The Biology of Chronic Fatigue Syndrome

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Is Chronic Fatigue Syndrome Real?

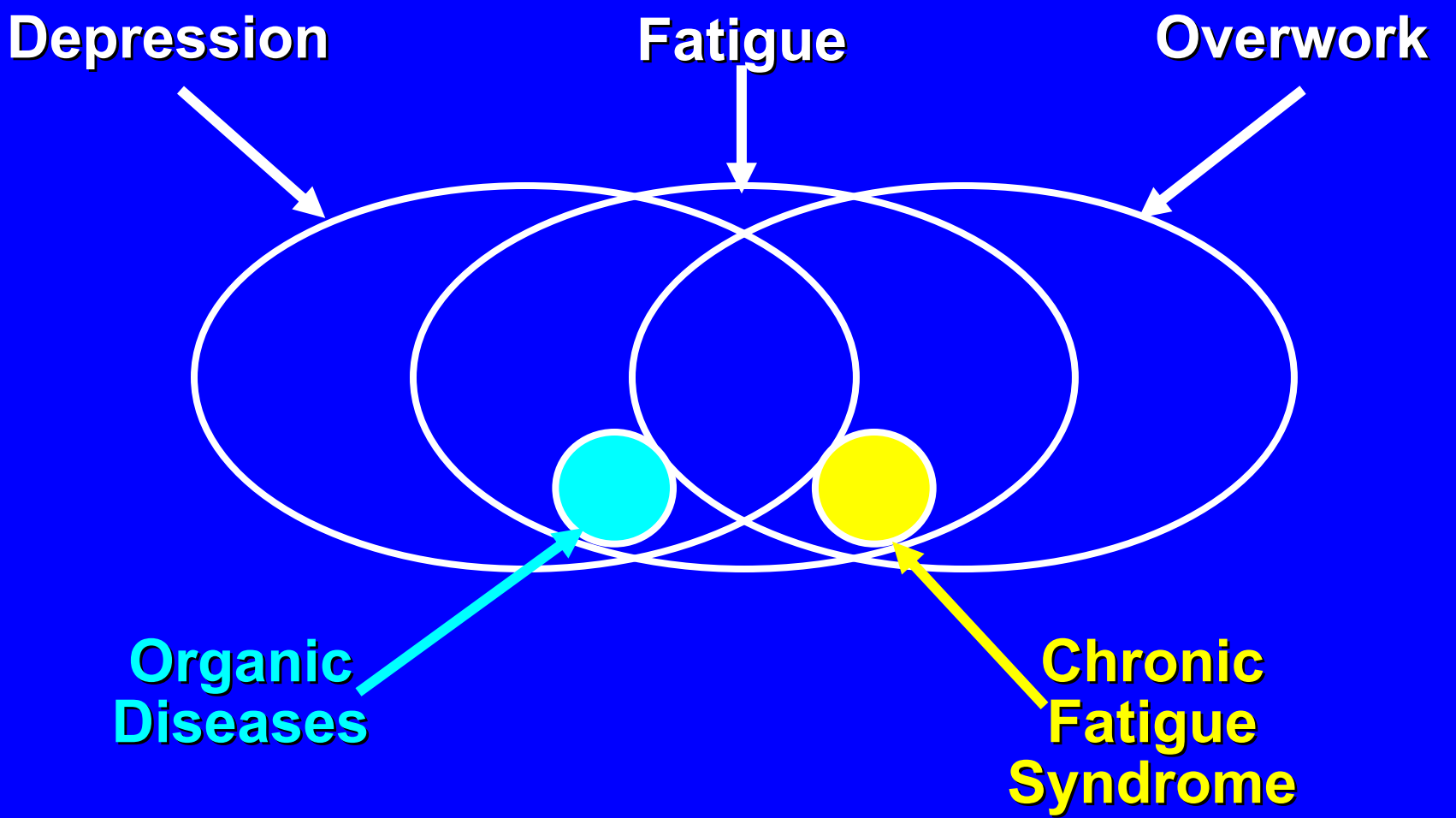
CFS is a syndrome defined just by symptoms, not by objective abnormalities. Are the symptoms imaginary, and not real?

- Are there objective biological markers that are abnormal in CFS?
- Do we understand the pathogenesis of CFS?

International Research/Recognition

- Intramural and extramural research programs at NIH and CDC
- Many international research conferences
- Over 4,500 peer-reviewed publications
- CDC survey of U.S. physicians finds that today over 40% have seen patients with CFS in their practices

Causes of Fatigue in a Primary Care Practice



CDC Case Definition of Chronic Fatigue Syndrome

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

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

Who Are The Patients?

- *Age:* Mid-30's (5-65 years)
- *Sex:* 65% female
- *Socioeconomic:* Middle-class, but more common among African-American/Latino minority populations on population-based surveys
- *Education:* 50% college graduates in office-based samples
- *Severity:* 50% intermittently bedridden/shut-in
- *Duration:* 14 years (4-36 years) in our patients

Sudden Onset

In 80-90% of our patients, the chronic fatigue syndrome started suddenly with a “flu”, “virus”, “bad cold”:

- Sore throat
- Cough
- Rhinorrhea
- Swollen glands
- Myalgias
- Fever
- Headache
- Diarrhea

Why Isn't Chronic Fatigue Syndrome "Just" Depression?

- Differences in objective neuroendocrine studies
- Results of treatment studies
- Results of formal psychiatric assessment

Hypothalamic-Pituitary Abnormalities In Chronic Fatigue Syndrome

	CFS	Depression
ACTH release after stimulation		↑
Prolactin release after stimulation		↓

Bakheit AM, et al. BMJ 1992; 304:1010

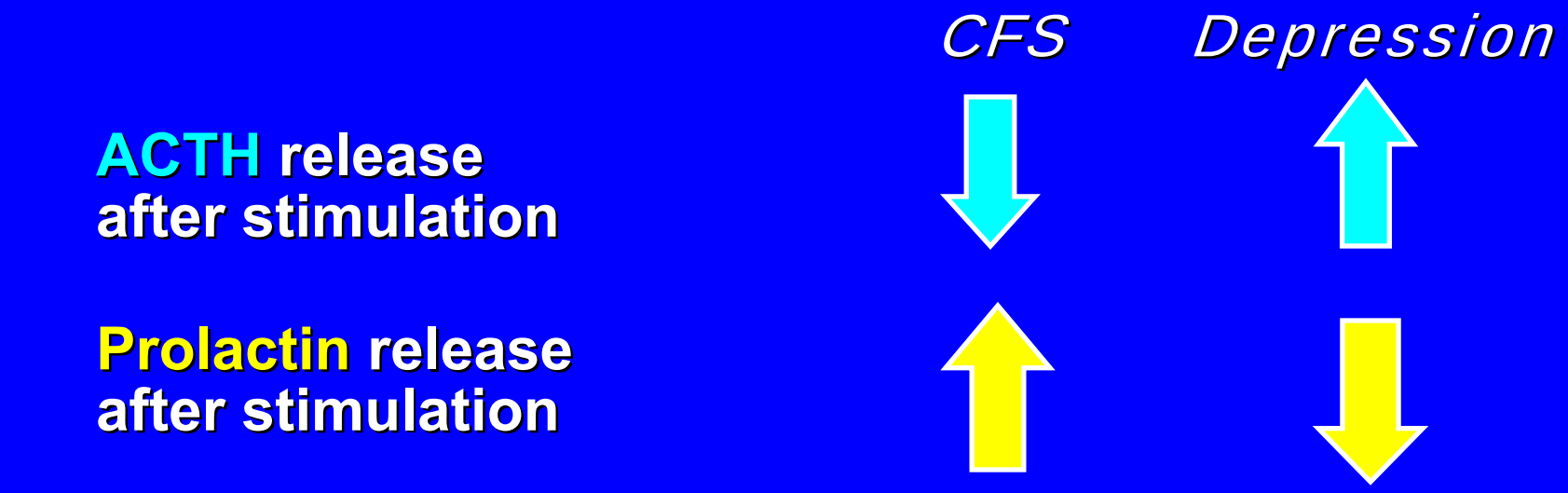
Cleare AJ, et al. J Affect Disord 1995; 35:283-9

Sharpe M, et al. BMJ 1997; 315:164

Demitrack MA, et al. J Clin Endocrinol Metab 1991; 173:1224

Dinan TG, et al. Psychoneuroendo 1997; 22:261.

