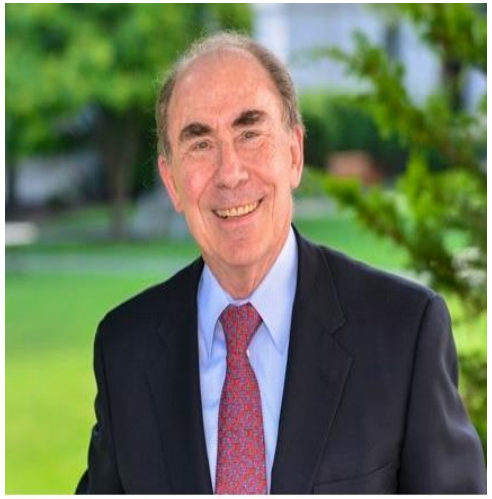
Solve ME/CFS Initiative

Leveraging patient-centered research to cure ME/CFS

2016 Webinar Series | Thursday, November 10, 2016 | 1:00 PM Eastern

Hot Areas in ME/CFS Research with Anthony Komaroff, MD



Dr. Anthony Komaroff

Simcox – Clifford – Higby professor of medicine at Harvard Medical School and senior physician at Brigham and Women's Hospital in Boston,MA

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About Our Webinars

- Welcome to the 2016 webinar series!
- The audience is muted; use the question box to send us questions
- Webinars are recorded, and the recording is made available on our YouTube channel: http://YouTube.com/SolveCFS
- The Solve ME/CFS Initiative is a research organization and does not provide medical advice

Save the Dates!

- Thursday, December 15: **Zaher Nahle, PhD, MPA**
  - Zaher Nahle, PhD, MPA , Vice President for research and scientific programs at Solve ME/CFS Initiative

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Hot Areas in ME/CFS Research

Anthony L. Komaroff, M.D.

Simcox-Clifford-Higby Professor of Medicine, Harvard Medical School

SolveME/CFS Webinar, November 10, 2016

Goal for Today

- Briefly revisit the “controversy” about ME/CFS that began in the mid-1980s
- Review the evidence that should put the controversy to rest
- Describe the hottest areas today in understanding the biological underpinnings to ME/CFS

Controversy: "Is ME/CFS Real?"

- 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?

2015 Reports/Initiatives on ME/CFS

Institute of Medicine, National Academy of Sciences: **300-page report reviewing all (9,000+ articles) of the published literature. Concludes CFS/ME is a biologically-based illness, proposes new case definition and new name**

National Institutes of Health:

- **Conference report concludes CFS/ME is a biologically-based illness**
- **Announces expanded research program**

Centers for Disease Control & Prevention: **Expanded research program; Subject of Grand Rounds**

Institute of Medicine Report: Scope/Seriousness of ME/CFS

- **836,000 to 2.5 million Americans have CFS/ME**
- **Direct & indirect economic costs: $17-24 billion annually in the U.S.**

From: Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness. Institute of Medicine, 2015.

Growing Global Interest in ME/CFS

- There is growing interest in CFS from scientists all around the world
- Conference in Japan in late October, attended by some of Japan's top neurologists
- The 12th International IACFS/ME Conference has just concluded, with scientific presentations from scientists all over the world.

