Research References Update - December 2008

1. **J Infect Dis. 2008 Apr 15;197(8):1171-84.**

Gene expression subtypes in patients with chronic fatigue syndrome/myalgic encephalomyelitis. Kerr JR etc

http://tinyurl.com/582qfj

Chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) is a multisystem disease, the pathogenesis of which remains undetermined. We set out to determine the precise abnormalities of gene expression in the blood of patients with CFS/ME. We analyzed gene expression in peripheral blood from 25 patients with CFS/ME diagnosed according to the Centers for Disease Control and Prevention diagnostic criteria and 50 healthy blood donors, using a microarray with a cutoff fold difference of expression of >or=2.5. Genes showing differential expression were further analyzed in 55 patients with CFS/ME and 75 healthy blood donors, using quantitative polymerase chain reaction. Differential expression was confirmed for 88 genes; 85 were upregulated, and 3 were downregulated. Highly represented functions were hematological disease and function, immunological disease and function, cancer, cell death, immune response, and infection. Clustering of quantitative polymerase chain reaction data from patients with CFS/ME revealed 7 subtypes with distinct differences in Medical Outcomes Survey Short Form-36 scores, clinical phenotypes, and severity.

2.: **Curr Rheumatol Rep. 2008 Dec;10(6):482-91.**

Gene profiling of patients with chronic fatigue syndrome/myalgic encephalomyelitis.

Kerr JR.

http://tinyurl.com/6qsz3q

Chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) is a multisystem disease, the pathogenesis of which remains undetermined. Following two microarray studies, we reported the differential expression of 88 human genes in patients with CFS; 85 of these genes were upregulated and 3 were downregulated. The top functional categories of these 88 genes were hematologic disease and function, immunologic disease and function, cancer, cell death, immune response, and infection. Clustering of quantitative polymerase chain reaction data from CFS/ME patients revealed seven subtypes with distinct differences in Short Form (SF)-36 scores, clinical phenotypes, and severity. Gene signatures in each subtype implicate five human genes as possible targets for specific therapy. Development of a diagnostic test for subtype status is now a priority. The possibility that

these subtypes represent individual host responses to particular microbial infections is being investigated and may provide another route to specific therapies for CFS patients.

3. **Curr Rheumatol Rep. 2007 Dec;9(6):482-7.Links**

Chronic fatigue syndrome: inflammation, immune function, and neuroendocrine interactions.
Klimas NG, Koneru AO.

http://tinyurl.com/5wafdx

Investigations into the underlying cause of chronic fatigue syndrome have advanced the field considerably in the past year. Gene microarray data have led to a better understanding of pathogenesis. Recent research has evaluated genetic signatures, described biologic subgroups, and suggested potential targeted treatments. Acute viral infection studies found that initial infection severity was the single best predictor of persistent fatigue. Genomic studies showed that persistent cases express Epstein Barr virus-specific genes and demonstrate abnormalities of mitochondrial function. Studies of immune dysfunction extended observations of natural killer cytotoxic cell dysfunction of the cytotoxic T cell through quantitative evaluation of intracellular perforins and granzymes. Other research has focused on a subgroup of patients with reactivated viral infection. These advances should result in targeted therapies that impact immune function, hypothalamic-pituitary-adrenal axis regulation, and persistent viral reactivation.

4. **BMC Neurol. 2005 Dec 1;5:22.**

A Chronic Fatigue Syndrome - related proteome in human cerebrospinal fluid.

Baraniuk JN, Casado B, Maibach H, Clauw DJ, Pannell LK, Hess S S

http://tinyurl.com/5h53gt

BACKGROUND: Chronic Fatigue Syndrome (CFS), Persian Gulf War Illness (PGI), and fibromyalgia are overlapping symptom complexes without objective markers or known pathophysiology. Neurological dysfunction is common. We assessed cerebrospinal fluid to find proteins that were differentially expressed in this CFS-spectrum of illnesses compared to control subjects.

CONCLUSION: This pilot study detected an identical set of central nervous system, innate immune and amyloidogenic proteins in cerebrospinal fluids from two independent cohorts of subjects with overlapping CFS, PGI and fibromyalgia. Although syndrome names and definitions were different, the proteome and presumed pathological mechanism(s) may be shared.

5. **NMR Biomed. 2008 Oct 21. [Epub ahead of print] Ventricular cerebrospinal fluid lactate is increased in chronic fatigue syndrome compared with generalized anxiety disorder: an in vivo 3.0 T (1)H MRS imaging study.**

Mathew SJ, Mao X, Keegan KA, Levine SM, Smith EL, Heier LA, Otcheretko V, Coplan JD, Shungu DC.

http://tinyurl.com/63hh3t

CFS is associated with significantly raised concentrations of ventricular lactate, potentially consistent with recent evidence of decreased cortical blood flow, secondary mitochondrial dysfunction, and/or oxidative stress abnormalities in the disorder.

6. **In Vivo. 2008 Jan-Feb;22(1):115-21.Links**

Unravelling intracellular immune dysfunctions in chronic fatigue syndrome: interactions between protein kinase R activity, RNase L cleavage and elastase activity, and their clinical relevance.

Meeus M, Nijs J, McGregor N, Meeusen R, De Schutter G, Truijen S, Frémont M, Van Hoof E, De Meirleir K.

http://tinyurl.com/6xpzl5

This study examined possible interactions between immunological abnormalities and symptoms in CFS.....This study suggests that in CFS patients an increase in elastase activity and subsequent RNase L cleavage is accompanied by increased activity of both the PKR and RNase L enzymes. RNase L and elastase activity are related to daily functioning, thus evidence supporting the clinical importance of these immune dysfunctions in CFS patients was provided.

7. **Clin Physiol Funct Imaging. 2006 Mar;26(2):83-6.Click here to read Links**

Patients with chronic fatigue syndrome have reduced absolute cortical blood flow.

Yoshiuchi K, Farkas J, Natelson BH.

http://tinyurl.com/5uam7y

These data indicate that patients with CFS have reduced absolute cortical blood flow in rather broad areas when compared with data from healthy controls and that those devoid of psychopathology had the most reductions in cortical flow. These data support, in part, our earlier findings that

patients devoid of psychopathology are the group most at risk of having some of the symptoms of CFS due to brain dysfunction.