Hypothalamic-Pituitary Abnormalities In Chronic Fatigue Syndrome



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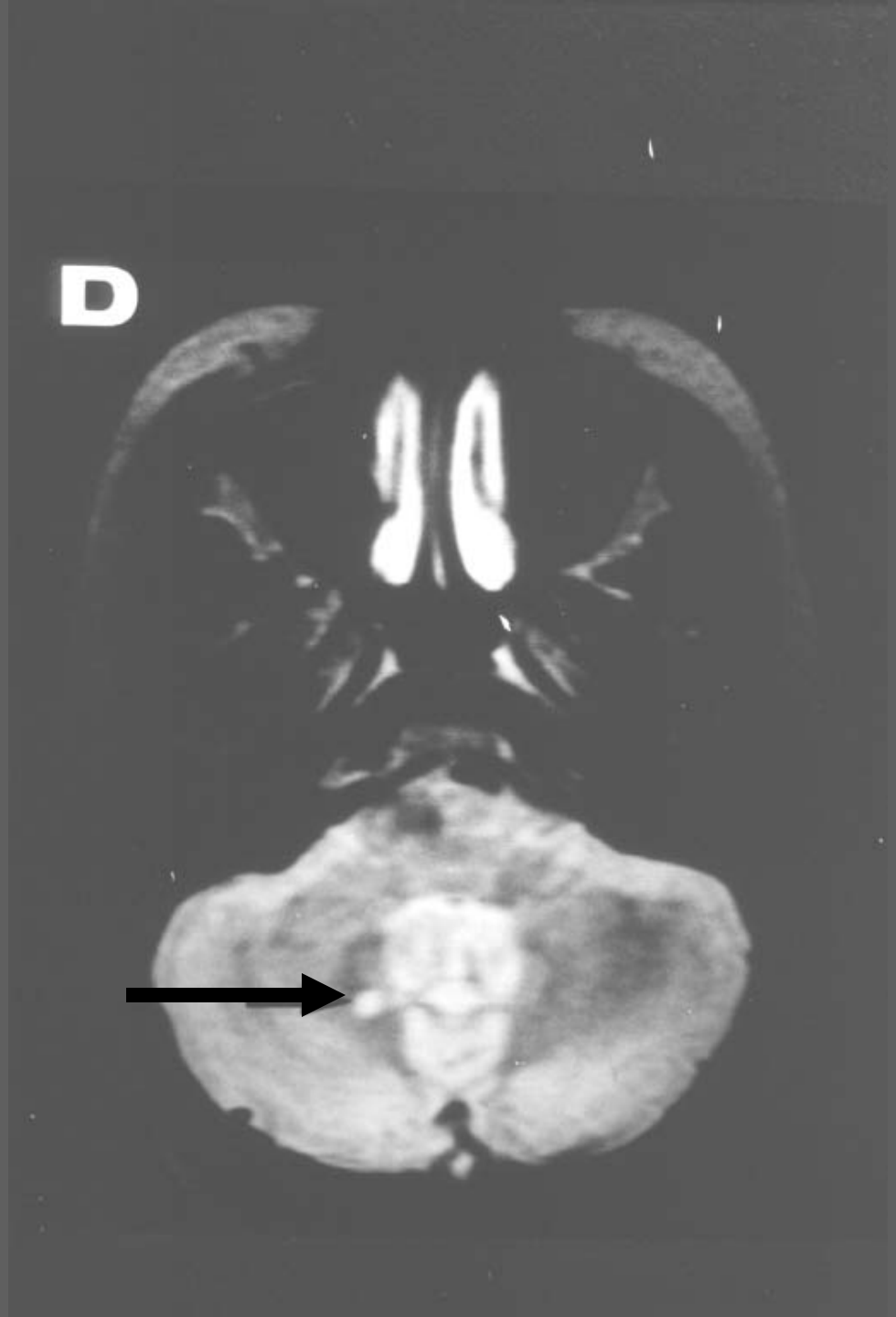
The Biology of CFS Involves…

- The brain and autonomic nervous system
- Chronic activation of the immune system
- Oxidative/nitrosative stress and abnormalities in energy metabolism
- Possible role of infectious agents in triggering and perpetuating the illness

Studies of the Brain and Autonomic Nervous System

Evidence of CNS Involvement in CFS

- ***MRI:*** **Punctate areas of high signal in white matter**
- ***SPECT:*** **Areas of reduced signal**
- ***Cognition:*** **Impairments in information processing speed, memory and attention - not explained by concomitant psychiatric disorders**
- ***Autonomic dysfunction:*** **Impaired sympathetic and parasympathetic function, 30-80%**
- ***Sleep disorders:*** **Disrupted sleep architecture**
- ***Neuroendocrine dysfunction:*** **Impairment of multiple limbic-hypothalamic-pituitary axes (involving cortisol, prolactin, & growth hormone) and serotonin (5-HT) system**


D

Hyperintense Signal In White Matter On Magnetic Resonance Imaging

Epidemic	*Endemic*	*Controls*
71/91 (78%)	42/53 (79%)	10/47 (21%)

P<0.000000001

Interobserver agreement 97%
between 3 neuroradiologists

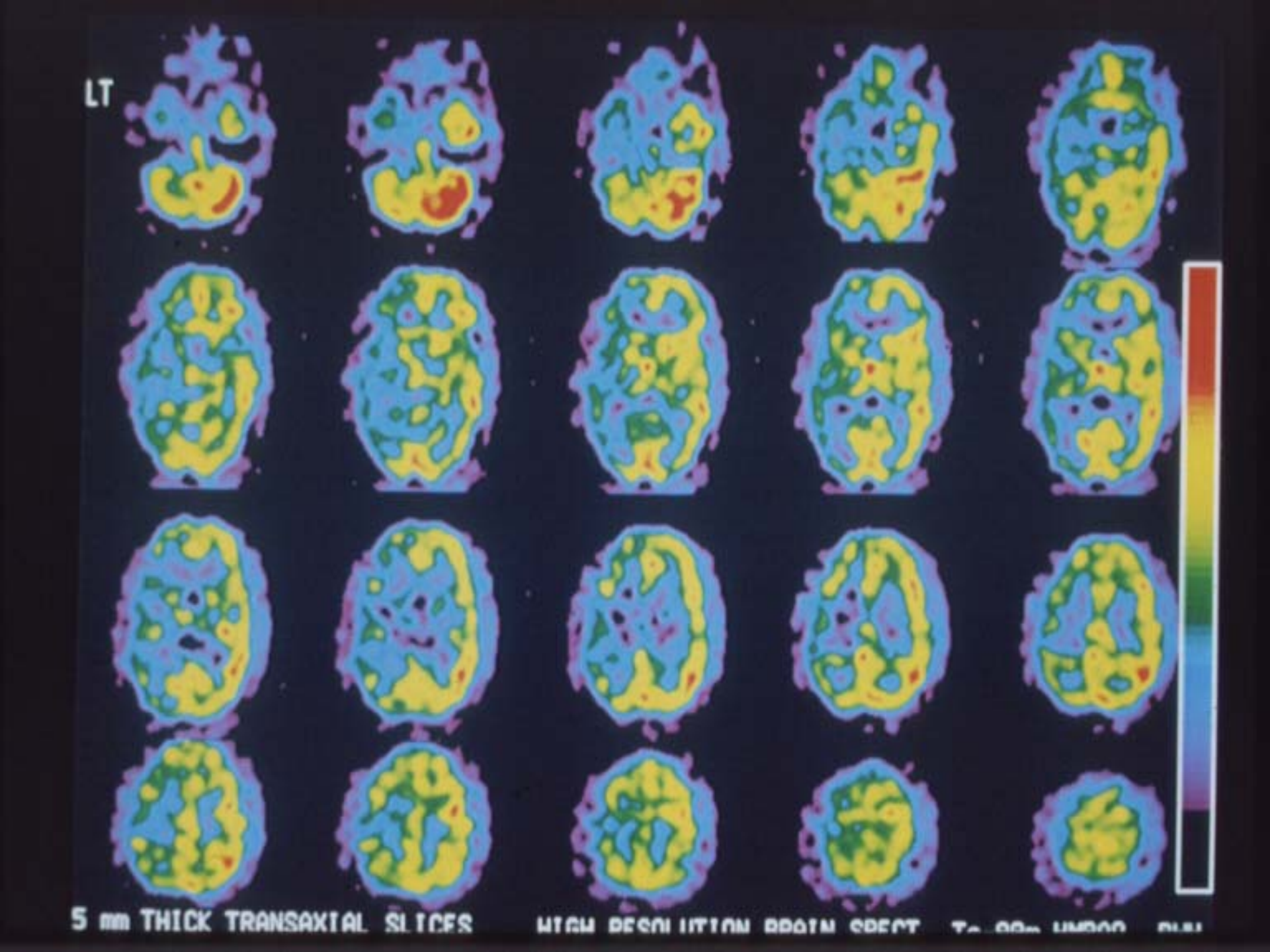
From: Buchwald D…Komaroff AL. Ann Intern Med 1992; 116:103.

