Commentary

The Concept of ME/CFS

Jonathan Edwards[1]

1. University College London, University of London, United Kingdom

The concept of ME/CFS (notionally standing for myalgic encephalomyelitis/chronic fatigue syndrome) has evolved over the last twenty years. This review compares it with the historical terms chronic fatigue syndrome, myalgic encephalomyelitis, and also post-viral fatigue syndrome, arguing that ME/CFS is better suited to both clinical and research needs, focusing on a symptom-based syndrome characterized by post-exertional malaise, orthostatic intolerance, and an unpredictable, fluctuating time course, rather than specific physiological markers. The need to dissociate the clinical concept from speculative theories of aetiology is emphasised. The breakdown in effective care, especially for severe cases, is highlighted and suggestions made for re-instituting a physician-led service that might allow both safe care and a clinical base for badly needed research.

Over the last two decades, the term ME/CFS has come to be widely used by both physicians and scientists[1]. In 2021, the UK National Institute for Health and Care Excellence (NICE) issued a set of ME/CFS Guidelines[2]. Nevertheless, I was only recently asked, by a sharp medical mind, what justified a specific concept of ME/CFS. The following is an attempt to answer.

ME/CFS appears to stand for myalgic encephalomyelitis and chronic fatigue syndrome but in an important sense it *stands for neither*. It is a newer concept, differing from both.

The NICE guideline gives a good overview of what is known, but two points may obscure the shift. It is suggested that ME/CFS is used for ‘consistency’. I think there is a more positive reason for using the term, which deserves emphasis. NICE points out that neither component term is satisfactory. The United States Institute of Medicine[3] suggested the name ‘Systemic Exertion Intolerance Disease’ but there has been no enthusiasm to use it. The ME/CFS acronym, rather than trying to find perfect words, reflects a desire for a pragmatic clinical term that both recognises and transcends various historical medical views, but also builds on the insights of people with ME/CFS who, importantly, have made

major contributions to research and the level of scientific rigour. It signifies not only what we have moved on from, but also *that* we have moved on.

Is everyone agreed on what the new concept is, though? I can only give a personal view, but one based on listening daily over a period of ten years, as someone 'interested but disinterested', to everyone involved, including patients, carers, clinicians and scientists.

NICE also describes ME/CFS as a 'complex, multi-system, chronic medical condition'. 'Complex' and 'multisystem' are probably not helpful. 'Complex' tends to tacitly imply unspecified psychological factors, which just obscures things (and was not intended). Without known pathology, 'multisystem' is unwarranted. Despite frequent claims of metabolic or immunological changes nothing consistent has been found that would explain the clinical presentation.

What 'ME/CFS' does provide is a concept of a specific clinical presentation, with two key elements, well illustrated in the Guideline text. Firstly, people with ME/CFS have persistent unpleasant and disabling symptoms, varied and hard to describe but, I will suggest, typically making them have to lie flat or nearly so, at least some of the time. This ties in to a recognised 'orthostatic intolerance' for most, but not necessarily any specific haemodynamic change. Secondly, symptoms relapse or worsen with a time relation to exertion that is delayed and prolonged but also unpredictable, in a way not explained by immediate physiologic change, or local tissue effects (in contrast to post-exercise muscle soreness). This is known as post-exertional malaise (PEM: see Carruthers et al.[1]). The clearest illustration of PEM is what is popularly known as a 'crash'.

I have not mentioned fatigue. Many people with ME/CFS say they do not have fatigue in its usual sense(s). People with renal failure or rheumatoid disease with fatigue do not 'crash'. Moreover, fatigue associated with most conditions is often best relieved by sitting in a comfortable, but *upright*, chair. Interest in fatigue in systemic disease has grown recently and there has been a tendency to see mechanisms as generic[4]. The use of pathway-specific drugs such as cytokine inhibitors[5] has, however, shown us that even for other systemic illnesses mechanisms are heterogeneous. More importantly, it is very uncertain that the core symptoms of ME/CFS are even subjectively the same thing.

