[…]
[…]
Subject: RFI ME/CFS

Research

- HHV-6 associated mononucleosis preceding onset of ME/CFS

- Pathogen-induced VDR dysfunction

- Gut Enterovirus infection

- Prevalence of SIBO in ME/CFS patients; Does treatment of SIBO improve symptoms of CFS in a subset of patients?

- Define Subsets of patients

- Sore throat causes in ME/CFS patients; Is it found only in a certain subset?

- Nutraceuticals trial

Education

- Include ME/CFS in Medical School Curriculum

[…]
[…]
Subject: CFS

I have had CFS for over 49 years and have consistently searched for a cause and a cure. Last year I was diagnosed with intestinal colonization of staph aureus and epidermis. I had no idea that it was possible to have an internal staph infection such as this. I am convinced that this is the initial cause of CFS. The colonization of staph produces biofilms and toxins which the immune system attempts to clear and cannot. Since 85 % of the immune system is in the intestines the immune system spirals down and the many viruses and bacteria , such as HHV 6, CMV , and EBV then can become active causing more severe health issues. Once health deteriorates to a certain level , whatever illnesses you may disposed to could take over. Internal staph infections are contagious and easily passed from person to person and can also be sexually transmitted.

I am suggesting to look at this first and determine if this could be correct. Dr. Davis is looking at the end result of CFS and the mitochondrial issues that are created. I think this happens later in the cycle. When I first became ill I knew almost immediately that something was wrong with my immune system. Any cut or scratch took much longer to heal but never healed completely. If I was around any person that had a cold or flu I would get it immediately.

I could write a book or two about my experiences, discoveries, what has helped, what I think will provide a cure going forward. However I wanted to keep this short. I hope there is interest in moving this forward to determine if I am correct. I think it is a good place to start.

[…]
[…]
Subject: ME/CFS

I am a patient that has had CFS for twenty years. I was unable to adequately care for my children who are now 21 for the majority of their childhood.(triplets) I was not as sick as my daughter. My daughter developed CFS with my identical symptoms two and half years ago. She was bedridden for most of this time. She lost twenty pounds, could not stand, could not eat, was short of breathe, slept 20 out of 24 hours , had horrific migraines, wore an eye mask due to light sensitivity, lost most of her hair, and after 9 months we thought she would die. No one would help us, no one understood what was happening to our goal oriented, highly productive child. We have been helped my Dr. Jose Montoya at Stanford University. The therapies that proved to have the most promise and improvement for me and my daughter have been antivirals, specifically, VALCYTE. My daughter improved on COLCHICINE due to its anti inflammatory properties as well as VALCYTE. My daughter had to leave her university and stay home where we can care for her. She was president of her high school student body and graduated with a 4.2 GPA. She was premed in college and wanted to travel to underdeveloped countries to aid in global healthcare. She will not realize her dream of becoming a physician. She hopes to someday in the future to finish college. She was strong, determined and had a plan for her future. All that has changed with her diagnosis of CFS. My husband is a very well trained physician having attended Dartmouth Medical School but do to his lack of training and education in this devastating disease he is completely helpless and ill equipped to treat out daughter. We went to no less that 25 physicians to receive a diagnosis,that stress alone greatly exacerbated our condition. Although I improved greatly from the Valcyte my daughter has had many relapses and her quality of life is poor. My daughter makes bracelets and donates the money to CFS research through Dr Montoya because she knows our government has not provided the research funds needed to help her fight her illness. There are no approved treatments and no bio markers to diagnosis our disease. I know so many children and adults wasting away in wheelchairs and in bed with no hope. We need to educate doctors to be able detect this illness and we need research funds to help find diagnostic markers and eventually treatments that will help. The fear and hopelessness I, a registered nurse and my husband, a physician feel as we care for our daughter at home without any guidance or or help from the healthcare community is paralyzing. We beg and implore the CDC and the NIH to make sure physicians are educated, research funds are equitably allocated, and to pursue a cause and a cure for this illness that effects more than 2.5 million Americans and people globally. We should not be alone in this battle to regain our health.

[…]
[…]
Subject: ME/CFS research

Anonymous submission

[…]

Emerging needs and opportunities:

Need to explore potential of immunomodulatory pharmacological treatments extensively.

Opportunity to consider both pharmacological and non-pharmacological treatments that reboot immune system e.g. bone marrow transplant.

Opportunities to collaborate with those researching both pathophysiology and treatments in other fatiguing illnesses e.g. MS, primary biliary cirrhosis, RA etc.

Opportunity to add an ME/CFS group to studies investigating treatments in other fatiguing diseases – this could be a cost-effective way of finding out which treatments might be worth pursuing in larger-scale studies in ME/CFS. As a patient it is frustrating to know that drugs and treatments known to reduce fatigue in other diseases have simply not been trialled in ME/CFS, e.g. Plaquenil in Sjogren's, various immunomodulators.

Again, opportunity to investigate possible common pathophysiology between cognitive fatigue/sensory overload across conditions e.g. ME/CFS, stroke, traumatic brain injury – very striking similarities based on my clinical and personal experience.

Challenges or barriers to progress:

Gross underestimation of the profoundly disabling nature of ME/CFS throughout medical field – resulting in reluctance to fund/do studies on "strong" drugs or non-pharmacological approaches that could actually help.

Lack of objective outcome measures has led to ineffective therapies being recommended. Very easy in modern world to quantify people's activity levels pre- and post-treatment.