SPECT Scan Results: Mid-Cerebral Uptake Index in 4 Groups

CFS (N=45)	*AIDS (N=27)*	*Depression (N=14)*	*Healthy (N=29)*
.67 ± .05	.65 ± .05	.73 ± .16	.72 ± .10

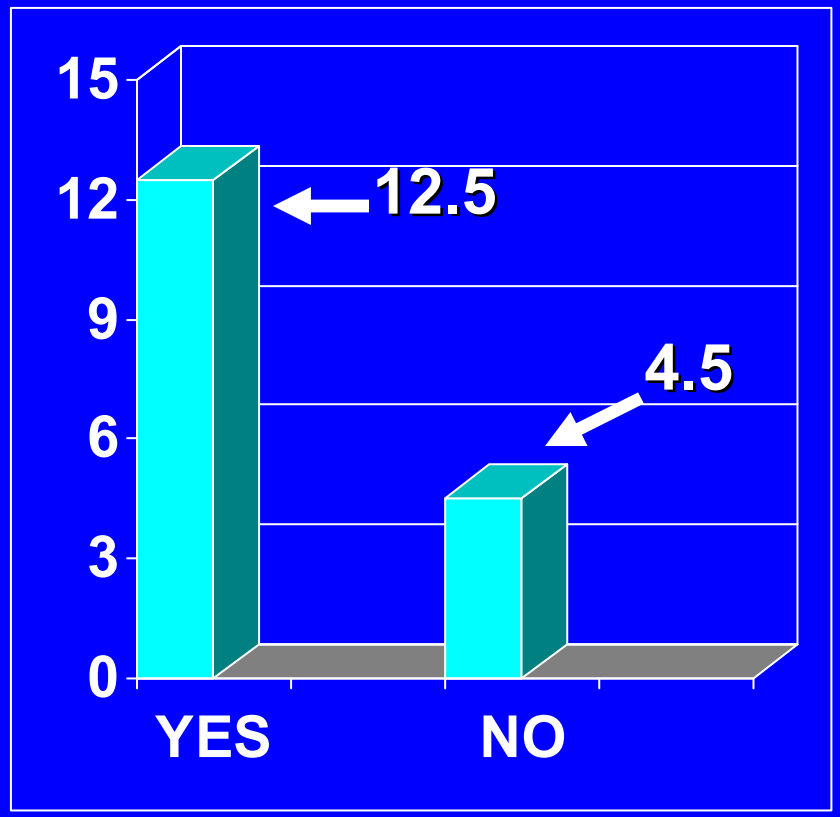
P<0.006

From: Schwartz RB, Komaroff AL… Holman BL. Am J Roentgen 1994; 162:943.

