

January 2, 2005

Dr. J. Gerberding, CDC Director
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Dr. Gerberding:

I appreciate your response (which is attached for your easy access) to my letter received October 6, 2004, on behalf of the current collective over 150 Myalgic Encephalomyelitis patients in the Sacramento, California area.

I am interested in addressing the concerns you raised in your letter.

You state that "a component of Myalgic Encephalomyelitis that continues to limit efforts to consider CFS as the same illness is the presence of measurable neurological findings in individuals with classical Myalgic Encephalomyelitis." You also stated that this and other unique characteristics that differentiate CFS from M.E. contributed to the naming of the syndrome in 1988. However, I would like to point out that one of the cardinal features of Myalgic Encephalomyelitis, neurological abnormalities, was reported to the original CDC representatives who came to Incline Village to confer with Dr. Cheney and Dr. Peterson; however, the committee that was formed by the CDC to produce a definition totally ignored these findings, which had been verified at the time by Dr. Sheila Bastien ("Patterns of Neuropsychological Abnormalities and Cognitive Impairment in Adults and Children") Further substantiation was provided by Ismael Mena, M.D., "Study of Cerebral Perfusion by NeuroSPECT in Patients with Chronic Fatigue Syndrome," The Cambridge Symposium on Myalgic Encephalomyelitis, 1990; 1: 21-22.

The epidemiologists from the CDC also failed to take into account the MRI scan abnormalities reported by Drs. Cheney and Peterson and verified by neuroradiologists in Reno and later substantiated by Dr. Komaroff at Harvard. In addition, see attached portion of Dr. Hyde's lecture at the Wisconsin conference which shows the inept CDC committee work on the definition of this disease as well as Dr. Hyde's clear presentation of the levels of disability in the disease, Myalgic Encephalomyelitis, by sophisticated use of brain SPECT scans.

The point I am making here is that the CDC's scattershot definition and criteria plus the name CFS itself have brought in patient cohorts that muddy the waters, whereas by following the definitions of M.E. cited below, the true nature of this neuroimmune and cardiac disease becomes clear. Dr. Hyde says that there is a group of CFS patients who are misdiagnosed and actually have some other disease. He also notes that there is a group that has a wide range of pathologies that may be mistaken for M.E.

By viewing three definitions of Myalgic Encephalomyelitis, we can also see an answer to your question of "how can all of these diverse findings describe the same illness?"

Dr. Melvin Ramsay, pioneer UK researcher and clinician, posits this description of M.E.: 1) Muscle myopathy, which Ramsay describes as a delay in muscle recovery after exercise. 2) Circulatory impairment including intolerance to temperature extremes. 3) Cerebral (brain) dysfunction including problems with memory and concentration, sleep disturbances, noise intolerance, palpitations and tachycardia.

The cardinal features of M. E. As described in Dowsett and Welsby (1992) and Macintyre (1992) are considered to be:

1. Generalised or localised muscle fatigue following minimal exertion with prolonged recovery time.
2. Neurological disturbances.
3. Variable involvement of cardiac and other bodily systems.
4. An extended relapsing course with a tendency to chronicity.
5. Marked variability of symptoms in the course of a day.

Dr. Hyde's definition of M.E.: "M.E. is a measurable, diffuse post-encephalitic illness. The illness is characterized by (1) its acute onset, (2) the diffuse, non-focal persisting nature of the encephalopathy, and (3) the chronicity of the resulting symptoms. These symptoms consist of the rapid exhaustion or loss of stamina of motor, sensory, intellectual, and cognitive abilities. M.E. is of infectious/autoimmune origin and less commonly, a toxic/autoimmune origin. M.E. occurs in epidemics and sporadic cases."