Potential harm to patients involved in research given negative consequences of cognitive and physical exertion. I think doctors often assume post-exertional malaise is temporary and reversible, and that patients do not deteriorate over time, but these are not safe assumptions. Extremely careful monitoring and reporting of harms should be part of all research. People with ME/CFS care about relapses/exacerbations/deteriorating over time, not just hospitalisations and death – researchers should too.

Some in medical field have strong beliefs in deconditioning and/or somatisation as cause of ME/CFS. This has stifled research, led to at best ineffective and at worst harmful therapies being widely recommended for people with ME/CFS, and shattered patients' trust in doctors. Patients' trust will be rebuilt only by a consistent commitment to research that is based in careful science, not beliefs.

Gaps and opportunities across the research continuum from basic through clinical studies

Long-term and retrospective studies detailing natural progression of disease to inform

- accurate prognosis
- pathophysiology

- accurate advice to prevent relapse and maximise chances of improvement/recovery.

As a patient interacting with other patients I see a number of potential patterns that are not mentioned anywhere in the literature – e.g. initial improvement followed by relapse(s) and subsequent ongoing deterioration, significant drop in functioning at approx. 3 years post-onset.

Opportunity for researchers to tap into resource of millions of patients worldwide with access to internet. Potential for extremely useful data to be collected.

I trust that ME/CFS researchers with a lot more energy than me will share valuable insights.

Looking forward to seeing the fruits of NIH-back research into ME/CFS.

[...]
Subject: ME/CFS: response to request for information. Notice Number: NOT-NS-16-024

Challenges or barriers to progress in research on ME/CFS.

The central blockage to ME/CFS research is the combined problem of a dearth of researchers in the field and the (widely reported) difficulty that existing ME/CFS researchers experience with respect to obtaining funding. The two issues together create a viscous cycle whereby new researchers refuse to enter the field because of a lack of funding, and the lack of new researchers means fewer researchers are applying for funds and researching ME/CFS. It is frequently reported that young researchers view a career in ME/CFS as career suicide because of the lack of career and funding opportunities, which in turn leads to a long-term shortage of new researchers in the field.

Many existing CFS researchers report that they experience disproportional difficulty in obtaining funding compared to other diseases. High profile scientists such as Prof Ian Lipkin and Prof Ron Davis, but also many others, have to resort to crowd funding in order to scrape together resources to enable then to carry out any research. Some of the more successful ME/CFS researchers manage to carry out research only by adding ME/CFS cohorts onto funded studies that primarily investigate other illnesses, such as gulf war illness, because the other illnesses are so much easier to attract funding.

Existing ME/CFS researchers have said that the reasons given by reviewers for the refusal of grant applications (for ME/CFS research) can be spurious. For example, a reviewer may make unfounded assumptions about the nature of ME/CFS, and declare that the research would be a waste of time based on ignorant and outdated prejudiced presumptions. Other reviewers may give other prejudiced and uninformed reasons (e.g. that ME/CFS isn't a serious illness so it doesn't warrant investigation of drugs with potentially serious side effects).

The NIH claims that a fair and rigorous funding mechanism is always adhered to, and that all researchers have a level playing field when applying for funding, however, ME/CFS researchers have repeatedly and

historically repeated the same claims about the disproportionate difficulties of attracting funding for biomedical investigations into ME/CFS. Perhaps this raises the question of whether there is an unidentified and unintentional institutional bias at the NIH, and other funding bodies, that may arise from factors such as: individual reviewer bias and ignorance about the illness; a lack of procedural oversight to ensure a fair playing field in funding opportunities for little-understood and low-profile or controversial illnesses; budget constraints that may result in an informal targeting of misunderstood, unrecognised or non-prioritised diseases.

The NIH must take responsibility for this historic problem and reverse the institutional issues that have historically caused funding problems. If it is widely known that research funds are available then the researchers will flock to the field. The Solve ME/CFS Initiative has has great success over the past few years in attracting new researchers to the field, who are currently experts in other firms, by making seed funding available and by providing access to a patient registry and biobank. However, the Solve ME/CFS Initiative is only able to provide small amounts of seed funding.

The funding issue is the most pressing issue within the field and must be transformed so that researchers can be confident that long-term investment in the field is guaranteed and that a move into ME/CFS research is a huge and exciting career opportunity and accelerators rather than a career end.

Gaps and opportunities across the research continuum from basic through clinical studies.

Recommendations for action:

1. Massively increased biomedical research funding, proportionate to funding for other diseases, such as cancer, MS, and Parkinson's.

2. Immediately fund (i.e. fast-track) research grant applications from existing experts who have had research applications declined, such as Prof Ron Davis, Prof Ian Lipkin, Dr Nancy Klimas, etc.

3. Promote, enable and instigate a massive and comprehensive hunt for biomarkers and pharmaceutical treatments.

4. Promote, enable and instigate a massive and comprehensive biomedical research program including (but not restricted to) research in the following areas:

i. The immune system and immune cell abnormalities/dysfunction;

ii. Cellular abnormalities/dysfunction (e.g. via metabolomics & proteomics etc);

iii. Cellular function e.g. genomics and epigenetics and miRNA;

iv. Endogenous retroviruses;

v. The potential role of common pathogens;

vi. The vagus nerve infection hypothesis.

vii. Clinical trials of rituximab and other promising pharmaceuticals, and interventions with potential to treat the illness, such as immune modulators and cytokine inhibitors. A very large repurposing study of immune related drugs would have enormous potential and could be run in coordination with pharmaceutical industry.

viii. A thorough investigation of a possible autoimmune connection. i.e. a comprehensive search for autoantibodies and auto-immune-type disease processes. Carry out a thorough full scale investigation of autoimmune possibilities or autoimmune-like activity (that isn't necessarily caused by autoantibodies, but could be caused by e.g. cell receptors that are abnormal by frequency, function, type or structure).