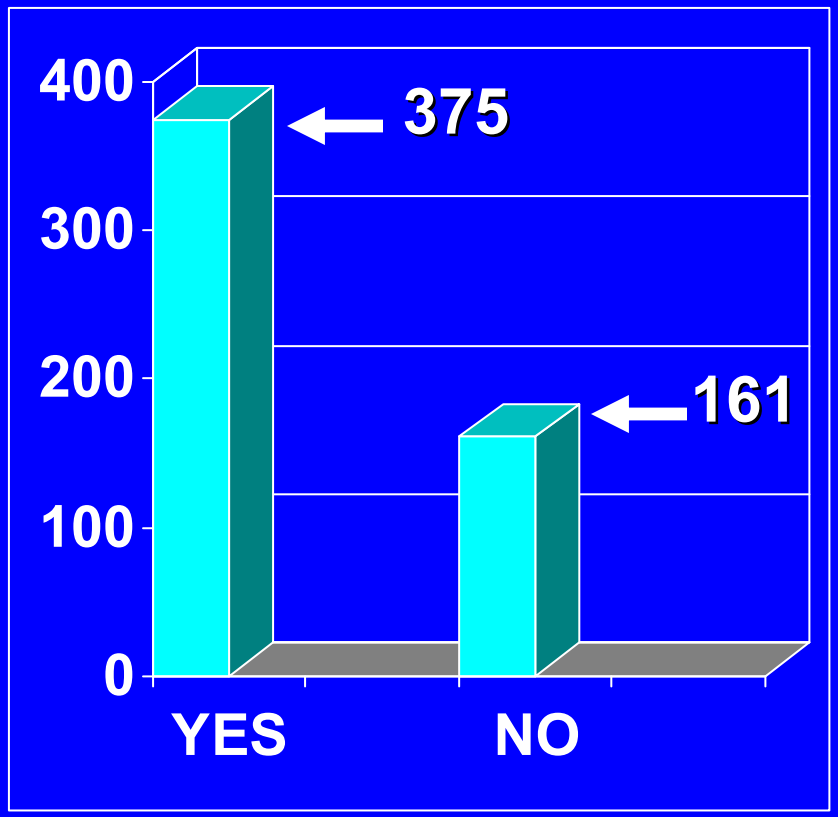

LT
5 mm THICK TRANSAXIAL SLICES

MRI/SPECT Studies in CFS: Results of Studies

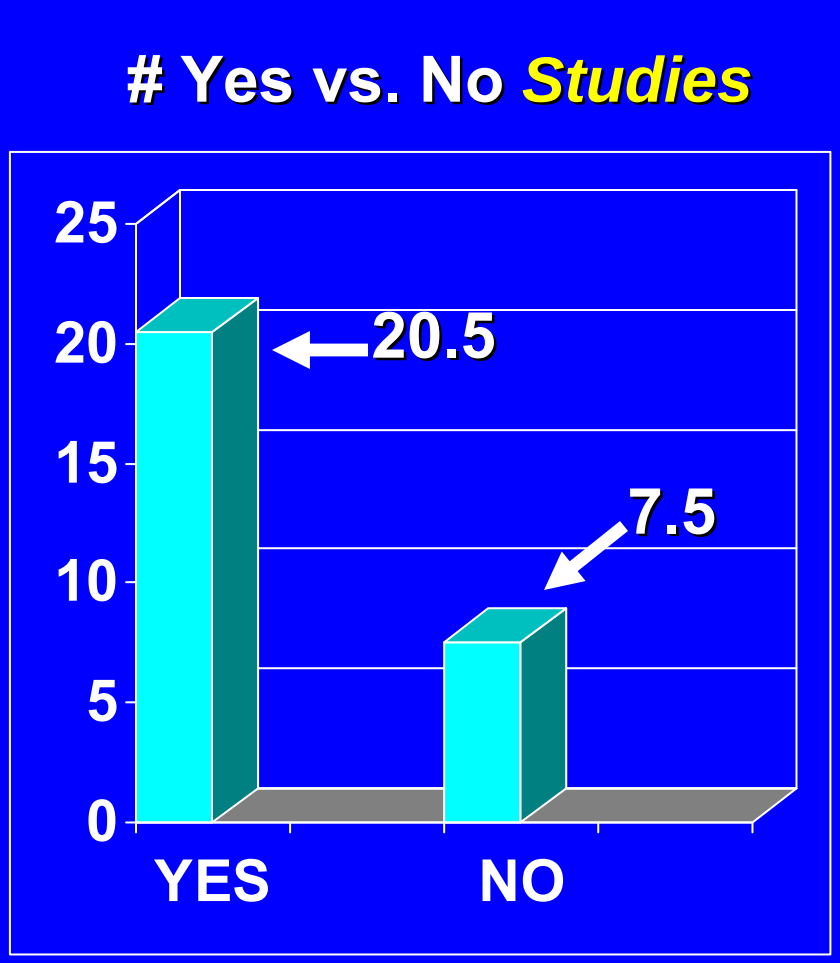
 # Yes vs. No *Studies*

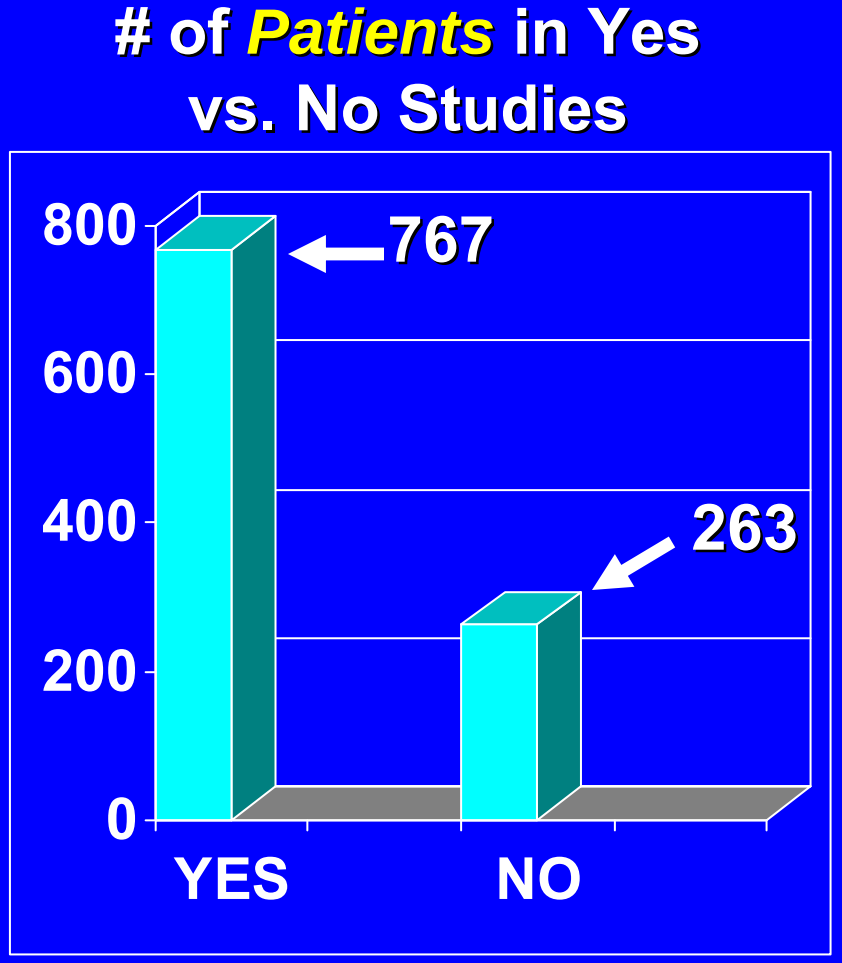


of *Patients* in Yes vs. No Studies



Autonomic Abnormalities in CFS: Results of Studies





Studies of Cognition in CFS

- IQ “normal”, but unclear if IQ has fallen from previous levels
- Deficiencies of:
  - Complex information processing (dealing simultaneously with multiple tasks)
  - Information processing speed
  - Initial acquisition of new information
  - Learning/recalling complex verbal material
- Higher order skills (e.g. planning, verbal fluency) intact
- Deficiencies not explained by coexistent psychiatric disorders

From: Tiersky LA, et al. J Clin Exp Neuropsychol 1997; 19:560.

EEG: Spectral Coherence Studies

Group	*Classified Accurately*	*# Subjects*
CFS-Unmedicated	89.4%	47
CFS-Medicated	73.9%	23
Healthy controls	87.4%	390
Depressed controls	100.0% (none Dx CFS)	24
Putative "CFS"	46.6%	148

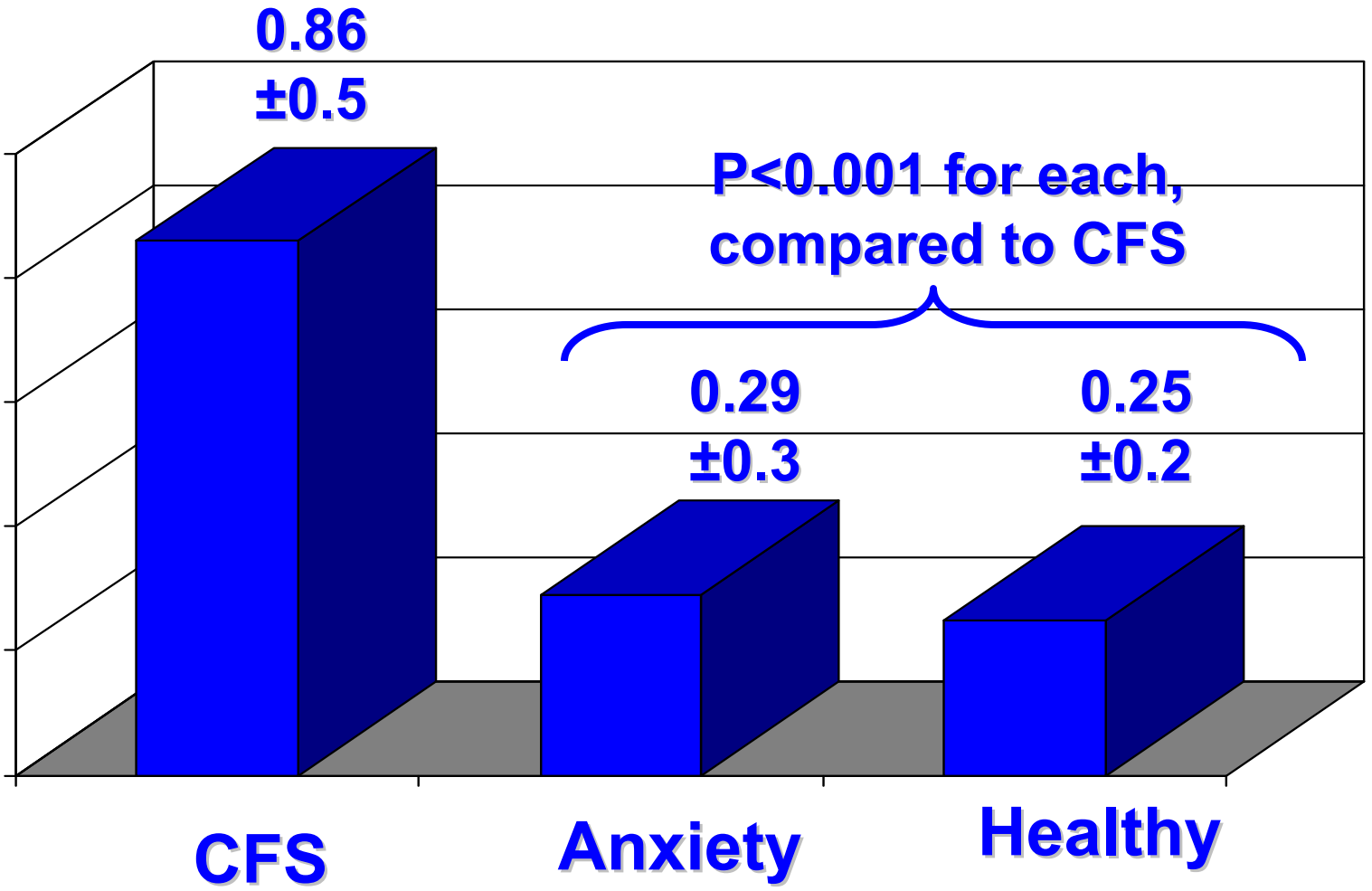
Duffy FH, et al. BMC Neurology 2011;11:82 (doi:10.1186/1471-2377-11-82)

Proteomic Markers in Spinal Fluid

	CFS N=10	Healthy N=10	P-Value	Function
α2-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

