

Eleanor Stein MD FRCP(C)
Psychiatry and Psychotherapy

**Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome,
Fibromyalgia, Multiple Chemical Sensitivity & Related Disorders**

**4523 – 16 A Street SW
Calgary, Alberta T2T 4L8
Phone: 403 287-9941 Fax: 403 287-9958
e-mail: espc@eleanorsteinmd.ca
web: www.eleanorsteinmd.ca**

March 2015 Newsletter

Sea Change for ME/CFS?

In the past few months three important reports have been published that will impact the future (and possible even the name) of ME/CFS.

This newsletter provides a brief summary of each reports and the links for those who want to read more. All three reports were sponsored by US Federal Agencies and they represent a success for the patient advocates who have been working tirelessly for the past 25 years to get more recognition and validation for ME/CFS. I summarize each report below with my editorial comments in brackets.

*****Save Tuesday evening May 19th on your schedules for the 2015 International Awareness Day Webcast event***** The keynote speaker will be Dr. Lucinda Bateman who will talk about her participation in the IOM committee and the Columbia led research study, both summarized below.

**AND LATE BREAKING NEWS
IMPORTANT FINDINGS FROM THE COLUMBIA STUDY
... see more at end of this newsletter**

NATIONAL INSTITUTES OF HEALTH
**Pathways to Prevention Workshop: Advancing the Research on
Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome**

DRAFT EXECUTIVE SUMMARY
December 9–10, 2014

<https://prevention.nih.gov/programs-events/pathways-to-prevention/workshops/me-cfs/workshop-resources>

This report task was to identify **research gaps and future research priorities**.

The National Institutes of Health is the federal US agency which provides funding and guidance for medical research. Researchers from around the world are successful in obtaining NIH funding including Canadians. This is fortunate because Canadian funding for ME/CFS researchers is virtually non-existent.

The NIH workshop was co-sponsored by the NIH Office of Disease Prevention (ODP) and the Trans-NIH Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) Research Working Group. During the 1½-day workshop, invited experts discussed the body of evidence, and attendees including many patient advocates had opportunities to provide comments during open discussion periods.

The P2P report is validating of the existence of ME/CFS, the challenges faced by patients and the need for better research and clinical care. They make many excellent recommendations and we hope that the NIH will follow through and remedy the needs identified. (My editorial comments are in round brackets).

Report Highlights

- ME/CFS exists and is not a psychological entity. (Great start!)
- We need a definition we can all agree on.
- Studying fatigue alone fails to capture the complexity of the condition.
- Research needs to include diverse patient groups including the severely ill.
- Existing treatment studies (cognitive behavioral therapy (CBT) and graded exercise therapy (GET) demonstrate measurable improvement, but this has not translated to improvements in quality of life (QOL). Thus, they are not a primary treatment strategy and should be used as a component of multimodal therapy. (Great to get validation about this from the NIH).
- There is not enough study about self-management and providers are not trained to guide patients with self-management. (music to my ears since to date self-management as outlined in my manual and Psychoeducational Group is a cornerstone of management).

- There is a failure to implement what we already know and patients are suffering. Lessons can be learned from palliative care, such as compassion, communication, and symptom management to improve the quality of care. (Excellent idea).
- A bank for de-identified data and samples needs to be created to facilitate research (They don't mention that Solve ME/CFS has already developed a working biobank).
- Primary care physicians are critical in care and need to be educated. (I couldn't agree more)
- Health professional licensing and accreditation agencies and professional societies should be enlisted to ensure that new trainees learn about ME/CFS. (Absolutely, if we don't train health care professionals to identify and treat ME/CFS, they can hardly be blamed for doing a bad job).

Agency for Healthcare Research and Quality (AHRQ)
Evidence Report/Technology Assessment Number 219

Diagnosis and Treatment of Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome

Executive Summary
December 11, 2014

<http://www.effectivehealthcare.ahrq.gov/ehc/products/586/2004/chronic-fatigue-report-141209.pdf>

This systematic literature review was commissioned by the Office of Disease Prevention at the National Institutes of Health (NIH), sponsored by the NIH Office of Research on Women's Health, and cosponsored by the Trans-NIH Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) Research Working Group to inform the NIH 2014 Pathways to Prevention Workshop. Articles between 1988 and September 2014 were considered.

The take home message from this report is that the quality of existing research on ME/CFS is poor. Most of the over 6000 published, peer reviewed research studies did not meet the quality criteria to be included in the analysis. This certainly supports the need for more research funding so that better quality studies can be done.

1. There is no accurate and reliable method for identifying patients or subgroups of patients with ME/ CFS in comparison with patients who may have conditions in which fatigue is a prominent symptom. (This is a big problem, possibly overstated since most of the literature was excluded from the review).

2. Overall, studies of counseling (mostly Cognitive Behavior Therapy) showed improved fatigue (7 of 11 trials showed a positive effect), measures of functioning, quality of life, and global improvement. **BUT** treatment effectiveness may not be generalizable to all patients because no study used a case definition that selected for more disabled patients.

