Input to the CFSAC Meeting October 29-30, 2009

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The Chronic Fatigue Syndrome Advisory Committee (CFSAC) of the Office of the Secretary of the Department of Health and Human Services of the Federal Government of the United States will hold a public meeting October 29-30, 2009, in Washington, DC. The public is invited to participate and/or submit printed material for the meeting. Here is the material that I want to submit to the CFSAC meeting.

What happens in the United States of America is important to the world because it is a leading nation in medical research. I live in Sweden, and what happens in your nation also influences my country. Myalgic Encephalomyelitis (ME) has been in the WHO list of diseases (ICD) for 40 years now, and research has been neglected in this field during all this time. People live their lives with the severe invalidity of ME, but nobody seems to be willing to be their guardian angel and assure that high quality biomedical research is performed. Who is going to change this or shall ME be continued to be discriminated in research? The Fukuda research definition for CFS has been used as a substitute for ME, but it is more of an imaginary condition, "created" by a group of people on a meeting, rather than based upon clinical observations. Many interesting research findings have been made with the Fukuda definition, but it has also been possible to produce conflicting results due to the fact that the Fukuda definition is diluted, vague and unspecific. People with ME are tired of not being listened to. People with ME are tired of scientists that are "creating" imaginary diseases on their office. Please, go out into the reality and learn what ME really is. We are humans too, and we are missing our lives a lot. Please, take part of literature and seminars of medical physicians that have experience in ME. Please, divert the funding for CFS research directed by CDC to biomedical research institutes for ME. It seems unlikely that funding to the CDC CFS program will result in large results for the money. Instead send the money to the already underfunded scientists and research institutes around the USA that have a serious interest in understanding ME and that perform high quality biomedical research.

Return of investment immense 6000:1

The United States together with Europe and Japan are the most important countries for ME research. ME strikes 0,4% of the population and the cost for the society is large. If ME could be understood, and a cure is found, then society can save a lot of money, as well as the devastation of lives.

ME cost society 30 billions of USD in the United states, given 1 million of ME sufferers and an annual cost of 30.000 USD per person due to loss in productivity.

The annual cost of 100 researchers full time is around 20 millions USD/year.

Let us assume that a cure is found by these researchers in 5 years. This would cost 100 millions of USD in salary for the researchers, but on the other hand this will mean that society gains 30 billions of USD every year on increased production, because of added productivity by the people not being disabled by ME. After e.g. 20 years 600 billions of USD have been gained. The invested 100 millions of USD becomes 600 billions. That gives a return on investment that is immense 6000/1! For each dollar originally invested, there is a return of 6000 dollars for each 20 year period!

Another important aspect is that a new field in medicine is opening now as tools have emerged (from for example the genome project) that allows us to analyse what is going on inside the cells on

a molecular basis. Diseases earlier not possible to understand due to limited technology and knowledge are now possible to understand. A new field has opened, and it is important for the United States to be a leader in this field. The medication industry depend upon a strong scientific basis in applied molecular cell biology, genomics or proteomics, in order to maintain a leading position on the world market.

CDC empiric CFS definition 2005 - Flaws in scientific approach

I have thought about how I would like to describe the flaws of the Reeves' methodology, with statistics, math and reasoning, but I do not have the energy, but I will make a short summary below.

I would have thought that the scientific way to go, would be to create distributions in a multidimensional space of persons with CFS in one set, of healthy people in one set, and sets of people with diseases that are differential diagnosis to CFS. Then I would have tried to create the largest distance between the points of the people with CFS to the points in the other sets, in order to try to separate the sets by a multidimensional plane. The location of the plane should be adjusted for the highest sensitivity and specificity.

I would have included physiological parameters and biomedical markers in a large amount in the multidimensional analysis, because CFS is a physiological disease. I would also have tried to include more signs and biomarkers instead of only having symptoms.

Although, I am not sure I would ever have used the multidimensional approach for defining CFS. Finally, it is what we put in the set of CFS patients (for the multidimensional study) that defines the disease. Therefore, one can simply use the original definition for CFS to define what is CFS. Why go cross the river to get water?

I would have required post-exertional malaise to be present in a definition of CFS. Post-exertional malaise should be present as a symptom, but also measured by objective test. The research is more and more showing a clear picture that post-exertional malaise lasting for 1-3 days, or more, is measurable by brain scans of blood flow, blood parameters (oxidative stress, ion channels, adrenergic receptors and immune molecules), and oxygen uptake for repeated exercise test. I think that a patient without post-exertional malaise, has a different pathophysiology and should be excluded from the CFS set. I also think that mental fog, that usually increases with upright posture, is a hallmark symptom.

What Reeves has done is to summarize a multidimensional space into ONE variable. This one-dimensional space is in simplified terms the sum of psychological and subjective symptoms. This means that an indefinite number of combinations of symptoms may score enough to be positive for CFS-Reeves-2005 (more appropriately labelled as "Reeves' Illness Melange"), so one can expect that a multitude of symptom clusters exist in the mix of CFS-Reeves-2005 [7]. No clear picture of symptoms can be distinguished. It is such a big insult to scientific and logical thinking, that I can not believe that one of the worlds largest and most important agency, CDC, can be the part of it.

