Current and Past Research on ME/CFS

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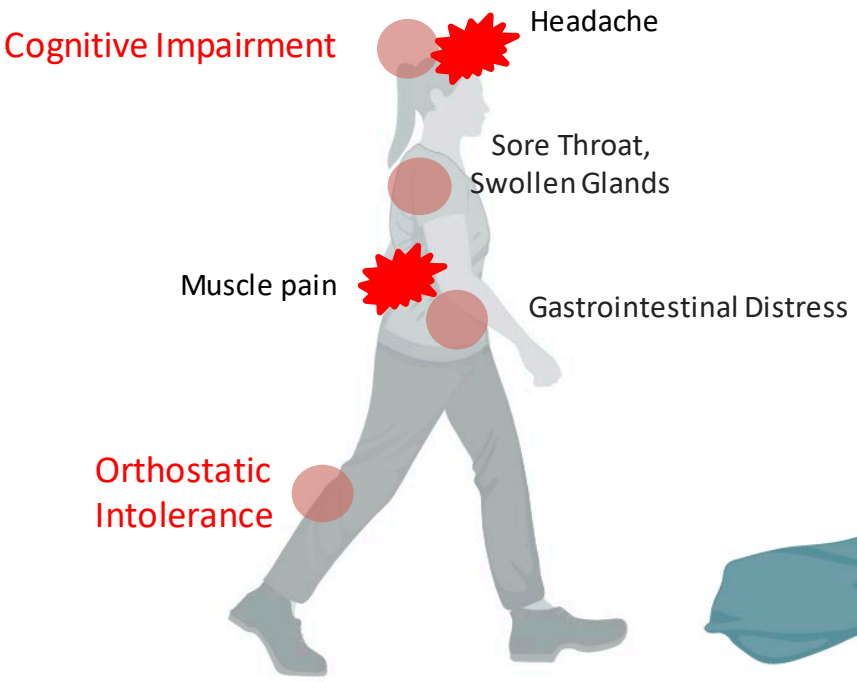
Cornell University in Ithaca, NY

Weill Cornell Medical College in Manhattan, NY

Predominant symptoms of ME/CFS



5 symptoms are recommended by the IOM committee for diagnosis

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Institute of Medicine clinician's guide:

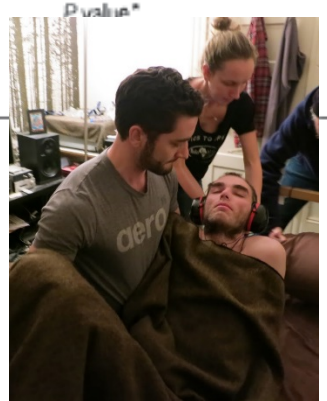
http://www.nationalacademies.org/hmd/Reports/2015/ME-CFS.aspx

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

TABLE II

Short-Form Health Survey (SF-36) Scores in Chronic Fatigue Syndrome (CFS) Compared with General Population Controls and Disease Comparison Groups

SF-36 Scales: Health Concepts		CFS Boston (n = 223)	General Population Controls MOS (n = 2,474)	Hypertension MOS (n = 2,089)	Congestive Heart Failure MOS (n = 216)	Diabetes Type II MOS (n = 163)	AMI MOS (n = 107)	Depression MOS (n = 502)	Multiple Sclerosis Boston (n = 25)
Physical functioning	Mean	54.5 ±	84.2 ±	73.4 ±	47.5 ±	67.7 ±	69.7 ±	71.6 ±	53.2 ±
	SD	25.9	23.3	26.4	31.0	28.7	26.1	27.2	24.4
	P value*		<0.00001	<0.00001	=0.00004	<0.00001	<0.00001	<0.00001	=0.4009
Role—physical	Mean	17.1 ±	81.0 ±	62.0 ±	34.4 ±	56.8 ±	51.4 ±	44.4 ±	33.0 ±
	SD	30.7	34.0	39.4	39.7	41.7	39.4	40.3	41.3
	P value*		<0.00001	<0.00001	<0.00001	<0.00001	<0.00001	<0.00001	<0.00001
Bodily pain	Mean	49.7 ±	75.2 ±	72.3 ±	62.7 ±	68.5 ±	72.8 ±	58.8 ±	70.9 ±
	SD	25.4	23.7	24.4	31.0	26.5	25.2	26.7	24.4
	P value*		<0.00001	<0.00001	<0.00001	<0.00001	<0.00001	<0.00001	<0.00001
General health perceptions	Mean	33.8 ±	72.0 ±	63.3 ±	47.0 ±	56.1 ±	59.2 ±	52.9 ±	44.8 ±
	SD	19.4	20.3	19.7	24.2	21.1	19.3	23.0	18.1
	P value*		<0.00001	<0.00001	<0.00001	<0.00001	<0.00001	<0.00001	<0.00001
Vitality	Mean	25.7 ±	60.9 ±	58.3 ±	44.3 ±	55.7 ±	57.7 ±	40.1 ±	27.0 ±
	SD	21.0	21.0	21.4	24.4	21.6	19.0	21.1	17.7
	P value*		<0.00001	<0.00001	<0.00001	<0.00001	<0.00001	<0.00001	=0.1369
Social functioning	Mean	45.8 ±	83.3 ±	86.7 ±	71.3 ±	82.0 ±	84.6 ±	57.2 ±	60.5 ±
	SD	26.2	22.7	20.7	33.1	25.0	21.2	27.7	26.1
	P value*		<0.00001	<0.00001	<0.00001	<0.00001	<0.00001	<0.00001	<0.00001
Role—emotional	Mean	62.9 ±	81.3 ±	76.7 ±	63.7 ±	75.6 ±	73.5 ±	38.9 ±	66.6 ±
	SD	42.0	33.0	35.7	43.0	36.6	38.0	39.8	44.1
	P value*		<0.00001	<0.00001	=0.3918	<0.00001	=0.00002	<0.00001	=0.1077
Mental health	Mean		74.7 ±	77.9 ±	74.7 ±	76.7 ±	75.8 ±	46.3 ±	66.9 ±
	SD		18.0	17.4	21.3	18.3	15.7	20.8	21.7
	P value*		<0.00001	<0.00001	<0.00001	<0.00001	<0.00001	<0.00001	=0.0005



