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**One Person's Highlights of the Biological
Research Presentations**

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Since the 2014 San Francisco Meeting

- **The report of the Institute of Medicine of the National Academy of Sciences, based on a review of over 9,000 published articles, concludes that ME/CFS is a “biologically-based illness”**
 - **Announcement of expanded research activities by the National Institutes of Health and educational efforts by the Centers for Disease Control and Prevention**
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Evidence from this Meeting of a “Biologically-Based Illness”

Studies of:

- Post-exertional malaise
 - Immunologic findings
 - Microbiome studies
 - Brain and nervous system studies
 - Epigenetic studies
 - Energy metabolism
 - Miscellany
 - Diagnostic Tests
 - Treatments
 - Formation of multi-site consortia
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Studies of Post-Exertional Malaise (PEM)

Detailed analysis of the components of “post-exertional malaise” **(Stanford)**

- Physical and cognitive exertion trigger PEM more often than emotional distress.
 - PEM includes not only fatigue, but also cognitive difficulties, sleep disturbances, headaches, muscle pain and flu-like symptoms
 - PEM lasts 3 or more days in ~25% of people.
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Studies of Post-Exertional Malaise (PEM)

Exercise testing in patients with ME/CFS vs healthy controls:

- Triggers a characteristic gene expression “signature” involving 15 cytokines/adipokines/growth factors **(Stanford)**
 - When repeated 24 hours after a first exercise test leads to a significant decline in peak heart rate (“chronotropic incompetence”), which could contribute to post-exertional malaise **(U of the Pacific)**
 - Leads to postural tachycardia after exercise (as contrasted to after tilt table testing) in a subset of ME/CFS patients and Gulf War Illness patients, due to increased sympathetic activity **(Georgetown U)**
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Studies of Post-Exertional Malaise (PEM)

Exercise testing in patients with ME/CFS vs healthy control subjects:

- Leads to lower oxygen consumption and earlier conversion to anaerobic metabolism (**U. Wisconsin, Nova Southeastern University**)
 - Blood lactate levels in a 2nd exercise test repeated 24 hours after 1st test:
 - **ME/CFS:** lactate levels are *higher* at all work loads
 - **Healthy controls:** lactate levels are *lower* at all work loads (**Ithaca College/U of Oslo**)
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Immunology

Huge study: 192 cases, 392 healthy controls.

- Levels of 17/51 cytokines/adipokines/growth factors were significantly different in ME/CFS than healthy controls.
 - Most of the cytokines were pro-inflammatory, and their levels correlated significantly with the severity of symptoms **(Stanford University)**
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Immunology

The errant B cell:

- The early rituximab studies, indicating therapeutic benefit in some patients (**U. Bergen, Norway**)
 - Reduced diversity and increased clonality of B cells in ME/CFS (**NCNP, Japan**)
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How the Microbiome May Affect The Brain

- **The human microbiome:** 10 times as many bacterial cells as human cells, containing 5-8 million genes compared to our 20,000+ genes
- **Microbes in our gut:**
 - Synthesize hormones and neurotransmitters (e.g. norepinephrine, serotonin, dopamine, ACh, GABA)
 - Synthesize molecules of inflammation (cytokines, prostaglandins) and elicit the production of those molecules by the gut immune system
 - Through inflammation, create a “leaky gut”: the tight junctions that bind gut epithelial cells together become loosened—allowing bacteria and bacterial toxins to enter the blood

Microbiome

In addition to the recently-reported reduction in *bacterial* diversity in ME/CFS, the team reports finding an increased number of Caudovirales bacteriophage *viruses* in ME/CFS.

All of these findings point to low-level inflammation in the gut (**Cornell Univ**).