Unpleasant symptoms in ME/CFS include nausea, orthostatic intolerance and diffuse pain, (hence 'malaise') together with sensitivity to environmental stimuli such as light, sound, physical contact and odours. There is also difficulty organising thought processes, which for many is central to their

disability. The peculiar time course suggests a longer term and unstable disturbance of regulation, perhaps of the immune system or nervous system or both combined. It reminds me of the game of snakes and ladders in that a person coping quite well may, at any time, suddenly crash and return to bed (a snake) and, sadly much less often, may also, after struggling for months or even years, suddenly experience relief (a ladder). If that follows a therapy, it is often touted as a success, but so far there is no reliable evidence that any specific modality helps.

These features make ME/CFS a typical syndrome concept, in the sense of a pattern of clinical symptoms and/or signs that *suggest* some common mediating process, even if that remains unknown. Syndromes allow heterogeneity of contributing causes and need not be mutually exclusive with other clinical categories; grey areas may be extensive. But aspects of the pattern of presentation appear to justify looking for a specific, if unknown, process. Importantly, where ME and CFS have tended to be concepts based on what people guess the process might be (neurological or psychosocial), and therefore may be empty, ME/CFS focuses on something undeniable – that a number of people in the community are seriously disabled by a particular pattern of symptoms, a small number of whom die as a result.

A break from history

What was wrong with the old terms, ME and CFS? Their history is confusing and inconsistent. There are, however, certain points of interest.

The chief problem with CFS is that it emphasises a generic concept of fatigue, perhaps with a similar mechanism and treatment. That seems unhelpful, when we know of many different pathways to fatigue and fatiguability including cytokines, autoantibodies, hypoxia and poor neuromuscular transmission, each with a different treatment. And disabling symptoms of ME/CFS are neither just fatigue nor fatiguability, as indicated above.

The problem with 'ME' is that it confused two different illnesses. The term was originally devised to describe a supposed acute, polio-like, neurological illness due to an unknown virus, typified by an outbreak at the Royal Free Hospital in 1955 and also one in Iceland[6]. 'Encephalomyelitis' was used because patients appeared to have localising neurological signs consistent with central nervous system lesions[7]. The basis for these signs was never confirmed but that is not relevant to the *quite different* illness now called ME/CFS[8].

Confusingly, Ramsay took an interest in longer term symptoms in Royal Free cases and dubbed them 'chronic ME'[9]. Ramsay's account looks a bit like the current account of ME/CFS, except that he focused on persisting muscle fatiguability rather than other symptoms. Specific electromyographic findings were claimed but not confirmed. More recently 2-day cardiopulmonary exercise testing[10] has suggested that there is a fall in metabolic function during exercise in people with ME/CFS, but it remains unclear how this relates either to muscle function or symptoms.

What may have been a persistent mistake in trying to define ME/CFS is reliance on physical signs or tests suggestive of a favoured aetiology when what we are primarily trying to define is a symptom-based syndrome. Diagnostic and management strategies have drawn on all sorts of theoretical models, including neuroinflammatory, psychosocial, metabolic, immunological or haematological but until there is reliable evidence for any of these, ME/CFS remains a symptom complex. The Canadian Consensus Criteria (for 'ME/CFS') of 2003 have been useful in this respect. The re-introduction of assumptions about mechanism by the later International Consensus Criteria (for 'ME')[11] looks to have been a step backwards which, fortunately, has not been followed by many.

A further confusion is the relation to 'post-viral fatigue'[8]. Persistent symptoms following infections such as Epstein-Barr virus and Q fever have long been recognised. The Dubbo study[12] gives useful documentation. Ramsay must have thought that 'chronic ME' was not just post-viral fatigue, at least early on. Under Ramsay's influence 'ME' became a popular diagnosis with a small number of physicians, who may also have thought in terms of a specific causal agent. That now looks unlikely, unless there is some unknown endemic microbe whose effects can be triggered by one of several *other* microbes such as EBV or now Covid-19. The concept of ME/CFS is not focused on a specific agent. If anything, it is focused on the phenomenon of PEM. There is specificity, and that specificity does overlap with Ramsay's account, but not aetiological specificity.

