

# **The Latest Research on CFS**

**Anthony L. Komaroff, M.D.**

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

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# CDC Case Definition of Chronic Fatigue Syndrome

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Severe fatigue that persists or relapses for > 6 months, of new or definite onset, not substantially alleviated by rest, resulting in substantial reduction in activities;

AND four or more of the following symptoms are currently present for > 6 months:

- Impaired memory/concentration
- Sore throat
- Multi-joint pain
- Unrefreshing sleep
- Neck/axillary adenopathy
- Muscle pain
- New headaches
- Post-exertional malaise

AND does *not* have active medical condition to explain the chronic fatigue, nor any psychosis, melancholic depression, substance abuse, dementia, or anorexia nervosa/bulimia

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*From: Fukuda K, et al. Ann Intern Med. 1994;121:953-959*

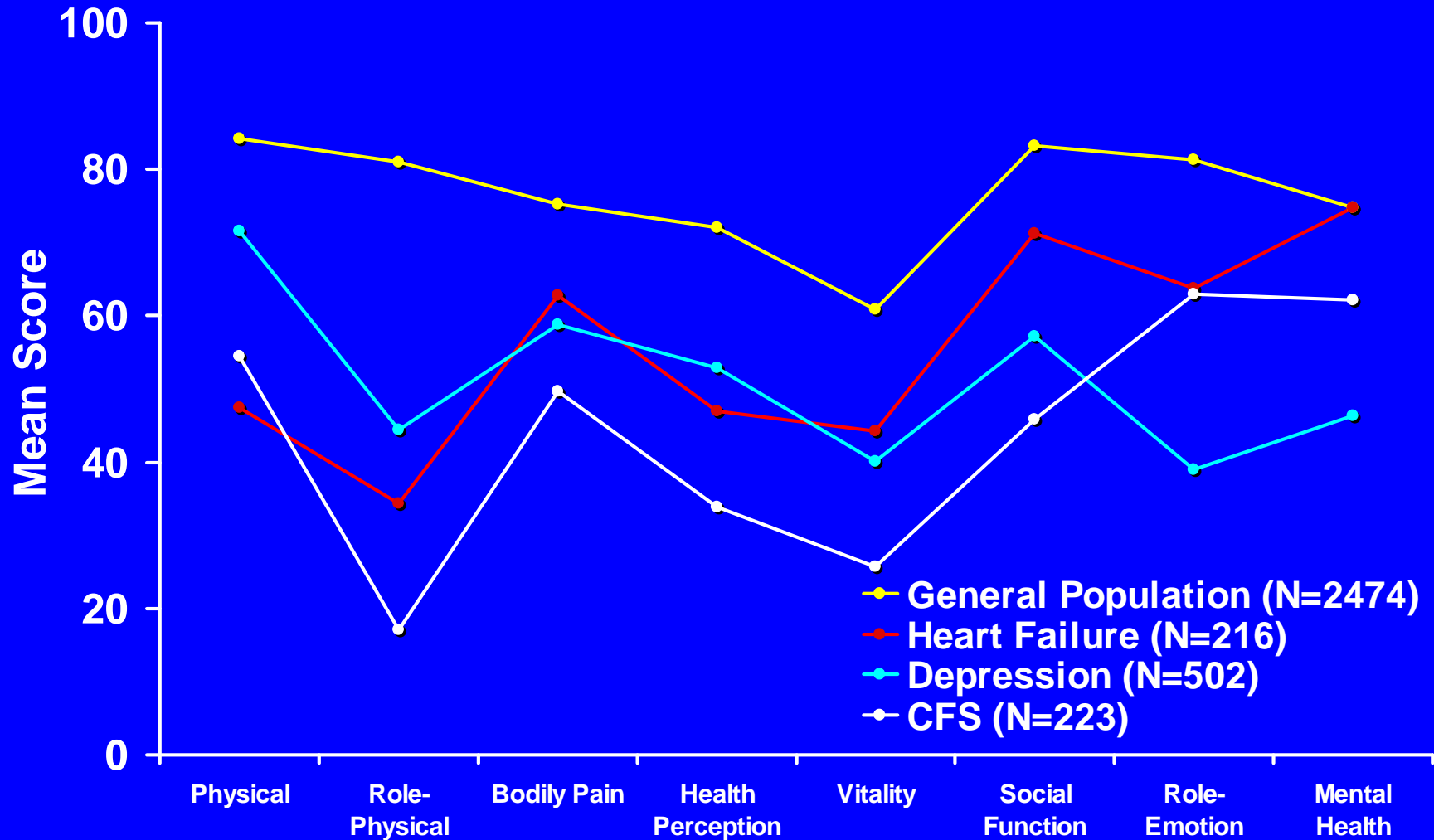
# Chronic Fatigue Syndrome Research

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- **Over 5,000 scientific articles published, over 300 in the most prestigious journals**
  - **8 international research conferences, the last of which had over 160 scientific presentations**
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# Severity of CFS