8. **Neuroimage. 2005 Jun;26(2):513-24. Epub 2005 Apr 7.Click here to read Links**

Objective evidence of cognitive complaints in Chronic Fatigue Syndrome: a BOLD fMRI study of verbal working memory.

Lange G, Steffener J, Cook DB, Bly BM, Christodoulou C, Liu WC, Deluca J, Natelson BH.

http://tinyurl.com/6gspt3

Findings showed that individuals with CFS are able to process challenging auditory information as accurately as Controls but utilize more extensive regions of the network associated with the verbal WM system. Individuals with CFS appear to have to exert greater effort to process auditory information as effectively as demographically similar healthy adults. Our findings provide objective evidence for the subjective experience of cognitive difficulties in individuals with CFS.

9. Clin Diagn Lab Immunol. 2005 Jan;12(1):52-5.Click here to read Click here to read Links

Spinal fluid abnormalities in patients with chronic fatigue syndrome.

Natelson BH, Weaver SA, Tseng CL, Ottenweller JE.

http://tinyurl.com/6owsb6

Arguments exist as to the cause of chronic fatigue syndrome (CFS). Some think that it is an example of symptom amplification indicative of functional or psychogenic illness, while our group thinks that some CFS patients may have brain dysfunction. To further pursue our encephalopathy hypothesis, we did spinal taps on 31 women and 13 men fulfilling the 1994 case definition for CFS and on 8 women and 5 men serving as healthy controls.....

The results support two hypotheses: that some CFS patients have a neurological abnormality that may contribute to the clinical picture of the illness and that immune dysregulation within the central nervous system may be involved in this process.

10. **From Am J Med. 1998 Sep 28;105(3A):54S-58S.Links**

Brain positron emission tomography (PET) in chronic fatigue syndrome: preliminary data.

Tirelli U, Chierichetti F, Tavio M, Simonelli C, Bianchin G, Zanco P, Ferlin G.

http://tinyurl.com/63vvs8

The PET images examined 22 cortical and subcortical areas. CFS patients showed a significant hypometabolism in right mediofrontal cortex (P = 0.010) and brainstem (P = 0.013) in comparison with the healthy controls. Moreover, comparing patients affected by CFS and depression, the latter group showed a significant and severe hypometabolism of the medial and upper frontal regions bilaterally (P = 0.037-0.001), whereas the metabolism of brain stem was normal. Brain 18FDG PET showed specific metabolism abnormalities in patients with CFS in comparison with both healthy controls and depressed patients. The most relevant result of our study is the brain stem hypometabolism which, as reported in a perfusion SPECT study, seems to be a marker for the in vivo diagnosis of CFS.

11. **J Clin Lab Anal. 2008;22(2):99-105.Click here to read Links**

Acute phase phospholipids related to the cardiolipin of mitochondria in the sera of patients with chronic fatigue syndrome (CFS), chronic Ciguatera fish poisoning (CCFP), and other diseases attributed to chemicals, Gulf War, and marine toxins.

Hokama Y, Empey-Campora C, Hara C, Higa N, Siu N, Lau R, Kuribayashi T, Yabusaki K.

http://tinyurl.com/6janc5

This study examined 328 CFS sera in a study with 17 CCFP, 8 Gulf War Veterans (GWV), 24 Prostate Cancer (PC), and 52 normal sera in the modified Membrane Immunobead Assay (MIA) procedure for CTX.

Preliminary chemical analyses have shown the lipids to be phospholipids associated with CL of the mitochondria. We designate this "Acute Phase Lipid" comparable to "Acute Phase Proteins" (C-reactive protein (CRP) and Serum Amyloid A (SAA)) in inflammatory conditions. (Copyright) 2008 Wiley-Liss, Inc.

12. **Biochem Biophys Res Commun. 2008 Nov 7;376(1):231-3. Epub 2008 Sep 5.Click here to read Links**

Lower frequency of IL-17F sequence variant (His161Arg) in chronic fatigue syndrome patients.

Metzger K, Frémont M, Roelant C, De Meirleir K.

http://www.ncbi.nlm.nih.gov/pubmed/18774769

Chronic fatigue syndrome (CFS) is characterized by immune dysfunctions including chronic immune activation, inflammation, and alteration of cytokine profiles. T helper 17 (Th17) cells belong to a recently identified subset of T helper cells, with crucial regulatory function in inflammatory and autoimmune processes. Th17 cells are implicated in allergic inflammation, intestinal diseases, central nervous system inflammation, disorders that may all contribute to the pathophysiology of CFS. IL-17F is one of the pro-inflammatory cytokines secreted by Th17 cells. We investigated the association between CFS and the frequency of rs763780, a C/T genetic polymorphism leading to His161Arg substitution in the IL-17F protein. The His161Arg variant (C allele) antagonizes the pro-inflammatory effects of the wild-type IL-17F. A significantly lower frequency of the C allele was observed in the CFS population, suggesting that the His161Arg variant may confer protection against the disease. These results suggest a role of Th17 cells in the pathogenesis of CFS.

13. **Free Radic Biol Med. 2005 Sep 1;39(5):584-9.Click here to read Links**

Oxidative stress levels are raised in chronic fatigue syndrome and are associated with clinical symptoms.

Kennedy G, Spence VA, McLaren M, Hill A, Underwood C, Belch JJ.

http://tinyurl.com/6y566j

The aetiology of chronic fatigue syndrome (CFS) is unknown; however, recent evidence suggests excessive free radical (FR) generation may be involved. This study investigated for the first time levels of 8-iso-prostaglandin-F(2 alpha)-isoprostanes alongside other plasma markers of oxidative stress in CFS patients and control subjects.....This is the first time that raised levels of the gold standard measure of in vivo oxidative stress (isoprostanes) and their association with CFS symptoms have been reported.

14. **In Vivo. 2005 Mar-Apr;19(2):387-90.Links**

Exercise capacity and immune function in male and female patients with chronic fatigue syndrome (CFS).

