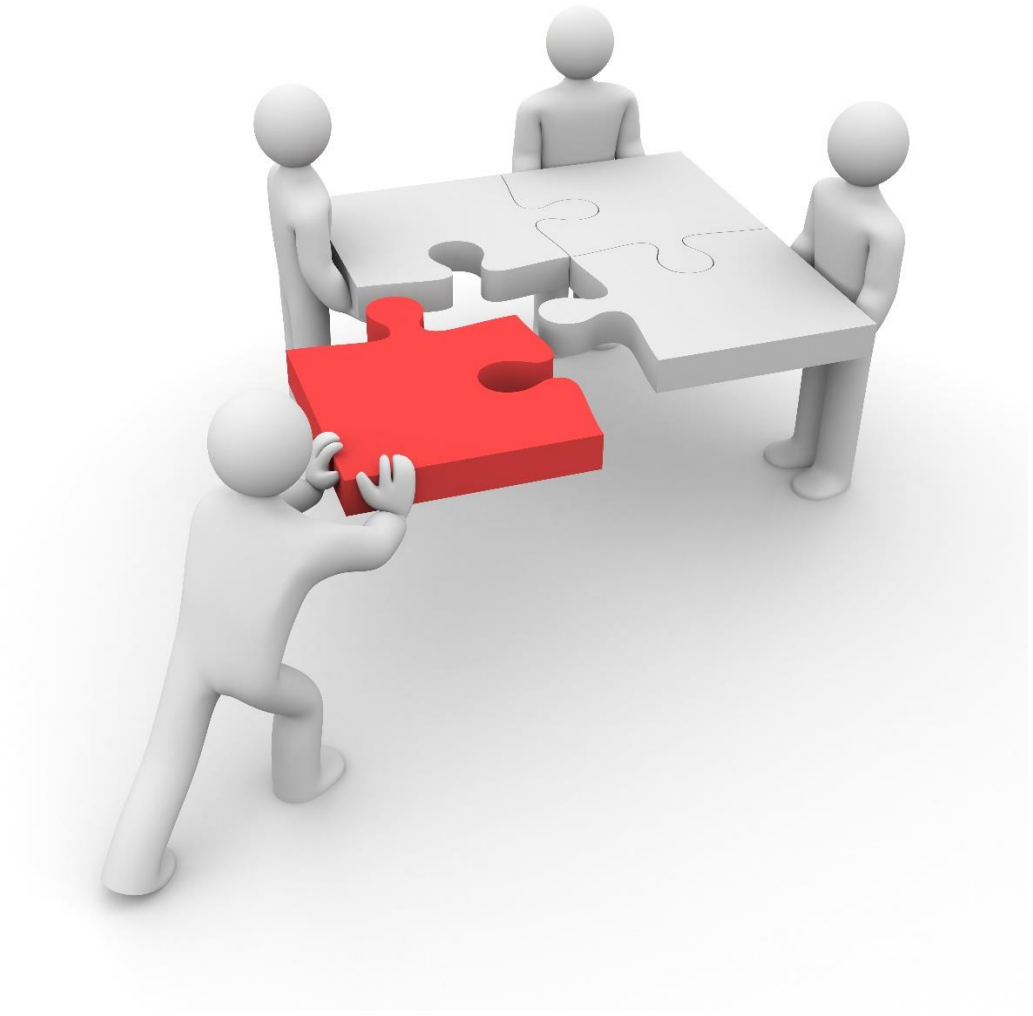
Understanding the pathophysiology of Myalgic Encephalomyelitis (ME)



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Compiled by: Sylvia Iversen

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"Eighteen months ago, after seeing thirteen different doctors and
undergoing multiple tests and investigations,
not only was I given a diagnosis of a condition that I didn't know about or understand,
it was an illness I didn't believe in" – Dr. Nina Muirhead (MD, surgeon)

"I split my time between ME/CFS and HIV, and I can tell you
if I had to choose between the two illnesses
I would rather have HIV" – Dr. Nancy Klimas (MD, Professor, Director)

"If you get ME/CFS – your life as you know it – is over"
Dr. Ronald Davis (PhD, Professor, Director, scientist)

"The symptoms caused by any illness should be suffering enough.
Yet, with some illnesses, the suffering often
is multiplied by skepticism about the illness.
That is the case with ME/CFS"
Dr. Anthony L. Komaroff (MD, Professor)

Understanding the pathophysiology of Myalgic Encephalomyelitis (ME)

Preface

Even though I am an ME patient with multiple comorbidities, I am also an autodidact who amongst others loves to learn about the pathophysiology of Myalgic Encephalomyelitis. This requires knowledge of many different medical specialties and takes me on a very interesting journey.

Sadly, once diagnosed with ME, ME patients struggle to find doctors who are willing and able to care for them. Most ME patients are therefore left on their own. Even the CDC has referred to ME/CFS as America's hidden health crisis. This crisis in healthcare is accompanied by unusually low research funding. But worst of all, the decades-long grip that a few psychiatrists with their biopsychosocial model had on ME, has caused tremendous harm and stigma, leaving a trail of suffering that continues to this day. Due to overwhelming biomedical evidence and the 2015 IOM report concluding that ME/CFS is a physiological, not a psychiatric illness, the situation is now slowly changing. Unfortunately, healthcare professionals are often unaware of recent biomedical research or the 2015 IOM report.

Like many ME patients, I have been following scientific research and conferences about ME for years. Initially, it was unusual for scientists to see so many ME patients attending scientific conferences. Now scientists are increasingly involving ME patients in their work, which turns out to be a great success. That is also why, with the current lack of knowledge in mind, I think that collaboration between medical professionals and ME patients can be mutually beneficial.

Due to my fluctuating memory problems, I eventually started to write down interesting scientific findings and my document started to grow. I had heard some of the most experienced ME doctors and scientists say that they understand a lot about the pathophysiology of ME. So, if they could understand it, maybe I could understand it too. Meanwhile, my first document has become very large and is a very rich source of possible explanations for many ME symptoms and their possible treatments. Nowadays I use that document to search for keywords and to refresh my memory.

My family and friends (some work as healthcare professionals) often asked me many questions about ME; they wanted me to explain and give an overview of this very complex disease. In order to give them the best information, I've created "Understanding the Pathophysiology of Myalgic Encephalomyelitis (ME)". It provides an overview of key biomedical findings, an in-depth understanding of today's pathophysiology of ME and a variety of other useful information. It even includes scientific studies which show a connection between Long COVID and ME. I have been working on this document until January 2022, but due to health reasons it was no longer possible to continue, except for a few studies that were added later.

Anyone can use this document; whether you want to quickly search for information or read it thoroughly to gain your own knowledge and understanding. You will find links to CPD/CME learning modules, short videos, documentaries and much more. I hope this overview will pique your interest in ME and will benefit the lives of many.

With the best wishes,

Sylvia Iversen
October, 2022
Sandnes, Norway

Contents

Understanding the pathophysiology of Myalgic Encephalomyelitis (ME)

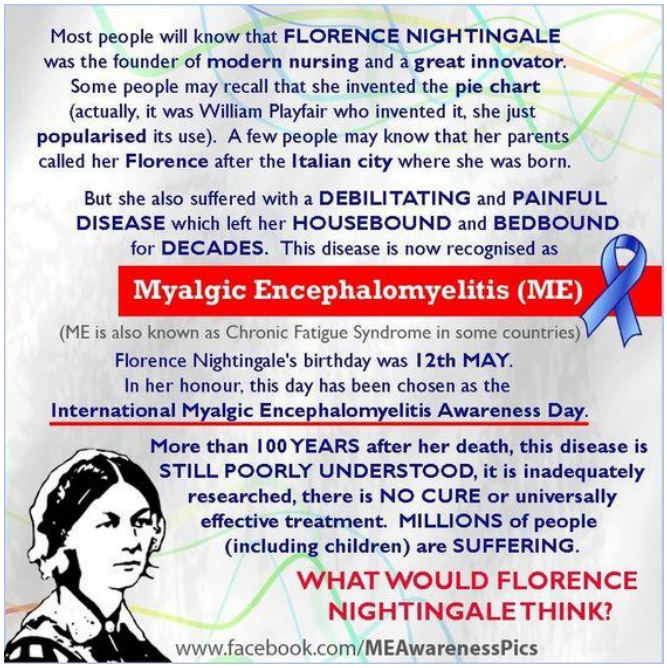
ME – A Life Altering Disease

[1 H, 2 H, 3 H, 4 H, 5 H, 6 H, 7 H, 8 H] Myalgic Encephalomyelitis is a serious, complex, multi-systemic disease that significantly impairs one's function and quality of life.

The most common symptoms of ME are:

- profound fatigue,
- unrefreshing sleep,
- sleep abnormalities,
- cognitive impairment (slowed information processing, memory impairments, concentration problems, difficulty comprehending, word-finding problems, reduced attention, impaired psychomotor function),
- hypersensitivities (light, sound, odor, touch, vibration, food, chemicals and medications),
- autonomic manifestations (orthostatic intolerance, cardiovascular irregularities, gastro-intestinal impairments, genitourinary impairments),
- immune manifestations (sore or scratchy throat, painful or tender axillary/cervical lymph nodes),
- neuroendocrine manifestations (loss of thermostatic stability, sweating episodes, intolerance of temperature extremes),
- pain (headaches, muscle pain, joint pain) and
- Post Exertional Malaise (worsening of symptoms upon even minimal exertion).

The extreme fatigue is not improved by rest and worsens after any activity, either physical or mental. Currently, there is no laboratory diagnostic test or cure.



[9 H] *May 12th is International Myalgic Encephalomyelitis (ME) Day.*
The month of May is ME Awareness Month.

[10 H] "The acronym ME/CFS may be used to describe Myalgic Encephalomyelitis. Different names may be used to indicate which of several sets of diagnostic criteria are being described. The disease defined by the Canadian Consensus Criteria (CCC) or Institute of Medicine Criteria is often described as ME/CFS, whereas the ICC criteria (ICC) is often described as Myalgic Encephalomyelitis. The Fukuda criteria connotates Chronic Fatigue Syndrome (CFS)".

[11 H, 12 H, 13 H] "Several other names have been used or proposed throughout the history of the disease, including atypical polio, Icelandic disease, benign ME, epidemic neuromyasthenia, Neuro-Inflammatory and Oxidative Fatigue (NIOF), CFS, and systemic exertion intolerance disease (SEID). This has led to much confusion as a variety of names have been used at different times to describe discrete outbreaks as well as a larger and potentially more heterogenous population of sporadic cases, defined by a wide variety of case definitions. A survey by The ME Action Network in 2016 found that the majority of patients prefer the name ME to other names including chronic fatigue syndrome. Myalgic encephalomyelitis (ME) was the original name for chronic fatigue syndrome (CFS); the names are used interchangeably or with the acronym ME/CFS."

[14 H,15 H, 16 H, 17 H, 18 H, 19 H, 20 H, Ref. 550 H] Post-Exertional Malaise (PEM) is considered to be the hallmark symptom of ME/CFS. It is a worsening of ME/CFS symptoms, often not occurring until 24-48 hours after minimal physical or mental exertion, and leading to a reduction in functional ability. PEM can be brought on by surroundings (hearing a voice, seeing lights), or by an effort (lifting a cup, reading, holding a conversation). The International Consensus Criteria uses Post Exertional Neuroimmune Exhaustion (PENE), which is "the pathological inability to produce sufficient energy on demand, with prominent symptoms primarily in the neuroimmune regions".

[21 H, 22 H, 23 H, 24 H, 25 H,26 H, 27 H, 28 H, Ref. 2 H, Ref. 225 H] When ME patients exceed their threshold, they will pay a tremendous price. "Patients experiencing PEM will often describe a "crash", "relapse", or "collapse" after even small amounts of mental or physical exertion that was previously tolerated. PEM is more than fatigue following a stressor; PEM exacerbates a patient's baseline symptoms. In some cases, patients experience new symptoms as part of the PEM response. If patients recover from PEM, it can take hours, days, a week, months or even years to come close to the previous baseline. But often, PEM doesn't just make the patients temporarily worse, it permanently lowers their energy limit every time they have PEM. It is therefore important to know that overexertion can damage a patient's health, sometimes permanently – and that patients cannot be cured by gradually increasing their exercise over time. Some patients may go through cycles of overexerting and crashing while others may have learned to reduce or change activities to minimize crashes. For some patients, even basic activities of daily living can result in PEM".

[29 H, 30 H, Ref. 142 H] "ME/CFS can be unpredictable and can change over time. Symptoms can fluctuate during the day, from day to day and throughout the illness". There are several scientific explanations for this phenomenon. Dr. Jarred Younger gives his explanation: "Primed microglia cells are like angry microglia cells. They are hypersensitive and it takes very little to set them off. There are quite a few things that can push them into that state. Once they are hypersensitive you may take a walk for two minutes and the cortisol you produce, or the beta endorphins you produce, might be enough to cause those, now primed microglia, to go into their fully activated state, pump out those pro-inflammatory cytokines and make you feel horrible. Someone may get sick multiple times a day, because they can move in and out of this state within a few seconds. You have these triggers that should not normally make you feel sick, that - because the central immune system is primed - it is reacting as if you just had a severe infection and all you did was take a walk. That's what we think is happening."

[Ref. 14 H, 31 H, 32 H, 33 H,34 H, 35 H, Ref. 138 H, Ref. 265 H, Ref. 272 H, Ref. 284 H, Ref. 291 H, Ref. 292 H, Ref. 315 H, 36 H, 37 H] "The distinctive characteristics of Post Exertional Malaise (PEM) are confirmed by scientific research. Exertion induces abnormalities in cognitive functioning, immune activation, gene expression and endogenous pain inhibition in ME/CFS patients that were not seen before exertion or in healthy controls. Most importantly PEM can be demonstrated by a 2-day cardiopulmonary exercise test (CPET)

procedure. On the second day CPET, ME/CFS patients display a significant drop in VO2 max and maximal workload, that is not seen in healthy controls or other diseases. These objective measures track strongly with the presence, severity and duration of PEM."

[38 H, 39 H, 40 H, 41 H] There are several severity scales for ME. The Hummingbird Scales are very detailed and give good insight into the level of severity of an ME patient. On the other hand, the most commonly used International Consensus Criteria (ICC) is much less precise and uses only 4 categories:

- mild (an approximate 50% reduction in pre-illness activity level),
- moderate (mostly housebound),
- severe (mostly bedridden) and
- very severe (totally bedridden and need help with basic functions).

[42 H, 43 H, 44 H, 45 H, 46 H, Ref. 505 H] An estimated 25-29% of patients with ME/CFS are severely ill and very low functioning. Some may be unable to move or speak. Very severe ME patients are amongst the sickest of the sick. Many of them are bedridden, in severe pain and the sickest ME patients are living in a semi-comatose state [47 H]. Some patients die from ME, like Brynmor John, Sophia Mirza and Merryn Crofts [48 H, 49 H, 50 H, 51 H, 52 H].

[53 H, 54 H, 55 H, 56 H, 57 H, 58 H, Ref. 5 H] "Very severe Myalgic Encephalomyelitis (ME), can lead to problems with nutrition and hydration. The reasons can be an inability to swallow, severe gastrointestinal problems tolerating food, or the patient being too debilitated to eat and drink. Some patients with very severe ME will require tube feeding, either enterally or parenterally. There can often be a significant delay in implementing this, due to professional opinion, allowing the patient to become severely malnourished. Healthcare professionals may fail to recognize that the problems are a direct consequence of very severe ME, preferring to postulate psychological theories rather than addressing the primary clinical need."

[59 H, 60 H, Ref. 61 H] "The prognosis for Myalgic Encephalomyelitis and Chronic Fatigue Syndrome (ME and CFS) is considered to be poor with only a minority (a median estimate of 2-5%) returning to pre-morbid levels of functioning. The majority of patients remains significantly impaired."

[61 H, 62 H] "Far more ME patients experience a deterioration rather than an improvement over time. The healthcare service and the welfare administration greatly contribute to a worsening of the course of the illness for an already seriously ill group of patients."

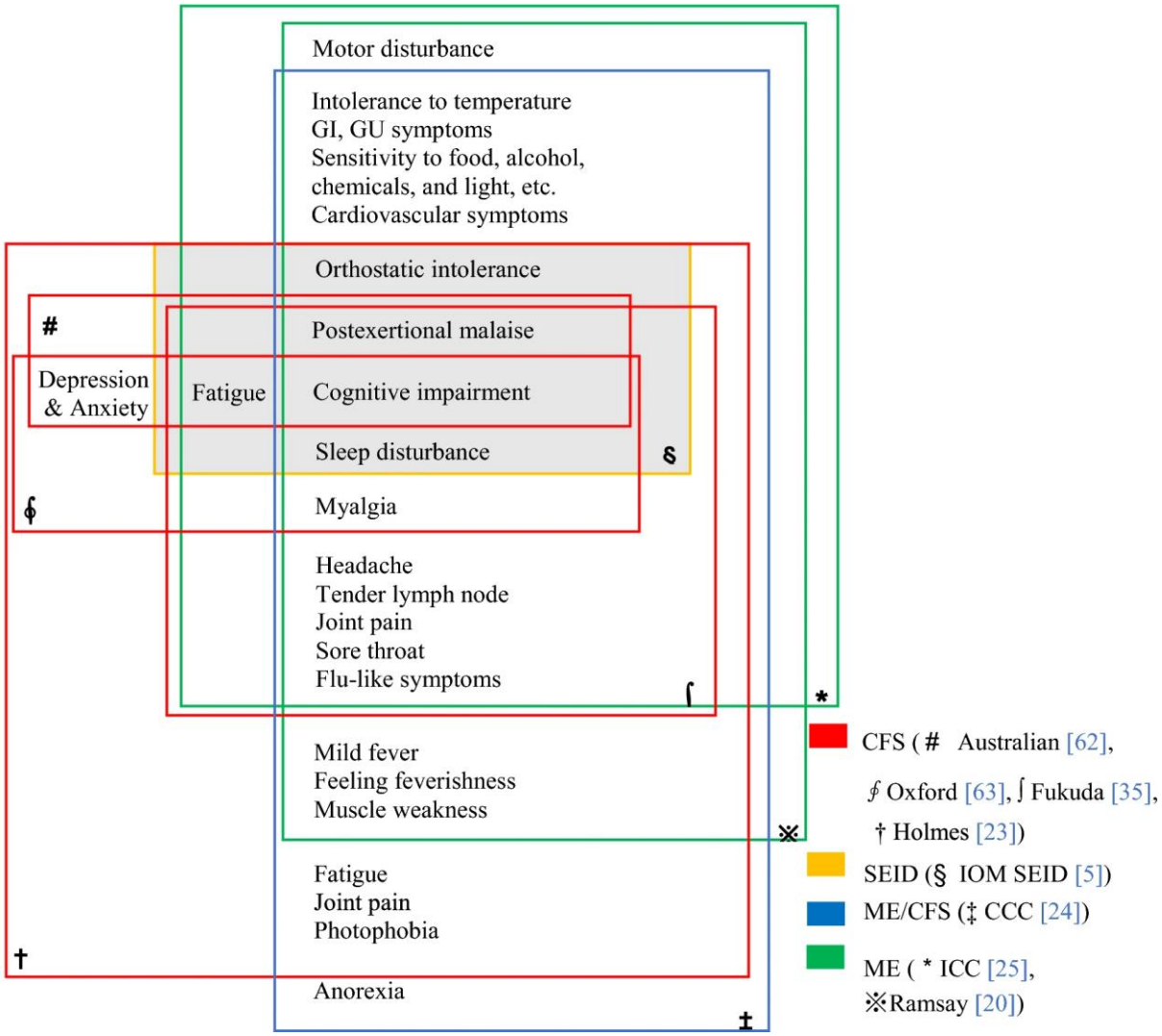
[63 H, 64 H, 65 H] Compared to other conditions ME/CFS patients have the lowest measured "Health-Related Quality of Life" score of 20 conditions, thus even worse than cancer, multiple sclerosis and stroke.

[66 H, 67 H, 68 H, 69 H, 70 H, Ref. 53 H, Ref. 651 H] "In spite of this level of debility, less than one-third of medical schools include ME/CFS in their core curricula, and the clinical guidance used by medical providers in practice includes treatments that are outdated, inappropriate, and potentially harmful. It is estimated that there are fewer than two dozen nationally recognized ME/CFS specialists in the USA. Patients struggle to find doctors willing and able to care for them. The US Centers for Disease Control and Prevention (CDC) has referred to ME/CFS as America's Hidden Health Crisis. This crisis in care is accompanied by a remarkably low level of research funding."

[Ref. 73 H, 71 H, 72 H, 73 H, 74 H, 75 H] "Norwegian researchers compared the main criteria (Oxford criteria, Fukuda criteria, Canadian Consensus Criteria, International Consensus Criteria and SEID). They say "it is important to distinguish between Myalgic Encephalomyelitis and Chronic Fatigue Syndrome" to improve understanding of the disease, treatment and patients' lives, as using incorrect criteria can lead to incorrect treatment. For instance, the Oxford criteria, which do not include PEM, would involve a large percentage of pure psychiatric conditions and should not be applied. False positive diagnosis may lead to inappropriate labelling and improper intervention and treatment of this vulnerable patient group."

[76 H, 77 H] "Different CFS criteria may at best be diagnosing a spectrum of disease severities and at worst different CFS phenotypes or even different diseases. This complicates research and disease management and may contribute to the significant stigma associated with the condition."

[78 H] This paper – "Review of case definitions for myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS)", Eun-Jin Lim & Chang-Gue Son, 2020 – gives an overview:



[Ref. 2 H, Ref. 5 H, 79 H, 80 H, 81 H, 82 H, 83 H, 84 H, 85 H] According to the Institute of Medicine (IOM) report published in 2015, "Patients often struggle with their illness for years before receiving a diagnosis, and an estimated 84 to 91 percent of patients affected by ME/CFS are not yet diagnosed."

Dr. Maureen R. Hanson, 2020: "The actual worldwide prevalence of ME/CFS is difficult to determine. Different studies have applied a variety of diagnostic criteria, so there is a substantial variation in prevalence estimates. Nevertheless, a close look at these reports indicates that it is not unreasonable to use the 0.86% prevalence rate worldwide, which gives a total of 67 million patients worldwide."
ME-Pedia gives an overview of the different prevalence rates over the years, varying from 0.03%-0,44%.
"The CDC estimates that one million people in the US have ME/CFS and as many as 17-24 million people worldwide have ME/CFS. A recent UK biobank study places that estimate at 30 million. In 2015, the Institute of Medicine Report estimated there were between 836,000 and 2.5 million ME/CFS patients in the United States." [86 H] The prevalence rate of ME in Norway is estimated at 0,5%-0,8%.

Common comorbidities

Orthostatic intolerance (OI), Chronotropic incompetence (CI), POTS, SIBO, IBS, Fibromyalgia, Mast Cell Activation Syndrome (MCAS), Multiple Chemical Sensitivities (MCS), Ehlers-Danlos Syndrome, Hashimoto's Thyroiditis, Endometriosis [87 H] and Sleep apnea.

Biomedical insights

Metabolomics and proteomics

Problems in metabolic cycles and pathways

- [88 H] Post-Exertional Malaise Is Associated with Hypermetabolism, Hypoacetylation and Purine Metabolism Deregulation in ME/CFS Cases, Neil R McGregor, Christopher W Armstrong, Donald P Lewis, Paul R Gooley, 2019.

  Abnormalities in the urea cycle metabolites.

- [89 H] The IDO Metabolic Trap Hypothesis for the Etiology of ME/CFS, Alex A. Kashi, Ronald W. Davis, Robert D. Phair, 2019

  IDO metabolic trap involving kynurenine pathways and tryptophan metabolism.

- [90 H] Tryptophan Metabolism Cytokines, and Fatty Acid Binding Protein 2 in ME/CFS, Manuela Simonato, 2021

- [91 H] Metabolic profiling of a myalgic encephalomyelitis/chronic fatigue syndrome discovery cohort reveals disturbances in fatty acid and lipid metabolism, Arnaud Germain, David Ruppert, Susan M. Levine, and Maureen R. Hanson, 2017.

  "Disturbances in fatty acid and lipid metabolism. Three main affected pathway categories: lipids, purine and amino acids, and energy metabolism."

  "Pathway analysis points to a few pathways with high impact and therefore potential disturbances in patients, mainly taurine metabolism and glycerophospholipid metabolism, combined with primary bile acid metabolism, as well as glyoxylate and dicarboxylate metabolism and a few other pathways, all involved broadly in fatty acid metabolism. Purines, including ADP and ATP, pyrimidines and several amino acid metabolic pathways were found to be significantly disturbed. Finally, glucose and oxaloacetate were two main metabolites affected that have a major effect on sugar and energy levels."

- [92 H] Insights into myalgic encephalomyelitis/chronic fatigue syndrome phenotypes through comprehensive metabolomics, Dorottya Nagy-Szakal, Mady Hornig, Oliver Fiehn & W. Ian Lipkin, 2018

  "Altered plasma levels of choline, carnitine and complex lipid metabolites. Patients with ME/CFS and IBS have increased plasma levels of ceramide."

- [93 H, 94 H] IACFS/ME Online Conference August 21, 2020 Iacfs/Me Conference Sep 02, 2020, *and* Upregulated PDK4 expression is a sensitive marker of increased fatty acid oxidation, Katrine Nitschke Pettersen, 2019

  "There is a block in the conversion of pyruvate to acetyl CoA. Upregulated PDK4 (pyruvate dehydrogenase kinase 4) expression appears as a sensitive marker for metabolic adaptations involving increased rates of mitochondrial fatty acid oxidation."

- [95 H, 96 H] Center for Enervating Neuroimmune Disease, Letter to the Editor of Metabolites explaining the estimate of 65 million people with ME/CFS worldwide, 2020 *and* Comprehensive Circulatory Metabolomics in ME/CFS Reveals Disrupted Metabolism of Acyl Lipids and Steroids, Arnaud Germain, Maureen R. Hanson, Susan M. Levine, 2020.

  Altered metabolites. "Acylcholines, belonging to the fatty acid metabolism sub-pathway of lipids, for which all compounds are consistently reduced in two distinct ME/CFS patient cohorts. Another class of lipids with far-reaching activity on virtually all organ systems are steroids; androgenic, progestin, and corticosteroids are broadly reduced in our patient cohort. We also report on lower dipeptides and elevated sphingolipids abundance in patients compared to controls. Disturbances in the metabolism of many of these molecules can be linked to the profound organ system symptoms endured by ME/CFS patients."

- [97 H] Sex-specific plasma lipid profiles of ME/CFS patients and their association with pain, fatigue, and cognitive symptoms, Nancy Klimas, August 2021

- [98 H] Widespread pain and altered renal function in ME/CFS patients, Neil R. McGregor, 2016

  "Increases in pain distribution were associated with reductions in serum essential amino acids, urea, serum sodium and increases in serum glucose and the 24-hour urine volume; however, the biochemistry was different for each pain area. Regression modelling revealed potential acetylation and methylation defects in the pain subjects".

  "Conclusions: These findings confirm and extend our earlier findings. These changes appear consistent with repeated minor inflammatory-mediated alterations in kidney function resulting in essential amino acid deprivation and inhibition of protein synthesis and genetic translation within tissues."

- [99 H] Advances in Clinical Chemistry, CHAPTER FIVE Metabolism in Chronic Fatigue Syndrome, Neil R McGregor, 2014.

  Fall in the purine metabolite hypoxanthine.

- [Ref. 136 H] Dysregulated Provision of Oxidisable Substrates to the Mitochondria in ME/CFS Lymphoblasts, Paul R. Fisher, 2021.

  "Elevated levels of enzymes involved in the TCA cycle, the pentose phosphate pathway, mitochondrial fatty acid β-oxidation and degradation of amino acids, including glutamine/glutamate, branched-chain amino acids and essential amino acids. Inefficient ATP synthesis by Complex V in ME/CFS lymphoblasts."

- [100 H] Prospective Biomarkers from Plasma Metabolomics of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Implicate Redox Imbalance in Disease Symptomatology, Arnaud Germain, David Ruppert, Susan M. Levine and Maureen R. Hanson, 2018.

  "Extensive analysis of the 832-metabolite dataset generated by Metabolon®, covering eight biological classes, generated important insight into metabolic disruptions that occur in ME/CFS."

  "We report on 14 metabolites with differences in abundance, allowing us to develop a theory of broad redox imbalance in ME/CFS patients, which is consistent with findings of prior work in the ME/CFS field."

  "The Metabolites Found to be Most Affected in ME/CFS Patients Belong to Four Classes."

“The nine metabolites discussed below belong to the following four super-pathways: “Cofactors and Vitamins”, “Energy”, “Nucleotides”, and “Peptides.”

“Four of those metabolites are classified as “Cofactors and Vitamins”. Heme, the pigment that gives blood its red color, is one of the most statistically different metabolites, with higher abundance in patients compared to controls (Figure 1a and Table 2). Heme consists of an iron ion centered in a large organic ring and is mainly found in hemoglobin, but also in a few other important hemoproteins, with varying functions all related to redox chemistry. Free heme is highly cytotoxic and deleterious to tissues via its pro-oxidative and pro-inflammatory properties, as it is capable of catalyzing free radical formation.”

“The other three metabolites are part of the vitamin E pathway, and were significantly lower in patients compared to controls (Figure 1b—d, and Table 2). Vitamin E is a fat-soluble antioxidant that can hinder the propagation of reactive oxygen species through lipid membranes. Gamma-CEHC is the oxidized form of dietary gamma-tocopherol and is anti-inflammatory, while the other two are glucuronide conjugates of alpha-CEHC and gamma-CEHC, both significant circulating forms in the blood.”

“Another metabolite of interest is alpha-ketoglutarate, as it is one of the ten “Energy” metabolites for which we have data in this study. Our data indicates it is higher in patients compared to controls, (Figure 1e and Table 2). Alpha-ketoglutarate is an essential biological compound found in many biological pathways, linked to amino acid metabolism and part of the TCA cycle, which occurs in the mitochondria, where chemical energy is produced from the oxidation of pyruvate.”

“The following three metabolites belong to the “Nucleotides” class and all three have lower abundance in patients compared to controls (Figure 1f—h, and Table 2). Not much is known about 2’-O-methylcytidine, apart from the fact that it is part of the pyrimidine metabolism. On the other hand, adenosine 3’,5’-cyclic monophosphate (cAMP) and inosine 5’-monophosphate (IMP) are part of the purine metabolism and both associated with ATP/AMP, respectively, and are thus linked to energy metabolism. While the function of IMP in blood is still being discussed, cAMP is known to be a central intracellular regulator affecting hormonal pathways.”

“Finally, gamma-glutamyl-threonine, a dipeptide part of the “Peptides” class, was detected at significantly higher levels in the blood of patients compared to controls (Figure 1i and Table 2). Apart from the fact that this compound is an intermediate breakdown product of protein degradation, very little is known about its physiological effect in blood. It is, however, cited in a patent as a potential biomarker for liver toxicity determination.”

“Out of the 7, two overlap with the statistically significant metabolites described in the above section, namely heme and IMP.”

“All the other metabolites identified in the volcano plot had higher abundances in patients compared to controls. These included tauroursodeoxycholate (TUDCA), reported both as a cytoprotective agent and a chemical chaperone; 3-hydroxybutyrylcarnitine 1 and 3-hydroxybutyrate (BHBA), both involved in ketosis, a metabolic process associated with energy and glucose; piperine, an alkaloid found in herbs and spices; and histamine, a compound known to be involved in many aspects of the human body, including local immune responses, acting as a central neurotransmitter and a vasodilator to name a few.”

“A notable condition found in the dataset analysis is anoxia (along with asphyxia) as this state is an extreme form of hypoxia, when the body, or a region of it, experiences extremely low oxygen. In a healthy person suffering from hypoxia, indicators include fatigue, confusion, headaches and numbness of extremities, which are all symptoms of ME/CFS patients. The oxygen status of tissue could possibly be affected by the disruption in heme abundance described in Figure 1a and Table 2.

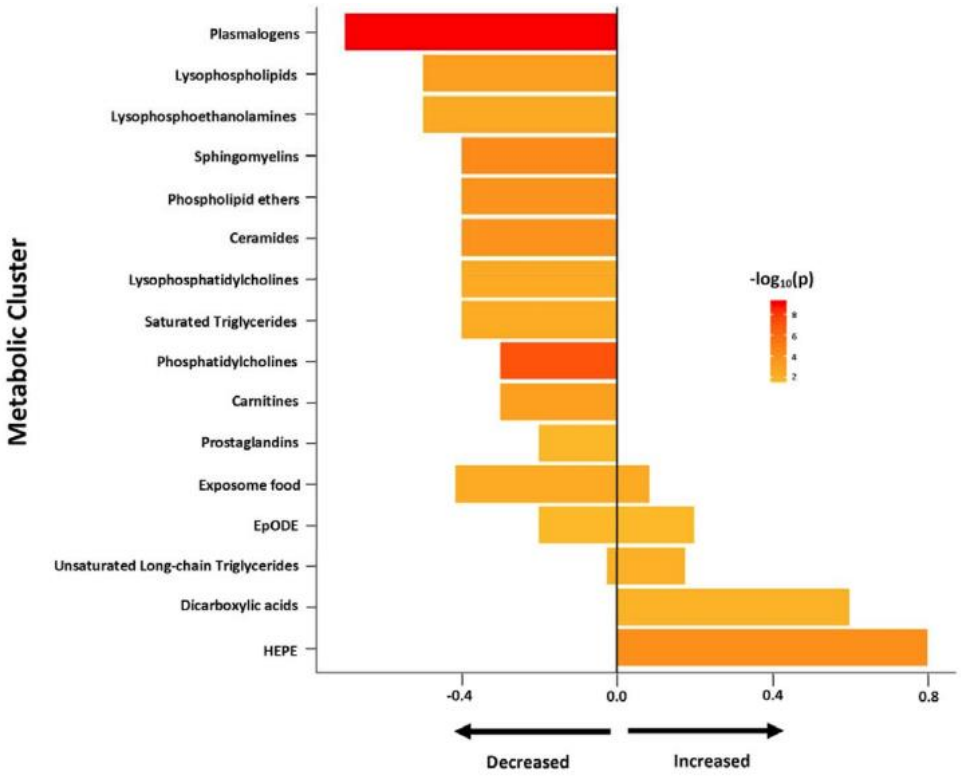
Reduced cerebral blood flow, which could result in inadequate brain oxygenation, has been hypothesized to be linked to cognitive impairment in ME/CFS patients."

- [101 H] In-Depth Analysis of the Plasma Proteome in ME/CFS Exposes Disrupted Ephrin-Eph and Immune System Signaling, by Arnaud GermainOrcID, Susan M. Levine and Maureen R. Hanson, 2021

  "Significant differences in the levels of 19 proteins between cohorts implicate pathways related to the extracellular matrix, the immune system and cell–cell communication. Outputs of pathway and cluster analyses robustly highlight the ephrin pathway, which is involved in cell–cell signaling and regulation of an expansive variety of biological processes, including axon guidance, angiogenesis, epithelial cell migration, and immune response."

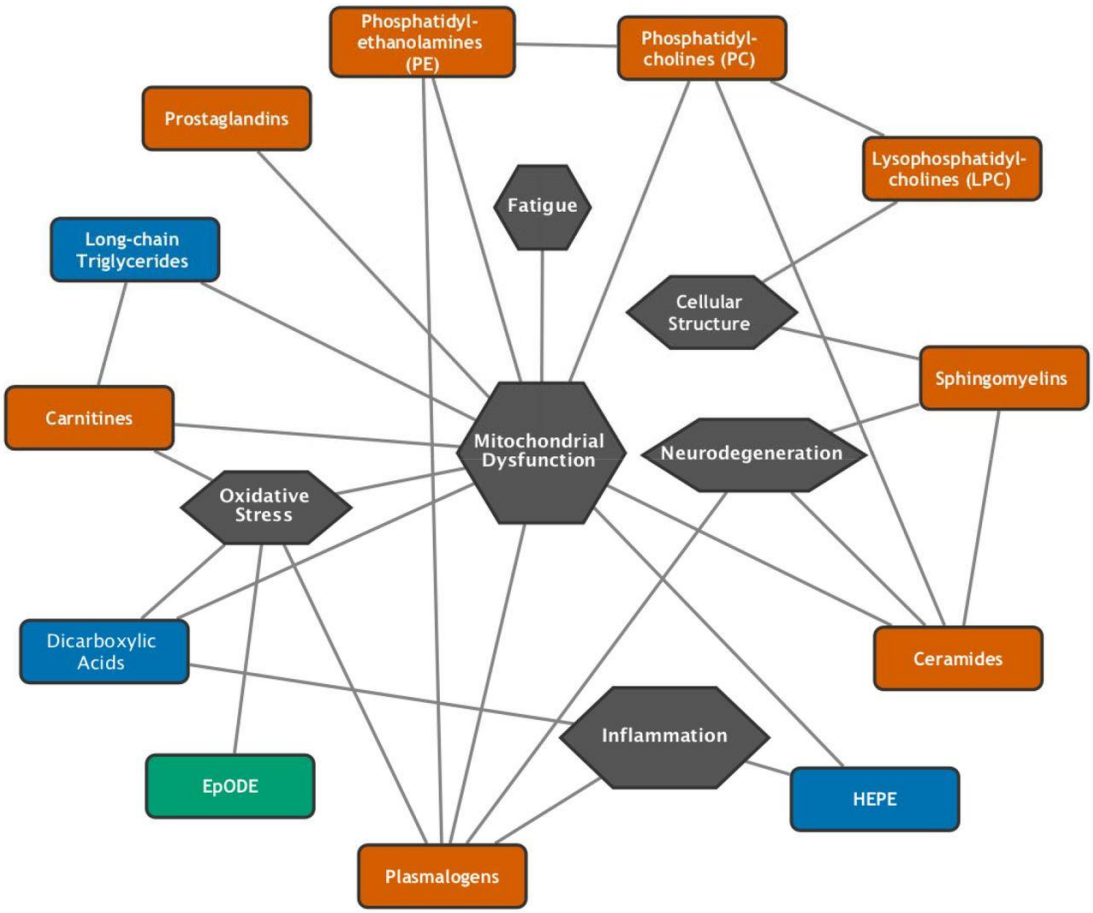
- [102 H, 103 H] Dysregulation of the Kennedy Pathway and Tricarboxylic Acid Cycle in Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome, Xiaoyu Che, Walter Ian Lipkin, 2021

  "…metabolomic analysis of 888 metabolic analytes in plasma samples of 106 ME/CFS cases and 91 frequency-matched healthy controls". "In ME/CFS cases, the regression, Bayesian and enrichment analyses all revealed abnormal levels of several membrane lipids indicating dysregulation of the Kennedy pathway: decreased plasma levels of plasmalogens, phosphatidylcholines, phosphatidylethanolamines, sphingomyelins, and phospholipid ethers. Enrichment analyses revealed decreased levels of cholines, ceramides and carnitines, and increased levels of long chain triglycerides, dicarboxylic acids, hydroxy-eicosapentaenoic acid, and the tricarboxylic acid cycle intermediates alpha-ketoglutarate and succinate." "Our findings are consistent with earlier ME/CFS work indicating compromised energy metabolism and redox imbalance, and highlight specific abnormalities that may provide insights into the pathogenesis of ME/CFS."



"*Figure 2.*
Chemical enrichment analyses using ChemRICH. A. All ME/CFS v. controls."
"The length of the bar represents altered ratio for each metabolic cluster. A bar restricted to the left of the centered vertical line indicates a metabolic cluster that is lower in ME/CFS patients. A bar

restricted to the right of the centered vertical line indicates a metabolic cluster that is higher in ME/CFS patients. A bar that crosses the vertical line indicates a metabolic cluster that is dysregulated in mixed directions. The color represents significance. EpODE: epoxy octadecadienoic acid. HEPE: hydroxy eicosapentaenoic acid. ME/CFS: myalgic encephalomyelitis/chronic fatigue syndrome. sr-IBS: self-reported physician diagnosed irritable bowel syndrome."



"Figure 4. Functional interaction network of altered metabolic clusters in ME/CFS
Metabolite levels that are decreased (orange), increased (blue), or mixed in direction (green) in the enrichment assay have been associated with oxidative stress, mitochondrial dysfunction, and neurodegeneration."

- [104 H] Human Herpesvirus-6 Reactivation, Mitochondrial Fragmentation, and the Coordination of Antiviral and Metabolic Phenotypes in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome, Philipp Schreiner, Robert K Naviaux, Bhupesh K Prusty, 2020

"Human herpesvirus (HHV)-6 and HHV-7 are two infectious triggers for which evidence has been growing. To understand possible causative role of HHV-6 in ME/CFS, metabolic and antiviral phenotypes of U2-OS cells were studied with and without chromosomally integrated HHV-6 and with or without virus reactivation using the histone deacetylase inhibitor trichostatin-A."

"Proteomic analysis was conducted by pulsed stable isotope labeling by amino acids in cell culture analysis. Antiviral properties that were induced by HHV-6 transactivation were studied in virus-naive A549 cells challenged by infection with influenza-A (H1N1) or HSV-1."

"Mitochondria were fragmented and 1-carbon metabolism, dUTPase, and thymidylate synthase were strongly induced by HHV-6 reactivation, whereas superoxide dismutase 2 and proteins required for

mitochondrial oxidation of fatty acid, amino acid, and glucose metabolism, including pyruvate dehydrogenase, were strongly inhibited."

"Adoptive transfer of U2-OS cell supernatants after reactivation of HHV-6A led to an antiviral state in A549 cells that prevented superinfection with influenza-A and HSV-1. Adoptive transfer of serum from 10 patients with ME/CFS produced a similar fragmentation of mitochondria and the associated antiviral state in the A549 cell assay."

"In conclusion, HHV-6 reactivation in ME/CFS patients activates a multisystem, proinflammatory, cell danger response that protects against certain RNA and DNA virus infections but comes at the cost of mitochondrial fragmentation and severely compromised energy metabolism."

- [105 H] Naviaux Lab - Chronic Fatigue Syndrome Research

  "A study by Bhupesh Prusty (University of Wurzburg) and Robert Naviaux (UCSD), found that mitochondria from ME patients show dramatic fragmentation in comparison to controls. Prusty and Naviaux found HHV-6 reactivation induced mitochondrial fragmentation, oxidative changes, and decreased antiviral resistance."

- [106 H] Investigation of Long COVID Prevalence and Its Relationship to Epstein-Barr Virus Reactivation, Jeffrey E. Gold, 2021

  Similar results are found in a Long Covid study 2021: "These findings suggest that many long COVID symptoms may not be a direct result of the SARS-CoV-2 virus but may be the result of COVID-19 inflammation-induced EBV reactivation."

- [107 H] The Hidden Enemy Within: Non-canonical Peptides in Virus-Induced Autoimmunity, Manivel Lodha, Florian Erhard, Lars Dölken and Bhupesh K. Prusty, 2022

  "Perspective article on Virus-induced autoimmunity, which revisits the idea of Cryptic peptides and their potential role in several human diseases including ME/CFS and Long-COVID."

- [108 H] Selective inhibition of microRNA processing by a herpesvirus-encoded microRNA triggers virus reactivation from latency, Bhupesh K Prusty, September 2021

  "Herpesviruses have mastered host cell modulation and immune evasion to augment productive infection, life-long latency and reactivation thereof 1,2. A long appreciated, yet elusively defined relationship exists between the lytic-latent switch and viral non-coding RNAs 3,4."

  "Here, we identify miRNA-mediated inhibition of miRNA processing as a novel cellular mechanism that human herpesvirus 6A (HHV-6A) exploits to disrupt mitochondrial architecture, evade intrinsic host defense and drive the latent-lytic switch."

  "We demonstrate that virus-encoded miR-aU14 selectively inhibits the processing of multiple miR-30 family members by direct interaction with the respective pri-miRNA hairpin loops. Subsequent loss of miR-30 and activation of miR-30/p53/Drp1 axis triggers a profound disruption of mitochondrial architecture, which impairs induction of type I interferons and is necessary for both productive infection and virus reactivation. Ectopic expression of miR-aU14 was sufficient to trigger virus reactivation from latency thereby identifying it as a readily drugable master regulator of the herpesvirus latent-lytic switch."

  "Our results show that miRNA-mediated inhibition of miRNA processing represents a generalized cellular mechanism that can be exploited to selectively target individual members of miRNA families. We anticipate that targeting miR-aU14 provides exciting therapeutic options for preventing

herpesvirus reactivations in HHV-6-associated disorders like myalgic encephalitis/chronic fatigue syndrome (ME/CFS) and Long-COVID."

- [109 H, 110 H, 111 H] Long COVID or Post-acute Sequelae of COVID-19 (PASC): An Overview of Biological Factors That May Contribute to Persistent Symptoms, Amy D. Proal and Michael B. VanElzakker, 2021

  "Some PASC patients meet the diagnostic criteria for myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) – a neuroinflammation-linked condition characterized by a range of debilitating chronic symptoms including severe fatigue, musculoskeletal pain, and post-exertional malaise (worsening of symptoms following exertion) (Carruthers et al., 2011; Clayton, 2015; Kedor et al., 2021; Komaroff and Bateman, 2021). Overlap between the PASC and ME/CFS diagnoses is not surprising, since most cases of ME/CFS begin with a viral infection, or involve multiple exposures to viral and bacterial pathogens over time (Rasa et al., 2018)."

  "Pathogens most commonly implicated in ME/CFS development include neurotrophic herpesviruses and enteroviruses. Several studies have found that active HHV-6 infection is more common in ME/CFS than controls (Komaroff, 2006). Enteroviruses, several species of which can be acquired via respiratory infection, have been identified in brain, skeletal muscle, and stomach biopsy specimens of certain patients with ME/CFS (Gow et al., 1991; McGarry et al., 1994; Richardson, 2001; Chia and Chia, 2008). Other respiratory pathogens have also been linked to the development of ME/CFS-like symptoms (Magnus et al., 2015). For example, one team studied 233 SARS survivors approximately 4 years after initial infection, and found that 27.1% met the modified 1994 Centers for Disease Control and Prevention (CDC) criteria for chronic fatigue syndrome (Lam et al., 2009)."