Similarly Graded Exercise Therapy (GET) shows improved measures of fatigue, function, and clinical global impression of change compared with controls but again results cannot be generalized to the severely ill. As well there was a tendency for patients receiving GET to report more adverse events, to have more withdrawals from the study or refuse repeat exercise testing. This suggests the therapy may have adverse effects.

The AQHC report concludes that:

1. We need a gold standard case definition
2. Treatment trials should refrain from using the Oxford definition (Sharpe, 1991) (hopefully this is a final nail in the coffin of this very inadequate definition).
3. Trials need to be better designed, have more people in them and recruit more men, minorities and severely ill individuals.
4. Studies need to report harms.
5. Given the devastating impact that this condition has had on patients and families, researchers planning and developing trials should consider involving the patient and/or advocate voice so that future research is relevant and meaningful to those affected by ME/CFS.

**Institute of Medicine of the National Academies
Committee on Diagnostic Criteria for ME/CFS**

**Beyond Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome:
Redefining an Illness**

February 10th, 2015

<http://iom.edu/Reports/2015/ME-CFS.aspx>

This report was sponsored by the Office on Women's Health within the Department of Health and Human Services (HHS), the National Institutes of Health (NIH), the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration, the Agency for Healthcare Research and Quality, and the Social Security Administration.

This report by the IOM is one of the most thorough and balanced that I have read. I am aware that some people are criticizing the report. I disagree and feel it is a useful addition to our knowledge base.

This review is divided into three sections: 1. commentary on the report itself, 2. commentary on the 4 recommendations made in the report and 3. commentary on the proposal to change the name and diagnostic criteria for ME/CFS.

1. Commentary on the IOM report:

- The full report (over 300 pages long) is very thorough and accurate. The language strongly validates the patient experience. Its presence will be a huge help to me in trying to explain the condition to others including in legal and disability cases.
- The committee listened to and understood patient concerns. They “got it”.
- The report recommends retiring the term Chronic Fatigue Syndrome as it trivializes the patient experience. Although I agree with this it is very hard in real life to use new terminology, even ME is confusing to many people.
- It stresses that ME/CFS is about more than FATIGUE
- The report states that the amount of **funding and research is deficient** given the number of people affected and the seriousness of the condition.
- The report recognizes the severely ill and the need to include them in research.

The IOM has just published a clinician’s guide to help guide clinicians in making the diagnosis of SEID using the new criteria.

<http://www.iom.edu/~media/Files/Report%20Files/2015/MECFSE/MECFSEcliniciansguide.pdf> The section which provides guidance about what questions to ask patients to discern if they meet the criteria will be very helpful. **HOWEVER** In my opinion it is very premature to conclude that the new criteria are any more useful than the Canadian Consensus Criteria from which the SEID criteria were derived. I recommend study to ensure that the criteria will accurately diagnose those who should have the label **before promoting their use.**

2. Comments on the 4 recommendations in the IOM report

Recommendation 1

Physicians should diagnose ME/CFS if diagnostic criteria are met following an appropriate history, physical examination, and medical work-up. ME/CFS is **NOT a diagnosis of exclusion.**

- This is very important for clinicians to understand. A diagnosis of exclusion makes ME/CFS a heterogeneous garbage bag category.

Recommendation 2.

The Department of Health and Human Services should develop a toolkit. The CDC toolkit and the 2014 primer can be used as starting points.

- **I DISAGREE with this recommendation.** The new definition needs to be validated before it can be widely recommended. A toolkit is premature.

Recommendation 3

A multidisciplinary group should re-examine the diagnostic criteria set forth in this report when firm evidence supports modification to improve the identification or care of affected individuals. Such a group should consider, **in no more than 5 years**, whether modification of the criteria is necessary. Funding for this update effort should be provided by non-conflicted sources, such as the Agency for Healthcare Research and Quality, through its Evidence Based Practice Centers process, and foundations.

- In my opinion, the research should be done before the criteria are sent to all clinicians in the US. **We don't yet know if the new criteria are valid or reliable.**
- Hopefully the recommendation for funding to review the criteria will be accepted.

Recommendation 4

The committee recommends that this disorder be renamed "Systemic Exertion Intolerance Disease" (SEID). SEID should replace Myalgic Encephalomyelitis/chronic Fatigue Syndrome for patients who meet the criteria set forth in this report. *The term "chronic fatigue syndrome" can result in stigmatization and trivialization and should no longer be used as the name of this illness.*

- The new name is growing on me. It describes the primary challenge in ME/CFS that of PEM. The problem with its introduction is that name changes are confusing and it takes time for new labels to be adapted.

3. Commentary on the proposed change in diagnostic criteria:

The committee determined that the name "Chronic Fatigue Syndrome" has done a disservice to many patients and that the name "Myalgic Encephalomyelitis" does not accurately describe the major features of the disease. In their place, the committee proposes "Systemic Exertion Intolerance Disease" (SEID) as a name that more fully captures the full scope of this disorder. Here are the proposed criteria.