5. Determine subgroups for whom experimental treatments (e.g. Rituximab, Ampligen and anti-virals are effective).

6. Investigate and quantify the biological post-exertional effects in ME/CFS. The specific post-exertional effects seen in ME/CFS are a unique biological feature of the illness, and may be a prime place to start to observe the biomedical mechanisms of the illness. For example, the following studies (please see below) carried out certain biomedical tests before and after exercise, and demonstrated clear and intriguing cytokine and epigenetic abnormalities after exertion compared to controls. This research objectively demonstrates post-exertional abnormalities (the central feature of ME/CFS) and needs to be replicated on a large scale in order to better understand the disease mechanism. This type of research demonstrates the disease process in action and it is vital to gaining insights into the biomedical mechanisms of the illness.

Studies:

White AT, Light AR, Hughen RW, Bateman L, Martins TB, Hill HR, Light KC. (2010) Severity of symptom flare after moderate exercise is linked to cytokine activity in chronic fatigue syndrome. Psychophysiology. 47:615-24. http://onlinelibrary.wiley.com/doi/10.1111/j.1469-8986.2010.00978.x/abstract

Light AR, Bateman L, Jo D, Hughen RW, Vanhaitsma TA, White AT, Light KC. (2012) Gene expression alterations at baseline and following moderate exercise in patients with Chronic Fatigue Syndrome and Fibromyalgia Syndrome. J Intern Med. 271:64-81. http://www.ncbi.nlm.nih.gov/pubmed/21615807

Other unmet needs.

Set up a network of in-patient clinical centres to care for severely ill patients at their time of greatest need, to be run by clinical experts who understand that ME has a biomedical basis. Currently, the needs of all patients are utterly neglected, but especially severely affected patients, who have access to practically no medical care our medical input. Typically, unsupported families are left to learn about the illness and to support their lived ones living at home in darkened rooms, or severely affected patients are driven to suicide because they cannot meet their basic care needs or their symptoms are

unmanageable or too severe to cope with. This group of patients can be considered an enormous research asset, who can help to inform researchers and clinicians about the illness in its most severe and most unrecognised form. The data collection potential from these patients is enormous, and the insights gained from these patients would help to alleviate the widespread stigma associated with the illness and to reverse the universal neglect experienced by most, if not all ME/CFS patients. A series of in-patient centres of excellence would be an enormous and very welcome asset to the patient community, and would definitely save lives. I know of numerous lives that would undoubtedly have been saved if adequate and trustworthy in-patient care (i.e. on a biomedical basis) had been available to patients at their time of greatest need.

A network of clinical centres of excellence to provide services to all patients would also provide essential, currently unmet, needs of the patient population. Centres of excellence would be an enormous clinical and research asset.

[…]
[…]
Subject: Response to Notice NOT-NS-16-024; Request for Information: Soliciting Input for New Research Strategies for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)

To: The Trans-National Institutes of Health (NIH) ME/CFS Working Group

Re: Response to Notice NOT-NS-16-024; Request for Information: Soliciting Input for New Research Strategies for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)

Dear Working Group:

The following is my response to NOT-NS-16-024; Request for Information: Soliciting Input for New Research Strategies for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS).

Emerging needs and opportunities that should be considered as new ME/CFS research strategies are developed:

Analyze samples of blood and spinal fluid taken during post-exertional malaise.

Analyze samples from the severely ill and from children for possible biomarkers.

Challenges or barriers to progress in research on ME/CFS:

The lack of a consensus case definition for ME/CFS poses a major stumbling block to progress in research.
Substantially greater funding is needed to address the complex problem of ME/CFS.

Gaps and opportunities across the research continuum from basic through clinical studies:

A carefully conceived, long-term research plan is needed.

Thank you for your consideration and your service.

[...]

Subject: Potential Research Pathways for Research Into ME/CFS

1) Muscle Failure, not Fatigue.

ME is a long illness, with a long acute phase and apparently whatever the pathogen is, is stimulated by exertion of any type, but especially muscular exertion.

The IOM states that this is a disease in which exertion of any type may adversely affect many organ systems, and the deleterious effects of exertion have been reported in the large survey of patients done by the UK ME Association, and in the Invest in Me book 'Lost Voices From A Hidden Illness', an account of patients who have severe ME, many of whom were very athletically active before the illness, and who became severely ill only after following a program of exercise.

http://www.ncbi.nlm.nih.gov/books/NBK284910/. Chapter 7, Page 14

http://www.meassociation.org.uk/2010/05/managing-my-me-me-association-publish-results-of-huge-survey-report/

'Lost Voices from a Hidden Illness, by Natalie Boulton, published by Invest in ME

The reason for this seems to lie in the fact that the body's aerobic muscle metabolism does not function properly. Even minimal exertion becomes anaerobic, with the consequences one would expect for a person engaging in ongoing anaerobic exertion - a build-up of metabolites, pain, eventual muscle failure, and damage. Severe ME is characterised by ongoing severe and intractable pain, non-epileptic involuntary contractions and spasms, and intermittent paralyses.

Myalgic Encephalomyelitis and Postviral Fatigue States, A Melvin Ramsay, MA, MD, published by the ME Association

Researchers during the polio era noted that during the period after the initial viral attack, when the virus was in the process of attacking the central nervous system, physical exertion was dangerous, as exercised muscles tended to be the ones which ultimately became permanently paralysed. They regarded complete rest as an essential protective measure during this stage of the disease.

http://www.positivehealth.com/article/cfs-me/lost-in-translation-the-me-polio-connection-and-the-dangers-of-exercise

Dr. Melvin Ramsay, (see above) the infectious disease consultant who dealt with the 1955 Royal Free Hospital outbreak noted that complete rest from the inception gave the best prognosis, and the impression gained from his writings was that a proportion of patients went on to become chronically ill, but not all. This implies that many made a complete recovery, which would be considered very rare these days, when the importance of rest is overlooked.