Brain & Nervous System

- Impaired speed in processing information is shown to be a critical deficit in both ME/CFS and Gulf War Illness (**CDC/MCAM**).
 - Compared to healthy children, pediatric patients with ME/CFS had impaired information processing speed and attention. After exertion, these deficits worsened and ME/CFS kids also had poorer performance on tasks of working memory (**Melbourne, Australia**)
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Brain & Nervous System

- Impairments in cerebral blood flow and cortical glutathione levels—not affected by comorbid psychiatric disease.
 - A third of ME/CFS, but no healthy controls, had high white cell count or elevated protein in spinal fluid **(Mt. Sinai School of Med)**
 - Altered heart rate variability, due to reduced cardiac vagal activity, in ME/CFS vs. healthy controls **(Multi-institutions, Barcelona, Spain)**
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Brain & Nervous System

Functional connectivity among different brain regions impaired:

- Following a cognitive test in ME/CFS vs. healthy controls, determined by PET (**Georgetown U**).
 - As determined by diffusion MRI in GWI patients (**Boston U, Nova Southeastern, Baylor**)
 - As determined by EEG (eLORETTA) in ME/CFS patients at rest (**DePaul U**)
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Epigenetic Studies

- **Disease is caused not just by mutated genes**
 - **It also is caused by perfectly normal, non-mutated genes, when those genes are not “expressed” (turned on or off) appropriately**
 - **Gene expression is controlled by many different “epigenetic” forces.**
 - **Epigenetic studies are increasingly being done in ME/CFS vs healthy controls**
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Epigenetic Studies

- ME/CFS: genes involved in signal transduction are hypomethylated more often, whereas genes involved in cell differentiation/cell death are hypermethylated more often **(Nova Southeastern)**.
 - ME/CFS: significantly different gene expression patterns for genes involved in immune regulation (JAK-STAT pathway), hormone regulation and mitochondrial dysfunction.
 - Gulf War Illness: 19 related groups of genes (“functional modules”) were found to have significantly altered gene expression. Specific immunosuppressant and hormonal therapies were identified that might target these dysregulated genes, and possibly improve symptoms. **(Nova Southeastern University)**
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Epigenetic Studies

- ME/CFS patients, compared to healthy controls, have 13 different gene loci, all involving glucocorticoid sensitivity, that are differentially methylated. The different methylation patterns correlated with clinical symptoms (U. of Toronto)
 - Characteristic expression of two particular microRNAs in plasma leads to elevated homocysteine levels identified in ME/CFS (U. of Montreal)
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Epigenetic Studies

- Three SNPs distinguished ME/CFS patients from healthy controls. All involve a gene that codes for a subunit of NADH dehydrogenase—an important energy molecule (**Nova Southeastern**)
 - MicroRNAs in spinal fluid predict orthostatic tachycardia after exercise (**Georgetown U**)
 - No clear gene expression differences in ME/CFS vs. healthy controls, at rest (**Cornell**)
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Energy Metabolism Studies

- Studies on patients in the rituximab trial have an energy metabolism deficit, and the key molecule is the enzyme pyruvate dehydrogenase (PDH). Speculate that autoantibodies may be the cause of this deficit. Upregulation of PDH inhibitors in white blood cells (U. Bergen, Norway).
 - Peripheral white blood cells from ME/CFS produce energy less well than WBCs from healthy subjects, particularly when the cells are exposed to stressors (Newcastle U., U.K.)
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Energy Metabolism Studies

- Citric acid cycle metabolites are depleted. Glucose as an energy source is being replaced by fatty acids and amino acids (**Stanford U**)
 - “Unbiased” metabolomics study finds that the metabolites that are most different between ME/CFS and healthy controls involve pathways harvesting energy from glucose, fatty acids and amino acids.
 - Also finds a general hypometabolic state, as did the recent paper from Naviaux (PNAS), though different metabolites were examined (**Cornell U**)
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Miscellaneous

- ME/CFS patients, but not healthy controls, experience a worsening of symptoms following true (but not sham) strain: neuromuscular strain (even sitting/driving for prolonged time) may contribute to symptoms of ME/CFS. Physical therapy likely to help **(Johns Hopkins)**
 - Five specific findings on physical examination were quite accurate in diagnosing ME/CFS. This is of interest, since ME/CFS is defined exclusively by symptoms. **(Perrin Clinic, Manchester, UK)**
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Miscellaneous

