Current and Past Research on ME/CFS

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Center for Enervating NeuroImmune Disease

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Cornell University in Ithaca, NY                    Weill Cornell Medical College in Manhattan, NY
Predominant symptoms of ME/CFS

- Unrefreshing sleep
- Cognitive Impairment
- Sore Throat, Swollen Glands
- Gastrointestinal Distress
- Orthostatic Intolerance
- Headache
- Muscle pain
- Fatigue

5 symptoms are recommended by the IOM committee for diagnosis.

Institute of Medicine clinician’s guide:

SF36 symptom survey indicates that ME/CFS patients have less quality of life than individuals with MS and Congestive Heart Failure

Table II

<table>
<thead>
<tr>
<th>SF-36 Scales: Health Concepts</th>
<th>CFS Boston (n = 223)</th>
<th>General Population Controls MOS (n = 2,474)</th>
<th>Hypertension MOS (n = 2,089)</th>
<th>Congestive Heart Failure MOS (n = 216)</th>
<th>Diabetes Type II MOS (n = 163)</th>
<th>AMI MOS (n = 107)</th>
<th>Depression MOS (n = 502)</th>
<th>Multiple Sclerosis Boston (n = 25)</th>
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<tr>
<td>Physical functioning</td>
<td>Mean 54.5 ±</td>
<td>84.2 ±</td>
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<td>Role—physical</td>
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<td>Bodily pain</td>
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<td>72.3 ±</td>
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<td>General health perceptions</td>
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<td>Vitality</td>
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<td>Role—emotional</td>
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<td>73.5 ±</td>
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<td>Mental health</td>
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<td>75.8 ±</td>
<td>75.8 ±</td>
<td>46.3 ±</td>
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Study performed by Anthony Komaroff at Harvard Medical School (chief editor of the Harvard Health Publications) “ask Doctor K”

Documented biological abnormalities in ME/CFS

Altered gut microbiome

Altered response to exercise by cardiopulmonary exercise testing

Altered levels of metabolites

Reduced natural killer cell function

Altered levels of inflammatory proteins, including cytokines

Changes in levels of molecules in the brain indicating increased oxidative stress or neuroinflammation

Differences in gene expression in immune cells
Conclusions from Gut Bacterial Microbiome study

Less bacterial diversity present in patients compared to healthy population

Anti-inflammatory bacterial species are reduced in ME/CFS patients

83% of the samples could be correctly classified as ME/CFS or healthy using microbiome data and blood assays

Reduced diversity and altered composition of the gut microbiome in individuals with myalgic encephalomyelitis/chronic fatigue syndrome

Ludovic Giloteaux¹, Julia K. Goodrich¹, William A. Walters¹, William A. Walters², Susan M. Levine³, Ruth E. Ley¹,² and Maureen R. Hanson⁴
Abnormalities in Leukocyte Function in ME/CFS

Chronic fatigue syndrome is associated with diminished intracellular perforin

K. J. Maher,* N. G. Klimas† and M. A. Fletcher*
*Department of Medicine, University of Miami
Miller School of Medicine, Miami, FL, USA, and
†Department of Medicine, Veterans Administration Medical Center, Miami, FL, USA

Longitudinal analysis of immune abnormalities in varying severities of Chronic Fatigue Syndrome/Myalgic Encephalomyelitis patients

Sharni Lee Hardcastle*, Ekua Weba Brenu, Samantha Johnston, Thao Nguyen, Teilah Huth, Sandra Ramos, Donald Staines and Sonya Marshall-Gradinisk

B-Lymphocyte Depletion in Myalgic Encephalopathy/ Chronic Fatigue Syndrome: An Open-Label Phase II Study with Rituximab Maintenance Treatment

Oystein Fluge1,², Kristin Risa3, Sigrid Lunde4, Kine Alme1, Ingrid Gurvin Rekeland4, Dipak Sapkota5,6, Elmar Kaaboe Kristoffersen1,7, Kari Sorland4, Ove Brueland2,8, Olav Dahl4, Olav Meila7,4,9

Immunologic Abnormalities Associated with Chronic Fatigue Syndrome

Edward Barker, Sue F. Fujimura, Mitchell B. Fadem, Alan L. Landay, and Jay A. Levy

From the Cancer Research Institute, Department of Medicine, University of California, San Francisco, California

Plasma cytokines in women with chronic fatigue syndrome

Mary Ann Fletcher1,2†, Xiao Rong Zeng1,2, Zachary Barnes1, Silvina Levis1 and Nancy G Klimas1,2

Deficient EBV-Specific B- and T-Cell Response in Patients with Chronic Fatigue Syndrome

Madlen Loebl1,2, Kristin Strohschein1,2, Carolin Giannini1, Uwe Koelsch3, Sandra Bauer1, Cornelia Doebis1, Sybille Thomas1, Nadine Unterwalder3, Volker von Baehr4, Petra Reinke3,6, Michael Knops1, Leif G. Hanitsch1, Christian Meisel1,8, Hans-Dieter Volk1,8, Carmen Scheibenbogen1,5

Biomarkers

Distinct plasma immune signatures in ME/CFS are present early in the course of illness

Mady Hornig1, José G. Montoya3, Nancy G. Klimas4, Susan Levine5, Donna Felsenstein6, Lucinda Bateman7, Daniel L. Peterson8, Gunnar Gottschalk9, Andrew F. Schultz1, Xiaoyu Che1, Meredith L. Eddy1, Anthony L. Komaroff1, W. Ian Lipkin1,2,10

Research Article

A Preliminary Comparative Assessment of the Role of CD8+ T Cells in Chronic Fatigue Syndrome/Myalgic Encephalomyelitis and Multiple Sclerosis

Ekua W. Brenu1, Simon Brodley1, Thao Nguyen1,3, Samantha Johnston1,3, Sandra Ramos1, Don Staines1 and Sonya Marshall-Gradinisk1,5
Our group investigated function of two types of T cells.