# SF36 Health Status Subscale Scores: CFS vs. Comparison Groups



Source: Komaroff AL....Ware JE, Bates DW. Amer J Med 1996; 101:281

# Lost Productivity from CFS: CDC Analysis

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**Survey of 56,000 persons contacted by  
random-digit dialing:**

- **37% decline in household productivity**
- **54% reduction in labor force productivity**
- **Total cost to United States each year  
from productivity losses caused by CFS:  
\$9.1 billion**

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*Reynolds KJ. BMC Cost Effect Res Alloc 2004;2:4.*

# Is Chronic Fatigue Syndrome Real?

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- **Are there objective biological markers that are abnormal in CFS?**
  - **Do we understand how CFS symptoms are caused?**
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# How Is The Body Affected by CFS?

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- **Brain (central nervous system)**
  - **Autonomic nervous system**
  - **Immune system**
  - **Energy metabolism/mitochondria**
  - **Genetic studies**
  - **Infectious agents**
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# **The Brain in CFS**

# Evidence of Brain Involvement in CFS

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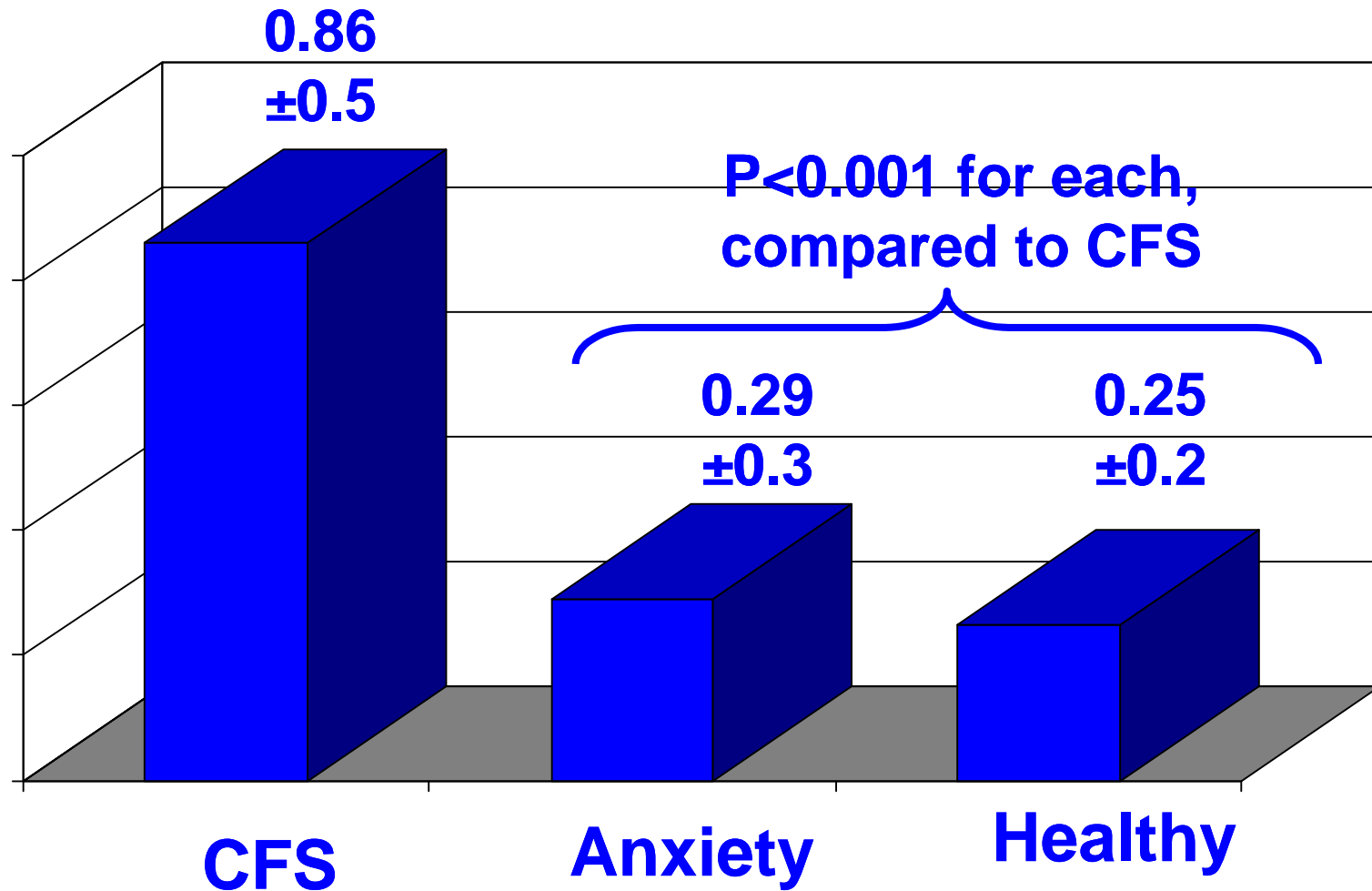
- ***Neuroendocrine dysfunction:*** Impairment of multiple limbic-hypothalamic-pituitary axes (involving cortisol, prolactin, & growth hormone) and serotonin (5-HT) system
  - ***Cognition:*** Impairments in information processing speed, memory and attention — not explained by concomitant psychiatric disorders
  - ***Autonomic dysfunction:*** Impaired sympathetic and parasympathetic function, 30-80%
  - ***MRI:*** Punctate areas of high signal in white matter
  - ***SPECT:*** Areas of reduced signal
  - ***EEG abnormalities:*** ↑ sharp/spike waves, distinctive spectral coherence pattern
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# Proteomic Markers in Spinal Fluid