- [112 H] Insights into Metabolite Diagnostic Biomarkers for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome, Emi Yamano, 2021

  "Common metabolic fluctuations were observed in fatigued animal models and human patients with ME/CFS and these findings could contribute to the elucidation of the pathophysiology of ME/CFS."

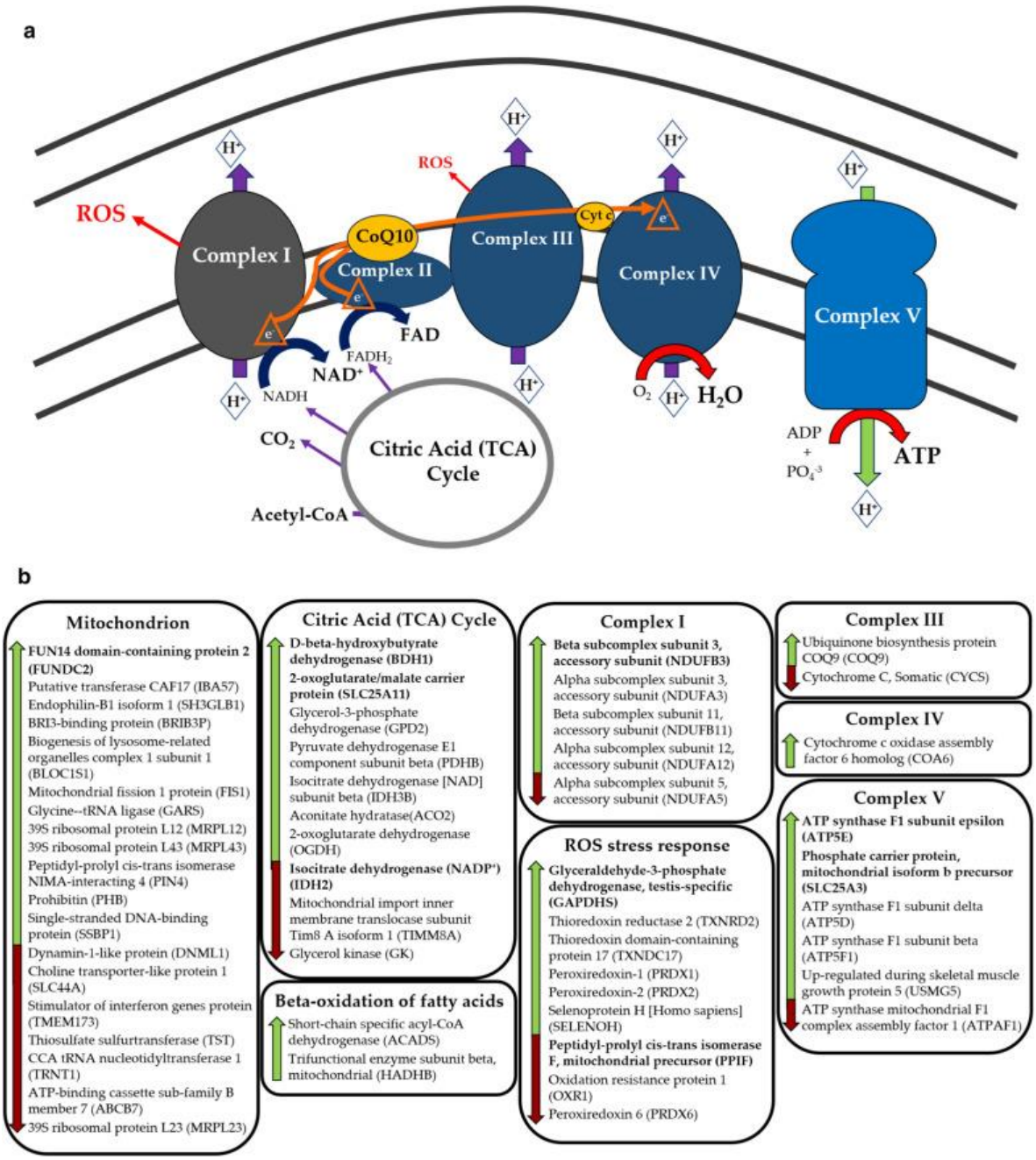
  "Biomarker research, to distinguish between patients with ME/CFS and healthy individuals, is still evolving."

  In previous studies, reactive oxygen metabolite-derived compounds (d-ROMs) in the blood, exosomes and inclusion proteins/micro RNAs, monocyte number, and lipoprotein profiles have been reported to be informative markers for discriminating patients with ME/CFS from healthy controls."

  "Furthermore, inflammation and immune system activation have been suggested by many previous studies to be the root causes of ME/CFS, and the results from many such studies have shown elevation of cytokines and lymphokines in plasma. Using positron emission tomography (PET), neuroinflammation was detected in wide-spread brain regions of patients with ME/CFS, which was associated with the severity of the specific neuro-psychologic symptoms."

  "We believe that in future, it will be possible to establish highly precise objective diagnostic biomarkers for ME/CFS, exhibiting diverse pathologies through the implementation of research that would integrate metabolomic markers reflecting the specific metabolism underlying the pathophysiology of fatigue with highly precise in vivo biomarkers."

- [113 H] A SWATH-MS analysis of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome peripheral blood mononuclear cell proteomes reveals mitochondrial dysfunction, Prof. Warren Tate, 2020



"*Fig. 4 a A schematic of the mitochondrial respiratory chain constructed by the authors to highlight the OXPHOS complexes, the major reactive oxygen species (ROS) production sites, and the ATP Synthase complex relevant to the differential expression of mitochondria-related proteins in the ME/CFS group b Highlighting differentially abundant proteins (P < 0.05, log10(Fold Change) > 0.114 and < −0.125) involved in mitochondrial function and energy metabolism. In bold are proteins with P < 0.01 and log10(Fold Change) > 0.2 and < −0.2. The green arrow represents increased relative abundance and the red arrow decreased relative abundance in the 'ME/CFS' PCA group, compared to controls*"

- [114 H] Bioenergetic and Proteomic Profiling of Immune Cells in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Patients: An Exploratory Study, Paula Fernandez-Guerra, 2021

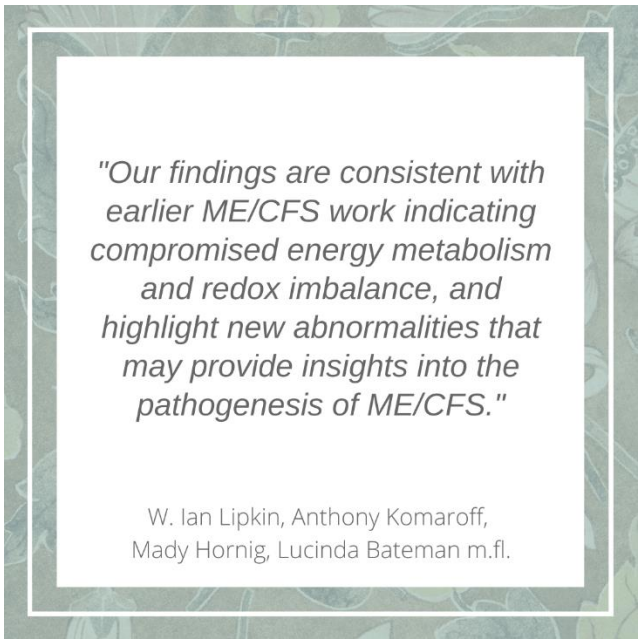
  "PBMCs from ME/CFS patients showed significantly lower mitochondrial coupling efficiency. They exhibited proteome alterations, including altered mitochondrial metabolism, centered on pyruvate dehydrogenase and coenzyme A metabolism, leading to a decreased capacity to provide adequate intracellular ATP levels. Overall, these results indicate that PBMCs from ME/CFS patients have a decreased ability to fulfill their cellular energy demands."

- [115 H] Induced pluripotent stem cells as suitable sensors for fibromyalgia and myalgic encephalomyelitis/chronic fatigue syndrome, María B Monzón-Nomdedeu, Karl J Morten, and Elisa Oltra, 2021

  "This opinion review explains our hypothesis that iPSCs could be developed as a screening platform to provide evidence of a metabolic imbalance in FM and ME/CFS."

  "To the best of our knowledge, this is the first comprehensive systematic review of ME/CFS and FM metabolic profiles. It is an update of the metabolic differences reported by more than one independent study, and the discrepancies that exist may reflect patient heterogeneity in these two overlapping diseases. Possible associations between dysregulated metabolites and disease symptoms were also found."

- [116 H] Evidence for Peroxisomal Dysfunction and Dysregulation of the CDP-Choline Pathway in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome, Levine, Bateman, Hornig, Lipkin, Komaroff, 2022



(*Picture: MillionsMissing Stavanger, January 2022*)

"Results In ME/CFS cases, regression, Bayesian and enrichment analyses revealed evidence of peroxisomal dysfunction with decreased levels of plasmalogens."

"To the best of our knowledge, this is the first study suggesting peroxisomal dysfunction in ME/CFS based on a comprehensive plasma metabolomic analysis."

"Other findings included decreased levels of several membrane lipids, including phosphatidylcholines and sphingomyelins, that may indicate dysregulation of the cytidine-5'-diphosphocholine pathway."

"Enrichment analyses revealed decreased levels of choline, ceramides and carnitines, and increased levels of long chain triglycerides (TG) and hydroxy-eicosapentaenoic acid. Elevated levels of dicarboxylic acids were consistent with abnormalities in the tricarboxylic acid cycle."

"Using machine learning algorithms with selected metabolites as predictors, we were able to differentiate female ME/CFS cases from female controls (highest AUC=0.794) and ME/CFS cases without self-reported irritable bowel syndrome (sr-IBS) from controls without sr-IBS (highest AUC=0.873)."

"Conclusion Our findings are consistent with earlier ME/CFS work indicating compromised energy metabolism and redox imbalance, and highlight new abnormalities that may provide insights into the pathogenesis of ME/CFS."

Mitochondria

- [117 H] Use of glucose for energy production in muscle cells from patients with ME/CFS, Cara Tomas, Joanna L Elson, Julia L Newton & Mark Walker, 2020

  "Muscle cells from people with ME/CFS are less able to use glucose as a fuel to produce energy. This impairment in energy production may underlie the muscle fatigue that is characteristic of the illness. These results help narrow down where in the metabolic pathway the abnormality occurs."

  "There are four steps to this process: glycolysis, pyruvate oxidation, the citric acid cycle and oxidative phosphorylation (OXPHOS). In this study, Cara concentrated on glycolysis and OXPHOS.
  Using a technique called extracellular flux analysis, Cara measured glycolysis in the skeletal muscle cells of nine people with ME/CFS and eleven healthy control subjects."

  "In summary, skeletal muscle cells from people with ME/CFS had a reduced ability to use glucose as a fuel to produce energy via OXPHOS, while they were able to use galactose and fatty acids normally, and glycolysis was also normal. This is important because glucose is one the body's preferred sources of fuel, and cells rely on OXPHOS as the final step in generating ATP for energy."

  "Furthermore, the results help narrow down where in the pathway this dysfunction occurs. Cara suggests that it could be in the pyruvate oxidation step which links glycolysis with the citric acid cycle (not the first time this has been implicated). The results are similar to those reported previously in white blood cells, but it is significant that the same abnormality is present in muscle cells, and strengthens the idea that ME/CFS affects multiple organs."

  "As part of the extended program of metabolic research in Newcastle over the last decade, these findings bring us another step closer to understanding fully the abnormalities in metabolism that underlie the muscle fatigue experienced by people with ME/CFS."

- [118 H] Abnormal blood lactate accumulation during repeated exercise testing in myalgic encephalomyelitis/chronic fatigue syndrome, Katarina Lien, 2019

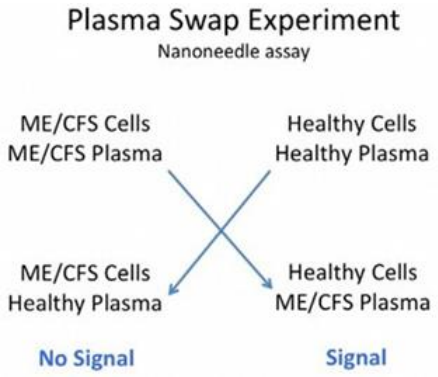
- [119 H] Broadband electrical impedance as a novel characterization of oxidative stress in single L6 skeletal muscle cells, Caroline Ferguson, 2021

  "Oxidative stress (OS) related diseases like ME/CFS lack unique biophysical markers.
  Differences between stressed and regular cells can be sensed via broadband sensing.
  Electrical signatures of cells experiencing OS have wider spread at GHz frequencies.
  Electrical difference can be tied to calcium flux within the cytoplasm."

- [120 H] ME International, Mitochondria and ME, Authored by John Duncan, updated 4/29/20

  "In 2019, in trying to develop an assay for ME, the Ron Davis group at Stanford found an altered electrical signal (impedance) in patients' cells when subjected to osmotic stress" [121] . "This suggests that in a harsh environment the patients' cells don't have the energy to maintain their voltage gradients – unlike normal cells which do. Besides its usefulness as a diagnostic, Davis's finding also implicates deficient cellular energy, and therefore the mitochondria, in ME patients."

- [122 H, 123 H, 124 H] Dr. Ron Davis presents ME/CFS Research, 2018 IIMEC Conference – amongst others the "Plasma Swap Experiment"



  Dr. Ron Davis's plasma swap experiment on the nanoneedle assay in 2018 showed that the signal tracks with the plasma, it's not the cell. "There's something in the plasma that's causing this effect. We don't know what it is yet, but that's something that we need to figure out, because it's going through the entire body. It may be causing some of the effects and if we can figure out what it is and what its size is, we might be able to find a way to remove it and that actually could be a treatment."

- [125 H] Metabolic profiling indicates impaired pyruvate dehydrogenase function in myalgic encephalopathy/chronic fatigue syndrome, Øystein Fluge, Olav Mella, 2016

  "It has been demonstrated that plasma from patients with moderate and severe ME/CFS alters the energy metabolism of cultured muscle cells suggesting cellular stress, with some indications that the effect could be immunoglobulin-mediated."

- [126 H] The effect of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) severity on cellular bioenergetic function, Cara Tomas, Julia L. Newton, 2020

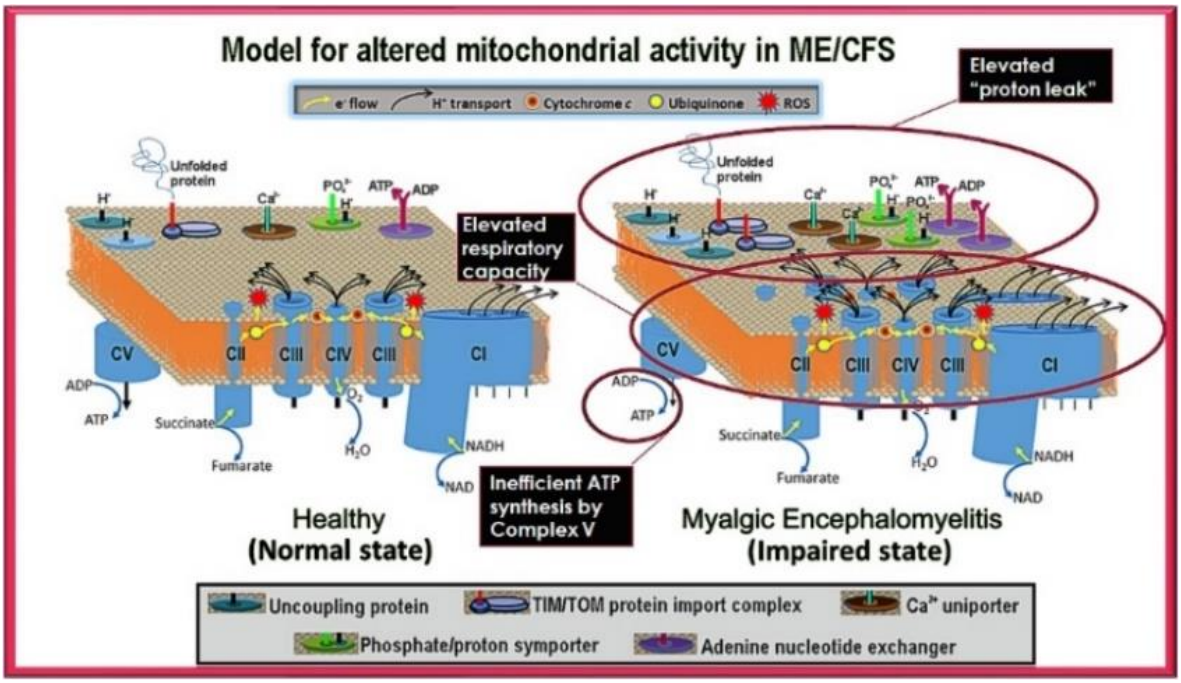
  "The lack of association between disease severity and mitochondrial function shown here indicates that abnormalities in mitochondrial function are a feature of the disease irrespective of severity. The lower glycolytic functioning in the severely affected patient group that we have identified is also vital as it shows that these patients have a glycolytic impairment in addition to the mitochondrial impairment which may explain why these patients present with a more severe phenotype. Lower levels of both mitochondrial and glycolytic functioning may be caused by a hypometabolic state in ME/CFS which is linked to disease severity. This work has increased our understanding of cellular energy production abnormalities in ME/CFS and how this alters with disease severity."

- [127 H] Metabolic abnormalities in chronic fatigue syndrome/myalgic encephalomyelitis: a mini-review Cara Tomas, Julia Newton, 2018

- [128 H, 129 H, 130 H] A map of metabolic phenotypes in patients with myalgic encephalomyelitis/ chronic fatigue syndrome, Karl J. Tronstad et al., August 2021

  "In summary, we report a map of common and context-dependent metabolic changes in ME/CFS, and some of them presented possible associations with clinical patient profiles. We suggest that elevated energy strain may result from exertion-triggered tissue hypoxia and lead to systemic metabolic adaptation and compensation. Through various mechanisms, such metabolic dysfunction represents a likely mediator of key symptoms in ME/CFS and possibly a target for supportive intervention."

- [131 H] An Isolated Complex V Inefficiency and Dysregulated Mitochondrial Function in Immortalized Lymphocytes from ME/CFS Patients, Daniel Missailidis, Sarah J Annesley, Claire Y Allan, Oana Sanislav, Brett A Lidbury, Donald P Lewis, Paul R Fisher, 2020



"*Fig. 4 a A schematic of the mitochondrial respiratory chain constructed by the authors to highlight the OXPHOS complexes, the major reactive oxygen species (ROS) production sites, and the ATP Synthase complex relevant to the differential expression of mitochondria-related proteins in the ME/CFS group b Highlighting differentially abundant proteins (P < 0.05, log10(Fold Change) > 0.114 and < −0.125) involved in mitochondrial function and energy metabolism. In bold are proteins with P < 0.01 and log10(Fold Change) > 0.2 and < −0.2. The green arrow represents increased relative abundance and the red arrow decreased relative abundance in the 'ME/CFS' PCA group, compared to controls*"

"Parameters of mitochondrial function and energy stress sensing were assessed by Seahorse extracellular flux analysis, proteomics, and an array of additional biochemical assays. Our results show that in ME/CFS lymphoblasts, there is an isolated Complex V inefficiency in ATP synthesis at the final step in mitochondrial oxidative phosphorylation. This is accompanied by multiple homeostatic compensations, including increased respiratory capacity, Complex V expression and capacity for fatty acid β oxidation. Together, these compensatory changes appear to be sufficient to meet the normal needs of active metabolism despite the inefficiency of ATP synthesis by Complex V. Thus, the steady state ATP levels and absolute ATP synthesis rates were both close to normal in these ME/CFS cells."

"However, this may leave the cells less able to respond to further acute increases in ATP demand, because the signaling and metabolic pathways involved are already chronically upregulated. AMPK activity in muscle cells cultured from CFS patients (Fukuda criteria) is reportedly unresponsive to electrical pulse-induced contraction in vitro, but not because AMPK itself is unresponsive to activation by either a mitochondrial Complex I inhibitor (metformin) or a direct AMPK activator (compound 991)."

"The authors suggested that the unresponsiveness of CFS cells to additional energy demands thus, seems to lie elsewhere. One possibility is the already elevated TORC1 activity, since TORC1 is an inhibitor of upstream pathways that activate AMPK. In any case, if this "cellular chronic fatigue" is present in other cell types, it may contribute to the unexplained fatigue experienced by ME/CFS patients, as suggested by the fact that all of the mitochondrial abnormalities we observed were correlated with the severity of patient symptoms measured by the Weighted Standing Time. These correlations also verify that the mitochondrial abnormalities we have found are of clinical relevance to the underlying cytopathological mechanisms and can serve as biomarkers of disease."

- [132 H, 133 H] Abnormalities of AMPK Activation and Glucose Uptake in Cultured Skeletal Muscle Cells from Individuals with Chronic Fatigue Syndrome, Audrey E. Brown, Julia L. Newton, 2015

  "We found four main differences in cultured skeletal muscle cells from subjects with CFS;
  - increased myogenin expression in the basal state,
  - impaired activation of AMPK,
  - impaired stimulation of glucose uptake and
  - diminished release of IL6."

  "The retention of these differences in cultured muscle cells from CFS subjects points to a genetic/epigenetic mechanism, and provides a system to identify novel therapeutic targets."

- [134 H] Pharmacological activation of AMPK and glucose uptake in cultured human skeletal muscle cells from patients with ME/CFS, Audrey E. Brown, 2018

  "The aim of the present study was to assess if AMPK could be activated pharmacologically in ME/CFS. Primary skeletal muscle cell cultures from patients with ME/CFS and healthy controls were treated with either metformin or compound 991. AMPK activation was assessed by Western blot and glucose uptake measured."

  "Both metformin and 991 treatment significantly increased AMPK activation and glucose uptake in muscle cell cultures from both controls and ME/CFS. Cellular ATP content was unaffected by treatment although ATP content was significantly decreased in ME/CFS compared with controls."

  "Pharmacological activation of AMPK can improve glucose uptake in muscle cell cultures from patients with ME/CFS. This suggests that the failure of EPS to activate AMPK in these muscle cultures is due to a defect proximal to AMPK. Further work is required to delineate the defect and determine whether pharmacological activation of AMPK improves muscle function in patients with ME/CFS."

- [135 H] Changes in the transcriptome of circulating immune cells of a New Zealand cohort with myalgic encephalomyelitis/chronic fatigue syndrome, Eiren Sweetman, Rosamund Vallings and Warren Tate, 2019

  "Functional network analysis of the altered gene transcripts ($P < 0.01$) detected interactions between the products related to inflammation, circadian clock function, metabolic dysregulation, cellular stress responses and mitochondrial function. Ingenuity pathway analysis ($P < 0.05$) provided further insights into the dysfunctional physiology, highlighting stress and inflammation pathways."

"This analysis provides novel insights into the molecular changes in ME/CFS and contributes to the understanding of the pathophysiological mechanisms of the disease."

- [136 H] Dysregulated Provision of Oxidizable Substrates to the Mitochondria in ME/CFS Lymphoblasts, Paul R. Fisher, 2021

  "Although understanding of the biomedical basis of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is growing, the underlying pathological mechanisms remain uncertain. We recently reported a reduction in the proportion of basal oxygen consumption due to ATP synthesis by Complex V in ME/CFS patient-derived lymphoblast cell lines, suggesting mitochondrial respiratory inefficiency. This was accompanied by elevated respiratory capacity, elevated mammalian target of rapamycin complex 1 (mTORC1) signaling activity and elevated expression of enzymes involved in the TCA cycle, fatty acid β-oxidation and mitochondrial transport."

  "These and other observations led us to hypothesize the dysregulation of pathways providing the mitochondria with oxidizable substrates. In our current study, we aimed to revisit this hypothesis by applying a combination of whole-cell transcriptomics, proteomics and energy stress signaling activity measures using subsets of up to 34 ME/CFS and 31 healthy control lymphoblast cell lines from our growing library."

  "While levels of glycolytic enzymes were unchanged in accordance with our previous observations of unaltered glycolytic rates, the whole-cell proteomes of ME/CFS lymphoblasts contained elevated levels of enzymes involved in the TCA cycle ($p = 1.03 \times 10{-}4$), the pentose phosphate pathway ($p = 0.034$, G6PD $p = 5.5 \times 10{-}4$), mitochondrial fatty acid β-oxidation ($p = 9.2 \times 10{-}3$), and degradation of amino acids including glutamine/glutamate (GLS $p = 0.034$, GLUD1 $p = 0.048$, GOT2 $p = 0.026$), branched-chain amino acids (BCKDHA $p = 0.028$, BCKDHB $p = 0.031$) and essential amino acids (FAH $p = 0.036$, GCDH $p = 0.006$). The activity of the major cellular energy stress sensor, AMPK, was elevated but the increase did not reach statistical significance."

  "The results suggest that ME/CFS metabolism is dysregulated such that alternatives to glycolysis are more heavily utilized than in controls to provide the mitochondria with oxidizable substrates."

- [137 H] Metabolism in Chronic Fatigue Syndrome, Dr. Neil McGregor, 2014

  "Studies on metabolism and CFS suggest irregularities in energy metabolism, amino acid metabolism, nucleotide metabolism, nitrogen metabolism, hormone metabolism, and oxidative stress metabolism. The overwhelming body of evidence suggests an oxidative environment with the minimal utilization of mitochondria for efficient energy production. This is coupled with a reduced excretion of amino acids and nitrogen in general."

  "Metabolomics is a developing field that studies metabolism within a living system under varying conditions of stimuli. Through its development, there has been the optimization of techniques to do large-scale hypothesis-generating untargeted studies as well as hypothesis-testing targeted studies. These techniques are introduced and show an important future direction for research into complex illnesses such as CFS."

- [138 H] Post-Exertional Malaise Is Associated with Hypermetabolism, Hypoacetylation and Purine Metabolism Deregulation in ME/CFS Cases, by Neil R. McGregor, 2019

  "This study revealed that post-exertional malaise is associated with changes in glycolysis and acetylation in ME/CFS cases. These changes are consistent with a hypoacetylation state and are likely

to significantly alter histone acetylation and the actions of acetylation and deacetylation in controlling cellular enzymatic events. Well-designed studies evaluating these important factors are warranted."

- [^{139} H] Hypothalamic-Pituitary-Adrenal Hypofunction in Myalgic Encephalomyelitis (ME)/Chronic Fatigue Syndrome (CFS) as a Consequence of Activated Immune-Inflammatory and Oxidative and Nitrosative Pathways, Gerwyn Morris, George Anderson, Michael Maes, 2016

  "Mechanistic explanations comprise increased levels of tumor necrosis factor-α, T regulatory responses with elevated levels of interleukin-10 and transforming growth factor-β, elevated levels of nitric oxide, and viral/bacterial-mediated mechanisms. HPA axis hypoactivity in ME/CFS is most likely a consequence and not a cause of a wide variety of activated immune-inflammatory and O&NS pathways in that illness."

The immune system

- [140 H] In the balance. Immune-system research in ME/CFS part 1, 26 April 2021

- [141 H] Distinct plasma immune signatures in ME/CFS are present early in the course of illness, Mady Hornig, 2015

  "We report here distinct alterations in plasma immune signatures early in the course of ME/CFS (n = 52) relative to healthy controls (n = 348) that are not present in subjects with longer duration of illness (n = 246). Analyses based on disease duration revealed that early ME/CFS cases had a prominent activation of both pro- and anti-inflammatory cytokines as well as dissociation of intercytokine regulatory networks. We found a stronger correlation of cytokine alterations with illness duration than with measures of illness severity, suggesting that the immunopathology of ME/CFS is not static. These findings have critical implications for discovery of interventional strategies and early diagnosis of ME/CFS."

- [142 H] Daily cytokine fluctuations, driven by leptin, are associated with fatigue severity in chronic fatigue syndrome: evidence of inflammatory pathology, Elizabeth Ann Stringer, Katharine Susanne Baker, Ian R Carroll, Jose G Montoya, Lily Chu, Holden T Maecker & Jarred W Younger, 2013

  "Studies have demonstrated elevated levels of inflammatory factors in patients with CFS, but findings are contradictory across studies and no biomarkers have been consistently supported. Single time-point approaches potentially overlook important features of CFS, such as fluctuations in fatigue severity. We have observed that individuals with CFS demonstrate significant day-to-day variability in their fatigue severity."

  "Daily fluctuations in self-reported fatigue (N = 250) were significantly correlated with daily leptin levels in participants with CFS, $r = 0.303$, $p < 0.01$. In contrast, healthy control data (N = 250) showed no correlation between fatigue and leptin, $r = -0.010$, $p < 0.873$."

  "Of particular interest are cytokines that can drive sickness behaviors such as fatigue and hypersensitivity to pain. While many studies have identified potential cytokine differences between individuals with CFS and healthy controls, results have been contradictory. The lack of consistent results across studies may be due partially to the use of cross-sectional designs in a condition driven by atypical, low-level inflammatory processes. We have observed that CFS symptom severity can change drastically in a short period of time, with abrupt shifts over just a couple of days. Such daily variability may blur the distinction between cases and controls in cross-sectional studies. We therefore propose a novel approach of daily immune monitoring to complement conventional cross-sectional studies. By capturing immune fluctuations every day, we can detect immune-fatigue relationships even when cytokine concentrations are highly variable over time, or when cytokines are driving symptoms at "normal" concentrations because downstream targets have been sensitized."

  "In our analyses of participants with CFS, the strongest relationship between cytokines and fatigue involved leptin. Although leptin is most broadly recognized as a pleiotropic peptide hormone secreted by adipocytes for regulating energy homeostasis, it is also an adipokine that modulates immune responses. Administration of endotoxin in both rodents and humans leads to increased gene expression for leptin and increased serum leptin levels. Likewise, leptin administration affects both the adaptive and innate immune systems, increasing the release of the proinflammatory cytokines TNF-alpha, IL-2, IL-6, and IL-12. Multiple studies have demonstrated elevated levels of circulating leptin in chronic inflammatory conditions. Serum leptin concentrations are also associated with fatigue severity in patients with chronic hepatitis C and irritable bowel syndrome."

"The relationship we observed between leptin and fatigue existed even though leptin levels were not abnormally elevated, and there was no statistical difference in leptin values between the CFS and control groups. Most of the body's leptin is secreted from white adipose tissue, and consequently, circulating leptin levels should be correlated with BMI. Leptin also demonstrates regular diurnal fluctuations that can change concentrations by over 50% in the course of a day. To mitigate the effect of diurnal rhythms on our results, we asked that participants complete their laboratory session at the same time each day, within a two-hour window. The percent change of leptin we observed over the study period was within the expected diurnal fluctuation range. The results suggest that absolute leptin levels were not abnormal, and therefore the relationship with symptom severity might only be observed with a longitudinal design."

"Our network analyses, using a simple massive univariate analysis approach, revealed that leptin was the only cytokine to covary significantly with fatigue in participants with CFS, while there was no relationship between fatigue and leptin (or any other cytokine tested) in the healthy controls. Even though leptin is reported to modulate other cytokines, specifically TNF-alpha, IL-2, IL-6, and IL-12, we did not observe relationships between those cytokines and fatigue variability."

"Our results support the role of cytokines in the pathophysiology of CFS."

- [143 H] Cytokine signature associated with disease severity in chronic fatigue syndrome patients, Jose G Montoya, 2017

  "Seventeen cytokines had a statistically significant upward linear trend that correlated with ME/CFS severity: CCL11 (Eotaxin-1), CXCL1 (GROα), CXCL10 (IP-10), IFN-γ, IL-4, IL-5, IL-7, IL-12p70, IL-13, IL-17F, leptin, G-CSF, GM-CSF, LIF, NGF, SCF, and TGF-α. Of the 17 cytokines that correlated with severity, 13 are proinflammatory, likely contributing to many of the symptoms experienced by patients and establishing a strong immune system component of the disease. Only CXCL9 (MIG) inversely correlated with fatigue duration."

- [144 H] Inflammatory proteins are altered in chronic fatigue syndrome-A systematic review and meta-analysis, Rebecca Strawbridge, 2019

  "Results were meta-analysed from 42 studies. Patients with CFS had significantly elevated tumour necrosis factor (ES = 0.274, $p < 0.001$), interleukin-2 (ES = 0.203, $p = 0.006$), interleukin-4 (ES = 0.373, $p = 0.004$), transforming growth factor-β (ES = 0.967, $p < 0.001$) and c-reactive protein (ES = 0.622, $p = 0.019$). 12 proteins did not differ between groups. These data provide some support for an inflammatory component in CFS, although inconsistency of results indicates that inflammation is unlikely to be a primary feature in all those suffering from this disorder."

- [145 H] Immunological abnormalities as potential biomarkers in Chronic Fatigue Syndrome/Myalgic Encephalomyelitis, Ekua W Brenu, Nancy G Klimas and Sonya M Marshall-Gradisnik 2011

  "Compared to healthy individuals, CFS/ME patients displayed significant increases in IL-10, IFN-γ, TNF-α, CD4+CD25+ T cells, FoxP3 and VPACR2 expression. Cytotoxic activity of NK and CD8+T cells and NK phenotypes, in particular the CD56bright NK cells were significantly decreased in CFS/ME patients. Additionally, granzyme A and granzyme K expression were reduced while expression levels of perforin were significantly increased in the CFS/ME population relative to the control population. These data suggest significant dysregulation of the immune system in CFS/ME patients."

- [146 H] A systematic review of natural killer cells profile and cytotoxic function in myalgic encephalomyelitis/chronic fatigue syndrome, Natalie Eaton-Fitch, Sonya Marshall-Gradisnik, 2019

  "A consistent finding among all papers included in this review was impaired NK cell cytotoxicity, suggesting that it is a reliable and appropriate cellular model for continued research in ME/CFS patients. Aberrations in NK cell lytic protein levels were also reported. Although additional research is recommended, current research provides a foundation for subsequent investigations. It is possible that NK cell abnormalities can be used to characterise a subset of ME/CFS due to the heterogeneity of both the illness itself and findings between studies investigating specific features of NK function."

- [147 H] The effect of IL-2 stimulation and treatment of TRPM3 on channel co-localisation with PIP2 and NK cell function in myalgic encephalomyelitis/chronic fatigue syndrome patients, Natalie Eaton-Fitch, Hélène Cabanas, Stanley du Preez, Donald Staines & Sonya Marshall-Gradisnik, 2021

  "Significant changes in co-localisation suggest PIP2-dependent TRPM3 function may be impaired in ME/CFS patients. Stimulation of NK cells with IL-2 significantly enhanced cytotoxic function in ME/CFS patients demonstrating normal function compared with HC. A crosstalk exists between IL-2 and TRPM3 intracellular signalling pathways which are dependent on Ca2+ influx and PIP2. While IL-2R responds to IL-2 binding in vitro, Ca2+ dysregulation and impaired intracellular signalling pathways impede NK cell function in ME/CFS patients."

- [Ref. 354 H, 356 H] "Altered T Cells in ME/CFS", Liisa Selin PhD and Anna Gil PhD, University of Massachusetts Medical School, 9/27/2020

  "CD8 T-cell exhaustion, increased CD4+CD8+ T-cells and aberrant cytokines in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)."

  "CD8 T-cell exhaustion arises during chronic infections and cancers in human and mice. Exhausted CD8 T-cells have progressive loss of function, sustained expression of inhibitory receptors (CTLA4, PD1), metabolic dysregulation poor memory recall and homeostatic self-renewal, and distinct transcriptional profile."

- [148 H] Myalgic encephalomyelitis/chronic fatigue syndrome patients exhibit altered T cell metabolism and cytokine associations, Maureen Hanson, 2020

  "We found that ME/CFS CD8+ T cells had reduced mitochondrial membrane potential compared with those from healthy controls. Both CD4+ and CD8+ T cells from patients with ME/CFS had reduced glycolysis at rest, whereas CD8+ T cells also had reduced glycolysis following activation. Patients with ME/CFS had significant correlations between measures of T cell metabolism and plasma cytokine abundance that differed from correlations seen in healthy control subjects. Our data indicate that patients have impaired T cell metabolism consistent with ongoing immune alterations in ME/CFS that may illuminate the mechanism behind this disease."

- [149 H] Immune cell metabolism altered in ME/CFS, NIH Research article Dr. Maureen Hanson, 2020

  "CD8+ T cells from people with ME/CFS showed a decrease in energy production after activation. Notably, they had changes in their mitochondria—the structures that produce most of the cell's energy."

  "Compared to cells taken from people without the disease, both CD4+ and CD8+ cells from people with ME/CFS had reduced glycolysis at rest. Glycolysis is another pathway that cells use to produce energy. CD8+ cells from people with ME/CFS also had reduced glycolysis after activation."

"The team found different patterns of cytokines in the blood of people with ME/CFS as well. Cytokines play important signaling roles in the immune system. Although many of these cytokines would normally promote immune activity, they correlated with reduced metabolism in CD8+ T cells in people with the disease."

- [150 H] Perturbation of effector and regulatory T cell subsets in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS), Lucinda Bateman, 2020

  "We found that the ratio of CD4+ to CD8+ T cells and the proportion of CD8+ effector memory T cells were increased, whereas NK cells were reduced in ME/CFS patients younger than 50 years old compared to a healthy control group. Remarkably, major differences were observed in Th1, Th2, Th17 and mucosal-associated invariant T (MAIT) T cell subset functions across all ages of patients compared to healthy subjects. While CCR6+ Th17 cells in ME/CFS secreted less IL-17 compared to controls, their overall frequency was higher."

  "Similarly, MAIT cells from patients secreted lower IFNγ, GranzymeA and IL-17 upon activation."

  "Together, these findings suggest chronic stimulation of these T cell populations in ME/CFS patients. In contrast, the frequency of regulatory T cells (Tregs), which control excessive immune activation, was higher in ME/CFS patients. Finally, using a machine learning algorithm called random forest, we determined that the set of T cell parameters analyzed could identify more than 90% of the subjects in the ME/CFS cohort as patients (93% true positive rate or sensitivity)."

  "In conclusion, these multiple and major perturbations or dysfunctions in T cell subsets in ME/CFS patients suggest potential chronic infections or microbiome dysbiosis. These findings also have implications for development of ME/CFS specific immune biomarkers and reveal potential targets for novel therapeutic interventions."

- [Ref. 383 H] "METHOD FOR THE TREATMENT OF CHRONIC FATIGUE SYNDROME USING AN INHIBITORY OR CYTOTOXIC AGENT AGAINST PLASMA CELLS", International application published under the Patent Cooperation Treaty (PCT), **Patent** Dr. Øystein Fluge, Dr. Olav Mella, 4 March, 2021

  Dr. Fluge and Dr. Mella: "Among immune cells, Cyclophosphamide has at our utilized trial doses an effect on both CD4+ and CD8+ T-cell subsets, and especially on T-regulatory cells. However, experience with the drug in autoimmune diseases show an effect of cyclophosphamide on proliferating B-cells that possibly halts the production of autoantibodies and reduces the formation of short-lived plasma cells, thus also the recruitment of mature plasma cells."

- [151 H] Diverse functional autoantibodies in patients with COVID-19, Eric Y. Wang, 2021

  "COVID-19 manifests with a wide spectrum of clinical phenotypes that are characterized by exaggerated and misdirected host immune responses1,2,3,4,5,6. Although pathological innate immune activation is well-documented in severe disease1, the effect of autoantibodies on disease progression is less well-defined. Here we use a high-throughput autoantibody discovery technique known as rapid extracellular antigen profiling7 to screen a cohort of 194 individuals infected with SARS-CoV-2, comprising 172 patients with COVID-19 and 22 healthcare workers with mild disease or asymptomatic infection, for autoantibodies against 2,770 extracellular and secreted proteins (members of the exoproteome)."

  "We found that patients with COVID-19 exhibit marked increases in autoantibody reactivities as compared to uninfected individuals, and show a high prevalence of autoantibodies against immunomodulatory proteins (including cytokines, chemokines, complement components and cell-surface proteins). We established that these autoantibodies perturb immune function and impair virological control by inhibiting immunoreceptor signalling and by altering peripheral immune cell

composition, and found that mouse surrogates of these autoantibodies increase disease severity in a mouse model of SARS-CoV-2 infection. Our analysis of autoantibodies against tissue-associated antigens revealed associations with specific clinical characteristics. Our findings suggest a pathological role for exoproteome-directed autoantibodies in COVID-19, with diverse effects on immune functionality and associations with clinical outcomes."

- [152 H] Myalgic Encephalomyelitis/Chronic Fatigue Syndrome – Evidence for an autoimmune disease, Franziska Sotzny, Carmen Scheibenbogen, EUROMENE, 2018

  "Immune dysregulation in ME/CFS has been frequently described including changes in cytokine profiles and immunoglobulin levels, T- and B-cell phenotype and a decrease of natural killer cell cytotoxicity. Moreover, autoantibodies against various antigens including neurotransmitter receptors have been recently identified in ME/CFS individuals by several groups. Consistently, clinical trials from Norway have shown that B-cell depletion with rituximab results in clinical benefits in about half of ME/CFS patients. Furthermore, recent studies have provided evidence for severe metabolic disturbances presumably mediated by serum autoantibodies in ME/CFS. Therefore, further efforts are required to delineate the role of autoantibodies in the onset and pathomechanisms of ME/CFS in order to better understand and properly treat this disease."

  "Several studies described autoantibodies in ME/CFS mostly against nuclear and membrane structures and neurotransmitter receptors.
  This paper mentions autoantibodies against:
  ANA, Nuclear envelope, reticulated speckles, 68/48 kDa protein, dsDNA, phospholipids, cardiolipin, phosphatidylserine, gangliosides, M AChR, M1 AChR, M3/4 AChR and ®2-AdR, 5-HT, Cytoplasmic intermediate filaments, dUTPase and Neopitopes formed by oxidative or nitrosative damage."

- [153 H] Cytokine profiling of extracellular vesicles isolated from plasma in myalgic encephalomyelitis/chronic fatigue syndrome: a pilot study, Maureen Hanson, 2020

  "Elevated levels of 30-130 nm EVs were found in plasma from ME/CFS patients and inter-cytokine correlations revealed unusual regulatory relationships among cytokines in the ME/CFS group that were different from the control group in both plasma and EVs. These disturbances in cytokine networks are further evidence of immune dysregulation in ME/CFS."

- [154 H] Environmental, Neuro-immune, and Neuro-oxidative Stress Interactions in Chronic Fatigue Syndrome, Geir Bjørklund, August 2020

  "The most frequently reported immune dysregulations in CFS are modifications in immunoglobulin contents, changes in B and T cell phenotypes and cytokine profiles, and decreased cytotoxicity of natural killer cells. Some of these immune aberrations display a moderate diagnostic performance to externally validate the clinical diagnosis of CFS, including the expression of activation markers and protein kinase R (PKR) activity. Associated with the immune aberrations are activated nitro-oxidative pathways, which may explain the key symptoms of CFS."

  "This review shows that viral and bacterial infections, as well as nutritional deficiencies, may further aggravate the immune-oxidative pathophysiology of CFS. Targeted treatments with antioxidants and lipid replacement treatments may have some clinical efficacy in CFS. We conclude that complex interactions between immune and nitro-oxidative pathways, infectious agents, environmental factors, and nutritional deficiencies play a role in the pathophysiology of CFS."

- [155 H] Back to the Future? Immunoglobulin Therapy for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome, Helen Brownlie and Nigel Speight, 2021

  "The findings of controlled trials on use of intravenous immunoglobulin G (IV IgG) to treat myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) are generally viewed as representing mixed results. On detailed review, a clearer picture emerges, which suggests that the potential therapeutic value of this intervention has been underestimated. Our analysis is consistent with the propositions that: (1) IgG is highly effective for a proportion of patients with severe and well-characterised ME/CFS; (2) responders can be predicted with a high degree of accuracy based on markers of immune dysfunction. Rigorous steps were taken in the research trials to record adverse events, with transient symptom exacerbation commonly experienced in both intervention and placebo control groups, suggesting that this reflected the impact of participation on people with an illness characterised by post-exertional symptom exacerbation."

  "Worsening of certain specific symptoms, notably headache, did occur more commonly with IgG and may have been concomitant to effective treatment, being associated with clinical improvement. The findings emerging from this review are supported by clinical observations relating to treatment of patients with severe and very severe ME/CFS, for whom intramuscular and subcutaneous administration provide alternative options."

  "We conclude that: (1) there is a strong case for this area of research to be revived; (2) pending further research, clinicians would be justified in offering a course of IgG to selected ME/CFS patients at the more severe end of the spectrum. As the majority of trial participants had experienced an acute viral or viral-like onset, we further suggest that IgG treatment may be pertinent to the care of some patients who remain ill following infection with SARS-CoV-2 virus."

- [156 H] Chronic fatigue syndrome and subsequent risk of cancer among elderly U.S. adults, Cindy M. Chang, 2012

  "CFS was associated with an increased risk of non-Hodgkin lymphoma (NHL). Among NHL subtypes, CFS was associated with diffuse large B cell lymphoma, marginal zone lymphoma and B-cell NHL not otherwise specified. CFS associations with NHL overall and NHL subtypes remained elevated after excluding patients with medical conditions related to CFS or NHL, such as, autoimmune conditions. CFS was also associated (although not after multiple comparison adjustment) with cancers of the pancreas, kidney, breast and oral cavity and pharynx."
  This is consistent with a chronic B-cell activation.