If, as seems likely, the pathogen(s) involved in ME remain in the system and are stimulated by exertion,

this would serve to reinforce the importance of rest as an immediate and urgent treatment recommendation (ME diagnosed by interview, exclusion, and recognition of the complex but easily identifiable constellation of symptoms of muscle metabolism failure, cognitive difficulties, failure in endocrine regulation, and signs of an activated immune system. A differential diagnosis from depression is relatively simple: a depressed person suffers from sadness and apathy...not fatigue...and will find their mood improved by exercise. The ME sufferer is highly motivated, willing to attempt anything, encounters almost immediate muscle failure (not fatigue), and is likely then to become frustrated and upset. The differences in motivational state and the sequence of change of emotional state are very distinct. The misuse of the term 'fatigue', which is incorrect in both conditions, is the only thing that confabulates them. Several questionnaires used to diagnose depression do conflate depression with ME in this way.

The IOM (see above). sets a 6 month duration of symptoms as a diagnostic necessity, but also affirms that ME can be diagnosed by careful interview and routine tests, and that symptoms should be treated without waiting for the 6 months to pass. Clearly, if a treatment, such as complete rest, is urgent at the start, as Ramsay insisted, then waiting for six months may lose any opportunity the patient may have to make a complete recovery, so investigation into the potential of offering an extended period of complete rest from the inception should clearly be one line of research.

ME is expensive to health services, government disability services and medical insurers. Up to now, agencies concerned have used the labelling of ME/CFS as a psychiatric condition, and insistence on cooperation with 'the best treatments' e.g. CBT and GET as a way of attempting to deal with this. The result is that patients either do not fully engage with GET, or they engage with it in good faith and become too ill even to get to the places where the treatment is offered. In either case, financial help can then be denied on grounds of failure to cooperate. And no one gets better. If, instead, genuine improvement or even recovery can be brought about by offering nothing more complicated or expensive than several weeks of rest from the inception, this would benefit patients, make return to work a possibility, and be both much less expensive and much more effective than the present system of services which is in place.

http://www.nhsmanagers.net/guest-editorials/a-radical-care-pathway-for-mecfs/

It should be recognised that with an illness which at best has a very protracted acute stage, and at worst, becomes a permanent feature in the system (like the latent herpes viruses), then rehabilitative treatments, as differentiated from treatments aimed at attacking the cause of the disease, or enabling the immune system to launch an effective attack, are inappropriate. There is so much evidence that programmes based on increasing physical activity actually prolong and intensify the disease that it is surprising that this approach is still regarded as acceptable. If the evidence available in relation to exercise and ME/CFS were in relation to a drug treatment, that drug would have been withdrawn years ago. The PACE Trial, which is the source of support for CBT and GET, and has been internationally influential, has been widely discredited. During the trial, the original criterion for recovery (85 on the Chalder Fatigue Scale) was lowered to 60 on that scale. The criterion for being sick enough to enter the trial was a score of 65, so that a patient could become slightly worse during treatment and still be recorded as 'recovered'. It is not ethical to change an important criterion during a research study. It is

not easy to understand how, in view of these facts, this study have been given so much credence and had so much influence on policy.

http://www.stats.org/pace-research-sparked-patient-rebellion-challenged-medicine/

Leslie O Simpson, Ph.D., a researcher in hemorheology with a particular interest in chronic diseases, sheds light on a potential mechanisms for this. In many chronic illnesses, immediately-fixed sample of blood show distinct shape changes in the erythrocyte population, with a variety of non-discocyte forms which are unable to traverse the microcirculation. As the function of the red blood cells is to deliver oxygen and remove metabolites. This appears to provide a relatively simple explanation for the failure of the aerobic muscle metabolism, cognitive difficulties, and endocrine problems---all of these areas are particularly vulnerable to lack of oxygen and the build up of metabolites.

Ramsay's Disease - Myalgic Encephalomyelitis (ME) and The Unfortunate Creation of Chronic Fatigue Syndrome (CFS), by Leslie O Simpson, Ph.D. and Nancy Blake BA, CQSW.

The research implications of the above are that

1) A trial of complete rest upon diagnosis (made immediately, not after six months) should be done. A diagnostic protocol on the lines suggested above could be developed, patients interviewed, and those which met the criteria should be dividing into one group put on a regime of virtually complete rest for several weeks, and one given 'usual medical care', and the long-term outcomes studied.

2) A retrospective study of the effects of exercise programmes needs to be conduThere is much evidence of harm, but this needs to be formalised and the results made operational in future political and management policies.

3) Les Simpson's research needs to be revisited, carefully reproducing his protocols. The implications for treatment should be included in future recommendations and guidelines. Hemorrheology is not included in medical education and the medical canon, which means that treatments to improve blood flow, which would be beneficial in many chronic illnesses, particularly diabetes as well as ME/CFS, are not offered by doctors.

4) The narrative of many ME people includes a serious commitment to exercise. The role of exercise as both a precipitating and a perpetuating factor needs to be studied. The evident lack of a narrative that could explain a psychiatric condition has lead to the assertion, by psychiatrists, that a somatoform or functional disorder (psychiatric problem) can occur without a relevant narrative. The impllications of the much more common narrative involving commitment to exercise has not been explored because it is a cultural imperative to think of exercise as universally beneficial. The IOM, along with the early doctors (Ramsay, Acheson) are unequivocal in stating that exertion in this disease, can have systemic adverse effects, and the research into exercise and polio suggests one possible explanation.