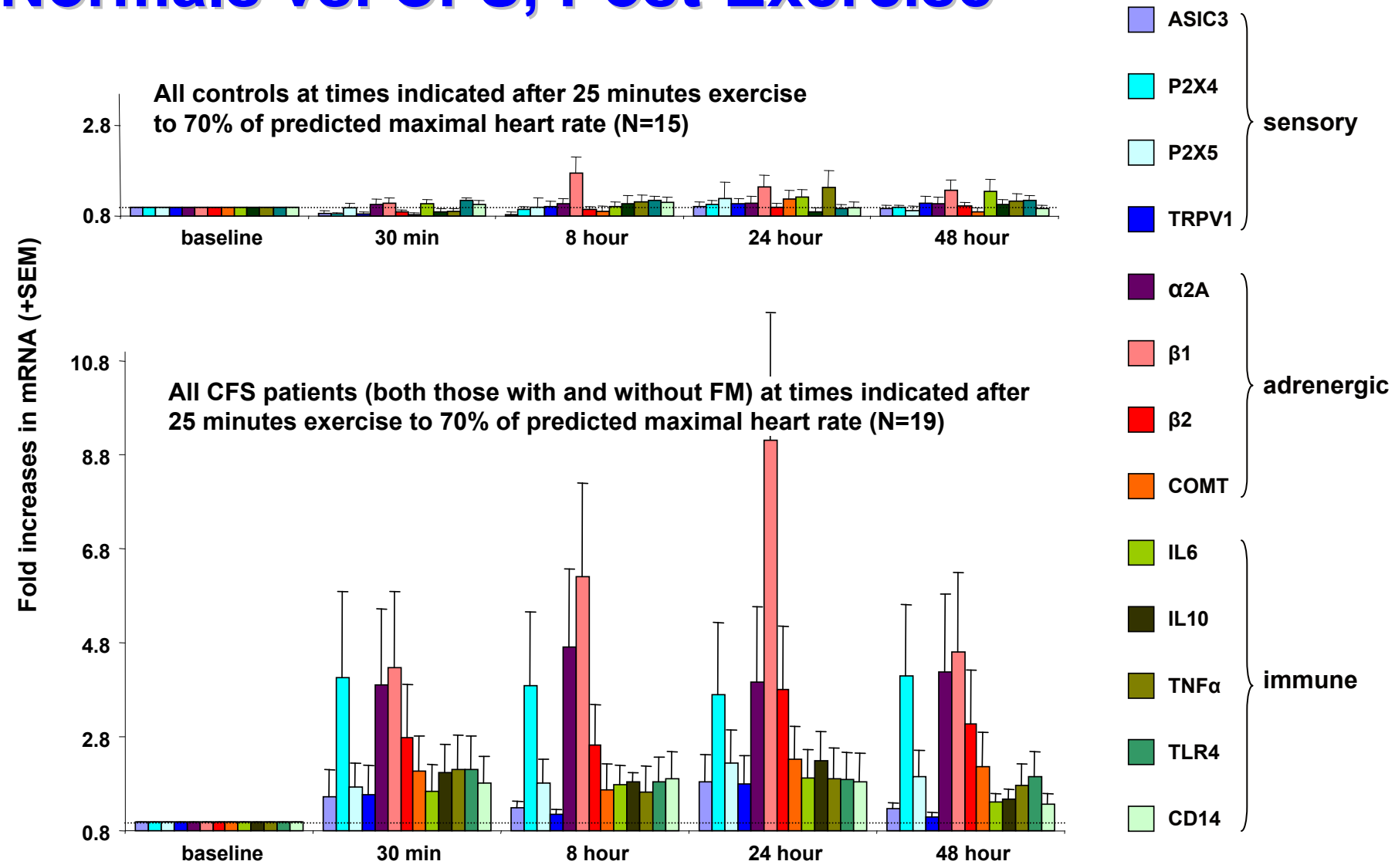
Baraniuk JN, et al. BMC Neurology 2005;5:1-19

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



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

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



Alan Light, *et al. J Pain 2009 (published online)*

Nature Reviews Neuroscience Panel Does CFS Involve the Nervous Sytem

27 july 2011; doi:10.1038/nrn3087

Well documented disorders of the autonomic nervous system, sleep disorders, defective attention, abnormalities in cognition, information processing and recall, stress and hypothalamus–pituitary axis abnormalities, altered sensory and pain perception, and reduced motor speed…point to major CNS involvement.

Stephen T. Holgate, UK MRC professor of immmunopharmacology at the School of Medicine, University of Southampton, UK.

I would be surprised if the pathology does not involve some dysfunction within the CNS.

Simon Wessely. professor and Chair of the Department of Psychological Medicine and also Vice Dean for Academic Psychiatry at the Institute of Psychiatry, King's College London, UK.

Studies of the 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.

- **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.

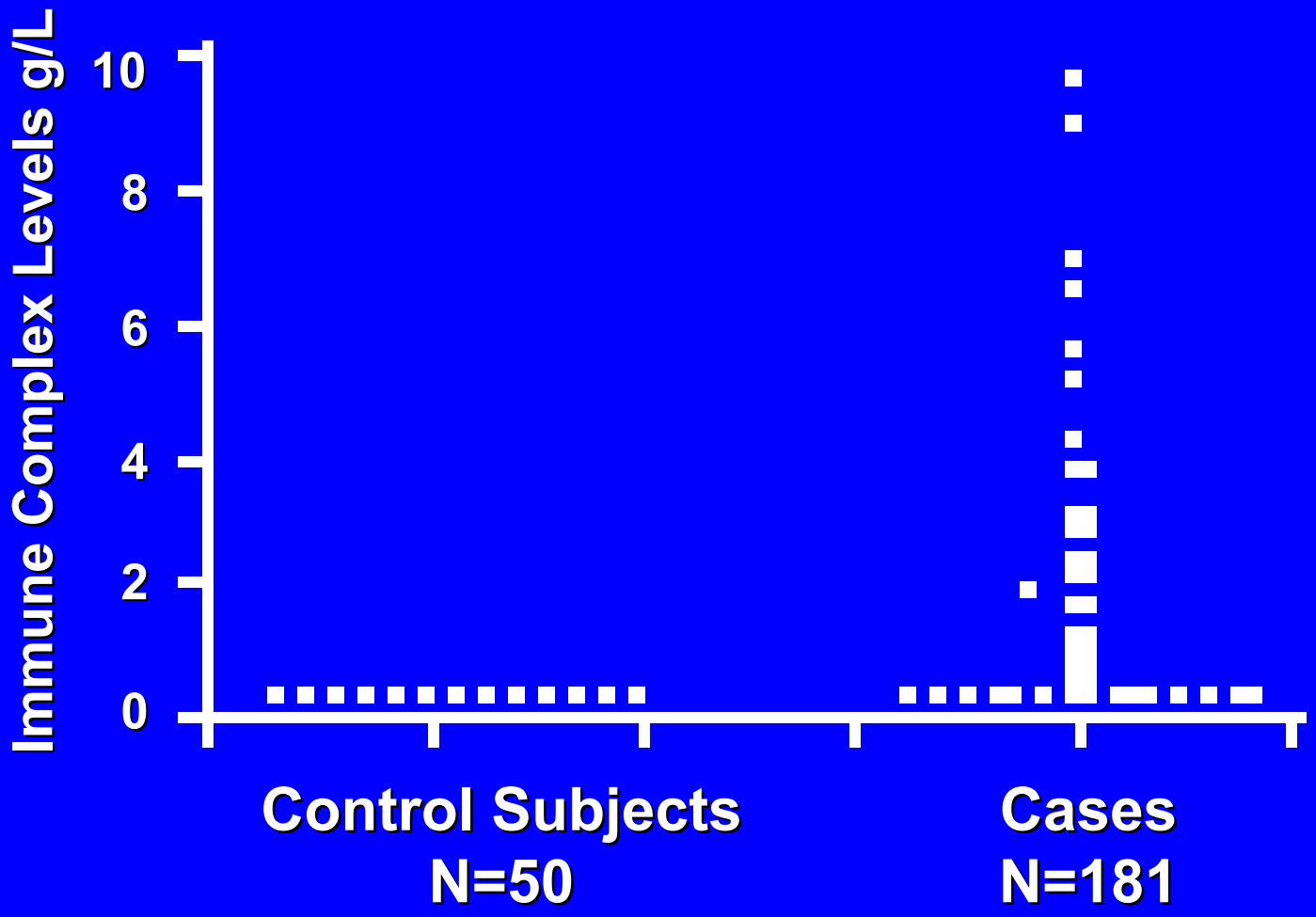
Common Laboratory Abnormalities in CFS

A Case-Control Study Involving Over 20,000 Laboratory Tests, in Over 700 Patients, in Two Geographic Areas, Over 10 Years

	Odds Ratios	95% C.I.	P-Value
Immune complexes	26.5	3.4 - 206	= 0.002
Immunoglobulin G	8.5	2.0 - 37	= 0.004
Atypical lymphocyte count above 2%	11.4	1.4 - 94	= 0.03

From: Bates DW. . .Komaroff AL. Arch Intern Med 1995; 155:97.

Elevated Immune Complex Levels in CFS



35% of cases had elevated levels (>0.23 g/L) vs. 2 % of controls.