	CFS N=10	Healthy N=10	P-Value	Function
$\alpha$ 2-macroglobulin	36%	0%	0.01	Protease
Orosomucoid	36%	0%	0.01	Protease
Pigment epith.- derived factor	45%	0%	0.005	Anti- oxidant
Keratin 16	45%	0%	0.005	Meningeal inflamm.
BEHAB	36%	0%	0.06	Structural repair

*Baraniuk JN, et al. BMC Neurology 2005;5:1-19*

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



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

# EEG: Spectral Coherence Studies

<b><i>Group</i></b>	<b><i>Classified Accurately</i></b>	<b><i># Subjects</i></b>
<b>CFS- Unmedicated</b>	<b>89.4%</b>	<b>47</b>
<b>CFS- Medicated</b>	<b>73.9%</b>	<b>23</b>
<b>Healthy controls</b>	<b>87.4%</b>	<b>390</b>
<b>Depressed controls</b>	<b>100.0%</b>	<b>24</b>
<b>Putative “CFS”</b>	<b>46.6%</b>	<b>148</b>

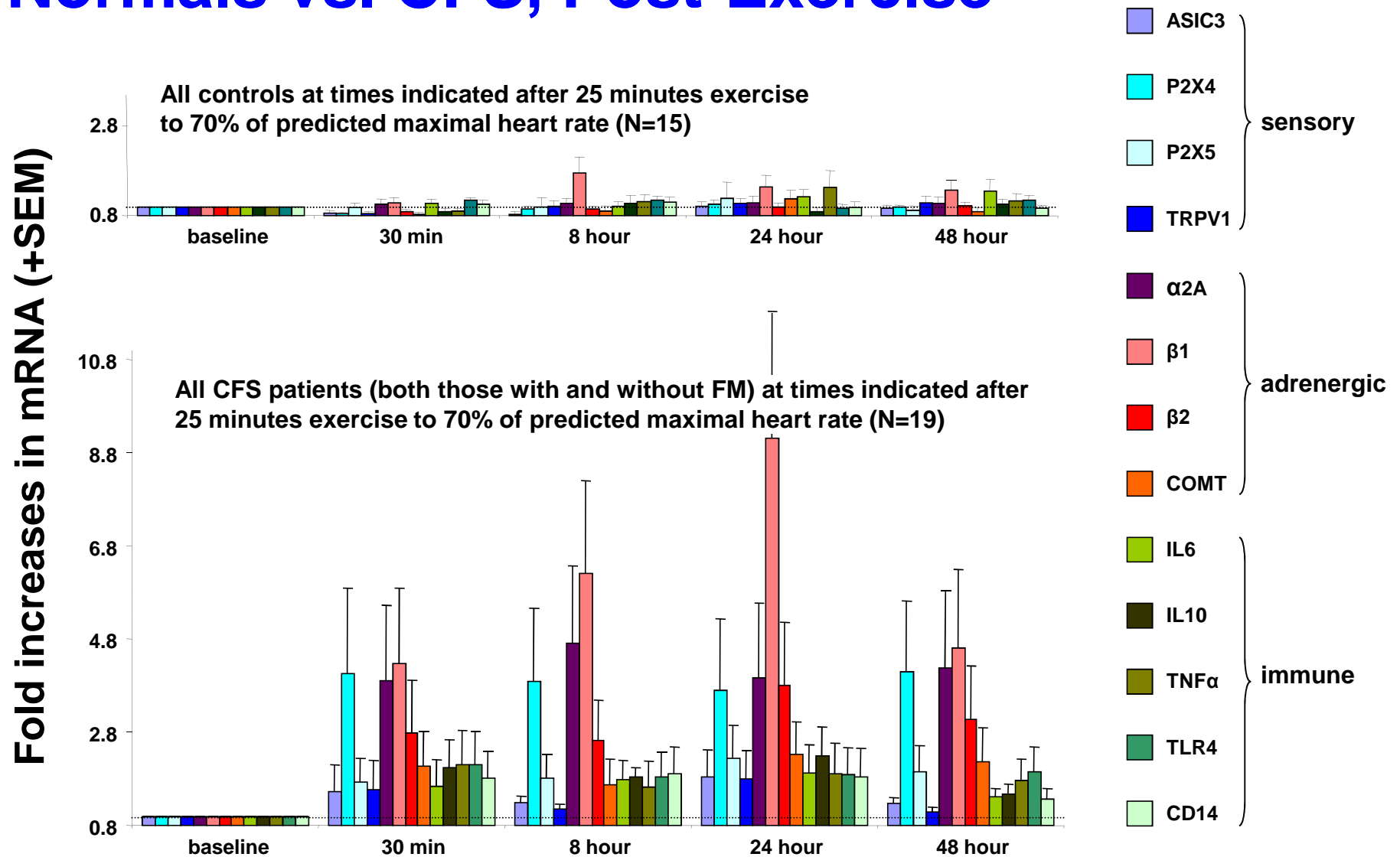
*Duffy FH, et al. Presented IACFS/ME Int. Conf, March 2009*