[Note by Rich Van Konynenburg, Ph.D, who reported on the Dr. Hyde's lecture at the recent Wisconsin conference of medical practitioners specializing in M.E./CFS which was also attended by Dr. Reeves -- "Basically, what he's saying here is that M.E. starts with an inflammation of the brain that occurs rather suddenly. This initial inflammation usually results from an infectious/autoimmune process, but it can also be caused by a toxic/autoimmune process. This sudden, short-term inflammation is followed by a disorder of the brain that continues over time. This chronic disorder of the brain is not localized to a small part of the brain, but is spread out over large regions of the brain, and it leads to chronic symptoms that can involve essentially all the normal functions of the brain. M.E. occurs both in epidemic-type clusters of cases as well as cases that are occasional and isolated."] Dr. Hyde said that though the primary injury in M.E. is the diffuse CNS encephalopathy, the illness may cause or be associated with measurable dysfunction in end organs and various body systems. The most commonly injured end organs and systems are (1) the thyroid gland, (2) the cardiovascular system and (3) the immune system. The CNS dysfunctions are caused by widespread, measurable, diffuse micro-vasculitis affecting normal cell operation and maintenance. He went on to say that in M.E., "the brain changes are not progressive but of acute onset and relatively stable over a period of years."

"The evidence would suggest that M.E. is caused primarily by a diverse group of viral infections that have neurotropic characteristics and that appear to exert their influence primarily on the CNS arterial bed. The available brain technology limits the viral site of action to the capillaries and microarterial CNS bed. This diffuse vascular site of injury rather than a neurological cellular site of injury explains the natural history of ME-type illness." [Note by Rich--What he is saying here is that there is evidence that the causes of M.E. are any of a group of viruses that are able to infect the brain. By means of high-resolution SPECT scanning, he can tell that they mainly affect the small arteries and capillaries in the brain.] "It is also noted that many M.E. patients also have generalized arterial pathophysiology [Note by Rich--In other words, there are problems with the arteries all over their bodies.], causing various vascular problems that include in numerous patients: (1) insufficient blood pressure increase on exertion, (2) hyperelasticity and hypercontractibility of arterial blood vessels, (3) various forms of arterial mediated vascular orthostatic pathophysiology [Note by Rich--In other words, they have difficulty standing up because of problems with their arteries] as demonstrated by Drs. David Streeten, David Bell, and Peter Rowe, and (4) cholinesterase dysfunction in the arterial wall, causing arterial elasticity dysfunction as demonstrated by Dr. Vance Spence at Dundee University, Scotland."

[Note by Rich--Dr. Spence and his group have found that when they inject acetylcholine into the forearms of CFS patients using a special electrochemical technique, the arteries dilate more than normal,

and stay dilated longer than normal.] Dr. Hyde noted that Dr. Erich Ryll had described the 1975 epidemic at the Mercy San Juan Hospital in Sacramento, California as epidemic vasculitis.

This goes along way to in answer your questioning of how the 18 bulleted observations of diverse abnormalities listed in my first letter could be found in one patient. Actually I have all but three of these abnormalities, as do most all patients with the real disease, M.E., not unusual after viral or toxic assault and the resulting CNS Encephalopathy/Vasculitis. The three exceptions which I personally have not yet been tested for, are however found in a number of M.E. patients. I am fortunate not yet to have clear indications of the end-stage organ failures mentioned by Dr. Richardson & Dr. Hyde, and I have not been tested for enteroviral invasion, while the other two findings are difficult to obtain testing for the broad M.E. population: 1) the heart biopsy results by Dr. Lerner, and 2) the head-up tilt test. Dizziness is, too, a recognized symptom, but just as heart failure patients do not present with the same symptom set, neither do M.E. or CFS patients.

Attached is research included in the statement of the U.S.D.H.H.S.-appointed Name Change Working Group as well as specific cardiac & muscle myopathy research, which substantiate these numerous abnormalities in solid scientific studies.

Also, I am a little mystified about your criticism of the 2003 Canadian Consensus Criteria, specifically your comments that it:

1. "... is plagued by the primary shortcoming of all definitions by committee efforts" and;
2. "... a lack of irrefutable data upon which the definition is constructed."

Correlating with your comments above:

1. I posit first of all that the Canadian panel was not any old committee (as was the case with the CDC definition committees in 1988 and 1994, see quote below), but was rather comprised of internationally respected experts in the field of M.E./CFS – both hands-on clinicians and long-time researchers, including top-notch American doctors such as Dr. Klimas and Dr. Lerner among others.