Snell CR, Vanness JM, Strayer DR, Stevens SR.

http://tinyurl.com/6hayy8

Hyperactivition of an unwanted cellular cascade by the immune-related protein RNase L has been linked to reduced exercise capacity in persons with chronic fatigue syndrome (CFS). This investigation compares exercise capacities of CFS patients with deregulation of the RNase L pathway and CFS patients with normal regulation, while controlling for potentially confounding gender effects.....These results implicate abnormal immune activity in the pathology of exercise intolerance in CFS and are consistent with a channelopathy involving oxidative stress and nitric oxide-related toxicity.

15. **J Intern Med. 2005 Mar;257(3):299-310. Chronic fatigue syndrome: assessment of increased oxidative stress and altered muscle excitability in response to incremental exercise.**

Jammes Y, Steinberg JG, Mambrini O, Brégeon F, Delliaux S.

http://tinyurl.com/57oreu

OBJECTIVES: Because the muscle response to incremental exercise is not well documented in patients suffering from chronic fatigue syndrome (CFS), we combined electrophysiological (compound-evoked muscle action potential, M wave), and biochemical (lactic acid production, oxidative stress) measurements to assess any muscle dysfunction in response to a routine cycling exercise.

CONCLUSIONS: The response of CFS patients to incremental exercise associates a lengthened and accentuated oxidative stress together with marked alterations of the muscle membrane excitability. These two objective signs of muscle dysfunction are sufficient to explain muscle pain and postexertional malaise reported by our patients.

16. **Clin Sci (Lond). 2004 Feb;106(2):183-9.Click here to read Links**

Peripheral cholinergic function in humans with chronic fatigue syndrome, Gulf War syndrome and with illness following organophosphate exposure.

Khan F, Kennedy G, Spence VA, Newton DJ, Belch JJ.

http://tinyurl.com/5q7rll

In the present study, we have investigated whether the peripheral cholinergic abnormalities that we have reported previously [Spence, Khan and Belch (2000) Am. J. Med. 108, 736-739] in patients with

chronic fatigue syndrome (CFS) are also present in those with Gulf War syndrome (GWS) and agricultural workers exposed to organophosphate pesticides, where cholinesterase inhibition is specifically implicated.....Although there are many clinical similarities between these three illnesses, our results indicate peripheral cholinergic abnormalities in the vascular endothelium of only patients with CFS, suggesting that this syndrome has a different aetiology, which might involve inhibition of vascular cholinesterase.

17. **Clin Physiol Funct Imaging. 2003 Sep;23(5):282-5. Prolonged acetylcholine-induced vasodilatation in the peripheral microcirculation of patients with chronic fatigue syndrome.**

Khan F, Spence V, Kennedy G, Belch JJ.

http://tinyurl.com/5h23pn

Although the aetiology of chronic fatigue syndrome (CFS) is unknown, there have been a number of reports of blood flow abnormalities within the cerebral circulation and systemic blood pressure defects manifesting as orthostatic intolerance. Neither of these phenomena has been explained adequately, but recent reports have linked cerebral hypoperfusion to abnormalities in cholinergic metabolism.....Prolongation of ACh-induced vasodilatation is suggestive of a disturbance to cholinergic pathways, perhaps within the vascular endothelium of patients with CFS, and might be related to some of the unusual vascular symptoms, such as hypotension and orthostatic intolerance, which are characteristic of the condition.

18. **J Clin Pathol. 2008 Jan;61(1):43-8. Epub 2007 Sep 13. Chronic fatigue syndrome is associated with chronic enterovirus infection of the stomach.**

Chia JK, Chia AY.

http://tinyurl.com/6rlseb

BACKGROUND AND AIMS: The aetiology for chronic fatigue syndrome (CFS) remains elusive although enteroviruses have been implicated as one of the causes by a number of studies.....RESULTS:135/165 (82%) biopsies stained positive for VP1 within parietal cells, whereas 7/34 (20%) of the controls stained positive (p< or =0.001).....CONCLUSION: Enterovirus VP1, RNA and non-cytopathic viruses were detected in the stomach biopsy specimens of CFS patients with chronic abdominal complaints. A significant subset of CFS patients may have a chronic, disseminated, non-cytolytic form of enteroviral infection, which could be diagnosed by stomach biopsy.

19. **J Clin Pathol. 2005 Nov;58(11):1126-32. The role of enterovirus in chronic fatigue syndrome.**

Chia JK.

http://tinyurl.com/5z36qh

Observations from in vitro experiments and from animal models clearly established a state of chronic persistence through the formation of double stranded RNA, similar to findings reported in muscle biopsies of patients with CFS. Recent evidence not only confirmed the earlier studies, but also clarified the pathogenic role of viral RNA through antiviral treatment. This review summarises the available experimental and clinical evidence that supports the role of enterovirus in chronic fatigue syndrome.

20. **Am J Med Sci. 2003 Aug;326(2):55-60. Abnormal impedance cardiography predicts symptom severity in chronic fatigue syndrome.**

Peckerman A, LaManca JJ, Dahl KA, Chemitiganti R, Qureishi B, Natelson BH.

http://tinyurl.com/6m8cah

BACKGROUND: Findings indicative of a problem with circulation have been reported in patients with chronic fatigue syndrome (CFS). We examined this possibility by measuring the patient's cardiac output and assessing its relation to presenting symptoms.....RESULTS: The patients with severe CFS had significantly lower stroke volume and cardiac output than the controls and less ill patients. Postexertional fatigue and flu-like symptoms of infection differentiated the patients with severe CFS from those with less severe CFS (88.5% concordance) and were predictive ($R2 = 0.46$, $P < 0.0002$) of lower cardiac output. In contrast, neuropsychiatric symptoms showed no specific association with cardiac output. CONCLUSIONS: These results provide a preliminary indication of reduced circulation in patients with severe CFS. Further research is needed to confirm this finding and to define its clinical implications and pathogenetic mechanisms.

21. **Redox Rep. 2000;5(1):35-41.**

Blood parameters indicative of oxidative stress are associated with symptom expression in chronic fatigue syndrome.