# Molecular Sensors of Fatigue & Pain

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- Ion channel receptors
- Adrenalin receptors
- Immune system molecules

# Fatigue & Pain Sensing Molecules: Normals vs. CFS, Post-Exercise



Alan Light, et al. *J Pain* 2009;10:1099

# **The Immune System in CFS**



# Immunological Abnormalities in CFS

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- **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.*

- **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.*

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# **Energy Metabolism in CFS**

# The Energy Metabolism Hypothesis

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

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# Genetic Component to CFS

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- Significantly increased prevalence of DR4, DR3 and DQ3<sup>1</sup> (RR 4-6)
- Significantly increased DQ1 (RR 3.2)<sup>2</sup>
- Twin studies show heritability estimate of 51%<sup>3</sup>
- Neuroendocrine gene variants (*TPH2*, *COMT*, *NR3C1*) associated with CFS<sup>4</sup>

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<sup>1</sup>Keller RH, et al. *Clin Infect Dis* 1994;18:S154

<sup>2</sup>Schacterle R, et al. *JCFS* 2003;11:33.

<sup>3</sup>Buchwald D, et al. *Psychosom Med* 2001;63:936

<sup>4</sup>Goertzel BN, et al. *Pharmacogenomics* 2006;7:429.

# Gene Expression Studies in CFS

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Using nucleic acid microarray analysis, the CDC and a team from Southampton University in U.K. compare genes that are activated in patients with CFS and in healthy controls

Find genes encoding proteins involved in immune activation, energy metabolism, and neuro-hormones involved in the stress response are activated more often in patients with CFS.

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*Whistler T, et al. J Trans Med 2003;1:1-8*

*Powell R, et al. Clin Exp Allerg 2003;33:1450-6.*

*Kaushik N, et al. J Clin Pathol 2005;58:826-32.*

*Kerr JR, et al. J Clin Pathol 2008;61:730-9.*

# Infections in CFS

# Infection: Temporary vs. Permanent

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- Most infections come and go—for example, the common cold
  - Some infections come and stay: the immune system can never eradicate them completely, although it can keep them suppressed most of the time, with occasional flare-ups—for example, cold sores caused by *Herpes simplex* virus
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# **Infections and Syndromes: More Than One Microbe**

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- **Many infectious syndromes can be caused by multiple different microbes**
  - **Some diseases may require the interaction of more than one microbe**
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# **Viruses and CFS: Mass CFIDS Talk, 1989**

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- **Infectious agents probably can trigger and perpetuate CFS**
  - **The agents cannot be fully eradicated by the immune system**
  - **There is evidence that CFS can follow a new infection**
  - **It is possible that in CFS different infectious agents interact to cause symptoms**
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# Infectious Agents Linked to CFS

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- Epstein-Barr Virus<sup>1,2</sup>
- Post Q fever (*Coxiella burnetii*)<sup>2,6,7</sup>
- Ross River virus<sup>2</sup>
- Lyme (*B burgdorferi*) (yes, but unusual)<sup>3</sup>
- Parvovirus (yes, but unusual)<sup>4</sup>
- Enteroviruses (probably sometimes)<sup>5</sup>
- *Borna disease virus* ??
- Human herpesvirus-6 (HHV-6)<sup>8</sup>
- *Xenotropic murine leukemia-related virus (XMRV)*<sup>9</sup>

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1. White PD, et al. *Br.J.Psychiatry*. 173:475-481, 1998. 2. Hickie I, et al. *BMJ*. 333:575-578, 2006. 3. Sigal LH. *Am.J.Med*. 88:577-581, 1990. 4. Kerr JR, et al. *J.Gen.Virol*. 2010;91:893. 5. Chia JKS. *J Clin Pathol* 2005;58:1126. 6. Ayres JG, et al. *Lancet*. 347:978-979, 1996. 7. Marmion BP, et al. *Lancet*. 347:977-978, 1996. 8. Komaroff AL. *J Clin Virol* 2006;37:S39. 9. Lombardi VC, et al. *Science* 326:585, 2009.

