New Jersey Chronic Fatigue Syndrome Association
2011 Medical Student Scholarship Program

"Ennumerate the various possible causes of Chronic Fatigue Syndrome (also referred to as Myalgic Encephalomyelitis). Discuss the evidence for and against these causes."

Beth A. Warren

D.O. Candidate

UMDNJ School of Osteopathic Medicine

Chronic Fatigue Syndrome (CFS) is a complex, physically debilitating disorder that encompasses severe unrelenting fatigue, muscle and joint pain, flu-like symptoms such as sore throat and swollen lymph nodes, unrefreshing sleep and concentration difficulties. It was first established as a diagnosis in 1988 by the Centers for Disease Control (CDC) which issued the first working case definition, which was later revised in 1994 to the current case definition (Bell, 1995). Ever since it was first defined in 1988, CFS has been the subject of controversy as patients experienced debilitating and disabling symptoms but a cause has not been identified. The search for a cause is made more difficult because the symptoms CFS patients experience overlap with many other disorders making it hard to narrow down the possibilities. Over the past 32 years, a great deal of research has been performed into potential causes of CFS; most of these fall into five main categories: infection/viruses, immune dysfunction, endocrine dysfunction and neuropsychiatric factors and genetics (Gluckman, 2011).

Viruses

Viruses were one of the first theories suggested when CFS was first recognized as a distinct illness in the mid 1980s. Following several outbreaks of CFS, the idea of a virus or infectious agent causing CFS gained popularity and many studies were performed in an attempt to identify the virus that might be responsible for causing CFS. Over the past 30+ years, viruses studied have included the Epstein-Barr Virus, Human Herpesvirus-6, Cytomegalovirus, Parvovirus B-19, Coxsackie-B virus, Borna disease virus, and Xenotropic Murine Leukemia Virus-Related Virus (XMRV) (Natelson et al, 2002)

Epstein-Barr virus was initially thought to be a likely cause of CFS, to the extent that early in the illness, before being named Chronic Fatigue Syndrome, patients were told they had chronic Epstein-barr virus. (Natelson et al, 2002) The researchers beliefs as to why EBV was a strong contender for causing CFS were based on 3 observations: EBV was known to lie dormant and reactivate, making it possible to cause chronic symptoms like CFS; many patients had tested positive for recent or active infection of EBV, outbreaks of CFS had occurred leading some doctors to believe a virus was a likely cause; and a number of patients reported becoming ill after a mononucleosis-type illness. (Gluckman, 2011) However, despite multiple studies showing a substantial number of patients had evidence of recent or active EBV infection (Buchwald et al, 1992; Sairenji et al, 1995), later studies suggested EBV was not the cause of CFS (Natelson et al, 2002). One study examined 20 patients; 5 CFS patients with primary EBV infection, 5 CFS patients with acute viral infection not caused by EBV, and 10 matched controls with resolution of EBV infection. Although CFS patients experienced increases in EBV titers, their levels did not differ from those of the control patients and the study found no evidence of ongoing or reactivated EBV in the pathogenesis of CFS. (Cameron et al, 2010).

Another herpesvirus, human herpesvirus-6, was also the subject of numerous studies. One study examined 259 patients with a "CFS-like" illness (study conducted prior to development of the case definition), and age and gender matched controls and found active replication of HHV6 in 70% of CFS patients versus 20% of controls. (Buchwald et al, 1992). Seven studies employing assays that could detect active infection found a link between CFS and active HHV6, while several smaller studies were unable to replicate their findings; however 717 patients (from the 7 positive studies) were found to have evidence of HHV6 infection while only 48 patients were not found to have evidence of infection. (Komaroff, 2006). A more recent study examined 10 CFS patients positive for HHV6, and 10 matched controls with past HHV6 infection and found that although patients had high antibody titers at infection baseline, the levels of CFS patients did not differ significantly from controls, contradicting the earlier studies (Cameron et al, 2010)