Richards RS, Roberts TK, McGregor NR, Dunstan RH, Butt HL.

http://www.ncbi.nlm.nih.gov/pubmed/10905542

Full blood counts, ESR, CRP, haematinics and markers for oxidative stress were measured for 33 patients diagnosed with chronic fatigue syndrome (CFS) and 27 age and sex matched controls. All participants also completed symptom questionnaires. CFS patients had increases in malondialdehyde (P <0.006), methaemoglobin (P <0.02), mean erythrocyte volume (P <0.02) and 2,3-diphosphoglycerate (P <0.04) compared with controls. Multiple regression analysis found methaemoglobin to be the principal component that differentiated between CFS patients and control subjects. Methaemoglobin was found to be the major component associated with variation in symptom expression in CFS patients (R(2) = 0.99, P <0.00001), which included fatigue, musculoskeletal symptoms, pain and sleep disturbance. Variation in levels of malondialdehyde and 2,3-diphosphoglycerate were associated with variations in cognitive symptoms and sleep disturbance (R(2) = 0.99, P <0.00001). These data suggest that oxidative stress due to excess free radical formation is a contributor to the pathology of CFS and was associated with symptom presentation.

22. **Dyn Med. 2007 Jan 30;6:2. Hypocapnia is a biological marker for orthostatic intolerance in some patients with chronic fatigue syndrome.**

Natelson BH, Intriligator R, Cherniack NS, Chandler HK, Stewart JM.

http://tinyurl.com/5pshs4

CONTEXT: Patients with chronic fatigue syndrome and those with orthostatic intolerance share many symptoms, yet questions exist as to whether CFS patients have physiological evidence of orthostatic intolerance.....CONCLUSION: A substantial number of CFS patients have orthostatic intolerance in the form of orthostatic hypocapnia. This allows subgrouping of patients with CFS and thus reduces patient pool heterogeneity engendered by use of a clinical case definition.

23. **Biochem Biophys Res Commun. 2006 Jul 14;345(4):1513-6. Epub 2006 May 22.**

Spectroscopic diagnosis of chronic fatigue syndrome by visible and near-infrared spectroscopy in serum samples.

Sakudo A, Kuratsune H, Kobayashi T, Tajima S, Watanabe Y, Ikuta K.

http://tinyurl.com/6xjkhd

To investigate visible and near-infrared (Vis-NIR) spectroscopy enabling chronic fatigue syndrome (CFS) diagnosis, we subjected sera from CFS patients as well as healthy donors to Vis-NIR spectroscopy.....The SIMCA model predicted 54 of 54 (100%) healthy donors and 42 of 45 (93.3%) CFS patients of Vis-NIR spectra from masked serum samples correctly. These results suggest that Vis-NIR spectroscopy for sera combined with chemometrics analysis could provide a promising tool to objectively diagnose CFS.

24. **In Vivo. 2004 Jul-Aug;18(4):417-24.**

Prevalence of abnormal cardiac wall motion in the cardiomyopathy associated with incomplete multiplication of Epstein-barr Virus and/or cytomegalovirus in patients with chronic fatigue syndrome.

Lerner AM, Dworkin HJ, Sayyed T, Chang CH, Fitzgerald JT, Beqaj S, Deeter RG, Goldstein J, Gottipolu P, O'Neill W.

http://tinyurl.com/6mz7mx

We reported unique incomplete herpesvirus (Epstein-Barr Virus (EBV) and/or nonstructural (HCMV) cytomegalovirus) multiplication in 2 distinct subsets of CFS patients.....A progressive cardiomyopathy caused by incomplete virus multiplication of EBV and/or HCMV in CFS patients is present.

25. **Chest. 1993 Nov;104(5):1417-21. Repetitively negative changing T waves at 24-h electrocardiographic monitors in patients with the chronic fatigue syndrome. Left ventricular dysfunction in a cohort.**

Lerner AM, Lawrie C, Dworkin HS.

http://tinyurl.com/624d5d

This study surveys the occurrence of repetitively negative to flat T waves, alternating with normal upright T waves in 24-h electrocardiographic recordings from a subspecialty infectious diseases outpatient practice during the years 1982 to 1990.....

Although resting ejection fractions (EFs) were normal (mean, 60 percent), with increasing work loads (Kilopon meters [Kpms]), gross left ventricular dysfunction occurred. The fatigue of patients with CFS may be related to subtle cardiac dysfunction occurring at work loads common to ordinary living.

26. **Int J Clin Exp Med 2(1):1-16,2009**

Chronic fatigue syndrome and mitochondrial dysfunction

Sarah Myhill, Norman E. Booth, John McLaren Howard

http://www.ijcem.com/812001A.html

Abstract: This study aims to improve the health of patients suffering from chronic fatigue syndrome (CFS) by interventions based on

the biochemistry of the illness, specifically the function of mitochondria in producing ATP (adenosine triphosphate), the energy currency

for all body functions, and recycling ADP (adenosine diphosphate) to replenish the ATP supply as needed. Patients attending a private

medical practice specializing in CFS were diagnosed using the Centers for Disease Control criteria. In consultation with each patient,

an integer on the Bell Ability Scale was assigned, and a blood sample was taken for the “ATP profile” test, designed for CFS and other

fatigue conditions. Each test produced 5 numerical factors which describe the availability of ATP in neutrophils, the fraction complexed

with magnesium, the efficiency of oxidative phosphorylation, and the transfer efficiencies of ADP into the mitochondria and ATP into the

cytosol where the energy is used. With the consent of each of 71 patients and 53 normal, healthy controls the 5 factors have been

collated and compared with the Bell Ability Scale. The individual numerical factors show that patients have different combinations of

biochemical lesions. When the factors are combined, a remarkable correlation is observed between the degree of mitochondrial

dysfunction and the severity of illness (P<0.001). Only 1 of the 71 patients overlaps the normal region. The “ATP profile” test is a

powerful diagnostic tool and can differentiate patients who have fatigue and other symptoms as a result of energy wastage by stress

and psychological factors from those who have insufficient energy due to cellular respiration dysfunction. The individual factors indicate

which remedial actions, in the form of dietary supplements, drugs and detoxification, are most likely to be of benefit, and what further

tests should be carried out. (IJCEM812001).