The “Hot Areas” of Research

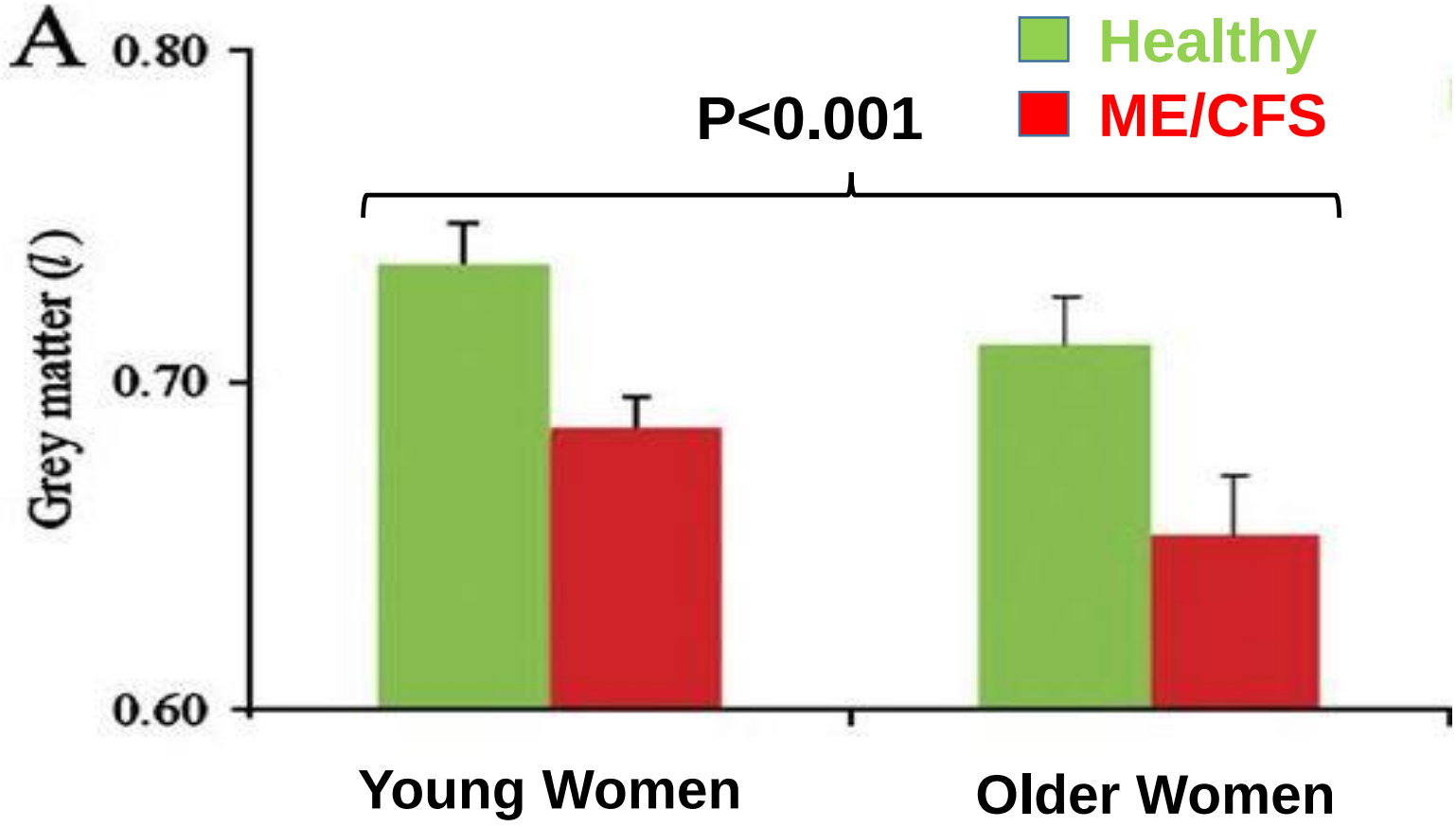
- Brain (central nervous system)
- Exercise (& post-exertional malaise)
- Immune system (& Infectious agents)
- Energy metabolism/mitochondria
- Epigenetic studies
- A Hypothesis: Low-grade brain inflammation, often triggered by brain-immune-gut connections)