- **Bone Marrow**
  - CD4
  - CD8

- **Thymus**
  - Secrete cytokines to induce other immune cells to respond to antigens
  - Cause death of pathogen-infected cells or cancer cells
  - Circulation
T cells use various types of energy sources to maintain themselves and to respond to activation signals.

The energetic functioning of T cells can be examined by measures of metabolic pathways and mitochondrial characteristics.

Agilent Seahorse assays to measure activity of:
- Oxidative phosphorylation
- Glycolysis
- Fatty acid oxidation

Fluorescence microscopy
Flow cytometry

Mitochondrial size, shape, membrane potential

Red Fluorescence Detector
Green Fluorescence Detector

Created with Biorender: Jessica Maya
Patient population for T cell study

Controls               ME/CFS

45                     53
Illness duration       21.7 ± 12 yrs

Daniel Peterson, M.D.
Gunnar Gottschalk
Marco Maynard
Jineet Patel
Incline Village, Nevada

Simmaron Research
Scientifically Redefining ME/CFS
Dysfunction of CD4+ and CD8+ T Cells in ME/CFS

CD4+ T cells       CD8+ T cells

Mitochondria

No significant differences          Mitochondrial membrane potential
Normal mitochondrial mass

Glycolysis

Basal and compensatory glycolysis at rest          Basal and compensatory glycolysis at rest and after activation

More in:

Harvard OMF Symposium
https://www.youtube.com/watch?v=QAdZNU6D7Gs

Videos from InvestinME Conference and the April NIH Conference at https://neuroimmune.cornell.edu/news/

Myalgic encephalomyelitis/chronic fatigue syndrome patients exhibit altered T cell metabolism and cytokine associations

Alexandra H. Mandarano,1 Jessica Maya,1 Ludovic Giloiteaux,1 Daniel L. Peterson,2 Marco Maynard,2 C. Gunnar Gottschalk,2 and Maureen R. Hanson1

Our current studies use samples before and after a provocation.

An exacerbation of a patient’s ME/CFS symptoms following exertion that would have been easily tolerated prior to becoming ill.
The molecular basis of post-exertional malaise can be studied by induction of symptoms by two successive CPETs.

In 94 patients tested at Ithaca College:

- Physiologic dysfunction: 34%
- Anaerobic dysfunction: 39%
- Autonomic dysfunction: 43%
- Reproduced normally: 29%

Betsy Keller, Ph.D.
Plasma metabolite comparisons may reveal differences in functioning of tissues and organs.
Plasma metabolites analyzed by Metabolon, Inc.

933 metabolites identified

30 Sedentary controls
45 ME/CFS subjects

LA
Ithaca
NYC
Exercise increases the number of metabolites significantly different between controls and patients.

$q<0.05$

933 metabolites identified
Work in Progress

Pathway Analysis

Integration of physiological measures and clinical information
Graded Exercise Therapy

No accepted evidence that such programs result in recovery from ME/CFS

An infamous study known as the PACE trial, carried out in the UK, claimed recovery due to flawed performance and analysis

Patients forced into such programs often report permanent harm

Recommendation made by ME/CFS expert physicians:

Balance activity and rest ("Pacing")

Avoid over-exertion, prevent induction of post-exertional malaise

Will usually require part-time work at most, or part-time school with physical education modification
Some ways to improve quality of life for ME/CFS patients

By treating symptoms with appropriate drugs:

Headaches (often migraines)
Muscular pain and tightness
Low blood volume
Orthostatic intolerance
Unrefreshing sleep

Recommending pacing to avoid post-exertional malaise

By not expressing disbelief in the physical nature of the illness

If psychological counseling seems advisable, explaining that it can help with coping with a chronic physical illness

By not recommending counterproductive “therapies” such as unmonitored aerobic exercise
The Cambridge Dictionary defines "Enervating" as:

adjective

causing you to feel weak and lacking in energy

Foremost among cryptic neuroimmune diseases is one variously known as Myalgic Encephalomyelitis or Chronic Fatigue Syndrome or Systemic Exertion Intolerance Disease. The Center’s mission is to promote research to identify its cause(s), biomarkers, and pathophysiology in order to lead to prevention and effective treatments.

Webinars available under News tab
Acknowledgments

The Hanson Lab Biomedical Group

Cornell NIH Center
Betsy Keller
Geoffrey Moore
Susan Levine
John Chia
Staci Stevens
Jared Stevens
Dikoma Shungu
Xiangling Mao

Carl Franconi
Jessica Maya
Ludovic Giloteaux
Arnaud Germain
Adam O’Neal
Alex Mandarano
Ivan Falstyn
Madeline McCanne
Vivian Huang

Jesús Castro-Marrero

Metabolon, Inc.
Cornell NIH Center
Cornell proteomics: Sheng Zhang

Daniel Peterson
Gunnar Gottschalk
Marco Maynard
Ivan Falstyn
Jineet Patel

Simmaron Research
Scientifically Redefining ME/CFS

Cornell University
Sloan Foundation
Private donors
Simmaron Research