# Documentation of Post-Infectious Chronic Fatigue Syndrome

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- 256 patients with acute laboratory-documented EBV, Q fever, or Ross River virus infection in one town, followed systematically for over 12 months
- 11% develop CFS—similar with each pathogen
- CFS more likely to occur in patients with initially severe clinical symptoms, which were associated with higher *ex vivo* production of pro-inflammatory cytokines
- CFS *not* more likely in patients with particular premorbid psychiatric and demographic factors

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*Hickie I, et al. BMJ 2006;333:575.*

# Enteroviral Infection in CFS: Gastric Antrum Biopsy Positive

CFS	Controls	P-Value
135/165 (82%)	7/34 (20%)	<0.001

Immunoperoxidase stain with EV-specific mAb

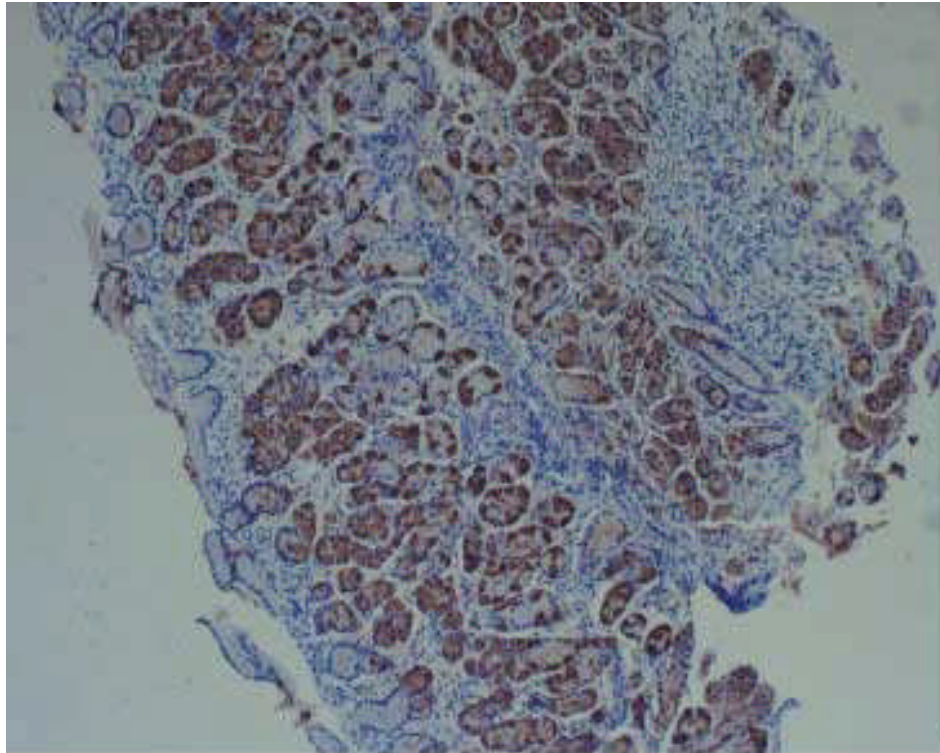
Stain with CMV-specific mAb negative in all samples

EV RNA also detected more often in CFS (P<0.01)

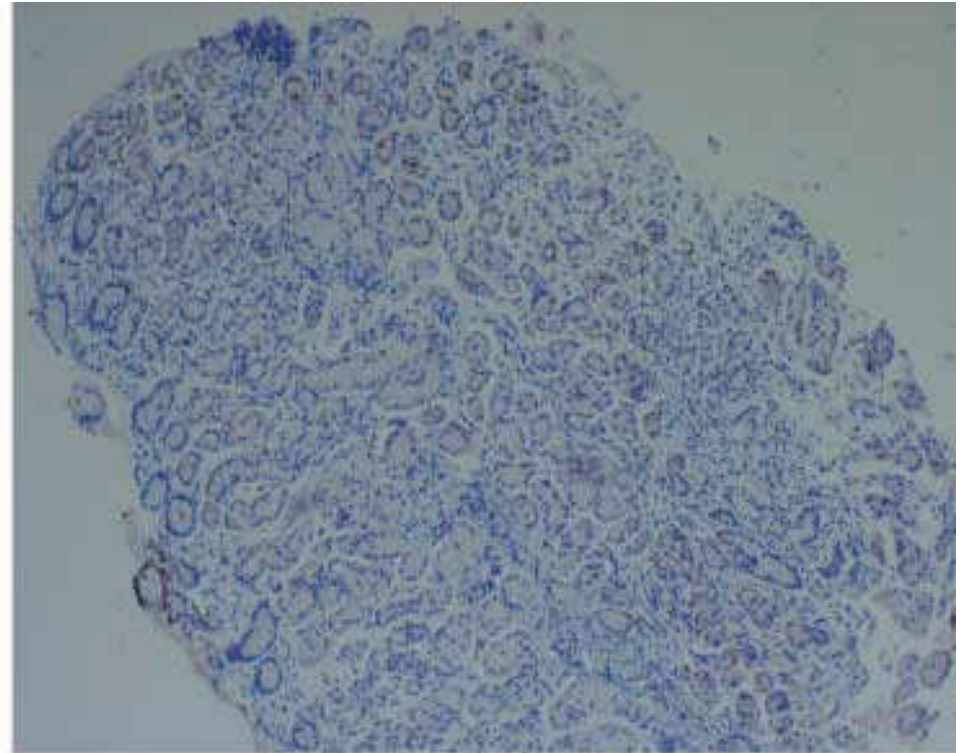
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<sup>1</sup> Chia JKS, Chia AY. *J Clin Pathol* 2008;61:43.