- [157 H] Plasma proteomic profiling suggests an association between antigen driven clonal B cell expansion and ME/CFS, Lucinda Bateman, Mady Hornig, Nancy G. Klimas, Susan Levine, Jose G. Montoya, Daniel L. Peterson, Anthony L. Komaroff, W. Ian Lipkin, 2020

  "Our findings are consistent with a significant association of ME/CFS with immune dysregulation and highlight the potential use of the plasma proteome as a source of biomarkers for disease."

- [158 H] Human Leukocyte Antigen alleles associated with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS), Asgeir Lande, 2021

  "Human Leukocyte Antigen (HLA) associations are hallmarks of autoimmune disease, and have not been thoroughly investigated in a large ME/CFS patient cohort. We performed high resolution HLA -A, -B, -C, -DRB1, -DQB1 and -DPB1 genotyping by next generation sequencing in 426 adult, Norwegian ME/CFS patients, diagnosed according to the Canadian Consensus Criteria."

  "ME/CFS is a complex disease, potentially with a substantial heterogeneity. We report novel HLA associations pointing toward the involvement of the immune system in ME/CFS pathogenesis."

- [159 H] Fine mapping of the major histocompatibility complex (MHC) in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) suggests involvement of both HLA class I and class II loci, Riad Hajdarevic, Asgeir Lande, August 14, 2021

  "Highlights:
  - By far the largest genetic study in ME/CFS.
  - Multi-level HLA and SNP analysis.
  - Independent HLA class I and II associations.
  - Positive association of HLA-DQB1 amino acid residue 57D."

  "SNP association analysis revealed two distinct and independent association signals (p≤0.001) tagged by rs4711249 in the HLA class I region and rs9275582 in the HLA class II region. Furthermore, the primary association signal in the HLA class II region was located within the HLA-DQ gene region, most likely due to HLA-DQB1, particularly the amino acid position 57 (aspartic acid/alanine) in the peptide binding groove, or an intergenic SNP upstream of HLA-DQB1. In the HLA class I region, the putative causal locus might map outside the classical HLA genes as the association signal spans several genes (DDR1, GTF2H4, VARS2, SFTA2 and DPCR1) with expression levels influenced by the ME/CFS associated SNP genotype."

  "Taken together, our results implicate the involvement of the MHC, and in particular the HLA-DQB1 gene, in ME/CFS. These findings should be replicated in larger cohorts, particularly to verify the putative involvement of HLA-DQB1, a gene important for antigen-presentation to T cells and known to harbor alleles providing the largest risk for well-established autoimmune diseases."

- [160 H, 161 H] Genetic Predisposition for Immune System, Hormone, and Metabolic Dysfunction in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: A Pilot Study, Melanie Perez, Nancy Klimas, 2019

  "The May 2019 pilot study, which used the Fukuda criteria for chronic fatigue syndrome only, looked for the SNPs that were more common in CFS patients than in healthy people, predicted which 50 of these were most likely to be harmful, and reported on the 10 genes found in at least 70% of those with CFS."

  "Three main clusters of pathways were found to share over 30% of genes common in ME/CFS patients:
  Immune-related genes: Cytokine Signaling in Immune System pathway; includes other immune-related pathways such as interferon signaling, autoimmune responses, and T-cell receptor signaling.
  Hormone-related genes: Nuclear-Receptors Meta-Pathway including hormone related pathways.
  Metabolism-related genes: Labelled as pathways in cancer but showing many metabolic processes, signaling and enzymes that are all involved in the regulation of glycogen, sugar and lipid metabolism."

- [162 H] Plasma proteomic profiling suggests an association between antigen driven clonal B cell expansion and ME/CFS, Milica Milivojevic, Lipkin, Klimas, 2020

  "Our findings are consistent with a significant association of ME/CFS with immune dysregulation and highlight the potential use of the plasma proteome as a source of biomarkers for disease."

- [163 H] Hypothalamic-Pituitary autoimmunity and related impairment of hormone secretions in chronic fatigue syndrome, Annamaria De Bellis, Jose G. Montoya, 2021

  "Objective: To investigate the occurrence of anti-pituitary (APA) and anti-hypothalamic (AHA) antibodies and possible related hypothalamic/pituitary dysfunctions in ME/CSF patients."

"Results: Patients in Group 1 showed a high prevalence of AHA (33%) and APA (56%) and significant lower levels of ACTH/cortisol, and GH peak/IGF1 vs controls (all AHA/APA negative). Patients in Group 1A (13 patients positive at high titers, ≥1:32) showed ACTH/cortisol and GH peak/ IGF1 levels significantly lower and more severe forms of ME/CFS with respect to patients in Group 1B (7 positive at middle/low titers,1:16-1:8) and 1C (10 Ab negative patients)."

"Conclusions: Both AHA and/or APA at high titers associated with hypothalamic/pituitary dysfunction suggest that hypothalamic/pituitary autoimmunity may play an important role in the manifestations of ME/CFS, especially in its more severe forms."

- [164 H] Lessons From Heat Stroke for Understanding Myalgic Encephalomyelitis/Chronic Fatigue Syndrome, Dominic Stanculescu, Jonas Bergquist, 2021

  "We here provide an overview of the pathophysiological mechanisms during heat stroke and describe similar mechanisms found in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). Both conditions are characterized by disturbed homeostasis in which inflammatory pathways play a central role. Splanchnic vasoconstriction, increased gut permeability, gut-related endotoxemia, systemic inflammatory response, central nervous system dysfunction, blood coagulation disorder, endothelial-cell injury, and mitochondrial dysfunction underlie heat stroke. These mechanisms have also been documented in ME/CFS. Moreover, initial transcriptomic studies suggest that similar gene expressions are altered in both heat stroke and ME/CFS. Finally, some predisposing factors for heat stroke, such as pre-existing inflammation or infection, overlap with those for ME/CFS."

  "Notwithstanding important differences - and despite heat stroke being an acute condition - the overlaps between heat stroke and ME/CFS suggest common pathways in the physiological responses to very different forms of stressors, which are manifested in different clinical outcomes. The human studies and animal models of heat stroke provide an explanation for the self-perpetuation of homeostatic imbalance centered around intestinal wall injury, which could also inform the understanding of ME/CFS. Moreover, the studies of novel therapeutics for heat stroke might provide new avenues for the treatment of ME/CFS. Future research should be conducted to investigate the similarities between heat stroke and ME/CFS to help identify the potential treatments for ME/CFS."

Sleep

- [165 H] Circadian rhythm disruption in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Implications for the post-acute sequelae of COVID-19, Michael J. McCarthy, 10 January 2022

  "Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is characterized by major disruptions in activity, sleep and energy that implicate the circadian clock."

  "The incidence of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is expected to increase dramatically as a result of the SARS-CoV2 pandemic and the post-acute sequelae of COVID-19."

  "Biomarker studies in ME/CFS patients implicate Transforming Growth Factor B (TGFB). TGFB has previously unrecognized roles in synchronizing circadian rhythms in peripheral cells. Identification of viable biomarkers and the development of new methodologies may facilitate progress in the chronobiological basis of ME/CFS."

  "We propose that disrupted TGFB signaling in ME/CFS may play a role in disrupting physiological rhythms in sleep, activity, and cognition, leading to the insomnia, energy disturbances, cognition problems, depression, and autonomic dysfunction associated with ME/CFS. Since SARS-like coronavirus infections cause persistent changes in TGFB and previous coronavirus outbreaks have

caused ME/CFS-like syndromes, chronobiological considerations may have immediate implications for understanding ME/CFS in the context of the COVID-19 pandemic and possibly suggest new avenues for therapeutic interventions."

- [166 H] *New Study Underway*: "Sleep Disturbances in ME/CFS", Open Medicine Foundation, 2021

  "…It is possible that inflammation of the Central Nervous System (CNS) plays a role in the symptom of unrefreshing sleep. Direct evidence for CNS inflammation in ME/CFS was revealed in a 2014 report, which demonstrates that microglial activation is one of the main cell types involved in neuro-inflammation. This activation was seen in the thalamus (structure in the center of the brain) in nine ME/CFS patients."

  "Despite the fact that ME/CFS includes symptoms of profound fatigue and cognitive dysfunction or "brain fog", no CNS biomarker, sleeping or brain biomarker have been identified to date."

  "The study will examine EEG frequencies (electrical activity occurring in the brain) of sleep and wakefulness in ME/CFS patients. Concurrently, Dr. Jonas Bergquist will evaluate cerebrospinal fluid proteomics at the Uppsala Collaborative Research Center. Dr Bergquist hopes to identify orexin (a neuropeptide that regulates arousal, and wakefulness) and related proteomic inflammatory markers in patients who have developed ME/CFS."

  "This project will help us better understand how to eventually treat devastating sleep deficiencies and fragmentation that is associated with ME/CFS."

- [167 H] Dr. Matthew Walker on Sleep for Enhancing Learning, Creativity, Immunity, and Glymphatic System, February 28th 2019

  "Shorter sleep duration: ↓NK-cell's activity to 70% of normal.
  Sympathetic nervous system is↑ amplified in people with insomnia.
  Poor sleep ↓glucose metabolism, ↓testosterone levels, ↑ amount of amyloid beta (Aβ) found in their cerebrospinal fluid by as much as 25-30% and the crucial role that slow-wave sleep plays in helping us clear amyloid beta.
  Beta cells (β-cells) in the pancreas become less sensitive to high glucose levels and other cells in the body become less sensitive to insulin when a person doesn't get enough sleep. People who sleep poorly tend to eat 200 to 300 calories more per sitting than those who sleep well and overall have more desire for caloric rich food — a phenomenon that, overall, tracks with a generalized pro-metabolic disorder quality that is associated with poor sleep and shorter sleep durations. Certain dietary macronutrients may differentially affect sleep. Poor sleep disrupts the gut microbiome. One cup of coffee in the evening can decrease deep sleep by about 20%."

- [168 H] Understanding Myalgic Encephalomyelitis - The new polio and chronic fatigue syndromes, Byron Hyde (2021)

  Dr Hyde has released 2 chapters of this new book. This is a quote from his new book:
  "Hyper-somnambulism, which tends to be replaced by sleep reversals, various sleep dysfunctions and chronic unrewarding sleep. Hypnagogic and hypnapagogic changes occur infrequently. Almost all M.E. patients develop various sleep dysfunction states. Although many patients eventually recover and return to a normal sleep pattern, a few do not. (The habit-forming use of narcotics or analgesics and electronic media appears to perpetuate both chronic sleep and pain dysfunction)."

- [169 H] Systematic Review of Sleep Characteristics in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome, Sonya Marshall-Gradisnik et al., 2021

"Conclusions — Many of the parameters measured including slow-wave sleep, apnea-hypopnea index, spectral activity and multiple sleep latency testing were inconsistent across the studies. The available research on sleep quality in ME/CFS was also limited by recruitment decisions, confounding factors, small sample sizes and non-replicated findings. Future well-designed studies are required to understand sleep quality in ME/CFS patients."

- [170 H] "Decoding Health Media: Beyond Hype & Headlines" – Dr Mark Donohoe mentioned sleep apnea, without obstruction in patients with ME/CFS at 36:43:

  Andrew Whitfield-Cook mentions that ME patients sigh a lot, they almost gasp for air, they don't breathe and it's almost like an apnea. Dr. Mark Donohoe answers:

  "It actually is a type of apnea. Many years ago, we had a hospital unit in Manly (Australia) and we had Chronic Fatigue Syndrome patients and there we did the breathing monitoring at night. And these people, on an official basis, suffered a type of sleep apnea, but it was not obstructive sleep apnea. This was a type of failing to breathe for up to 40 seconds and then a catchup breathing on the other side when we did the area around the curve the oxygen exchange over the night was about 70% of what you normally would have. Not Cheyne-Stokes breathing, nothing like that, but it is almost like the brain forgets to breathe for a period of time, but what we were told on the pattern of it, is it is just like cot death babies, accept cot death babies don't have the escape mechanism on the other side. So, there was hypopnea, which is the failure of fuel delivery. They woke up tired in the morning and it was entirely explainable by the underbreathing that happened over the night. You can't easily catch up that way. Retraining breathing is not a thing we ever expect to have to do. It's on autopilot, you know in the midbrain, and it just is on automatic."

- [171 H] Cytokines in immune function and sleep regulation, James M. Krueger, 2011

- [172 H] Human immune system during sleep, Nayyab Asif, 2017

- [173 H] The Sleep-Immune Crosstalk in Health and Disease, Luciana Besedovsky, Tanja Lange, and Monika Haack, 28 March 2019

- [174 H] Circadian rhythm abnormalities and autonomic dysfunction in patients with Chronic Fatigue Syndrome/Myalgic Encephalomyelitis, Trinitat Cambras, 2018

  "These findings suggest that circadian regulation and skin vasodilator responses may play a role in CFS/ME."

- [175 H] 2021 Conference - Understanding ME/CFS Today: A Clinical & Research Approach (0:30:50) Irina Rozenfeld, DNP, MSHS, APRN, ANP-BC, The Role of Sleep in the Control of ME/CFS Symptoms

- [176 H] The Cortisol Awakening Response with Dr Carrie Jones, 2020

  "Low morning cortisol Influences T-cell response, memory (recall), autoimmune problems, problems hippocampus, hypothalamus, reticular activating system etc. Irregular menstrual cycles are connected to the cortisol awakening response. Circadian rhythm, sleep and melatonin are important.
  Cortisol imbalance:
  If you are the type of person that gets a second wind late at night or wakes up between 1am-4am and can't get back to sleep, you may be suffering from a cortisol imbalance (Seriphos or Phosphorylated Serine can be very useful in cases of insomnia that are a result of elevated nighttime cortisol levels). Be aware of medications that can affect sleep like Prednisone, which is suppressive of the HPA axis."

- [Ref. 241 H and "nervous system – the brain"] Enlarged basal ganglia perivascular spaces and sleep parameters, Oscar H. Del Brutto, 2019

"Poor sleep efficiency is independently associated with enlarged basal ganglia-PVS, suggesting that sleep may influence structural changes in these fluid-filled cavities."

- [177 H] Control Pain & Heal Faster with Your Brain, Andrew Huberman, Professor of Neurobiology and Ophthalmology at Stanford University, Huberman Lab Podcast #9, (at 42:30), 2021

  Prof. Andrew Huberman: "Sleeping on one's side or with feet slightly elevated (using a pillow) increases the amount of wash through of the glymphatic system function and the rate of clearance of some of the debris. The glymphatic system has a physical pressure dynamic to it, which allows it to work more efficiently when one is sleeping on their side or feet slightly elevated. It also helps to sleep more deeply and one wakes up much more refreshed."

- [178 H, 179 H] Master Your Sleep & Be More Alert When Awake, Huberman Lab Podcast #2, Prof. Andrew Huberman, 2021 *And*
  The Science of Vision, Eye Health & Seeing Better, Huberman Lab Podcast #24, at 29:08, 2021

  Professor Huberman explains the importance of sunlight for a minimum of 2-10 minutes early in the morning (from sunrise 05.00 to 10.00) and 2-10 minutes in the evening (sunset) per day. "Melanopsin retinal ganglion cells (intrinsically photosensitive cells) communicate to areas of the brain when particular qualities of lights are present and signal to the brain that it's early in the day or late in the evening. This is important for our internal clock. If we don't get natural light at these times, then severe disruptions occur in our sleep patterns, metabolism (how fast), blood sugar levels, hormones, dopamine levels, temperature rhythms, our pain threshold and many other factors including the ability to learn and remember information."

  Prof. Huberman mentions the importance of blue and yellow light. Blue light is essential for waking up early in the day:
  [180 H] The inner clock—Blue light sets the human rhythm, Siegfried Wahl, 2019

  "Visible light synchronizes the human biological clock in the suprachiasmatic nuclei of the hypothalamus to the solar 24-hour cycle."

Gastrointestinal and genitourinary problems

- [181 H, 182 H] The Emerging Role of Gut Microbiota in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS): Current Evidence and Potential Therapeutic Applications, Angelica Varesi, 2021

  "An altered composition and overall decrease in diversity of gut microbiota (GM) has been observed in ME/CFS cases compared to controls. In this review, we reflect on genetics, infections, and other influences that may factor into the alterations seen in the GM of ME/CFS individuals, we discuss consequences arising from these changes, and we contemplate the therapeutic potential of treating the gut to alleviate ME/CFS symptoms holistically."

  Article in ME Centraal:
  "In recent years, studies have been conducted on the types of changes in the gut microbiome in ME and their implications. For example, an altered microbiome was found in saliva, intestines, and stool of ME patients, suggesting a link between the microbiome and the disease."
  "A striking decrease was observed in the relative abundance and diversity of Firmicutes bacteria, and a higher number of Bacteroidetes. Often a lower Bacteroides/Firmicutes ratio is accompanied by an increase in Enterobacteria, indicating a complete rearrangement of the composition of the gut microbiota."

"GM dysbiosis may also be a cause of increased gut permeability. In this regard, some studies have observed an association between changes in GM and higher levels of inflammation. One hypothesis is that the increase in Enterobacteria found in dysbiosis may play a role in intestinal inflammation and permeability."

"Another possibility is that bacterial metabolites contribute to the disease by interfering with the estrogen receptor and the vitamin D receptor, since the latter is also involved in the development of autoimmune diseases, which often occur as comorbidities of ME."
"The gut-brain axis, the autonomic nervous system, and the digestive nervous system should also be considered."

"The results are not reproducible between studies, probably due to the study designs. Taken together, these data suggest that changes in the gut microbiota are characteristic in ME patients, but the role of the gut microbiota in the onset and progression of the disease needs further investigation."

- [183 H] Examining clinical similarities between myalgic encephalomyelitis/chronic fatigue syndrome and D-lactic acidosis: a systematic review, Amy Wallis, 2017

  "The majority of neurological disturbances reported in D-la episodes overlapped with ME/CFS symptoms. Of these, the most frequently reported D-la symptoms were motor disturbances that appear more prominent during severe presentations of ME/CFS. Both patient groups shared a history of gastrointestinal abnormalities and evidence of bacterial dysbiosis, although only preliminary evidence supported the role of lactate-producing bacteria in ME/CFS."

- [184 H] Reduced diversity and altered composition of the gut microbiome in individuals with myalgic encephalomyelitis/chronic fatigue syndrome, Ludovic Giloteaux, Maureen R. Hanson, 2016

  "We observed elevated levels of some blood markers for microbial translocation in ME/CFS patients; levels of LPS, LBP, and sCD14 were elevated in ME/CFS subjects. Levels of LBP correlated with LPS and sCD14 and LPS levels correlated with sCD14. Through deep sequencing of bacterial rRNA markers, we identified differences between the gut microbiomes of healthy individuals and patients with ME/CFS."

  "We observed that bacterial diversity was decreased in the ME/CFS specimens compared to controls, in particular, a reduction in the relative abundance and diversity of members belonging to the Firmicutes phylum."

  "In the patient cohort, we find less diversity as well as increases in specific species often reported to be pro-inflammatory species and reduction in species frequently described as anti-inflammatory. Using a machine learning approach trained on the data obtained from 16S rRNA and inflammatory markers, individuals were classified correctly as ME/CFS with a cross-validation accuracy of 82.93 %."

  "Our results indicate dysbiosis of the gut microbiota in this disease and further suggest an increased incidence of microbial translocation, which may play a role in inflammatory symptoms in ME/CFS."

- [185 H, 186 H, 187 H] Endothelial Senescence and Chronic Fatigue Syndrome, a COVID-19 Based Hypothesis, Adonis Sfera, June 2021
  (+ Intoxication With Endogenous Angiotensin II: A COVID-19 Hypothesis
  + The Big Merge? Are Long COVID and ME/CFS Hypotheses Meshing?)

  "In a previous article, we hypothesized that COVID-19-upregulated angiotensin II triggered premature endothelial cell senescence, disrupting the intestinal and blood brain barriers. Here, we hypothesize further that post-viral sequelae, including myalgic encephalomyelitis/chronic fatigue syndrome, are promoted by the gut microbes or toxin translocation from the gastrointestinal tract into other tissues, including the brain. This model is supported by the SARS-CoV-2 interaction with host proteins and bacterial lipopolysaccharide. Conversely, targeting microbial translocation and cellular senescence may ameliorate the symptoms of this disabling illness."

  Health Rising:
  "… In June 2020, researchers proposed that the renin-angiotensin-aldosterone system had become discombobulated in COVID-19, and that high Ang II levels were causing damage to the blood vessels and the mitochondria. Despite the fact that high Ang II levels are also found in ME/CFS, they did not mention it."

  "One of the great mysteries in ME/CFS and POTS has been something called the renin-angiotensin-aldosterone (RAAS) paradox. The paradox lies in the fact that despite the very low blood volume levels in the disease, the RAA system – which is designed to increase them – is never activated."

  "One part of the RAA system is, though. Angiotensin II levels are greatly increased. Wirth and Scheibenbogen provided a possible explanation for the paradox. Balky beta-adrenergic receptors and plus a vasodilator called bradykinin were "annihilating" the signal the RAA system needed to proceed."

  "A year later, the long-COVID researchers were back with a hypothesis they believe explains both long COVID and ME/CFS. It was centered squarely on those high Ang II levels found in ME/CFS."

  "Ang II levels, it turns out, can cause more problems than we knew. Besides possibly producing blood vessel and mitochondrial problems, they can damage the gut lining, jack up oxidative stress levels, interfere with cellular cleanup, and even damage telomeres."

  "The authors proposed that the high Ang II levels were causing the guts of both long-COVID and ME/CFS patients to leak bacterial molecules into the bloodstream – triggering an immune reaction reaching all the way to the brain."

  "The authors even believe that the adrenergic autoantibodies that have received so much attention in ME/CFS may have been produced to deal with the bacterial molecules making their way into the gut."

  "The authors outlined a variety of possible treatments not currently being used in ME/CFS that might help. Time will tell whether the current flock of ME/CFS and long-COVID hypotheses will win out, but the fact that most (Systrom, Wirth and Scheibenbogen, Fluge/Mella, Patterson, Sfera at. al.) involve problems with the blood vessels, and some are even focusing on the RAA system (which hasn't gotten much attention in ME/CFS), is nothing if not encouraging…."

- [188 H] The association of fecal microbiota and fecal, blood serum and urine metabolites in myalgic encephalomyelitis/chronic fatigue syndrome, Christopher W. Armstrong, Neil R. McGregor, 2016

  "The workflow was validated using the non-ME/CFS cohort where fecal short chain fatty acids (SCFA) were associated with serum and urine metabolites indicative of host metabolism changes enacted by SCFA. In the ME/CFS cohort a decrease in fecal lactate and an increase in fecal butyrate, isovalerate

and valerate were observed along with an increase in Clostridium spp. and a decrease in Bacteroides spp. These differences were consistent with an increase in microbial fermentation of fiber and amino acids to produce SCFA in the gut of ME/CFS patients. Decreased fecal amino acids positively correlated with substrates of gluconeogenesis and purine synthesis in the serum of ME/CFS patients."

"Increased production of SCFA by microbial fermentation in the gut of ME/CFS patients may be associated with deleterious effects on the host energy metabolism."

- [189 H] Deficient butyrate-producing capacity in the gut microbiome of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome patients is associated with fatigue symptoms, Cheng Guo, Nancy Klimas, 2021

  "Using shotgun metagenomics and qPCR and rigorous statistical analyses that controlled for important covariates, we identified decreased relative abundance and quantity of Faecalibacterium, Roseburia, and Eubacterium species and increased bacterial load in feces of subjects with ME/CFS."

  "These bacterial taxa play an important role in the production of butyrate, a multifunctional bacterial metabolite that promotes human health by regulating energy metabolism, inflammation, and intestinal barrier function. Functional metagenomic and qPCR analyses were consistent with a deficient microbial capacity to produce butyrate along the acetyl-CoA pathway in ME/CFS."

  "Metabolomic analyses of short-chain fatty acids (SCFAs) confirmed that fecal butyrate concentration was significantly reduced in ME/CFS. Further, we found that the degree of deficiency in butyrate-producing bacteria correlated with fatigue symptom severity among ME/CFS subjects."

  "Finally, we provide evidence that IBS comorbidity is an important covariate to consider in studies investigating the microbiome of ME/CFS subjects, as differences in microbiota alpha diversity, some bacterial taxa, and propionate were uniquely associated with self-reported IBS diagnosis."

- [190 H] The Gut Microbiome in Myalgic Encephalomyelitis (ME)/Chronic Fatigue Syndrome (CFS), Rahel S. König, Carmen Scheibenbogen, 2022

  "Here we review the current state of knowledge on the interplay between ME/CFS and the microbiome, to identify potential diagnostic or interventional approaches, and propose areas where further research is needed. We iteratively selected and elaborated on key theories about a correlation between microbiome state and ME/CFS pathology, developing further hypotheses."

  "Based on the literature we hypothesize that antibiotic use throughout life favours an intestinal microbiota composition which might be a risk factor for ME/CFS. Main proposed pathomechanisms include gut dysbiosis, altered gut-brain axis activity, increased gut permeability with concomitant bacterial translocation and reduced levels of short-chain-fatty acids, D-lactic acidosis, an abnormal tryptophan metabolism and low activity of the kynurenine pathway. We review options for microbiome manipulation in ME/CFS patients including probiotic and dietary interventions as well as fecal microbiota transplantations. Beyond increasing gut permeability and bacterial translocation, specific dysbiosis may modify fermentation products, affecting peripheral mitochondria."

  "Considering the gut-brain axis we strongly suspect that the microbiome may contribute to neurocognitive impairments of ME/CFS patients. Further larger studies are needed, above all to clarify whether D-lactic acidosis and early-life antibiotic use may be part of ME/CFS etiology and what role changes in the tryptophan metabolism might play. An association between the gut microbiome and the disease ME/CFS is plausible. As causality remains unclear, we recommend longitudinal studies. Activity levels, bedridden hours and disease progression should be compared to antibiotic exposure, drug intakes and alterations in the composition of the microbiota. The therapeutic

potential of fecal microbiota transfer and of targeted dietary interventions should be systematically evaluated."

- [191 H] Myalgic Encephalomyelitis/Chronic Fatigue Syndrome in the Era of the Human Microbiome: Persistent Pathogens Drive Chronic Symptoms by Interfering With Host Metabolism, Gene Expression, and Immunity, Amy Proal and Trevor Marshall, 2018

  "The history of ME/CFS strongly suggests that infectious agents play a central role in driving the disease process. However, the discovery of the human microbiome has revolutionized the manner in which persistent infection and chronic inflammation are understood and studied. Humans harbor extensive microbiome communities of bacteria, viruses, and fungi in nearly all tissue and blood."

  "Many inflammatory disease states, including neurological conditions and cancers, are tied to dysbiosis or imbalance of human microbiome communities in various body sites. While gut microbiome dysbiosis has already been identified in ME/CFS, distinct microbial and viral communities may additionally persist in ME/CFS blood and brain tissue. Possible identification of these microbiomes should be a priority for the ME/CFS research community, but analysis requires the use of very specific technologies and methodologies."

  "Treatments that support or activate the human immune system could allow ME/CFS patients to improve microbiome health by better targeting pathogens over time. Like the novel immunotherapies being developed for cancers, these immunostimulatory therapies would be expected to generate temporary immunopathology. Institutional reviewers hesitant to approve immunopathology-based therapies should consider that ME/CFS quality of life is typically very low, with patients demonstrating a substantial increase in mortality from suicide."

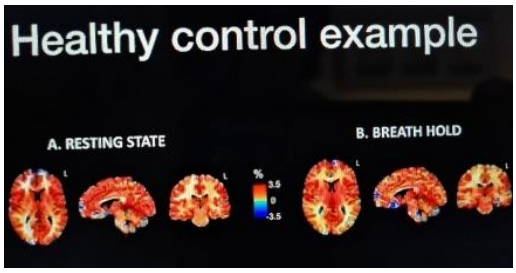
- [192 H] Chronic Fatigue Syndrome, Viruses, and the Innate Immune System, Theodore Henderson, MD, PhD, 2020

  1. "HHV6 and HSV1 and therefore likely the other neurotrophic herpes family viruses can invade the brain and replicate there, potentially spreading to many neurons
  2. HHV6 can integrate into the human genome
  3. HHV6 partial reactivation impairs mitochondrial function, including decreased ATP production and induces a pro-inflammatory state
  4. Serum from patients with CFS/ME carry the ability to impede mitochondrial function in naïve cells
  5. Serum from patients with CFS/ME may carry some factor that can impart protection from viral infection to naïve cells
  6. This protective factor raises exciting possibilities for a new approach to protection from COVID-19
  7. The protective factor can be developed into a diagnostic assay for CFS/ME giving the first definitive test for this much beleaguered and neglected disease.
  8. A definitive test is the first step to better research, more funding, and greater federal attention to CFS/ME, which affects an estimated 24 million worldwide."

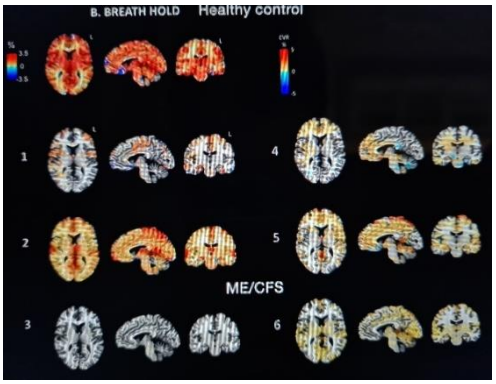
The nervous system

The brain

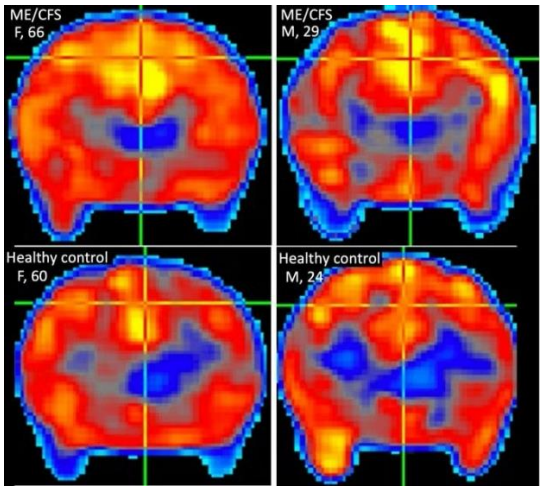
[193 H, 194 H, 195 H, 196 H, 197 H, 198 H, 199 H, 200 H, 201 H, 202 H, 203 H, 204 H, 205 H, 206 H, 207 H, 208 H, 209 H, 210 H, 211 H, 212 H, 213 H, 214 H, 215 H, 216 H, Ref. 77 H]



[Ref. 195 H, Ref. 206 H] Resting state - breath hold HC ME/CFS



Breath hold Healthy Control vs



[217 H, 218 H] Picture 7-Tesla MRI scanner, 30 Nov. 2021,
Dr. Michael VanElzakker on Twitter:
"Some prelim data from my ongoing neuroinflammation study at Harvard Med/@MGHMartinos/@MGH_RI. Longer-term ICC-ME and more recent-onset ”Long-COVID”, both with increased [11C] PBR28 uptake in cingulate cortex vs. age and genotype-matched healthy controls. @PolyBioRF"

Metabolite abnormalities in the brain

“Choline (CHO), myo-inositol (MI), lactate (LAC), and N-acetylaspartate (NAA) were quantified in 47 regions, expressed as ratios over creatine (CR), and compared between ME/CFS patients and controls using independent-samples t-tests. Most notably elevated CHO/CR (choline/creatine) in the left anterior cingulate. Raised lactic acid and lowered glutathione levels in the brain.
Myo-inositol (MI): higher values represent greater microglia proliferation or gliosis.
Lactate (Lac): higher values represent more severe inflammatory activity.
Choline (Cho): higher values indicate greater cell turnover (inflammation, gliosis, or demyelination).
N-acetylaspartate (NAA): lower values represent neurodegeneration.”

Increased temperature

"Brain temperature increases converged with elevated LAC/CR in the right insula, putamen, frontal cortex, right thalamus, and cerebellum."

Brain inflammation

"Choline and Lactate (a byproduct of glycolysis in an oxygen-limited environment) increased in a number of brain areas consistent with brain inflammation. Inflammation in the cingulate cortex, occipital cortex, hippocampus, amygdala, thalamus, basal ganglia, midbrain, and pons was correlated with the symptoms. Neuroinflammation is evidenced by activation of microglia or astrocytes, and activated glial cells exhibit an increase in expression of the 18-kDa translocator protein (TSPO)."

- [Ref. [198] H] "The BP(ND) values of (11)C-(R)-PK11195 in the cingulate cortex, hippocampus, amygdala, thalamus, midbrain, and pons were 45%-199% higher in CFS/ME patients than in healthy controls. In CFS/ME patients, the BP(ND) values of (11)C-(R)-PK11195 in the amygdala, thalamus, and midbrain positively correlated with cognitive impairment score, the BP(ND) values in the cingulate cortex and thalamus positively correlated with pain score, and the BP(ND) value in the hippocampus positively correlated with depression score."

  "Conclusion: Neuroinflammation is present in widespread brain areas in CFS/ME patients and was associated with the severity of neuropsychologic symptoms. Evaluation of neuroinflammation in CFS/ME patients may be essential for understanding the core pathophysiology and for developing objective diagnostic criteria and effective medical treatments."

- [[219] H, Ref. [199] H] "In a series of three studies, Prof. Dikoma C. Shungu found high levels of lactic acid in ventricular cerebrospinal fluid and significant correlation between lactic acid levels and the severity of mental fatigue in ME/CFS patients. He later went on to discover levels of the antioxidant glutathione (GSH) reduced by 36% in brain tissue and suggested oxidative stress was playing a role in ME/CFS."

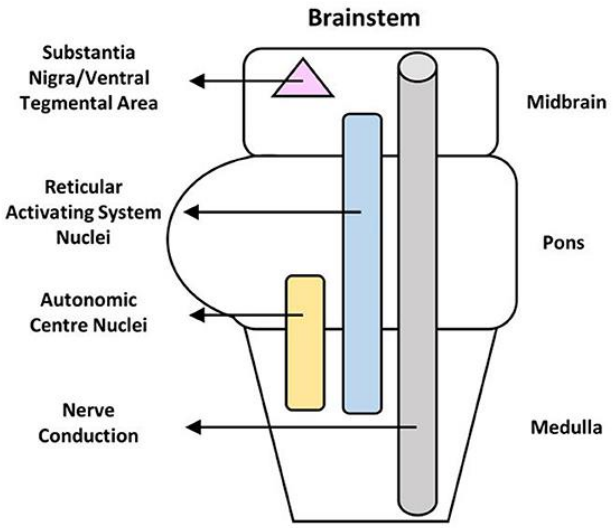
Impaired intra brainstem connectivity

"Reticular activation system (RAS) connectivity is diminished in ME/CFS in the brainstem and to the hippocampus. "RAS nuclei generate oscillatory signals which facilitate thalamocortical signal coherence. Impaired RAS affects cortical coherence necessary for attention, memory and problem solving."

- [[220] H] Brainstem Abnormalities in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: A Scoping Review and Evaluation of Magnetic Resonance Imaging Findings, Todd Nelson, 2021

  "Findings: Data showed that MRI studies frequently reported structural changes in the white and gray matter. Abnormalities of the functional connectivity within the brainstem and with other brain regions have also been found. The studies have suggested possible mechanisms including astrocyte dysfunction, cerebral perfusion impairment, impaired nerve conduction, and neuroinflammation involving the brainstem, which may at least partially explain a substantial portion of the ME/CFS symptoms and their heterogeneous presentations in individual patients."

  "Conclusions: This review draws research attention to the role of the brainstem in ME/CFS, helping enlighten future work to uncover the pathologies and mechanisms of this complex medical condition, for improved management and patient care."



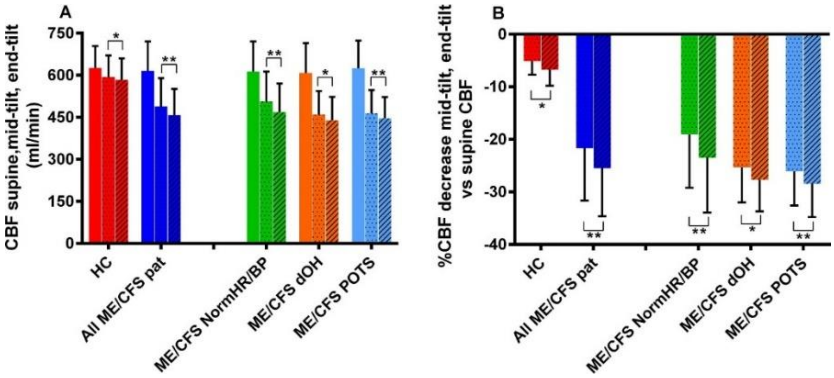
	Function	MRI findings	ME/CFS symptoms
Substantia Nigra/Ventral Tegmental Area	Dopaminergic control of motivation, concentration and learning	1) Reduced white matter volume in midbrain 2) Abnormal axon calibre or axonal/myelin density in midbrain	Concentration deficits, fatigue
Reticular Activating System Nuclei	Control of sleep/wakefulness cycles and consciousness	1) Reduced white matter volume in midbrain and pons 2) Functional connectivity deficits between cuneiform nucleus and medulla, and between brainstem and the hippocampus and intralaminar thalamus 3) Abnormal axon calibre or axonal/myelin density in midbrain and pons	Fatigue, sleep dysfunction, deficits with problem solving, sensory perception, attention and memory
Autonomic Centre Nuclei	Regulation of heart rate, blood pressure and breathing	1) Reduced white matter volume in pons 2) Varied correlation patterns between autonomic centre nuclei (myelination, volume, T2 signal) and physiological measures (heart rate, blood pressure) in ME/CFS	Cardiac dysfunction (*e.g.,* orthostatic intolerance, postural orthostatic tachycardia syndrome), respiratory dysfunction (*e.g.,* abnormal breathing), sweating episodes
Nerve Conduction	Passage of nerves	1) Reduced white matter volume in pons and medulla 2) Different brainstem myelination or iron (decreased in grey matter and increased in white matter) 3) Connectivity deficits within the brainstem	Sensory input and motor output dysfunction (*e.g.,* temperature hypersensitivity, slowed motor conduction, musculoskeletal and abdominal pain)

"Figure 3. Associations of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) symptoms with brainstem dysfunction based on MRI findings."

[221 H, 222 H, 223 H, 224 H, 225 H, 226 H, 227 H, 228 H, Ref. 206 H] **Reduced cerebral blood flow** in the distribution of both right and left middle cerebral arteries. The data indicate that patients with CFS have reduced absolute cortical blood flow in rather broad areas when compared with data from healthy controls.

One of many studies:

- [Ref. 223 H] "Cerebral blood flow is reduced in ME/CFS during head-up tilt testing even in the absence of hypotension or tachycardia: A quantitative, controlled study using Doppler echography", C. (Linda) M.C. van Campen, Freek W.A. Verheugt, Peter C. Rowe, and Frans C. Visser, 2020



*"Fig. 2. (A) CBF in ml/min of healthy controls and the 3 patient groups during head-up tilt. The left colored column is supine, the dotted column is mid-tilt, and the hatched column is end-tilt. (B) This shows the % decrease from supine for mid and end tilt data in patients and controls. CBF: cerebral blood flow; HC: healthy controls; ME/CFS dOH: ME/CFS patients with delayed orthostatic hypotension; ME/CFS NormHR/BP: ME/CFS patients with a normal heart rate and blood pressure response; ME/CFS POTS: ME/CFS patients with postural orthostatic tachycardia syndrome. Comparison between mid and end tilt data: *=P < .005; **=P < .0005."*

Reduced electrical activities

- [229 H] Electroencephalogram characteristics in patients with chronic fatigue syndrome, Tong Wu, 2016

  "BEAM results showed that spontaneous brain electrical activities in CFS patients were significantly reduced. The abnormal changes in the cerebral functions were localized at the right frontal and left occipital regions in CFS patients. These results indicate that there is a significant increase of slow brain electrical activities in CFS patients. Slower activity generally indicates more severe underlying cerebral dysfunction."

Abnormal neurovascular coupling

- [230 H] Neuroimaging characteristics of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS): a systematic review, Zack Y. Shan, Leighton R Barnden, 2020

  "A balance between neuronal activity and local blood supply is facilitated by neurovascular coupling. Disturbances in neurovascular coupling have critical consequences for brain function. Both insufficient blood supply and abnormal hyperperfusion can disturb O2 delivery and be detrimental for neuronal function."

- [Ref. [230] H] Neuroimaging characteristics of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS): a systematic review, Zack Y. Shan, Leighton R Barnden, 2020

  "Additional brain area recruitment for cognitive tasks and abnormalities in the brain stem are frequent observations in 11 and 9 studies using different modalities from different research teams respectively. Also, sluggish blood oxygenation level-dependent (BOLD) signal responses to tasks, reduced serotonin transporters, and regional hypometabolism are consistent observations by more than two research teams. Single observations include abnormal brain tissue properties, regional metabolic abnormalities, and association of brain measures with ME/CFS symptoms. Reduced resting cerebral blood flow and volumetric brain changes are inconsistent observations across different studies."

  "Neuroimaging studies of ME/CFS have frequently observed additional brain area recruitment during cognitive tasks and abnormalities in the brain stem. The frequent observation of additional brain area recruitment and consistent observation of sluggish fMRI signal response suggest abnormal neurovascular coupling in ME/CFS."

- [[231] H] Submaximal Exercise Provokes Increased Activation of the Anterior Default Mode Network During the Resting State as a Biomarker of Postexertional Malaise in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome, Rakib U. Rayhan and James N. Baraniuk, 2021

  "The most striking exercise-induced effect in ME/CFS was the increased spontaneous activity in the medial prefrontal cortex that is the anterior node of the Default Mode Network (DMN). In contrast, this region had decreased activation for controls. Overall, controls had higher BOLD signals suggesting reduced global cerebral blood flow in ME/CFS."

  "Conclusion: The dynamic increase in activation of the anterior DMN node after exercise may be a biomarker of postexertional malaise and symptom exacerbation in CFS. The specificity of this postexertional finding in ME/CFS can now be assessed by comparison to post-COVID fatigue, Gulf War Illness, fibromyalgia, chronic idiopathic fatigue, and fatigue in systemic medical and psychiatric diseases."

Myelin

- [[232] H, [233] H] Intra brainstem connectivity is impaired in chronic fatigue syndrome – 2019 - Dr. Leighton Barnden et al. *and*
  Evidence in chronic fatigue syndrome for severity-dependent upregulation of prefrontal myelination that is independent of anxiety and depression, Leighton R Barnden 1, Benjamin Crouch, Richard Kwiatek, Richard Burnet, Peter Del Fante, 2015

  "Severity dependent upregulated myelin in prefrontal white matter ↑ implies weakened nerve signals from brainstem. Earlier reports of WM volume losses and neuroinflammation in the midbrain, together with the upregulated prefrontal myelination suggested here, are consistent with the midbrain changes being associated with impaired nerve conduction which stimulates a plastic response on the cortical side of the thalamic relay in the same circuits."

- [[234] H] Progressive brain changes in patients with chronic fatigue syndrome: A longitudinal MRI study, Zack Y. Shan PhD, Sonya M. Marshall-Gradisnik PhD, Leighton R. Barnden PhD, 2016

  "The results suggested that CFS is associated with inferior fronto-occipital fasciculus WM deficits which continue to deteriorate at an abnormal rate."

- [235 H] Mapping of pathological change in chronic fatigue syndrome using the ratio of T1- and T2-weighted MRI scans, Kiran Thapaliya, Sonya Marshall-Gradisnik, July 31, 2020

  "We showed increased T1w/T2w in ME/CFS in contrast to other neurodegenerative diseases. Higher T1w/T2w occurred in basal ganglia and white matter tracts."

  "Increased T1w/T2w indicates increased myelin and/or iron levels."

  "T1w/T2w regressions vs clinical measures were abnormal in cingulate cortex and white matter foci."

- [236 H, 237 H] Neuroinflammation and Cytokines in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS): A Critical Review of Research Methods, Michael B. VanElzakker, 2019 *and* Mapping of pathological change in chronic fatigue syndrome using the ratio of T1- and T2-weighted MRI scans, Kiran Thapaliya, Sonya Marshall-Gradisnik, July 31, 2020

  "Our study demonstrates that the T1w/T2w approach is very sensitive and shows increases in myelin and/or iron in WM and basal ganglia in ME/CFS."

  "Myo-inositol is a carbocyclic sugar residing largely in astrocytes, and is upregulated during astrocyte activation. Myo-inositol also upregulates during myelin decay."

More and enlarged perivascular spaces

- [238 H, 239 H, 240 H, 241 H, 242 H]
  "Enlarged and more numerous Virchow-Robin perivascular spaces in the midbrain, hippocampi, basal ganglia, and centrum semiovale. Perivascular spaces (PVS) are involved in mechanisms of brain interstitial fluid and metabolic waste clearance."

Summary abnormalities in the brain

Metabolite abnormalities, increased brain temperature, brain inflammation, impaired intra brainstem connectivity, reduced cerebral blood flow, reduced electrical activities, abnormal neurovascular coupling (disturbed O2 delivery), more and enlarged Virchow-Robin perivascular spaces in midbrain, hippocampi, basal ganglia, and centrum semiovale.
Nerve signal conduction between medulla, pons and midbrain are ↓, and to the hippocampus is ↓.
Myelin in brainstem is ↓ and is compensated in other regions.
Brainstem compensation in sensorimotor cortex is ↑.
Severity dependent upregulated myelin in prefrontal white matter ↑ implies weakened nerve signals from the brainstem.