The most recent virus connected with CFS is a retrovirus, Xenotropic Murine Leukemia Virus-Related Virus (XMRV) – previously only detected in prostate cancer patients. The initial study, published in 2009, found evidence of XMRV in 67% of 101 CFS patients and only 3.7% of 218 healthy controls (Lombardi et al, 2009) However, 4 follow-up studies failed to find any link between XMRV and CFS (Silverman et al, 2010) One comprehensive follow-up study examined 100 CFS patients, 200 healthy controls from the same geographic region and 14 patients who tested positive for XMRV in the initial study; this study processed, tested and analyzed the samples using the same methods as the initial study but failed to detect XMRV in any of the samples. (Shin et al, 2011) Several studies published in the 2010 issue of Retrovirology found evidence that XMRV was the result of contamination of mouse DNA. (Hue et al, 2010, Robinson et al, 2010). More follow-up studies are scheduled to take place and may settle the issue of whether XMRV is a human pathogen or the result of lab contamination, and what role it plays (if any) in the etiology of CFS.

Immune Dysfunction

With evidence that CFS patients have been exposed to multiple viruses, researchers then turned to immune dysregulation as an explanation for CFS and to explain why patients test positive for multiple viruses. Scientists hypothesized that patients had an initial infection or virus that caused their immune system to malfunction so that even after the virus or infection went away, their immune system remained hyperactive (Pollack, 2002). Among the differences seen in CFS patients are lower than normal levels of circulating immune complexes, reduced numbers of natural killer cells, depressed natural killer cell function, altered levels of immunoglobulins, elevated titers of antiviral antibodies, lower levels of autoantibodies, decreased mitogen responses, decreased cell-mediated immunity,

enhanced interferon activity, increased levels of interleukin-2, and altered CD4/CD8 ratios. (Bell, 1995) One study of 147 CFS patients found a reduced CD8 suppressor cell population and increased activation markers (CD38, HLA-DR) on CD8 cells, not present in 80 healthy controls or 43 patients with other diseases (Landay et al, 1991) Another study of 259 CFS patients found higher CD4/CD8 T-cell ratios compared to healthy controls (Buchwald et al, 1992) A study of 30 CFS patients meeting CDC criteria and 86 healthy controls found all CFS patients to have multiple immune abnormalities, the most consistent of which was low natural killer cell cytotoxicity. Patients had elevated numbers of natural killer cells but diminished function, as well as increases in the percentage of suppressor-cytotoxic T lymphocytes, CD8, and proportionally larger increase in the number of CD8 cells expressing class II activation marker. The authors stated the pattern of immune abnormalities suggested CFS was an acquired immune deficiency. (Klimas et al, 1990) However other studies have failed to replicate these findings. A case control study of 26 CFS patients and age matched controls examined immune function and found no differences in white blood cell numbers, immune complexes, complement or serum immunoglobulin levels, delayed type hypersensitivity, and allergic responses, natural killer cell function and proliferative responses to mitogens and antigens. However when assessing the CFS patients based on onset (gradual versus sudden), subtle immunologic differences were seen (Mawle et al, 1997). The conflicting findings suggest while there may be some immune dysfunction, it may be a result of the disorder and not have a causal role.

Endocrine and Metabolic Dysfunction

Endocrine and metabolic abnormalities are another area which has held interest for many CFS researchers; adrenal insufficiency shares a number of symptoms with CFS including fatigue, muscle pain, flu-like symptoms, sleep abnormalities, headaches, and memory problems). These similarities have led researchers to investigate the hypothalamic-pituitary-adrenal (HPA) axis of CFS patients. (Papanicolaou, 2009). Part of the interest in categorizing the endocrine and metabolic abnormalities of CFS was to use those findings to help differentiate CFS from depression, which has characteristic endocrine findings. Patients with depression have been shown to have central up-regulation of the HPA axis resulting in mild hypercortisolism while CFS patients have been found to have down-regulation of the HPA axis yielding hypocortisolism. (Demitrack et al, 1991). An additional study supported these findings, it examined urinary free cortisol (UFC) excretion in 21 patients with CFS, 10 patients with major depression and 15 healthy controls. The study found that patients with depression had UFC levels significantly higher than healthy controls, and CFS patients had UFC excretion rates significantly lower than the controls. Additionally, 5 of the CFS patients had comorbid depression but that subgroup retained the UFC excretion profile of the patients with CFS alone leading the authors to suggest a different pathophysiological