5) Not related to anything above, Dr. Gary Kaplan has explored the role of sequential challenges to the microglia in producing permanent upregulation, inflammation and chronic pain, and this seems an avenue to explore in relation to the pain of severe ME, as well as the apparent range of events which

can led up to ME, as well as the common co-morbidities. This, and his description of the myofacial pain, how it is caused and how it operates offer further avenues to explore the mechanisms of widespread, variable, fluctuating pain which cannot be explained neurologically. Kaplan's attitude of treating his patients' account of their symptoms and using that as information guiding his diagnostic efforts is much more productive in producing effective resolutions than simply declaring that if the medical explanation isn't forthcoming, let's call that a psychiatric condition. The myofascial system and the role of microglia need further exploration in relation to ME and Fibromyalgia, as well as more recent developments in terms of the discovery of hitherto unknown parts of the immune system in the brain.

"Total Recovery - Solving the Mystery of Chronic Pain and Depression" by Dr. Gary Kaplan, DO, with Donna Beech covers Dr. Kaplan's research and clinical work.

The fundamental change that needs to take place is understanding that this is a complex, multisystem physical disease, and as the IOM report insists, this has to be the assumption underlying all efforts at research if any real progress is to be mad.

[...]
Subject: A Reply for LDN Trust

Good day,

I do not know exactly to whom I am writing to but this link was suggested by the LDN Trust.

Not wanting to complain but, I live with an extreme pain disorder including; chronic high levels of intense pain, sleep disorders, muscle degeneration (probably due to not being able to properly exercise due to the pain), chronic fatigue and several others.

For many years (almost 30) I have been on high levels of morphine for about 12 of those years I have been on ever-increasing doses of the Fentanyl patch. As of February 2016 I was on the equivalent of 240 mgs of morphine (as converted). I decided that I had had enough of all the side effects of the med so I (along with my Family Doctor) went on a 'Fentanyl diet'. As of the 1st week of May I have had no opioids at all. It was a very tough program to go through but I am very pleased I am off.

Although my pain level was 'over the top' I managed through to be clean for about 3 weeks.

In a long story, I re-discovered my cousin who has been working with LDN for over 25 years. I re-connected & he offered suggestions as to how to proceed.

I started on LDN at 3.5 mgs & found that had little or no effect. I now have been taking LDN at 4.5 mgs for about 2 weeks & have found a modicum of relief. I realize now what the opioids have been masking & many of the original injury areas are being rediscovered as well as some secondary probs. Without the opioids I have re-found my senses of smell, taste and better hearing - so far.

I look forward to the LDN kicking in to offer more assistance for the mega-pain. I have been told it might take a while to become fully functional in one's body so therefore I am willing to push through the pain on a minute-to-minute basis until it can 'filter through'.

I do not know if this is the type of information you are seeking but I offer it freely & (for now) anonymously for data only. Perhaps in the future I may be willing to have the above & perhaps additional info posted under my name.

Be well.

[...]
[...]
Subject: Request for Information: Soliciting Input for New Research Strategies for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)

Dear NIH,

I'm a patient, and here is my response to your **Request for Information: Soliciting Input for New Research Strategies for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS).**

In my opinion, the following are research priorities:

1. Identifying biomarkers.

2. Using objective tests such as cardiopulmonary exercise testing and brain imaging to search for abnormalities, especially during and after physical or mental exertion, infection, and other stressors.

3. Developing means to distinguish between subgroups (under the assumption that CFS may actually be several illnesses with some superficial similarities).

4. Investigating B cell depletion as treatment, and developing a test to identify patients that are likely to respond to this treatment.

5. Investigating immune system abnormalities.

6. Investigating energy metabolism.

7. Investigating mitochondrial function.

8. Investigation gut health and the intestinal microbiota.

In my opinion, the following are barriers to research:

1. Lack of appropriate research funding (thankfully this appears to be changing, but it needs to be said that this was probably the biggest barrier).

2. CFS is considered a career suicide for researchers. It needs to become a respectable and attractive career choice.

3. An abundance of low quality research that brings more confusion than clarity. Enforcing higher standards in study design would help. I don't know what could be done but I think this is a problem.

4. Lack of industry involvement.

5. Lack of centers of excellence which could provide the patients needed to conduct studies.

8. There aren't enough conferences for researchers where they can exchange ideas and findings.

In my opinion, the following are gaps in research:

1. Severely sick patients have never been studied because they are housebound.

2. The natural history of the illness is poorly understood.

3. From discussions with patients it appears that a subset of patients have poor glucose tollerance consistent with postprandial hypoglycemia and will go into hypoglycemia during a glucose tollerance test or simply due to fasting, and a larger portion of patients report the need to eat frequently. To my knowledge, this problem has never been acknowledged in the literature, even if it's relatively common and simply to demonstrate. This doesn't appear to be due to a known endocrine disease.

[...]
[...]
Subject: Ldn

I believe ldn should be researched for me CFS. I was under a doctor getting positive results. Effective Y sorting my own healthcare I a country with a dysfunctional health care system run for the few. No worthwhile treatment is available. we need something.

[...]
[...]

Why don't you call people with CFS. You can learn Sooooo much if you ask the riight questions.