Studies of the Brain

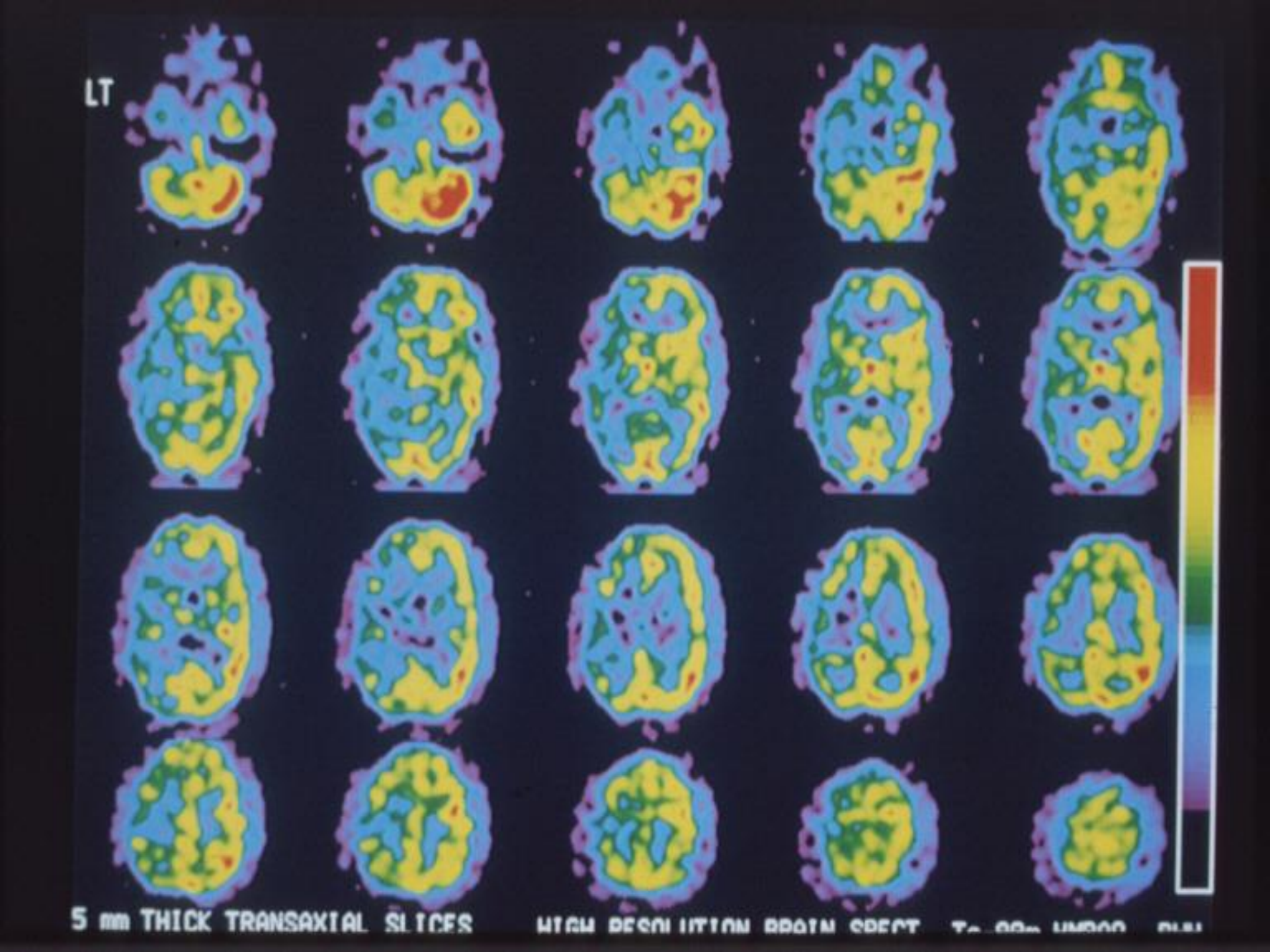
CNS Involvement in ME/CFS

- ***Neuroendocrine dysfunction:*** **Impairment of multiple limbic-hypothalamic-pituitary axes (involving cortisol, prolactin, & growth hormone) and serotonin (5-HT) system**
- ***Cognition:*** **Impairments in information processing speed, memory and attention — not explained by concomitant psychiatric disorders**
- ***Autonomic dysfunction:*** **Impaired sympathetic and parasympathetic function, 30-80%**
- ***MRI:*** **Multiple abnormalities**
- ***SPECT:*** **Areas of reduced signal**
- ***PET:*** **Immune cell activation (neuroinflammation)**
- ***EEG abnormalities:*** **↑ sharp/spike waves, distinctive spectral coherence pattern, impaired connectivity**

Reduced Grey Matter in ME/CFS:
Voxel-Based Morphometric (Unbiased) Study



From: de Lange F, et al. NeuroImage 2005;26:777.


LT
5 mm THICK TRANSAXIAL SLICES

Functional "Connectivity" in Brain

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)**

Summary: The Brain in CFS

Many different techniques for looking at the brain all say something is wrong

They do not say that the problem is a permanent or a progressive problem

The cause of the problem remains obscure: infection of the brain and nervous system, or an immune system attack on parts of the brain, are reasonable but unproven possibilities

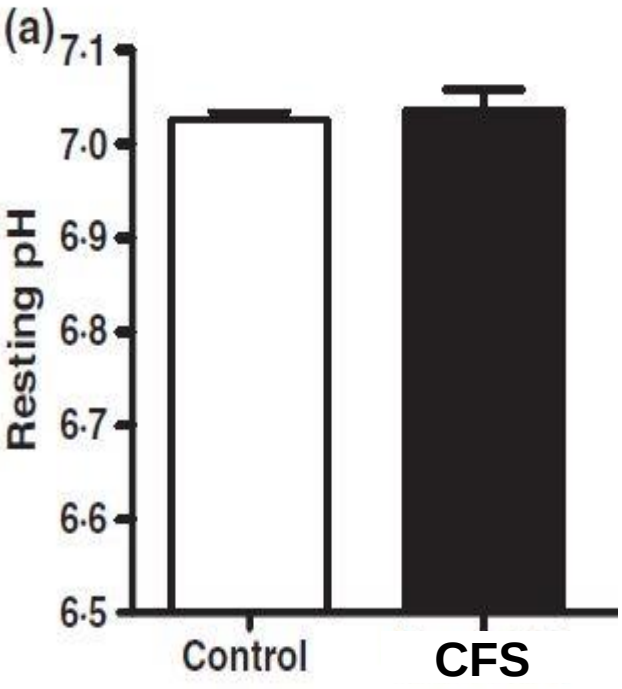
Effects of Exercise/ Causes of Post-Exertional Malaise in ME/CFS