Study performed by Anthony Komaroff at Harvard Medical School (chief editor of the Harvard Health Publications) "ask Doctor K"

AL Komaroff et al. *Am J Med*. 1996 101:281-90.

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 Giloteaux[1], Julia K. Goodrich[1,2], William A. Walters[1,2], Susan M. Levine[3], Ruth E. Ley[1,2] and Maureen R. Hanson[1*]

Abnormalities in Leukocyte Function in ME/CFS

Clinical and Experimental Immunology ORIGINAL ARTICLE doi:10.1111/j.1365-2249.2005.02935.x

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

PLOS | ONE

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-Gradisnik

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

Øystein Fluge[1]*, Kristin Risa[1], Sigrid Lunde[1], Kine Alme[1], Ingrid Gurvin Rekeland[1], Dipak Sapkota[1,2], Einar Kleboe Kristoffersen[3,4], Kari Sørland[1], Ove Bruland[1,5], Olav Dahl[1,4], Olav Mella[1,4]*

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

BIOMARKERS

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

Mady Hornig,[1,2]* José G. Montoya,[3] Nancy G. Klimas,[4] Susan Levine,[5] Donna Felsenstein,[6] Lucinda Bateman,[7] Daniel L. Peterson,[8] C. Gunnar Gottschalk,[8] Andrew F. Schultz,[1] Xiaoyu Che,[1] Meredith L. Eddy,[1] Anthony L. Komaroff,[9] W. Ian Lipkin[1,2,10]

Research

Plasma cytokines in women with chronic fatigue syndrome

Mary Ann Fletcher*†[1,2], Xiao Rong Zeng[1,2], Zachary Barnes[1], Silvina Levis[1] and Nancy G Klimas†[1,2]

OPEN ACCESS Freely available online PLOS | ONE

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

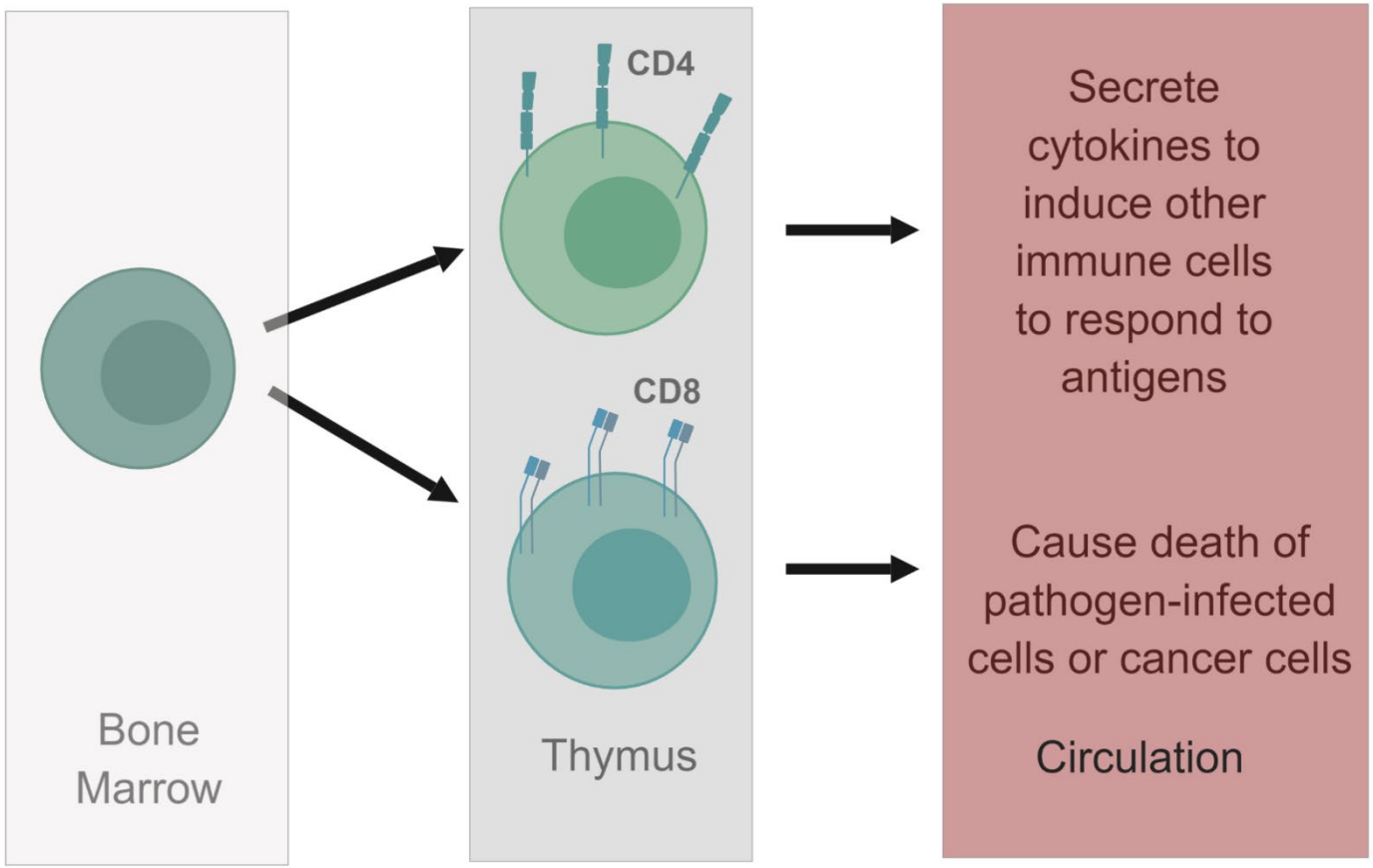
Madlen Loebel[1]*, Kristin Strohschein[1,2], Carolin Giannini[1], Uwe Koelsch[3], Sandra Bauer[1], Cornelia Doebis[4], Sybill Thomas[1], Nadine Unterwalder[3], Volker von Baehr[4], Petra Reinke[5,6], Michael Knops[1], Leif G. Hanitsch[1], Christian Meisel[1,3], Hans-Dieter Volk[1,5], Carmen Scheibenbogen[1,5]