- ME/CFS patients have significantly higher anti-citrullinated protein antibodies than matched healthy controls, as is seen in several autoimmune diseases (**U. Vermont**)
 - Particular mutations in two nucleosome transport genes distinguish ME/CFS patients from healthy controls (**Australian centers**)
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Miscellaneous

- A second case of ME/CFS caused by an enteroviral infection of the brain (**U. Vermont**)
 - Impressive hypothesis: dysregulation in the production/release of H₂S could explain many of the symptoms and objective abnormalities seen in ME/CFS (**Nova Southeastern U**)
 - A subset of ME/CFS patients with sinusitis and/or hives has more pain and other symptoms (**Columbia U**)
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Possible Diagnostic Tests for ME/CFS?

Four biomarkers—IL-8, sCD14, PGE2 and CD3-/CD57+ count—correctly predicted ME/CFS in 97% of female cases (**U. Nevada**)

An ideal diagnostic test would:

- Have very low false positive and false negative rates, compared to healthy controls ***and other fatiguing diseases, when retested on a large number of new people***
 - Be easy to perform reliably by many labs
 - Be inexpensive
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Treatment Studies

- **Magnetic resonance spectroscopy revealed 15% lower levels of the natural antioxidant, glutathione, in the brain in ME/CFS patients compared to controls. N-acetyl-cysteine (NAC) treatment improved both brain glutathione levels and symptoms, and reduced oxidative stress, in the ME/CFS patients. (Cornell U)**
 - **Randomized trial of low-dose methylphenidate plus a nutritional regimen designed to improve mitochondrial function. At 12 weeks, a trend toward reduced symptoms that was not statistically significant; more severely ill patients did seem to benefit. (Bateman-Horne Center, Utah)**
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Treatment Studies

- A careful study of 990 ME/CFS patients found that patients' beliefs about the cause of their illness did not explain their level of activity, a result that does not support the theoretical benefit of cognitive behavioral therapy. **(DePaul U)**
 - Multimodal physical therapy improves symptoms in adolescents and young adults with ME/CFS and impaired range of motion. **(Johns Hopkins)**
 - Quantitative modeling identifies drugs that are already FDA-approved and that might target TNF- α , IL-2 and the glucocorticoid receptor—targets that may be important in causing the symptoms of GWI **(Nova Southeastern University)**
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Multisite Consortia to Standardize and Pool Clinical and Biosample Data

- **CDC: Multi-Site Clinic Assessment (MCAM)**, with 7 collaborating centers. Biospecimens (serum, plasma, saliva, and white blood cell DNA) from nearly 700 ME/CFS cases and healthy control subjects.
 - **The National Institute of Neurological Disorders and Stroke at the NIH** announced that it was partnering with the CDC to develop common data elements for standardized testing.
 - **European Network on ME/CFS (EUROMENE)**: practices in 14 countries, most of which conduct ongoing research.
 - **U.K. ME/CFS Biobank**
 - **CFI (Hutchins Family Fnd)**: clinical data and biosamples from ~300 patients and matched controls
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The Questions Addressed By Many of the Presentations

- In an illness defined exclusively by subjective symptoms, is there evidence of objective underlying biological abnormalities?
 - Could those biological abnormalities *theoretically* explain the symptoms?
 - Do the abnormalities *in fact correlate* with the symptoms?
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In Summary...

- **Case-control studies comparing patients with CFS to both disease comparison groups and healthy control subjects find robust evidence of an underlying biological process involving:**
 - **the brain and autonomic nervous system**
 - **immune system**
 - **energy metabolism**
 - **oxidative and nitrosative stress**
 - **The illness is not simply the expression of physical symptoms by people with a primary psychological disorder**
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