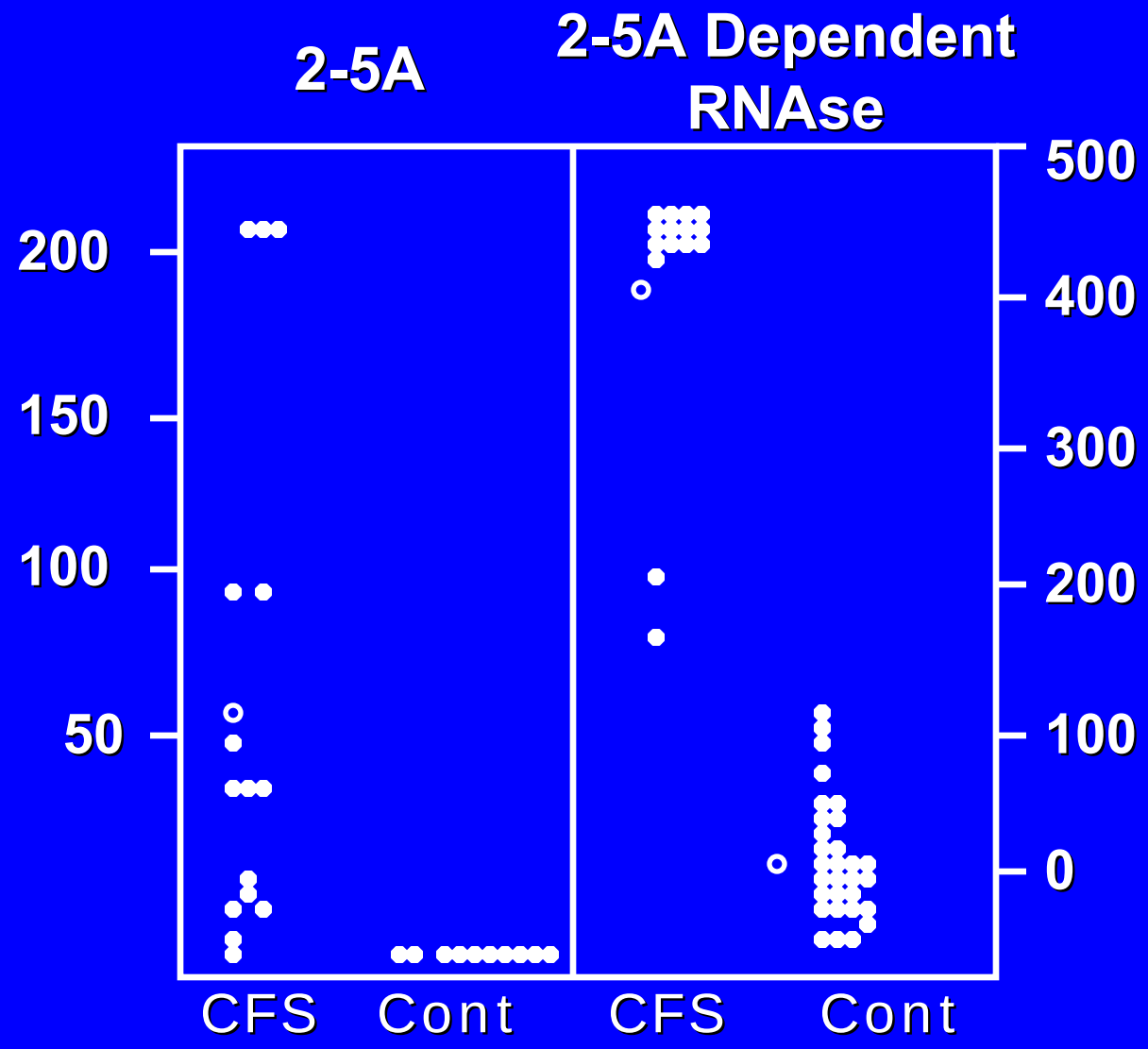
Source: Bates DW, et al. Arch Intern Med 1995; 155:97-103

Cytokine Abnormalities in CFS

- Dysregulated pro-inflammatory cytokines, primarily TNF-α, IL-1 family, IL-6, IF-γ
- Increased TGF-β, possibly in response to upregulation 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.
Bennett AL, et al. J Clin Immunol 1997;17:160.
Kavelaars A, et al. J Clin Endocrin Metab 2000;85:692.

Up-Regulation of 2-5A System in CFS



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

Studies of Infectious Agents

Viruses and CFS—My View

- Infectious agents probably can trigger and perpetuate CFS—but no proof yet
- Agents associated with CFS typically share two properties: they cannot be fully eradicated by the immune system, and they can infect the CNS
- 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