Research Article

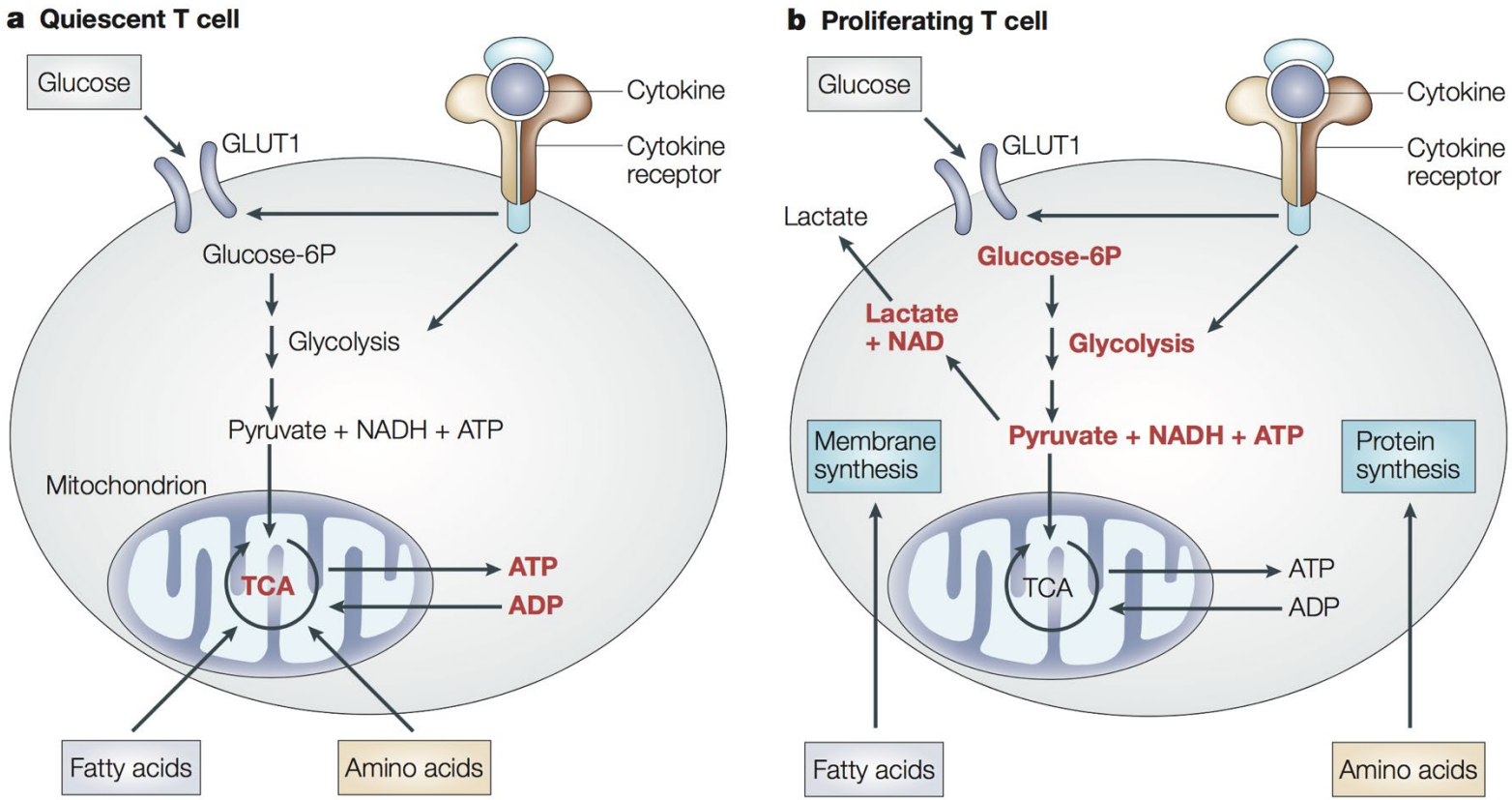
A Preliminary Comparative Assessment of the Role of CD8+ T Cells in Chronic Fatigue Syndrome/Myalgic Encephalomyelitis and Multiple Sclerosis