If a change of the CFS definition is made, it shall never be made over one night. One should use the new criteria in parallel with the old criteria for several years in order to keep comparability with research made with the old definition, and in order to validate the new definition.

The general reader of scientific articles will never understand that different definitions have been used unless it is clearly stated, and they will assume that all articles with "chronic fatigue syndrome" studies the same kind of patients, and this can make huge harm to the progress in scientific research into CFS. If CFS-Reeves is used, I think it should be referred to for example "Reeves' Illness Melange (RIM)" in the scientific articles in order to avoid misunderstandings and to separate it from CFS-Fukuda [6].

The Fukuda definition of CFS

Because of the hijacking of the term CFS by Reeves and CDC, by replacing the Fukuda definition of CFS [6] with the mishmash of CFS-Reeves [7], I think it is important for the scientists that use CFS-Fukuda to describe what kind of definition that has been used in the title of the scientific articles, otherwise things will start to be mixed up. I have no really good suggestion in how to do that.

Maybe by referring to "CFS - Fukuda definition" in the title, while "chronic fatigue syndrome according to the Fukuda definition" will very long.

Add ME [1,2,3] as exclusionary condition in the CFS-Fukuda-1994 [6] definition in order to make cohorts/sets mutually exclusive (disjoint), e.g. a person diagnosed with ME should not have a CFS-Fukuda diagnosis as well. CDC states that ME is different from CFS [8], therefore it should not be included in the set of CFS. See references [10,11,12].

CFS-Fukuda [6] is regarded as very diluted, vague and unspecific by the patients with ME. While the description of Ramsay [1] is excellent. I think one has to have Ramsay's clinical description in the back of ones head when dealing with ME. It is very insightful and contains many important features that one should not forget about. Patients with ME feel that CFS-Fukuda could be everything or nothing at the same time, and it is of no wonder that physicians do not take it seriously, as even the patients do not understand it.

I think the Holmes [5] definition is the most interesting of the CFS definitions, but it lacks post-exertional malaise and mental fog as mandatory symptoms in order to be a candidate for a definition for ME. Also, it has mild fever as a symptom, but in fact almost everybody with established ME note that their temperature is subnormal (typically 36,5° C). CFS-Holmes had a more complete list of exclusionary diagnosis and obligatory laboratory tests than CFS-Fukuda, making it more strict. It is stated that it is a definition for research. I can not see the reason for diluting the Holmes definition with the Fukuda definition. If they had stuck to the Holmes definition, I think research had been more fruitful.

I want to stress that it is important to stick to the original descriptions and not to change the meaning of an established condition, as has happened with CFS over the years. The 1988 Holmes CFS definition was more specific and it was a construct on the hypothesis that it was a physical disease, but later definitions (Fukuda and Reeves) have stepwise gone into the direction of the hypothesis a psychiatric disease. One shall always look back on the original descriptions from time to time in order too see if one is on the same track or has deviated from its course, otherwise one loses comparability between research articles and results, and that is really not a very intelligent way to make science.

Set up an ME advisory committee and funding of biomedical research of ME

ME has been totally neglected in research for over 50 years, and its time to be taken up on the agenda. There is as far as I know no funding from CDC for studies of ME, which is different from CFS according to CDC [8]. Citation from CDC: *"ME is accompanied by neurologic and muscular signs and has a case definition distinct from that of CFS*" [8]. See references [9,10,11,12].

Move economic resources from the CFS program into a program of high quality biomedical research into ME, with Ramsay [1], Wallis [2], and Acheson [3] as the clinical *descriptions*, and ME/CFS-Canada [4] as one interim research and clinical *definition*.

At this time the Canada definition for ME/CFS [1] is the most interesting candidate for use in ME research. CFS-Fukuda or CFS-Holmes do not require mandatory ME symptoms as for example post-exertional malaise lasting 1-3 days or more. They do not require mental fog or problem with information processing. Neither temperature dysregulation. Intolerances to medications and alcohol, problem with hyperacusis and sensory overload is quite common and should at least be non-mandatory criteria for ME. CFS-Fukuda is perceived as very vague and diluted by ME patients, while CFS-Canada-2003, is perceived as a very good description of their condition and something they can relate to. Do not deviate over time from the original clinical descriptions of ME [1,2,3] into something different, because it hijacks the name of an established condition, and comparability between scientific articles is lost. Comparability is a fundamental concept in science. Keep on studying ME until the puzzle of pathogenesis and aetiology is completed. As ME is more specific than CFS, research is likely to give more value for the money, because it will yield more consistent and significant abnormalities, and so research will be more productive and quicker.