basis for depressive symptoms in CFS (Scott et al, 1998). Researchers have shown CFS patients had subnormal adrenal response to different doses of ACTH indicating chronic HPA axis underactivity (Demitrack et al, 1991) A later study supported those findings by demonstrating patients with CFS had small adrenal glands compared to healthy controls using computed axial tomography. (Scott et al, 1998). These findings led researchers to hypothesize that the chronic hypocortisolism could lead to increased production of inflammatory cytokines and tested that hypothesis by administering corticotropin-releasing hormone (CRH) and checking to see if plasma levels of interleukin-6, an inflammatory cytokine, increased; this study was performed on healthy adults. The study found that CRH administration led to elevated levels of circulating IL-6 in healthy volunteers. A study was performed to determine whether administration of low-dose hydrocortisone would improve symptoms in CFS patients, and found that only 30% of patients experienced mild improvement. (Cleare, 2003). While there is clearly evidence of endocrine dysfunction in CFS patients, conflicting studies show the need for more research; newer studies are taking a multipronged approach by examining the relationship between the immune system, HPA axis, and stress (Van Houdenhove et al, 2009).

Neuropsychiatric Factors

One of the largest category of studies is that of neuropsychiatric factors, encompassing psychiatric factors, autonomic nervous system abnormalities, and sleep disturbances. When CFS was first recognized, many physicians suggested the disorder was psychiatric in origin due to the lack of objective test findings, and the overlap of CFS symptoms with those of depression (fatigue, memory loss, sleep difficulties). One study examined 87 patients with severe CFS, and found after psychiatric testing that 33 had a psychiatric illness that began with or after the onset of their CFS. They compared the degree of anger, depression and anxiety in depressive patients and patients with CFS and with MS, and found the CFS and MS patients had fewer problems than those with depression. Depression scores in CFS patients were compared with those of MS patients and patients with depression; and the CFS patients resembled MS patients in that they experienced less self-reproach but experienced more somatic symptoms than depressed patients. (Johnson et al, 1996) A meta-analysis of 244 studies examined medically unexplained physical symptoms, anxiety and depression in patients with irritable bowel syndrome, nonulcer dyspepsia, fibromyalgia and chronic fatigue syndrome, and found that depression and anxiety were more severe and occurred at a higher prevalence in patients with chronic fatigue syndrome compared to healthy controls or patients with similar medical diseases of known organic pathology. However the study did not differentiate between secondary depression, or depression that occurred after the onset of CFS, and primary depression that occurred prior to the onset of CFS. (Henningsen et al, 2003). Other studies have examined the difference between depression and CFS; one study compared 53 CFS patients with 20 depressed patients and 38 healthy controls on perceptions of their health, illness attributions, self-esteem, cognitive distortions of

general and somatic events, symptoms of distress and coping. The study determined CFS patients could be differentiated from depressed patients because depressed patients attitudes were dominated by a negative view of the self while CFS patients were primarily concerned about their poor health. The authors concluded that the results of their study supported evidence that argued against CFS being a version of depression. (Moss-Morris et al, 2001). In addition, studies comparing the HPA axis findings of CFS patients with patients with major depression show a significant difference; depressed patients have up-regulation of the HPA axis while CFS patients have down-regulation of the HPA axis. (Komaroff et al, 1998)

Studies have also examined autonomic nervous system abnormalities in CFS. Patients with CFS often complain of dizziness, particularly following changes in posture. Orthostatic intolerance is defined as the development of symptoms (dizziness, fatigue) and a drop in blood pressure during upright positions, relieved by changing to a reclining position. (Stewart, 2002) One study suggested a link between neurally mediated hypotension (also referred to as orthostatic intolerance) and CFS. Neurally mediated hypotension In this study 23 subjects with CFS underwent tilt table testing and 22 were found to have an abnormal test (compared to 4 out of 14 unmatched controls). The patients who tested positive were treated with fludrocortisones, atenolol or disopyramide, and most reported at least partial resolution of symptoms (Rowe et al, 1998). However, this study and other initial studies were not placebo-controlled, blinded or randomized. A later study of 21 pairs of monozygotic twins, in which one twin had CFS and the other did not have it, found abnormal tilt table tests to occur at the same rate in both twins (19% of abnormal tilt tests in those with CFS and 19% in those without CFS). (Poole et al, 2000)