Abnormalities of Muscle in ME/CFS

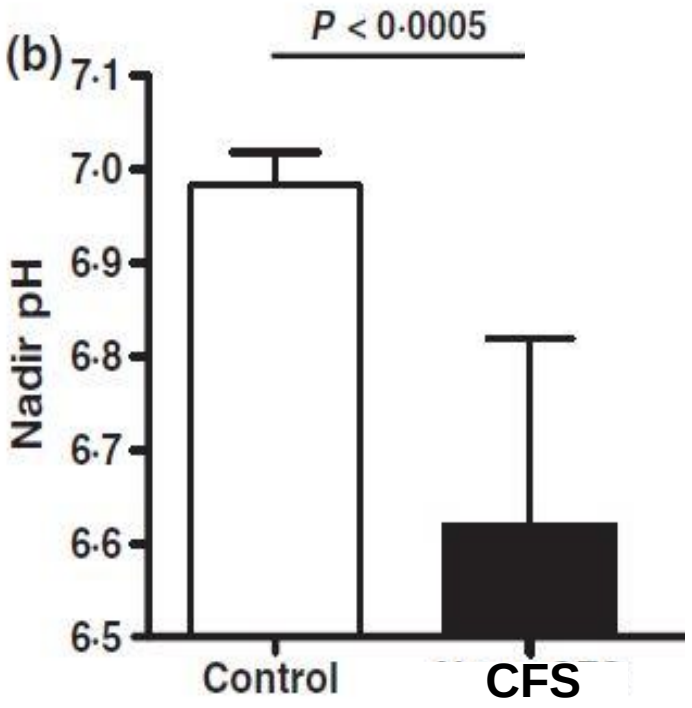
- ***Central sensitization:*** **Decreased pain threshold, generalized hyperalgesia**
- ***Oxidative and nitrosative stress:*** **Elevated TBARS (products of lipid peroxidation)**
- ***Mitochondrial dysfunction:*** **Reduced levels of succinate reductase, cytochrome-C oxidase, and coenzyme Q10**
- ***Bioenergetic dysfunction:*** ⇩ **proton efflux after exercise;** ⇧ **intramuscular acidosis (?) with exercise**

Adapted from: Rutherford G, et al. J Aging Res 2016; doi: 10.1155/2016/2497348

Muscle Acidosis During Exercise:
Determined by MR Spectroscopy



Muscle pH at Rest



Muscle pH at Max Exercise

Reduced anaerobic threshold causes ⬆ lactic acid

From: Jones DEJ, et al. Eur J Clin Invest 2012;42:186.

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)**

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)**

Studies of Immune System

Immunological Abnormalities in CFS

- **CD8 + "cytotoxic" T cells bearing activation antigens (CD38 +, HLA-DR)**

  Landay AL.. Levy JA. Lancet 1991; 338:702.

  Barker E, Landay AL, Levy JA. Clin Infect Dis 1994;18:S136

- **Poorly functioning natural killer (NK) cells**

  Caligiuri M…Komaroff AL.. Ritz J. J Immunol 1987; 139:3306.

  Klimas NG, et al. J Clin Microbiol 1990; 28:1403.

  Herberman R, et al. Clin Immunol Immunopathol 1993; 69:253.

  Brenu EW et al. J Translat Med 2012, 10:88

- **Upregulation of the 2,5A system**

  Suhadolnik RJ, et al. Clin Infect Dis 1994; 18-S96

  De Meirleir K, et al. Am J Med 2000; 108:99-105

- **Increased production of pro-inflammatory cytokines**

  Patarca R. Ann NY Acad Sci 2001;933:185-200.

  Moss RB, et al. J Clin Immunol 1999;19:314.

  Kerr JR, et al. J Gen Virol 2001;82:3011.

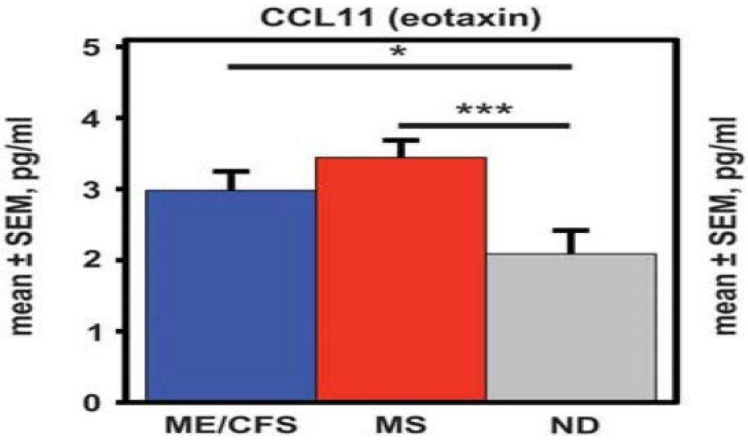
Cytokine Levels: Dramatic Differences in Short-Term vs. Long-Term Patients

- Study of 298 ME/CFS patients enrolled at six sites vs. 348 age-, gender-matched healthy controls
- Patients ill less than 3 years compared to those ill for more than 3 years, and to healthy controls
- Levels of 51 cytokines measured in same sample
- 28/51 cytokines (both pro- and anti-inflammatory) were ***up-regulated*** in the ***short-term*** group, but most of these were ***slightly depressed*** in the ***long-term*** group: due to lymphocyte "exhaustion"?

From: Hornig M, et al. Science Advances 2015 (Feb 27);1:e1400121

Cytokines in Spinal Fluid, in ME/CFS

- 32 ME/CFS vs. 40 MS vs. 19 age- & sex-matched healthy controls
- 51 different cytokines measured in spinal fluid
- Highly significant differences between ME/CFS and healthy for most cytokines: ME/CFS often like MS
- "Consistent with immune activation in the CNS, and a shift toward a T helper type-2 pattern."