# Enterovirus VP1 Ag in Gastric Antrum



**Enterovirus Staining**



**Cytomegalovirus (control)  
Staining**

# **Neurological Findings in Many (But Not All) Patients with CFS**

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- Initial episode of encephalitis**
  - White matter abnormalities on MRI**
  - EEG abnormalities (spike & sharp waves, characteristic spectral coherence pattern)**
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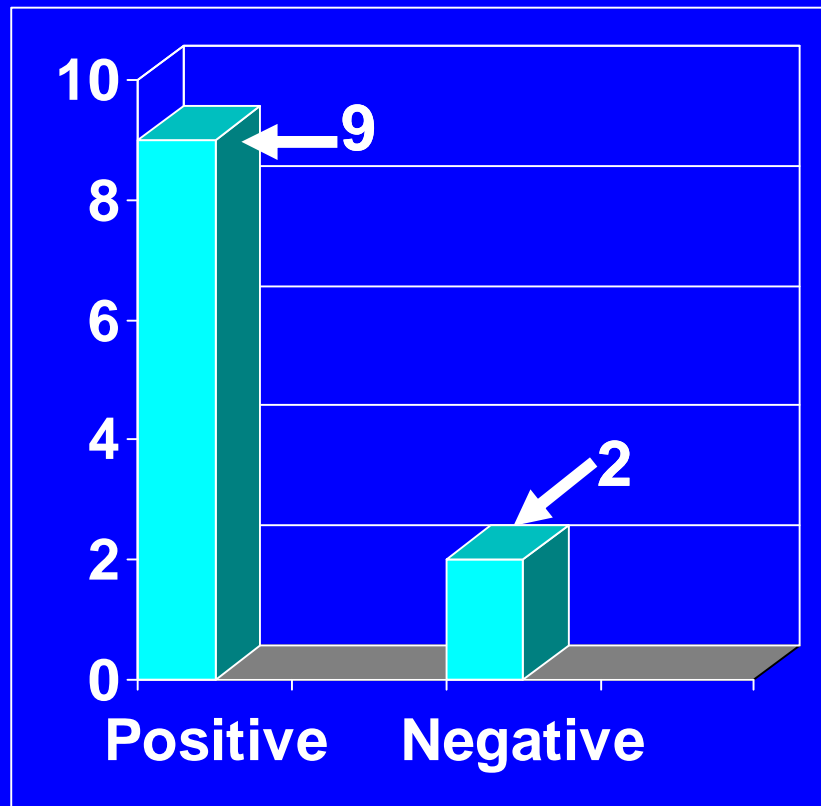
# HHV-6 and the Brain