Ekua W. Brenu,[1] Simon Broadley,[2] Thao Nguyen,[1,3] Samantha Johnston,[1,3] Sandra Ramos,[1] Don Staines,[1] and Sonya Marshall-Gradisnik[1,3]

Our group investigated function of two types of T cells



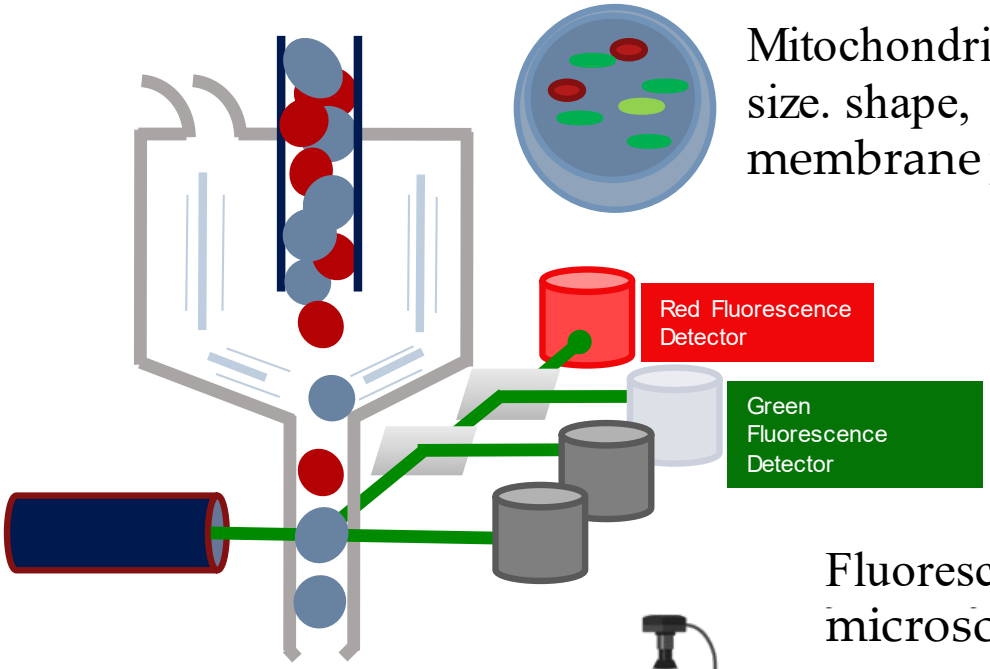
T cells use various types of energy sources to maintain themselves and to respond to activation signals



Fox et al. Nat. Rev. Immun. 2005

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

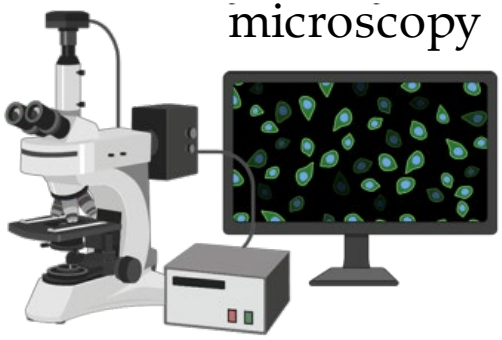
Agilent Seahorse assays
to measure activity of:
Oxidative phosphorylation
Glycolysis
Fatty acid oxidation



Flow cytometry

Mitochondrial size. shape, membrane potential

Fluorescence microscopy



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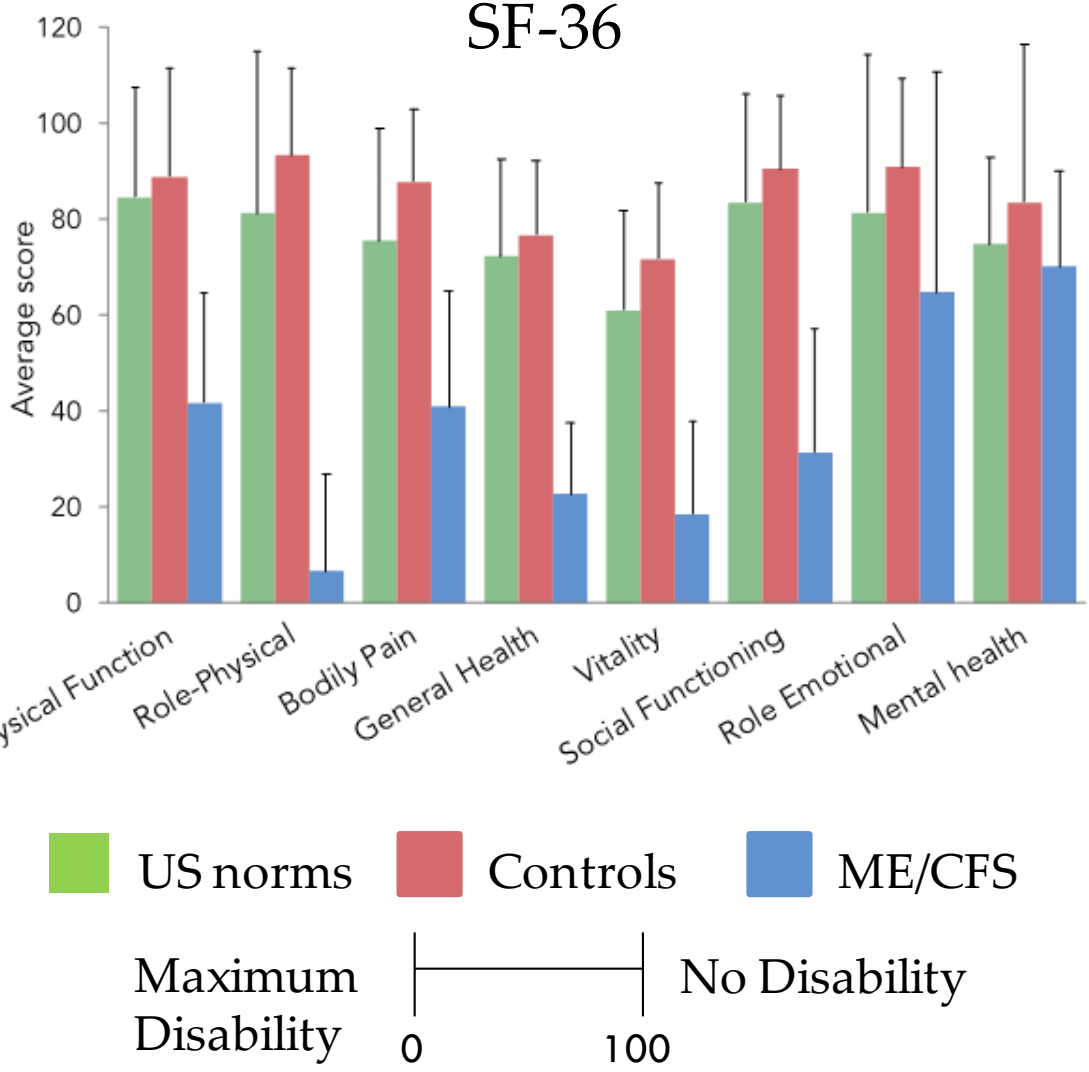
Patient population for T cell study