By contrast, please note at the 2004 AACFS-Wisconsin Dr Reeves, one of the many authors of the Fukuda '94 definition, was very candid about the shortcomings of that CDC committee & the definition it produced: "The current case definition is what we have. It was basically, being an author I can do this in the crudest terms--a bunch of old cronies... writing on their favorite symptoms... There were people in fact who deal with CFS patients for a living, but the definition was not based on empiric data."

I hope you will agree this demonstrates a primary shortcoming, emanating from the CDC, that is causing untold harm to millions around the world.

2. Addressing your need for irrefutable data, there are 237 references in the Canadian Criteria that cite reliable data. The attached citations from the Name Change Working Group provide additional reliable data (plus additional important cardiac & muscle myopathy abnormalities substantiated by research).

3. The recent study by Dr. Leonard Jason ["Comparing the Fukuda et al. Criteria and the Canadian Case Definition for Chronic Fatigue Syndrome," J of Chronic Fatigue Syndrome, Vol. 12 Issue 1, pp. 37-52, 2004, E-mail: ljason@depaul.edu] revealed that the Canadian Case Definition is a far superior tool in the clinical setting for diagnostic purposes (see attached abstract of study). Much of the inability of research studies to reach consistent results is due to the failure to work on research-based subsets under M.E./CFS, as well as the inherent problems of heterogeneity caused by the Fukuda criteria. Fatigue, as commonly understood, is not the central feature of the illness, but rather it's the relapsing of a

number of neurological, circulatory, immune, musculoskeletal-weakness like symptoms, all of which are described under the Canadian Clinical Case Definition.

4. Australia has adopted the Canadian Clinical Case Definition for their country along with the name, Myalgic Encephalopathy/CFS. This would be an excellent & efficient example for us to follow.

Finally, Dr. Carruthers has said that this document could be readily modified for research purposes. Therefore, this Canadian Criteria (which is actually by international consensus of experts) could provide both solid clinical and research definition documents in a short amount of time - notably without a lot of government expense.

Again, thank you for your letter, and for your consideration of these matters. I think it's possible to get these issues resolved in short order with your cooperation before more undue suffering and inhumane deprivations occur due to the loose 1994 Fukuda definition, and the name itself. A new name needs to be found for CFS (whether it be Myalgic Encephalomyelitis, Myalgic Encephalopathy, CNS Encephalopathy or CNS Vasculitis) because patients cannot get medical care and are routinely dismissed when they mention the name CFS. (reference: "Suffering, Science and Sabotage," by M. B. Yunus, M.D., Journal of Musculoskeletal Pain, Vol. 12(2) 2004), which shows in bright light the bias that medical practitioners continue to exhibit in their clinical treatment of M.E./CFS patients)

Sincerely,

Steven Du Pre, Representing:
Capital Area CFIDS/M.E. Assoc. & Sacramento Valley CFIDS/M.E. Assoc.
P.O. Box 60101
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CC: Senator Barbara Boxer, Senator Diane Feinstein, Representative Dan Lungren, Dr. Larry Fields, Dr. David Bell, Dr. Anthony Komaroff, Valerie Strauss from The Washington Post

Portion of report on Dr. Hyde's comments at the conference:

When the original board met at the CDC in 1988 to establish a case definition for CFS, Dr. Hyde was in attendance, because those interested in this type of diseases were invited to come. He said that "it was obvious to those who had actually seen M.E./CFS patients that the vast majority of the people on the board were researchers who had never seen an M.E. patient clinically."

Dr. Hyde said that the definition this board developed totally warped the whole concept of M.E./CFS-type disease, because the authors introduced the word "fatigue" into the name. Fatigue can be produced by many things, and it is a totally undefinable term in his view. Furthermore, in the 50 epidemics up to that time, fatigue had only occurred in one. What actually did occur in these epidemics again and again was central nervous system (CNS) derangement: sleep dysfunction, cognitive problems, and in general, difficulties with any tasks the brain is required to perform.

According to Dr. Hyde, the second factor that came into the picture in 1988 and was perpetuated as well in the development of the revised 1994 Fukuda et al. case definition process as well those carried out in other countries, was that they brought in more psychiatrists. The overall result was that the definitions were developed primarily either by epidemiologists who were in his view forced by the government to go

and start looking at these patients and produce a definition, or by people who did not believe that there was any physical thing wrong with any of the people who had what they called CFS.