27. **J. Clin Virol. 2006 Dec;37 Suppl 1:S39-46. Is human herpesvirus-6 a trigger for chronic fatigue syndrome?**

Komaroff AL.

http://tinyurl.com/5fpm44

Chronic fatigue syndrome (CFS) is an illness currently defined entirely by a combination of non-specific symptoms. Despite this subjective definition, CFS is associated with objective underlying biological abnormalities, particularly involving the nervous system and immune system. Most studies have found that active infection with human herpesvirus-6 (HHV-6)--a neurotropic, gliotropic and immunotropic virus--is present more often in patients with CFS than in healthy control and disease comparison subjects, yet it is not found in all patients at the time of testing. Moreover, HHV-6 has been associated with many of the neurological and immunological findings in patients with CFS. Finally, CFS, multiple sclerosis and seizure disorders share some clinical and laboratory features and, like CFS, the latter two disorders also are being associated increasingly with active HHV-6 infection. Therefore, it is plausible that active infection with HHV-6 may trigger and perpetuate CFS in a subset of patients.

28. **J Clin Virol. 2006 Dec;37 Suppl 1:S47-51. Activation of human herpesviruses 6 and 7 in patients with chronic fatigue syndrome.**

Chapenko S, Krumina A, Kozireva S, Nora Z, Sultanova A, Viksna L, Murovska M.

http://tinyurl.com/5w3za7

BACKGROUND: Human herpesvirus 6 (HHV-6) and 7 (HHV-7) have been suggested as possible triggering agents for chronic fatigue syndrome (CFS). OBJECTIVES: To determine the possible

association of HHV-6 and HHV-7 infections with CFS....CONCLUSIONS: HHV-6 and HHV-7 may be involved in the pathogenesis of CFS and reactivation of both viruses may provoke changes in the phenotype of circulating lymphocytes.

29. **Behav Brain Funct. 2008 Sep 26;4:44. Evidence of inflammatory immune signaling in chronic fatigue syndrome: A pilot study of gene expression in peripheral blood.**

Aspler AL, Bolshin C, Vernon SD, Broderick G.

http://tinyurl.com/6aoe2

BACKGROUND: Genomic profiling of peripheral blood reveals altered immunity in chronic fatigue syndrome (CFS) however interpretation remains challenging without immune demographic context. The object of this work is to identify modulation of specific immune functional components and restructuring of co-expression networks characteristic of CFS using the quantitative genomics of peripheral blood.....CONCLUSION: Dissection of blood microarray profiles points to B cell dysfunction with coordinated immune activation supporting persistent inflammation and antibody-mediated NK cell modulation of T cell activity. This has clinical implications as the CD19+ genes identified could provide robust and biologically meaningful basis for the early detection and unambiguous phenotyping of CFS.

30. **BMC Physiol. 2005 Mar 24;5(1):5. Exercise responsive genes measured in peripheral blood of women with chronic fatigue syndrome and matched control subjects.**

Whistler T, Jones JF, Unger ER, Vernon SD.

http://tinyurl.com/5pc27o

BACKGROUND: Chronic fatigue syndrome (CFS) is defined by debilitating fatigue that is exacerbated by physical or mental exertion. To search for markers of CFS-associated post-exertional fatigue, we measured peripheral blood gene expression profiles of women with CFS and matched controls before and after exercise challenge.....Exercise-responsive genes differed between CFS patients and controls. These were in genes classified in chromatin and nucleosome assembly, cytoplasmic vesicles, membrane transport, and G protein-coupled receptor ontologies. Differences in ion transport and ion channel activity were evident at baseline and were exaggerated after exercise, as evidenced by greater numbers of differentially expressed genes in these molecular functions.

31. **Genomics. 2008 Sep 30. [Epub ahead of print] Neuroendocrine and immune network re-modeling in chronic fatigue syndrome: An exploratory analysis.**

Fuite J, Vernon SD, Broderick G.

http://tinyurl.com/6pwh7k

This work investigates the significance of changes in association patterns linking indicators of neuroendocrine and immune activity in patients with chronic fatigue syndrome (CFS).....Results indicate statistically significant differences between CFS and control networks determined mainly by re-modeling around pituitary and thyroid nodes as well as an emergent immune sub-network. Findings align with known mechanisms of chronic inflammation and support possible immune-mediated loss of thyroid function in CFS exacerbated by blunted HPA axis responsiveness.

32. **J Interferon Cytokine Res. 1997 Jul;17(7):377-85.Links**

Biochemical evidence for a novel low molecular weight 2-5A-dependent RNase L in chronic fatigue syndrome.

Suhadolnik RJ, Peterson DL, O'Brien K, Cheney PR, Herst CV, Reichenbach NL, Kon N, Horvath SE, Iacono KT, Adelson ME, De Meirleir K, De Becker P, Charubala R, Pfleiderer W.

http://tinyurl.com/674z35

Previous studies from this laboratory have demonstrated a statistically significant dysregulation in several key components of the 2',5'-oligoadenylate (2-5A) synthetase/RNase L and PKR antiviral pathways in chronic fatigue syndrome (CFS).....Evidence is provided indicating that the RNase L enzyme dysfunction in CFS is more complex than previously reported.

33. **Am J Med. 1996 Sep;101(3):281-90. Health status in patients with chronic fatigue syndrome and in general population and disease comparison groups.**

Komaroff AL, Fagioli LR, Doolittle TH, Gandek B, Gleit MA, Guerriero RT, Kornish RJ 2nd, Ware NC, Ware JE Jr, Bates DW.

http://tinyurl.com/6fvdqg

PURPOSE: To measure the functional status and well-being of patients with chronic fatigue syndrome (CFS), and compare them with those of a general population group and six disease comparison groups.CONCLUSION: Patients with CFS had marked impairment, in comparison with the general population and disease comparison groups. Moreover, the degree and pattern of impairment was different from that seen in patients with depression.