Controls	ME/CFS
45	53

Illness duration
21.7 ± 12 yrs

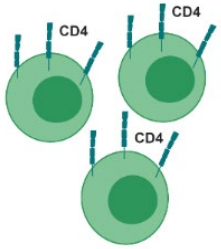


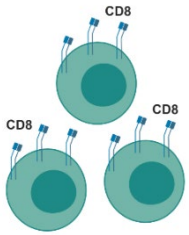
Simmaron Research
Scientifically Redefining ME/CFS

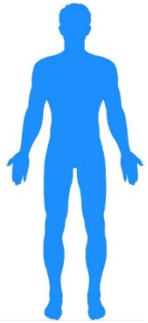
Daniel Peterson, M.D.
Gunnar Gottschalk
Marco Maynard
Jineet Patel
Incline Village, Nevada

Dysfunction of CD4+ and CD8+ T Cells in ME/CFS

CD4+ T cells CD8+ T cells







	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

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

Alexandra H. Mandarano,[1] Jessica Maya,[1] Ludovic Giloteaux,[1] Daniel L. Peterson,[2] Marco Maynard,[3] C. Gunnar Gottschalk,[3] and Maureen R. Hanson[1]

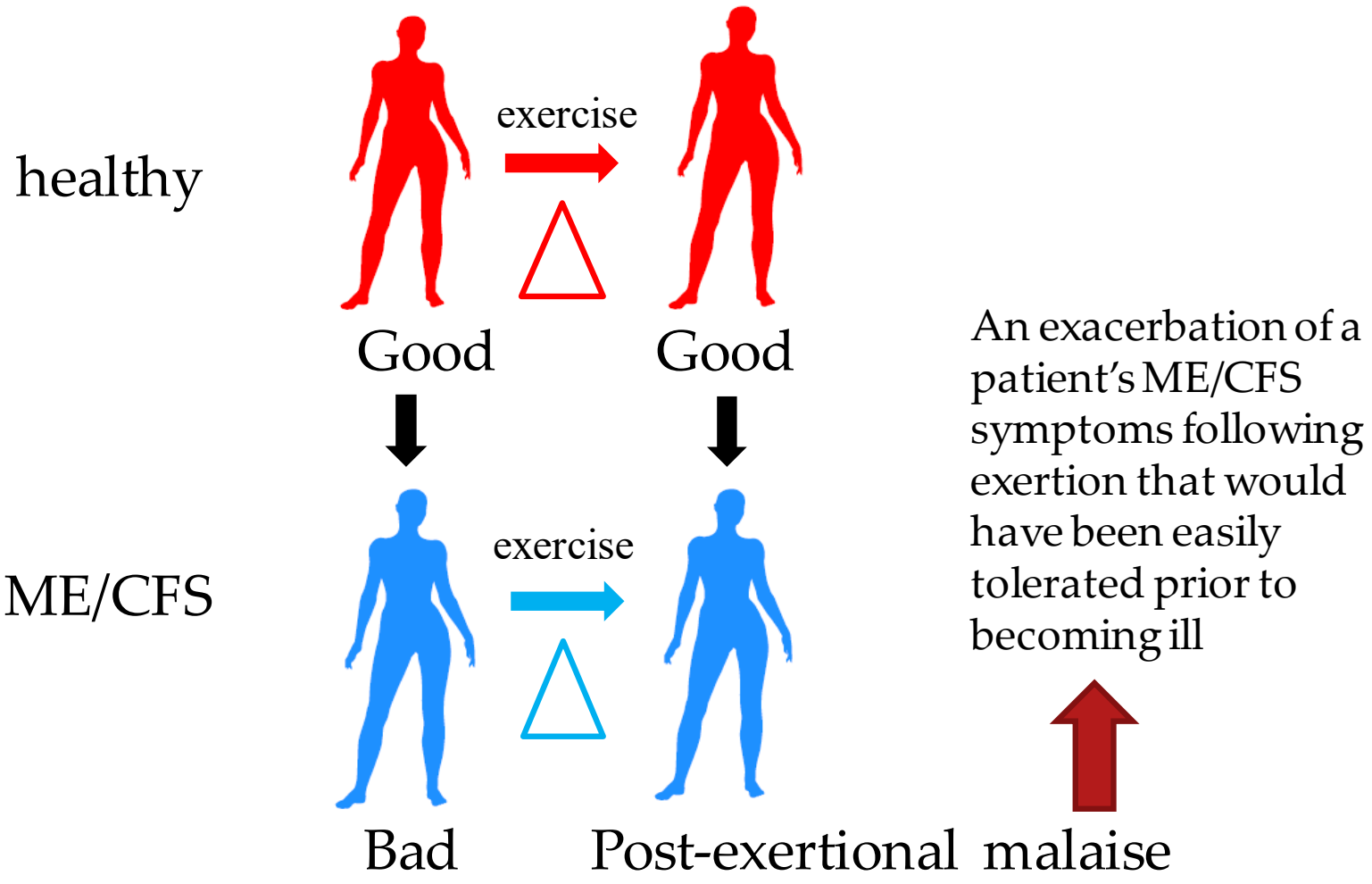
J Clin Invest. 2020;130(3):1491-1505.

