



ME/CFS RESEARCH SUMMARY

by Jamie Seltzer

GENERAL INFORMATION

THE INSTITUTE OF MEDICINE REPORT, 2015

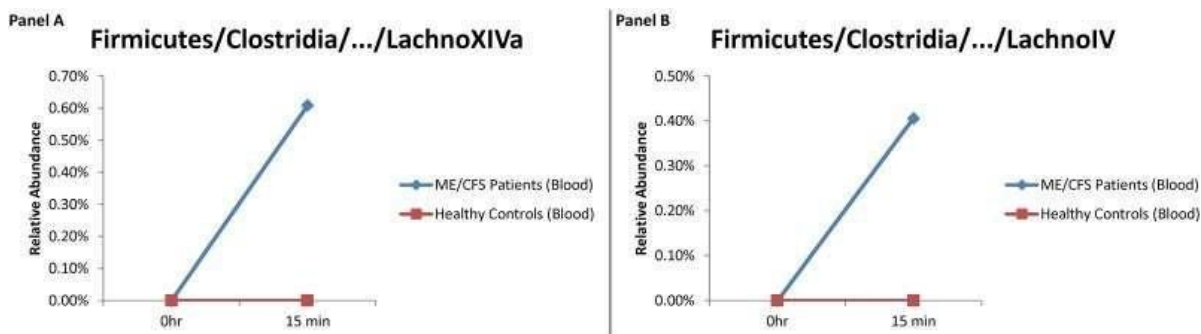
[Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness](#) is a literature review conducted by the then-IOM. A panel of experts reviewed over 9,000 separate studies to produce it. It concluded that ME/CFS is a multi-system disease often preceded by an immune challenge.

METABOLISM

- [Fluge and Mella, 2016](#); [Armstrong et al., 2015](#) – Identified errors in cellular energy production in patients, including a reduction in glycolysis, the process that breaks down carbohydrates and sugars. Other energy-producing reactions' metabolites were elevated, which may indicate a kind of metabolic compensation for this dysfunction. For example, amino acids and proteins show signs of being broken down at an accelerated rate. Diet showed no difference in protein intake than in controls, so this could not have been the source of the difference. Bathing normal cells in ME patients' blood serum caused them to show the same metabolic abnormalities as patient cells.
- [Naviaux et al., 2016](#) -- Found significant decreases in metabolites that led to the idea of slowed metabolism in ME/CFS patients overall. He also found changes in important cell membrane compounds, like sphingolipids and cholesterol. Naviaux's group also discovered that they could identify patients 19 times of 20 using a mix of 8 metabolites in women and 13 in men.

MICROBIOME

- [Giloteaux et al., 2016](#) -- Maureen Hanson of Cornell's team ([Giloteaux, 2016](#)) confirmed previous results showing that ME patients have different kinds of gut bacteria than healthy individuals, with specific kinds of bacteria elevated (*Firmicutes* and *Bacterioides*). Blood markers also indicated elevated response to bacteria post-exercise, implying leakage of gut bacteria into the blood.
- [Shukla et al., 2015](#): Sepsis as a Feature of PEM -- [Shukla et al. \(2015\)](#) found that blood samples collected 15 minutes after exercise showed different bacteria in patients than in controls. These researchers also found that certain bacteria increased in the bloodstream only in patients, and not in healthy controls.



[\(Shukla et al. 2015 -- Changes in Gut and Plasma Microbiome following Exercise Challenge in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome \(ME/CFS\)\)](#)

Other studies have verified dysregulation in the intestinal bacteria in patients ([Frémont, Coomans, Massart, & De Meirlier, 2013](#)).

EXERCISE STUDIES

Numerous studies have found unusual reactions to exercise in ME, including:

- Reduced blood flow to the brain and heart ([Neary et al., 2008](#); [Peterson et al., 1994](#))
- Reduced oxygen uptake in hemoglobin ([Miller et al., 2015](#)) and reduced oxygen use on second-day exercise testing ([Jones et al., 2012](#); [Keller, Pryor, & Giloteaux, 2014](#))
- This oxygen use is not caused by a general lack of physical activity (known as 'deconditioning') ([Vermeulen, & Vermeulen van Eck, 2014](#))