Dr. Hyde said that at a meeting initiating the development of the 1994 definition there was not a single clinician on the entire board, with one exception, and he therefore got up and said, "Why don't you put some people on this board who have actually seen patients?" He said they accommodated by adding one more who had. Dr. Hyde said the people on the board were brilliant, but they had never seen a case of CFS. According to Dr. Hyde, bringing in so many physicians who had never actually seen CFS patients, and particularly psychiatrists, who wanted to say that these patients had depression or anxiety or some other psychiatric problem, and trying to accommodate these extremes in the definitions destroyed the reality in the definitions that resulted.

Dr. Hyde quoted a 1993 paper by Dr. William Reeves of the CDC, to wit, "Chronic fatigue syndrome has no confirmatory physical signs or characteristic laboratory abnormalities, and the etiology and pathophysiology remain unknown." In Dr. Hyde's view, any reasonable physician who did not actually deal with CFS would conclude from reading this that CFS had to be a form of psychiatric or somatizing illness. He said that we need to redefine what is going on, and that there is a lot of good evidence with which to do so.

Recovery of ME Patients

Dr. Hyde distinguished the following three types of ME, based on his SPECT observations "Type I ME: Patients who demonstrate primarily a mild persisting encephalopathy of only one of the brain hemispheres are most likely to have some chance of recovery.

"Type II ME: Patients who demonstrate an encephalopathy involving both cerebral hemispheres rarely or never recover.

"Type III ME: These patients have both a bilateral cortical hemisphere and a subcortical encephalopathy. Type III patients have the most severe and most chronic form of illness and demonstrate the largest degree of increased end-organ pathophysiology."

Dr. Hyde emphasized that the changes he observes on the SPECT scan in ME patients are not found in healthy people, and that they are clear evidence of disease.

He believes that the causes of these changes could be viral, chemical, or autoimmune agents.

He further believes that "These central nervous system changes can potentially affect other body organs and systems that are controlled by the specific CNS areas injured, and that these organ and system changes are also measurable."

Abstract of Dr. Leonard Jason study:

Comparing the Fukuda et al. Criteria and the Canadian Case Definition for Chronic Fatigue Syndrome
Journal: J of Chronic Fatigue Syndrome, Vol. 12 Issue 1, pp. 37-52, 2004 ISSN: 1057-3321 Pub Date:
10/14/2004 Authors Leonard A. Jason PhD, DePaul University, Center for Community Research,
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Abstract

Because the pathogenesis of Chronic Fatigue Syndrome (CFS) has yet to be determined, case definitions have relied on clinical observation in classifying signs and symptoms for diagnosis. The selection of diagnostic signs and symptoms has major implications for which individuals are diagnosed with CFS and

how seriously the illness is viewed by health care providers, disability insurers and rehabilitation planners, and patients and their families and friends.

Diagnostic criteria also have implications for whether research based on varying definitions can be synthesized.

The current investigation examined differences between CFS as defined by Fukuda et al. (1994) and a set of criteria that has been proposed for a clinical Canadian Case definition.

There were twenty-three participants who met the Canadian criteria, 12 in the CFS (Fukuda et al. (7) criteria) group and the 33 from the chronic fatigue (CF)-psychiatric group. Dependent measures included: work status, psychiatric comorbidity, symptoms, and functional impairment (measured by the Medical Outcomes Study). People meeting the Fukuda et al. and Canadian criteria were compared with people who had a chronically fatiguing illness explained by a psychiatric condition. Statistical tests used included binomial logistic regression and analysis of variance.

The Canadian criteria group, in contrast to the Fukuda et al. criteria group, had more variables that statistically significantly differentiated them from the psychiatric comparison group. Overall, there were 17 symptom differences between the Canadian and CF-psychiatric group, but only 7 symptom differences between the CFS and CF-psychiatric group.