More in:

Harvard OMF Symposium https://www.youtube.com/watch?time_continue=1&v=QAdZNU6D7Gs

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

Our current studies use samples before and after a provocation



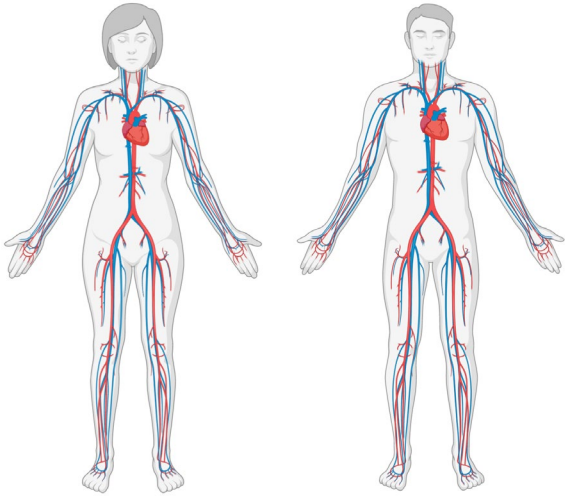
The molecular basis of post-exertional malaise can be studied by induction of symptoms by two successive CPETs

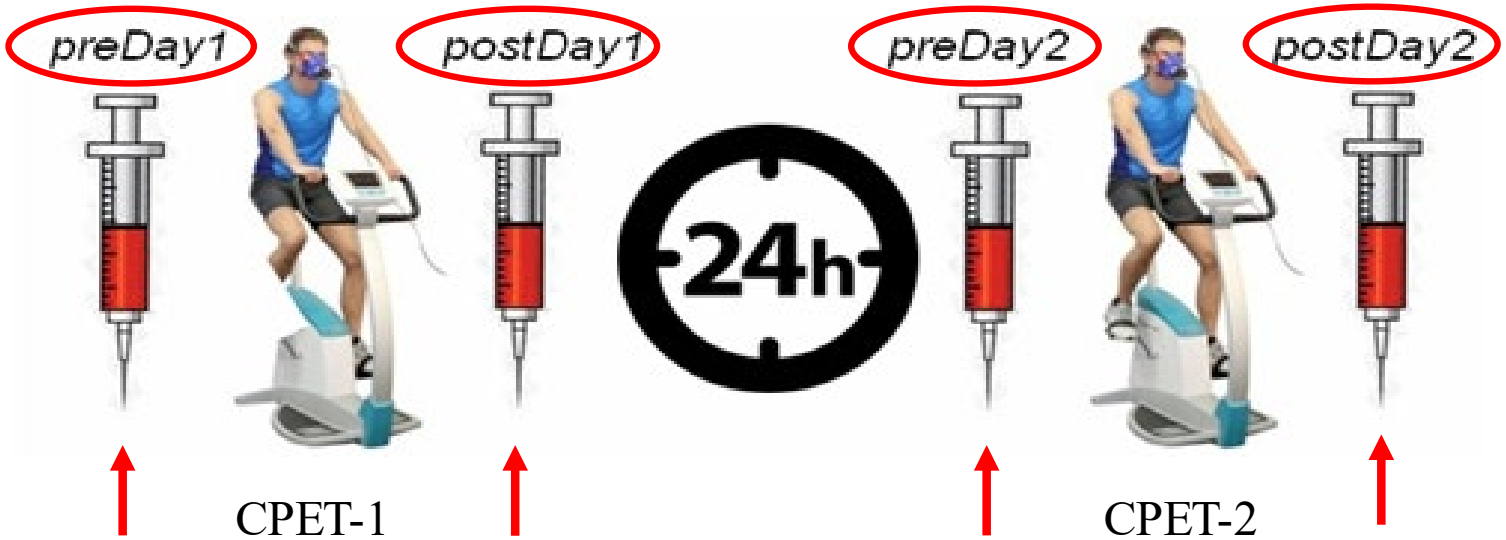
In 94 patients tested at Ithaca College:

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

Betsy Keller, Ph.D.