34. **Exp Biol Med (Maywood). 2007 Sep;232(8):1041-9. Hematologic and urinary excretion anomalies in patients with chronic fatigue syndrome.**

Niblett SH, King KE, Dunstan RH, Clifton-Bligh P, Hoskin LA, Roberts TK, Fulcher GR, McGregor NR, Dunsmore JC, Butt HL, Klineberg I, Rothkirch TB

http://www.ncbi.nlm.nih.gov/pubmed/17720950

.....Blood biochemistry and full blood counts were unremarkable and fell within normal laboratory ranges. However, the case-control comparison of the blood cell data revealed that CFS patients had a significant decrease in red cell distribution width and increases in mean platelet volume, neutrophil counts, and the neutrophil-lymphocyte ratio. Evaluation of the urine excretion parameters also revealed a number of anomalies. The overnight urine output and rate of amino acid excretion were both reduced in the CFS group ($P < 0.01$). Significant decreases in the urinary excretion of asparagine ($P < 0.0001$), phenylalanine ($P < 0.003$), the branch chain amino acids ($P < 0.005$), and succinic acid ($P < 0.0001$), as well as increases in 3-methylhistidine ($P < 0.05$) and tyrosine ($P < 0.05$) were observed.It was concluded that the urinary excretion and blood parameters data supported the hypothesis that alterations in physiologic homeostasis exist in CFS patients.

35. **Neuro Endocrinol Lett. 2007 Aug;28(4):477-83. Decreased expression of CD69 in chronic fatigue syndrome in relation to inflammatory markers: evidence for a severe disorder in the early activation of T lymphocytes and natural killer cells.**

Mihaylova I, DeRuyter M, Rummens JL, Bosmans E, Maes M..

http://tinyurl.com/6kjrel

Patients with CFS show defects in T and NK cell activation. Since induction of CD69 surface expression is dependent on the activation of the protein kinase C (PKC) activation pathway, it is suggested that in CFS there is a disorder in the early activation of the immune system involving PKC.

36. Arzneimittelforschung. 2006;56(6):399-404. Clinical activity of folinic acid in patients with chronic fatigue syndrome.

Lundell K, Qazi S, Eddy L, Uckun FM.

http://www.ncbi.nlm.nih.gov/pubmed/16889122

A high incidence of severe B-cell immunodeficiency and chronic reactivated Epstein-Barr virus (EBV) infection in patients with chronic fatigue syndrome (CFS) is reported herein. Of the 58 patients evaluated, 100% had evidence of prior EBV exposure and 72% had evidence for reactivated EBV infection. Notably, 94% of CFS patients had B-cell immunodeficiency with a marked depletion of their CD19+IgM+ mature B-lymphocyte population. A remarkable 81% of CFS patients experienced subjective improvement of their symptoms after treatment with folinic acid (CAS 58-05-9, leucovorin). The findings provide unprecedented evidence that CFS frequently is a folinic acid responsive clinical entity accompanied by B-cell immunodeficiency and inappropriate antibody responses to EBV.

37. **Neuroreport. 2003 Feb 10;14(2):225-8. Proton magnetic resonance spectroscopy of basal ganglia in chronic fatigue syndrome.**

Chaudhuri A, Condon BR, Gow JW, Brennan D, Hadley DM.

http://www.ncbi.nlm.nih.gov/pubmed/12598734

Fatigue is a common symptom of neurological diseases that affect basal ganglia function. We used proton magnetic resonance spectroscopy ((1)H MRS) to study the metabolic functions of the basal ganglia in chronic fatigue syndrome (CFS) to test the hypothesis that fatigue in CFS may have a neurogenic component. (1)H MRS of left basal ganglia was carried out in eight non-psychiatric patients with CFS and their results were compared to age- and sex-matched healthy asymptomatic healthy controls. A highly significant increase in the spectra from choline-containing compounds was seen in the CFS patient group ($p < 0.001$). In the absence of regional structural or inflammatory pathology, increased choline resonance in CFS may be an indicator of higher cell membrane turnover due to gliosis or altered intramembrane signalling.

38. **Int J Neurosci. 2001 Mar;107(1-2):1-6. Relationship of brain MRI abnormalities and physical functional status in chronic fatigue syndrome.**

Cook DB, Lange G, DeLuca J, Natelson BH.

http://tinyurl.com/6oawx3

Chronic Fatigue Syndrome (CFS) is an unexplained illness that is characterized by severe fatigue. Some have suggested that CFS is a "functional somatic syndrome" in which symptoms of fatigue are inappropriately attributed to a serious illness. However, brain magnetic resonance imaging (MRI) data suggest that there may be an organic abnormality associated with CFS.....These results demonstrate that the presence of brain abnormalities in CFS are significantly related to subjective reports of physical function and that CFS subjects with MRI brain abnormalities report being more physically impaired than those patients without brain abnormalities.

39. **Med Sci Sports Exerc. 2001 Sep;33(9):1463-70. Physiological responses to incremental exercise in patients with chronic fatigue syndrome.**

Inbar O, Dlin R, Rotstein A, Whipp BJ.

http://tinyurl.com/6yar7c

Results: As a group, the CFS patients demonstrated significantly lower cardiovascular as well as ventilatory values at peak exercise, compared with the control group.....It was found that the primary exercise-related physiological difference between the CFS and the control group was their significantly lower heart rate at any equal relative and at maximal work level. Assuming maximal effort by all (indicated by RER, PETCO(2), and subjective exhaustion), these results could indicate either cardiac or peripheral insufficiency embedded in the pathology of CFS patients.

40. **J Clin Virol. 2006 Dec;37 Suppl 1:S33-8. Use of valganciclovir in patients with elevated antibody titers against Human Herpesvirus-6 (HHV-6) and Epstein-Barr Virus (EBV) who were experiencing central nervous system dysfunction including long-standing fatigue.**

Kogelnik AM, Loomis K, Hoegh-Petersen M, Rosso F, Hischier C, Montoya JG.

http://www.ncbi.nlm.nih.gov/pubmed/17276366

OBJECTIVES: We sought to determine whether elevated antibodies to EBV and HHV-6 indicated chronic viral activation in patients with CNS dysfunction and if their symptoms could be improved by suppressing viral activity with oral valganciclovir.....

