Institute of Medicine (IoM) Report, study sponsored by the Department of Health and Human Services (HHS), the NIH, the Centres for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), the AHRQ and the Social Security Administration. [3]

- USA 2015 the Chronic Fatigue Syndrome Advisory Committee (CFSAC) provides recommendations to the Secretary for Health and Human Services, informed by the above developments, the conclusions of which drew on comprehensive reviews of peer reviewed research papers and testimony from expert researchers and clinicians in the field. The CFSAC advise:[4]
  - That both the IoM and P2P reports have identified definitive evidence of biological impairment.
  - That the disease is not psychiatric in nature and should not be equated with neurasthenia, somatic symptom disorder, or functional somatic syndrome.
  - That there is strong scientific evidence of immunologic and inflammatory pathologies, neurotransmitter signaling disruption, microbiome perturbation, and metabolic or mitochondrial abnormalities in the disease.
  - That the disease is not synonymous with "chronic fatigue," "idiopathic fatigue" or "fatigue syndrome."

- England and Wales 2015 - in view of these developments in the USA, the National Institute for Health and Care Excellence (NICE) conclude *The new criteria may affect the interpretation of all preceding evidence that may have used different inclusion criteria for study participants.*[5]

- Publication, Fatigue: Biomedicine, Health & Behavior 2016 - analysis of PACE trial data on 'recovery' according to the original trial protocol.[6] Findings include:
  - Previously reported recovery rates in respect of 'graded exercise therapy' and a specialised form of cognitive behavioural therapy (CBT) [7] were based on a

definition that differed markedly from that specified in the trial protocol, and so lax that it was possible to score below the level required for trial entry, and/or to deteriorate over the course of the trial, yet be rated as 'recovered'.

- Defined according to the original protocol, recovery rates in the 'graded exercise therapy' and CBT groups were 4% and 7%, respectively.
- *"The claim that patients can recover as a result of CBT and GET is not justified by the data, and is highly misleading to clinicians and patients considering these treatments"*

- England and Wales 2016 - NICE begin a formal check of the requirement to update their 2007 guideline (CG53), noting (i) that the US reports imply that there are likely to be changes in diagnostic criteria that will have implications for the guideline; (ii) that they have been made aware of new information about the PACE trial.[8]

- England and Wales 2017 - NICE decide to fully update their guideline.[9] Evidence deemed to point to potential need for change included:
  - *'Neurohumoral and haemodynamic profile in postural tachycardia and chronic fatigue syndromes.'*[10] The authors conclude: *"Because there were no distinguishing features between POTS patients with and without CFS, we propose that CFS–POTS is not a separate clinical entity distinct from POTS without CFS. Rather, CFS seems to be part of the spectrum of POTS, associated with greater sympathetic activation and/or a more severe form of this condition."*
  - *'Clinical characteristics of a novel subgroup of chronic fatigue syndrome patients with postural orthostatic tachycardia syndrome.'*[11] NICE identify the potential relevance: *"The presence of POTS marks a distinct clinical group of CFS patients, with phenotypic features differentiating them from those without POTS. A combination of validated clinical assessment tools can determine which CFS patients have POTS with a high degree of accuracy, and thus potentially identify those who require further investigation and consideration for therapy to control heart rate."*
  - *'Myalgic encephalomyelitis/chronic fatigue syndrome patients' reports of symptom changes following cognitive behavioural therapy, graded exercise therapy and pacing treatments: Analysis of a primary survey compared with secondary surveys'.*[12] Based on reports from around 18,000 patients across multiple surveys from the UK and Europe, this analysis identified that, with regard to these approaches: cognitive behavioural therapy is of benefit to a small percentage of patients; graded exercise brings about large negative responses in patients; pacing has the lowest negative response rate and the highest reported benefit.
- Publication, BMC Psychology 2018 - Outcomes in respect of the PACE trial based on the original protocol-specified procedures.[13]
  - Conclusion: *"These findings raise serious concerns about the robustness of the claims made about the efficacy of CBT and GET."*

- Publication, JAMA 2019 - *Advances in Understanding the Pathophysiology of Chronic Fatigue Syndrome by* Anthony Komaroff MD, Professor of Medicine at Harvard Medical School.[14] Prof Komaroff advises:

- *"Over the past 35 years, thousands of studies from laboratories in many countries have documented underlying biological abnormalities involving many organ systems in patients with ME/CFS, compared with healthy controls: in short, there is something wrong."*
- *"Moreover, most of the abnormalities are not detected by standard laboratory tests."*
- *"It is clear that many biological measurements clearly distinguish patients with ME/CFS from healthy control individuals."*