What remains unclear is to what extent the majority of cases of post-viral fatigue resemble ME/CFS or are more like the fatigue associated with conditions like rheumatoid arthritis and heart failure. A proportion of people with symptoms following Covid-19 report the spectrum of ME/CFS symptoms, with PEM, some unable to leave their beds or speak. Most cases probably do not. Unfortunately, the descriptions of symptoms in accepted criteria for ME/CFS are not that precise and estimates of proportions of post-Covid cases who fit ME/CFS criteria are likely to be misleading.

Differences in temporal profile may also be critical. Active EBV infection can produce severe malaise for several weeks and post-EBV 'fatigue' may be seen simply as a failure of resolution of those symptoms with normalisation of the blood picture. Long term ME/CFS is recognised after EBV infection, but it may not be merely a longer version of a 'PVFS' category (that need not include 'crashes' and sensitivity to light and sound). When ME/CFS occurs after infection there may be a symptom-free window with subsequent 'crash', suggesting a new process. Even if there is no window it is typified by a fluctuating course.

Covid-19 has joined the group of infections with a high rate of post-infective problems, much like EBV. Sifting out different clinical patterns may be crucial to useful explanatory research, and detailed time course may be as important as symptom categories. Very likely the situation is not simple, just as the relationship of 'palindromic arthritis' and 'transient synovitis' to 'definite rheumatoid arthritis' or 'psoriatic arthritis' is something we still lack a black and white answer to. Nevertheless, that does not stop us from being sure that definite rheumatoid arthritis relates to at least one specific pathogenic pathway in which autoantibody production occurs.

There is more work to do to get the concept of ME/CFS as clear as it could be. More precise delineation of symptom patterns, perhaps backed up by detailed posture-sensitive actimetry studies, could be very useful. Nevertheless, a huge amount of progress has been made in the last decade. Clear clinical definition has allowed unproductive theories such as deconditioning cycles to have been shown to be off target. To a considerable extent progress has been driven by citizen scientist patients, or carers and friends with biomedical science skills. The science community must swallow the unpalatable truth that it is the patient community that has brought methodological rigour to the subject, not the academics. For more than one reason, physicians should listen to patients.

'Non-existent' care

What has come to public attention through the media in the UK in recent months is that alongside progress in scientific enquiry there has been a more or less total collapse of NHS services for people with ME/CFS. There have been unnecessary deaths from inanition[13]. There is a stark comparison between the death of Maeve Boothby O'Neill in the UK, for whom the NHS found no way to provide feeding support, and Whitney Dafoe, a Californian who has been on either parenteral or enteral feeding for several years. Whitney's quality of life may not be good, but he has made it clear that he

feels fortunate in comparison to Maeve. Others have had parenteral and enteral feeding support and been weaned off[14].

The precise reasons for failure of care in individual cases are complex. Some possible contributing factors have been discussed elsewhere[15]. In general terms, however, my perception is that there has been a deliberate policy amongst physicians not to get involved with ME/CFS care. The justification seems to have been that psychosocial factors are likely to be perpetuating the clinical state and that what is needed is psychological 'support' or therapy. What appears to be forgotten is that (a) there is no reliable evidence for a role for psychosocial factors. It is easy to assume they must be involved, but medicine needs to move on from 'clinical impression'. Lots of people with unhelpful beliefs, unhappy relationships, and past histories of adversity remain very well. The bottom line, (b), is that, whatever roles psychological factors might play, psychological medicine has shown no useful understanding of what they are or how to treat them. The only trial methodologically adequate to provide any information at all[16] indicates that psychosocial theories have been wrong and that psychological intervention gives no worthwhile benefit.

Worryingly, not only has the psychological medicine approach failed but its proponents have shown no recognition of their lack of understanding of either the illness or research methodology needed to identify effective treatment[17]. Claims of benefit from psychotherapy are hard to justify when there is no evidence for reduction in the prevalence of the illness and people are still dying of avoidable dehydration and starvation.