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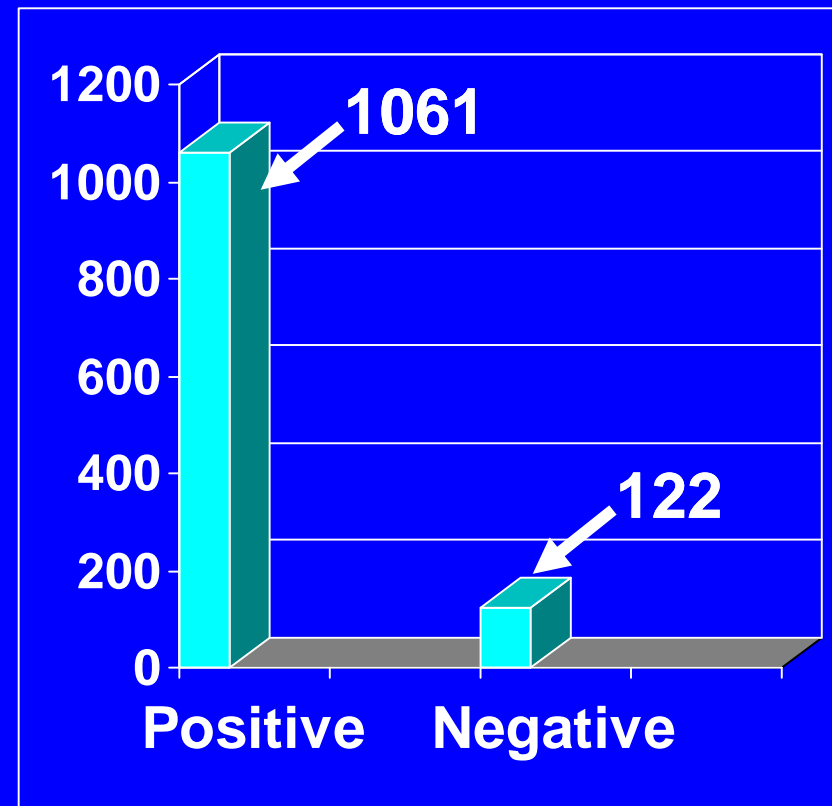
- **Infects neuroblastoma and glioma cells, glial cells (astrocytes, oligodendrocytes) & neurons**
  - **Most common cause of infant febrile seizures**
  - **Persists in CNS after primary infection**
  - **Causes encephalitis in immunosuppressed and (commonly) in immunocompetent**
  - **Causes demyelination in immunosuppressed and in immunocompetent infants/children**
  - **Associated with multiple sclerosis**
  - **Associated with temporal lobe seizure disorders**
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# Active HHV-6 Infection in CFS: Results of Studies

# of Positive vs.  
Negative *Studies*

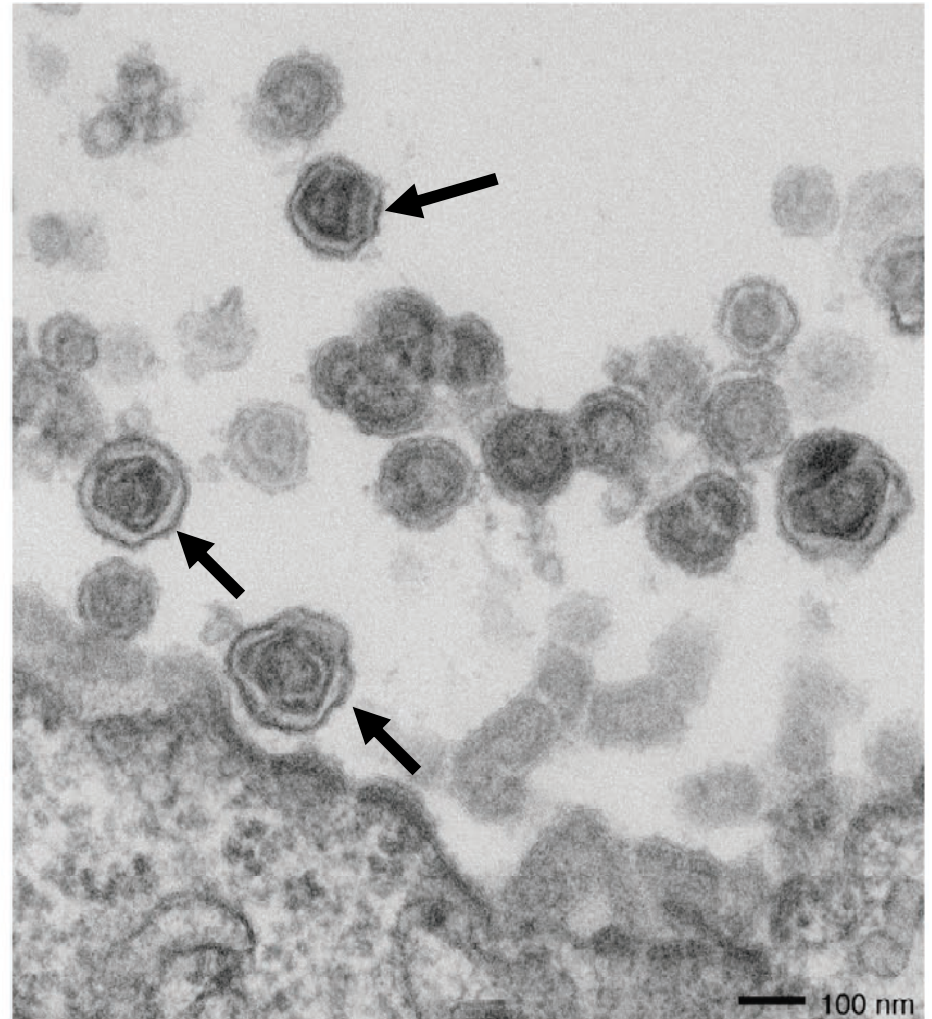
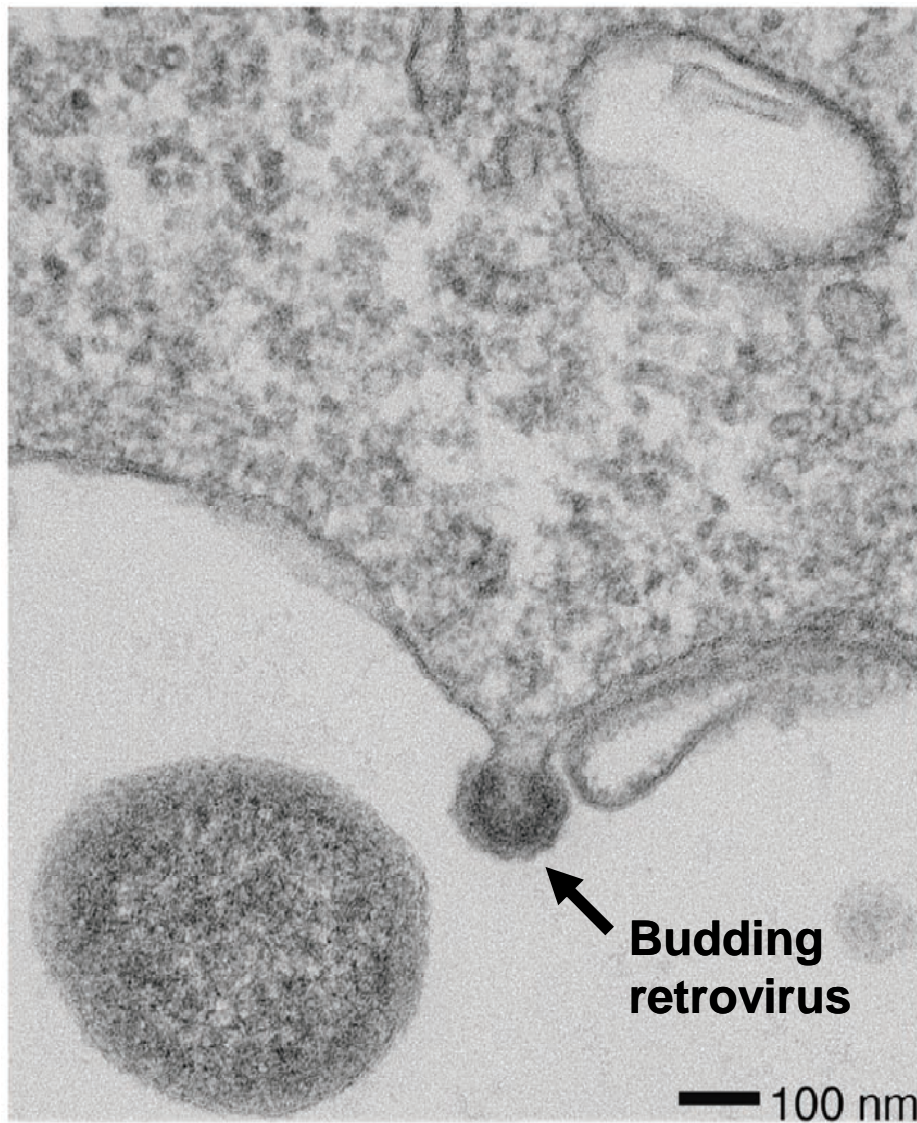