- [Ref. 77 H, 243 H] Diffusion tensor imaging reveals neuronal microstructural changes in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome, by Kiran Thapaliya, Sonya Marshall-Gradisnik, Don Staines, Leighton Barnden in European Journal of Neuroscience, August 6, 2021

  "Our DTI study detected axonal microstructural abnormalities in ME/CFS patients. The group analysis using a voxel-based method detected differences in diffusion metrics in ascending and descending tracts in the medulla, pons and midbrain of the brainstem in ME/CFS patients, but only for those meeting ICC criteria."

  "This demonstrated the importance of strict case definitions for ME/CFS. Our DTI parameter interaction-with-group regressions with clinical measures showed involvement of multiple brain

regions. These novel analyses can contribute to understanding the pathophysiology of ME/CFS patients. Brainstem abnormality may be an imaging diagnostic marker for ME/CFS."

- [[244] H, [245] H] Capillary-associated microglia regulate vascular structure and function through PANX1-P2RY12 coupling in mice, Kanchan Bisht, September 2021

  "School of Medicine researchers have revealed a vital but previously unknown role for immune cells that protect the brain from disease and injury: The cells, known as microglia, also help regulate blood flow and maintain the brain's critical blood vessels."

  "In addition to revealing a new aspect of human biology, the findings may prove important in cognitive decline, dementia and stroke, among other conditions linked to diseases of the brain's small vessels, the researchers say."

  "Precise blood vessel function is critical to accommodate the extreme energy demands of the brain for normal brain function," said Ukpong B. Eyo, PhD, of UVA's Department of Neuroscience, the UVA Brain Institute and UVA's Center for Brain Immunology and Glia (BIG). "These findings suggest previously unknown roles for these brain cells in the proper maintenance of blood delivery to the brain and provide novel opportunities to intervene in contexts where blood perfusion to the brain is impaired."

- [Ref. [216] H] Differential Effects of Exercise on fMRI of the Midbrain Ascending Arousal Network Nuclei in Myalgic Encephalomyelitis / Chronic Fatigue Syndrome (ME/CFS) and Gulf War Illness (GWI) in a Model of Postexertional Malaise (PEM), James N Baraniuk, 2021

  "Conclusions: Exercise caused opposite effects with increased activation in ME/CFS but decreased activation in GWI indicating different pathophysiological responses to exertion and mechanisms of disease. Midbrain and isthmus nuclei contribute to postexertional malaise in ME/CFS and GWI."

- [[246] H, [247] H] Signs of Intracranial Hypertension, Hypermobility, and Craniocervical Obstructions in Patients With Myalgic Encephalomyelitis/Chronic Fatigue Syndrome, Björn Bragée, 2020

  "In their research, they found displacement in the neck in 4 out of 5 patients. A little less than half of the patients also had a lowering of the cerebellum, causing a narrow foramen magnum. They also found that a large number of the patients had fibromyalgia, and only a few of the patients had a normal pain threshold."

  "In addition to this, a lot of the patients had changes in the optic nerve that indicates an increased pressure in the fluid surrounding the brain. The width of the optic nerve was measured with an ultrasound apparatus against the eye. Increased brain pressure can cause inflammation, cloudy vision, "brainfog" and headache."

  "Summary:
  - Displacement in the neck/brain might be a normal result of ME
  - Increased brain fluid pressure might be a normal result of ME
  - Increased pressure might cause inflammation in the central nervous system
  - It is necessary to verify these findings in further studies."

- [[248] H] Cytokine network analysis of cerebrospinal fluid in myalgic encephalomyelitis/chronic fatigue syndrome, M. Hornig, 2015

  "Group-specific differences were found for the majority of analytes with an increase in cases of CCL11 (eotaxin), a chemokine involved in eosinophil recruitment. Network analysis revealed an inverse relationship between interleukin 1 receptor antagonist and colony-stimulating factor 1, colony-

stimulating factor 2 and interleukin 17F, without effects on interleukin 1α or interleukin 1β, suggesting a disturbance in interleukin 1 signaling. Our results indicate a markedly disturbed immune signature in the cerebrospinal fluid of cases that is consistent with immune activation in the central nervous system, and a shift toward an allergic or T helper type-2 pattern associated with autoimmunity."

- [249 H, 250 H, 251 H] Immune network analysis of cerebrospinal fluid in myalgic encephalomyelitis/chronic fatigue syndrome with atypical and classical presentations, M Hornig, 2017

- [252 H] Moderate exercise increases expression for sensory, adrenergic and immune genes in chronic fatigue syndrome patients, but not in normal subjects, Alan R. Light, 2009

  "Previous studies implicated dysregulation of the sympathetic nervous system (SNS), and immune system (IS) in CFS and FMS. We recently demonstrated that Acid Sensing Ion Channel (likely ASIC3), purinergic type 2X receptors (likely P2X4 and P2X5), and the transient receptor potential vanilloid type 1 (TRPV1) are molecular receptors in mouse sensory neurons detecting metabolites that cause acute muscle pain and possibly muscle fatigue. These molecular receptors are found on human leukocytes along with SNS and IS genes. Real-time, quantitative PCR showed that 19 CFS patients had lower expression of β-2 adrenergic receptors but otherwise did not differ from 16 controls before exercise."

  "After a sustained moderate exercise test, CFS patients showed greater increases than controls in gene expression for metabolite detecting receptors ASIC3, P2X4 and P2X5, for SNS receptors α-2A, β-1, β-2 and COMT, and IS genes for IL10 and TLR4 lasting from 0.5–48 hours (P< .05). These increases were also seen in the CFS subgroup with comorbid FMS and were highly correlated with symptoms of physical fatigue, mental fatigue and pain. These new findings suggest dysregulation of metabolite detecting receptors as well as SNS and IS in CFS and CFS-FMS."

- [253 H] The Neuro-Immune Pathophysiology of Central and Peripheral Fatigue in Systemic Immune-Inflammatory and Neuro-Immune Diseases, Gerwyn Morris, 2015

  "Many patients with systemic immune-inflammatory and neuro-inflammatory disorders, including depression, rheumatoid arthritis, systemic lupus erythematosus, Sjögren's disease, cancer, cardiovascular disorder, Parkinson's disease, multiple sclerosis, stroke, and chronic fatigue syndrome/myalgic encephalomyelitis, endure pathological levels of fatigue. The aim of this narrative review is to delineate the wide array of pathways that may underpin the incapacitating fatigue occurring in systemic and neuro-inflammatory disorders."

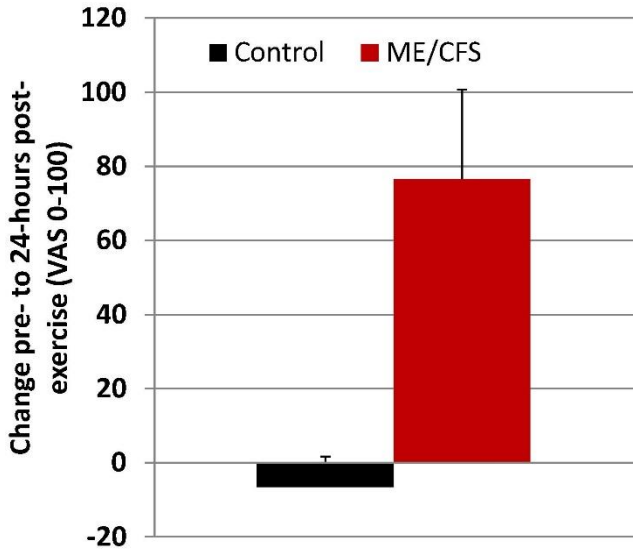
  "A wide array of immune, inflammatory, oxidative and nitrosative stress (O&NS), bioenergetic, and neurophysiological abnormalities are involved in the etiopathology of these disease states and may underpin the incapacitating fatigue that accompanies these disorders. This range of abnormalities comprises: increased levels of pro-inflammatory cytokines, e.g., interleukin-1 (IL-1), IL-6, tumor necrosis factor (TNF) α and interferon (IFN) α; O&NS-induced muscle fatigue; activation of the Toll-Like Receptor Cycle through pathogen-associated (PAMPs) and damage-associated (DAMPs) molecular patterns, including heat shock proteins; altered glutaminergic and dopaminergic neurotransmission; mitochondrial dysfunctions; and O&NS-induced defects in the sodium-potassium pump."

  "Fatigue is also associated with altered activities in specific brain regions and muscle pathology, such as reductions in maximum voluntary muscle force, downregulation of the mitochondrial biogenesis master gene peroxisome proliferator-activated receptor gamma coactivator 1-alpha, a shift to glycolysis and buildup of toxic metabolites within myocytes. As such, both mental and physical fatigue, which frequently accompany immune-inflammatory and neuro-inflammatory disorders, are the consequence of interactions between multiple systemic and central pathways."

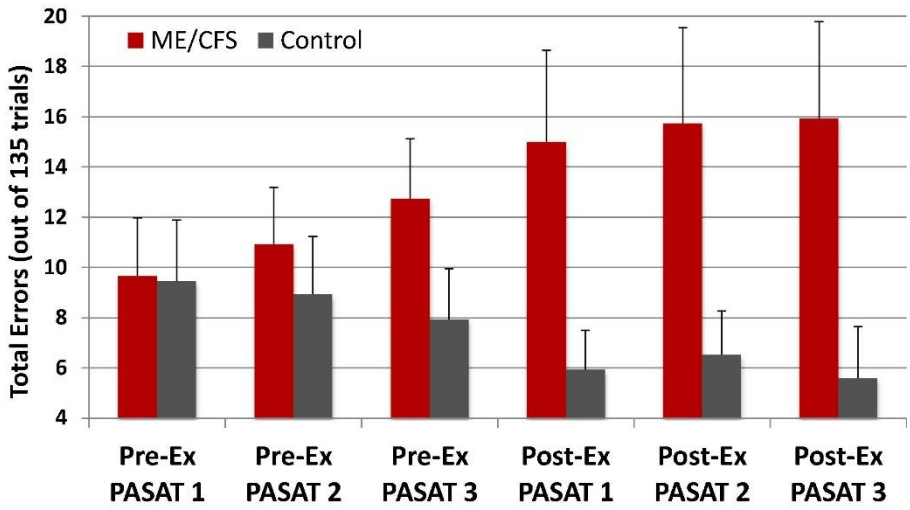
- [254 H] Gene expression alterations at baseline and following moderate exercise in patients with Chronic Fatigue Syndrome and Fibromyalgia Syndrome, A. R. Light, 2011

  "At least two subgroups of patients with CFS can be identified by gene expression changes following exercise. The larger subgroup showed increases in mRNA for sensory and adrenergic receptors and a cytokine. The smaller subgroup contained most of the patients with CFS with orthostatic intolerance, showed no postexercise increases in any gene and was defined by decreases in mRNA for α-2A. FM-only patients can be identified by baseline increases in three genes. Postexercise increases for four genes meet published criteria as an objective biomarker for CFS and could be useful in guiding treatment selection for different subgroups."

- [Ref. 32 H] Neural consequences of post-exertion malaise in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome, Dane B. Cook, Alan. R. Light, 2017



"Fig. 1. Total symptom changes for ME/CFS and control pre- to 24-h post-exercise. Total symptoms are based on the sum of 10 VAS ratings derived from 10 items contained in the CDC symptom inventory; see Table 3 for complete symptom list."



"Fig. 2. VAS ratings of mental fatigue measured during functional brain imaging pre- and 24-h post-exercise. Data are presented during each PASAT segment (1, 2 &3). Participants provided ratings of mental fatigue following each PASAT segment (1, 2 & 3). There were significant main effects for Time

(F = 20.2, p < 0.001) and Group (F = 86.3, p < 0.001) and a significant Group by Time interaction (F = 5.5, p = 0.005).”

“During number recognition, controls exhibited greater brain activity (p<0.05) in the posterior cingulate cortex, but only for the pre-exercise scan. For the Paced Serial Auditory Addition Task, there was a significant Group by Time interaction (p<0.05) with patients exhibiting increased brain activity from pre- to post-exercise compared to controls bilaterally for inferior and superior parietal and cingulate cortices. Changes in brain activity were significantly related to symptoms for patients (p<0.05). Acute exercise exacerbated symptoms, impaired cognitive performance and affected brain function in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome patients. These converging results, linking symptom exacerbation with brain function, provide objective evidence of the detrimental neurophysiological effects of post-exertion malaise.”

- [[255] H] A compromised paraventricular nucleus within a dysfunctional hypothalamus: A novel neuroinflammatory paradigm for ME/CFS, Angus Mackay and Warren P Tate, 2018

- [[256] H] Central Autonomic Network Disturbance in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: A Pilot Study, Mark Zinn, Marcie L. Zinn, Leonard A. Jason, 2021

Peripheral nervous system

Small fiber polyneuropathies: Ref. [259] H and Ref. [284] H, Ref. [383] H, [257] H.

- [[258] H, Ref. [771] H] Insights From Invasive Cardiopulmonary Exercise Testing of Patients With Myalgic Encephalomyelitis/Chronic Fatigue Syndrome, Phillip Joseph, MD, David M. Systrom, MD, 2021
  And The Tangled Story of ME/CFS: Controversy, Denigration and Ignorance, Natalie Boulton, Dialogues for ME/CFS, 2021

  “These results identify two types of peripheral neurovascular dysregulation that are biologically plausible contributors to ME/CFS exertional intolerance—depressed Qc from impaired venous return, and impaired peripheral oxygen extraction. In patients with small-fiber pathology, neuropathic dysregulation causing microvascular dilation may limit exertion by shunting oxygenated blood from capillary beds and reducing cardiac return.”

  [Ref. [771] H, at 57:25] Dr. Systrom on distinct differences in ME/CFS vs. deconditioning:
  “On the venous side we see low filling pressures in ME, whereas in deconditioning we see higher filling pressure. And what we are seeing on the arterial side is a significant abnormality of systemic oxygen extraction, which is not a feature of deconditioning. When we see evidence of preload failure or, subsequently, when we see hard evidence of arterial-vascular dysregulation during exercise. And when we do a skin biopsy in these patients and we find evidence of a small fiber neuropathy and we say, “there is no way this abnormality is in your head”, they will break down and cry, because they have been rejected by so many for so long.”

- [[259] H] The Pathophysiology of Chronic Fatigue Syndrome: Results from an Invasive Cardiopulmonary Exercise Laboratory, P. Joseph, D. M. Systrom, 2019

  “Small fiber (autonomic) polyneuropathy may be an underlying mechanism behind the exertional intolerance of preload failure and ME/CFS. SFPN is associated with a lack of peripheral sympathetic tone, impaired venoconstriction during exercise, low cardiac filling pressures, decreased cardiac output, and exertional intolerance.”

- [[260] H] Insights From Invasive Cardiopulmonary Exercise Testing of Patients With Myalgic Encephalomyelitis/Chronic Fatigue Syndrome, M. Systrom, MD, 2019

"These results identify two types of peripheral neurovascular dysregulation that are biologically plausible contributors to ME/CFS exertional intolerance—depressed Qc from impaired venous return, and impaired peripheral oxygen extraction. In patients with small-fiber pathology, neuropathic dysregulation causing microvascular dilation may limit exertion by shunting oxygenated blood from capillary beds and reducing cardiac return."

- [[261] H, [262] H] Autoantibodies to Vasoregulative G-Protein-Coupled Receptors Correlate with Symptom Severity, Autonomic Dysfunction and Disability in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome, Carmen Scheibenbogen et al., 2021

  "Correlations of specific AAB against G-protein-coupled receptors (GPCR) with symptoms provide evidence for a role of these AAB or respective receptor pathways in disease pathomechanism."

- [[263] H] Evidence for generalized hyperalgesia in chronic fatigue syndrome: a case control study, Mira Meeus, Jo Nijs, Sven Huybrechts & Steven Truijen, 2010

  "These findings provide evidence for the existence of hyperalgesia even in asymptomatic areas (generalized secondary hyperalgesia). The generalized hyperalgesia may represent the involvement of a sensitized central nervous system."

- [[264] H] Neuromuscular Strain Increases Symptom Intensity in Chronic Fatigue Syndrome, Peter C. Rowe, 2016

  "Compared to individuals with CFS in the sham strain group, those with CFS in the true strain group reported significantly increased body pain (P = 0.04) and concentration difficulties (P = 0.02) as well as increased composite symptom scores (all P = 0.03) during the maneuver. After 24 hours, the symptom intensity differences were significantly greater for the CFS true strain group for the individual symptom of lightheadedness (P = 0.001) and for the composite symptom score (P = 0.005). During and 24 hours after the exposure to the true strain maneuver, those with CFS had significantly higher individual and composite symptom intensity changes compared to the healthy controls."

  "We conclude that a longitudinal strain applied to the nerves and soft tissues of the lower limb is capable of increasing symptom intensity in individuals with CFS for up to 24 hours. These findings support our preliminary observations that increased mechanical sensitivity may be a contributor to the provocation of symptoms in this disorder."

- [[265] H, [266] H] The Role of Autonomic Function in Exercise-induced Endogenous Analgesia: A Case-control Study in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome and Healthy People, Jessica Van Oosterwijck, Uros Marusic, 2017

  "Patients with myalgic encephalomyelitis / chronic fatigue syndrome (ME/CFS) are unable to activate brain-orchestrated endogenous analgesia (or descending inhibition) in response to exercise. This physiological impairment is currently regarded as one factor explaining post-exertional malaise in these patients. Autonomic dysfunction is also a feature of ME/CFS."

  "Results: Some relationships of moderate strength between autonomic and pain measures were found. The change (post-exercise minus pre-exercise score) in pain severity was correlated (r = .580, P = .007) with the change in diastolic blood pressure in the healthy group. In the ME/CFS group, positive correlations between the changes in pain severity and low frequency (r = .552, P = .014), and between the changes in bodily pain and diastolic blood pressure (r = .472, P = .036), were seen. In addition, in ME/CHFS the change in headache severity was inversely correlated (r = -.480, P = .038) with the change in high frequency heart rate variability."

"Conclusions: Reduced parasympathetic reactivation during recovery from exercise is associated with the dysfunctional exercise-induced analgesia in ME/CFS. Poor recovery of diastolic blood pressure in response to exercise, with blood pressure remaining elevated, is associated with reductions of pain following exercise in ME/CFS, suggesting a role for the arterial baroreceptors in explaining dysfunctional exercise-induced analgesia in ME/CFS patients."

- [267 H] Analgesia following exercise: a review, K F Koltyn, 2000

  "Currently, the mechanism(s) responsible for exercise-induced analgesia are poorly understood. Although involvement of the endogenous opioid system has received mixed support in human research, results from animal research seem to indicate that there are multiple analgesia systems, including opioid and non-opioid systems. It appears from animal research that properties of the exercise stressor are important in determining which analgesic system is activated during exercise."

- [268 H, 269 H] Chronic fatigue syndrome: Abnormally fast muscle fiber conduction in the membranes of motor units at a low-level static force load (Vermeulen), 2021

  "In chronic fatigue patients, muscle conduction increases abnormally with force. Surface EMG can elicit abnormalities in both fibromyalgia and chronic fatigue."

  "Our results suggest disturbed membrane function in CFS patients, in their motor units involved in low force generation. Central neural deregulation may contribute to these findings."

  Cort Johnson (Health Rising):
  "The membranes surrounding the muscle cells were more excitable in both ME/CFS and FM patients compared to the healthy controls."

The cardiovascular system

- [270 H, 271 H, 338 H] The Workwell study found overwhelming evidence for Chronotropic Incompetence (the inability of the heart to keep pace with increased activity) in ME/CFS patients, relative to healthy subjects.

  "According to Dr. Mark VanNess, 89% of people with ME/CFS have CI. An older study by Montague and colleagues found a similar result (87% of ME/CFS subjects had CI). Furthermore, CI worsens both on disease severity and on day 2 of repeat exercise testing. A blunted heart rate contributes to the already low oxygen uptake (VO2) found in ME/CFS, placing further limits on levels of activity."

- [272 H] Ventilatory Functioning During Serial Cardiopulmonary Exercise Testing in People With and Without Myalgic Encephalomyelitis/Chronic Fatigue Syndrome, Todd Davenport, DPT, MPH; Staci R. Stevens, MA; Jared Stevens, MPH; Christopher R. Snell, PhD; J. Mark Van Ness, PhD, Workwell, 2021

  "People with ME/CFS demonstrate abnormal pulmonary measurements on CPET that may correlate with abnormal metabolic and cardiac functioning. Potential effects on pulmonary function of short-term PEM induced by CPET remain unclear."

- [273 H, 274 H, 275 H, Ref. 546 H] "Orthostatic intolerance in ME due to impaired tissue oxygen uptake or VO2Max. Impaired VO2Max has been traced to low right atrial filling pressure, leading to impaired cardiac output as a result of cardiac preload failure."

- [276 H] Hemodynamics during the 10-minute NASA Lean Test: evidence of circulatory decompensation in a subset of ME/CFS patients, Jihyun Lee, Suzanne D. Vernon, Lucinda Bateman, 2020

  "Circulatory decompensation characterized by increased heart rate and abnormally narrow pulse pressure was identified in a subgroup of ME/CFS patients who have been sick for < 4 years. This suggests inadequate ventricular filling from low venous pressure. The 10-minute NLT can be used to diagnose and treat the circulatory decompensation in this newly recognized subgroup of ME/CFS patients. The > 10 ME/CFS group had less pronounced hemodynamic changes during the NLT possibly from adaptation and compensation that occurs over time. The 10-minute NLT is a simple and clinically useful point-of-care method that can be used for early diagnosis of ME/CFS and help guide OI treatment."

- [277 H] Unexplained exertional dyspnea caused by low ventricular filling pressures: results from clinical invasive cardiopulmonary exercise testing, Dr. Systrom, 2016

  "Before exercise, all patients received up to 2 L of intravenous normal saline to target an upright pulmonary capillary wedge pressure (PCWP) of ≥5 mmHg. Despite this treatment, biventricular filling pressures at peak exercise were lower in the impaired group than in the normal group (right atrial pressure [RAP] : 6 [IQR: 5-8] vs. 9 [7-10] mmHg, P = 0.004; PCWP: 12 [10-16] vs. 17 [14-19] mmHg, P < 0.001), associated with decreased stroke volume (SV) augmentation with exercise (+13 ± 10 [standard deviation (SD)] vs. +18 ± 10 mL/m(2), P = 0.014). A review of hemodynamic data from 23 patients with low RAP on an initial iCPET who underwent a second iCPET after saline infusion (2.0 ± 0.5 L) demonstrated that 16 of 23 patients responded with increases in Qtmax ([+24% predicted [IQR: 14%-34%]), V̇o2max (+10% predicted [7%-12%]), and maximum SV (+26% ± 17% [SD]). These data suggest that inadequate ventricular filling related to low venous pressure is a clinically relevant cause of exercise intolerance."

- [278 H] Unexplained exertional intolerance associated with impaired systemic oxygen extraction, Kathryn H. Melamed, David M. Systrom, 2019

  "We identified a cohort of patients whose exercise limitation is due only to systemic oxygen extraction, due to either an intrinsic abnormality of skeletal muscle mitochondrion, limb muscle microcirculatory dysregulation, or hyperventilation and left shift the oxyhemoglobin dissociation curve."

- [279 H] Phenylephrine alteration of cerebral blood flow during orthostasis: effect on n-back performance in chronic fatigue syndrome, Marvin S. Medow, Shilpa Sood, Zachary Messer, Seli Dzogbeta, 15 Nov. 2014

- [Ref. 225 H] Reductions in Cerebral Blood Flow Can Be Provoked by Sitting in Severe Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Patients, (Linda) MC van Campen, Peter C. Rowe, Frans C Visser, 2020

  "A sitting test in severe ME/CFS patients was sufficient to provoke a clinically and statistically significant mean CBF decline of 24.5%. Patients with a previous diagnosis of POTS had a larger CBF reduction while seated, compared to patients without POTS. The magnitude of these CBF reductions is similar to the results in less severely affected ME/CFS patients during head-up tilt, suggesting that a sitting test is adequate for the diagnosis of orthostatic intolerance in severely affected patients."

- [280 H] Cerebral blood flow remains reduced after tilt testing in myalgic encephalomyelitis/chronic fatigue syndrome patients, C. Linda M.C .van Campen, Peter C.Rowe, Frans C.Visser, Sept. 2021

  "During tilt testing, extracranial Doppler measurements show that cerebral blood flow is reduced in ME/CFS patients and recovery to normal supine values is incomplete, despite cardiac index returning to pre-tilt values. The delayed recovery of cerebral blood flow was independent of the hemodynamic findings of the tilt test (normal heart rate and blood pressure response, POTS, or delayed orthostatic hypotension), or the presence/absence of hypocapnia, and was only related to clinical ME/CFS severity grading. We observed a significantly slower recovery in cerebral blood flow in the most severely ill ME/CFS patients."

  "A significant difference was found in the degree of abnormal cerebral blood flow reduction in the supine post-test in mild, moderate, and severe ME/CFS: mild: cerebral blood flow: −7 (2)%, moderate: −16 (3)%, and severe :-25 (4)% (p all < 0.0001). Cardiac index declined significantly during the tilt test in all 3 severity groups, with no significant differences between the groups. In the supine post-test cardiac index returned to normal in all patients."

- [281 H] Orthostatic Symptoms and Reductions in Cerebral Blood Flow in Long-Haul COVID-19 Patients: Similarities with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome, C. (Linda) M. C. van Campen, Peter C. Rowe and Frans C. Visser, 2021

- [282 H] Compression Stockings Improve Cardiac Output and Cerebral Blood Flow during Tilt Testing in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) Patients: A Randomized Crossover Trial, C. (Linda) M. C. van Campen, Peter C. Rowe and Frans C. Visser, 2021

  "Results: There were no differences in supine measurements between the 2 baseline measurements. There were no differences in heart rate and blood pressure at either end-tilt testing period. Compared to the test with the stockings off, the mean percentage reduction in cardiac output during the test with compression stockings on was lower, 15 (4)% versus 27 (6)% (p < 0.0001), as was the mean percentage CBF reduction, 14 (4)% versus 25 (5)% (p < 0.0001). Conclusion: In ME/CFS patients with orthostatic intolerance symptoms, cardiac output and CBF are significantly reduced during a tilt

test. These abnormalities were present without demonstrable heart rate and blood pressure changes and were ameliorated by the use of compression stockings."

- [283 H] Evidence of altered cardiac autonomic regulation in myalgic encephalomyelitis/chronic fatigue syndrome, A systematic review and meta-analysis, Maximillian J. Nelson, 2019

  "The differences in HR parameters identified by the meta-analysis indicate that ME/CFS patients have altered autonomic cardiac regulation when compared to healthy controls. These alterations in HR parameters may be symptomatic of the condition."

- [284 H] New Findings Elucidate Potentially Treatable Aspects of ME/CFS, Medscape, 2019

  "…patients with ME/CFS have distinct defects in both ventricular filling pressure and oxygen extraction from the muscles."

  "Neither of those are features of deconditioning, in which the major defect is decreased stroke volume and cardiac output. In ME/CFS patients, he found supranormal pulmonary blood flow compared with VO2 max, indicating left-to-right shunting."

  "In addition, Systrom found that a large proportion of ME/CFS patients with these cardiopulmonary defects also have biopsy-demonstrated small fiber polyneuropathy, suggesting that PEM may be due to an underlying autonomic nervous system dysfunction."

  "…findings showing that, in patients with ME/CFS who have OI, cerebral blood flow drops significantly compared with controls on tilt-table testing even without changes in heart rate or blood pressure. And this was true regardless of VO2 max or recorded steps, suggesting again that the phenomenon isn't simply due to illness-related inactivity."

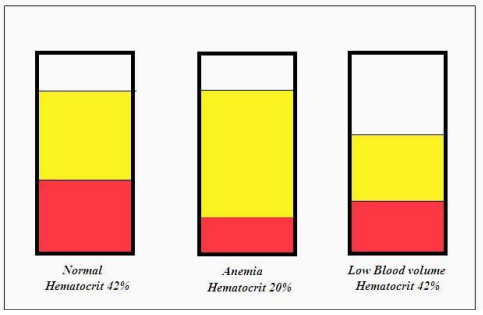
  "Systrom is now conducting a phase 3 clinical trial testing pyridostigmine bromide (Mestinon, Valeant Pharmaceuticals) in patients with ME/CFS." "The rationale for using pyridostigmine in ME/CFS, Systrom said, is that enhancement of cholinergic stimulation of norepinephrine release at the postganglionic synapse may improve venoconstriction at the site of exercising muscles, leading to improved return of blood to the heart and better distribution of oxygenated blood to the skeletal muscle mitochondrion during exercise."

  "Two phenomena appear to be contributing to the OI simultaneously, Rowe said: increased pooling of blood in the legs and decreased vasoconstriction, along with a decrease in circulating blood volume. But in a new and potentially paradigm-shifting finding, Van Campen and colleagues used transcranial Doppler echography of the internal carotid and vertebral arteries during the tilt-table test in over 400 ME/CFS patients. They displayed a greater than 20% reduction in cerebral blood flow compared with a 6% reduction found previously in healthy volunteers."

  "It was quite a profound change," Rowe said, noting, "Maybe we've been looking in the wrong place. If symptoms are due to decreasing cerebral blood flow, maybe that's where we should focus."

- [285 H, 286 H] Dr. David Bell on Low Blood Volume in Chronic Fatigue Syndrome, Health Rising, 2015

  "The first slide is a description of what is meant by low blood volume as distinct from anemia."



  "The first is a healthy person with roughly five quarts of blood divided into two portions, the red blood cells which carry oxygen and the plasma. The second is a person with anemia. In this person the total volume of blood is normal, but the proportion is not. In anemia, the red cells are reduced compared to normal, and this reduction causes fatigue. In the third bucket, a person with ME has low blood volume, but the proportion of red blood cells and plasma is normal. The accumulated volume, instead of being five quarts is down to three or four quarts."

  "In the first study of blood volume in ME, eighty percent of ME patients were abnormal compared to historical controls. This was subsequently confirmed by a study out of Miami. In addition, the volume has been studied in POTS which can co-exist with ME in up to 40%. And the blood volume can be strikingly low."

  "Furthermore, Dr. Bell explains Mechanisms of Blood Volume Loss, Reductions in Anti-diuretic Hormone (ADH), Reductions in Blood Vessel Diameter, Treatment Anecdotes, IV Saline Given Early in the Illness, Blood Transfusion, IV Saline II, IV Saline III – Sleep, Military Anti-Shock Trousers."

- [287 H] Deconditioning does not explain orthostatic intolerance in ME/CFS (myalgic encephalomyelitis/chronic fatigue syndrome), C. (Linda) M. C. van Campen, Peter C. Rowe & Frans C. Visser, 2021

  "This study shows that in ME/CFS patients' orthostatic intolerance is not caused by deconditioning as defined on cardiopulmonary exercise testing. An abnormal high decline in cerebral blood flow during orthostatic stress was present in all ME/CFS patients regardless of their %peak VO2 results on cardiopulmonary exercise testing."

- [288 H] Cognitive Function Declines Following Orthostatic Stress in Adults With Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS), C. (Linda) M. C. van Campen, 2020

  "Orthostatic intolerance (OI) is common among individuals with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). Cognitive dysfunction has been demonstrated during head-up tilt testing (HUT) in those with ME/CFS: worse scores on cognitive tests occur with increasing tilt angles and increasing complexity of the cognitive challenge."

  "Conclusion: As measured by the N-back test, working memory remains impaired in adults with ME/CFS following a 30-min head-up tilt test."

- [289 H] Psychogenic Pseudosyncope: Real or Imaginary? Results from a Case-Control Study in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) Patients, by C. (Linda) M. C. van Campen and Frans C. Visser, 2022

  "This study demonstrates that in ME/CFS patients suspected of having PPS, or conversion, CBF measurements end-tilt show a large decline compared with a control group of ME/CFS patients. Therefore, hypoperfusion offers an explanation of the orthostatic intolerance and syncopal spells in these patients, where it is clear that origin might not be behavioral or psychogenic, but have a clear somatic pathophysiologic background."

- [290 H] Early Cerebral Hypoperfusion in Patients with Orthostatic Intolerance Without Tachycardia During Head-Up Tilt Test is Independent of Vasovagal Response, J Antonio González-Hermosillo, 2021

  "Patients with chronic OI without tachycardia have early postural cerebral hypoperfusion, regardless of the VVR during HUTT."

- [291 H, 292 H] OMF, Multi-omics of iCPET Plasma Samples

  "Aspects of this preload failure (PLF) are highly consistent with mechanisms that result in POTS and post-exertional malaise (PEM), which are seen in many ME/CFS patients. These proposed studies offer significant opportunities for the identification of new drug targets and drug therapies for ME/CFS."

  "Preliminary data analysis shows significantly higher levels of cytokines in patients post-exercise compared to healthy controls."

  "There is a strong likelihood that using proteomic and metabolic analysis, critical clues to what causes fatigue and inability to exercise may be identified in the blood of people with ME/CFS using an iCPET. We hope that as we receive further results, researchers will gain a better understanding of the underlying biology behind ME/CFS and PLF and be able to identify new drug targets and therapies for patients."

- [293 H] Cerebral blood flow changes during tilt table testing in healthy volunteers, as assessed by Doppler imaging of the carotid and vertebral arteries, C. (Linda) M.C. van Campen, Freek W.A. Verheugt and Frans C. Visser, 2018

- [294 H] MEA Summary Research Review: Abnormal cardiac changes in ME/CFS not due to deconditioning By: Charlotte Stephens 26th November 2018

- [295 H, 296 H, 297 H, 298 H] Simmaron Research article: The Blood Vessel Crunch: A Unifying Hypothesis for ME/CFS – about paper: "A Unifying Hypothesis of the Pathophysiology of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS): Recognitions from the finding of autoantibodies against ß2-adrenergic receptors", Scheibenbogen, 2020

  "We found elevated ß2 adrenergic receptor (ß2AdR) and M3 acetylcholine receptor antibodies in a subset of CFS/ME patients. As both ß2AdR and M3 acetylcholine receptor are important vasodilators, we would expect their functional disturbance to result in vasoconstriction and hypoxemia. An impaired circulation and oxygen supply could result in many symptoms of ME/CFS. There are consistent reports of vascular dysfunction in ME/CFS. Muscular and cerebral hypoperfusion has been shown in ME/CFS in various studies and correlated with fatigue. Metabolic changes in ME/CFS are also in line with a concept of hypoxia and ischemia."

"Here we try to develop a unifying working concept for the complex pathomechanism of ME/CFS based on the presence of dysfunctional autoantibodies against ß2AdR and M3 acetylcholine receptor and extrapolate it to the pathophysiology of ME/CFS without an autoimmune pathogenesis."

"The cardiovascular situation in ME/CFS patients is unique and not found in any other condition or disease. Low vascular, atrial and ventricular filling suggesting hypovolemia, and preload failure has been found in a number of studies leading to a low stroke volume and a lower than normal cardiac output (CO) at rest while the RAAS activity is low. Therefore, ME/CFS is frequently associated with orthostatic dysfunction (OD) and the postural tachycardia syndrome (POTS)."

- [299 H, 300 H, 301 H] Mestinon (pyridostigmine bromide) trial "The Exercise Response to Pharmacologic Cholinergic Stimulation in Myalgic Encephalomyelitis / Chronic Fatigue Syndrome", Dr. David Systrom

  "… exertional dyspnea, and post-exertional malaise. The latter two symptoms are caused in part by abnormal cardiopulmonary hemodynamics during exercise thought to be due to a small fiber polyneuropathy. This manifests as low biventricular filling pressures throughout exercise seen in patients undergoing a level 3 CPET along with small nerve fiber atrophy seen on skin biopsy."

  "After diagnosis, patients are often treated with pyridostigmine (off-label use of this medication) to enhance cholinergic stimulation of norepinephrine release at the post-ganglionic synapse. This is thought to improve venoconstriction at the site of exercising muscles, leading to improved return of blood to the heart and increasing filling of the heart to more appropriate levels during peak exercise. Retrospective studies have shown that noninvasive measurements of exercise capacity, such as oxygen uptake, end-tidal carbon dioxide, and ventilatory efficiency, improve after treatment with pyridostigmine. To date, there are no studies that assess invasive hemodynamics after pyridostigmine administration."

- [302 H] Reduced cardiac volumes in chronic fatigue syndrome associate with plasma volume but not length of disease: a cohort study, Julia L Newton, 2016

  "This study confirms an association between reduced cardiac volumes and blood volume in CFS. Lack of relationship between length of disease, cardiac and plasma volumes suggest findings are not secondary to deconditioning. The relationship between plasma volume and severity of fatigue symptoms suggests a potential therapeutic target in CFS."

- [303 H] Chronic Fatigue Syndrome and Cardiovascular Disease: JACC State-of-the-Art Review, Benjamin H Natelson, 2021

  "Although rarely considered to have cardiac dysfunction, ME/CFS patients frequently have reduced stroke volume with a significant inverse relation between cardiac output and PEM severity. Magnetic resonance imaging of ME/CFS patients compared with normal control subjects found significantly reduced stroke, end-systolic, and end-diastolic volumes together with reduced end-diastolic wall mass. Another cardiovascular abnormality is reduced nocturnal blood pressure assessed by 24-hour monitoring. Autonomic dysfunction is also frequently observed with postural orthostatic tachycardia and/or hypocapnia. Two consecutive cardiopulmonary stress tests may provide metabolic data substantiating PEM."

- [304 H] Reduced heart rate variability predicts fatigue severity in individuals with chronic fatigue syndrome/myalgic encephalomyelitis, Rosa María Escorihuela, 2020

  "Our findings suggest that ANS dysfunction presenting as increased sympathetic hyperactivity may contribute to fatigue severity in individuals with ME/CFS. Further studies comparing short- and long-term HRV recording and self-reported outcome measures with previous studies in larger CFS/ME cohorts are urgently warranted."

- [305 H] Reduced Parasympathetic Reactivation during Recovery from Exercise in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome, Jessica Van Oosterwijck, 2021

  "This is the first study showing reduced parasympathetic reactivation during recovery from physical exercise in ME/CFS. Delayed HR recovery and/or a reduced HRV as seen in ME/CFS have been associated with poor disease prognosis, high risk for adverse cardiac events, and morbidity in other pathologies, implying that future studies should examine whether this is also the case in ME/CFS and how to safely improve HR recovery in this population."

- [306 H] Analysis of Gender Differences in HRV of Patients with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Using Mobile-Health Technology, Lluis Capdevila, 2021

  "No differences in any HRV parameter appear between male ME/CFS patients and controls, in contrast to our findings in women."

  "However, we have found negative correlations of ME/CFS symptomatology with cardiac variability (SDNN, RMSSD, pNN50, LF) in men. We have also found a significant relationship between fatigue symptomatology and HRV parameters in ME/CFS patients, but not in healthy control men."

  "Gender effects appear in HF, LF/HF, and HFnu HRV parameters. A MANOVA analysis shows differential gender effects depending on the experimental condition in autonomic dysfunction symptoms and HF and HFnu HRV parameters."

  "A decreased HRV pattern in ME/CFS women compared to ME/CFS men may reflect a sex-related cardiac autonomic dysfunction in ME/CFS illness that could be used as a predictive marker of disease progression. In conclusion, we show that HRV analysis using mHealth technology is an objective, non-invasive tool that can be useful for clinical prediction of fatigue severity, especially in women with ME/CFS."

- [307 H] Abnormal impedance cardiography predicts symptom severity in chronic fatigue syndrome, Arnold Peckerman, Benjamin H Natelson, 2003

  "The patients with severe CFS had significantly lower stroke volume and cardiac output than the controls and less ill patients. Postexertional fatigue and flu-like symptoms of infection differentiated the patients with severe CFS from those with less severe CFS (88.5% concordance) and were predictive ($R2 = 0.46$, $P < 0.0002$) of lower cardiac output. In contrast, neuropsychiatric symptoms showed no specific association with cardiac output."

  "Conclusions: These results provide a preliminary indication of reduced circulation in patients with severe CFS. Further research is needed to confirm this finding and to define its clinical implications and pathogenetic mechanisms."

- [308 H] Elevated brain natriuretic peptide levels in chronic fatigue syndrome associate with cardiac dysfunction: a case control study, Cara Tomas, Julia L. Newton, 2017

  "This study confirms an association between reduced cardiac volumes and BNP in CFS. Lack of relationship between length of disease suggests that findings are not secondary to deconditioning. Further studies are needed to explore the utility of BNP to act as a stratification paradigm in CFS that directs targeted treatments."

- [309 H] North Carolina/Ohio ME & FM Support Group: Summary Cardiologist handout 2021

- [310 H] Use of Cardiopulmonary Stress Testing for Patients With Unexplained Dyspnea Post–Coronavirus Disease, Donna M. Mancini, Benjamin H. Natelson, 2021

  "The authors used cardiopulmonary exercise testing (CPET) to define unexplained dyspnea in patients with post-acute sequelae of severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infection (PASC). We assessed participants for criteria to diagnose myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS)."

  "Circulatory impairment, abnormal ventilatory pattern, and ME/CFS are common in patients with PASC. The dysfunctional breathing, resting hypocapnia, and ME/CFS may contribute to symptoms. CPET is a valuable tool to assess these patients."

Endothelial dysfunction

[311 H, 312 H, 313 H, 314 H] Patients with ME/CFS had reduced endothelial function affecting both large and small vessels compared to healthy controls.

"Peripheral ED is frequent in patients with ME/CFS and associated with disease severity and severity of immune symptoms. As ED is a risk factor for cardiovascular disease, it is important to elucidate if peripheral ED is associated with increased cardiovascular morbidity and mortality in ME/CFS."

- [Ref. 383 H] METHOD FOR THE TREATMENT OF CHRONIC FATIGUE SYNDROME USING AN INHIBITORY OR CYTOTOXIC AGENT AGAINST PLASMA CELLS, International application published under the Patent Cooperation Treaty (PCT), **Patent** Dr. Øystein Fluge, Dr. Olav Mella, 4 March, 2021

  "CFS patients have a marked endothelial dysfunction assessed by Flow- Mediated Dilation (FMD), a test that (under standardized conditions) largely reflect Nitric Oxide (NO) synthesis in endothelial cells after shear stress. A markedly reduced FMD, transient clinical responses after long-acting nitrates (like isosorbide mononitrate) and the clinical picture of CFS, are the basis for a hypothesis according to the present invention in which a main mechanism for CFS symptom maintenance is a relative lack of endothelial-cell derived Nitric Oxide (NO) availability."

  "This results in reduced NO diffusion from endothelial cells to surrounding cells such as smooth muscle cells in blood vessel walls, and with a resulting inadequate regulation of blood flow to meet the metabolic demands of tissues."

  "Also, a relative lack of endothelial-cell derived NO may result in cognitive disturbances, sleep problems, a low anaerobic threshold, and lactate accumulation in tissues after modest exertion, a low NK cell function, all reported to be associated with CFS."

- [315 H, 316 H, 317 H] Effects of Post-Exertional Malaise on Markers of Arterial Stiffness in Individuals with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome, Joshua Bond, 2021

  "Evidence is emerging that individuals with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) may suffer from chronic vascular dysfunction as a result of illness-related oxidative stress and vascular inflammation."

  "Conclusions: The findings suggest that those with ME/CFS may not experience exercise-induced vasodilation due to chronic vascular damage, which may be a contributor to the onset of post-exertional malaise (PEM)."

- [318 H] Autoantibodies to beta-adrenergic and muscarinic cholinergic receptors in Myalgic Encephalomyelitis (ME) patients, Carmen Scheibenbogen, Jonas Bergquist, 2020

  “Significant increases in autoantibody levels in ME patients compared to controls were found for M3 and M4-receptors in both cohorts and β1, β2, M3 and M4-receptors in one cohort. No significant correlations were found between autoantibody levels and disease severity. No significant levels of autoantibodies were detected in the CSF samples.”

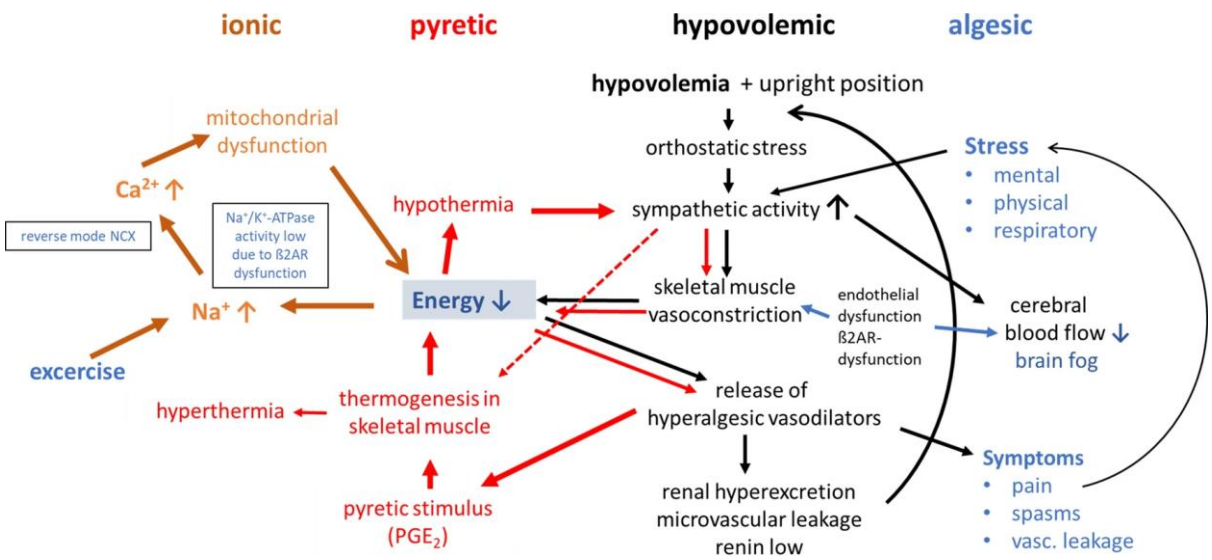
  “These findings support previous findings that there exists a general pattern of increased antibody levels to adrenergic and muscarinic receptors within the ME patient group. However, the role of increased adrenergic and muscarinic receptor autoantibodies in the pathogenesis of ME is still uncertain and further research is needed to evaluate the clinical significance of these findings.”