[...]
[...]
Subject: Notice number NOT-NS-16-024 request for information ... new research strategies for ME/CFS

Dear Sir/Madam
I am responding as an individual person with ME/CFS and as a researcher, to your Request for Information: Soliciting Input for New Research Strategies for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)
I have attached my response as a word document. I have also copied my response below.

Response to Request for Information: Soliciting Input for New research Strategies for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)

I am a UK ex-General Practitioner who developed ME/CFS as a result of viral meningitis in 1988. I had very severe ME/CFS, improving gradually to moderate and remaining at this level until 2000, when my illness responded well to the drug naltrexone in low dosage (termed low dose naltrexone or LDN). After attempts to persuade others to conduct clinical trials of LDN in ME/CFS patients failed, I returned to university to study a Masters in Research with the long term aim of conducting such a trial myself. I am therefore approaching the research community as an outsider.

Emerging needs and opportunities

The primary need for patients is clinical trials of drugs in ME/CFS. In conversation with patients this need is repeatedly highlighted – patients are desperate to enrol in any worthwhile clinical trial. There are already several drugs licensed for the treatment of fibromyalgia, a condition which may co-exist in some patients with ME/CFS. These treatments could be usefully trialled in ME/CFS, as could drugs such as rintatolimod (Ampligen), intravenous immunoglobulin, or antiviral agents, all of which may be beneficial in some patients but clinical trials failed to show significance or results have not been replicated in larger trials. There is a specific need for clinical trials of low dose naltrexone in patients with ME/CFS (see below).

Challenges or barriers to progress in ME/CFS research

The comparative lack of clinical drug trials for ME/CFS patients means that there is little consensus on the optimum drug trial design, including entry criteria and exclusions, and outcome measures. Due to lack of consensus, those trials which have been conducted have used varying entry criteria and outcome measures, and mostly are of too small a size and too short a duration to obtain statistically significant results even when the drug may be potentially useful. This was well summarised by Smith et al in the Evidence Report (Smith MEB, Nelson HD, Haney E, Pappas M, Daeges M, Wasson N, 2014) and by Green et al (Green, Cowan, Elk, O'Neil, & Rasmussen, 2015) following the Pathways to Prevention workshop on ME/CFS in 2014.

The lack of specialist clinics to treat patients with ME/CFS and the lack of academics, particularly senior academics, interested in ME/CFS research are major barriers to ME/CFS research. One fundamental way that this needs to be addressed is by raising the profile of ME/CFS generally. Education of medical students and student nurses about ME/CFS needs to be greatly increased. There is still too much perception of ME/CFS as a psychological illness in the medical world, and this hampers potential researchers from becoming interested. In the UK there is also a perception that patients are antagonistic towards researchers. This antagonism has arisen due to the prevailing psychological school of thought previously dominating research and due to the frustration of the patient community. Conversely, I have found patient groups to be both supportive and eager to engage with my research ideas.

As a person attempting to design and carry out a clinical trial of a drug in patients with ME/CFS, these shortcomings create further barriers, as I have experienced fewer possibilities of interacting with fellow researchers, difficulties with engaging a committed senior researcher to oversee my studies, few clinics from which well characterised patients could be sourced and a lack of funding opportunities. There are no ready-made pathways for a person such as myself to slot into an existing research programme; the

university I am studying at (Manchester University, one of the largest and most distinguished for research in the UK) has no dedicated ME/CFS research programme.

Gaps and opportunities

I believe that a culture needs developing in which clinical trials are routinely offered to patients attending specialist ME/CFS clinics, as happens frequently in cancer and lymphoma/leukemia clinics. This needs a massive increase in specialist clinics, in funding for clinical trials, and a consensus on entry criteria and outcome measures for such trials. The research community will only develop knowledge of optimum clinical trial designs including suitable outcome measures through repeatedly conducting clinical trials, as occurred in the field of malignancies. It is not appropriate to wait until further advances in understanding the aetiology of ME/CFS, or more potent potential treatments emerge. Conducting trials, even of drugs with supposed limited usefulness, refines methodology and attracts researchers into the field; they are then more likely to remain interested in research into ME/CFS.

Opportunities exist when developing outcome measures of using portable actigraphy devices. The non-research use of actigraphy devises is now part of routine life for people using mobile phones. More sophisticated devises measuring temperature, skin conductivity as well as posture and motion would provide interesting complex outcome measures, and may enable subgroup analysis of responders v non-responders, but have not yet been successfully deployed as an outcome measure in ME/CFS clinical trial research.

The need for clinical trials of low dose naltrexone (LDN)

Description of need or opportunity and scientific rationale

Naltrexone is a pure opiate antagonist, counteracting the effects of both exogenous opiates (morphine, heroin etc) and endogenous opiates (endorphins and enkephalins). At full dosage (50 to 100 mg) it has been licensed since 1984 to treat drug addiction and, more recently, alcoholism (Anton et al., 2006), for which it is widely used. Naltrexone is off-patent, cheap and widely available.

At low dosage (3 to 4.5 mg), naltrexone acts as an immune modulator, though the exact mechanism is still unknown in ME/CFS. Possible mechanisms for immune modulation are; short term blockade of opioid receptors causing a rebound increase in endorphins, which then act on the immune system; specific temporary blockade of opioid growth factor receptors; or antagonism of Toll-like receptor-4 on microglial cells, preventing release of pro-inflammatory cytokines. LDN also reduces pain in chronic pain syndromes, though the mechanism of action is again not clear.