The findings suggest that both the Canadian and Fukuda et al. case definitions select individuals who are statistically significantly different from psychiatric controls with chronic fatigue, with the Canadian criteria selecting cases with less psychiatric co-morbidity, more physical functional impairment, and more fatigue/weakness, neuropsychiatric, and neurological symptoms.

From Recommendations of the Name Change Workgroup Presented to the DHHS Chronic Fatigue Syndrome Advisory Committee

The number of symptoms reported by patients with the syndrome is very large (4). However, most of the commonly reported symptoms are associated with or may be indicative of an aberration or dysfunction of the neurologic, neuroendocrine, and/or immunologic systems. The following selected scientific publications provide a sound basis for a new name that reflects common symptoms associated with these systems. The articles were selected because they have withstood scientific scrutiny and represent critical findings. While other publications are available, the chosen articles are widely respected, cited, and felt to be representative of the current understanding of the science. For purposes of this document, the articles have been categorized into their relevant subsections pertaining to each of the body systems.

A. Neurologic System

Autonomic nervous system (including orthostatic intolerance)

Several authors have published findings demonstrating that some of the symptoms seen with this syndrome are associated with autonomic nervous system dysfunction, predominantly blood pressure control.

Bou-Holaigah I, Rowe PC, Kan J, Calkins H. The relationship between neurally mediated hypotension and the chronic fatigue syndrome. *JAMA* 1995; 274:961-967.

Schondorf R, Freeman R. The importance of orthostatic intolerance in the chronic fatigue syndrome. 1999 *Am J Med Sci* 1999;317(2):117-123.

Freeman R, Komaroff A. Does the chronic fatigue syndrome involve the autonomic nervous system? *Am*

J Med 1997;102:357-364.

Neuroendocrine System

The best studied evidence of neuroendocrine dysfunction involves the hypothalamic-pituitary-adrenal axis.

Demitrak MA, Dale JK, Straus SE, et al. Evidence for impaired activation of the hypothalamic-pituitary-adrenal axis in patients with chronic fatigue syndrome. J Clin Endocrinol Metab 1991;73:1223-1234.

Scott LV, Medbak S, Dinan TG. Blunted adrenocorticotropin and cortisol responses to corticotropin-releasing hormone stimulation in chronic fatigue syndrome. Acta Psychiatr Scand 1998;97:450-457.

Neurocognitive Problems

Neurocognitive symptoms are reported with relatively high frequency in **the** syndrome. In addition to problems with memory and concentration, information processing functions appear to be abnormal. Many meritorious articles have been published, but at least one seems to be scientifically robust and has not been substantially challenged by other publications.

DeLuca J, Johnson SK, Ellis SP, Natelson BH. Cognitive functioning is impaired in patients with chronic fatigue syndrome devoid of psychiatric disease. J Neurol Neurosurg Psychiatry 1997;62:151-155.

B. The Immune System

Several articles have been published investigating the relationship between the immunologic system and chronic fatigue syndrome. The best validated work and most consistent findings demonstrate decreased function of natural killer cells and reduced responses of T cells to mitogens and other specific antigens. The literature also supports evidence of chronic immune activation in CFS, with increasing emphasis on cytokine dysregulation.

Caligiuri M, Murry C, Buchwald D, et al. Phenotypic and functional deficiency of natural killer cells in patients with chronic fatigue syndrome. J Immunol 1987;139:3306-3313.

Klimas NG, Salvato FR, Morgan R, Fletcher MA. Immunologic abnormalities in chronic fatigue syndrome. J Clin Microbiol 1990;28:1403-1410.

Patarca R, Klimas N, Sandler D, Garcia MV, Fletcher MA. Interindividual immune status variation patterns in patients with chronic fatigue syndrome: association with gender and tumor necrosis factor system. J of CFS 2(1):7-41, 1996.

Cannon JG, Angel JB, Abad LW, Vannier E, Mileno MD, Fagioli L, Wolff SM, Komaroff AL. Interleukin-1 beta, interleukin-1 receptor antagonist, and soluble interleukin-1 receptor type II secretion in chronic fatigue syndrome. Journal of Clinical Immunology 17(3):253-61, 1997.