From: Hornig M, et al. Molecular Psychiatry (2016) 21, 261–269.

Cytokines in ME/CFS

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)**

Autoantibodies in ME/CFS

- Increased numbers of B cells
- Anti-nuclear antibodies
- Anti-cardiolipin, anti-phospholipid antibodies
- Anti-neuronal antibodies
- Anti-ganglioside antibodies
- Anti-serotonin antibodies
- Anti-muscarinic cholinergic receptor antibodies (M3, M4)
- Anti-β adrenergic receptor

Hokama Y. J Clin Lab Anal 2008;22:99. Konstantinov K. J Clin Invest 1996;98:1888. Buchwald D. Arthritis Rheum 1991;34:1485. Nishikai M. Nippon Rinsho 2007;65:1067. Klein R. Eur J Med Res 1995;1:21. Tanaka S. Int J Mol Med 2003;12:225.; Loebel M, et al. Brain, Behav & Immun 2016;52:32.

Infection and ME/CFS—My Current View

- There now is solid evidence that ME/CFS can follow a new infection: i.e., some cases appear to be ***triggered*** by infection
- Infectious agents may ***perpetuate*** ME/CFS in some patients, but this has not been proven
- Several agents associated with ME/CFS cannot be fully eradicated by the immune system, and infect the central nervous system: could the symptoms result from a chronic low-grade encephalitis?

Summary: The Immune System in ME/CFS

Something has activated several different parts of the immune system

What has activated the immune system is unclear, but infectious agents are a plausible possibility

Immune system activation in or near the brain and the nerves that come from it could explain many of the symptoms of CFS