RESULTS: Nine out of 12 (75%) patients experienced near resolution of their symptoms, allowing them all to return to the workforce or full time activites. In the nine patients with a symptomatic response to treatment, EBV VCA IgG titers dropped from 1:2560 to 1:640 (p = 0.008) and HHV-6 IgG titers dropped from a median value of 1:1280 to 1:320 (p = 0.271).

41. **BMC Infect Dis. 2006 Jan 31;6:15. Preliminary evidence of mitochondrial dysfunction associated with post-infective fatigue after acute infection with Epstein Barr virus.**

Vernon SD, Whistler T, Cameron B, Hickie IB, Reeves WC, Lloyd A.

http://tinyurl.com/6pf45k

BACKGROUND: Acute infectious diseases are typically accompanied by non-specific symptoms including fever, malaise, irritability and somnolence that usually resolve on recovery. However, in some individuals these symptoms persist in what is commonly termed post-infective fatigue. The objective of this pilot study was to determine the gene expression correlates of post-infective fatigue following acute Epstein Barr virus (EBV) infection.....

RESULTS: Those who developed post-infective fatigue had gene expression profiles indicative of an altered host response during acute mononucleosis compared to those who recovered uneventfully. Several genes including ISG20 (interferon stimulated gene), DNAJB2 (DnaJ [Hsp40] homolog and CD99), CDK8 (cyclin-dependent kinase 8), E2F2 (E2F transcription factor 2), CDK8 (cyclin-dependent kinase 8), and ACTN2 (actinin, alpha 2), known to be regulated during EBV infection, were differentially expressed in post-infective fatigue cases. Several of the differentially expressed genes affect mitochondrial functions including fatty acid metabolism and the cell cycle.

42. **Physiol Behav. 2007 Dec 5;92(5):963-8. Epub 2007 Jul 25. A real-time assessment of the effect of exercise in chronic fatigue syndrome.**

Yoshiuchi K, Cook DB, Ohashi K, Kumano H, Kuboki T, Yamamoto Y, Natelson BH.

http://tinyurl.com/63w66m

Patients with chronic fatigue syndrome (CFS) report substantial symptom worsening after exercise. However, the time course over which this develops has not been explored.....Following exercise, physical symptoms did get worse but not until a five-day delay in CFS patients. Despite this, there was no difference in the temporal pattern of changes in psychological symptoms or in cognitive function after exercise between CFS patients and controls. In conclusion, physical symptoms worsened after several days delay in patients with CFS following exercise while psychological symptoms or cognitive function did not change after exercise.

43. **Am J Med. 1998 Sep 28;105(3A):54S-58S. Brain positron emission tomography (PET) in chronic fatigue syndrome: preliminary data.**

Tirelli U, Chierichetti F, Tavio M, Simonelli C, Bianchin G, Zanco P, Ferlin G.

http://tinyurl.com/6mysb7

The PET images examined 22 cortical and subcortical areas. CFS patients showed a significant hypometabolism in right mediofrontal cortex (P = 0.010) and brainstem (P = 0.013) in comparison with the healthy controls. Moreover, comparing patients affected by CFS and depression, the latter group showed a significant and severe hypometabolism of the medial and upper frontal regions bilaterally (P = 0.037-0.001), whereas the metabolism of brain stem was normal. Brain 18FDG PET showed specific metabolism abnormalities in patients with CFS in comparison with both healthy controls and depressed patients. The most relevant result of our study is the brain stem hypometabolism which, as reported in a perfusion SPECT study, seems to be a marker for the in vivo diagnosis of CFS.

44. **In Vivo. 2007 Sep-Oct;21(5):707-13. Valacyclovir treatment in Epstein-Barr virus subset chronic fatigue syndrome: thirty-six months follow-up.**

Lerner AM, Beqaj SH, Deeter RG, Fitzgerald JT.

http://tinyurl.com/5z5456

After six-months, Group 1 CFS patients receiving valacyclovir experienced an increased mean least square EI point score +1.12 units (122 kcal/day), while the placebo cohort increased +0.42 EI units (65 kcal/day). EI point scores at Group 2 increased progressively. Sinus tachycardias decreased and

abnormal cardiac wall motion improved. Serum antibody titers to EBV VCA IgM decreased. Patients resumed normal activities.

45. **J Clin Pathol. 2008 May;61(5):623-6. Epub 2007 Nov 23. Immunoassay with cytomegalovirus early antigens from gene products p52 and CM2 (UL44 and UL57) detects active infection in patients with chronic fatigue syndrome.**

Beqaj SH, Lerner AM, Fitzgerald JT.

http://tinyurl.com/5e4xxk

AIMS: To investigate whether the use of recombinant early antigens for detection of antibodies to human cytomegalovirus (HCMV) gene products CM(2) (UL44, UL57) and p52 (UL44) is specific in the diagnosis and differentiation of active HCMV infection in a subset of patients with chronic fatigue syndrome (CFS), a diagnosis which is often missed by the current ELISA assay that uses crude viral lysate antigen.

CONCLUSIONS: Immunoassays that use early antigen recombinant HCMV CM(2) and p52 are five times more sensitive than HCMV ELISA assay using viral lysate, and are specific in the detection and differentiation of active HCMV infection in a subset of patients with CFS.

46. **Health Care Women Int. 2006 Aug;27(7):615-26. Causes of death among patients with chronic fatigue syndrome.**

Jason LA, Corradi K, Gress S, Williams S, Torres-Harding S.

http://tinyurl.com/5nro5n

Chronic fatigue syndrome (CFS) is a debilitating illness affecting thousands of individuals. At the present time, there are few studies that have investigated causes of death for those with this syndrome. The authors analyzed a memorial list tabulated by the National CFIDS Foundation of 166 deceased individuals who had had CFS. There were approximately three times more women than men on the list. The three most prevalent causes of death were heart failure, suicide, and cancer, which accounted for 59.6% of all deaths. The mean age of those who died from cancer and suicide was 47.8 and 39.3 years, respectively, which is considerably younger than those who died from cancer and suicide in the general population. The implications of these findings are discussed.