BOX 7-1

Proposed Diagnostic Criteria for ME/CFS

Diagnosis requires that the patient have the following three symptoms:

1. A substantial reduction or impairment in the ability to engage in pre-illness levels of occupational, educational, social, or personal activities, that persists for more than 6 months and is accompanied by fatigue, which is often profound, is of new or definite onset (not lifelong), is not the result of ongoing excessive exertion, and is not substantially alleviated by rest, and
2. Post-exertional malaise,* and
3. Unrefreshing sleep*

At least one of the two following manifestations is also required:

1. Cognitive impairment* or
2. Orthostatic intolerance

* Frequency and severity of symptoms should be assessed. The diagnosis of ME/CFS should be questioned if patients do not have these symptoms at least half of the time with moderate, substantial, or severe intensity.

The positives:

- ✓ The rationales for the proposed changes are to make it easier for physicians to diagnose and to include only symptoms for which there are objective tests. (This is a valid concern because many clinicians find the Canadian Criteria confusing and don't use the checklist.)
- ✓ The new definition requires the presence of Post Exertional Malaise after physical, cognitive or emotional stressors. (This is a big improvement from the Fukuda criteria which does not require PEM.)
- ✓ The definition requires moderate to severe symptoms be present more than 50% of the time. Good idea but I would choose 80 – 100% of the time. I don't see any patients who are 100% well even 1% of the time.)

The negatives:

- ✗ The sleep criteria exclude the very large group of patients who are unable even with medication to get "several hours" of sleep.
- ✗ Choosing orthostatic intolerance as the only marker of autonomic dysfunction leaves out all the people with irritable bowel syndrome and other autonomic symptoms (if indeed IBS is autonomic).
- ✗ **Cognitive symptoms are measurable and universal and should not be an optional criterion.**

- ✘ Immune symptoms are prominent in about 50% of patients with ME/CFS (SEID). When they occur they validate that the condition in question is ME/CFS and not some other condition. **Leaving immune symptoms entirely out of the definition will increase the chances of false positive diagnoses** and is an error (especially in light of the Lipkin paper just released of which a summary follows).
- ✘ Making the criteria simpler in the way proposed increases the probability of false positives. The proposed definition should NOT be used for research until it is validated.

AND LATE BREAKING NEWS IMPORTANT FINDINGS FROM THE COLUMBIA STUDY of ME/CFS

“Distinct plasma immune signatures in ME/FS are present early in the course of illness.”

Hornig et al Sci. Adv. 2015;1:e1400121 Feb 27, 2015

<http://advances.sciencemag.org/content/1/1/e1400121>

This study led by Drs. Mady Hornig and Ian Lipkin at Columbia University included carefully screened patients from the practices of Drs. Jose Montoya, Nancy Klimas, Susan Levine, Lucinda Bateman and Dan Peterson. The study combined cases from two research samples: one referred to as the NIH study group and another from the Chronic Fatigue Initiative group (privately funded).

Blood samples were drawn between 10 am and 2 pm. All the participants met BOTH the Fukuda and Canadian criteria. In addition, all had viral infection like symptoms prior to the onset of their illness. Each participant gave a blood sample after filling out the study questionnaires (to serve as a mild stressor). Three groups were included: “short duration illness (52 subjects ill for less than 3 years), long duration illness (246 subjects ill longer than 3 years) and healthy controls (348 subjects). In total, this is the largest sample tested to date.

Analyses were done for a large number of cytokines – the chemicals produced by immune cells to communicate with each other and with the rest of the body. The group used very fancy statistics to compare the short duration vs long duration vs controls for each cytokine and to study the relationships between the cytokines ie. which influence the others and in which direction.

The important finding from this study is that significant differences were found between the short and long duration subjects and between each of these groups and the healthy controls.

- Those with short duration illness had a general upregulation (increase) in most of the cytokine levels compared with healthy controls.

- Those with longer duration illness had a general decrease in cytokine levels. The authors hypothesize that there may be an immune burnout after 3 years of having ME/CFS.
- HOWEVER when short and long duration groups were taken together the combined group didn't differ from the healthy controls. **This is an important finding as it may explain why previous smaller studies have failed to demonstrate consistent findings.** ME/CFS (SEID) changes over time and most studies lump everyone together cancelling out differences.
- A major finding in the short duration cases was an elevation of interferon gamma. This has been reported repeatedly by Dr. Kenny De Meirleir and others over the years. This cytokine is activated by viral infection suggesting a viral connection.
- The Columbia group has reported previously that they can't find evidence of active viral infection in this sample. Therefore ME/CFS (SEID) may be a case of "hit and run". A virus triggers illness and causes long lasting immune changes even after the virus itself is gone from the body.
- Interferon gamma accelerates the breakdown of tryptophan and melatonin, maybe explaining in part the energy, mood and sleep problems experience by people with ME/CFS (SEID).
- They found an increase in leptin in the long duration illness group, similar to the findings of Dr. Jared Younger in patients with Fibromyalgia. Leptin is involved with metabolism, hunger and satiety.
- Another finding is a deficiency of CD40L. In other research low levels of this cytokine are associated with chronic sinus and lung infections and a pattern of encephalitis unrelated to any known pathogen... very interesting.
- Many other findings ...

This newsletter is pretty heavy going with lots of important information for those who have or are supporting people with ME/CFS (SEID). These reports give hope that we are moving ahead.

Ellie Stein