I hope the scientific world will continue to study abnormalities in ME patients during post-exertional malaise. Many tests have been in the normal range, when ME patients were studied in a state of rest, but when one studies what happens after exertion one really begins to discover that there are indeed abnormalities. The abnormalities are discovered in the dynamic response to exertion. I think this is the way to go. Scientists are discovering things, now when they start to test things that never crossed their minds to test for several years. Biomedical and physiological findings are consistent

with the patients reports of feeling awful after exertion. This direction of research should be continued and be extended into new areas of physiological and biomedical tests.

I think it is important to use well defined patients in scientific studies in order to be able to stratify and find relationships. Scientific research centres for ME are encouraged to use a research database for their patients where all the results of laboratory tests and clinical evaluations are stored. Also, a tissue bank (tissues collected post mortem and in vivo) can be connected to the research database. A multidimensional approach is suggested to be used in order to find biomarkers, to make advances in the knowledge of pathophysiology, to identify possible sub-groups, and to separate ME patients from patients with conditions that are differential diagnoses to ME in a clinical setting. Use level of disability as variable in analysis. A database also allows studies to be longitudinal, and is also important for properly describe the patients for post mortem samples.

Every scientific study should include a proportion of severely affected patients, i.e. those that are completely bedridden. Those patients shall not be forgotten about in research, because they are likely to have the most significant abnormalities, but also because they are the ones that suffer the most.

Do not a priori assume that the ME cohort/set is homogeneous. Instead, assume heterogeneity. Put special efforts in order to find objective tests for ME and its possible sub groups. Focus biomedical research on the abnormalities of the dynamics of post-exertional malaise, and on finding out more about the pathophysiology, with the aim to understand the pathogenesis, and finding a cure. See references [10,11,12].

Major Suggestions

1. Stop using the CFS-Reeves-2005 definition [7] or at least prohibit it to be labelled as Chronic Fatigue Syndrome (CFS). Call it for example "Reeves' Illness Melange (RIM)". See references [11,12] for background information and motivation.

2. CDC states that ME is different from CFS [8], therefore it should not be included in the set of CFS. Add ME [1,2,3] to the list of exclusionary conditions in the CFS-Fukuda-1994 definition [6] in order to make things coherent. See references [10,11,12].

3. Move economic resources from the CFS program into a program of high quality biomedical research into ME, with Ramsay [1], Wallis [2], and Acheson [3] as the clinical *descriptions*, and ME/CFS-Canada [4] as one interim research and clinical *definition*, until the pathogenesis is understood.

4. Remove CFS-Reeves and CFS-Fukuda from WHO ICD-10 code G93.3, and have Ramsay [1], Wallis [2], and Acheson [3] as the disease *descriptions* and ME/CFS-Canada [4] as one interim disease *definition* for this code. See reference [11].

Abbreviations

CDC	Centers for Disease Control and Prevention (USA)
CFS	Chronic Fatigue Syndrome
CFSAC	Chronic Fatigue Syndrome Advisory Committee (U.S. Department of Health and Human Services)
ICD	International Statistical Classification of Diseases and Related Health Problems (WHO)
ME	Myalgic Encephalomyelitis
WHO	World Health Organization (United Nations)

References

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8 **CDC citation:** *"The name myalgic encephalomyelitis (ME) was coined in the 1950s to clarify well-documented outbreaks of disease; however, ME is accompanied by neurologic and muscular signs and has a case definition distinct from that of CFS."*
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9 Kasper Ezelius. **Use the Canadian criteria 2003 for CFS in the USA.** June 22, 2008.
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Letter to the President and Congress of the United States of America, U.S. Department of Health and Human Services, U.S. National Institutes of Health, and U.S. Centers for Disease Control.

10 Kasper Ezelius. **Resolution in order to make cohorts less heterogeneous.** September 1, 2008.
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Research into CFS (Chronic Fatigue Syndrome) and ME (Myalgic Encephalomyelitis) has been blurred through many decades due to heterogeneous patient populations (cohorts). One problem is that researchers, as well as clinicians, have different interpretations of what is CFS. Some researchers/clinicians would (incorrectly) not set a CDC CFS diagnosis if post-exertional malaise is not present, although the CDC CFS definition does not require post-exertional malaise.

11 Kasper Ezelius. **How to categorize ME and CFS.** October 23, 2008.
http://me-cfs.se/dok/081023-categorize.pdf
This document is a brief sketch for further discussion on how to proceed with taxonomy in research related to Myalgic Encephalomyelitis (ME) and Chronic Fatigue Syndrome (CFS).

12 Kasper Ezelius. **CFS is no longer CFS, and it was never ME.** December 5, 2008.
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The Centres for Disease Control and Prevention in the USA has adopted a more including criterion for chronic fatigue syndrome which is important to be aware of when reading scientific papers. It is important to know that the new criteria is so much "loosened up" that it encompasses 2,5% of the general population instead of around 0,4% as with the earlier criteria. How to stratify and group patients in future research is proposed. The use of disjoint sets of patients is encouraged.