- England 2019 - Dr Nina Muirhead appears before the NICE Guideline Committee in the capacity of Expert on Medical Education in ME/CFS. Her testimony includes the following points:[15]
  - *"In the past, ME/CFS has been characterized as a syndrome of medically unexplained fatigue responsive to talk therapy and graded exercise. But scientific advances are revealing a complex, multisystem disease involving neurological, immunological, autonomic, and energy metabolism impairments. There is a critical need for a different approach to management of the disease and accompanying comorbidities."*[16]
  - *"Education based on theories of deconditioning and fear avoidance of exercise lead the professional to believe that the patient will respond to reconditioning and may recover with cognitive behavioural therapy. This is in direct conflict with the neuroimmune exhaustion, exacerbation of symptoms and post exertional malaise described by patients, supported by research showing that exercise deteriorates physical performance and increases lactate in patients with ME/CFS."*[17]
  - *"New education on this topic is required to reflect: 1) The huge paradigm shift in understanding of this illness; 2) Up-to-date international biomedical research and education on ME/CFS; 3) The experience of patients whose lives are completely changed by the illness."*

- England & Wales, 2020 - with a new guideline in development, Paul Chrisp, director of Centre for Guidelines at NICE, advises:[18]
  - *"ME/CFS can cause profound, long-term illness and disability, and much of the distress surrounding it is caused by difficulties in recognising, acknowledging and accepting the condition and its impact. This has been compounded further by a lack of effective treatments, wide variation in access to services, and by controversy over the use of graded exercise therapy and CBT that has served only to alienate many people with ME/CFS and in some cases undermine the confidence of those caring for them."*

- Worldwide 2020 - with a novel coronavirus rife, a growing number of cases emerge of people who do not recover their previous levels of health following SARS-CoV-2 infection, showing a clinical picture that bears striking similarities to ME/CFS. As early as May 2020, Dr Muirhead included the case of a patient who had had COVID-19 several months previously in her CPD accredited learning module, advising: *"ME/CFS is emerging as an important diagnosis to consider in this context due to the post-viral onset and multisystem nature of symptoms together with a clear history of PEM (Post-Exertional Malaise)."*[19]

- Scotland 2020 - recognising the need to improve knowledge relating to diagnosis and management of ME-CFS, the Scottish Government began to fund *'Learn about M.E. – the ME-CFS Professional Development Project'* through the Health Department's Neurological Framework, promoting and disseminating Dr Muirhead's on-line learning module to student and qualified doctors.

- British Medical Journal, December 2020 - Opinion piece *'Confronting the pathophysiology of long-Covid'* advises: *"There are many precedents for perturbation of immune and inflammatory responses by acute viral infection leading to long term sequelae. These range from the autoimmune/inflammatory conditions that can persist for years after Ebola virus or Chikungunya virus, to the profound immune subset perturbations that can be provoked by Epstein-Barr virus (EBV) in infectious mononucleosis."*[20]

- Publication, Trends in Molecular Medicine, September 2021 - Professors Komaroff and Lipkin summarise what is known about the pathogenesis of ME/CFS and of acute COVID-19, in the context of post-acute COVID-19 syndrome (PASC). They report:[21]
  - *"PASC also includes a post–coronavirus disease 2019 (COVID-19) syndrome ('long COVID') with features that can follow other acute infectious diseases and myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS)."*
  - *"We propose molecular mechanisms that might explain the fatigue and related symptoms in both illnesses."*

- England, October 2021 - the National Institute for Health and Care Excellence (NICE) publishes their current guideline on diagnosis and management of ME/CFS.[22] This advises that:
  - The committee agreed that 'fatigue' as it is commonly used is not a true description of the symptoms in someone with ME/CFS.[23]
  - In the committee's experience recognition of orthostatic intolerance and the appropriate treatment can improve people's functioning.[24]
  - 'Graded exercise therapy' must not be offered for ME/CFS patients.
  - CBT may be offered to support people with ME/CFS to manage symptoms, improve their functioning and reduce distress associated with having a chronic illness; CBT should not be offered based on the assumption that 'abnormal' illness beliefs and behaviours are an underlying cause of ME/CFS.

- England, May 2022 - then Secretary of State for Health and Social Care, the Rt. Hon. Sajid Javid MP, announces the intention to develop a cross-Government Delivery Plan on ME/CFS.[25] 'Attitudes and Education' are soon identified as a core area requiring attention and a Working Group established on this topic, which Dr Muirhead is asked to co-chair.