Energy Metabolism, Oxidative Stress and Nitrosative Stress

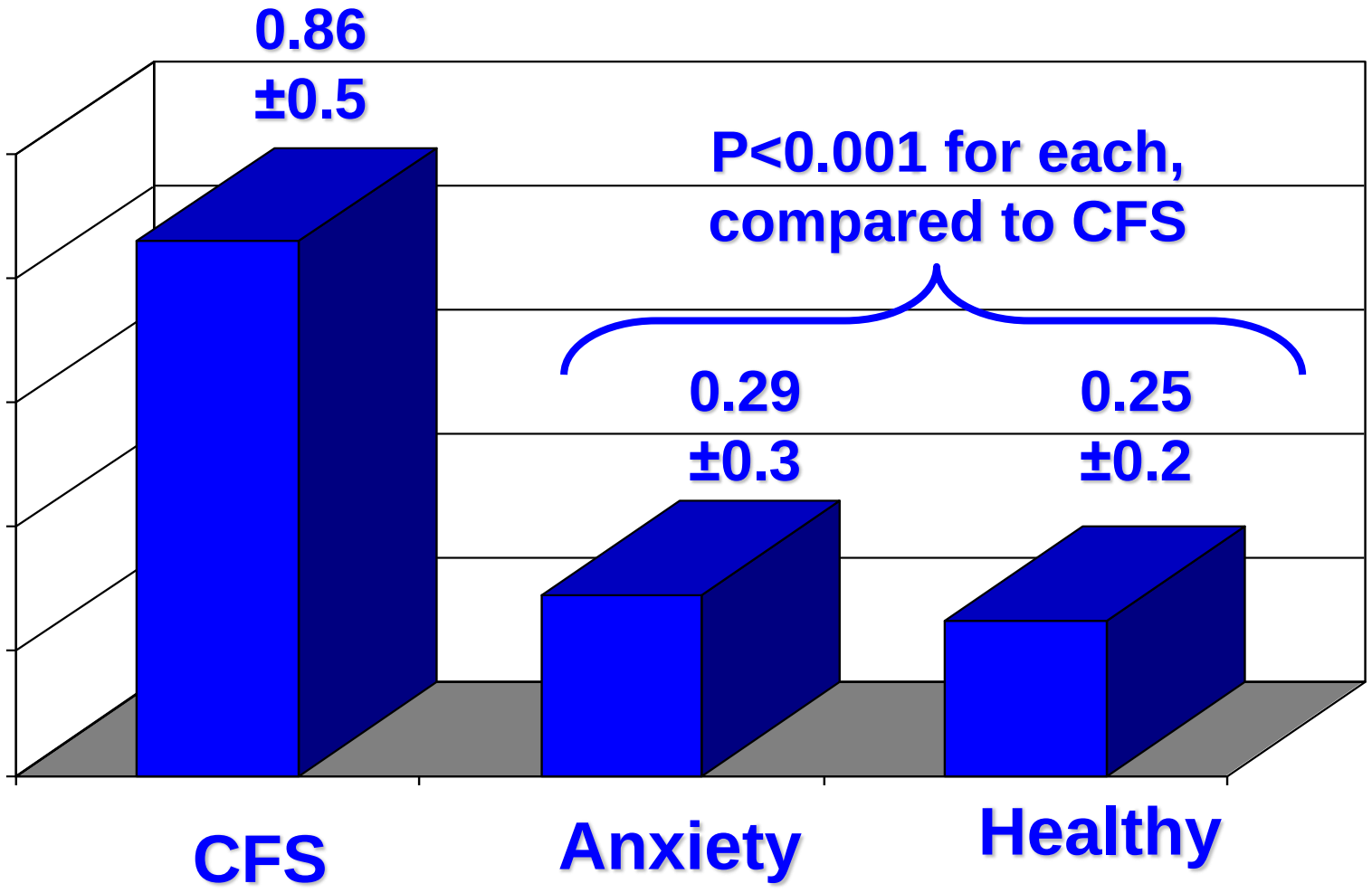
The Energy Metabolism Hypothesis

If the organism experiences a lack of energy, perhaps there is a defect in energy metabolism at the cellular level.

Documented Abnormalities Of Energy Metabolism in ME/CFS

- Defective production of molecules that gives cells energy
- Physical abnormalities of the mitochondria, the “energy pack” inside every cell that produce energy
- “Oxidative stress”, which can damage mitochondria

Lactate in Spinal Fluid in CFS:
In vivo Proton MR Spectroscopy



Mathew SJ, et al. NMR Biomed 2008 (DOI 10.1002/nbm.1315)

Energy Metabolism Studies in ME/CFS

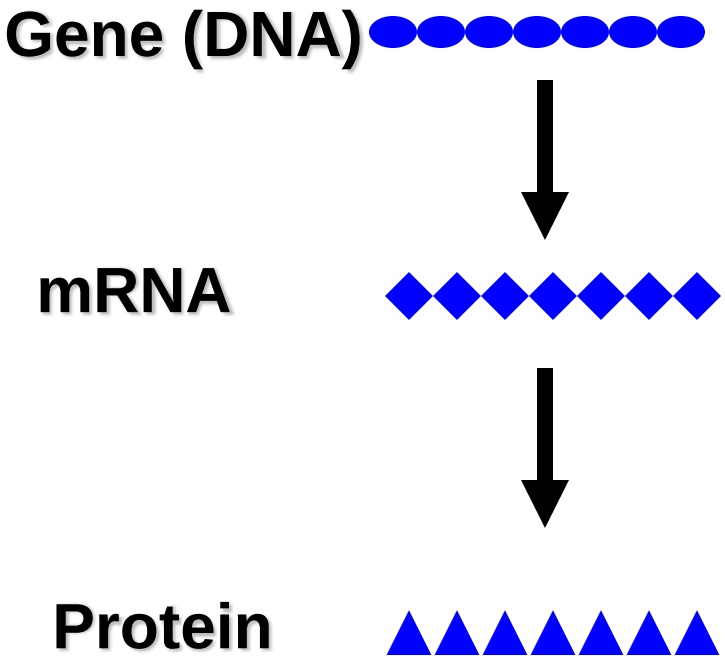
- Studies on patients in the rituximab trial have an energy metabolism deficit, and the key molecule is the enzyme pyruvate dehydrogenase (PDH). Speculate that autoantibodies may be the cause of this deficit. Upregulation of PDH inhibitors in white blood cells **(U. Bergen, Norway).**
- Peripheral white 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.)**