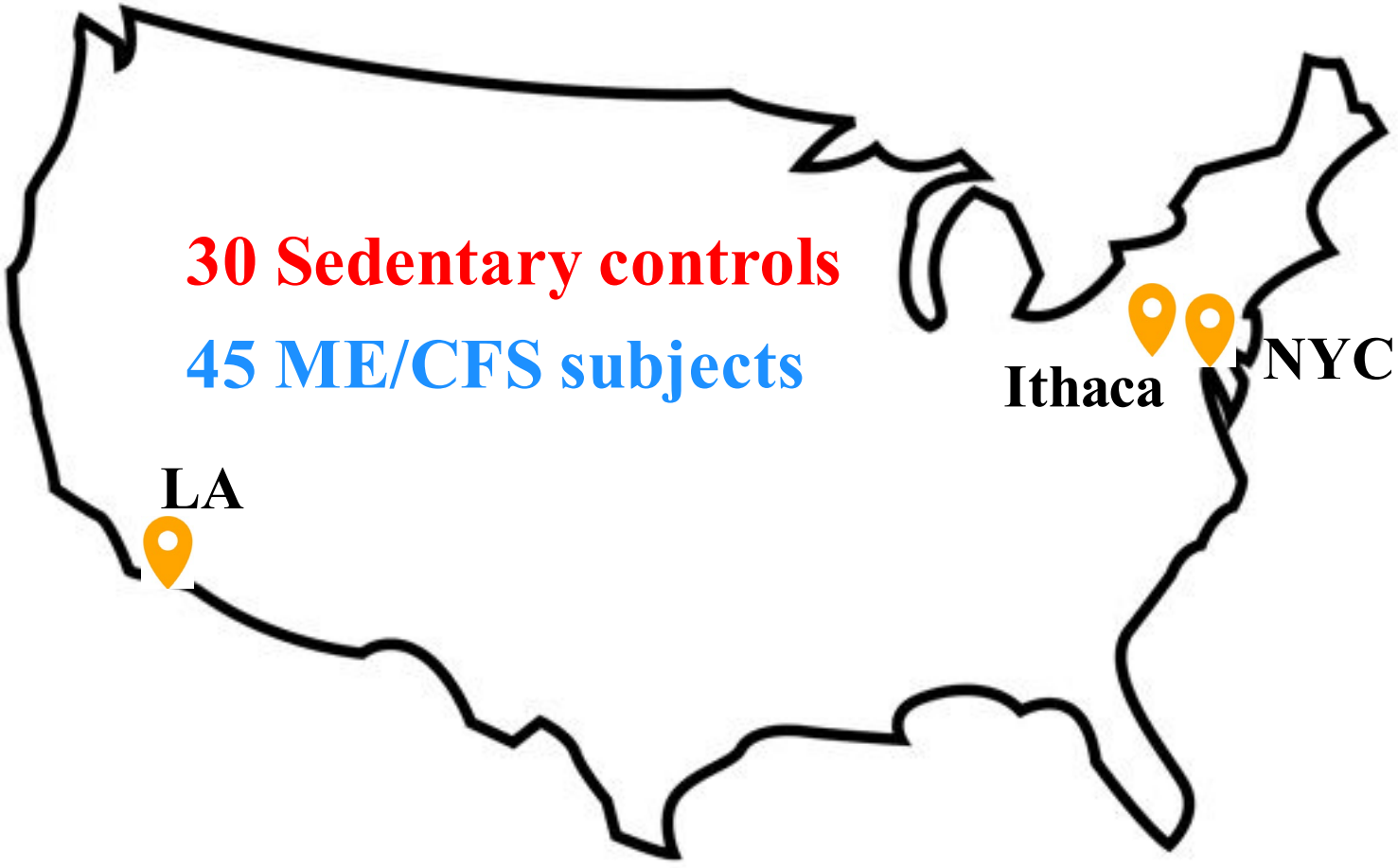
Plasma metabolite comparisons may reveal differences in functioning of tissues and organs