- England, May 2022 - All Party Parliamentary Group (APPG) on Myalgic Encephalomyelitis publish *'Rethinking ME'*.[26]
  - This report refers to *"the failure of the medical education establishment to update teaching in line with the ever-expanding evidence base demonstrating that ME is biomedical multisystem disease rather than a psychological condition."*[27] leading the chair to conclude that *"It is clear that radical action, including mandatory education for relevant health professionals, is needed to ensure appropriate medical intervention and care".*

- Publication, Advances in Bioengineering & Biomedical Science Research, January 2023 - Review of the most recent studies of ME/CFS patient treatment harms following CBT and graded exercise:[28]
  - *"A significant body of research suggests that CBT and GET are not only ineffective, but harmful for many patients with ME/CFS."*
- Publication, Blood Reviews, March 2023 - summarises the published literature on cardiovascular and haematological findings documented in ME/CFS patients and discusses the potential role of previously-implicated pathogens:[29]
  - *Viruses, including herpes viruses such human herpesvirus (HHV)-4 (also known as Epstein-Barr virus (EBV)), HHV-6, and HHV-7, are implicated in ME/CFS.*
  - *Viral reservoirs of herpesviruses exist in ME/CFS, and most likely contribute to cardiovascular and haematological dysfunction directly or indirectly.*
  - *While atherosclerotic heart disease is not significantly associated with ME/CFS, suboptimal cardiovascular function defined by reduced cardiac output, impaired cerebral blood flow, and vascular dysregulation are, and these abnormalities do not appear to be influenced by deconditioning. Rather, these cardiac abnormalities may result from dysfunction in the (autonomic) nervous system.*[30]
- Publication, Frontiers in Medicine June 2023 - Professors Komaroff and Lipkin provide *"a current road map to the extensive literature on the underlying biology"* of ME/CFS and Long COVID:[31]
  - *"We compare the symptoms of ME/CFS and Long COVID, noting the considerable similarities and the few differences."*
  - *"We then compare in extensive detail the underlying pathophysiology of these two conditions, focusing on abnormalities of the central and autonomic nervous system, lungs, heart, vasculature, immune system, gut microbiome, energy metabolism and redox balance. This comparison highlights how strong the evidence is for each abnormality, in each illness."*
- Publication, PLOS Pathogens, August 2023 - paper on viral connection by Professor Maureen Hanson of Cornell University USA, reviewing prior evidence on ME/CFS in the context of post-SARS-CoV-2 infection syndromes. Prof Hanson reports that:[32]
  - *History offers persuasive evidence to suspect the enterovirus (EV) family of causing ME/CFS.*
  - *Ignoring the abundant evidence for EV involvement in ME/CFS has slowed research into the possible dire but hidden consequences of EV infections, including persistence in virus reservoirs.*
  - *Prior to the SARS-CoV-2 pandemic, the ability of RNA viruses to persist in tissues for long periods was largely ignored.*
- England, August 2023 - Interim Cross Governmental Delivery Plan published.[33] On the subject of medical education and training, this states:
  - *"There is limited appropriate undergraduate and postgraduate healthcare professional training on ME/CFS."*
  - *"We need to reach people while they are training to qualify and staff who are already qualified, particularly as experienced practitioners may have received outdated or very little education on ME/CFS."*

- England, November 2023 - opinion piece, The Guardian Newspaper by Professor Danny Altmann *'There are new scientific insights into long Covid – but political will is waning'.*[34] Regarding new scientific insights, Prof Altmann refers to the recently published paper *'Serotonin reduction in post-acute sequelae of viral infection.'*[35]

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[2] P2P Workshop Report Executive Summary: https://prevention.nih.gov/docs/programs/mecfs/ODP-P2P-MECFS-FinalReport.pdf. Published article: Green, C.R., Cowan, P., Elk, R., O'Neil, K.M. and Rasmussen, A.L. (2015) *National Institutes of Health Pathways to Prevention Workshop: Advancing the Research on Myalgic Encephalomyelitis/Chronic Fatigue Syndrome,* Annals of Internal Medicine, 162(12), pp. 860–865. Available at: https://doi.org/10.7326/M15-0338

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[5] *Ad hoc surveillance report*, NICE, October 2015.

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[16] Dr Muirhead referred to work by the US Clinician Network in this connection, available at the website of the Open Medicine Foundation: https://www.omf.ngo/2019/09/01/new-guidelines-for-diagnosing-and-treating-me-cfs. Since published as: Bateman, L. *et al.* (2021) *Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Essentials of Diagnosis and Management*, Mayo Clinic Proceedings, 96(11), pp. 2861–2878. Available at: https://doi.org/10.1016/j.mayocp.2021.07.004.

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[24] ibid. page 51. Note that *"**POTS** patients who meet CFS criteria were found to have a similar clinical, autonomic and neurohumoral profile to other POTS patients (Okamoto et al. 2012* Pubmed ID 21906029*). Because there were no distinguishing fea-tures between POTS patients with and those without CFS, the researchers propose that CFS–POTS is not a separate clinical entity distinct from POTS without CFS. Rather, CFS seems to be part of the spectrum of POTS, associated with greater sympathetic activation and/or a more severe form of this condition."*

[25] This intention was published in a Written Ministerial Statement laid in Parliament https://questions-statements.parliament.uk/written-statements/detail/2022-05-12/hcws23.

[26] https://appgme.co.uk/wp-content/uploads/2022/05/Rethinking-ME-a-report-by-the-APPG-on-ME-2022.pdf

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