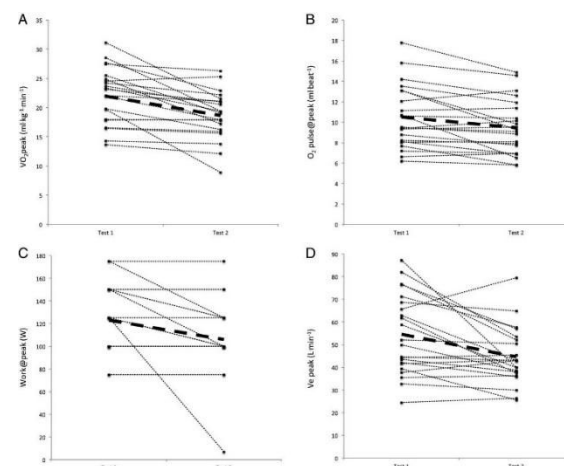
Note that exercise studies are usually only performed on minor or minor-moderate-presenting patients. Many patients are incapable of exercise. Also note that exercise testing, which measures metabolites in the blood through a catheter placed in the artery and may measure breaths in and out, cannot be 'fooled' by poor effort on the part of the patient.

- [Light et al., 2009](#): Gene expression post-exercise -- Light's group found different gene function after exercise in patients, including in genes related to immunity, metabolism, and the nervous system. Genes with increased expression included those responsible for regulating function of the heart, cell death, and inflammation.
- [Snell et al., 2013](#), [Keller et al., 2014](#), and [Vermeulen & Vermeulen, 2014](#): Second-day CPET and VO₂

Post-exertional malaise, or a worsening of all symptoms after exertion, is considered the cardinal features of ME/CFS. However, patients do not always experience the consequences of PEM right away; they may experience a 'crash' 8, 24, or 48 hours after the initial exertion.

Snell et al. (2013) found that, while a single exercise test showed no noticeable differences between CFS patients and controls, a second test performed 24 hours later showed significant abnormalities in oxygen use and how hard patients were able to work. Keller (2014) also found significant differences in ability to perform during a second test.

[Vermeulen et al. \(2014\)](#) compared sedentary controls (active less than 1 hr / week) to ME/CFS patients to show that these findings were not merely a matter of low activity level (deconditioning). O₂ extraction in patients was still found to be less than half of that of inactive controls.



The second-day test is often used to diagnose ME/CFS.

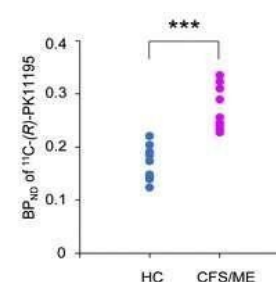
- PACE trial and refutations -- The PACE trial was a trial of graded exercise therapy for ME/CFS initially heralded as a success. Patients, researchers and clinicians were skeptical of these claims, as The Institute of Medicine describes exercise intolerance as the distinguishing feature of the disease.

Numerous issues with the trial were identified. Most significantly, the original authors found no difference between activity levels on follow-up with the original participants ([Sharpe et al., 2015](#))¹: even the subjective improvements that were reported dissipated within a few months. The same null result was found in their similar FINE trial on long-term follow-up ([Wearden et al., 2010](#)). *The Lancet* has not yet retracted the study, but [PLOS ONE has flagged it](#) and issued an [expression of concern](#).

There have been a series of articles discussing the flaws of the PACE trial, notably David Tuller of Berkeley's series, [Trial By Error](#), posed on Racaniello of Columbia's Virology Blog. Additionally, the Journal of Health Psychology just released a [series of solicited opinions on PACE](#).

NEUROLOGICAL

- [Mathew et al., 2008; 2010; 2012; 2017](#): Increased ventricular lactate -- Several imaging studies (with a great deal of author overlap) show **increased cerebrospinal lactate** in ME/CFS patients as compared to various control groups. This is significant because lactate is produced by cells when oxygen is low. This implies poor blood flow to the brain in ME patients.
- [Nakatomi et al., 2014](#): Neuroinflammation -- Nakatomi et al. (2014) performed an imaging study using ¹¹C-(R)PK11195, a protein used to visualize brain inflammation, since it is a marker for damage of



¹ Their abstract reports the opposite to be the case. Reading the full text is necessary.

neurons (brain cells). The ^{11}C -(R)-PK11195 in the brain was between 1.5 and 3 times as high as that of healthy people.