Epigenetic Studies

Genetic Studies

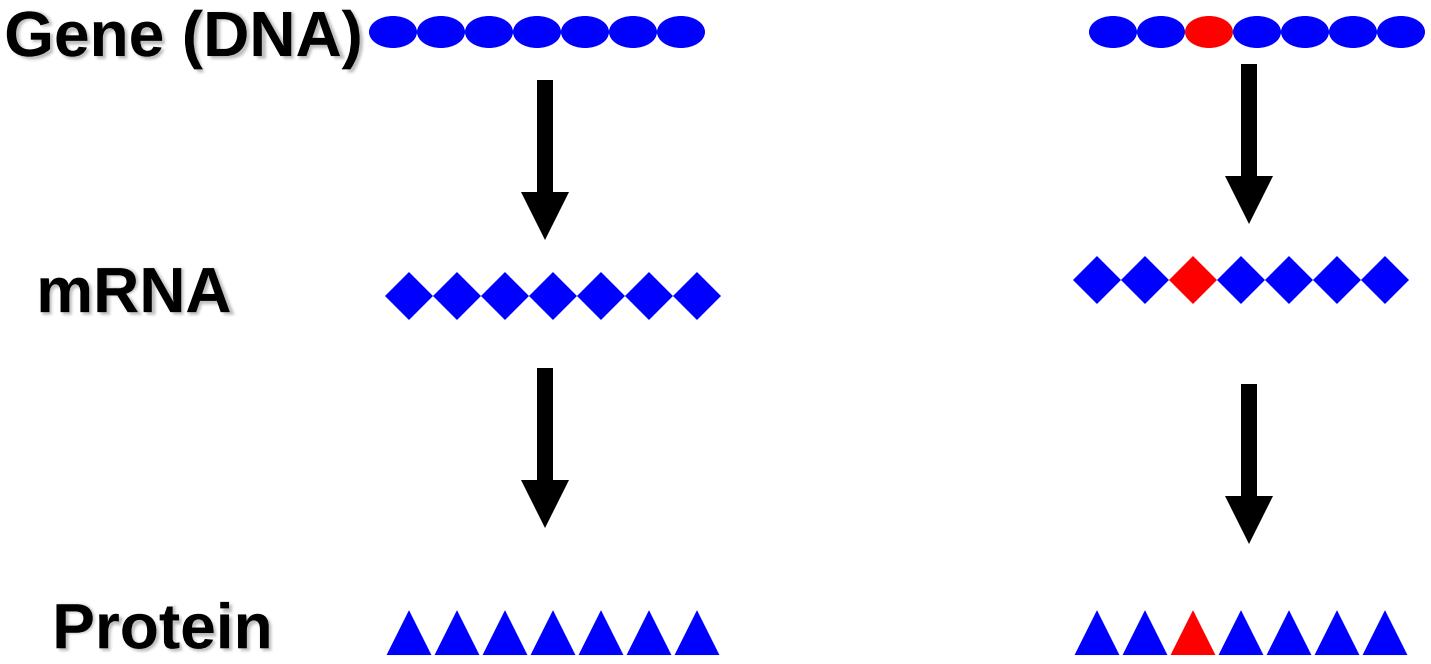
- Before talking about epigenetic studies, let's talk about genetic studies
- In 1949, a particular defect in the *structure* of a particular gene was found to cause a terrible disease—sickle cell anemia.
- Since then, we've tried to understand disease by looking for defects in gene structure
- "For a gene to work normally, it must be built normally"

Genes (DNA)→mRNA→Protein



Normal gene makes normal protein

Genes (DNA)→mRNA→Protein



Normal gene makes normal protein

Abnormal gene variant makes abnormal protein

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

Epigenetic Studies in ME/CFS

- Abnormal expression of many genes have been reported
- Different epigenetic mechanisms are involved. Two of the more common are:
  - MicroRNAs
  - Abnormal methylation of genes

Hypothesis: Low Grade Brain Inflammation Causes Symptoms of ME/CFS

Brain-Immune System-Gut Connection

Hypothesis: ME/CFS is Caused By Low-Grade Brain Inflammation

- **ME/CFS can be triggered by *different* factors, but all the factors end up causing low-grade inflammation in the brain. That inflammation causes the symptoms of ME/CFS.**
- **The inflammation could be caused by infection *inside* the brain that the immune system can constantly attack, but cannot eradicate: minimal or no cellular damage**
- **Or by an autoimmune process *inside* the brain**
- **Or by chronic infection or inflammation *outside* the brain that sends signals to the brain**

Sickness Behavior

- Seen in most animals, even invertebrates
- A *temporary* response to injury and infection: to focus body's energy stores on fighting infection/healing injury (***acute*** inflammation & fever), the brain directs a decrease in energy-consuming activities: lethargy, social withdrawal, achiness, sleepiness, loss of libido, difficulty thinking, depression, anorexia
- Sickness behavior comes from activation of the innate immune system in the brain, caused by inflammation ***inside*** or from ***outside*** of the brain?
- Are there circumstances in which this physiology could become ***chronic?***

From: Morris G, et al. BMC Medicine 2013;11:64.

How Can Inflammation *Outside* the Brain Lead to Activation of Innate Immune System *Inside* the Brain?

Innate immune system in the brain can be activated by infection elsewhere in the body due to:

- ***Humoral:*** A blood-brain barrier made "leaky" by inflammation, allowing entry into the brain of circulating immune cells and molecules (via circumventricular organs and brain endothelial cells)
- ***Neural:*** Retrograde signals up the vagus nerve to the brain, triggered by any peripheral infection