The discovery of the immune modulating properties of LDN in mice in 1983 (Zagon & McLaughlin, 1983, 1984), rapidly led to its use in humans to reduce inflammation in a range of conditions (Younger, Parkitny, & McLain, 2014; Zagon & McLaughlin, 1984). It was trialled by researchers such as Bihari treating patients with HIV infection and then more widely prescribed for Multiple Sclerosis, Parkinson's disease and inflammatory bowel disease. So far only small scale clinical trials of LDN, for example, in Crohn's Disease, M.S. and HIV infection, have been carried out but these show it to be effective and/or with less toxicity than established treatments (Cree, Kornyeyeva, & Goodin, 2010; Smith et al., 2011;

Smith, Field, Bingaman, Evans, & Mauger, 2013; Traore et al., 2011). A small randomised double-blind placebo-controlled counterbalanced crossover study of LDN in fibromyalgia, an overlapping syndrome with CFS/ME, has shown benefits, particularly in pain reduction (Younger, Noor, McCue, & Mackey, 2013). In this trial there was a trend for patients with higher-normal ESRs to respond to LDN more than those with low-normal ESRs. There are no clinical trials of LDN in CFS/ME though there are numerous anecdotal reports (Health Rising, 2015; LDN world database, 2015), and several notable CFS/ME specialists recommend its use (Health Rising, 2015).

Naltrexone is unlicensed for any indication at low dose. As it is unlicensed, doctors must take personal responsibility for prescribing it and in the UK this means most patients obtain it privately. About 10,000 patients in the UK reportedly take LDN for a variety of conditions (LDNNow, 2015), mostly via private prescription. There is widespread use of LDN amongst patient communities throughout the world including USA, UK and Scandinavian countries, and there are many internet support groups. Because LDN is unlicensed, systematic collection of data on effectiveness is lacking. It appears that about 2/3 of patients who try it obtain some benefit, though the degree of benefit varies.

Because the immune modulating properties of LDN were discovered when the drug was nearing the end of its patent, there was no drug development work at low dosage by the pharmaceutical industry. There have been no dosing studies in humans of naltrexone at low dosage, apart from a small study of endorphin responses to different doses of naltrexone by Bihari in the 1980's, which he described on a Youtube video (Bihari, 2014) but is unpublished. The patient community in general is very reluctant to try doses other than between 1.5mg to 4.5mg because of Bihari's work. However, there is accumulating anecdotal evidence that patients with ME/CFS respond better to higher doses (personal communications Dr Jarred Younger, Prof Jose Montoya and Dr Ros Vallings), possibly in the range 9 to 12 mg though the highest recorded dose for optimum response is 24mg (personal communication Dr Tom Gilhooly, G.P. Glasgow, UK).

Naltrexone in full dosage has a good safety record. The UK system used by all doctors for notifying potential drug reactions (the yellow card system) has recorded only 9 deaths since 1984 in which full dose naltrexone was possibly implicated. Apart from 2 sudden deaths without further explanation, all of these were single incidents and most appear connected with underlying disorders of the patient rather than the drug, for example, aspiration. I attach the ADR report as information.

No serious side-effects with LDN are known and there have been no reported deaths. There are 32 registered clinical trials of low dose naltrexone on the clinicaltrials.gov website, of which 22 were completed, and data on around 12 is published or available on the website. Side-effects recorded in these trials were mild and generally self-limiting. Younger et al (2013)(Younger et al., 2013) reported that in 31 patients enrolled in the fibromyalgia cross-over study the only side effect occurring more frequently during treatment than during placebo was disturbance of sleep particularly through vivid dreams. The Cochrane systematic review of clinical trials of LDN in Crohn's disease concluded there were no statistically significant differences between LDN and placebo, though patient numbers were small (Segal, Macdonald, & Chande, 2014). Anecdotally, headaches and increasing fatigue may occur on initiating treatment or increasing dosage in CFS/ME patients (Health Rising, 2015). All symptoms settle with time, though temporary reduction in dosage may be needed in some patients.

Potential public health impact, and anticipated challenges to be addressed.

It would appear that LDN is a potentially useful treatment for ME/CFS which is not more widely available due to lack of clinical trial evidence of efficacy and consequent drug licensing. There is therefore a pressing need for clinical trials of LDN to establish the degree of efficacy and whether particular subgroups (for example those with higher levels of inflammation or possible auto-immunity) respond more. Initially a dosing study of LDN in patients with ME/CFS is needed to establish the optimum dose or range of doses as this is currently unknown. This information could then be used to design and conduct a large scale randomised controlled trials (RCTs) to test efficacy.

As the drug is out of patent, any clinical trial will need funding by government agencies. I suggest the NIH could directly fund such studies by announcing a Funding Opportunity centred on the development of clinical trials of LDN in ME/CFS. The knowledge gained conducting RCTs of LDN might contribute to understanding the mechanisms causing or perpetuating ME/CFS by studying characteristics of responders. The trials would also contribute useful knowledge towards optimising the design of future trials of potentially more specific drugs.

If LDN is shown to be effective, even if only partially so, this could rapidly lead to it being prescribed to alleviate symptoms in patients with ME/CFS, as the drug is already widely available, cheap and known to be non-toxic. It could then become the first readily available treatment within a relatively short time period. This would lead to rapid health and economic benefits if patients were able to return to work as a consequence.