47. **Neuropsychol Rev. 2005 Mar;15(1):29-58. Chronic fatigue syndrome: the need for subtypes.**

Jason LA, Corradi K, Torres-Harding S, Taylor RR, King C.

http://tinyurl.com/65d8jo

Chronic fatigue syndrome (CFS) is an important condition confronting patients, clinicians, and researchers. This article provides information concerning the need for appropriate diagnosis of CFS subtypes.....This review suggests that there is a need for greater diagnostic clarity, and this might be accomplished by subgroups that integrate multiple variables including those in cognitive, emotional, and biological domains.

48. **The Story of Sophia and M.E. and her death.**

http://tinyurl.com/uxqza

From the Autopsy Report:

“unequivocal inflammatory changes affecting the special nerve cell collections (dorsal root ganglia) that are the gateways (or station) for all sensations going to brain through spinal cord. The changes of dorsal root ganglionitis seen in 75% of Sophia‘s spinal cord were very similar to that seen during active infection by herpes viruses (such as shingles).”

And link to a website revealing the full story of Sophia's case, how she was treated and documentation:

http://www.sophiaandme.org.uk/

49. **The Inquest into the Death of Sophia Mirza**

http://tinyurl.com/35cgqa

The cause of death was stated as

'The verdict was Acute aneuric renal failure due to dehydration arising as a result of CFS'

Two pathologists could not agree which name to use - CFS, ME or ME/CFS.

In the end it was stated that CFS is a modern word for ME.

This is why CFS was used on the death certificate.

The pathologist also said -

'ME describes inflammation of the spinal chord and muscles. My work supports the inflammation theory. There was inflammation in the basal root ganglia.'

50. **"ME/CFS: A Clinical Case Definition and Guidelines For Medical Practitioners - An Overview of the Canadian Consensus Document"**

http://tinyurl.com/6jh8fa

And:

"Assessment and Treatment of Patients with ME/CFS:

Clinical Guidelines for Psychiatrists"

http://tinyurl.com/yr27vl

51. **MEResearchUK,**

http://www.meresearch.org.uk/

"ME Research UK is a national charity funding biomedical research into Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (also known as ME/CFS). Our principal aim is to

commission and fund high-quality scientific (biomedical) investigation into the causes, consequences and treatment of ME, but we also have a mission to 'Energise ME Research'."

They hold an international biomedical research conference every year.

52. **Invest in ME.**

http://www.investinme.org/index.htm

"an independent UK charity campaigning for bio-medical research into Myalgic Encephalomyelitis (M.E.), as defined by WHO-ICD-10-G93.3.

We have links nationwide and also internationally."

They too hold an international biomedical research conference every year.

53. **CFS Research Foundation**

http://www.cfsrf.com/goals.html

"The aims of the CFS Research Foundation are three-fold; first, to gain a workable understanding of how the disease is caused (pathogenesis), and second, with that knowledge, to develop useful treatments which will lead to a cure in most cases. And thirdly, to develop a diagnostic test for the disease which is simple enough to be used widely and specific only to Chronic Fatigue Syndrome (CFS)."

They fund Dr Jonathan Kerr's gene expression research see numbers 1 and 2

above.

54. **The Whittemore-Peterson Institue for Neuro-Immune Disease**

http://www.wpinstitute.org/index.html

http://www.wpinstitute.org/research/research_basic.html

“The first institute in the world dedicated to neuro-immune

disease integrating patient treatment, basic and clinical research, and medical education.”

“The Whittemore Peterson Institute for Neuro Immune Disease exists to bring discovery, knowledge, and effective treatments to patients with illnesses that are caused by acquired dysregulation of both the immune system and the nervous system, often resulting in life long disease and disability.

Our first goal is to work towards developing a better understanding of the natural history of these diseases, thereby diagnosing and treating patients accurately and efficiently. Generating and sustaining a blood and tissue repository and a clinical database for ME/CFS and ultimately for other neuroimmune diseases is a primary focus of the Institute.”

55. Here are quotations from three professors on the organic basis of ME/CFS:

1) From Antony Komaroff, Professor of Medicine at Harvard University,

at a CDC press conference to raise international awareness of the

seriousness and economic impact of ME/CFS in Washington DC, November,

2006:

"There are now over 4,000 published studies that show underlying

biological abnormalities in patients with this illness. It is not an

illness that people can simply imagine that they have and it's not a

psychological illness."

2) From Professor Nancy Klimas, University of Miami in her initial

address, as incoming President of the American Association of ME/CFS

in 2005 stated:

"Our patients are terribly ill, misunderstood, and suffer at the hands

of a poorly informed medical establishment and society"

And also form Professor Klimas Nancy: "Defining Moments – 20 years of making CFS History", published by the CFIDS Association of America, January 2008).

"As an immunologist, I once would have said (ME)CFS is clearly an immune dysfunction state, while an endocrinologist would have called attention to the adrenal gland irregularities, and a specialist in the autonomic nervous system would be convinced (ME)CFS is all about blood pressure abnormalities. Given what we've discovered about the illness, I now tell people (ME)CFS is all of these things. We know that (ME)CFS has identifiable biologic underpinnings because we now have research documenting a number of pathophysiological processes involving the brain, the immune system, the neuroendocrine system and the autonomic nervous system"

3) Professor Malcolm Hooper, Emeritus Professor of medicinal chemistry at the University of Sunderland and Margaret Williams. "Wessely's Way: Rhetoric or Reason?

March 2008**,** http://www.meactionuk.org.uk/Wesselys_Way.htm

"That ME/CFS is not a somatisation disorder is now beyond doubt because there is overwhelming evidence confirming it to be a multi-system organic disorder in which there is disruption of virtually every system in the body (for evidence, see http://www.meresearch.org.uk/information/researchdbase/index.html andhttp://www.meactionuk.org.uk "

For details of further research studies dating back decades visit http://www.meactionuk.org.uk/SUBJECT_INDEX.htm