Documentation of Post-Infectious Chronic Fatigue Syndrome

- 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

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

Infectious Agents Linked to CFS

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

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

HHV-6 and the Brain

- 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

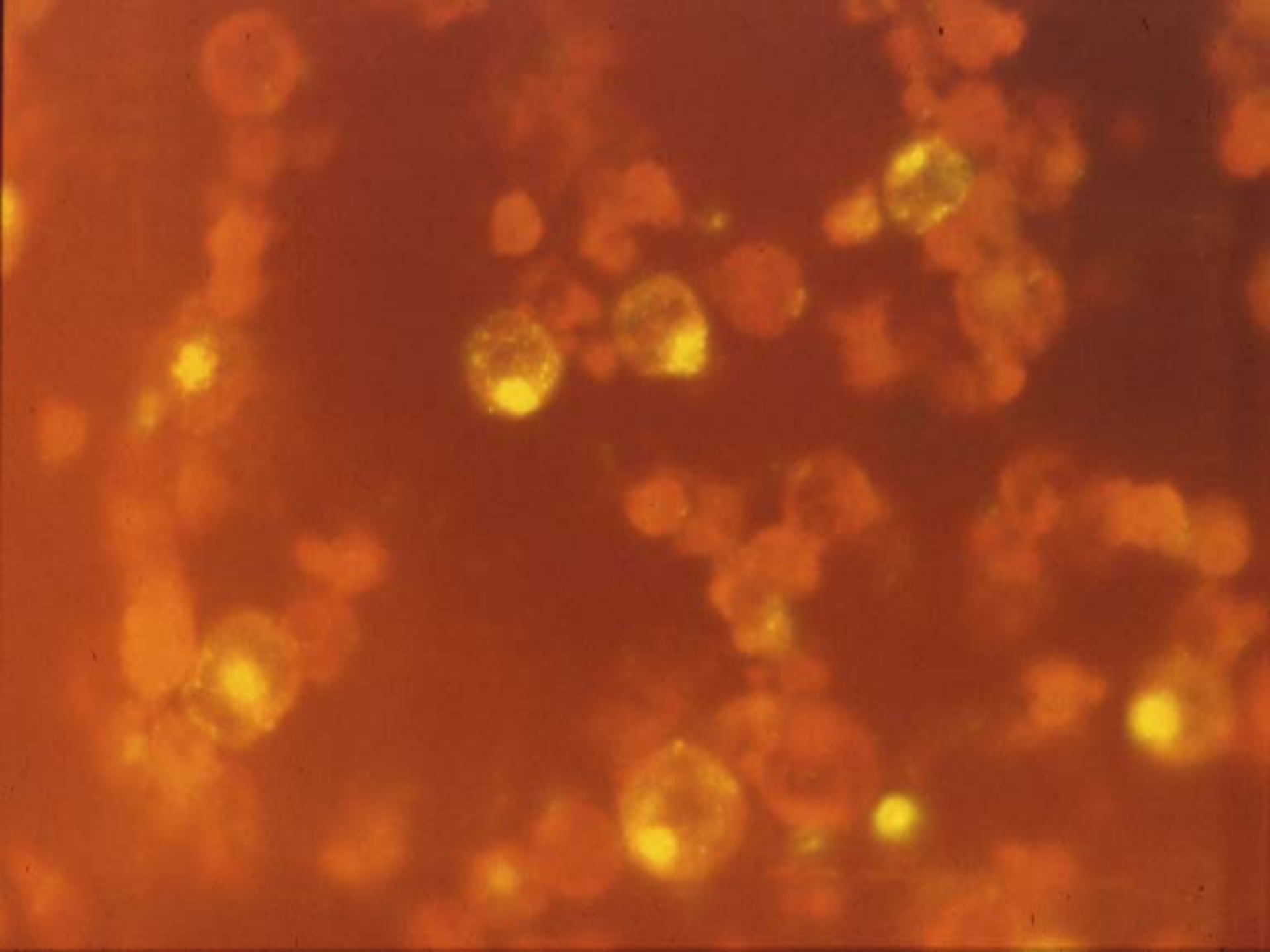
Evidence of Active HHV-6 Infection

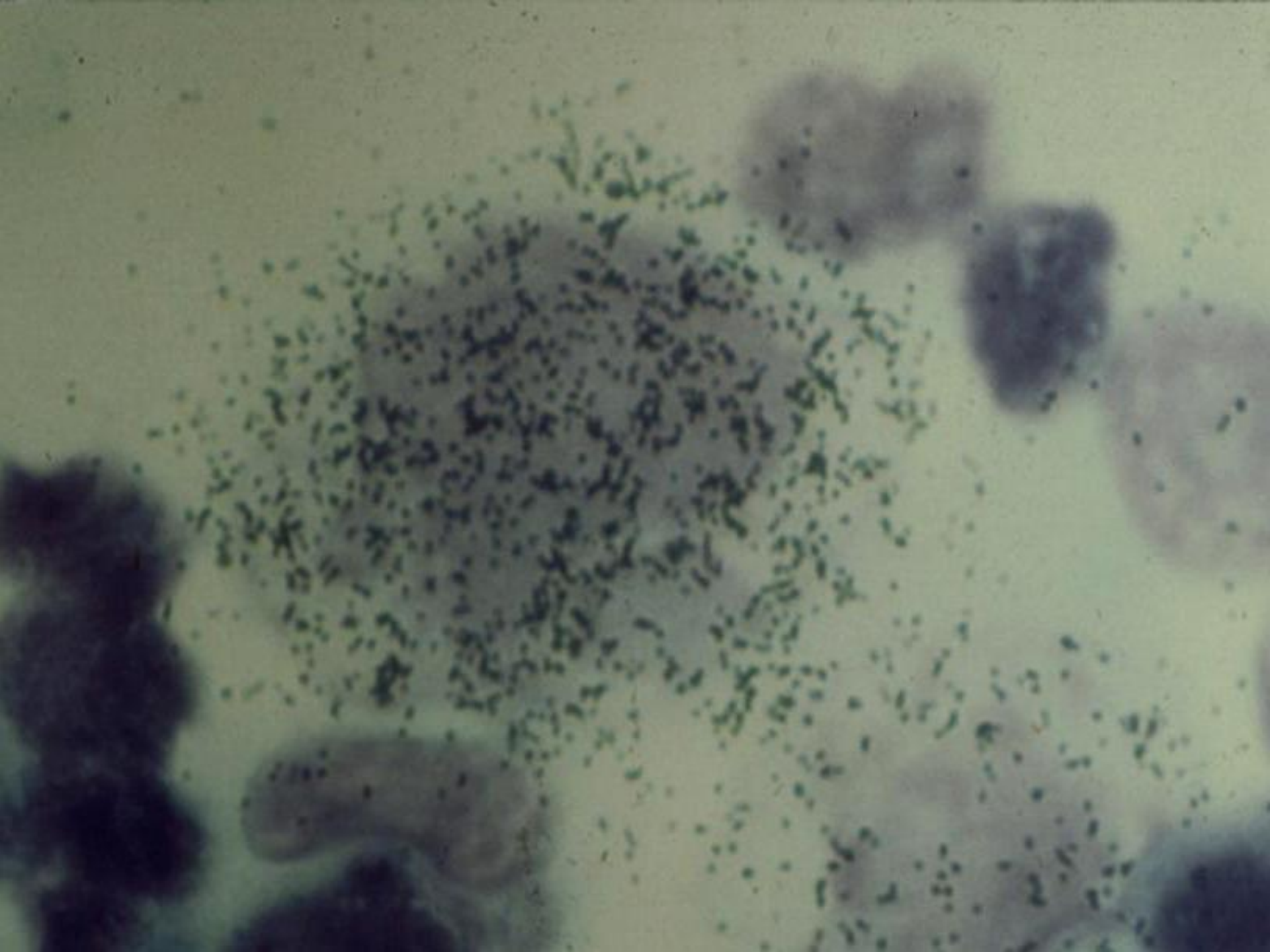
Criteria: Primary cell culture produces large refractile giant cells in 4-8 days which fluoresce with antisera known to have high levels of antibody to HHV-6.

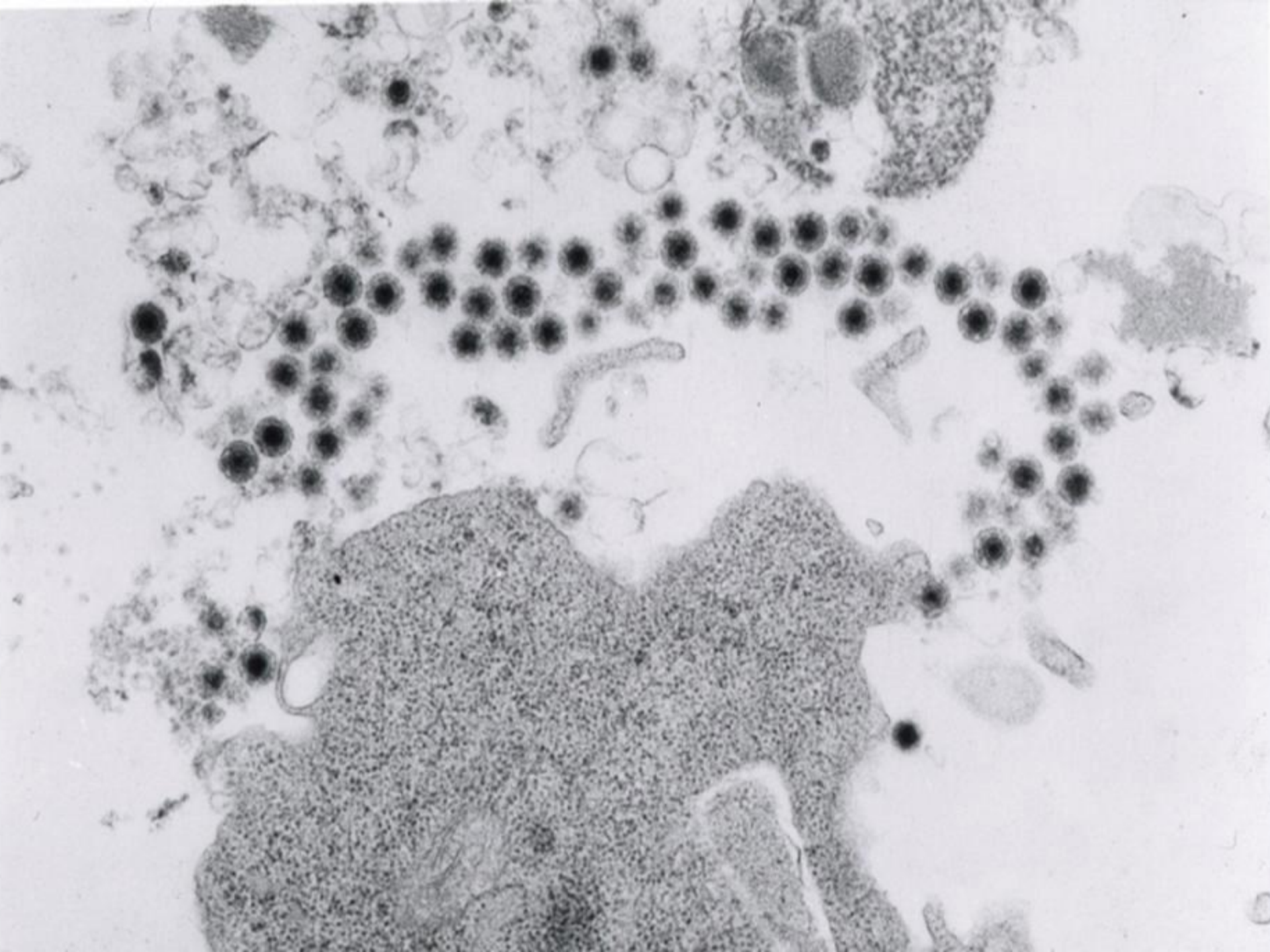
Epidemic	*Endemic*	*Controls*
45/71 (63%)	34/42 (81%)	8/40 (20%)

P<0.00000001

From: Buchwald D, et al. Ann Intern Med 1992; 116:103.