  “It has been suggested that adrenergic and muscarinic autoantibodies interfere with the binding of norepinephrine/epinephrine, influence the normal receptor function and contribute to symptoms seen in ME. Adrenergic receptors are involved in the normal function of the autonomous nervous system by regulating the sympathetic and parasympathetic reactions that control energy metabolism, immune system activation, heart muscle activity and neurocognitive function. Muscarinic receptors are important for neurological and neuromuscular transmission.”

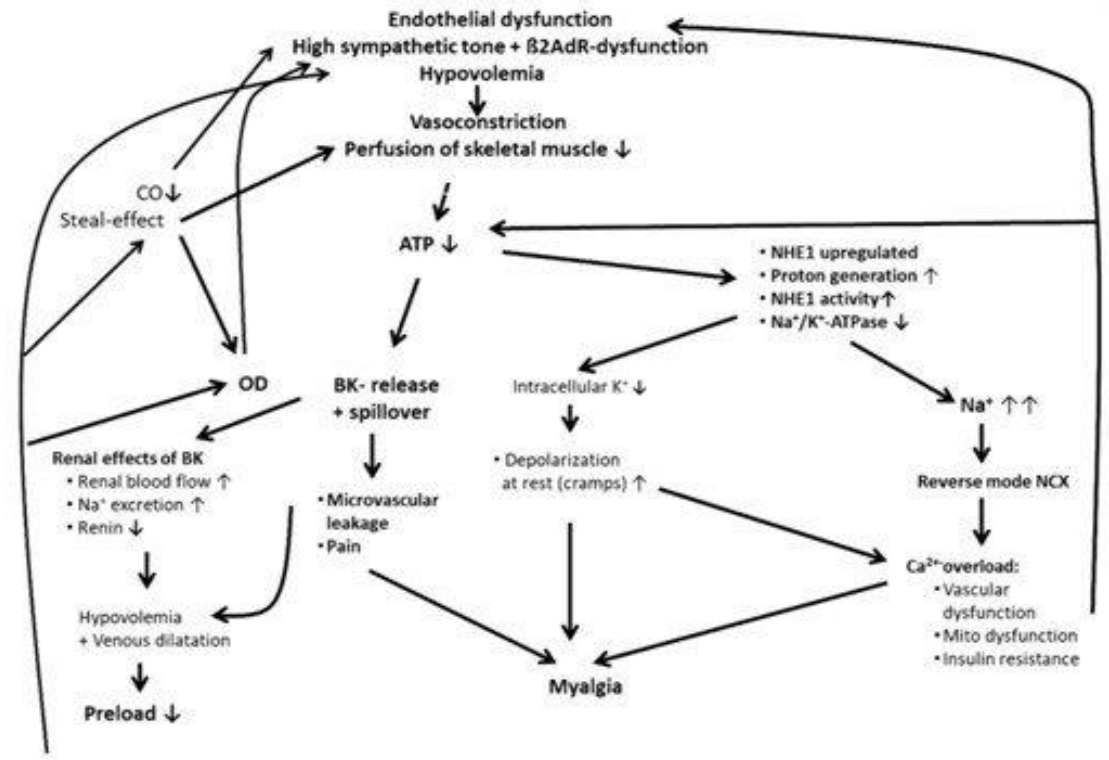
  “Dysfunction in adrenergic and muscarinic receptors introduced by autoantibody-binding have been suggested to contribute to autonomic dysfunction associated with symptoms of orthostatic intolerance, vertigo, bladder dysfunction, malaise, gastro intestinal disturbances, short term memory loss, concentration difficulties, muscle weakness and problems with information processing (Loebel et al., 2016; Johnston et al., 2016; Haga et al., 2012). However, little evidence exists regarding the receptor-autoantibody interactions and pathological significance of the autoantibodies leaving a knowledge gap that needs to be filled.”

  “It is yet to be explored whether the autoantibodies to Beta-adrenergic and muscarinergic cholinergic receptors have any clinical significance, whether they bind to the receptors and whether treatment options including blood purificating techniques (eg plasmaphoresis or immunoadsorbtion) improve symptoms and/or disease severity (Scheibenbogen et al., 2018).”

- [319 H, 320 H] Pathophysiology of skeletal muscle disturbances in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS), Klaus J. Wirth & Carmen Scheibenbogen, 2021



"Figure 4: Exercise, Hypovolemia, Stress and Disturbed Thermoregulation in ME/CFS: A Self-stabilizing Interplay between Vicious Circles"



"Figure 5: Hypothetical pathomechanisms in skeletal muscle and in cardiovascular system in ME/CFS explaining fatigue and myalgia. Bradykinin (BK), Cardiac output (CO), Orthostatic dysfunction (OD)"
"According to our hypothesis dysfunctions of the ß2AdR or post-receptor mechanisms, of the NHE1, the Na+/K+ATPase, the NCX, the RAAS and the KKS could be causally involved in ME/CFS and should therefore be further investigated. This concept offers potential novel strategies for the treatment of this debilitating disease."

- [321 H] Altered endothelial dysfunction-related miRs in plasma from ME/CFS patients, J. Blauensteiner, 2021

  “Although the etiology is unknown, evidence supports immunological abnormalities, such as persistent inflammation and immune-cell activation, in a subset of patients. Since the interplay between inflammation and vascular alterations is well-established in other diseases, endothelial dysfunction has emerged as another player in ME/CFS pathogenesis.”

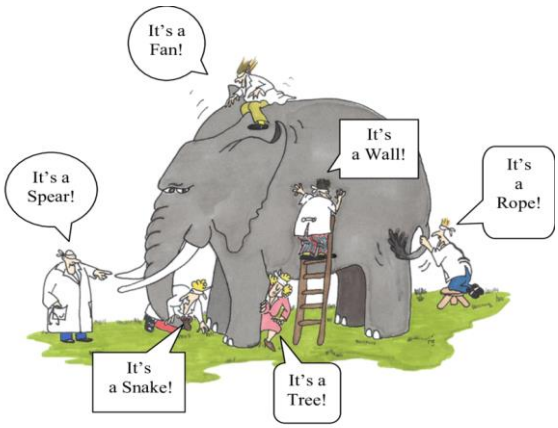
  “Endothelial nitric oxide synthase (eNOS) generates nitric oxide (NO) that maintains endothelial homeostasis. eNOS is activated by silent information regulator 1 (Sirt1), an anti-inflammatory protein. Despite its relevance, no study has addressed the Sirt1/eNOS axis in ME/CFS. The interest in circulating microRNAs (miRs) as potential biomarkers in ME/CFS has increased in recent years. Accordingly, we analyze a set of miRs reported to modulate the Sirt1/eNOS axis using plasma from ME/CFS patients. Our results show that miR-21, miR-34a, miR-92a, miR-126, and miR-200c are jointly increased in ME/CFS patients compared to healthy controls.”

  “A similar finding was obtained when analyzing public miR data on peripheral blood mononuclear cells. Bioinformatics analysis shows that endothelial function-related signaling pathways are associated with these miRs, including oxidative stress and oxygen regulation. Interestingly, histone deacetylase 1, a protein responsible for epigenetic regulations, represented the most relevant node within the network. In conclusion, our study provides a basis to find endothelial dysfunction-related biomarkers and explore novel targets in ME/CFS.”

- [322 H] Decreased NO production in endothelial cells exposed to plasma from ME/CFS patients, R. Bertinat, J. Blauensteiner, 2022

  “Highlights:
  - ME/CFS-plasma reduced the ability of ECs to produce NO.
  - Decreased NO production was linked to higher inhibitory phosphorylation of eNOS at Thr495 at the basal state.
  - We provide new methodological approaches to study in vitro ED in ME/CFS.”

Research summaries



- [323 H, 324 H] On July 5, 2019, Anthony L. Komaroff, MD, published a paper in Jama with an overview: "Advances in Understanding the Pathophysiology of Chronic Fatigue Syndrome".
  This paper has had 83,036 views and is in the top 5% of all research outputs scored by Altmetric.

- [325 H] Harvard Health Blog, Chronic fatigue syndrome: Gradually figuring out what's wrong, Author: Anthony Komaroff, MD, Editor in Chief, Harvard Health Letter, November 14, 2019

  "Here's an overview of what the current science suggests".

- [326 H] "International ME/CFS Research: an overview" by Professor Anthony Komaroff, MD, at RME Sweden October conference 2021

- [327 H, 328 H] CDC Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Stakeholder Engagement and Communication (MECFS-SEC) Webinar/Conference Call, Anthony L. Komaroff, M.D.
  The Biology of ME/CFS: Emerging Models, September 16, 2019

- [Ref. 74 H] Myalgic Encephalomyelitis (ME) in the Young. Time to Repent, Ola Didrik Saugstad, December 2019

- [329 H] Biomedical Insights that Inform the Diagnosis of ME/CFS, Dr. Brett Lidbury and Dr. Paul Fisher (2020)

  This Special Edition reports on a conference centered on biomedical discoveries, and on the translation of these results into tangible, quantitative, and predictive markers, which could diagnose ME/CFS. The book includes 11 published papers and a PDF of the book can be downloaded.

- [330 H] Current Research Provides Insight into the Biological Basis and Diagnostic Potential for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS), Warren Tate, 2019

- [331 H] Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: A Comprehensive Review, Mateo Cortes Rivera, 2019

  A short overview of the pathophysiology of ME/CFS.

- [332 H] ME Research Summary 2019

- [333 H] Article “Milestone” Meeting Highlights NIH Efforts to Combat ME/CFS, Miriam E. Tucker, April 17, 2019

  Immunologist Derya Unutmaz, MD: "There Is Something Biologically Terribly Wrong With These People".

- [334 H] The ME Association Index of Published ME/CFS Research, 2020

- [335 H] How Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) Progresses: The Natural History of ME/CFS, Luis Nacul, 2020

- [336 H, 337 H, 338 H] Insights from Myalgic Encephalomyelitis/Chronic Fatigue Syndrome May Help Unravel the Pathogenesis of Post-Acute COVID-19 Syndrome, Anthony L. Komaroff, W. Ian Lipkin, 2021

  “What’s the state-of-the-science, regarding ME/CFS?
  I and Dr. Ian Lipkin, Director of the Center, have just published an article summarizing the state-of-the science. It was published online in late June 2021, in the journal Trends in Molecular Medicine.
  As summarized in more detail in that article, we note that people with ME/CFS have:
  - Larger numbers of inflammation-causing bacteria, and smaller numbers of inflammation-fighting bacteria, in their gut, changes that correlate with symptoms;
  - Higher numbers of activated immune cells called T cells, as if the cells are fighting a battle against something;
  - Depressed function of another type of virus-fighting cell called natural killer (NK) cells;
  - Higher levels of certain chemicals (cytokines) that the immune system uses to fight battles;
  - Various autoantibodies—evidence of an autoimmune process in which the body’s immune system attacks not some foreign invader but attacks parts of the body, itself;
  - An impaired ability to make energy molecules (ATP);
  - Various abnormalities in the brain and autonomic nervous system.”

  “Finally, our recent article discusses how the growing knowledge about ME/CFS may affect our understanding of the lingering illness that can occur in people who develop COVID-19—postacute COVID-19 syndrome, or “long COVID”—and vice versa.”

  “We also propose a research agenda for both ME/CFS and postacute COVID-19 syndrome. We need to know whether the underlying biological abnormalities of ME/CFS are similar or identical to those in postacute COVID-19 syndrome. Although we don’t yet know how many people will develop postacute COVID-19 syndrome, it is plausible that the number in the U.S. soon will match the number who already suffer from ME/CFS—as many as 2.5 million people.”

  “In summary, the recent article summarizes in some detail what is known about the underlying biology of ME/CFS. It also highlights the fact that understanding a disease sometimes awaits the development of new scientific technologies. The article also emphasizes why physicians should never dismiss an illness just because they don’t understand it. With dedication, new tools and an open mind, the answers are coming.”

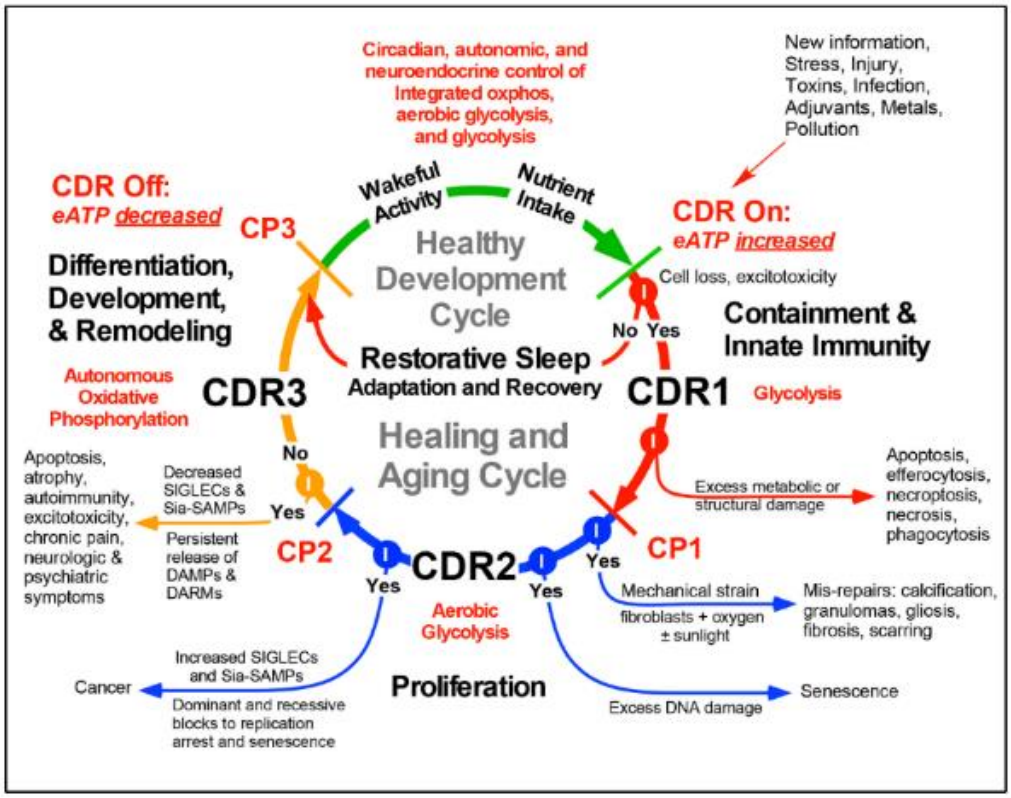
- [339 H] Index of ME/CFS Published Research, An A-Z index of the most important published research, The ME Association, 1st October 2021

Hypotheses and possible solutions

- [340 H, 341 H] **Dr. Robert Naviaux – dauer state and cell danger response (CDR)**

  "Just removing the trigger does not cure the illness. The cause of disease persistence is a biological failure of the normal healing cycle. Treatments of chronic illness require a detailed knowledge of the molecular controls and governing dynamics of healing. New treatments of chronic illness will seek to identify and remove blocks to the healing cycle to restore health, i.e., lead to cures. Dr. Naviaux sees that many chronic illnesses share one common feature and that is that the persistent cell danger response creates blocks in healing."

  "Essential facts when a cell is injured or stressed:
  (CDR1) M1 mitochondria in cells using glycolysis: pro-inflammatory form of defense.
  (CDR2) M0 mitochondria in cells using aerobic glycolysis: uncommitted form for growth and biomass replacement.
  (CDR3) M2 mitochondria in cells using oxidative phosphorylation: anti-inflammatory form for standard conditions."



  "We need M1 mitochondria as a response against i.e. a microbial attack.
  The cell danger response coordinates all the mitochondrial functions after every injury."

  "The healing cycle is a genetically programmed, 3-step sequence used to ensure recovery after any kind of injury. It has a beginning, a middle and an end. Metabolism controls progression through the healing cycle by using metabolites as signaling molecules. These are called "metabokines". The beginning of the healing cycle starts with M1, then M0 and at the end M2."

  "Physicians and scientists are taught to think in snapshots and not in dynamics; healing is a process, not a state. It is not just the removal of the pathogens that brought you to the chronic illness, but now adding, the addition of factors that will promote progress through the healing cycle. Instead of just

focusing on pathogens, which we need to in order to prevent disease epidemiologically, but once you have it you also need to talk about salugens. And having a systematic pharmacological search for medicines and natural products and interventions that can relieve abnormalities that have resulted in repeating cycles (being stuck) in one of the stages of healing. 30% of children and 60% of adults are caught in chronic illness. Maybe a way out of that is to unpack this healing process and to understand the molecular details of going from one stage CDR1 to CDR2 and CDR3 back to health. And maybe if we do that, we can start to having cures for chronic illnesses."

"Dr. Naviaux looked at what causes "dauer" (a kind of hibernation state) and they studied the C. Elegans worms. These worms can go into a dauer stage and live for 4 months, instead of its normal 2 week's life cycle. Dauer can be triggered by hypoxia, caloric restriction, predator stress, dehydration, heat stress, parasites, microbial infections."

"When they looked at what happens metabolically in the C. Elegans worms, they discovered that the path back to health is different than the normal path that got you to health. And it is also not a reversal of the pathway that got you into dauer."

"The worms in dauer have hypersensitivity to multiple chemicals, brittle behavior responses and post exertional crashes. So, after they have been touched, they were not able to respond to that for a long period after the stimulus, until they recover. It is a lot like post exertional malaise in ME/CFS."

"Dauer is an energy reallocation state with increased autophagy, and increased AMPK activation:
- Basal glucose utilization/PDH declines
- Basal fatty acid oxidization preferred
- Lipid stores increase (calories → fat)
- Methylation and acetalization decreased
- Polyamines increased
- SAMe diverted for polyamines
- Heat shock proteins increased
- Muscle preservation, connective tissue (collagen) turnover
- Bile acid-like sterol dafachronic acid low
- Cuticular/cutaneous receptor hypersensitivity to multiple chemicals
- Brittle behavioral response and post-excitatory/exertional "crashes"."

"Dauer is just one of many stress-related energy-reallocation, and survival states in nature. It is a way to survive environmental stress."

"For example, Lyme and Tuberculosis have both persister cells where they decrease their metabolic rate to make them resistant to environmental stress or antibiotics. Basically, it leads to core metabolic pathways of energy reallocation for survival."

"The fact that healing is a process and not a state is so fundamental that you will make mistakes if you do not get this."

"Once the healing cycle is complete, the extracellular ATP is reduced."

"The first stage of the healing cycle (CDR1) is involved in containment & innate immunity and it involves glycolytic metabolism. The underlying metabolic features of each stage allow for the steps of that stage to be completed. We have to have glycolysis before aerobic glycolysis, before oxidative phosphorylation and before a reblending of all the different metabolic states during the circadian rhythms."

"ME/CFS and autism appear more to be in a block towards the end of CDR3."

"Mitochondria in health are mostly in M2 in oxidative phosphorylation, CDR1 during inflammation they go glycolytic and become M1, then rise to proliferation in CDR2 and become M0, and finally CDR3 is a remodeling stage and then back to health in M2."

"If you look at an inflammatory disease, which is in CDR1, then you forget that you cannot go back to health. You actually have to proceed through the CDR2, CDR3 steps. So, knowledge of where a person is stuck does not actually tell you exactly the path to recovery. That is part of this hidden biology, the root causes that underlie virtually every chronic illness."

"In the dauer-worms they found that amongst others that the metabolite Acetylcholine must rise to go to recovery, 3 Methylhistidine must decrease, and Hypoxanthine (has a purine base) has to increase."

"A genetically modified mustard plant Arabidopsis will fluoresce when free calcium is released. There is a little cricket bite and if you add either glutamate or ATP, then that injury is signaled to the rest of the plant. So why APT and glutamate? They have very high concentrations inside the cell, but very low concentrations immediately outside the cell. So that when a cell is injured and releases these molecules, it is a very clear signal that there has been damage."

"Metabolomic pathways in Gulf War Illness were compared to metabolomic pathways in ME/CFS. There are some shared pathways in ceramides, sphingolipids, phospholipids and branch chain amino acids. But it turns out in Gulf War Illness those typically are increased and are decreased in ME/CFS. The only thing that was the same was that purines were decreased in both illnesses."

"Every stressed cell releases ATP and other metabolites through stress gated channels that are opened under increased oxidative stress. Mitochondria talk to the nucleus through a short path and they coordinate. There is also a long pathway that involves the release of these molecules and bind to receptors and then change gene expression."

"So, if there is a dissipated loss of ATP from the cell, what would happen if we have a drug that might be able to block that release of ATP from the cell? There would be more ATP that could be used inside the cell for purposes of growth and healing."

"It turns out that a P2X4 receptor is upregulated in ME/CFS compared to controls. So, when we went looking and there is one drug, Suramin, that could be an inhibitor of extracellular ATP signaling through several of the 19 Purinergic receptors. Suramin is a 100-year-old drug that is used to treat African sleeping sickness. It is actually related to ME/CFS. Dr. Naviaux has an FDA approval for a Suramin randomized, double blind, placebo controlled clinical trial for ME/CFS, for 3 years. They are now (April 2019) waiting for Suramin and a sponsor."

This paper confirms Dr. Naviaux's theory about extracellular ATP:

- [342 H] Metabolic and behavioral features of acute hyperpurinergia and the maternal immune activation mouse model of autism spectrum disorder, Dr. Naviaux, 2021

- [343 H] Oxidative shielding or oxidative stress? Robert K Naviaux, 2012

- [344 H] Mitochondrial: Cell Danger Response, Andrew Heyman, MD MHSA discussing Orchestration of Metabolism and the Cell Danger Response, 2021

- [345 H, 346 H] Episode #121: Cell Danger Response with Dr. Neil Nathan, MD, 2020

Dr. Nathan, MD, works with and explains the cell danger response in depth in this interview:

"….. [00:14:21.22] Scott: "When we think of Cell Danger Response, I think most people think that the entire body is either stuck or not stuck. But can various groups of cells or tissues or organs be in a Cell Danger Response when others maybe are not? Or possibly some areas in the body are in a different phase or stage of the Cell Danger Response? Is that possible?"

[00:14:48.09] Dr. Nathan: "It is. Generally, what is affecting a cell ultimately will affect the whole body. However, and Dr. Naviaux uses the term mosaic to describe the process that at any given moment in time, you can have certain tissues of the body in Cell Danger Response 1 and other tissues will be in Cell Danger Response 2, and others will be in Cell Danger Response 3. So it is not a clean, we're always in the same thing in a uniform way. Different parts of the body are operating in different ways with different capacities, with different genetics. So, it's a tad more complicated than just every cell in the body is going through this at the same time, not quite."

[00:15:42.25] Scott: "You mentioned mitochondria, so let's talk about that a little bit about ATP. I think many people think that to heal that we need to support the mitochondria that we need to produce more ATP. But that may not necessarily be the case in this Cell Danger Response model. So talk to us about extracellular ATP, the role that it plays as a danger signal. Can that be measured in some way, and why might attempts to create more ATP potentially backfire?"

[00:16:14.26] Dr. Nathan: "Okay, wonderful questions. So, we all know that ATP is the major energy molecule of the body. And accordingly, we think of it as a good thing exclusively. Which is if we're fatigued, make more ATP, that's a nice, simplistic answer. However, as an intrinsic part of the Cell Danger Response, one of the first things that happen when a cell feels threatened is it changes ATP from an energy molecule to a signaling molecule."

"So, it stops using it for energy. And think of this in terms of let's say you have a flu, your body grounds you, you're exhausted, absolute fatigue, malaise. Don't want to get out of bed, that is a part of the healing response, it's part of these Cell Danger Response to convince the organism to not attempt to overdo or do what you can't do. You don't have the ATP resources, you don't have the energy right now, shut it down, rest, go to bed, sleep that is a part of the healing response."

"So, we're stopping the way we use ATP, and instead, it is leaving the cell as a signaling molecule, and it is the creator of beep, beep danger, it is the molecule that's doing it for us. So when the extracellular percentage of ATP goes up, that is a signal to the entire body we're under threat right now, shut it down. And Dr. Naviaux has outlined beautifully a host of other biochemical changes that accompany this. And so you're absolutely right, to tell someone with a chronic illness that they have a mitochondrial dysfunction, tells us nothing."

"Of course, you have a mitochondrial dysfunction, it comes with the territory. You have to, your body is changing the way you use energy to deal with this chronic illness, regardless of which threat it is, the body doesn't care, it's going to do this anyway. So, if you use strategies to stimulate the body to make more ATP, it will either do nothing or make you worse, it's the wrong way to go. And I see a ton of people referred to me who are on all kinds of mitochondrial building materials. They're taking Coq10 and L-taurine and L-carnitine and D-ribose and malic acid, whatever your favorite products are, and their physicians are baffled that it's not doing anything."

"Well, you're dealing with an organism that can't use it, it's on survival mode, it can't use that. And so one of the most important concepts of the Cell Danger Response is, it's really important to try to figure out which part of that response that organism is in, or you're going to be giving treatments that will either do nothing or hurt the person, and you're going to spin your wheels for a long time because you're not addressing the cause."

[00:19:57.26] Scott: "Is there a way to measure extracellular ATP or is that not available?"

[00:20:02.10] Dr. Nathan: “Not clinically no, not yet. I know that Dr. Naviaux's working currently on a variety of things that may help us to understand what stage of the Cell Danger Response you're in, but we don't have that currently available.”

[00:20:17.22] Scott: “So, before we jump into the shallow end of the pool because we'll never get into the deep end of the pool in this topic in 90 minutes. Talk to us about what is purinergic signaling, what are purinergic receptors? How do they fit into a Cell Danger Response discussion?”

[00:20:34.10] Dr. Nathan: “So, ATP is a purine, so purinergic simply refers to ATP and some of the similar molecules of which ATP is the best known. A purinergic receptor is one that like all receptors, you've got a structure on the edge of every cell and that cell is intended to bind to ATP when it comes around. So a purinergic receptor simply accepts ATP.”

“There are 19 known purinergic receptors, and they respond to ATP in such a way that they participate in this shutting down process. So if we're talking about using a medication like Suramin, which is an anti-purinergic, it blocks the receptor site so that it the ATP can do its job and is no longer blocking. In other words, it reverses this process and has the capacity to turn off that danger signal.”

[00:21:41.29] Scott: “At a very high level in some of your prior talks, you talk about eight key changes that happen when we enter this Cell Danger Response. So can you tell us what actually happens, what are these eight key changes that we see?”

[00:21:54.16] Dr. Nathan: “Well, sure and these all occur virtually simultaneously and almost instantaneously once it gets triggered. So just to tell you how it gets kicked off, the mitochondria in a cell are exposed to a threat, either a toxin or an infection. They immediately register that threat as a drop in voltage in the cell, and that drop in voltage triggers the body immediately to go into what we call oxidative shielding. Now for years, people have talked about oxidative stress in which there's free radicals that are produced, reactive oxygen species that come into play and that's always been thought of as the cause of the illness.”

“In point of fact, that isn't necessarily the cause of the illness, in one of Dr. Naviaux's profound papers is literally titled “Oxidative shielding versus activated stress”. Where he's trying to shift consciousness that this oxidative shielding is the oxygen level in the cell rises, shutting off a whole lot of other processes inside the cell and that is protective. It's not intended to harm the cell, it doesn't need to be treated.”

“So, in the same way that we just talked about maybe treating mitochondrial dysfunction isn't the right strategy initially, maybe using antioxidants isn't the right strategy, we are messing with the body's innate intelligence and its knowledge that no, I’m creating the correct milieu, chemical milieu in which healing can occur. Don't mess with me, and again by understanding this we can make progress. So once that gets triggered, there are eight specific things that are a part of that. One is that the body immediately changes its metabolism, it goes from what's called polymer metabolism to monomer metabolism.”

“Now to translate that into English, polymer metabolism is we are making proteins out of our amino acids, we're making complicated sugars that we work with and polysaccharides. Well, the microbes that are trying to infect that love that, because they can't make all of that for themselves. Literally, they are hijacking our chemistry to make those materials, so we shut it down intentionally. So we shift from making those complicated materials that they can't make but need, and we instead shift to monomer metabolism, which is simply simple sugars, simple amino acids, simple fats, that's one. Another thing that we do is we change the way we metabolize sulfur.”

“Now that's much more relevant in terms of glutathione, one of the most important sulfur-containing materials in the body. We need glutathione to help process toxins; we need glutathione to help with

oxidative reduction reactions. And unfortunately, we use it up very quickly in the initial stages of the Cell Danger Response. So how do we make glutathione? With methylation. So the cell intentionally shuts down methylation to stop making glutathione, so that the body can't harness methylation either."

"For example, viruses can't replicate unless they hijack our ability to methylate, our ability to make histones so that they can replicate their DNA which is what they do. They can't do it, unless we're offering them here, methylate to your heart's content you know make all the materials you need, we shut it down. So, again another area that is often misunderstood is oh, you're not methylating very well. Well duh, of course, you're not methylating well, it's part of the deal. So again, many practitioners have discovered that attempting to give methylation early on in the course of illness will backfire."

"In my patients who tend to be very sensitive, the vast majority can't take methylation materials, it'll make them worse and for other people, it won't do anything. So, do you need to methylate?"

"Eventually. But not in the beginning phases, because we shut it down. We shut down, we change tryptophan metabolism. We make tryptophan into, there are two different big pathways you can take depending on the enzyme that's working on the tryptophan, which is just an amino acid."

"We can either make serotonin from which we make melatonin, or we can make kynurenic acid and quinolinic acid. Now the latter will trigger IL-6 it's inflammatory and it's long associated with a great deal of psychological issues like anxiety and depression. Obviously, serotonin helps us to cure depression and feel better. Which pathway does the body use, that depends on that person's innate chemistry and genetics, but that's another part of the deal. It changes how we process vitamin D. The enzyme that normally we utilize to bind and work with vitamin D shifts."

"So, our vitamin D levels drop, it changes the way we metabolize B6, the biome changes. There's an automatic shift in the biome through the Cell Danger Response because it is becoming less open if you will to all of these exogenous issues. An interesting paper by the way on the biome reboot, Dr. Naviaux did a paper with mice that can be autistic. And he took Suramin and he gave them to the autistic mice, and he measured a whole host of parameters including their biome. One injection of Suramin normalized the biome completely in these mice doing no other interventions. So again, we do elaborate treatments to reboot our gut. We are taught in functional medicine, the gut is the most important area that needs to be treated first."

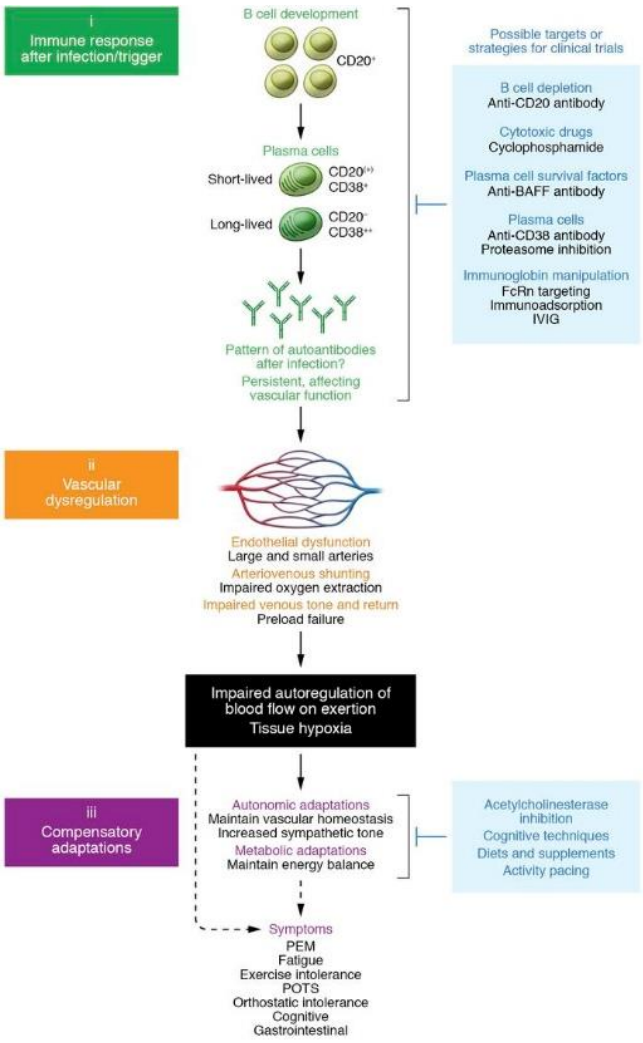
"Well, you're going to find for example if you have mold toxicity that you won't be able to fix that biome until you fix the mold, because it's triggering the Cell Danger Response, you're just not going to do it. Fix the Cell Danger Response in many ways the biome will often reboot itself. So the wisdom in Dr. Naviaux's work here is it's helping us to understand when we need to intervene with our knowledge of functional medicine."

"It's not enough to know what's deficient, we need to know when is that organism able to use that in the service of healing, or are we just piling up a whole bunch of supplements that it's got a process, it's on survival mode, it can't possibly deal with that. So those are some of the eight basic principles that this contains…."

- [347 H] #59: Dr. Jill interviews Dr. Eric Gordon on the Cell Danger Response (at 27:35), 1. April 2021

Dr. Gordon says that unexplained air hunger/dyspnea is caused by extracellular ATP:
"…. there were some studies in the '90s where they tried to use injectable ATP for Cachexia (weight loss in cancer), because they thought that this would give them some strength and restore their energy. One of the big side effects was air hunger. You see, because it is a danger signal. ATP is supposed to be inside the cell."

- [348 H] **Pathomechanisms and possible interventions in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS)**, Øystein Fluge, Karl J. Tronstad and Olav Mella, July 2021



"Figure 1 - Proposed model for ME/CFS pathomechanisms."

"Proposed model for ME/CFS pathomechanisms. We suggest three principal steps underlie the initiation and maintenance of ME/CFS. (i) **Immune response** after infection serves as a triggering event, with a role for B cells/plasma cells and autoantibodies in the underlying pathology. (ii) The vascular system and possibly GPCRs are potential targets for **autoantibodies**, which may affect endothelium or neurovascular control and autonomic small nerve fibers. The autoantibodies could be pathogenic IgGs or functional autoantibodies that normally occur after infection, but persist and fail to resolve over time. This disturbed homeostasis involves endothelial dysfunction in large and small arteries, impaired venous return and preload failure, and arteriovenous shunting, presumed to result in impaired autoregulation of blood flow and tissue hypoxia on exertion. (iii) **Secondary compensatory efforts** may add to the clinical presentation and symptoms. They include autonomic adaptations, often with increased sympathetic tone, and metabolic adaptations aiming to restore energy supply. Possible strategies for clinical trials targeting these pathways are also indicated."

- [Ref. 128 H,129 H, 349 H] **Hypothesis: An autoimmune mechanism blocks the oxygen supply to the cells during exertion**, Trondstad et al, August 2021

"The findings by Tronstad and colleagues support a theory that ME is associated with a persistent disturbance in the cells' ability to satisfy energy needs."

"According to Tronstad, some changes are expressed differently in different patients because the body has distinct ways of dealing with threatening situations."

"By ways of example, he mentions the body's response to fasting: When you fast, you limit the normal supply of nutrition to the cells, and the body will respond by supplying the cells with alternative sources of energy via the blood. Such metabolic compensatory mechanisms can be triggered by illness and may vary from individual to individual."

"Among the ME patients, we found characteristic features of two types of metabolic adaptations, one of which was associated with a more severe symptomatology. Possible contributing factors include diets, drugs, genetics, and lack of physical activity", says Tronstad

"Hypothesis: An autoimmune mechanism blocks the oxygen supply to the cells during exertion The findings are also compatible with the fact that symptoms often intensify during and after physical activity. During physical activity, the demand for energy supply to the cells increases. If the energy supply is not working properly, it increases the strain on the cells."

"The assumption that the changes in energy supply are caused by a flaw in the immune system is only a hypothesis, but this too agrees with the present findings: "To be specific, an autoimmune mechanism could be affecting the blood supply during exertion. When we are physically active, our blood flow is adjusted to enable activity, but in ME patients this autoregulation may be impaired", says Tronstad."

"As a consequence, the cells receive too little oxygen. Our metabolic findings are compatible with this kind of changes", says Tronstad, emphasizing that this is a hypothesis that requires further research.

Tronstad, Fluge and Mella have recently published an article where they describe their hypothesis in further detail: https://www.jci.org/articles/view/150377".

- [350 H] **An attempt to explain the neurological symptoms of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome**, Klaus J. Wirth, Carmen Scheibenbogen & Friedemann Paul, November 2021

  "There is accumulating evidence of endothelial dysfunction, muscle and cerebral hypoperfusion in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS). In this paper we deduce the pathomechanisms resulting in central nervous pathology and the myriad of neurocognitive symptoms. We outline tentative mechanisms of impaired cerebral blood flow, increase in intracranial pressure and central adrenergic hyperactivity and how they can well explain the key symptoms of cognitive impairment, brain fog, headache, hypersensitivity, sleep disturbances and dysautonomia."

  "Decreased CBF, disturbed local blood flow regulation and neurovascular coupling, central adrenergic hyperactivity, hypocapnia and increase in intracranial pressure seem to play a strong role in the pathophysiology of the neurological symptoms in ME/CFS (Fig. 1). They can well explain cognitive impairment, brain fog, headache, psychomotor slowing, ataxia and loss of coordination of movements, hypersensitivity, sleep disturbances and dysautonomia."

- [351 H, 352 H] **The Enterovirus Theory of Disease Etiology in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: A Critical Review**, Adam J. O'Neal and Maureen R. Hanson, 2021

  "We conclude that there is considerable evidence that prior outbreaks of ME/CFS were caused by one or more enterovirus groups. Furthermore, we find that the methods used in prior studies were inadequate to rule out the presence of chronic enteroviral infections in individuals with ME/CFS. Given the possibility that such infections could be contributing to morbidity and preventing recovery, further studies of appropriate biological samples with the latest molecular methods are urgently needed."

- [353 H] **Salivary DNA Loads for Human Herpesviruses 6 and 7 Are Correlated With Disease Phenotype in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome**, Ji-Sook Lee1, Eliana M. Lacerda2, Luis Nacul2,3,4, Caroline C. Kingdon2, Jasmin Norris2, Shennae O'Boyle2, Chrissy h. Roberts2, Luigi Palla2,5, Eleanor M. Riley1,6 and Jacqueline M. Cliff, 2021

  "The results indicate that fluctuating viral DNA load correlates with ME/CFS symptoms: this is in accordance with the hypothesis that pathogenesis is related to herpesvirus reactivation state, and this should be formally tested. Herpesvirus reactivation might be a cause or consequence of dysregulated immune function seen in ME/CFS. The sampling strategy and molecular tools developed here permit such large-scale epidemiological investigations."

- [354 H, 355 H] **CD8 T-cell exhaustion, increased CD4+CD8+ T-cells and aberrant cytokines in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)**, summary poster, Solve ME/CFS Initiative and Massachusetts ME/CFS & FM *and*
  "Altered T Cells in ME/CFS" on Vimeo, Liisa Selin PhD and Anna Gil PhD, University of Massachusetts Medical School, 9/27/2020

  "Clinical implications:
  - Potential biomarkers: low CD8, altered CD4:CD8 ratio, high CD4+CD8+ frequency, CD8 functional studies for exhaustion
  - Therapy:
    - Check point inhibitors (anti-PD1, anti-CTLA4) are being used to reverse CD8 T cell exhaustion in tumor therapy and chronic viral infections.
    - Anti-cytokine therapies such as anti-IL17 is being developed for other autoimmune conditions like inflammatory bowel disease
    - Due to CD8 T cell exhaustion do ME/CFS patients have difficulty controlling their commensal bacteria, funguses (Candida albicans) and viruses such as EBV, HHV6, CMV?
    - Would antivirals help, anti-fungal, microbiome therapy help, hyperbaric oxygen
    - Understanding the pathogenesis of ME/CFS
    - IL9 and IL17 have receptors in the CNS (may contribute to CNS disease)
    - IL9 is a potent mast cell inducer (may contribute to the allergies and mastocytosis in ME/CFS)
    - CD8 T cell exhaustion is known to be associated with increased systemic levels of IFNa/b and TGFb . These cytokine abnormalities associated with CD8 T cell exhaustion lead to the types of metabolic dysregulation observed in ME/CFS.
    - Potentially use TCR sequencing to identify the major antigens whether viral or auto-antigen that are driving or contributing to this aberrant immune activation in ME/CFS"

  [356 H] "On March 8, 2021, NIH awarded a $2.5 million grant to researchers Liisa Selin, MD, PhD, and Anna Gil, PhD, for their work on the highly disabling disease ME/CFS (Myalgic Encephalomyelitis / Chronic Fatigue Syndrome). This NIH RO1 grant, titled "Altered T cell Responses in ME/CFS" allows the researchers to examine the role of aberrant T cell responses in the immunopathogenesis of ME/CFS patients. Selin and Gil's recent research findings could point to potential biomarkers, treatments and ways of tracking response to therapy for the disease, things that have been sorely missing."

- [357 H, 358 H, Ref. 322 H] **Nitrogen Metabolism and Testing Nitrogen Hypothesis in ME/CFS**, OMF, Dr. Christopher Armstrong

  "We hypothesize that toxic nitrogen-containing by-products of energy metabolism accumulate more readily in the cells of ME/CFS patients. This accumulation, in turn, creates a cycle of energy generation to overcome a stressed state while generating more toxic nitrogen by-products in the process. We will also identify the compounds that can circumvent the production of toxic nitrogen by-products and release patients from this cycle."

- [359 H, 360 H] **Hypothesis: Mechanisms That Prevent Recovery in Prolonged ICU Patients Also Underlie Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)**, OMF, Dr. Jonas Bergquist, 2021

  "Here the hypothesis is advanced that maladaptive mechanisms that prevent recovery in some intensive care unit (ICU) patients may also underlie Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). Specifically, these mechanisms are: (a) suppression of the pituitary gland's pulsatile secretion of tropic hormones, and (b) a "vicious circle" between inflammation, oxidative and nitrosative stress (O&NS), and low thyroid hormone function."

  Treatment paper:
  "Notably, the early successes to reactivate the pulsatile secretions of the pituitary in prolonged critically ill patients with pituitary secretagogues—and the resulting positive metabolic effects—would indicate that this also could be an important avenue for ME/CFS treatments. The simultaneous reactivation of suppressed endocrine axes so far remains unexplored in ME/CFS. Conversely, the findings from ME/CFS related to the dysfunctions at the cellular and mitochondrial level can likely provide important complementary insights to the understanding of critical illness. In addition, the positive impacts from thyroid hormone supplementation described in some of the trials for both conditions merit further investigation."

Methylation cycle hypotheses

- [361 H] Glutathione and the Methylation Cycle by Rich Van Konynenburg Ph.D.

- [362 H] A Simplified Treatment Approach Based on the Glutathione Depletion-Methylation Cycle Block Pathogenesis Hypothesis for Chronic Fatigue Syndrome (CFS) by Rich Van Konynenburg, Ph.D.

- [363 H] Methylation cycle hypothesis (several protocols: Rich's Protocol, Yasko's Protocol, Freddd's Protocol).

  "This Glutathione Depletion-Methylation Cycle Block hypothesis for CFS proposes that glutathione depletion and a partial block in the methylation cycle impact the detox system in a big way, causing toxins to continue to build up in the body while the person has CFS, among other deleterious effects on the body's systems in CFS that stem from these same root causes.
  Glutathione is important for both phases I and II of the detox process in the liver. Other substances that are impacted by the GD-MCB mechanism, that are also important for the detox system, include SAMe, cysteine, taurine, and sulfate."

  "When the partial methylation cycle block is lifted and glutathione comes up to normal, the function of the detox system is restored, and the backlog of stored toxins begins to be mobilized. This results in some unpleasant additional symptoms for a while, until the toxins are cleared out."