Unrefreshing sleep is part of the case definition of CFS, therefore some researchers have suggested sleep disturbance as a possible cause of CFS. One study evaluated polysomnograms of CFS patients with and without fibromyalgia, to determine if patients had increased rates of sleep-disturbed breathing; or if feelings of unrefreshing sleep were associated with differences in sleep architecture. The study found CFS patients had significant differences in polysomnographic findings from healthy controls and felt sleepier and experienced more fatigue after a night's sleep than controls. CFS patients also had less total sleep time, lower sleep efficiency, and less rapid eye movement sleep than controls. These findings were not attributable to any diagnosable sleep disorders nor to coexisting fibromyalgia. (Togo et al, 2008). While sleep abnormalities have been demonstrated in CFS patients, it is not known whether they play a causal role or are secondary to the disorder.

The Role of Genetics

Genetic studies have also been performed; many patients have reported having one or more family members with the disease causing physicians to question whether there is a genetic role in the development of CFS. One study examined 146 pairs of female twins

where one twin had chronic fatigue lasting greater than 6 months and found a concordance rate higher in monozygotic twins (55% versus 19% for dizygotic twins). (Buchwald et al, 2001) Another study was performed investigating the possibility of a heritable predisposition to CFS; the analysis of familial clustering of CFS in a computerized genealogical resource found evidence of significantly elevated risks for CFS among first, second and third degree relatives of CFS patients. The authors stated that the results supported a genetic predisposition to CFS (Albright et al, 2011) However, the mechanism of inheritance was not examined. A recent study looked at patients with CFS and unexplained fatigue; this study found that CFS patients have different levels of expression of genes with roles in the HPA axis and sympathetic nervous system; these resulted in differences in how the body responded to hormones and other chemical messengers released in response to various stressors (Smith et al, 2006).

Concluding Remarks

With conflicting reports for most findings, it seems unlikely that any of the studies have pinpointed the cause. Subjective reports from patients have indicated that patients have become ill following a variety of triggers; ranging from infection/viruses to surgery to car accidents (Bell, 1995). It seems most likely that the cause of CFS is multi-factorial, incorporating a genetic predisposition that can be triggered by a virus or infection, a car accident or other stressful event, that may lead to immune dysregulation and endocrine abnormalities in the HPA axis. (Shor, 2003) Future studies focusing on the new field of psychoneuroimmunology may help explain the interrelationship between these areas and result in a better understanding of the pathophysiology of CFS and lead to the discovery of more effective treatments for CFS patients.

References:

Albright, F., Light, K., Light, A., Bateman, L., and Cannon-Albright, L.A. Evidence for a heritable predisposition to chronic fatigue syndrome. *BMC Neurology* 2011 11:62

Bell, D.S. *The Doctor's Guide to Chronic Fatigue Syndrome: Understanding, Treating and Living with CFIDS.* 1st Edition, Reading, MA. Addison-Wesley Publishing Company, 1995.

Buchwald, D., Cheney, P.R., Peterson, D.L. et al. A chronic illness characterized by fatigue, neurologic and immunologic disorders and active human herpesvirus type 6 infection. *Annals of Internal Medicine* 1992, 116:103

Buchwald, D., Herrell, R., Ashton, S., Belcourt, M., Schmaling, K., Sullivan, P., Neale, M., and Goldberg, J. A twin study of chronic fatigue. *Psychosomatic Medicine* 2001 Nov-Dec 63(6): 936-943

Cameron, B., Flamand, L., Juwana, H., Middledorp, J., Naing, Z., Rawlinson, W., Ablashi, D. and Lloyd, A. Serological and virological investigation of the role of the herpesviruses EBV, CMV and HHV-6 in the post-infective fatigue syndrome. *Journal of Medical Virology* 2010 82:1684-1688

Cleare, A. The neuroendocrinology of chronic fatigue syndrome. *Endocrine Reviews* 2003 24(2): 236-252

Gluckman, S.J. Clinical features and diagnosis of chronic fatigue syndrome. In: *UpToDate*, Rose, BD (Ed), UpToDate, Waltham, MA, 2011

Henningsen, P.; Zimmerman, T., and Sattel, H. Medically unexplained physical symptoms, anxiety and depression: a meta-analytic review. *Psychosomatic Medicine* 2003 65:528-533.