# of *Patients* in Pos.  
vs. Neg. Studies





# XMRV (Retrovirus) in CFS



*From: Lombardi VC, et al. Science 2009;326:585.*

# XMRV (Retrovirus) in CFS

	<b>CFS</b>	<b>Healthy Controls</b>	<b>P Value</b>
<b>Viral nucleic acid</b>	68/101 (67%)	8/218 (4%)	<.0001
<b>Viral protein</b>	19/30 (63%)	0/16 (0%)	<.00001
<b>Infectious agent in plasma</b>	10/12 (83%)	0/12 (0%)	<.00003
<b>Antibodies to virus in serum</b>	9/18 (50%)	0/7 (0%)	<.02

*From: Lombardi VC, et al. Science 2009;326:585.*

# XMRV (Retrovirus) in CFS

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- Is the virus real? **Yes.**
- Is the virus associated with CFS? ***Remains to be confirmed.***
- Is the virus present in 67% or more of CFS cases? ***Remains to be confirmed.***
- Is the virus a cause of CFS? ***Remains to be confirmed.***

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*From: Lombardi VC, et al. Science 2009;326:585.*

# What if XMRV Is Associated With CFS?

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***The Virus is Primary:*** It is a cause of CFS, either acting alone or in combination with other viruses that live within us... OR

***The Virus is Secondary:*** It is inside most of us, asleep, but gets reawakened by immune dysfunction—it is not a cause

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# **Viruses and CFS—My Current View**

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- **Infectious agents probably can trigger and perpetuate CFS**
  - **The agents cannot be fully eradicated by the immune system**
  - **There now is solid evidence that CFS can follow a new infection**
  - **It is possible that in CFS different infectious agents interact to cause symptoms**
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**In Closing...**