Who is best placed to manage ME/CFS?

Who should provide care? Certainly physicians, since the key skills required are the evaluation of ongoing symptoms for signs of alternative or additional diagnoses and early preventive measures for problems such as osteoporosis and, in rare cases, nutritional failure. But which? Neurologists? Rheumatologists? Infectious Disease Physicians? This may be the wrong question. We have so little theoretical base for ME/CFS care that it may not matter what specialty training carers have received, other than, crucially, a training in critical thinking that prevents them sliding into poorly grounded theory-driven practice.

ME/CFS has been flying under physicians' radar for some years. I see an important driver for this as the fashion for 'multidisciplinary teams'. Where we have complex technical knowledge in many

disciplines relevant to the care of someone with renal lupus or head and neck malignancy, multidisciplinary team meetings are essential, but that has little to do with the diffusion of personal responsibility and decision-making that allows someone with ME/CFS to be sent off to three different therapists, none of whom have any idea what modalities are of clinical value – because *nobody* knows.

There are ongoing discussions amongst people with ME/CFS as to what would constitute a necessary and sufficient team for care. A popular suggestion is that a physician and a specialist nurse could provide all routine requirements, including review to ensure other diagnoses were not missed and practical management of coping with the illness. Acquisition of skills such as activities of daily living assessment and protection against tendon contractures would be important but these are not beyond the scope of a specialist nurse, any more than chemotherapy infusions are.

Building an effective care system for people with ME/CFS that does justice to the NICE NG206 Guideline is going to take time and it will depend critically on education of health professionals. That can only start with a clear concept of ME/CFS. At present there is not only persistent confusion relating to adherence to historic theory-laden concepts but resulting antagonism both between groups of health care professionals and between professionals and patients.

I would suggest that the first lesson to learn is that whatever confusion has arisen it is our fault, not the patients'. An unspoken assumption for many doctors' approaches to ME/CFS is that patients have acquired unhelpful ideas about what is wrong with them and that these ideas may directly or indirectly inhibit recovery. There is no reliable evidence for this. However, if patients are given inappropriate advice on levels of activity, whether too much or too little, or given drugs to combat speculated haemodynamic, cognitive or metabolic problems, adverse effects are very possible. What may get forgotten is that, ultimately, all potentially unhelpful beliefs originate from the speculations of medical professionals. The names used go in a never-ending progression, each with a rather different 'meme' attached: neurasthenia, ME, fibromyalgia, functional neurological disorder, diseases of gut-brain axis, and so on. The names may convey very different concepts but have one thing in common – an implication that the user has some understanding of the problem when they do not. The advantage of ME/CFS is that it is overtly a pragmatic compromise term that implies an illness with a reasonably well-established epidemiology that we understand nothing about and for precisely that reason need to turn our attention to.

A concept to build on

It is time for physicians to take ME/CFS seriously as an unsolved disabling illness, with no presuppositions about causal mechanisms. The time course of deterioration following exertion is not explained by any currently understood type of mechanism. Neo-Freudian psychodynamics or 'predictive coding' theories, as proposed for notional 'functional neurological' problems (which themselves appear to give the wrong predictions), have nothing coherent to offer. Metabolic deficits do not fit well either. Failures in immunological or autonomic control might explain things but even there, no simple story fits.

Some humility is in order. ME/CFS appears to be based on a process at the interface between central nervous and immune systems at a level that currently we have no way of modelling. Popular quips about 'mind-body interaction' replacing Cartesian Dualism simply reveal as deep an ignorance of great philosophers as of human biology. It might turn out to be as simple as another error of acetyl choline metabolism, with complicated secondary effects. It might involve misdirection of tissue-bound complement regulatory proteins. Who knows? The history of medicine is full of situations where illness is entirely misunderstood until some empirical finding makes sense of it. Until then there is a need to get as clear as possible the clinical concept we are trying to explain, so that research studies have the very best chance of finding clues to what is going on.