Sudaholnik RJ, Peterson DL, O'Brien K, Cheney PR et al. Biochemical evidence for a novel low molecular weight 2-5A-dependent RNase L in chronic fatigue syndrome. J of Interferon&Cytokine research. 17(7):377-85, 1997.

(Additional studies on serious cardiac & muscle myopathy abnormalities in M.E./CFS)

Lerner AM, Dworkin HJ, Sayyed T, Chang CH, Fitzgerald JT, Beqaj S, Deeter RG, Goldstein J, Gottipolu P, O'Neill W. 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. *In Vivo*. 2004 Jul-Aug;18(4):417-24.

Peckerman A, LaManca JJ, Dahl KA, Chemitiganti R, Qureishi B, Natelson BH. "Abnormal impedance cardiography predicts symptom severity in chronic fatigue syndrome." *Am J Med Sci*. 2003 Aug;326(2):55-60.

Arnold Peckerman, Rahul Chemitiganti, Caixia Zhao, Kristina Dahl, Benjamin H. Natelson, Lionel Zuckier, Nasrin Ghesani, Samuel Wang, Karen Quigley and S. Sultan Ahmed. "Left Ventricular Function in Chronic Fatigue Syndrome (CFS): Data From Nuclear Ventriculography Studies of Response to Exercise and Postural Stress," Findings presented at the American Physiological Society conference, Experimental Biology 2003, being held April 11-15, 2003, at the San Diego Convention Center, San Diego, CA

Lerner, A. M., Goldstein, J., O'Neill W., et al. "Cardiac involvement in patients with chronic fatigue syndrome as documented with Holter and biopsy data in Birmingham, Michigan, 1991-1993." *Inf Dis in Clin Pract*, 1997; 6:327-333.

Muscle myopathy: Muscle Metabolism/Mitochondrial Myopathy

Behan, W. M., More, I.A., Behan, P.O. "Mitochondrial abnormalities in the postviral fatigue syndrome." *ACTA Neuropathol (Berl)*, 1991;83(1):61-5.

Zhang C., Baumer A., et al. "Unusual pattern of mitochondrial DNA deletions in skeletal muscle of an adult human with chronic fatigue syndrome." *Hum Mol Genet*, 1995 Apr.; 4(4):751-4.

McCully K.K., Natelson B.H., et al. "Reduced oxidative muscle metabolism in chronic fatigue syndrome." *Muscle Nerve*, 1996 May; 19(5):621-5.

Behan, W.M.H., Holt, I.J., et al. "In vitro study of muscle aerobic metabolism in chronic fatigue syndrome." *JCFS*, 5.1(1999):np.

Lane, R. J., et al. "Heterogeneity in chronic fatigue syndrome: evidence from magnetic resonance spectroscopy of muscle." *Neuromuscular Disorders* 83 (4):204-209.

Lane, R.J., et al. "Muscle fiber characteristics and lactate responses to exercise in chronic fatigue syndrome." *J of Neurol, Neurosurgery, and Psychiatry* 64(3):362-367.

McCully, K.K., Natelson, B.H. "Impaired oxygen delivery to muscle in chronic fatigue syndrome." *Clin Sci (Colch)* 1999, Nov; 97(5):603-8;discussion 611-3.

Kuratsune H., Yamaguti K., et al. "Acylcarnitine deficiency in chronic fatigue syndrome." *Clin Inf Dis* 1994; 18(suppl1):62-67.

Griggs R.C., Karpati G. "Muscle pain, fatigue, and mitochondriopathies." *NEJM* 1999; 341:1077-78.

Manfredi, G., Beal M.S. "The role of mitochondria in the pathogenesis of neurodegenerative diseases." *Brain Pathol* 2000 Jul; 10(3):462-72.

LaManca, JJ., Sisto, SA., DeLuca., Johnson, SK., Lange, G., Pareja, J., Cook, S and Natelson, BH. Influence of exhaustive treadmill exercise on cognitive functioning in chronic fatigue syndrome. *American Journal of Medicine*, 1998, 105, 3A, 59s-65s

Paul, L., Wood, L., Behan, WMH and Maclaren, WM. Demonstration of delayed recovery from fatiguing exercise in chronic fatigue syndrome. *European Journal of Neurology*, 1999, 6, 63-69.