(Right: [Nakatomi et al., 2014](#) -- *Neuroinflammation in Patients with Chronic Fatigue Syndrome/Myalgic Encephalomyelitis: An ^{11}C -(R)-PK11195 PET Study* : BP_{ND} of ME/CFS patients versus healthy controls)

- [Shan et al., 2016](#) and [Puri et al., 2012](#): Brain changes on MRI – [Shan et al. \(2016\)](#) found that white matter volume (MWV) had decreased in some regions, and that the grey matter volume (GMV) had decreased in others. These changes correlated to symptoms. [Puri et al., \(2012\)](#) also saw findings on MRI that support patient reports of impaired memory, visual processing, and discrepancies between intended actions and consequent movements.
- [Cook et al., 2017](#) : MRI abnormalities post-exertion -- Patients and healthy controls had similar responses to an initial exercise test, but they could not replicate the level of effort of healthy controls, and they experienced greater pain and fatigue on exertion. Patient response to other tasks was then examined post-exercise. Patients performed significantly worse in difficult mental tasks post-exercise; this impairment could be correlated to changes on MRI.

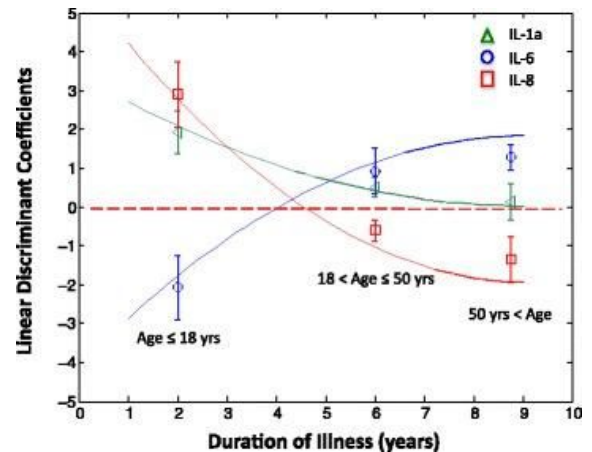
IMMUNOLOGICAL

The search for a specific virus or bacteria that causes ME has not been successful, although there is evidence that some infections are more likely to result in the illness, including Epstein-Barr Syndrome and other herpes viruses, echovirus, and enterovirus ([Institute of Medicine, 2015](#))². ME/CFS may appear in epidemic outbreaks³, implicating an infectious agent or agents in onset, coupled with a genetic susceptibility; many patients report onset occurs after a severe infection.

- Cytokine studies – Many cytokines, chemicals related to inflammatory response, have been found to be elevated in patient serum. Some researchers have discovered a general pattern of increased inflammation early in the disease and a more immunosuppressed picture after long-term illness ([Lipkin & Hornig, 2015](#); [Russell et al., 2016](#)). A second set of researchers found that these cytokines fluctuated with severity rather than timecourse ([Montoya et al., 2017](#)).

Right: [Russell et al., 2016](#) – *Illness progression in chronic fatigue syndrome: a shifting immune baseline*. Different patterns of cytokine expression over disease progression

- NK function studies – [A summary by Strayer et al. \(2015\)](#) found that out of 17 studies in ME/CFS studying natural killer cell function, 15 had discovered lowered NK cell function in patients. One of the most recent studies on NK function is by [Fletcher et al., 2010](#), who shows a significant difference between NK cell function in healthy controls and patients with ME/CFS.
- B-cells, T-cells, and Rituximab – One of the most important recent studies showed that Rituximab, a chemotherapy drug, resulted in complete remission for some patients. Accidental discovery in a patient with cancer and ME/CFS led to a phase I, II, and III clinical trial using the drug by [Fluge and Mella](#). The paper posited that the B cell depletion's success provided evidence for ME/CFS as an autoimmune disease. Finally, Curriu and colleagues also found significant elevations of the T cell exhaustion markers PD-1 and CD95 ([2013](#)).



Altered immune reactions to some types of infection have recently been identified in ME in several studies, including a deficiency in EBV-specific B- and T-cell memory response in CFS patients ([Lerner et al., 2012](#)).

- Autoantibody studies-- Multiple studies have found signs of autoimmunity in ME/CFS patients, including:
 - Elevated ANA
 - Anti-cholinergic muscarinic antibodies ([Loebel et al., 2016](#))
 - B-adrenergic antibodies ([Loebel et al., 2016](#))
 - Anti-serotonin antibodies elevated in nearly 2/3 of patients in a 117 patient study ([Maes et al., 2013](#))
 - Anti-P_i (phosphatidylinositol) antibodies modestly elevated in patients in comparison to healthy controls ([Maes et al., 2007](#))

² You can find a patient-created list of enteroviral research with links [here](#).

³ You can find a list of outbreaks of myalgic encephalomyelitis 1934-1980 with attendant references [here](#).

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