From: Poon DC-H, et al. Neuroscience and Biobehavioral Reviews 2015;57:30–45

How the Microbiome May Affect The Brain

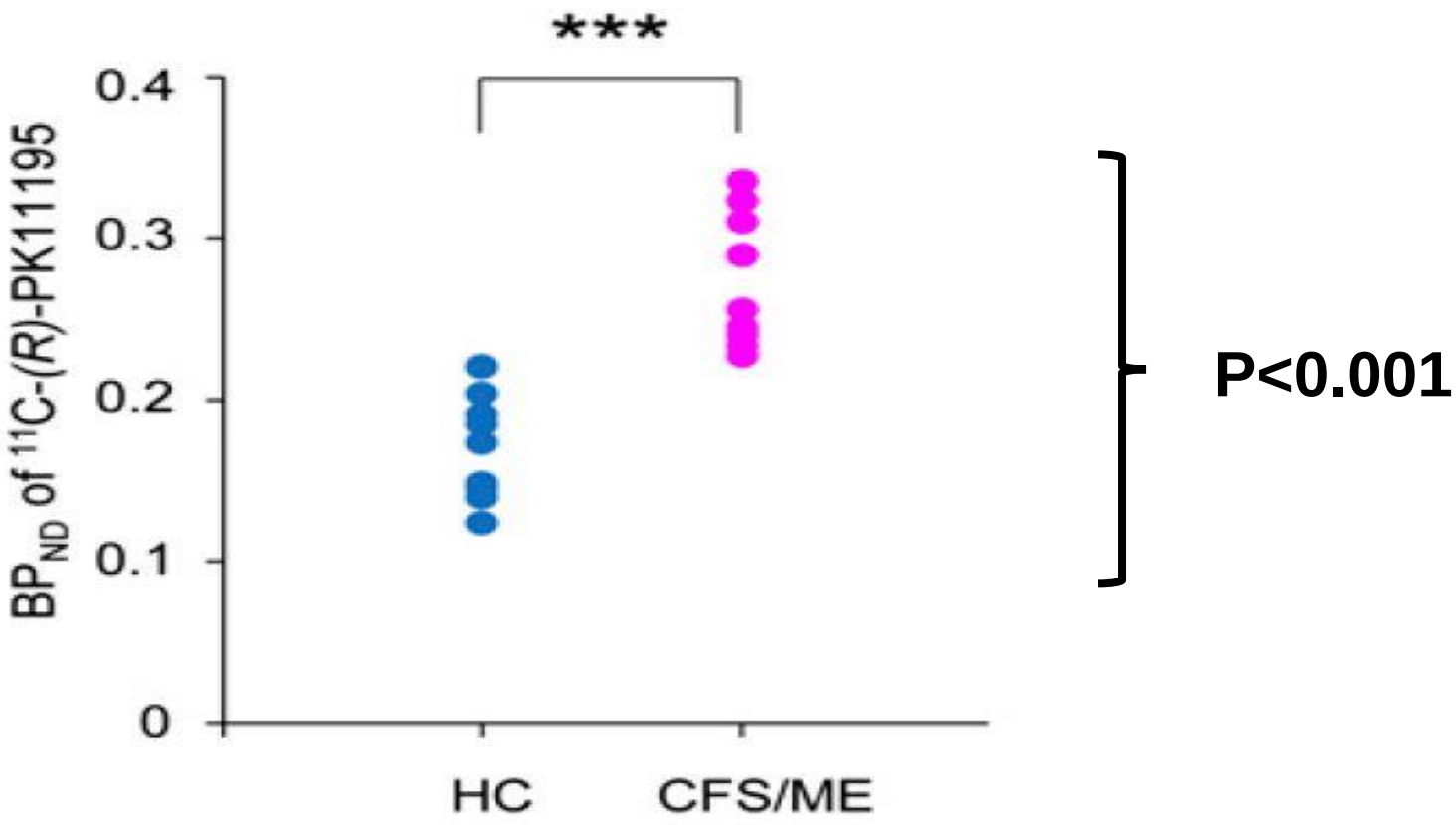
- **The human microbiome:** 10 times as many bacterial cells as human cells, containing 5-8 million genes compared to our 20,000+ genes
- Microbes in our gut:
  - Synthesize hormones and neurotransmitters (e.g. norepinephrine, serotonin, dopamine, ACh, GABA)
  - Synthesize molecules of inflammation (cytokines, 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

From: Navaneetharaja N, et al. J Clin Med 2016;5:55

Is There Evidence the Brain's Innate Immune System is Chronically Activated?

- The brain-immune-gut chronic sickness behavior hypothesis states that the ongoing symptoms and suffering of this illness stem from chronic activation of the brain's innate immune system—due to low-grade infection of the brain or to chronic inflammation outside the brain that sends signals to the brain
- So, is there any evidence of such chronic activation of the brain's innate immune system?

PET Evidence of Brain Inflammation Distinguishes CFS from Healthy



CFS: N=9 Controls: N=10.

From: Nakatomi Y, et al. J Nucl Med 2014; 55:945–950

ME/CFS: In Summary…

- The pathogenesis is still obscure, and the causes are probably multiple
- The case definition of CFS likely encompasses several illnesses with similar symptoms, but different triggers
- No tests yet have adequate sensitivity and specificity for diagnosis
- No proven treatments

But…

ME/CFS In Summary…

- The illness is not simply the expression of somatic symptoms by people with a primary psychological disorder
- Case-control studies comparing ME/CFS patients 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

ME/CFS: In Summary

- ME/CFS may be caused by the same physiology that causes “sickness behavior” in acute infections—a physiology that persists because infection and inflammation persist
- The long-held hypothesis that the symptoms of ME/CFS are caused by activated innate immunity in the brain is increasingly plausible
- The possibility that the gut microbiome may influence this process is plausible

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Leveraging patient-centered research to cure ME/CFS

Thank you for joining us!

Our mission

To make ME/CFS understood, diagnosable, and treatable

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