Holmes, G.P., Kaplan, J.E.; Stewart, J.A., Hunt, B., Pinsky, P.F., and Schonberger, L.B. A cluster of patients with a chronic mononucleosis-like syndrome. Is Epstein-Barr virus the cause? *Journal of the American Medical Association.* 1987 257(17): 2297-2302

Hue, S., Gray, E.R., Gall, A., Katzourakis, A., Tan, C.P., Houldcroft, C.J., McLaren, S., Pillay, D., Futreal, A., Garson, J.A., Pybus, O.G., Kellam, P., and Towers, G.J. Disease-associated XMRV sequences are consistent with laboratory contamination. *Retrovirology* 2010 7:111

Johnson, SK; Deluca, J, Natelson BH. Depression in fatiguing illness: comparing patients with chronic fatigue syndrome, multiple sclerosis and depression. *Journal of Affective Disorders* 1996 32:21-30.

Klimas, N.G., Salvato, F.R., Morgan, R. and Fletcher, M.A. Immunologic abnormalities in chronic fatigue syndrome. *Journal of Clinical Microbiology* 1990 28(6):1403-1410

Komaroff, A.L. Is human herpesvirus-6 a trigger for chronic fatigue syndrome? *Journal of Clinical Virology* 2006 37 (S1): S39-S46.

Komaroff, A.L., Buchwald, D.S. Chronic Fatigue Syndrome: An Update. *Annual Reviews of Medicine* 1998 49: 1-13

Landay, A.L., Jessop C., Lennette, E.T., Levy, J.A. Chronic fatigue syndrome: clinical condition associated with immune activation. *Lancet* 1991; 338:707

Lombardi, V.C., Ruscetti, F.W., Das Gupta, J., Pfost, M.A., Hagen, K.S., Peterson, D.L, Ruscetti, S.K., Bagni, R.K., Petrow-Sadowski, C., Gold, B., Dean, M., Silverman, R.H., and Mikovits, J.A. Detection of an infectious retrovirus, XMRV, in blood cells of patients with chronic fatigue syndrome. *Science* 2009 326(5952):585-589

Mawle, A.C.; Nisenaum, R.; Dobbins, J.G.; Gary, H.E.; Stewart, J.A.; Reyes, M.; Steele, L.; Schmid, D.S.; and Reeves, W.C. Immune responses associated with chronic fatigue syndrome: a case-control study. *The Journal of Infectious Diseases* 1997, 175: 136-141

Mawle, AC, Reyes, M., and Schmid, D.S. "Is Chronic Fatigue Syndrome an Infectious Disease? *Infectious Agents and Disease* 1994 2: 333-341.

Moss-Morris R., and Petrie, K.J. Discriminating between chronic fatigue syndrome and depression: a cognitive analysis. *Psychological Medicine* 2001 31:469-479.

Natelson, B.H. *Facing and Fighting Fatigue: A Practical Approach* 1st edition, New Haven, CT. Yale University Press, 1998.

Natelson, B.H., and Lange, G. A Status Report on Chronic Fatigue Syndrome. *Environmental Health Perspectives* 2002 110(Suppl4): 673-677

Natelson, B.H., LaManca, J.J, Denny, T.N., Vladutiu, A., Oleske, J., Hill, N., Bergen, M.T., Korn, L. and Hay, J. Immunologic parameters in chronic fatigue syndrome, major depression and multiple sclerosis. *American Journal of Medicine* 1998 105(3A): 43S-49S.

Nijs J, De Meirleir K. Impairments of the 2-5A synthetase/RNase L pathway in chronic fatigue syndrome. *In Vivo*. 2005 Nov-Dec;19(6):1013-21.