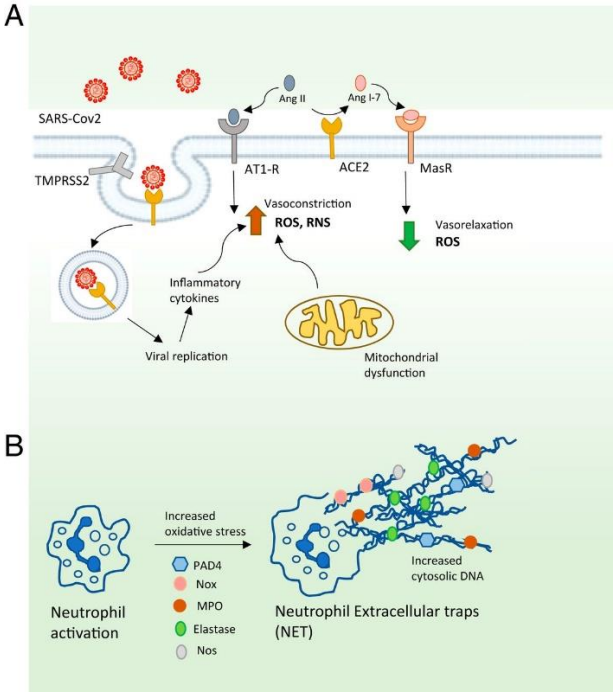
- [364 H] Changes in DNA methylation profiles of myalgic encephalomyelitis/chronic fatigue syndrome patients reflect systemic dysfunctions, A. M. Helliwell, W.P. Tate, 2020

- [365 H] Histamine, Homocysteine and Health with Joanne Kennedy, 2021

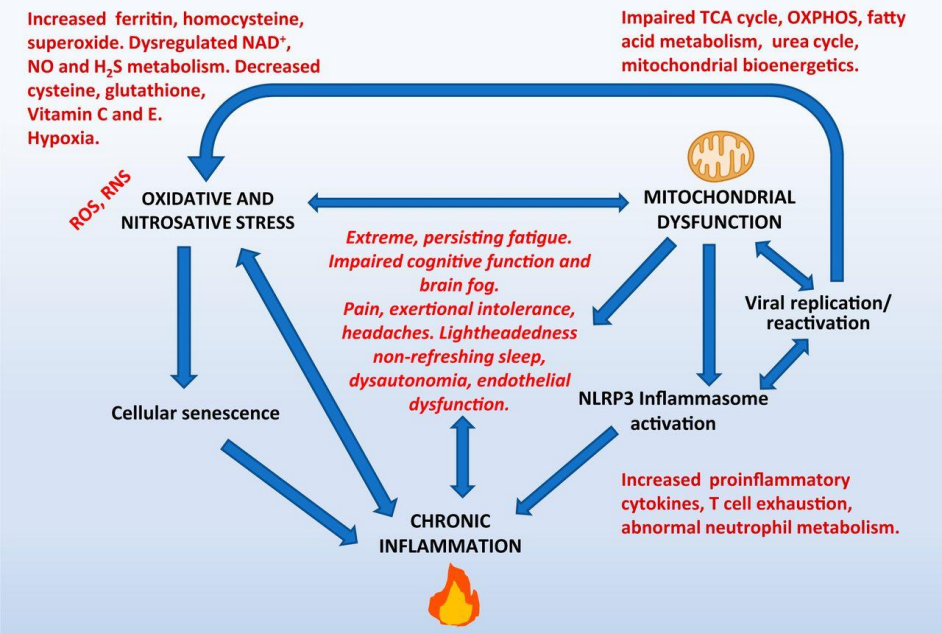
- [366 H] Hypothesis: chronic fatigue syndrome is caused by **dysregulation of hydrogen sulfide metabolism,** Marian Dix Lemle, 2009

  "Marian Lemle theorized that the hydrogen sulfide (H2S) was possibly affecting the body's ability to fully utilize oxygen. That insight led to the development of the "hibernation" theory of illness in CFS/ME, and represented the first comprehensive theory of hydrogen sulfide in chronic illness. ME/CFS patients may be experiencing a hypometabolic state akin to hibernation."

- [367 H, 368 H, 369 H] **Redox imbalance links COVID-19 and myalgic encephalomyelitis/chronic fatigue syndrome**, Bindu D. Paul, Marian D. Lemle, Anthony L. Komaroff, and Solomon H. Snyder, 2021



"Fig. 1.
Oxidative stress in COVID-19. (A) The ACE2 pathway. SARS-CoV-2 infects cells harboring ACE2 and the protein transmembrane protease, serine 2 (TMPRSS2); together, these molecules prime the viral spike protein S, facilitating its entry by endocytosis. ACE2 converts angiotensin II (Ang II) to angiotensin 1 to 7 (Ang 1–7). This decreases ACE2 and elevates Ang II, which acts through the angiotensin 1 receptors (AT1-Rs), causing accumulation of superoxide radicals (O2•−) leading to hypertension and inhibition of vasodilation. Ang 1–7 binds the G-protein–coupled Mas receptor MasR, mediates vasorelaxation, and decreases O2•− production. SARS-CoV-2 induces formation of reactive oxygen radicals (ROS) and RNS by eliciting mitochondrial dysfunction and production of proinflammatory cytokines. (B) The NETs. NETs are web-like structures extruded from activated neutrophils, comprising proteins assembled on a scaffold of decondensed chromatin, which target invading pathogens. The component proteins include oxidative and proinflammatory enzymes such as NADPH oxidase (Nox), neutrophil elastase, myeloperoxidase (MPO), NOS, and peptidyl arginine deiminase 4 (PAD4), which deaminates arginine to citrulline, resulting in the formation of citrullinated proteins (such as histone H3, causing its dissociation from DNA). Excessive accumulation of NETs causes inflammation and damage in COVID-19."



"Fig. 2.
The interactions between redox imbalance, mitochondrial dysfunction, chronic inflammation, and related symptoms. As explained in the text, redox imbalance, mitochondrial dysfunction, and inflammation are bidirectionally related to each other and may cause some of the symptoms of both long COVID-19 and ME/CFS. The bidirectional connections mean that an initial abnormality in one component can trigger abnormalities in other components and can precipitate a persistent, self-reinforcing pathological process."

"People with acute COVID-19 and people with ME/CFS share redox imbalance, systemic inflammation and neuroinflammation, impaired production of ATP and other abnormalities in common (Fig. 2), abnormalities that have bidirectional connections (169).
The syndrome of long COVID-19 that can develop in some COVID-19 survivors (people called "long haulers") is very similar to ME/CFS, so it may well be that the group of abnormalities seen in acute COVID-19 and in ME/CFS also will be seen in long COVID-19. Presumably, redox abnormalities in COVID-19 are secondary to the infection with SARS-CoV-2. The same may be true among those ME/CFS patients whose illness began with an "infectious-like" illness."

Prof. Jonas Blomberg:

- [370 H] Infection Elicited Autoimmunity and Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: **An Explanatory Model**, Jonas Blomberg, 2018

- [Ref. 410 H, 371 H, 372 H, 373 H] **Dr. Nancy Klimas: Reset Homeostasis**

"If you think of ME being a homeostatic disruption, then you can also think about homeostasis as a way to reboot. Interactive systems are working in a different balance: immune, autonomic, endocrine HPA, HPG, neuropeptides. Homeostasis in the setting of the environment of the patient: toxin exposures, stress responses, infections etc. We know that all the systems (i.e. brain, nervous system, endocrine system) are interactive. So, when they are doing their homeostatic modelling and try to find interventions, they found out that there is no one trick, no one button to force this back into balance. It is always 2 or more buttons. Big surprise, we are working in multiple systems here. So, just fixing the immune system is not enough. Just fixing the endocrine system is not enough. But when we start doing things in combinations, at least in the computer modelling systems, then we start seeing really good things."
[374 H, 375 H] In Gulf War Illness, a human trial started (March 2020) with the same "homeostatic reset" model, using Etanercept and Mifepristone.

Cortene drug CD38 (Daratumumab) hypotheses
See latest update September 2021, Ref. [420] H, Ref. [421] H
"Clinical trial provides preliminary evidence of a cure for myalgic encephalomyelitis / chronic fatigue syndrome (ME/CFS) and Long Covid".

- [[376] H, [377] H] Cortene to Move Forward on New Drug for Chronic Fatigue Syndrome (ME/CFS), by Cort Johnson, Aug 29, 2019
  and
  The Cortene Drug Trial Results for ME/CFS Are In, Cort Johnson, Sep 3, 2021
  "These data support there being a pathological hypersensitivity in the CRFR2 pathway."

  "Cortene believes the pathway they've targeted – the CRFR1/CRFR2 pathway – plays a special, even fundamental role in homeostasis. Cortene became particularly interested in ME/CFS because it presented the most extreme case of "dyshomeostasis" they could find. Where else, after all, do you find dramatic declines in functionality, such difficulties responding to stressors such as exertion, mental activity, even such seemingly innocuous things like lights or sounds?"

  "Cortene believes a neuronal "switch" exists in the limbic system which turns the threat response on and off. The switch is found in the corticotropin-releasing factor (or hormone) system which regulates serotonin. Two receptors – the CRFR1 and CRFR2 – are involved."

  "Under minor stress or at baseline, CRFR1 dominates; sitting on the surface of GABA-producing neurons, the CRFR1 receptors trigger the release of GABA – a neurotransmitter that inhibits serotonin. During these low-stress periods, CRFR2 is inactive and remains embedded inside serotonin neurons."

  "Under high (or prolonged) stress levels, the two receptors switch places. CRFR1 drops inside the GABA neurons and goes dormant. CRFR2, on the other hand, pops up onto the surface of serotonin-producing neurons and triggers the release of serotonin."

  "Once the stress/threat is resolved, the CRFR2 receptors should drop back into the neurons and the CRFR1 receptors should return to the surface – thus restoring the calm state one usually associates with health. Cortene doesn't believe that happens in ME/CFS."

  "They believe the CRFR2 receptor remains upregulated, leaving the stress response system in a hypersensitive, easily-provoked state – which can have major consequences. From the metabolic to the autonomic, to the immune, to the endocrine systems, the authors cite papers demonstrating the wide reach of the CRFR1/CRFR2 system. They believe everything from movement problems, to energy issues, to stimuli sensitivities, to the cognitive and emotional ramifications of ME/CFS, could potentially be caused by an upregulation of this system. Because the upregulation exists on the neurons, the type of symptoms any one person with ME/CFS experiences would depend on which neurons are affected."

  "The fact that we can't actually measure what's happening with the CRFR1/CRFR2 switch Cortene is attempting to turn off means problems with it will not show up in the blood tests – which, potentially fits ME/CFS – the disease that perpetually seems to fall between the cracks – quite well. The only way to assess if CRFR2 has been turned on or off is to hit it with a drug. Fortunately, CT38 is a good drug to do that as, so far as we know, it only interacts with CRFR2. If an effect with this drug is seen then, we can assume that it was because CT38 impacted CRFR2."

  "Cortene chose an interesting way to damp down what they believe is an overactive CRFR2 pathway. Instead of using an antagonist to block the pathway – as is usually done – their objective was to use an agonist to overstimulate the pathway."

"It might seem strange to attempt to overstimulate an already hyped-up pathway, but that approach simply takes advantage of how neurons function. If they get overstimulated, they basically fold; i.e. they turn themselves off. Faced with the CT38 agonist, the neurons should move the CRFR2 receptors back inside the cell – returning it to its normal resting state – and turning off a multitude of problems. Cortene's approach is different, but it potentially has some real advantages. Pathway blockers (antagonists) may stop the final expression of the pathway, but because they don't turn it off, they often need to be taken for life. An agonist which overstimulates the pathway, on the other hand, might allow it to reset itself and return to a healthy state."

- [[378] H] Prof Tate's Lecture on his research groups results, Nov 2019

  Prof. Warren Tate talks about the Cortene drug CD38, and shows that their epigenetics study found changes in the genes involved in serotonin metabolism, corticotrophin metabolism and genes involved in energy production.

- [[379] H] InTime: the results of Cortene's CT38 trial, ME/CFS, Michiel Tack, September 12, 2021

  "Unfortunately, we can't conclude much from the findings of the InTime trial except that they contradict claims about a cure for ME/CFS. Although It is great that a pharmaceutical company wants to test a new drug to treat ME/CFS, the results do not look that promising. The researchers stated that they plan to test CT38 using longer or additional infusions in future trials. We can only hope that these will show more encouraging results."

- [[380] H] Dr. Bateman on Cortene and CT38, by Lucinda Bateman, MD, BHC News, Home, Long COVID, ME/CFS, Research News, Sep 9, 2021

  "We should be careful how we use or react to the word "cure" at this stage of the scientific process. None of us know what CT38 can really do for a larger pool of people with ME/CFS or anyone with Long COVID until larger, controlled trials are complete. Cortene asserts that if the disease mechanism reversed by CT38 is a primary cause of ME/CFS, then the drug has the potential to be curative rather than supportive. That is exciting but remains to be proven. The preliminary results from the first, small, proof-of-concept CT38 trial in ME/CFS provide a strong enough signal to move forward with the next steps. Given the known heterogeneity of ME/CFS, it is unlikely any treatment breakthrough will have the same response in everyone who meets the diagnostic criteria. We must be prepared for that outcome. But for all with ME/CFS, I hope that CT38 proves to be an effective treatment for as many as possible."

- [[381] H, [382] H] **AXA1125** Now in Phase 2a and 2b Development, ME Association, Oxford to test potential treatment for fatigue in long COVID patients, Dr. Charles Shepherd, October 2021

  To test potential treatment for fatigue in long COVID patients Dr Shepherd says:
  "A new drug treatment for fatigue in Long Covid?
  This is an interesting report about the use of an experimental drug from America called AXA1125 that is now being assessed by researchers in Oxford as a possible form of treatment for fatigue in Long Covid."

  "As we keep reporting, there are important clinical and pathological overlaps between Long Covid and ME/CFS - one of which is known as mitochondrial dysfunction. Mitochondria are the vital battery like structures that create energy at a cellular level and the MEA has been funding research into mitochondrial dysfunction in ME/CFS in both Oxford (Dr Karl Morten) and Newcastle (Professor Julia Newton) for many years."

  "If this clinical trial demonstrates that this drug does help to reduce fatigue in Long Covid there could be important implications for people with ME/CFS."

"It is also interesting to note that mitochondrial function in the AXA 1125 study will be looked at using magnetic resonance spectroscopy (MRS) - as I used my own skeletal muscle in a study we carried out in Oxford back in the early 1980s with MRS to demonstrate the presence of mitochondrial dysfunction in ME/CFS. This research was published in The Lancet back in 1984!"

"More information on AXA 1125:
https://axcellatx.com/pipeline/axa1125/
Dr Charles Shepherd, Hon Medical Adviser, MEA"

- [383 H] Method for the treatment of Chronic Fatigue Syndrome using an **inhibitory or cytotoxic agent against plasma cells**, Patent **Dr. Øystein Fluge and Dr. Olav Mella**, 4 March 2021

Some highlights of the patent:
"CFS in a subset of patients may be a post-infectious immune dysregulation, possibly a variant of autoimmune mechanisms, possibly with a genetic predisposition, in which B lymphocytes are important for symptom maintenance."

"Patients responding to Rituximab may have autoantibody production from immature plasma cells (plasmablasts). For most ME/CFS patients with autoantibody-production from the mature plasma cells, not responding to Rituximab, a possible way to treat ME/CFS could thus be by using a regimen that targets mature plasma cells, either because of plasma cell vulnerability to a drug with a general mode of action, or to a molecular targeted therapy directed against specific epitopes on mature plasma cells."

"Consequently, ME/CFS can be treated with drugs that induce apoptosis and reduce autoantibody production in plasma cells. Specifically, this may be achieved by a proteasome inhibitor like Bortezomib. The class of drugs denoted as proteasome inhibitors act by inhibiting the chymotrypsin activity of the proteasome, accumulating misfolded proteins particularly in cells with high levels of protein turnover and especially in immunoglobulin-producing plasma cells. In myeloma, this will eventually lead to apoptosis of the malignant plasma cells. Experimental data indicate that these drugs also are beneficial in auto immune disease by depleting activated T- and B-cells and by inhibition of type I interferon production in monocytes and plasmacytoid dendritic cells. Because of toxicity (especially peripheral neuropathy), and also the influence on long-lived plasma cells responsible for normal antibodies such as vaccine-induced antibodies, the drugs should preferably be given in a few (1-4) courses over a limited period of time."

"An alternative approach for plasma cell depletion is to target the mature plasma cells directly, including memory cells, with antibodies directed toward epitopes on their surface. Such epitopes are not necessarily specific for plasma cells and must be used with care. A commercially available drug directed at CD38 (Daratumumab) is used for treatment of myeloma, because the myeloma cells typically have high densities of CD38 antigen. The drug will however also target other immune cells, such as activated T- and B-cells as well as myeloid- derived suppressor cells. The attenuation of this suppression may induce T-cell activity after the use of Daratumumab. Thus, even though targeting the plasma cells, Daratumumab may induce recruitment of other B-cells and therefore given alone maybe not achieve the goal of effective and long-lasting suppression of long-lived plasma cells."

"An embodiment of the present invention, a combination of at least two inhibitory or cytotoxic agent against plasma cells may be provided."

- [384 H] Emerge, Australia, **Research** Interview: **Professor Ken Walder** (Australia, 2021)

  “Hypothesis: there may be a systemic problem with the ability of the mitochondria to produce the energy the body needs to function and that leads to feelings of fatigue as well as some of the other symptoms people with ME/CFS get.”

  "For ME/CFS patients the most exciting aspect of Walder’s work is that it culminates in drug testing. After Walder and his team learn how to stress and dysregulate ME/CFS cells, the grant will fund the use of 1300 well-known, off-patent drugs to see which is best at restoring the cells to looking like healthy control cells.”

  “Walder considers it likely that several drugs will show promise. If they do, then the option exists to proceed to trials on patients.”

  “If we find a drug that makes ME/CFS cells look like healthy control cells, we immediately know what its safety profile is, what the dosage regimen that works is, any drug-drug interactions that we might need to be careful of, and because it has already been approved and marketed you can go straight to a Phase 2 trial.”

- [385 H] **Dr. Sarah Myhill**, CFS - The Central Cause: Mitochondrial Failure. CFS is **low cardiac output secondary to mitochondrial malfunction**.

  “Low cardiac output explains the symptoms of CFS:
  The job of the heart is to maintain blood pressure. If the blood pressure falls, organs start to fail. If the heart is working inadequately as a pump, then the only way blood pressure can be sustained is by shutting down blood supply to organs. Organs are shut down in terms of priority, i.e. the skin first, then muscles, followed by liver, gut, brain and finally the heart, lung and kidney. As these organ systems shut down, this creates further problems for the body in terms of toxic overload, susceptibility to viruses which damage mitochondria further, thus exacerbating all the problems of the CFS sufferer. This is called POTS Postural orthostatic tachycardia syndrome or POTs.”

  Dr. Myhill explains symptoms: chest pain, effects on the skin (heat intolerance), symptoms in muscles, symptoms in the liver and gut, effects on the brain, effects on the heart, effects on lung and kidney, and gives an explanation of the fatigue problems in CFS patients.

- [386 H] **Dr. Ron Davis**, Emerge Australia 2019 conference video, at 24:53 (Establishing New Mechanistic & Diagnostic Paradigms for ME/CFS).

  Dr. Ron Davis tested several medications on his **Nanoneedle biosensor** (2019). Drugs that make the signal go away are: Copaxone (immune modulator and MS drug) and SS31.

- [387 H] Myalgic Encephalomyelitis/Chronic Fatigue Syndrome in the Era of the Human Microbiome: **Persistent Pathogens Drive Chronic Symptoms** by Interfering With Host Metabolism, Gene Expression, and Immunity, **Amy Proal** and Trevor Marshall, 2018

  Dr. Amy Proal thinks that tissue research is very important. Viruses can hide in tissue and reactivation of viruses is not detectable in the blood.
  “The illness ME/CFS has been repeatedly tied to infectious agents such as Epstein Barr Virus. Expanding research on the human microbiome now allows ME/CFS-associated pathogens to be studied as interacting members of human microbiome communities. Humans harbor these vast ecosystems of bacteria, viruses and fungi in nearly all tissue and blood. Most well-studied inflammatory conditions are tied to dysbiosis or imbalance of the human microbiome.”

"While gut microbiome dysbiosis has been identified in ME/CFS, microbes and viruses outside the gut can also contribute to the illness. Pathobionts, and their associated proteins/metabolites, often control human metabolism and gene expression in a manner that pushes the body toward a state of illness. Intracellular pathogens, including many associated with ME/CFS, drive microbiome dysbiosis by directly interfering with human transcription, translation, and DNA repair processes. Molecular mimicry between host and pathogen proteins/metabolites further complicates this interference. Other human pathogens disable mitochondria or dysregulate host nervous system signaling."

"Antibodies and/or clonal T cells identified in patients with ME/CFS are likely activated in response to these persistent microbiome pathogens. Different human pathogens have evolved similar survival mechanisms to disable the host immune response and host metabolic pathways. The metabolic dysfunction driven by these organisms can result in similar clusters of inflammatory symptoms."

"ME/CFS may be driven by this pathogen-induced dysfunction, with the nature of dysbiosis and symptom presentation varying based on a patient's unique infectious and environmental history. Under such conditions, patients would benefit from treatments that support the human immune system in an effort to reverse the infectious disease process."

- [388 H] Tolerability and Efficacy of **s.c. IgG Self-Treatment** in ME/CFS Patients with IgG/IgG Subclass Deficiency: A Proof-of-Concept Study, **Carmen Scheibenbogen**, 2021

  "Our data indicate that self-administered s.c. IgG treatment is feasible and led to clinical improvement in a subset of ME/CFS patients."

- [389 H, 390 H] OMF ongoing **Study of Thrombospondin-1 (TSP1) in ME / CFS pathogenesis** (STOP-ME)

  "We propose that elevation of circulating thrombospondin-1 (TSP-1), a multifunction protein, in the blood could reduce brain-blood flow in some persons suffering from ME / CFS leading to a brain fog and post-exertional malaise (PEM). Conversely, a rapid decrease in TSP-1 blood levels in some ME/CFS patients could induce a hypotension resulting in orthostatic intolerance or even POTS."

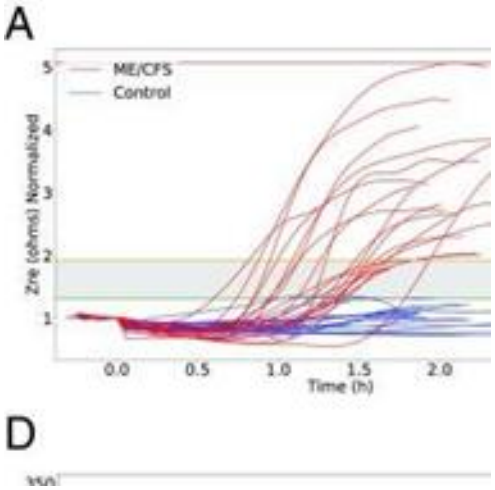
- [391 H] Lessons From Heat Stroke for Understanding Myalgic Encephalomyelitis/Chronic Fatigue Syndrome, Dominic Stanculescu, Nuno Sepúlveda, Chin Leong Lim and Jonas Bergquist, 2021

- [392 H] **Transient Receptor Potential (TRP) ion channels** in ME/CFS: A portrait of discovery – Sonya & Don, 2021

  "Professor Sonya Marshall-Gradisnik and Professor Donald Staines, NCNED, Griffith University, Australia give an overview of their studies. Significant reduction in TMPR3 expression on unstimulated Bright CD56+ NK cell surface. Significant reduction in cytoplastic and storage of calcium Bright CD56+ NK cell surface. Significant reduction in TMPR3 expression in ME/CFS. Confirmed significant changes in expression of TRP on cell surface and calcium entry/storage in cells from ME/CFS patients. TMPR3 function was faulty in 4 separate ME/CFS cohorts. μ-opioid receptor acts as inhibitor on TMPR3 channels. Naltrexone is an opioid antagonist and acts as antagonist to μ-opioid receptor. Naltrexone negates inhibitory effect of the μ-opioid receptor on TRPM3. Naltrexone may promote functional activity of TRPM3 (**LDN** (Low Dose Naltrexone) normalizes this dysfunction)."

Biomarkers

Dr. Ron Davis' Nanoneedle Assay



"Every ME patient shows this response. No healthy control has this response."

- [393 H] Biomarker for chronic fatigue syndrome identified, Stanford Medicine News Center, 2019
- [394 H] A nanoelectronics-blood-based diagnostic biomarker for myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), R.W. Davis, 2019
- [395 H] Red blood cell deformability is diminished in patients with Chronic Fatigue Syndrome, Amit K Saha, Ronald W Davis, 2019

  "We observed from various measures of deformability that the RBCs isolated from ME/CFS patients were significantly stiffer than those from healthy controls. Our observations suggest that RBC transport through microcapillaries may explain, at least in part, the ME/CFS phenotype, and promises to be a novel first-pass diagnostic test."

- [396 H, 397 H] Open Medicine Foundation Project "Improving diagnostic tools for ME/CFS", Dr. Ron Davis, 2021

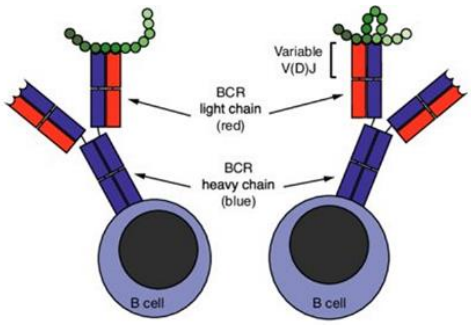
  "OMF has recently funded a project, under my direction, at University of California, Davis to improve a microfluidic diagnostic device to measure red blood cell deformability in people with ME/CFS."

  "Several prior studies have implicated a role of "oxidative" stress in ME/CFS. Red blood cells (RBCs) are potent scavengers of oxidative stress and their shape changes noticeably in response to oxidative stress; this has also been observed in certain inflammatory conditions including obesity and diabetes."

  "The shape of RBCs determines how well these cells can move through blood vessels, so it seems pertinent to determine if RBCs in ME/CFS patients are affected. This has led to the development of a microfluidic device that mimics blood flow through microcapillaries."

  "We are developing a recording device using electrical flow to measure RBC movement and measure differences in cell velocity. It will be inexpensive and easy to operate in different clinical settings, and in a relatively short time."

- [398 H] Discovery of Immune Biomarkers for Myalgic Encephalomyelitis / Chronic Fatigue Syndrome (ME/CFS) based on B cell receptor repertoire analysis, Prof. Takashi Yamamura (National Institute of Neuroscience, NCNP), 2021



B cell receptor（BCR）

- ✓ ME/CFS is characterized by skewed B cell receptor gene usage.
- ✓ Upregulation of specific IGHV genes correlated to infection-related episodes at onset.
- ✓ Plasmablasts of ME/CFS patients upregulated interferon response genes.
- ✓ B cell receptor repertoire analysis can provide a useful diagnostic marker in ME/CFS.

1. "They revealed a previously unknown abnormality of B cell receptor repertoire in ME/CFS.
2. B cell receptor repertoire analysis could provide a useful blood diagnostic test for ME/CFS."

"It has been reported that B cell depletion therapy and immunoadsorption therapy can be effective for some ME/CFS patients. This method could be utilized to develop such immune-targeted therapy for ME/CFS patients." (For Immunoadsorption therapy see Ref. 414 H)

- [399 H] Inability of myalgic encephalomyelitis/chronic fatigue syndrome patients to reproduce VO_2peak indicates functional impairment, Betsy A Keller, 2014

"ME/CFS participants were unable to reproduce most physiological measures at both maximal and ventilatory threshold intensities during a CPET performed 24 hours after a prior maximal exercise test. Our work confirms that repeated CPETs warrant consideration as a clinical indicator for diagnosing ME/CFS. Furthermore, if based on only one CPET, functional impairment classification will be mis-identified in many ME/CFS participants."

- [Ref. 162 H] Plasma proteomic profiling suggests an association between antigen driven clonal B cell expansion and ME/CFS, Milica Milivojevic, Lipkin, Klimas, 2020

"Our findings are consistent with a significant association of ME/CFS with immune dysregulation and highlight the potential use of the plasma proteome as a source of biomarkers for disease."

- [400 H] Cell-Based Blood Biomarkers for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome, Daniel Missailidis, Paul R. Fisher, 2020

"We reported previously that, after recovery from frozen storage, lymphocytes (peripheral blood mononuclear cells, PBMCs) from ME/CFS patients die faster in culture medium than those from healthy controls. We also found that lymphoblastoid cell lines (lymphoblasts) derived from these PBMCs exhibit multiple abnormalities in mitochondrial respiratory function and signaling activity by the cellular stress-sensing kinase Target Of Rapamycin Complex 1 (TORC1). These differences were correlated with disease severity, as measured by the Richardson and Lidbury weighted standing test. The clarity of the differences between these cells derived from ME/CFS patient blood and those from healthy controls suggested that they may provide useful biomarkers for ME/CFS."

"We found that results from three different tests—lymphocyte death rate, mitochondrial respiratory function and TORC1 activity—could each individually serve as a biomarker with better than 90% sensitivity but only modest specificity vís a vís healthy controls. However, in combination, they provided a cell-based biomarker with sensitivity and specificity approaching 100% in our sample."

"This level of sensitivity and specificity was almost equalled by a suggested protocol in which the frozen lymphocyte death rate was used as a highly sensitive test to triage positive samples to the more time consuming and expensive tests measuring lymphoblast respiratory function and TORC1 activity. This protocol provides a promising biomarker that could assist in more rapid and accurate diagnosis of ME/CFS."

- [401 H] A new approach to find biomarkers in chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) by single-cell Raman micro-spectroscopy, Jiabao Xu, M. Potter, Cara Tomas, 2019

  "Single-cell Raman spectra (SCRS) are label-free biochemical profiles, indicating phenotypic fingerprints of single cells. In this study, we applied a new approach using single-cell Raman microspectroscopy (SCRM) to examine ρ0 cells that lack mitochondrial DNA (mtDNA), and peripheral blood mononuclear cells (PBMCs) from CFS patients and healthy controls. The experimental results show that Raman bands associated with phenylalanine in ρ0 cells and CFS patient PBMCs were significantly higher than those of the wild-type model and healthy controls."

  "As similar changes were observed in the ρ0 cell model with a known deficiency in the mitochondrial respiratory chain as well as in CFS patients, our results suggest that the increase in cellular phenylalanine may be related to mitochondrial/energetic dysfunction in both systems."

  "Interestingly, phenylalanine can be used as a potential biomarker for the diagnosis of CFS by SCRM. A machine learning classification model achieved an accuracy rate of 98% correctly assigning Raman spectra to either the CFS group or the control group. SCRM combined with a machine learning algorithm therefore has the potential to become a diagnostic tool for CFS."

- [402 H, 403 H] Cornell, Center for Enervating NeuroImmune Disease, ongoing research projects, *and* Cornell, Center for Enervating NeuroImmune Disease, research project: "Probing the Pathophysiology of ME/CFS through Proteomics and Metabolomics", ongoing study.

  Ongoing research projects: Oxidative Stress in the Brain and Neuroinflammation, Extracellular Vesicles in Regulation of Inflammation and Metabolism, and Gene Dysregulation in the Immune System.

  Ongoing research project: "Extracellular Vesicles in Regulation of Inflammation and Metabolism".

  "By analyzing, in conjunction with physiological data, metabolites, circulating inflammatory molecules, and extracellular vesicle (EV) cargo in blood samples from before and after exercise sessions, we aim to uncover markers and mechanisms of post-exertional malaise in ME/CFS. Our broad survey of possible molecular responses to exercise will include inflammatory proteins and immunogenic mitochondrial DNA fragments, targeted and untargeted metabolomics of blood serum, and a detailed proteomic and metabolomic characterization of EVs."

  "EVs are released into the circulation during exercise and could therefore contain biomarkers or contain cargo that plays an active role in mediating the abnormal response to physical activity in ME/CFS. We expect to provide comprehensive data on metabolomic and proteomic changes associated with post-exertional malaise in ME/CFS that will enable identifications of previously unknown biomarkers and mechanisms associated with this disease."

- [404 H,405 H] Profile of circulating microRNAs in myalgic encephalomyelitis and their relation to symptom severity, and disease pathophysiology, Alain Moreau, November 2020
  + Article about this paper and biomarker: New Test for Chronic Fatigue Syndrome Could Help COVID-19 Patients, December 2020.

  "In order to test a patient, researchers attached an inflatable arm cuff to a patient's arm, which then provided mechanical stimulation. The result causes post-exertional malaise, one of the most common symptoms of ME, and provides an exact molecular signature. This makes it possible to differentiate between ME patients and those without the condition, as well as from patients living with related conditions such as fibromyalgia."

  "Next comes a blood test. The test detected a change in abundance of 11 microRNAs in patients' blood compared with blood drawn before the test. MicroRNAs are small non-coding RNA molecules that act inside cells to regulate gene expression—and have been the subject of research interest as potential diagnostic tools for several conditions."

  "Most of these 11 microRNAs found were involved in regulating immunity, which supports the idea that immune dysfunction plays a key role in ME. The findings are the first step in developing a molecular diagnostic test for the disease."

  "An increase or reduction of some of the microRNAs measured in the test can also help predict the patient's therapeutic response to certain drugs, which improves the chances of finding the right therapy to personalize treatment."

- [406 H] Deep phenotyping of myalgic encephalomyelitis/chronic fatigue syndrome in Japanese population, Toshimori Kitami, 2020

- [407 H] Rethinking ME/CFS Diagnostic Reference Intervals via Machine Learning, and the Utility of Activin B for Defining Symptom Severity, Brett A. Lidbury, 2019

- [408 H, 409 H] "Hand Grip Strength as a Clinical Biomarker for ME/CFS and Disease Severity", Luis Carlos Nacul, Kathleen Mudie, Caroline C. Kingdon, 2018 *and*
  "Hand grip strength and fatigability: correlation with clinical parameters and diagnostic suitability in ME/CFS", Bianka Jäkel, Carmen Scheibenbogen, 2021

  "Hand grip strength (HGS) has been used as an objective measure of muscle strength and fatigue, which is a primary symptom of ME/CFS. HGS is markedly reduced in ME/CFS, particularly in patients with more severe disease, and may indicate muscle and fatigue related symptoms. HGS is a potential diagnostic tool in ME/CFS, and could also be used to enhance patient phenotyping and as an outcome measure following interventions."

  "ME/CFS patients have a significantly lower Fmax and Fmean HGS compared to HC ($p < 0.0001$). Further, Fatigue Ratio assessing decline in strength during repeat maximal HGS measurement (Fmax/Fmean) was higher ($p \leq 0.0012$). The Recovery Ratio after an identical second testing 60 min later was significantly lower in ME/CFS compared to HC (Fmean2/Fmean1; $p \leq 0.0020$). Lower HGS parameters correlated with severity of disease, post-exertional malaise and muscle pain and with higher CK and LDH levels after exertion."

  "Conclusion:
  Repeat HGS assessment is a sensitive diagnostic test to assess muscular fatigue and fatigability and an objective measure to assess disease severity in ME/CFS."

- [410 H] Discovery Forum 2017: Presentation of Dr. Nancy Klimas

  "Deficiency of IL-15 (↓) is a good biomarker. In vitro, when you add IL-15, you completely correct the NK-cell abnormality (NK-cells are ↓ [411 H, 412 H]). This is just one of the many things they found and they get a tremendous signature in ME patients."

- [413 H] Complement Component C1q as a Potential Diagnostic Tool for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Subtyping, Jesús Castro-Marrero, 2021

  "The results show three symptom-based clusters, classified as severe, moderate, and mild, presenting significant differences ($p < 0.05$) in five blood parameters. Unexpectedly the study also revealed high levels of circulating complement factor C1q in 107/250 (43%) of the participants, placing C1q as a key molecule to identify an ME/CFS subtype/subgroup with more apparent pain symptoms. Conclusions: The results obtained have important implications for the research of ME/CFS etiology and, most likely, for the implementation of future diagnosis methods and treatments of ME/CFS in the clinic."

Promising treatments

- [[414] H, [415] H, Ref. 398 H] Immunoadsorption (Prof. Dr. Carmen Scheibenbogen):

  "IA can remove autoantibodies against ß2 adrenergic receptor and lead to clinical improvement. B cell phenotyping provides evidence for an effect of IA on memory B cell development."

- [[416] H] CellTrend Germany, POTS/ME/LongCovid diagnostics.

- [[417] H] Chronic post-COVID-19 syndrome and chronic fatigue syndrome: Is there a role for extracorporeal apheresis? Stefan R. Bornstein, June 2021

  "Extracorporeal apheresis using a special filter seems to be effective in reducing these antibodies in a significant way clearly improving the debilitating symptoms of patients with chronic fatigue syndrome. Therefore, such a form of neuropheresis may provide a promising therapeutic option for patients with post-COVID-19 syndrome. This method will also be effective when other hitherto unknown antibodies and inflammatory mediators are involved."

- [[418] H] BBC News – Dr. Beate Jaeger and Dr. Asad Khan on "Apheresis" Long Covid treatment, 2021

  "Dr. Beate Jaeger has found a successful treatment for Long Covid. Dr. Asad Khan is a patient of hers who went from wheelchair to walking in just a few weeks."

  "Dr. Jaeger uses Heparin extracorporeal LDL precipitation (HELP) apheresis. She explains that they have been doing this treatment in Germany for 37 years now."

  "It is a last resort treatment for patients suffering repeated heart attacks, myocardial infarctions, after heart transplantations, severe peripheral lymph disease and hypercholesterolemia. This treatment eliminates clotting factors, LDL cholesterol, bacterial toxins and cytokines."

- [[419] H] Persistent clotting protein pathology in Long COVID/ Post-Acute Sequelae of COVID-19 (PASC) is accompanied by increased levels of antiplasmin, Etheresia Pretorius, 2021

- [Ref. [410] H] Discovery Forum 2017: Presentation of Dr. Nancy Klimas

  Dr. Nancy Klimas is doing a phase II trial in Gulf War Illness targeting nfKb with curcumin vs liposomal glutathione vs placebo. *Pro-inflammatory nfKb* (nuclear factor κB (NF-κB) *also plays a role in ME/CFS*, so this is interesting.

- [Ref. [410] H] Dr. Nancy Klimas, Reset Homeostasis (Discovery Forum 2017: Presentation of Dr. Nancy Klimas)

- [420 H, 421 H, Ref. 376 H, 377 H, 378 H, 380 H] Cortene, CT38 (Daratumumab): a proprietary peptide agonist, selective/specific for Corticotropin-Releasing Factor Receptor Type 2 (CRFR2).
  Cortene Press Release: "Clinical trial provides preliminary evidence of a cure for myalgic encephalomyelitis / chronic fatigue syndrome (ME/CFS) and Long Covid"
  And "Acute Corticotropin-Releasing Factor Receptor Type 2 Agonism Results in Sustained Symptom Improvement in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome," Gerard Pereira1, Hunter Gillies1, Sanjay Chanda1, Michael Corbett1, Suzanne D. Vernon2, Tina Milani2 and Lucinda Bateman2, September 2021

  "BURLINGAME, CA, September 1, 2021 – Cortene Inc. announces publication of its InTiME clinical trial in which a short subcutaneous infusion of its experimental drug, CT38, achieved sustained symptom improvement in ME/CFS. "The company intends to test CT38 in Long Covid, the post-acute stage of COVID-19 infection, which is considered by many to be the latest trigger for ME/CFS."

  "Cortene believes the CRFR2 pathway is upregulated and therefore overactive, leading to the wide variety of symptoms in ME/CFS."

  "The conventional approach would be to block the overactive pathway," said Sanjay Chanda, PhD, Cortene's Chief Development Officer."

  "Instead, our counterintuitive approach seeks to overstimulate CRFR2, causing it to downregulate, without the need for chronic treatment."

  "CT38 was subcutaneously infused at one of four infusion rates for a maximum of 10.5 hours, in 14 ME/CFS patients. CT38 treatment was safe and generally well-tolerated. It was associated with significant reduction in mean 28-day, total daily symptom score (TDSS), which aggregated 13 patient-reported, daily symptom scores. At an infusion rate of 0.03 µg/kg/h, mean TDSS improved by 26% ($p < 0.01$, $n = 7$)."

  "Infusing CT38 is known to cause temporary cardiovascular changes and InTiME revealed that patients were significantly more sensitive to these changes than healthy subjects from a previous safety study", said Hunter Gillies, MD, InTiME's medical monitor."

  "These data support there being a pathological hypersensitivity in the CRFR2 pathway. Given that InTiME showed i) dose-dependent improvements in TDSS; and ii) additional infusions provide additional benefit, the next trial should test CT38 using longer or additional infusions. While infusion rates are somewhat limited by tolerability, it is total exposure at low rates that appears to drive symptom improvement."

  "The persistent improvement in symptoms over weeks using a limited exposure is encouraging. Many patients are still showing signs of improvement almost 2 years after treatment," said Lucinda Bateman, MD, founder and Medical Director of the Bateman Horne Center, scientific advisor to Cortene, and the Principal Investigator of the InTiME study. "In fact, a few patients expressed a desire for "just a little bit more drug"."

  "Full details of the trial have been peer reviewed and published in Frontiers in Systems Neuroscience, Acute corticotropin-releasing factor receptor type 2 agonism results in sustained symptom improvement in myalgic encephalomyelitis / chronic fatigue syndrome."

  "The publication explains how the CRFR2 pathway controls homeostasis (maintaining biological system stability), how this pathway can become disrupted at the neuronal level leading to the individual symptoms of ME/CFS and how these same symptoms manifest in many other chronic diseases. Cortene plans to conduct additional trials in patients with ME/CFS and other diseases with similar symptoms using well-tolerated infusion rates and greater total exposure."

- [Ref [379] H] InTime: the results of Cortene's CT38 trial, ME/CFS, Michiel Tack, September 12, 2021

  "Unfortunately, we can't conclude much from the findings of the InTime trial except that they contradict claims about a cure for ME/CFS. Although It is great that a pharmaceutical company wants to test a new drug to treat ME/CFS, the results do not look that promising. The researchers stated that they plan to test CT38 using longer or additional infusions in future trials. We can only hope that these will show more encouraging results."

Symptom management

It is understandable that ME patients have many questions. Why do specific symptoms appear? What are the possible underlying pathophysiological mechanisms? And can I do something about them? My “first document” is the result of my search for those possible answers. In addition, all research papers and scientific summaries mentioned here also provide many clues to form your own opinion and answers.

Differences in severity and predominant symptoms can vary, which makes a personalized and holistic approach very suitable. Holistic physicians take the time to unravel and treat different symptoms in 1- or 2-hour long consultations. GPs on the other hand, just have 15 minutes for their patients. This does not mean that GPs cannot help their patients. On the contrary, by using telehealth, by believing in their patients and working together with them, they can be very beneficial and accomplish a lot.

Medical doctors specialized in ME, like the ME/CFS Clinician Coalition, have treatment recommendations which they use in their own practices. I think the medications mentioned can be suggestions and helpful for some patients. Other patients might benefit from totally different treatments. Due to the current lack of a qualified biomarker and a cure, everyone is doing their best to manage symptoms in all kinds of ways. No matter what helps, every little improvement is a win.

Medical disclaimer

All information given in this document is for educational purposes only and is not intended to substitute for professional medical advice or treatment. Always seek the advice of your physician or other qualified health care provider with any questions you may have regarding your health. Any application of the information provided in this document is at the reader’s discretion and is his or her sole responsibility.

General rule of thumb

ME patients tend to be highly sensitive to medications, so start low and go slow.

Medications

- [[422] H] ME/CFS treatment recommendations, ME/CFS Clinician Coalition, Version 1, February 20, 2021

- [[423] H] The US ME/CFS Clinician Coalition Treatment Recommendations, Cort Johnson, Health Rising, 2021

- [Ref. [539] H] Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Essentials of Diagnosis and Management, U.S. Clinical Coalition, August 2021

  "There are many steps that clinicians can take to improve the health, function, and quality of life of those with ME/CFS, including those in whom ME/CFS develops after COVID-19. Patients with a lingering illness that follows acute COVID-19 who do not fully meet criteria for ME/CFS may also benefit from these approaches."

- [[424] H] 10 min. video: "ME & possible treatments/ME & mogelijke behandelingen" - Dr. Charles Shepherd, 2014

- [[425] H] ME Action Encyclopedia, Pain killers

- [[426] H] The ME Association, Symptoms, Testing and Assessment

- [[427] H] Headaches, ME Association UK, Dr Charles Shepherd, 2017

- [Ref. [448] H] Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Essentials of Diagnosis and Management, Lucinda Bateman, MD, 2021

- [[428] H] Latest ME/CFS research, COVID-19 vaccine & illness management, Dr Rosamund Vallings, February 2021, at 20:40 "Potential Medications", at 1:05:47 "studies and benefits of B12 injections"

These are some of the medications mentioned for ME, although not all can be used at the moment: Mestinon/Pyridostigmine (Dr. Systrom), Melatonin, Circadin, Vallergan, Dexamethasone (Dr. Klimas), Cyclophosphamide (Dr Fluge/Mella), Copaxone and SS31 (according to Nanoneedle), sensory overload crash sometimes responds to gentle, low dose benzodiazepines like Lorazepam or Alprazolam, low dose Abilify (Dr. Ron Davis/Whitney Dafoe), [[429]] Low-Dose Dextromethorphan (Dr. Jarred Younger, study result: no good evidence for use), Minocycline (especially in the initial disease stage [[430]]), antivirals like Valganciclovir can work in a small subgroup early-stage ME patients, Rintatolimod (Ampligen), Suramin (Dr. Naviaux), promethazine and fludrocortisone for POTS (Rosamund Vallings, MD) and many more.

- [[431] H, [432] H, [433] H, see also Ref. [422] H] Low-Dose Naltrexone (LDN), recommended for a long time by Dr. Jarred Younger.

  LDN is known to improve symptoms for some ME patients. LDN is also mentioned by Professor Sonya Marshall-Gradisnik for correcting TRPM3 channels [Ref. [392] H] .

- [[434] H, see also Ref. [422] H] Modafinil:

  "It is a narcolepsy drug which is also used to enhance cognitive function. It is often used by people with MS. It gives a physical energy boost. It makes it impossible to pace which can lead to terrible crashes and can lead to a decrease in functionality because of repeated overexerting. Another side effect mentioned is paranoia. Air Force Pilots use it to keep them awake and alert."

- [[435] H, [436] H, see also Ref. [422] H] Gabapentin receptor alpha2delta-1 is a neuronal thrombospondin receptor responsible for excitatory CNS synaptogenesis, Cagla Eroglu, 2009

  "Abstract: Synapses are asymmetric cellular adhesions that are critical for nervous system development and function, but the mechanisms that induce their formation are not well understood. We have previously identified thrombospondin as an astrocyte-secreted protein that promotes central nervous system (CNS) synaptogenesis."

  "Here, we identify the neuronal thrombospondin receptor involved in CNS synapse formation as alpha2delta-1, the receptor for the anti-epileptic and analgesic drug gabapentin. We show that the VWF-A domain of alpha2delta-1 interacts with the epidermal growth factor-like repeats common to all thrombospondins. alpha2delta-1 overexpression increases synaptogenesis in vitro and in vivo and is required postsynaptically for thrombospondin- and astrocyte-induced synapse formation in vitro."