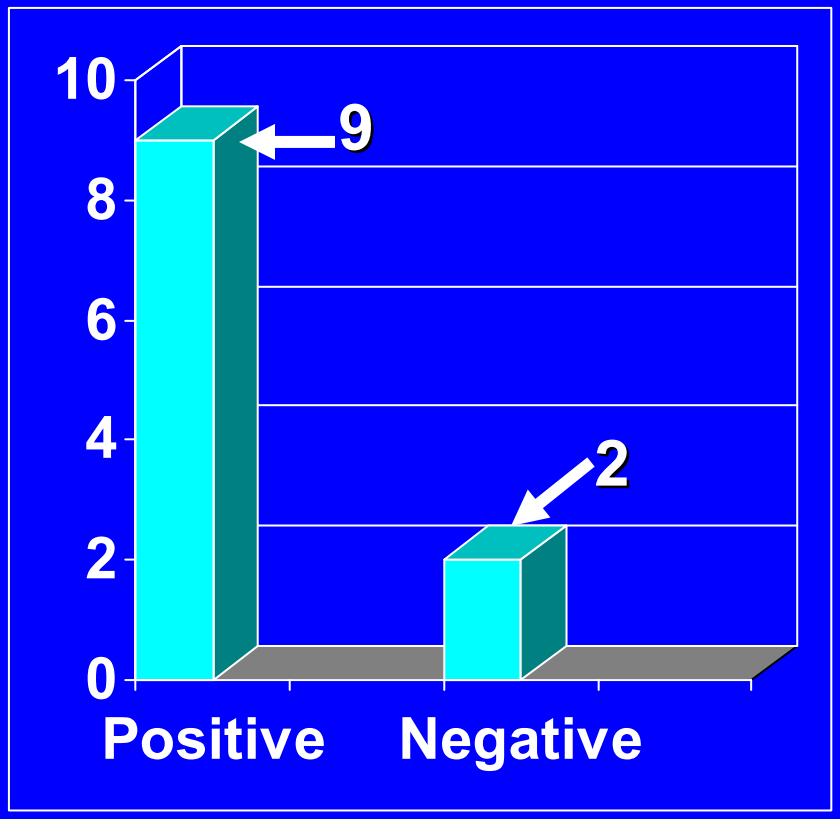




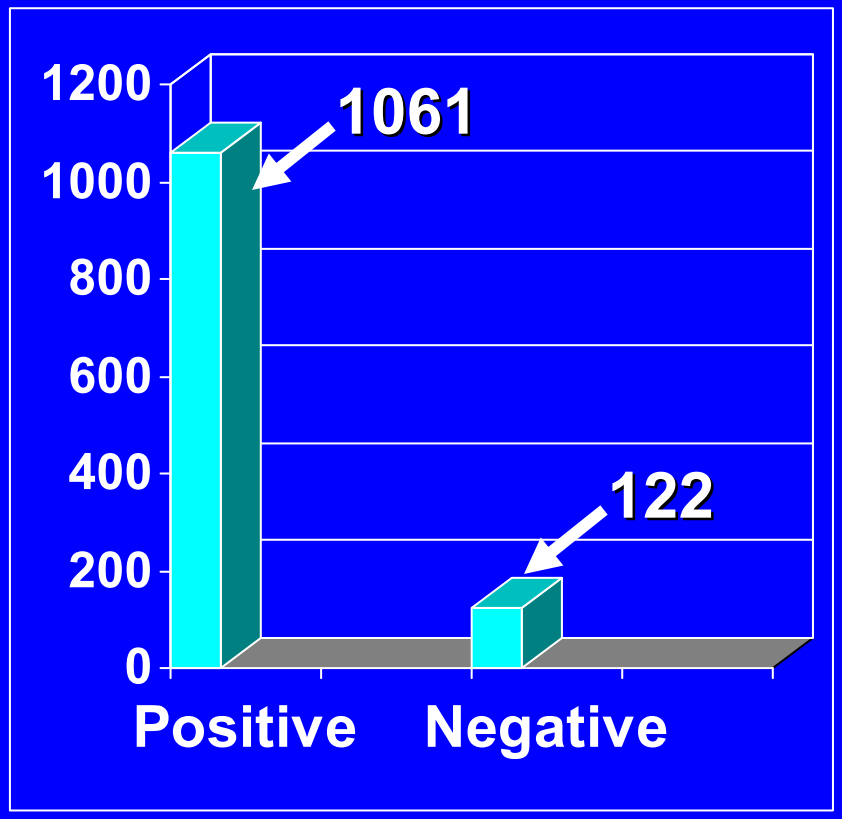


Active HHV-6 Infection in CFS: Results of Studies

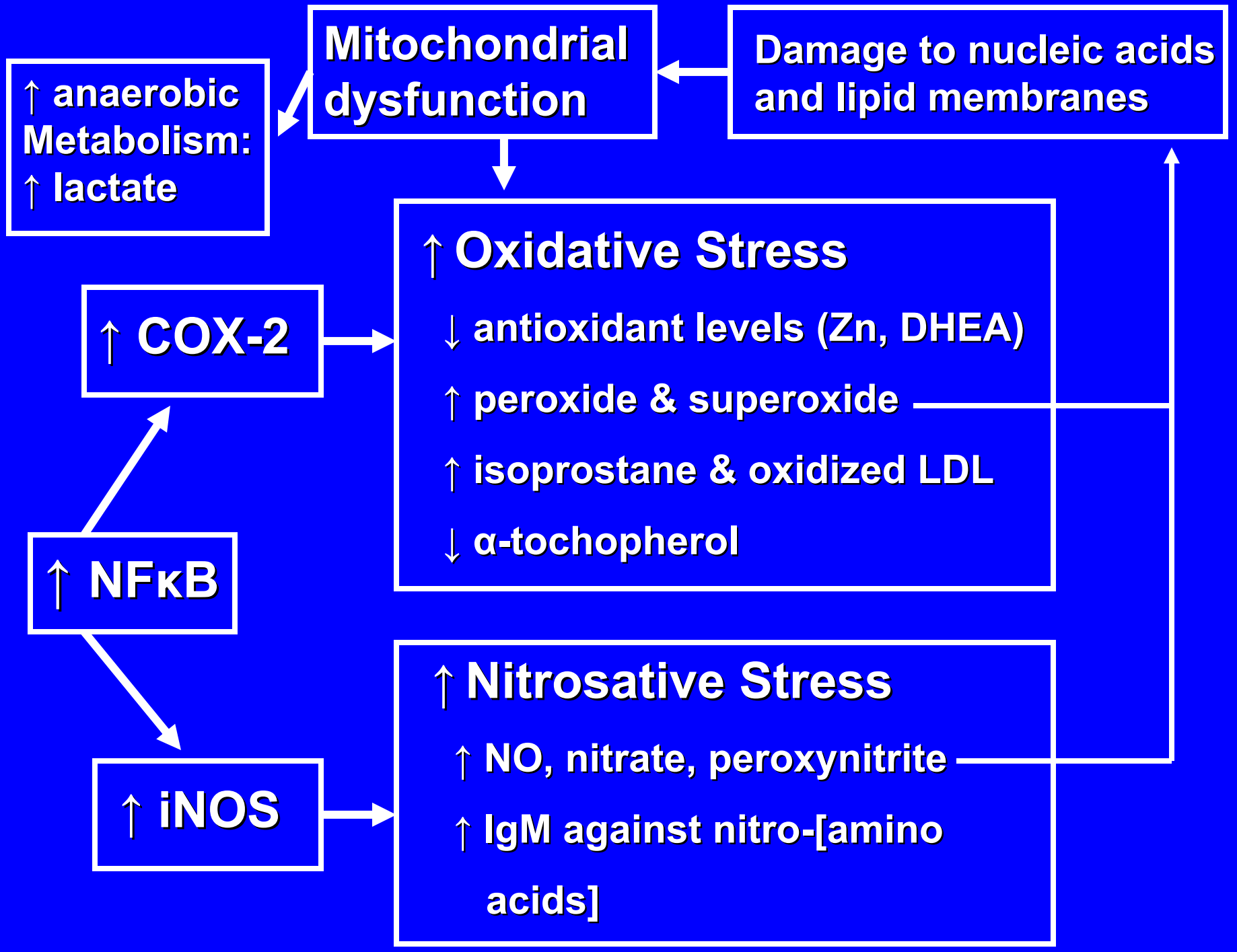
# of Positive vs. Negative *Studies*



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



Energy Metabolism/ Oxidative and Nitrosative Stress/ Inflammation


↑ anaerobic Metabolism: ↑ lactate
Mitochondrial dysfunction
Damage to nucleic acids and lipid membranes
↑ Oxidative Stress
↓ antioxidant levels (Zn, DHEA)
↑ peroxide & superoxide
↑ isoprostane & oxidized LDL
↓ α-tochopherol
↑ COX-2
↑ NFκB
↑ iNOS
↑ Nitrosative Stress
↑ NO, nitrate, peroxynitrite
↑ IgM against nitro-[amino acids]

The Biology of Chronic Fatigue Syndrome

- The CNS and autonomic nervous systems are involved
- There is a state of chronic immune activation, as if the immune system is attacking something foreign
- There are oxidative/nitrosative stress
- Energy metabolism is impaired
- Infection can *trigger* the illness in many, if not all, patients. Can it *perpetuate* illness??

Is Chronic Fatigue Syndrome Real?

- Do we understand the causes or pathogenesis of CFS?
- Are there objective biological markers that are abnormal in CFS?

Is CFS “real”?