Papanicolaou, D. Corticotropin-Releasing Hormone in Chronic Fatigue Syndrome. The CFS Research Review *2009* Fall 4(2): 4-8.

Pollack, S. Chronic Fatigue Syndrome and Immune Dysfunction: Cause or Effect? *Israeli Medical Association Journal* 2002 Vol 4(Supplement): 883-885.

Poole, J., Herrell, R.; Ashton, S. et al. Results of isoproterenol tilt table testing in monozygotic twins discordant or chronic fatigue syndrome. *Archives of Internal Medicine* 2000; 160:3461

Robinson, M.J., Erlwin, O., Kaye, S., Weber, J., Cingoz, O., Patel, A., Walker, M.M., Kim, W-J., Uiprasertkul, M., Coffin, J.M., and McClure, M. Mouse DNA Contamination in human tissue tested for XMRV. *Retrovirology* 2010 7:108

Rowe, PC., and Calkins, H. Neurally mediated hypotension and chronic fatigue syndrome. *American Journal of Medicine* 1998; 105:15S

Sairenji, T., Yamanishi, K., Tachibana, Y., Bertoni, G., and Kurata, T. Antibody responses to Epstein-Barr virus, human herpesvirus 6 and human herpesvirus 7 in patients with chronic fatigue syndrome. *Intervirology* 1995. 38(5):269-273

Scott, L., and Dinan, T.G. Urinary free cortisol excretion in chronic fatigue syndrome, major depression and in healthy volunteers. *Journal of Affective Disorders* 1998 47: 49-54.

Shin, C.H., Bateman, L., Shlaberg, R., Bunker, A.M., Leonard, C.J., Hughen, R.W., Light, A.R., Light, K.C., and Singh, I.R. Absence of XMRV Retrovirus and other murine leukemia virus-related viruses in patients with chronic fatigue syndrome. *Journal of Virology* 2011 85(14):7195-7202

Shor, S. Pathogenesis of Chronic Fatigue Syndrome: A Multisystem Hypothesis. *Journal of Chronic Fatigue Syndrome* 2003; 11(3):51-68

Silverman, R.H., Nguyen, C., Weight, C.J., and Klein, E.A. The human retrovirus XMRV in prostate cancer and chronic fatigue syndrome. *Nature Review Urology* 2010 7: 392-402

Smith, A.K., White, P.D., Aslakson, E., Vollmer-Conna, U., and Rajeevan, M.S. Polymorphisms in genes regulating the HPA axis associated with empirically delineated classes of unexplained chronic fatigue. *Pharmacogenomics* 2006 7(3): 387-394.

Stewart, J. Dizziness in CFS. In J.F. John & J.M. Oleske (Eds.) *A Consensus Manual for the Primary Care and Management of Chronic Fatigue Syndrome* (29-33). 2002 Lawrenceville, NJ: The Academy of Medicine of NewJersey.

Suhadolnik RJ, Reichenbach NL, Hitzges P, et al. Upregulation of the 2-5A synthetase/RNase L antiviral pathway associated with chronic fatigue syndrome (Abstract). *Clinical Infectious Disease*s 1994 Jan; 18 Suppl 1:596-104.

Swanink, C.M.A., Melchers, W.J.G., Van der Meer, J.M.M. et al "Enteroviruses and the chronic fatigue syndrome" *Clinical Infectious Diseases* 1994 19:860-864.

Togo, F., Natelson, B.H., Cherniack, N.S., FitzGibbons, J., Garcon, C., and Rapoport, D.M. Sleep structure and sleepiness in chronic fatigue syndrome with or without fibromyalgia. *Arthritis Research Therapy* 2008 10(3):R56

Van Houdenhove, B.; Van Den Eede, F.; and Luyten, P. Does hypothalamic-pituitary-adrenal axis hypofunction in chronic fatigue syndrome reflect a 'crash' in the stress system? *Medical Hypotheses.* 2009 72: 701-705.

Yousef, GE, Mann, GF; Smith, DG et al "Chronic enterovirus infection in patients with postviral fatigue syndrome" *British Medical Journal* 1991 302:140-143