References

1. a, b *Carruthers BM, Jain AK, De Meirleir KL, Peterson DL, Klimas NG, et al. (2003). Myalgic encephalomy elitis/chronic fatigue syndrome: clinical working case definition, diagnostic and treatment protocols. Jo urnal of Chronic Fatigue Syndrome 11(1):7-115.*
2. ^ *NICE Guideline NG206 (2021). https://www.nice.org.uk/guidance/ng206*
3. ^ *Institute of Medicine (of the National Academies, USA) (2015). Beyond myalgic encephalomyelitis/chr onic fatigue syndrome: redefining an illness. https://web.archive.org/web/20170615034241/https://ww w.nap.edu/resource/19012/MECFSclinicians guide.pdf*
4. ^ *Hackett KL, Lambson RL, Strassheim V, Gotts Z, Deary V, Newton JL (2016). A concept mapping study e valuating the UK's first NHS generic fatigue clinic. Health Expect. 19(5):1138-49.*
5. ^ *Moreland LW, Genovese MC, Sato R, Singh A (2006). Effect of etanercept on fatigue in patients with re cent or established rheumatoid arthritis. Arthritis Rheum. 55(2):287-93.*

6. ^Acheson ED (1957). Benign myalgic encephalomyelitis. Lancet 272(6973):834-5.
7. ^Ramsay AM, O'Sullivan E. Encephalitis simulating poliomyelitis. Lancet. 1956;270(6926):761-4.
8. a, bAcheson ED (1991). Introduction. British Medical Bulletin 47(4):793-5.
9. ^Ramsay AM (1986). Postviral Fatigue Syndrome: The saga of Royal Free disease. London, Gower Medic al.
10. ^Keller B, Receno CN, Franconi CJ, Harenburg S, Stevens J, Mao X, et al. (2024). Cardiopulmonary and metabolic responses during a 2-day CPET in myalgic encephalomyelitis/chronic fatigue syndrome: tran slating reduced oxygen consumption to impairment status to treatment considerations. Journal of Trans lational Medicine 22 Article number: 627.
11. ^Carruthers BM, van de Sande MI, De Meirleir KL, Klimas NG, Broderick G, Mitchell T, et al. (2011). Myal gic Encephalomyelitis: International Consensus Criteria. Journal of Internal Medicine 270(4):327–38.
12. ^Hickie I, Davenport T, Wakefield D, Vollmer-Conna U, Cameron B, Vernon SD, et al. (2006). Post-infec tive and chronic fatigue syndromes precipitated by viral and non-viral pathogens: prospective cohort st udy. BMJ 333(7568):575.
13. ^Courts and Tribunals Judiciary (2024). Maeve Boothby O'Neill: Prevention of Future Deaths Report. htt ps://www.judiciary.uk/prevention-of-future-death-reports/maeve-boothby-oneill-prevention-of-fu ture-deaths-report/
14. ^Baxter H, Speight N, Weir W (2021). Life-Threatening Malnutrition in Very Severe ME/CFS. Healthcare 9(4):459. doi:10.3390/healthcare9040459.
15. ^Edwards JCW (2024). Management of Nutritional Failure in People with Severe ME/CFS: Review of the Case for Supplementing NICE Guideline NG206. Qeios. doi:10.32388/T9SXEU.
16. ^Wilshire CE, Kindlon T, Courtney R, et al. (2018). Rethinking the treatment of chronic fatigue syndrom e-a reanalysis and evaluation of findings from a recent major trial of graded exercise and CBT. BMC Psy chol 6(1):6.
17. ^White P, Abbey S, Angus B, Ball HA, Buchwald DS, Burness C, et al. (2023). Anomalies in the review pro cess and interpretation of the evidence in the NICE guideline for chronic fatigue syndrome and myalgic encephalomyelitis. J Neurol Neurosurg Psychiatry 94(12):1056-1063.

Declarations

Funding: No specific funding was received for this work.

Potential competing interests: No potential competing interests to declare.