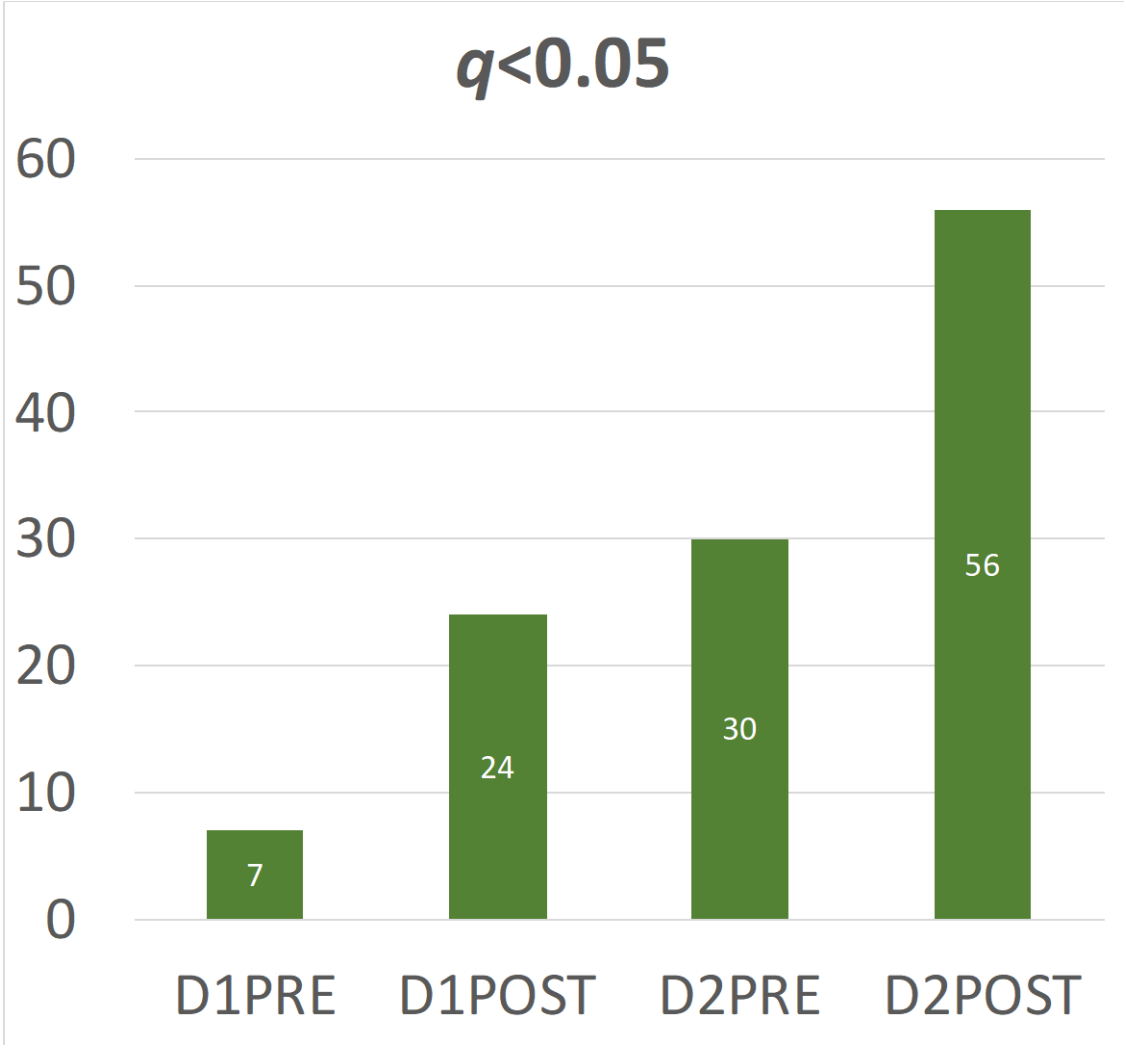


Plasma metabolites analyzed by Metabolon, Inc.

933 metabolites identified



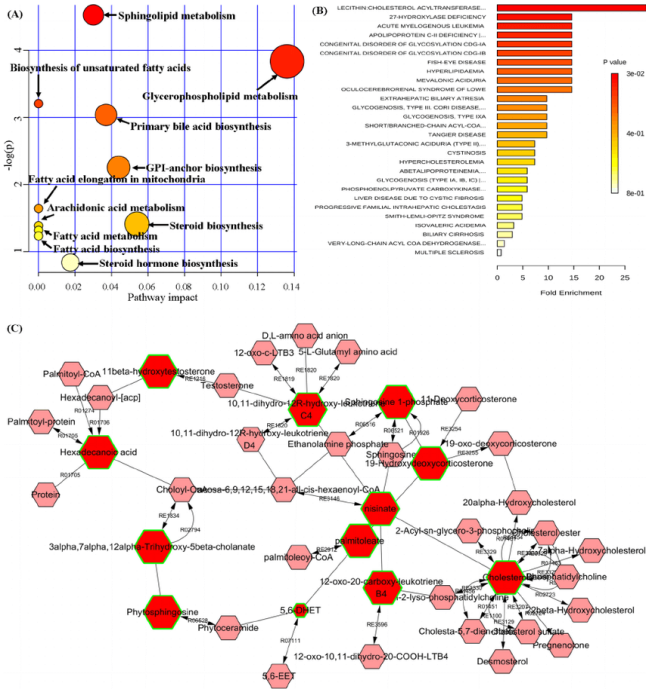
Exercise increases the number of metabolites significantly different between controls and patients



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

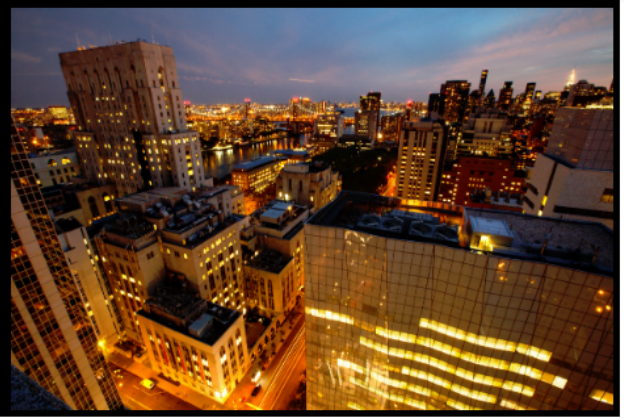
By not expressing disbelief in the physical nature of the illness

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

Center for Enervating NeuroImmune Disease

Cornell University in Ithaca, NY



Weill Cornell Medicine in Manhattan, NY

The Cambridge Dictionary defines "**Enervating**" as:

adjective

causing you to feel weak and lacking in energy

About the Cornell ENID Center

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

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Simmaron Research
Scientifically Redefining ME/CFS

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