  "Gabapentin antagonizes thrombospondin binding to alpha2delta-1 and powerfully inhibits excitatory synapse formation in vitro and in vivo. These findings identify alpha2delta-1 as a receptor involved in excitatory synapse formation and suggest that gabapentin may function therapeutically by blocking new synapse formation."

- [[437] H] Amitriptyline for Fibromyalgia & Chronic Fatigue Syndrome, Adrienne Dellwo, 2020
  And Dr. Mark Donohoe mentions Low Dose Amitriptyline:

  [Ref. [438] H] The Complexity of Pain Management: Part 2 with Dr Mark Donohoe (at 29:20)

- [[438] H] The Complexity of Pain Management: Part 2 with Dr Mark Donohoe

  "Pain:
  - Low dose Amitriptyline is a low-dose tricyclic antidepressant that may be prescribed to help ease muscle pain.
  - Oxytocin: Due to its analgesic, anxiolytic, antidepressant and other central nervous system effects, there is strong evidence that oxytocin and other drugs acting through the oxytocin receptor could act as multifunctional analgesics with unique therapeutic value.
  - Low Dose Naltrexone"

- [[439] H] Lecture Dr. Nigel Speight, about his experience as a pediatrician and about good effect of Immunoglobulin, 2019

- [Ref [388] H] Tolerability and Efficacy of s.c. IgG Self-Treatment in ME/CFS Patients with IgG/IgG Subclass Deficiency: A Proof-of-Concept Study, Carmen Scheibenbogen, 2021

- [Ref. [155] H] Back to the Future? Immunoglobulin Therapy for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome, Helen Brownlie and Nigel Speight, 2021

  "The findings emerging from this review are supported by clinical observations relating to treatment of patients with severe and very severe ME/CFS, for whom intramuscular and subcutaneous administration provide alternative options."

  "We conclude that:
  1. there is a strong case for this area of research to be revived;
  2. pending further research, clinicians would be justified in offering a course of IgG to selected ME/CFS patients at the more severe end of the spectrum.

  As the majority of trial participants had experienced an acute viral or viral-like onset, we further suggest that IgG treatment may be pertinent to the care of some patients who remain ill following infection with SARS-CoV-2 virus."

- [[440] H] Off label use of **Aripiprazole** shows promise as a treatment for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS): a retrospective study of 101 patients treated with a low dose of Aripiprazole, L. D. Crosby, 2021

  "Dopamine D2 receptor agonists have been shown to mediate neuroinflammation, microglial activation, and cell death in animal models and humans. This suggests that dopamine-modulating drugs like aripiprazole may lead to clinical improvement in fatigue and cognitive symptoms in ME/CFS. Given the lack of approved drugs for treating this condition, we were interested in exploring the potential benefit of low doses of aripiprazole in our Stanford University ME/CFS clinical practice."

  "In summary, the number of positive responders in a group of 101 patients taking aripiprazole was significantly greater than the number of patients who did not respond or had negative experiences. Also, the magnitude of perceived improvement was significant. Some patients failed to observe any benefit, and a small subset of patients experienced side effects that required the medication to be discontinued. Overall, these results suggest that aripiprazole may effectively reduce symptoms of ME/CFS and warrants further investigation in a randomized clinical trial. Exploring the mechanism of action for aripiprazole in neuroinflammatory conditions may also provide new insight into the pathogenesis of ME/CFS."

- [[441] H] Inspiritol – A New Investigational Drug Announced for ME/CFS and Long COVID, Cort Johnson, Oct 30, 2021

- [Ref. [175] H] 2021 Conference - Understanding ME/CFS Today: A Clinical & Research Approach, at 0:00:10 (Dr. Nancy Klimas)

  - "Inflammation (brain and body). Treatments need to cross BBB (e.g. low dose naltrexone, nanocurcumin, omega 3)
  - Bioenergetics (depleted antioxidants, reduced mitochondrial function). Treatments need to cross the BBB (e.g. NAC, intranasal glutathione, others)
  - Poor antiviral function with reduced cytotoxic function, chronic immune activation (bioenergetic approaches, antivirals, control allergens, toxins exposures)
  - Mast cell activation – mast cell stabilizers, nonsedating antihistamines
  - Evidence of viral reactivation (e.g. HHV6, EBV, Coxackie B) – perhaps antivirals
  - Hypercholinergic state with dysautonomia, low blood volume – electrolyte solutions, perhaps low dose beta blockers, midodrine (alpha I agonist)
  - Dysregulation of hypothalamic and pituitary function – deep endocrine evaluation
  - Poor sleep quality – sleep study to rule out upper airway resistance, avoid alpha wave trappers (sedatives) consider low dose TCA (e.g. doxepin 5-10 mg) or melatonin if need be."

- [[442] H, [443] H, [444] H] Larazotide: Publication in Journal of Clinical Investigation Describing Successful Use of Larazotide for Treating Multisystem Inflammatory Syndrome in Children, Lael Yonker, M.D., Massachusetts General Hospital, 2021

  Sylvia: Larazotide is used for leaky gut, IBS and inflammation.

- [[445] H] Treatment and management of chronic fatigue syndrome/myalgic encephalomyelitis: all roads lead to Rome, Jesus Castro-Marrero, 2017

- [446 H] Treatment Avenues in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: A Split-gender Pharmacogenomic Study of Gene-expression Modules,
  Mary G. Jeffrey, M.A., Nancy G. Klimas, M.D., 2019

  "In conclusion, this study supports established literature pointing toward immunologic dysfunction, especially in TNF-α, while identifying potential targets for known pharmaceuticals to inform further research."

- [447 H] Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS): Where will the drugs come from? Peter L. Toogood, 2021

- [Ref. 514 H] European Network on Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (EUROMENE): Expert Consensus on the Diagnosis, Service Provision, and Care of People with ME/CFS in Europe,
  Luis Nacul et al., 2021

- [448 H] Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Essentials of Diagnosis and Management, Lucinda Bateman, M.D., 2021

- [449 H] Biomedical Insights That Inform the Diagnosis of ME/CFS (PDF book download, 2020),
  Brett A. Lidbury and Paul R. Fisher, 2020

  "In practice, pharmacological or non-pharmacological treatments have been directed toward relieving symptoms and improving quality of life."

- [450 H] Antibiotic Treatment of ME/CFS, 2020

  "Research of Professor Kenny De Meirleir (M.D.) focuses on a subgroup of ME patients who show evidence of chronic bacterial infection and gut dysbiosis. These patients are responding to specific antibiotic/ probiotic therapy."

- [451 H] Drug Repurposing I: Antibiotics to Reduce Microglial Activation in ME/CFS and Fibromyalgia?
  Cort Johnson, 2014

- [452 H] M.E. and Enterovirusses, Amy Proal interviewing Dr. John Chia,
  ME Centraal, Dr. Chia talks about medications: Epivir or Lamivudine, IVIG (immunoglobulin), Dihydroquercitine, Remdesivir, and
  Chinese herbs – "Equilibrant" [453] :

  "the primary ingredient is oxymatrine, an immunomodulator which is found within the shrubby sophora (Sophora flavescens) root extract constituent of Equilibrant. Equilibrant also contains the immunomodulatory herbs astragalus, olive leaf, shiitake mushrooms and licorice, as well as Vitamin A, Vitamin D, Calcium and Selenium."

  "Dr Chia finds that the overall response rate of ME/CFS patients to oxymatrine is 52%, and the response rate for Equilibrant is a few percent higher at 56%

Sensitivities

- [454 H] The Effects of Influenza Vaccination on Immune Function in Patients with Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (2012)

- [455 H] Dr. Naviaux, at 42:45 - How vaccination produces changes in sphingolipids, purines, krebs cycle etc. Dr. Naviaux refers to this paper by Li et al:
  [456 H] Metabolic Phenotypes of Response to Vaccination in Humans, Cell, Li et al, 2017

- [457 H] Expert says chronic fatigue syndrome sufferers should be exempt from Covid-19 vaccination, Prof. Warren Tate, 2021

- [458 H] Experts talk COVID-19 vaccine for people with ME/CFS, October 21, Dr. Ros Vallings, Prof. Warren Tate, Dr. Nancy Klimas and Dr. Lucinda Bateman, 2021 by ANZMES

- [459 H] After Vaccination, Health of People with Long Covid More Likely to Improve or Worsen Compared to Controls, You and ME registry by Solve ME/CFS, December 21, 2021

- [460 H] American Myalgic Encephalomyelitis and Chronic Fatigue Syndrome Society (AMMES), COVID-19 and ME/CFS

- [461 H] ME/CFS and FM Experts on Whether to Take the Coronavirus Vaccine – Plus The Vaccine Polls, (i.e. "ME/CFS Expert's Recommendations") Health Rising, Cort Johnson, 2021

- [462 H] To Vaccinate or Not - with ME/CFS, Nancy Klimas, MD, Director, INIM, 2020/2021

- [463 H] Dr. Nancy Klimas discussing what you should do about COVID-19, if you have ME/CFS.

Alcohol intolerance is very common, but is not always mentioned in ME symptom lists.

Energy management and preventing PEM

- [464 H] The Energy Envelope Theory for Patients with ME, by Prof Leonard Jason, 2022

- [465 H] Energy systems and pacing in ME/CFS, Frozen Amber, Dr. Caroline Elisabeth (scientist, writer, and mother with ME/CFS), June 29, 2020

- [466 H] Pacing vs Graded Exercise Therapy, The Academic Battle - in Reality (for both ME/CFS and Long Covid), 2021

- [467 H] Spoon theory

- [468 H] Activity and Energy Management – Pacing (video 2020)

- [469 H] Classic Pacing for a Better Life with ME by Ingebjørg Midsem Dahl

- [470 H] Using a heart rate monitor to prevent PEM in ME/CFS

- [471 H] Lessons from Myalgic Encephalomyelitis/Chronic Fatigue Syndrome for Long COVID Part 4: Heart Rate Monitoring to Manage Postexertional Symptom Exacerbation,
  Todd E. Davenport, Staci R. Stevens, Jared Stevens, Christopher R. Snell, J. Mark Van Ness, 2022

- [472 H] Lessons from Myalgic Encephalomyelitis/Chronic Fatigue Syndrome for Long COVID Part 3: "Energy System First Aid" for People With Postexertional Symptom Exacerbation, Todd E. Davenport, Staci R. Stevens, Jared Stevens, Christopher R. Snell, J. Mark Van Ness, 2022

"

- [473 H] Lessons from Myalgic Encephalomyelitis/Chronic Fatigue Syndrome for Long COVID Part 2: Physiological Characteristics During Acute Exercise Are Abnormal in People With Postexertional Symptom Exacerbation, Todd E. Davenport, Staci R. Stevens, Jared Stevens, Christopher R. Snell, J. Mark Van Ness, 2022

- [474 H] Lessons from Myalgic Encephalomyelitis/Chronic Fatigue Syndrome for Long COVID: Postexertional Symptom Exacerbation is an Abnormal Response to Exercise/Activity, Todd E. Davenport, Staci R. Stevens, Jared Stevens, Christopher R. Snell, J. Mark Van Ness, 2022

- [475 H] Pacing by Numbers: Using Your Heart Rate To Stay Inside the Energy Envelope, Bruce Campbell
- [476 H] Learning to pace, Emerge Australia

- [477 H] Pacing with a Heart Rate Monitor, Emerge Australia

- [478 H] Why Graded Exercise Therapy Doesn't Work - M.E/CFS Recovery: Toby Morrison uses a program with a different, more flexible and holistic approach (amongst others "less is more approach")

- [Ref. 271 H] Blunted heart rate and implications for pacing in ME/CFS.

- [479 H] "Gregg Fisher, who coined the term Aggressive Rest Therapy (ART), describes:

  "The concept of ART is not just to rest when you feel horribly ill or even merely to eliminate "pushing." This is a program of aggressive rest. Even when you feel you have a little energy, you should rest."

  Gregg Fisher, "Chronic Fatigue Syndrome: A Comprehensive Guide to Symptoms, Treatments, and Solving the Practical Problems of CFS."

("No clinical trials have been conducted on the effectiveness of aggressive rest therapy. Only very limited accounts of individual patient experiences exist.")

"Aggressive Rest Therapy (ART) is a management technique where you alternate between rest and activities that are tolerated. The goal is to stay out of PEM and possibly increase your baseline functioning. Rest means lying down in a dark quiet space. No music, no podcasts, no audiobooks, etc. Literally doing nothing but rest."

"Activities are anything else like listening to an audiobook, reading, using Facebook etc. The trick is the timing of the rest and activity periods. This can be 30 minutes of activity and 20 minutes of rest, or 90 minutes of activity and 30 minutes of rest, or 30-30, or 20-60, it is personal, and you will have to find the right balance and see what works best for you."

"Pacing with a Heart Rate Monitoring (HRM) and ART can also work well together. HRM Pacing can help people tackle the tasks that raise their HR (heart rate) the most, break them down and then can help calm the ANS (autonomic nervous system). ART strengthens this by giving the whole body a gentle time out; time to restore and recover. This in turn helps to calm the ANS and can help keep the HR lower, thus helping HRM Pacing."

[480] Interestingly, "the basic rest–activity cycle (BRAC), also called the "ultradian rhythm", is a physiological arousal mechanism in humans proposed by Nathaniel Kleitman, hypothesized to occur during both sleep and wakefulness. Empirically, it is an ultradian rhythm of approximately 90 minutes (80–120 minutes) characterized by different levels of excitement and rest. The cycle is mediated by the human biological clock. It is most readily observed in stages of sleep, for example, rapid eye movement sleep (REM) and the delta activity cycle."

"When awake, brainwaves are faster during the first half of the cycle which corresponds to feeling alert and focused. During the last 20 minutes brainwaves slow and as the body feels dreamy or tired. In this phase the body is being readied for the alertness that comes at the beginning of the following cycle."

Ways that healthcare professionals can help minimize the symptoms

- using telehealth/online consultations or home visits when needed
- keeping lights dimmed
- minimizing strong smells (no perfume)
- reducing noise
- keep in mind that speaking, listening, reading and concentrating is very energy consuming and not always possible for very severe ME patients
- be aware that severe and very severe ME patients need a low-stimulus environment, for example a dark quiet room with interaction at a level of their need (this may be little or no social interaction, calm movements and gestures).

More tips can be found in these 2 links:

- [Ref. [557] H] Tips for Visiting Someone Living with Myalgic Encephalomyelitis, North Carolina/Ohio ME & FM Support, 2019

- [[481] H] 12 basic rules for handling Myalgic Encephalopathy (ME), © Sidsel Kreyberg, Head of The registry for myalgic encephalopathy in Norway

- [[482] H, [483] H] Respiratory influence on cerebrospinal fluid flow – a computational study based on long-term intracranial pressure measurements, Vegard Vinje, 2019

  The importance of breathing for cerebrospinal fluid clearance.

  "Current theories suggest that waste solutes are cleared from the brain via cerebrospinal fluid (CSF) flow, driven by pressure pulsations of possibly both cardiac and respiratory origin."

  "No significant differences in pressure gradient pulsations were found in the sleeping versus awake state. Pressure gradients underlying CSF flow in the cerebral aqueduct are dominated by cardiac pulsations, but induce CSF flow volumes dominated by respiration."

  "Vinje explains why deep, slow breaths have a greater effect on the flow of cerebrospinal fluid than short, shallow breathing. Longer waves bring with them more volume. He believes it can be compared to ocean waves hitting land:
  Imagine a beach with rubbish on it. A long wave will remove debris and clutter on a beach much more effective than a short one. Short, sharp waves will not hit as far up the beach as longer waves of the same height. A tsunami has extremely long waves that cascade far inland, although the wave is not necessarily that much higher."

  "The patients in this study had as many as 15 breaths per minute, on average. This is typically superficial or normal breathing. Vinje points out that breathing is something we can consciously control."

  "Deep breathing can be only five breaths per minute, for example. This is typical in various yoga exercises, says Vinje. Much research has been done on whether and how breathing may have a health-promoting effect. It is not impossible that some of the answers may lie in the influence of breathing techniques on the flow of spinal fluid, which in turn has been linked to the clearance of waste products from the brain, Vinje believes."

- [[484] H] Technology To Improve Quality Of Life, Whitney Dafoe, 28/06/2021

- [[485] H] Book: "How to Be Sick", Tony Bernard, 2010, second edition 2018

  Many ME patients find this book very helpful. The writer, Tony Bernard, has had ME since 2001.

  "Chronic illnesses or conditions – such as arthritis, heart disease, and diabetes (three among dozens) – while not immediately life-threatening, are life-disrupting and stressful. The book is unique in that each chapter contains easy-to-learn tools and practices to help the chronically ill and their caregivers live skillfully, maintain equanimity, and even find joy despite the profound changes in their lives. A recurring theme in the book is that, although one's body may be sick, one's mind can be at peace."

Natural remedies

- [[486] H, [487] H] Mitochondrial Enhancers for ME/CFS and Fibromyalgia, Pt III: Magnesium
  Health Rising, Cort Johnson, 2021
  Mitochondrial Enhancers for Chronic Fatigue Syndrome (ME/CFS) and Fibromyalgia Series, with links to earlier articles about:
  Pt I: D-Ribose, CoQ10 and PQQ
  Pt II: L-carnitine and Acetylcarnitine
  Pt. III: Magnesium
  Pt IV: N-acetyl cysteine (NAC)

- [488 H] Effect of Dietary Coenzyme Q10 Plus NADH Supplementation on Fatigue Perception and Health-Related Quality of Life in Individuals with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: A Prospective, Randomized, Double-Blind, Placebo-Controlled Trial, Jesús Castro-Marrero, 2021

  "A significant reduction in cognitive fatigue perception and overall FIS-40 score ($p < 0.001$ and $p = 0.022$, respectively) and an improvement in HRQoL (health-related quality of life (SF-36)) ($p < 0.05$) from baseline were observed within the experimental group over time. Statistically significant differences were also shown for sleep duration at 4 weeks and habitual sleep efficiency at 8 weeks in follow-up visits from baseline within the experimental group ($p = 0.018$ and $p = 0.038$, respectively). Overall, these findings support the use of CoQ10 plus NADH supplementation as a potentially safe therapeutic option for reducing perceived cognitive fatigue and improving the health-related quality of life in ME/CFS patients."

- [489 H, 490 H] Novel Microbiome Therapeutics, Shahram Lavasani Ph.D., 2021 (RME conference Sweden, 14-10-'21, video recording on their YouTube channel)

  "ImmuneBiotech discovers and develops novel probiotics for therapeutic effect based on lactic acid bacteria and symbiotic formulations targeting gut microbiota and the immune system. We deliver transformational solutions to modulate the microbiome, heal leaky gut and reduce inflammation to prevent and treat autoimmune and other chronic inflammatory conditions."

- [491 H] Neurochemical abnormalities in chronic fatigue syndrome: a pilot magnetic resonance spectroscopy study at 7 Tesla, Beata R. Godlewska, 2021

  "The changes in glutathione and creatine are consistent with the presence of oxidative and energetic stress in CFS patients and are potentially remediable by nutritional intervention. A reduction in myo-inositol would be consistent with glial dysfunction. However, the relationship of the neurochemical abnormalities to the causation of CFS remains to be established, and the current findings require prospective replication in a larger sample."

- [492 H, 493 H] Dr. Naviaux mentions that they will start a trial with Enol-Oxaloacetate (see at 13:30). More info on the product "benaGene" (Oxaloacetate): "How Oxaloacetate CFS may Help with ME/CFS".

  "Oxaloacetate is an energy metabolite found in every cell of the human body. It holds a key place in the Krebs Cycle within the mitochondria, providing energy to the cells. It is also a critical early metabolite in gluconeogenesis, which provides glucose for the heart and brain during times of low glucose."

  "Oxalacetic acid can be found in a number of food items such as daikon radish, sacred lotus, cucurbita (gourd), and tarragon, which makes oxalacetic acid a potential biomarker for the consumption of these food products."

- [494 H, 495 H, 496 H] Creatine and Creatinine Metabolism, Markus Wyss, and Rima Kaddurah-Daouk, 1 July 2000 (Methylation and Creatine etc.).

- [497 H] 10 tips for getting started on a ketogenic diet with ME/CFS, Frozen Amber/Caroline Elizabeth Christian, December 18, 2019

Information for physicians/health care providers

- [[498] H] ME International, A medical practitioners guide for diagnosing and treating Myalgic Encephalomyelitis (ME), page 2:

  "Severe ME constitutes a major challenge, not only for the patient and the family, but also for the doctor confronted with it, often for the first time. It requires from the doctor commitment, calmness, courage and compassion, indeed many of the qualities of the ideal doctor." Dr. Nigel Speight (2021)

- [[499] H] Health Care Responsibility and Compassion-Visiting the Housebound Patient Severely Affected by ME/CFS, Caroline Kingdon, 2020 [see also Ref. [500] H, [501] H]

  "Many people with severe Myalgic Encephalopathy/Chronic Fatigue Syndrome (ME/CFS) commonly receive no care from healthcare professionals, while some have become distanced from all statutory medical services."

  "Paradoxically, it is often the most seriously ill and needy who are the most neglected by those responsible for their healthcare. Reasons for this include tensions around the complexity of making an accurate diagnosis in the absence of a biomarker, the bitter debate about the effectiveness of the few available treatments, and the very real stigma associated with the diagnosis."

  "Illness severity often precludes attendance at healthcare facilities, and if an individual is well enough to be able to attend an appointment, the presentation will not be typical; by definition, patients who are severely affected are home-bound and often confined to bed."

  "We argue that a holistic model, such as "Compassion in Practice", can help with planning appointments and caring for people severely affected by ME/CFS. We show how this can be used to frame meaningful interactions between the healthcare practitioners (HCPs) and the homebound patient."

- [[502] H] Elements of Suffering in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: The Experience of Loss, Grief, Stigma, and Trauma in the Severely and Very Severely Affected, Patricia A. Fennell, Nancy Dorr and Shane S. George, 2021

  This MDPI article describes how ME impacts all facets of life.

  Sylvia: A paper worth reading, but in my opinion, one should keep in mind that ME patients can react differently, so a personalized approach is always best. Secondly, the scientists of this paper are apparently unaware that most ME patients are not able to tolerate alcohol at all.

- [[503] H] MGH Institute of Health Professions, "Students Hear of Little-Known Illness". Myalgic Encephalomyelitis, also known as Chronic Fatigue Syndrome, is topic at 2019 Caldwell Interprofessional Rounds.

  Panelists (l-r):
  Dr. Ronald Tompkins, Lisa Hall, RN, Robie Robitaille and Rivka Solomon, January 22, 2019.

- [[504] H] "Dialogues for ME/CFS", Natalie Boulton and Josh Biggs

  "The collection of videos covers a variety of topics, giving a multi-faceted understanding of the disease from the perspectives of medical professionals, exercise scientists, and research professionals specializing in ME/CFS. Importantly it also features the experiences of patients and carers – with about a dozen patients interviewed, including donors from the UK ME/CFS Biobank and patient

advocates. The project is a resource which appears to be filling a gap, as the videos are being hosted or linked to by UK charities (ME Research UK and ME Association) and included in medical education resources both in the UK and the US. (Study PRN continuing professional education, the US ME/CFS Clinicians Coalition, Workwell Foundation and Healthcare Special Issue: Severe ME)."

- [505 H] Severe and very severe ME, Contributors to the Severe & Very Severe ME/CFS videos: Dr Nigel Speight, Dr William Weir, Dr Luis Nacul, Dr Nina Muirhead, Mrs Caroline Kingdon, Dr Charles Shepherd, Prof Todd Davenport and patients and carers

  "Very severe ME/CFS can be a very frightening disease, not only for the family and carers of the severely ill patient, but also for doctors who are unlikely to have any previous experience of these most severe presentations. Patients can die from very severe ME/CFS and its complications, and this is more likely to happen when their condition is badly managed by ill-informed doctors. It is important that doctors listen to the patient, or if the patient wishes, to their carers. Specialist help should be available for these very severe cases."

- [506 H] Caring for the Patient with Severe or Very Severe Myalgic Encephalomyelitis/Chronic Fatigue Syndrome, Jose G. Montoya, 2021

  "ME/CFS can cause a wide range of severity and functional impairment with the most severely ill homebound and bedbound, sometimes in need of total care. Yet, as sick as they are, these patients are often not seen by medical providers because they cannot travel to doctors' offices. Some patients no longer try because they have previously faced disbelief or received treatment recommendations that made them worse."

  "For their part, primary care providers may not have seen this level of debility before. They often lack accurate information on the nature of the disease and how to care for patients with severe or very severe ME/CFS, a problem compounded by the lack of research on these patients."

  "Caring for such vulnerable patients requires a patient-centered, collaborative approach in all clinical interactions, one that is grounded in compassion, humility, and respect for the nature and severity of the patient's disease. Use of carefully selected pharmacological and non-pharmacological treatments and management approaches can help protect against worsening of the patient's health while decreasing symptom burden and improving the patient's quality of life."

  "Partnerships with the patient, the caregiver and a targeted network of providers along with use of enablers such as telemedicine and remote monitoring are key to providing the needed care without overwhelming either the patient or the busy provider. Using these approaches, the primary care provider can make a significant difference in the lives of these underserved patients."

- [507 H] Excerpt from "Why we do it", website Doctors with ME:

  "High quality evidence-based care is worse than rare – the disease is largely unaddressed or mismanaged, at best. Despite being common and having clear diagnostic criteria, the empirical consensus documents unusually low levels of understanding amongst medical professionals of ME epidemiology, disability and management. Current norms versus ME are analogous to prejudices that were previously psychologised versus other physical conditions, such as multiple sclerosis, asthma or autism."

  "ME patients are not just unusually neglected. Quality of life scores are shocking – worse than nearly all conditions encountered in primary and secondary care (with little difference in emotional or mental health, despite repeated confirmation of ME as a greater physical disability). They are unusually vulnerable, often with little physical capacity to address issues that affect them, implying the need for additional care in clinical frontline services and administrative contexts..."

- [508 H] Doctors' knowledge and understanding of Myalgic Encephalomyelitis, Dr. K.N. Hng, 2018

- [509 H] An Audit of UK Hospital Doctors' Knowledge and Experience of Myalgic Encephalomyelitis, Keng Ngee Hng, Keith Geraghty and Derek F. H. Pheby, 2021

- [510 H] Short video: "Hospital Admission, Issues and alternatives for severely ill ME/CFS patients", Dialogues for ME.

  "While it may be understood from a written page that the severe and very severe ME/CFS patient should receive advanced medical care outside of the hospital setting, this video brings the depth of understanding and acceptance of this concept to the viewer's core. A must see for physicians accepting the responsibility for these patients and a must see for carers confronting the decision as to whether the patient in their care needs to go to hospital and, if so, how best to manage it."

- [511 H] Medical School Education on Myalgic Encephalomyelitis, Nina Muirhead, 2021

  "This exploratory study reveals inadequacies in medical school teaching on ME/CFS. Many medical schools (64% of respondents) acknowledge the need to update ME/CFS education by expressing an appetite for further educational materials. The General Medical Council (GMC) and Medical Schools Council (MSC) are called upon to use their considerable influence to bring about the appropriate changes to medical school curricula so future doctors can recognise, diagnose and treat ME/CFS. The GMC is urged to consider creating a registered specialty encompassing ME/CFS, post-viral fatigue and long Covid."

- [512 H] Royal College of Physicians, "Doctors believe in ME", Dr. Nina Muirhead, 2021

- [513 H] Medical Board of California News, Myalgic Encephalomyelitis/Chronic Fatigue Syndrome and Long COVID: What Every Physician Needs to Know, 2021

- [514 H] European Network on Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (EUROMENE): Expert Consensus on the Diagnosis, Service Provision, and Care of People with ME/CFS in Europe, Luis Nacul, 2021

- [515 H] Confronting Our Next National Health Disaster — Long-Haul Covid, Steven Phillips, M.D., M.P.H., and Michelle A. Williams, Sc.D., June 30, 2021

  "The relationship of long Covid to ME/CFS has been brought into focus by the CDC, the NIH, the WHO, and Anthony Fauci, the chief medical advisor to President Joe Biden and director of the National Institute of Allergy and Infectious Diseases. Going forward, research may yield complementary insights into the causation and clinical management of both conditions. The CDC has developed guidelines and resources on the clinical management of ME/CFS that may also be applicable to patients with long Covid."

- [516 H] AMA Journal of Ethics, The Importance of Listening in Treating Invisible Illness and Long-Haul COVID-19, Dorothy Wall, MA, 2021

- [517 H] Article in The Guardian – "I felt betrayed": how Covid research could help patients living with chronic fatigue syndrome - includes stories of health care professionals giving insight, June 2021

- [518 H] US ME/CFS Clinician Coalition Letter: Post-COVID "Long Haulers" and ME/CFS, October 30, 2020

- [519 H] Medical Societies and new Komaroff-Lipkin Paper Highlight Long COVID and ME/CFS Links, by David Tuller, DrPH, July 2021

- [520 H, 521 H, 522 H] A Comprehensive Examination of Severely Ill ME/CFS Patients, Chia-Jung Chang, Ronald W. Davis, September 2021

  Open Medicine Foundation:
  "The goal of this Severely Ill Patient Study (SIPS) is to better characterize these patients' clinical conditions and discover the underlying biological abnormalities causing the symptoms. In this first publication, we reported the results of a comprehensive examination of the symptoms and clinical laboratory tests of the patients. The quality of life of the SIPS patients was negatively correlated with that of clinical depression."

  "The most troublesome symptoms included fatigue (85 percent), pain (65 percent), cognitive impairment (50 percent), orthostatic intolerance (45 percent), sleep disturbance (35 percent), post-exertional malaise (30 percent), and neurosensory disturbance (30 percent)."

  "Sleep profiles and cognitive tests revealed distinctive impairments. Lower morning cortisol levels and alterations in its diurnal rhythm were observed in the patients, and antibody and antigen measurements showed no evidence for acute infections by common viral or bacterial pathogens. These results highlight the urgent need to develop molecular diagnostic tests for ME/CFS. In addition, there was a striking similarity in symptoms between long COVID and ME/CFS. This underscores the value of research to understand the mechanisms of ME/CFS for efforts to treat and prevent long COVID and other debilitating post-viral conditions, which together affect millions in the United States alone."

  Michiel Tack:
  "The authors note: "While physical functioning, energy/fatigue, and related functioning were extremely low in these patients, emotional well-being was clearly less impacted – a clear distinction from the frequent misdiagnosis of clinical depression in these patients."

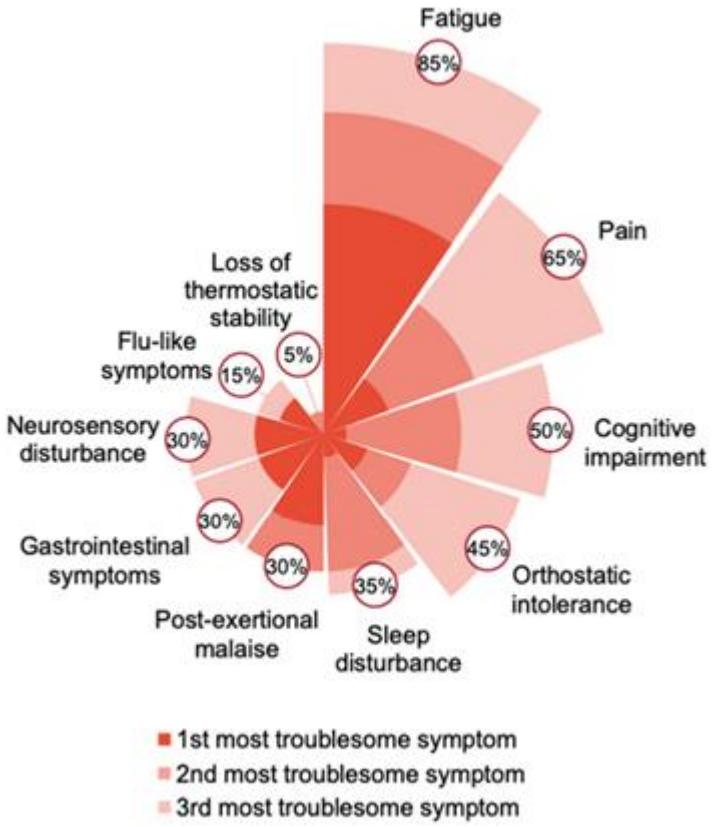
  "The authors tested all sorts of antibody and antigen tests of viral and bacterial pathogens but these were no different in patients versus controls. They also tested some popular blood tests done in ME/CFS patients such as Lymphocyte subsets, Natural Killer Cell function, hormones (TSH/T3/T4, FSH/LH, testosterone, estrogen…), vitamins (B12/folate...) but these also showed no significant differences."

  "The most striking difference between severe ME/CFS and the controls was seen in salivary cortisol levels. These were significantly lower in patients during the morning."

  "Non-invasive sleep monitoring suggested that most of the severely ill patients had an abnormally high number of awakenings and abnormally long wake time after sleep onset."

  "Cognitive tests showed slower reaction times and problems with identifying emotions."

  "The researchers also asked which symptoms patients found most disturbing. Fatigue and pain (and not post-exertional malaise) came out on top as the graph below shows:



Researchers interested in learning more: the data of the Severely Ill Patient Study has been made available through a web-based data portal at: https://endmecfs.stanford.edu "

- [523 H] Interview with Dr. Nina Muirhead, Director in Doctors with ME, and Dr. David Strain, Medical Advisor for Action for ME (13 min.), ME/CFS and the pause of NICE Guidelines - Woman's Hour - BBC Radio 4.

- [524 H] New 10-minute professionally made video, Dialogues, "Prologue to Dialogues for a neglected illness ME/CFS-2021. NICE - a turning point becomes a debacle".

- [525 H, 526 H, 527 H] "The most severe ME patients: disease burden and public assistance services" (original title: "De alvorligste ME syke: sykdomsbyrde og hjelpetilbud"), Norwegian ME Association, Trude Schei, Arild Angelsen, Elin Myklebust, 2019

  Worth reading. Please use document translate for the full English version, or you can read the English summary [Ref. 525 H] .

  "That 2 out of 3 severe ME patients have had such negative experiences with actors in the health care system that they do not dare or want to contact them again is one of the most serious findings in the report."
  - "The sickest are so ill that if it was another disease, one would think they were dying, but they live that way, year after year – without being able to move, without being able to communicate, with great pain," says Trude Schei".
  - "Mette and her two children have ME: - You work in the dark and must be careful"
  - Article: "New report on ME: Among the sickest in Norway and do not get enough medical help"
  - Article: "New report on severe ME: - They've been left out in the cold", ABC Nyheter, 2019

- [528 H] Disease progression in ME – A large survey amongst Norwegian patients, ME Foreningen Norway, Arild Angelsen and Trude Schei, 2019

Primers and handouts

- [[529] H] International Consensus Primer Adult & Paediatric: For Medical Practitioners, 2012 Authors - International Consensus Panel: Carruthers BM, van de Sande MI, De Meirleir KL, Klimas NG, Broderick G, Mitchell T, Staines D, Powles ACP, Speight N, Vallings R, Bateman L, Bell DS, Carlo-Stella N, Chia J, Darragh A, Gerken A, Jo D, Lewis D, Light AR, Light K, Marshall Gradisnik S, McLaren-Howard J, Mena I, Miwa K, Murovska M, Steven S, Co-Editors: Carruthers B. M. & van de Sande M. I. © Copyright 2012: Carruthers & van de Sande

- [[530] H] NICE ME/CFS 2021: Q&A summary for GPs, DoctorsWithME, 2021

- [[531] H] ME/CFS: A Primer for Clinical Practitioners, 2014 Edition (based on SEID criteria)

- [[532] H] Pediatric ME/CFS: Fact Sheet for Healthcare Professionals, CDC

- [[533] H] Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Diagnosis and Management in Young People: A Primer, Peter C. Rowe, 2017

- [[534] H] Initiating Care of a Patient With Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS), Charles W Lapp, 2019

- [[535] H] A Guide for GPs Completing an Access Request Form, Emerge Australia, September 2018

- [[536] H] Severe ME in Children, Dr. Nigel Speight, 2020

  Dr. Speight shares his experience; challenges for the doctor faced with a case of severe ME/CFS, lessons learned, how not to manage severe ME/CFS, etc.

- [Ref. [439] H] Lecture, Dr. Nigel Speight, sharing his experience as a pediatrician, 2019

- [[537] H] Testing Recommendations for suspected ME/CFS, U.S. ME/CFS Clinical Coalition, Version 1, 2021

- [[538] H] Diagnosing and treating Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS), U.S. Clinical Coalition, Version 2, July 2020

- [[539] H, [540] H] Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Essentials of Diagnosis and Management, U.S. Clinical Coalition, August 25, 2021

- [[541] H] Supporting people with severe Myalgic Encephalomyelitis, Nursing Standard, Crowhurst G., 2005

- [[542] H] Questionnaire for diagnosing ME, using the ICC criteria, ME Advocacy, 2016

- [[543] H] DIAGNOSIS OF ME/CFS, The importance of having an early and accurate diagnosis, Dr Charles Shepherd, 2020
- [Ref. [27] H] Diagnosis & management of myalgic encephalomyelitis, ME Action

- [[544] H, [545] H] "Hours of upright activity (HUA)" diagnostic tool and wearable development (a method to test the severity of ME), Bateman Horne Center, 2020

- [[546] H] , Ref. [273] H, Ref. [274] H, Ref. [275] H, Ref. [276] H] 10-Minute NASA Lean Test, Clinician Instructions (to test Orthostatic Intolerance in a GP's office), Bateman Horne Center

- [547 H] Orthostatic Intolerance* Questionnaire (OIQ), Orthostatic Intolerance* Daily Activities Scale (OIDAS), Bateman Horne Center, 2012 (*We have substituted the word "intolerance" for "hypotension" in this questionnaire)

- [548 H] Upright Activity and Exercise Intolerance: Critical Concepts in the Evaluation of Chronic Fatigue, Lucinda Bateman, MD, October 2019

- [549 H] Healthcare Provider Toolkit, CDC

- [550 H] (3-minute video) "ME and PEM", (Once you've understood what PEM is about, you'll know a lot more about the debilitating chronic disease ME), Norwegian ME Association, 2020

- [551 H] Managing Post-Exertional Malaise (PEM) in ME/CFS, CDC

- [552 H] Pacing and management guide for ME/CFS, ME Action

- [Ref. 498 H] A medical practitioners guide for diagnosing and treating Myalgic encephalomyelitis (ME), Based on the International Consensus Criteria (ICC) and International Consensus Primer (ICP) 2012, ME International

- [553 H] Basics for treating Myalgic Encephalomyelitis (ME) - What Should be included in Medical Textbooks Based on Expert and Patient Experience, North Carolina/Ohio ME & FM Support Group, 2019

- [554 H] An Introduction For Physicians and Patient To Modern SPECT Technology, Simon Lawrence, 2021

- [555 H] Handouts for cardiologists, neurologists, immunologists and emergency room, ME International

- [556 H] ME/CFS Surgery and Anesthesia Recommendations, Charles W. Lapp, MD, Feb 2020

- [Ref. 531 H] Recommendations for persons with ME/CFS prior to surgery, International Association for ME/CFS. Primer for clinical practitioners, 2014 Edition (page 30)

- [557 H] Tips for Visiting Someone Living with Myalgic Encephalomyelitis, North Carolina/Ohio ME & FM Support, 2019

- [558 H, 559 H] "Post-viral ME/CFS, Diagnosing & Treating ME/CFS in the time of COVID" *and* "Resources: Post-viral ME/CFS", Dr. Lucinda Bateman, MD, Dr. Katherine Rowe, MD, Dr. Mark VanNess, PhD

- [560 H] Wetenschap voor Patienten - ME/cvs Vereniging, series of 6-10 min video interviews with ME experts on all kinds of topics.

- [561 H] Treating COVID-19 in patients with ME/CFS & severe FM, Bateman Horne Center, Dr. Lucinda Bateman

- [562 H] Long COVID & ME, understanding the connection, ME Action

- [563 H] Treating COVID-19 in patients with ME/CFS & severe FM, Dr. Lucinda Bateman, Bateman Horne Center, 2021

- [564 H] Index of ME/CFS Published Research, An A-Z index of the most important published research, 1 st January 2022, The ME Association

- [565 H] For healthcare professionals – Learn about M.E., Action for M.E.

- [566 H] Medical considerations when treating urgently ill patients with underlying myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), Bateman Horn Center, 2022

- [567 H] MEDICAL MATTERS with Dr Charles Shepherd, Q&A, Medical Matters features questions asked by Members of the ME Association on health-related topics, 2022

Norway:

- [568 H] An offer to severe ME patients in Norway

- [569 H] Project "Adapted education for ME patients, a good way to social inclusion and improved quality of life" and the associated toolbox prepared by the Norwegian ME Association Rogaland Fylkeslag.
  The project now includes Norway, Denmark, Finland and Sweden.
  The toolbox is relevant for everyone in the school system (teachers, counselors, school nurses) who is in contact with students with ME.

Accredited ME learning modules for physicians/health care providers (CPD/CME)

I would like to recommend General Practitioners to start with the two modules from ThinkGP.

- [570 H] Busting the myths and redefining myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), ThinkGP Australia, 2020

- [571 H] Ensuring a patient-centered approach to care for people living with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), ThinkGP Australia, 2021

- [572 H] Myalgic Encephalomyelitis / Chronic Fatigue Syndrome CPD, FREE online resource composed of 10 clinical cases assessing your knowledge of ME/CFS. You'll receive 1 hour of CPD on successful completion of the resource. Author: Dr Nina Muirhead, 2020

- [573 H] Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Test Your Strengths and Gaps in Knowledge, Author: Dr. Nancy Klimas, MD, 2020

- [574 H] Diagnosing Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: The Experts Weigh In Authors: Lucinda Bateman, MD; Natalie Azar, MD; Nancy Klimas, MD; José Montoya, MD, 2020

- [575 H] Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: A Case-Based Learning Module Authors: Stephen J. Gluckman, MD, 2020

- [576 H] ME/CFS Part 1: Introduction and Identification, Part 2: Etiology and Analeptic Management, presented by Todd Davenport, PT, DPT, MPH, OCS, Staci Stevens, MA, and Mark VanNess, PhD

- [577 H] Clinical Education Initiative, Post-Viral Syndrome and Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS): What Every Clinician Needs to Know, David Kaufman, MD, Release Date: 9/30/2020, Termination Date: 09/30/2023

- [578 H] Watch Unrest and Receive Continuing Medical Education (CME / CE) Credit

- [579 H] New Zealand Doctor HOW TO TREAT article, MYALGIC ENCEPHALOMYELITIS / CHRONIC FATIGUE SYNDROME, 1 CPD credit (free access code: CFS), 2021

  “Myalgic encephalomyelitis/chronic fatigue syndrome is a common, debilitating and costly disease. Diagnosing and managing complex chronic conditions such as this is not easy with a 15-minute consultation, but this article, by Cathy Stephenson and Rose Silvester, provides a framework of evidence-based information for GPs working with patients with ME/CFS.”

- [580 H] Medscape CME & Education - A Fresh Look at Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Diagnosis and Management of a Multisystem Illness,
  Authors: Benjamin Natelson, MD; Donna Felsenstein, MD; Mitchell Miglis, MD; Dale Strasser, MD, CME / ABIM MOC / CE Released: 12/21/2021, Valid for credit through: 12/21/2022

Reviews and important changes

- [Ref. [2] H, [581] H, [582] H, [583] H] ***2015 - Institute of Medicine report***
  The committee revied more than 9000 research articles.
  Key findings:
  - "Between 836,000 and 2.5 million Americans suffer from myalgic encephalomyelitis/chronic fatigue syndrome."
  - ME "is a ***medical*** - not a psychiatric or psychological - ***illness***"
  - "This disease is characterized by profound fatigue, cognitive dysfunction, sleep abnormalities, autonomic manifestations, pain, and other symptoms that are made worse by exertion of any sort."
  - "Many people with ME/CFS report difficulty completing everyday tasks, and at least one quarter have been home- or bed-bound at some point as a result of their illness."
  - "The total economic costs of ME/CFS are estimated at $17 to $24 billion annually."
  - "ME/CFS can severely impair patients' ability to conduct their normal lives."

- [[584] H, [585] H, [586] H, [587] H, [588] H] ***2020 – Draft Changes in NICE Guidelines (Final guidelines expected August 18, 2021)***

- [[589] H, [590] H, [591] H, [592] H] ***August 17, 2021: NICE pauses publication of updated guideline on diagnosis and management of ME/CFS***
  Some highlights:
  "Section 1.11.16 Do NOT offer people with ME/CFS:
  - any therapy based on physical activity or exercise as a treatment or cure for ME/CFS
  - generalised physical activity or exercise programmes – this includes programmes developed for healthy people or people with other illnesses
  - any programme based on fixed incremental increases in physical activity or exercise, for example graded exercise therapy
  - structured activity or exercise programmes that are based on deconditioning as the cause of ME/CFS
  - therapies derived from osteopathy, life coaching and neurolinguistic programming (for example the Lightning Process)."

  "Section 1.3.1 When ME/CFS is suspected, give people personalised advice about managing their symptoms.
  Also advise them:
  - not to use more energy than they perceive they have − they should plan their daily activity to stay within their energy envelope and not push through activity
  - to rest as they need to
  - to maintain a healthy balanced diet, with adequate fluid intake."

  "The way in which activity-induced fatigue is described in Long Covid is no different to that found in ME/CFS. This is hardly surprising as they are both extremely debilitating post-viral conditions." *
  "Section 1.8.4 Service providers should be proactive and flexible in delivering services to people with severe or very severe ME/CFS, who may have particular difficulty accessing services and articulating their needs. This could include home visits, online consultations, written communication, and supporting their applications for aids and appliances."

  * *Sylvia*: Several ME organizations are currently doing research on Long Covid and ME/CFS; amongst others, Solve M.E. and The Open Medicine Foundation [[593] H, [594] H, [595] H, [596] H, [597] H, [598] H, [599] H, Ref. [371] H] .

- [600 H] Myalgic encephalomyelitis (or encephalopathy)/chronic fatigue syndrome: diagnosis and management
  NICE guideline [NG206] Published: 29 October 2021
  Some highlights:
  "1.11.14
  Do not offer people with ME/CFS:
  - any therapy based on physical activity or exercise as a cure for ME/CFS
  - generalised physical activity or exercise programmes – this includes programmes developed for healthy people or people with other illnesses
  - any programme that does not follow the approach in recommendation 1.11.13 or that uses fixed incremental increases in physical activity or exercise, for example, graded exercise therapy (see box 4)
  - physical activity or exercise programmes that are based on deconditioning and exercise avoidance theories as perpetuating ME/CFS.

  1.12.27
  Do NOT offer the Lightning Process, or therapies based on it, to people with ME/CFS
  1.12.28
  Discuss cognitive behavioural therapy (CBT) with adults, children and young people with ME/CFS (and their parents or carers, as appropriate).
  Explain its principles, including that it may help them manage their symptoms but it is NOT curative"

- [601 H] AN ME ASSOCIATION SUMMARY OF THE 2021 NICE CLINICAL GUIDELINE FOR ME/CFS, ESSENTIAL INFORMATION FROM THE NEW NICE GUIDELINE, ME Association, December 2021

- [602 H] NICE, Media & Statements, Sissel Sunde, November 1, 2021

- [603 H] Dialogues for a neglected illness (Dialogues for ME/CFS), Natalie Boulton and Josh Biggs, "A dangerous model abandoned as NICE seeks to reform care for ME/CFS patients in 2021" (11-minute video, explaining the changes)

May 2021 - WHO Changes diagnostic code for ME
ICD-11 for Mortality and Morbidity Statistics (Version: 05/2021)

- [604 H] WHO has now removed "benign" from ME, CFS and Postviral Fatigue Syndrome in the new diagnostic system ICD-11. The new code is called 8E49 and replaces the current G93.3.
  "Code 8E49 Postviral Fatigue Syndrome:
  - Other disorders of the nervous system

  Inclusions:
  - chronic fatigue syndrome
  - myalgic encephalomyelitis

  Exclusions:
  - Fatigue (MG22)"

Medical harm, GET, CBT and Lightning Process

Harmful treatments originating from the biopsychosocial model "The Mental Health Movement", GET, CBT and Lightning Process are still being used by ignorant health care professionals.

- [605 H] Articles on ME/CFS by Professor Malcolm Hooper and Margaret Williams 1986-2019

  "A collection of articles by Margaret Williams and Professor Malcolm Hooper together with related documents written by other people (for example, the Countess of Mar, Professor George Szmukler, Professor Simon Wessely, Professor Michael Sharpe, as well as official reports and the PACE trial protocol). These articles have been available on the internet or elsewhere for many years but now for the first time have been brought together in one place. The intention is to provide a valuable historical resource for researchers, advocates, patients and anyone interested in the illness Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. These articles illustrate how the "Wessely School" have ignored the biomedical science on ME/CFS for almost 30 years."

- [606 H, 607 H, 608 H] The Mental Health Movement: Persecution of Patients? Malcom Hooper, 2003

  "A consideration of the role of Professor Simon Wessely and other members of the "Wessely School" in the perception of Myalgic Encephalomyelitis (ME) in the UK."

  "The document gives illustrations of the implementation of the Wessely School policy and describes amongst others the gross and barbaric abuse of patients/children with ME (Ean Proctor, page 12)."

  "The Mental Health Movement describes how the neurological illness myalgic encephalomyelitis has been incorrectly portrayed as a mental health condition, and the resulting effects on patients' health care, restrictions or denial of access to social security (for example, disability benefits), medical neglect and medical abuse, and forced treatment using controversial therapies."

- [609 H] MEpedia, Medical gaslighting, Forced treatment.

  "The belief of some health professionals that ME/CFS is entirely or partly psychological/behavioral in nature has led to some patients, including children, being forcibly admitted to locked psychiatric units in order to force them to participate in treatment that had previously declined."

  "Concerns over forced treatment of severely ill ME patients has led to some charities to produce advise for patients and carers about how to avoid unnecessary and harmful forced psychiatric admission. Patients known to have been subjected to inappropriate forced treatments in psychiatric units include Sophia Mirza, who died of M.E. just a few months after being released and Karina Hansen, who was later found to have been illegally detained."

  "ME/CFS is not classified as a psychological disorder, so patients typically have this diagnosis removed and are misdiagnosed with a psychiatric diagnosis that includes physical symptoms instead, e.g., bodily distress disorder, functional somatic syndrome, somitization or conversion disorder, or in the case of children, the unrecognised diagnosis of pervasive refusal syndrome."

  "The mental illness diagnosis can be used to claim patients are unable to make their own healthcare decisions or are not able to make decisions in their own best interests, which allows doctors to determine their treatment for them."

  "Forced treatments may include exercise, cognitive behavioral therapy (if patients can still speak), or behavioral approaches like removing disability aids and leaving food out of reach to "motivate" patients to over-exert in order to eat."

- [610 H] The rise and fall of the Wessely School, Marks, D. F., 2021, June 10.

  "Based on the "Biopsychosocial Model", the WS proposes that patients' dysfunctional beliefs, deconditioning and attentional biases cause illness, disrupt therapies, and lead to preventable deaths. The evidence reviewed here suggests that none of the WS hypotheses is empirically supported. The lack of robust supportive evidence, fallacious causal assumptions, inappropriate and harmful therapies, broken scientific principles, repeated methodological flaws and unwillingness to share data all give the appearance of cargo cult science. The WS approach needs to be replaced by an evidence-based, biologically-grounded, scientific approach to MUS/MECFS."

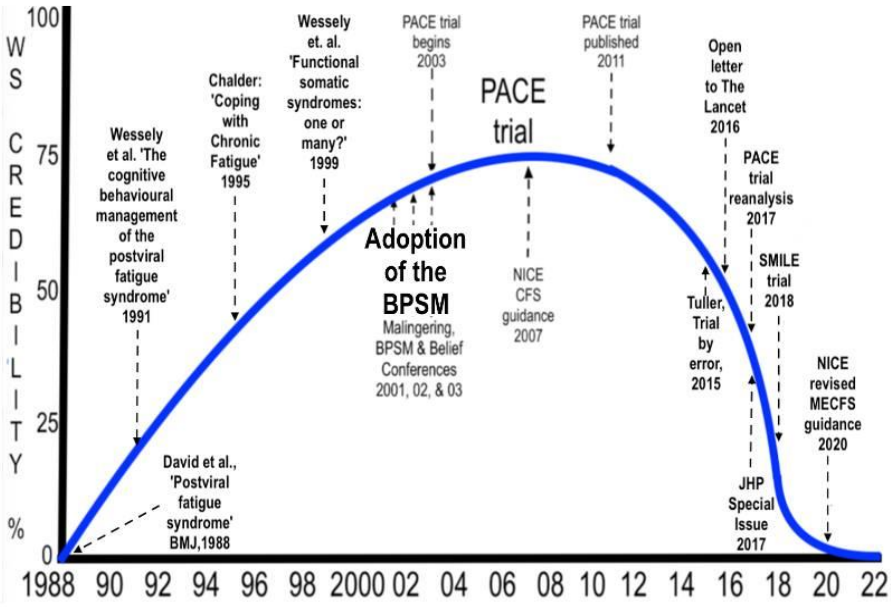


Figure 7. The rise and fall of the Wessely School, 1988-2021, indicating some key moments over the period. In this reviewer's assessment, the scientific credibility of the WS made a steady ascent over the period 1988-2010, peaked around the time of the PACE trial, and steeply descended over the period 2011-2021.

(*page 101*)

- [611 H] Magical medicine: how to make a disease disappear, Malcolm Hooper (Emeritus Professor of Medicinal Chemistry Department of Life Sciences, University of Sunderland), 2010

- [612 H] Summary: Structural dimensions of the biopsychosocial model, HEALTHCARE HUBRIS, Nemesis, Jo Hunt, August 8, 2021

  "...a series of four blogposts looking at structural (essentially, socio-political) dimensions of the biopsychosocial (BPS) model."

- [613 H] Myalgic encephalomyelitis/chronic fatigue syndrome and the biopsychosocial model: a review of patient harm and distress in the medical encounter, Keith J Geraghty, Charlotte Blease, 2018

- [614 H] Families facing false accusations: results of Action for M.E.'s survey, June 2017

- [615 H] For People With Chronic Fatigue Syndrome, More Exercise Isn't Better, Sara Wong for NPR, 2017. Article with statements from Dr. Nancy Klimas and Dr. Maureen Hanson about GET.

- [616 H] ME/CFS and treatment harms, Marks, D. F. (psychologist, professor, author), March 10, 2021

- [617 H] ME/CFS and the Wessely School, David F. Marks (psychologist, professor, author), March 11, 2021

- [618 H] ME/CFS: Past, Present and Future, William Weir and Nigel Speight, 2021

- [619 H] Science In The Age of Dogma: A Conversation with Dr. William Weir, Phoenix Rising Articles, 2021

  Dr William Weir says: "The adherence of some members of the medical establishment to [the use of] GET for ME/CFS is reminiscent of the use of bloodletting in cholera. In both cases, dogma is the driving force. Funding efforts for proper scientific (i.e. non-psychological) research into ME/CFS has been hampered by such dogma." He goes on to outline key findings of dysfunction in ME/CFS.

- [620 H] Can Long-Covid be Cured with the Mind: Expert Patient or Nutty Professor?
  Dr. Keith Geraghty, June 2021

- [621 H] The "cognitive behavioural model" of chronic fatigue syndrome: Critique of a flawed model, Keith Geraghty, Leonard Jason, Madison Sunnquist, 2019

- [622 H] CFS patients remain severely disabled after specialist treatment with CBT in the UK, Mark Vink, 2021

- [623 H] ME/CFS Sceptic, Summary of the CDC evidence review, Michiel Tack, June 2021

  "A deep-dive into why a much-touted meta-analysis should not be taken at face value. The meta-analysis findings suggested that blinding didn't really reduce bias even when studies relied on self-reported outcomes."

- [624 H] PRINCE Secondary: transdiagnostic CBT is not effective for persistent physical symptoms, Michiel Tack and David M. Tuller, August 17, 2021

- [625 H] The "medically unexplained symptoms" syndrome concept and the cognitive-behavioural treatment model, Michael J. Scott, Joan S Crawford, Keith J Geraghty, David F Marks, 2021

- [626 H] Psychiatrist Would Abandon Research on Long COVID and Chronic Fatigue Syndrome, Llewellyn King, 2021

- [627 H] Workwell Foundation hosts educational videos on GET, PEM and Pacing

- [628 H] Workwell Foundation, Letter to healthcare professionals "Opposition to Graded Exercise Therapy (GET) for ME/CFS", J. Mark VanNess, Ph.D, Todd E. Davenport, PT, DPT, MPH, OCS, Christopher R. Snell, PhD and Staci Stevens, MA, 2018

- [629 H] "I got a virus, I didn't die, but I never recovered. We are the #MillionsMissing". An ME Action Network video (7 min.) with amongst others Dr. Nina Muirhead warning about GET.

- [630 H] Fatigue, Pacing and PEM Management, Lessons from ME/CFS - With Dr Ben Marsh (about PEM/GET risk, NICE removal of GET, CBT etc.), June 2021

- [631 H, 632 H, 633 H, 634 H] Articles by David M. Tuller, DrPH on the flawed, harmful PACE trial and Lightning Process.

- [635 H] Trial By Error: Do the "Vast Majority" of Lightning Process Participants Achieve "Lasting Change"? David Tuller, DrPH, April 2021

- [636 H] Trial By Error: More Disinformation from Professor White in Journal of Psychosomatic Research, David Tuller, DrPH, June 2021

- [637 H] Trial By Error: Journal Corrects "Highlights" of GETSET Paper; A Letter about Prof White's GET Safety Paper, by David Tuller , 30 June 2021

- [638 H] Trial By Error: Null Outcomes Presented as Success in Yet Another CBT Trial from Prof Trudie Chalder, David Tuller, DrPH, 19 June 2021

- [639 H] Trial By Error: NICE Squares Off Against Royal College Bullies Over New ME/CFS Guidelines, By David Tuller, DrPH, August 19, 2021

- [640 H] Carol Monaghan on the PACE trial: "I think that when the full details of the trial become known, it will be considered one of the biggest medical scandals of the 21st century."

- [Ref. 524 H] New 10-minute professionally made video, Dialogues, "Prologue to Dialogues for a neglected illness ME/CFS-2021. NICE - a turning point becomes a debacle", 2021

- [641 H] Doctors with ME, Position Statement: 2021 NICE Guideline Update on Treatment and Management of Myalgic Encephalomyelitis / Chronic Fatigue Syndrome (ME/CFS), July 2, 2021

- [642 H] Post-Covid syndrome, Myalgic Encephalomyelitis, and the recurring pseudoscience of mass hysteria, Brian M. Hughes, Ph.D., Professor of Psychology, July 27, 2020

  "The people who want you to think that everything is "all in your mind" are back, their schtick now revised and updated for a COVID-19 world."

- [643 H,644 H] Sweden, July 2021, very severe ME patient Holger Klintenberg, forced institutionalization, ongoing tragedy, family has to go to court to protect the life of Holger.

  Dr Nigel Speight: "Regarding the care of patients with very severe ME, any form of stress (physical, psychological, sensory stimulation) should be avoided, as it can lead to further deterioration. Patients with severe ME who deteriorate are at risk of actually dying."

- [645 H] Is the Sunk Cost Fallacy "First Doing Harm" in Chronic Fatigue Syndrome?, Steven Lubet, 2021

- [646 H] ME, the insurance industry and psychiatry, MElivet, Nina E. Steinkopf, April 2021

- [647 H] Abuse of process & abuse of power: a NICE publication (with file download), Valerie Eliot Smith, September 13, 2021

- [Ref. 28 H] GET and CBT are ineffective or cause harm in ME-patients, ME Livet, Jørn Tore Haugen, October 2021

- [648 H] Trial By Error: Losers in NICE Guideline Fight Remain Defiant Despite Public Repudiation of Their Claims, David Tuller, October 31, 2021

- [649 H] On Lightning Process: "Self-styled medical leaders defend "neurolinguistic processing" as legit treatment for ME/CFS", Brian Hughes, October 31, 2021

- [650 H] Even Health-Care Workers With Long COVID Are Being Dismissed, Ed Young, The Atlantic, 2021

- [651 H] The circuit of symbolic violence in chronic fatigue syndrome (CFS)/myalgic encephalomyelitis (ME) (I): A preliminary study, Xavier Gimeno Torrent

- [652 H] Position statement on alternative medicine and therapy programmes including the Lightning Process or the Switch, ME Awareness NZ

Technological development

- [653 H] OMF works on Personalized Automated Symptom Summary (PASS), Using Computerized Adaptive Testing (CAT) that is intended to aid a clinician more efficiently to define the character and priorities of a patient's current symptoms of ME/CFS, Post-treatment Lyme Disease (PTLD), or Fibromyalgia (FM).

  "The overall strategy is to reduce the time spent by a clinician to perform a patient's evaluation. The intent is to provide a clinical quantitative metric that can be most efficiently administered, be highly reproducible, and address each of the many possible symptomologies."

  "This approach will provide a highly valid means to support the diagnosis, follow the progression or remission of an individual patient's disease, as well as provide a metric to assess whether treatment interventions are effectively improving symptoms within an individual patient or within a particular cohort in a clinical trial."

- [654 H, 655 H] Stanford symposium: the potential of smartphones to better understand diseases, including ME/CFS, Simon McGrath, 2019 *and*
  Michael Snyder, PhD, professor and chair of genetics, "Wearable sensors can tell when you are getting sick, Stanford Medicine News Center", By Jennie Dusheck, science writer, 2017

  "We think smartphones will be the most important health tool in future", said Dr Michael Snyder at the recent Stanford ME/CFS symposium. Snyder heads up the Stanford Centre for Genomics and Precision Medicine, as well as the Genetics Department at Stanford University."

  "His presentation highlighted the potential of technologies to monitor health and better understand diseases – including ME/CFS."

  "Snyder's work on personal, data-driven medicine kicked off with a landmark paper in 2012 (which wasn't covered in his talk). This revealed insights from deep molecular profiling over 14 months of a single person – Snyder himself."

  "The study tracked over 40,000 different biological molecules and integrated the findings with data from clinical tests and other sources. This is in addition to analyzing Snyder's full genome sequence."

Large research projects

“People with the illness are the true ME experts. As a scientist, it is hugely valuable to be able to consult regularly with them as colleagues.” - Professor Chris Ponting

- [656 H] UK:
  - “The “Prioritise ME initiative” is led by Sonya Chowdhury, CEO of the charity Action for ME. The project is supported by the UK’s two main public funders of medical research – the Medical Research Council and the National Institute for Health Research (NIHR).”
  - “The most radical way for researchers to engage with patients is to invite them onto the research team. That’s exactly the pioneering approach taken by the “DecodeME” study. It is a very large DNA study that is looking for biological causes of ME/CFS.”

Simon McGrath: “We need the approach pioneered by DecodeME and Prioritse ME to be the future, not an exception. It is time for researchers and funders to partner with patients and agree a research agenda. It is time for researchers to partner with patients as the new normal to carry out better research. And it is time to ensure that public funds spent on research deliver for people with ME/CFS. Let’s all work together to make this happen.”

Some of the most experienced scientists and physicians specialized in ME

- [657 H] Dr. Chris Armstrong, PhD (biochemistry and molecular biology) ("performs research in the Department of Biochemistry and Molecular Biology and the Bio21 Molecular Science & Biotechnology Institute at the University of Melbourne, Melbourne, Australia with an interest in the dysfunction of energy metabolism of people with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). Dr. Armstrong is a member of the Working Group which offers their expertise and resources to the ME/CFS Collaborative Research Center at Stanford University.")

- [658 H] Dr. Leighton Barnden (medical scientist) ("serving as a medical scientist at the National Centre for Neuroimmunology and Emerging Disease in Griffith's Menzies Health Institute Queensland.")

- [659 H] Dr. Lucinda Bateman, MD (physician, researcher, founder and Chief Medical Officer of the Bateman Horne Center. "Dr. Bateman was one of the authors of the 2011 case definition, International Consensus Criteria, and was one of the experts on the "Committee on the Diagnostic Criteria for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome" that was convened for the 2015 Institute of Medicine report.")

- [660 H] Dr. David Bell, MD ("serves at the Scientific Advisory Board of the Open Medicine Foundation and is a member of the Working Group the ME/CFS Collaborative Research Center at Stanford University")

- [661 H] Prof. Dr. Kenny DeMeirleir, MD, PhD (Internal Medicine doctor)

- [662 H] Dr. Jonas Bergquist, MD, PhD (Analytical Chemistry and Neurochemistry, "Chief Medical Officer & Director – The ME/CFS Collaboration at Uppsala University" "Dr. Bergquist is a Full Chair Professor in Analytical Chemistry and Neurochemistry in the Department of Chemistry at Uppsala University, Sweden, Adjunct Professor in Pathology at the University of Utah School of Medicine, and Distinguished Professor in Precision Medicine at Binzhou Medical University in Yantai, China.
His group develops tools for screening and discovery of biomarkers in different diseases. Dr. Bergquist studies numerous conditions, including neurodegenerative disorders. His research into ME/CS is focused on characterizing the neuroimmunological aspects of the disease using proteomics and metabolomics, with a special interest in cerebrospinal fluid studies and autoantibodies")

- [663 H] Dr. C. (Linda) M.C. van Campen, MD ("Cardiologist and Director at Stichting Cardiozorg, Hoofddorp, Netherlands.")

- [664 H] Dr. Mark Davis, PhD ("…Professor of Microbiology and Immunology and the Director of the Stanford Institute for Immunity, Transplantation and Infection at Stanford University School of Medicine. He is on the ME/CFS Advisory Board of the Stanford ME/CFS Initiative")

- [665 H] Dr. Ronald W. Davis, PhD (Professor of Biochemistry and Genetics, Director of the Stanford Genome Technology Center at Stanford University, Scientific Advisory Board Director Open Medicine Foundation)

- [666 H] Dr. Mark Donohoe, MD (GP and integrative medicine doctor, "GP and integrative medicine doctor based in Sydney, New South Wales, Australia, who mostly treats patients with chronic fatigue syndrome, myalgic encephalomyelitis, fibromyalgia, multiple chemical sensitivity, and chronic inflammation. According to Donohoe, "treating a person with CFS requires time, patience, a willingness to hear their story and a commitment not to abandon them." He also claims that about

half of patients referred to him by other GPs do not have CFS, but another diagnosis missed by basic tests.")

- [667 H] Dr. Paul Fisher PhD (Head of Microbiology, Department of Physiology, Anatomy and Microbiology)

- [668 H] Dr. Øystein Fluge, MD ("Senior Consultant supervising the ME/CFS research group at the Department of Oncology and Medical Physics at the University of Bergen, Haukeland University Hospital, Bergen, Norway." "Dr. Fluge is a member of the Working Group the ME/CFS Collaborative Research Center at Stanford University")

- [669 H] Prof. Maureen R. Hanson, PhD ("Liberty Hyde Bailey Professor in the Department of Molecular Biology & Genetics, and Director of the Cornell Center for Enervating NeuroImmune Disease, elected to the National Academy of Sciences")

- [670 H] Dr. K.N. Hng, MD ("General Internal Medicine and Gastroenterology, Founder Doctors with ME")

- [671 H] Prof. Mady Hornig ("physician-scientist and Associate Professor of Epidemiology")

- [672 H] Dr. Byron Marshall Hyde ("a family practice physician in Ottawa, who dedicated his practice solely to ME/CFS, Founder of The Nightingale Research Foundation")

- [673 H] Prof. Leonard Jason, PhD ("Professor of psychology at DePaul University in Chicago, Illinois, US and Director of the Center for Community Research at DePaul University, which includes the DePaul University Chronic Fatigue Syndrome Project")

- [674 H] Dr. David Lyons Kaufman, MD ("Internal Medicine physician at the Center for Complex Diseases")

- [675 H] Dr. Nancy G. Klimas, MD ("Director, Institute for Neuro-Immune Medicine, Nova Southeastern University, Director, Clinical Immunology Research, Miami VAMC, Professor of Medicine, Department of Clinical Immunology, College of Osteopathic Medicine, Nova Southeastern University, Chair, Department of Clinical Immunology, College of Osteopathic Medicine, Nova Southeastern University, Professor Emerita, University of Miami, School of Medicine")

- [676 H] Dr. Anthony L. Komaroff, MD ("is an Internal Medicine physician and a foremost expert in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) since the late 1980s. As of 1993, he has been a professor at Harvard Medical School in the United States, holding the title of the Steven P. Simcox, Patrick A. Clifford and James H. Higby Distinguished Professor of Medicine, he serves on the team for the Center for Solutions for ME/CFS at Columbia University, a Collaborative Research Center (CRC) partially funded by the National Institutes of Health (NIH)")

- [677 H] Dr. Susan M. Levine, MD ("clinician for the Center for Enervating NeuroImmune Disease at Cornell University, and a member of the Working Group which offers their expertise and resources to the ME/CFS Collaborative Research Center at Stanford University")

- Dr. Katarina Lien, MD, PhD and scientist (Department of Nutrition, Institute of Basic Medical Sciences, University of Oslo, Norway)

- [678 H] Dr. Alan R. Light Ph.D. ("Research Professor of Anesthesiology, Neurobiology and Anatomy at the Interdepartmental Program in Neuroscience at the University of Utah and member of the Working Group the ME/CFS Collaborative Research Center at Stanford University")

- [679 H] Dr. W. Ian Lipkin, MD, John Snow Professor of Epidemiology, Professor of Neurology and Pathology and Cell Biology, Director Center for Infection and Immunity

- [680 H] Prof. Dr. Michael Maes, MD, PhD (Neuropsychiatrist) ("In 2015, Maes developed a new case definition of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) called Neuro-Inflammatory and Oxidative Fatigue (NIOF) "based on pattern recognition methods and using neuro-immune, inflammatory, oxidative and nitrosative stress (neuro-IO&NS) biomarkers as external validating criteria.")

- [681 H] Prof. Sonya Marshall-Gradisnik, BSc (Hons), PhD ("neuroimmunologist, director of the National Centre for Neuroimmunology and Emerging Diseases (NCNED) at Griffith University in Australia")

- [682 H] Prof. Olav Mella, MD, PhD ("Adjunct Professor in the ME/CFS research group at the Department of Oncology and Medical Physics at the University of Bergen, Haukeland University Hospital, Bergen, Norway, and member of the Working Group the ME/CFS Collaborative Research Center at Stanford University")

- [683 H] Dr. Jose G. Montoya ("he was Professor of Medicine (Infectious Diseases and Geographic Medicine) at Stanford University Medical Center and head of the Stanford ME/CFS Initiative. Considered one of the foremost experts of ME/CFS, Dr. Montoya has served on numerous government and institutional committees on ME/CFS. He is also an ME/CFS researcher and frequent conference speaker")

- [684 H] Dr. Alain Moreau, PhD ("Professor in both the Department of Stomatology, Faculty of Dentistry and Dept of Biochemistry and Molecular Medicine, Faculty of Medicine, at Université de Montréal, Montréal, Québec, Canada and the Director of Network for Canadian Oral Health Research, and a member of the Working Group the ME/CFS Collaborative Research Center at Stanford University")

- [685 H] Dr. Nina Muirhead (dermatologist, "a specialist surgeon in dermatology who has myalgic encephalomyelitis. She is a graduate of Oxford University, UK, and has written a number of popular medical textbooks. Dr Muirhead educates other doctors about ME/CFS and is part of Forward-ME, a group of UK charities and advocates for people with ME/CFS")

- [686 H] Dr. Sarah Myhill ("British doctor running her own specialist M.E. clinic in Knighton, Wales, United Kingdom")

- [687 H] Dr. Benjamin Natelson, MD ("neurologist with post-doctoral training in Behavioral Medicine. He is head of the Pain and Fatigue Study Center in New York City which specializes in treating and researching ME/CFS|myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), fibromyalgia (FM), and severe pain and fatigue illnesses. He is, also, an Emeritus Professor of Neurology and Neurosciences at Rutgers and Professor of Neurology at the Icahn School of Medicine at Mt. Sinai")

- [688 H] Dr. Robert K. Naviaux, MD, PhD ("Professor of Medicine, Pediatrics, and Pathology at the University of California, San Diego (UCSD). He is the founder and co-director of the Mitochondrial and Metabolic Disease Center and former President of the Mitochondrial Medicine Society (MMS) and a founding associate editor of the journal Mitochondrion. He is an internationally known expert in human genetics, inborn errors of metabolism, metabolomics, and mitochondrial medicine….")

- [689 H] Dr. Julia L. Newton, PhD ("Clinical Professor of Ageing and Medicine at the University of Newcastle in the United Kingdom. She is a member of the UK CFS/ME Collaborative and is the Joint Medical Adviser of the charity Action for ME. She is Director of the Newcastle Fatigue Research Group and Associate Medical Director for Research for Newcastle upon Tyne Hospitals NHS Foundation

Trust. Dr. Newton serves on the editorial board of the journal, Fatigue: Biomedicine, Health & Behavior, published on behalf of the IACFS/ME.")

- [690 H] Dr. Daniel L. Peterson, MD "… a physician in Incline Village, Nevada specializing in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS)." "…serving on Simmaron Research's Scientific Advisory Board and the Faculty of Health Sciences and Medicine at Griffith University in Queensland, Australia. He helped establish the Whittemore Peterson Institute (WPI) which was renamed in 2016 the Nevada Center for Biomedical Research. He left in 2010 to return to private practice at Sierra Internal Medicine, Incline Village, Nevada. In 2019, he joined the scientific advisory board of the Open Medicine Foundation.")

- [691 H] Prof. Chris Ponting ("researcher with a special interest in genomics and bioinformatics". "Prof. Ponting is Section Head at Biomedical Genomics, Chair of Medical Bioinformatics, and a Principal Investigator at the MRC Human Genetics Unit, Institute of Genetics and Molecular Medicine at the University of Edinburgh". "Professor Ponting is principal investigator on a large study that will use the UK Biobank data to "investigate the biomolecular and genetic bases to myalgic encephalomyelitis (ME/CFS)")

- [692 H] Amy Proal, PhD ("… is a microbiologist who researches the role of the human microbiome and human virome in chronic inflammatory disease." "Proal serves as PolyBio's Research Team Coordinator.")

- [693 H] Dr. Bhupesh Prusty PhD "… is the Group Leader in the Department of Microbiology, Julius Maximilian University of Wuerzburg, Germany. His research expertise includes the molecular mechanisms of latency and activation of Human herpesvirus 6 and the finding of the chromosomal integration and inheritance of Human herpesvirus 7.")

- [694 H] Dr. Peter C. Rowe ("has been the director of the Johns Hopkins Children's Center Chronic Fatigue Clinic in Baltimore, Maryland, US, since 1996. He serves as a professor of Pediatrics at the Johns Hopkins University School of Medicine. In 2007, he became the inaugural recipient of the Sunshine Natural Wellbeing Foundation Chair in Chronic Fatigue and Related Disorders at Johns Hopkins University")

- [695 H] Prof. Ola Didrik Saugstad (researcher, "…Norwegian pediatrician and neonatologist….", "…Professor of Pediatrics at the University of Oslo and Director of the Department of Pediatric Research at the National Hospital")

- [696 H] Prof. Dr. Carmen Scheibenbogen ("Professor Doctor Carmen Scheibenbogen is an Internal Medicine physician, ME/CFS doctor and the Professor for Immunology and Deputy Chair, Institute of Medical Immunology, at the University Hospital Charité in Berlin, Germany.")

- [697 H] Dr. Charles B. Shepherd, MB, BS ("… the Honorary Medical Adviser to the ME Association, a patient charity in London, United Kingdom and the co-author with Dr Abhijit Chaudhuri of ME/CFS/PVFS: An Exploration of Key Clinical Issues, also known as The Purple Book, a health professional's guidebook published by the ME Association. He was on the Steering Committee of the National ME Observatory, a collaborative research project in the UK. His special interest in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) stems from having developed the illness in his twenties after a bout of chickenpox")

- [698 H] Prof. Kristian Sommerfelt (Pediatric neurologist at Haukeland University hospital in Bergen, Norway. "Professor Sommerfelt wrote the national guidelines (2019) for diagnosis, treatment and follow-up of ME/CFS children/ young people for the website NEL (Norsk Elektronisk Legehåndbok) - which is a web-based methods used the most by general practitioner doctors and is also used

extensively in hospitals. Over the last eight years he has given lectures and presentations at courses and conferences for health professionals and others in addition to teaching medical students.")

- [699 H] Dr. Nigel Speight ("Doctor Nigel Speight is a semi-retired British doctor based in the North East of England who specialises in Pediatric ME/CFS and has been involved in fighting many child protection cases in which children with ME/CFS were at risk of being removed from their parents. He has acted as a voluntary paediatric medical advisor for many ME/CFS charities.")

- [700 H] Prof. Donald Staines MBBS, MPH, FAFPHM, FAFOEM ("… Clinical Professor at Menzies Health Institute Queensland and the co-director (alongside Sonya Marshall-Gradisnik) of the National Centre for Neuroimmunology and Emerging Diseases (NCNED) at Griffith University in Queensland in north-eastern Australia. His research team is working towards discovery of diagnostic tools and treatments for chronic fatigue syndrome.")

- [701 H] Dr. David M. Systrom, MD ("… practices Pulmonary and Critical Care Medicine at Brigham and Women's Hospital and is the Director of the Massachusetts General Hospital Cardiopulmonary laboratory, both in Boston, Massachusetts, US. He teaches as an Assistant Professor of Medicine at Harvard Medical School.")

- [702 H] Prof. Warren Tate, CNZM FNZIC FRSNZ MA-PIMBN ("… a New Zealand biochemist and Professor of Biochemistry at the University of Otago, New Zealand. Emeritus Prof Warren Tate, though officially retired, is continuing his molecular-level research into myalgic encephalomyelitis/chronic fatigue syndrome at the university. His daughter Katherine was diagnosed with ME/CFS in the early 1990s.")

- [703 H] Prof. Ronald G. Tompkins, MD, ScD (†January 2022) ("… was a leading trauma and burn specialist physician at the Massachusetts General Hospital, a leading ME/CFS researcher, and Chief Medical Officer at the Open Medicine Foundation until he passed away in 2022." "Tompkins, along with Dr. Wenzhong Xiao, led the Harvard ME/CFS Collaborative Research Center, whose funding was provided by the Open Medicine Foundation.")

- [704 H] Prof. Karl Johan Tronstad, PhD (biochemist) ("… professor in the Department of Biomedicine, University of Bergen, Bergen, Norway, where he heads the Tronstad Lab which studies cell metabolism and mitochondrial involvement in cancer and Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)")

- [705 H] Dr. Rosamund Vallings MD, MNZM, MB, BS ("is one of New Zealand's leading authorities on Chronic Fatigue Syndrome. She served voluntarily for over 27 years as President of the Associated New Zealand ME Society (ANZMES) and later as Medical Adviser and Committee Member. She is one of the authors of the 2011 case definition, International Consensus Criteria and the 2017 Pediatric Primer for Physicians")

- [706 H] Dr. Michael VanElzakker, PhD ("… is a neuroscientist affiliated at Massachusetts General Hospital, Harvard Medical School, and Tufts University. He has two primary research interests: post traumatic stress disorder (PTSD), and chronic fatigue syndrome (CFS). He has proposed a vagus nerve infection hypothesis (VNIH) for ME/CFS." "Core Team Member at PolyBio", "Harvard Medical School/Massachusetts General Hospital neuroscientist with encyclopedic knowledge of brain circuits, brain signaling and the technologies needed to study them.")

- [707 H] Prof. dr. F.C. (Frans) Visser ("… is a Dutch cardiologist and researcher." "Cardiologist and Professor by special appointment at VUMC in Amsterdam, and acting tutor at the cardiology A study at VUMC. An university lecturer Chair regarding myocardial metabolism in cardiac failure. Since 2008 working in the independent treatment center Cardiozorg, Hoofddorp.")

- [708 H] Dr. Wenzhong Xiao PhD ("…Director of the Inflammation & Metabolism Computational Center, Massachusetts General Hospital and an Assistant Professor of Surgery (Bioinformatics) at Harvard Medical School, Boston, Massachusetts, US. He is a member of the scientific team of ME/CFS Collaborative Research Center at Stanford University. Along with Dr. Ronald Tompkins, Dr. Xiao leads the Harvard ME/CFS Collaborative Research Center, whose funding was provided by the Open Medicine Foundation")

- [709 H] Prof. Jarred Younger, B.A. PhD ("… an American researcher who leads the Neuroinflammation, Pain and Fatigue lab at the University of Birmingham, Alabama, United States. He previously worked at the Stanford ME/CFS Initiative with Jose Montoya, as an Assistant Professor involved in a notable study highlighting leptin levels and ME/CFS. He is currently funded by the U.S. National Institutes of Health and Department of Defense to study new techniques for diagnosing and treating neuroinflammation in ME/CFS, fibromyalgia and Gulf War Illness. In particular his work focuses on the role of microglia." Director of the Neuroinflammation, Pain and Fatigue Laboratory, University of Alabama at Birmingham. "Director and Associate Professor Prof. Younger's goal is to end the chronic pain and fatigue that is caused by inflammation in the brain. He is currently funded by the National Institutes of Health, Department of Defense, and several non-profit agencies to develop techniques for diagnosing and treating neuroinflammation, pain, and fatigue.")

Others

- [710 H] The Workwell Foundation: Staci Stevens, MA, Christopher R. Snell, Ph.D. and Dr. Mark VanNess,
  Betsy Keller PhD

- [711 H] "Physios for ME" is a group of physiotherapists in the United Kingdom with a special interest in
  Myalgic Encephalomyelitis ("ME")

- [712 H] David M. Tuller, DrPH (a Senior Fellow in Public Health in Journalism at the Center of Global Public Health, School of Public Health, University of California, Berkeley, California and regularly writes about research on myalgic encephalomyelitis and other frequently misunderstood illness).

ME organizations, websites, blogs, magazines and documentary films

ME Organizations

- [713 H] Open Medicine Foundation
- [714 H] ME Action, MEpedia, MillionsMissing
- [715 H] Action for ME, UK CFS/M.E. Research Collaborative
- [716 H] Forward ME
- [717 H] Solve M.E. Initiative
- [718 H] ME International
- [719 H] ME Advocacy
- [720 H] ME Research UK
- [721 H] Invest in ME Research
- [722 H] The ME Association
- [723 H] The Hummingbirds Foundation for M.E.
- [724 H] 25% M.E. Group
- [725 H] Massachusetts ME/CFS & FM Association
- [726 H] Emerge Australia
- [727 H] U.S. ME/CFS Clinical Coalition
- [728 H] The American Myalgic Encephalomyelitis and Chronic Fatigue Syndrome Society (AMMES)
- [729 H] Doctors with ME
- [730 H] IACFS/ME (International Association for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis)
- [731 H] World ME Alliance
- [732 H] European ME Alliance (EMEA)
- [733 H] European ME Clinicians Council (EMECC)
- [734 H] The European ME Research Group (EMERG) is a network of European ME researchers who are collaborating in biomedical research into myalgic encephalomyelitis (ME)
- [735 H] European Network on ME/CFS (EUROMENE)
- [736 H] ME Foreningen, Norway
- [737 H] Interagency meetings of the Trans-NIH ME/CFS working group, led by NINDS Director Dr. Walter J. Koroshetz, M.D. (the meetings include several ME patient organizations)
- [738 H] James Lind Alliance, Priority Setting Partnership. “The JLA brings together patients, carers, and clinicians in PSPs. The PSP has been formed with the support of Action for ME, Forward ME, the Science4ME Forum and the Patient Advisory Group to the UK CFS/ME Research Collaboration. With funding from the National Institute for Health Research, the Scottish Government Chief Scientist Office and the Medical Research Council.”
- [739 H] Dysautonomia International

ME websites, blogs and magazines

- [740 H] ME Global Chronicle
- [741 H] ME Association Magazine
- [742 H] Health Rising, Cort Johnson
- [743 H] Simmaron Research foundation
- [744 H] Phoenix Rising ME/CFS Forums and website
- [745 H] Science for ME, Forum
- [746 H] ME/CFS Research Review, Simon McGrath
- [747 H] Emerge, Research Digest
- [748 H] Prohealth, supplement company, blogs and forums
- [Ref. 712 H] Virology Blog, David M. Tuller, DrPH
- [749 H] The Science Bit, Brian M. Hughes, PhD, FPsSI (Professor of Psychology)
- [750 H] Science, Behaviour, Homeostasis, (category health psychology, ME/CFS), David F Marks
- [751 H] Stonebird: the experience of Severe ME, Greg Crowhurst
- [752 H] Life with ME by Sissel, Sissel Sunde
- [753 H] MELivet, Nina E. Steinkopf
- [754 H] ME/CFS Sceptic, A critical view into ME/CFS research, Michiel Tack and Evelien van den Brink
- [755 H] ME Centraal (Dutch with an English section)
- [756 H] Anil about ME, Anil van der Zee
- [757 H] Law and Health: due process and civil society, Valerie Eliot Smith
- [758 H] Frozen in Amber, Caroline Elizabeth (professor, scientist, writer, and mother with ME/CFS)
- [759 H] PolyBio, Mike VanElzakker, Amy Proal and Kris Fobes
- [760 H] Microbe Minded, Dr. Amy Proal
- [761 H] ME/CFS Alert, Llewellyn King
- [762 H] ME/CFS Research Network
- [763 H] Blue Ribbon Fellowship
- [764 H] Map MECFS, an interactive data portal providing access to research results across many biological disciplines from studies that are focused on advancing our understanding of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)
- [765 H] Search MECFS
- [766 H] North Carolina/ Ohio ME & F.M Support Facebook group, founder Colleen Steckel
- [767 H] Whitney Dafoe ME/CFS
- [768 H] HEALTHCARE HUBRIS, anonymous blogger Nemesis
- [769 H] MEE Medical, The magazine for Healthcare Professionals (the ME Association's new quarterly magazine for healthcare professionals, first issue Autumn 2021)
- [770 H] ICanCME Research Network

Documentary films

- [771 H] The Tangled Story of ME/CFS: Controversy, Denigration and Ignorance, Natalie Boulton and Josh Biggs, Dialogues for ME/CFS, 2021

  “The final film in Natalie Boulton's project "Dialogues for a neglected illness" is now available on the website (1 hr 11 mins). The film examines the historical and political context of the illness myalgic encephalomyelitis/ME (referred to in this project as "ME/CFS"). I contributed to the making of this film. I have lived with this illness since 1981. “The history of ME remains one of the worst examples of unacknowledged institutional abuse in modern times. ~ Valerie Eliot Smith 2019"

  “The tangled story of ME/CFS. Hard to believe that patients with ME have been treated so poorly for decades, but they have, and the stirring story of their resilience and unwillingness to be forgotten is brilliantly portrayed in these videos. If you really want to know about the most serious health challenge facing our planet, one that still has not been recognized, be sure to watch these videos and then demand the change that is so desperately needed. ~ Leonard Jason, PH.D., Professor of Psychology. Director, Center for Community Research, DePaul University, Chicago.”

- [772 H, 773 H, 774 H] “ME-skandalen”, part 1 and 2 (English subtitles), 2021

  “The Norwegian "ME scandal" tells the story that does not appear in the media about powerful networks, hidden conflicts of interest, money & prestige, attacks on the seriously ill, research misconduct and much more.”

- [775 H] LEFT OUT - ME/CFS Documentary, Pål Schaathun, 2018

  "It was a project birthed in hope. Pål Schaathun, a Norwegian filmmaker, would document what he hoped might be the end of chronic fatigue syndrome (ME/CFS). That, unfortunately, turned out not to be, but Schaathun ended up documenting – in strikingly beautiful fashion – the next best thing. He managed to vividly portray the needs, hopes and desires of a community desperately yearning for health as it embarked on its first real shot for success."

- [776 H] Unrest, Jennifer Brea, 2017

  “Jennifer Brea's Sundance award-winning documentary, Unrest, is a personal journey from patient to advocate to storyteller. Jennifer is twenty-eight years old, working on her PhD at Harvard, and months away from marrying the love of her life when a mysterious fever leaves her bedridden. When doctors tell her it's "all in her head," she picks up her camera as an act of defiance and brings us into a hidden world of millions that medicine abandoned.“

- [777 H] What about ME?
  Documentary, “20x the infection rate of AIDS, with no cure”, Susan Douglas, 2016

  “What About ME?” is an expose inside the dramatic search for a cure for Myalgic Encephalopathy (ME), also known as Chronic Fatigue Syndrome (CFS). 17 million people around the world suffer from ME/CFS which, unbelievably, until now, has been treated as a mystery illness or even as a psychological disorder by the medical community.”

- [778 H] Forgotten Plague, ME and the future of medicine, Ryan Prior and Nicole Castillo, 2015

  “Forgotten Plague is a journey into the hidden world of myalgic encephalomyelitis. It is a chilling tale of our medical system’s failures in addressing many chronic, complex diseases. Yet it is also a riveting story of science’s remarkable ability to transform medicine and improve human life itself.”

- [779 H] The Last Great Medical Cover Up, Change For M.E. Change For Us, 2015

  “Filming took the campaign across the UK, visiting six individuals living with Myalgic Encephalomyelitis, otherwise known as ME. Interviews discussed in detail the effects of suffering from a little-known disease, and how the lack of medical assistance has left British citizens fighting for recognition and treatment every day from their GPs and practitioners.”

- [780 H] The Invisible Ones – On Severe ME/CFS, RME, 2015

  “The Swedish National Association for ME Patients (RME) arranged in the autumn of 2015 the conference "The invisible ones – A conference on severe ME/CFS and the way forward", in Stockholm, Sweden Monday the 19th of October and in Gothenburg, Sweden Thursday the 22nd of October.” This short video (9 min.) was made for this occasion and shows 18 very severe ME patients, amongst others ME patient and advocate Anne Örtegren († January 2018).

- [781 H] Voices from the Shadows, Natalie Boulton and Josh Biggs, 2014

  “Voices from the Shadows” shows the brave and sometimes heartrending stories of five ME patients and their carers, along with input from Dr Nigel Speight, Prof Leonard Jason and Prof Malcolm Hooper. It was filmed and edited between 2009 and 2011 by the brother and mother of an ME patient in the UK. The film shows the devastating consequences that occur when patients are disbelieved and the illness is misunderstood. Severe and lasting relapse occurs when patients are given inappropriate psychological or behavioral management: management that ignores the reality of this physical illness and the severe relapse or exacerbation of symptoms that can be caused by increased physical or mental activity, over exposure to stimuli and by further infections.”

- [782 H] Perversely Dark (Norwegian documentary “Sykt Mørkt”), Pål Winsents, 2014

  “In each of their respective rooms, in two different places around the greater Oslo, Norway area lie ME/CF'S patients Kristine and Bjørnar sequestered in protective total darkness. In both cases, the tiniest amount of mental, social, or physical effort is detrimental and can completely overwhelm their bodies’ minimal energy reserves and function. Consequently, only health care assistants and immediate family are permitted whispered access into their isolation in order to feed, medicate, and tend them.”

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The reference number links to this "Reference list", with all information on that particular reference (which sometimes has more than one link).
Click once on "H" behind the reference number and you will go directly to one hyperlink of the reference.
Ref. + reference number is a cross-reference to an earlier mentioned reference.

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