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DRUG ANALYSIS PRINT

DRUG NAME: NALTREXONE

Jump to first report page

Drug name:	NALTREXONE	**Reporttype:**	Spontaneous
Report run date:	12-Mar-2016	**Report origin:**	UNITED KINGDOM
Data lock date:	11-Mar-2016 19:00:08	**Route of admin:**	ALL
Period covered:	01-Jul-1963 to 11-Mar-2016	**Reporter type:**	ALL
Earliest reaction date:	15-Aug-1988	**Reaction:**	ALL
MedDRA version:	MedDRA 18.1	**Age group:**	ALL

Total number of reactions*:	248	**Total number of ADR reports:**	88	**Total number of fatal ADR reports:**	9

Products included in this print - Single active constituent products (PBGs):

NALOREX

Drug name:	NALTREXONE	**Report type:**	Spontaneous
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MedDRA version:	MedDRA 18.1	**Age group:**	ALL

System Organ Class	**Single active constituent**		**Multiple active constituent**		**Total unique reports***	
	All	**Fatal**	**All**	**Fatal**	**All**	**Fatal**
Congenital disorders	1	0	0	0	1	0
Gastrointestinal disorders	48	0	0	0	48	0
Hepatic disorders	4	0	0	0	4	0
Infections	5	0	0	0	5	0
Investigations	16	0	0	0	16	0
Muscle & tissue disorders	13	0	0	0	13	0
Nervous system disorders	32	1	0	0	32	1
Renal & urinary disorders	7	0	0	0	7	0
Respiratory disorders	7	1	0	0	7	1
Surgical & medical procedures	1	0	0	0	1	0
TOTAL NUMBER OF REACTIONS	**248**	**9**	**0**	**0**	**248**	**9**

TOTAL NUMBER OF FATAL ADR REPORTS*		**9**		**0**		**9***
TOTAL NUMBER OF ADR REPORTS*	**88**		**0**		**88***	

Drug name:	NALTREXONE	**Report type:**	Spontaneous
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GLOSSARY/ABBREVIATIONS

ADR - Adverse Drug Reaction

Age group - lists which age groups are included in the Drug Analysis Print – either ALL, Adolescent, Adult, Child, Elderly, Infant or Neonate

Data lock date - shows data on the database at this specified date and time

HLT - High Level Term - see definition of MedDRA

MedDRA - this stands for **Med**ical **D**ictionary for **R**egulatory **A**ctivities, which is the internationally agreed list of terms used for Medicines Regulation. MedDRA groups related adverse drug reaction terms in a hierarchical structure whereby the *'preferred term' (PT)* (e.g. tunnel vision) is grouped under the broader heading the *'high level term' (HLT)* (e.g. visual field disorders). *'High level terms'* are contained within the *'system organ class' (SOC)* (e.g. eye disorders). The *'preferred term'* is the most specific term on the Drug Analysis Print, while the *'system organ class'* is the most general

Multi active constituent products - contain the drug constituent of interest plus one or more other drug constituents (e.g. co-codamol contains paracetamol and codeine)

NEC - appears in MedDRA and stands for Not Elsewhere Classified

NOS - appears in MedDRA and stands for Not Otherwise Specified

PBG - Product Brand Group – this means drug brand name e.g. Amoxil is a PBG for the drug substance amoxicillin

Products included in this print - this is a list of the products for which at least one suspected Adverse Drug Reaction (ADR) report has been received that specifies that product as a 'suspected drug' (i.e. suspected causal association with the reaction). It does not provide an exhaustive list of the products which contain the named drug substance

PT - Preferred Term - see definition of MedDRA

Reaction - defines which ADRs are included in the Drug Analysis Print – either ALL, Serious or Non-Serious

Reporter type - lists the reporter types which are included in the Drug Analysis Print – either Patient, Health Professional or ALL (i.e. both)

Report run date - the date the Drug Analysis Print was produced

Route of admin - lists the route of administration of the suspect drug for which reports are included in the Drug Analysis Print, e.g. ORAL only includes reports where the suspect drug was specified as having been taken by the oral route, or ALL which includes all routes of administration

Single active constituent products - contain only the drug substance of interest

Spontaneous - suspected ADR reports sent in to the Yellow Card Scheme are called spontaneous reports

Substance - is an active ingredient in a product

Substance Variant - is a more specific substance term. A substance may have zero, one or many linked variants. For example LITHIUM is linked to the variant LITHUM CARBONATE and LITHIUM CITRATE.

System Organ Class (SOC) - this is the highest level in MedDRA which groups together reactions that affect similar systems/organs in the body

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MedDRA version:	MedDRA 18.1	**Age group:**	ALL

	Single active constituent		Multiple active constituent		Total unique reports*	
Reaction Name	**All**	**Fatal**	**All**	**Fatal**	**All**	**Fatal**
SOC						
HLT						
PT						
Cardiac disorders						
Cardiac signs and symptoms NEC						
Palpitations	1	0	0	0	1	0
Heart failures NEC						
Cardiac failure	1	0	0	0	1	0
Supraventricular arrhythmias						
Atrial fibrillation	1	0	0	0	1	0
Sinus tachycardia	1	0	0	0	1	0
Ventricular arrhythmias and cardiac arrest						
Cardio-respiratory arrest	1	1	0	0	1	1
Ventricular fibrillation	1	0	0	0	1	0
Cardiac disorders SOC TOTAL	**6**	**1**	**0**	**0**	**6**	**1**

*This provides the number of individual reports and may be less than the sum of the single-active constituent and multi-active constituent columns. For example, if both a single- and multi-active constituent product are considered by the reporter to have a suspected causal relationship with the suspected reaction, then the same report will appear in both columns.

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MedDRA version:	MedDRA 18.1	**Age group:**	ALL

	Single active constituent		Multiple active constituent		Total unique reports*	
Reaction Name	**All**	**Fatal**	**All**	**Fatal**	**All**	**Fatal**
SOC						
HLT						
PT						
Congenital disorders						
Congenital disorders NEC						
Congenital anomaly	1	0	0	0	1	0
Congenital disorders SOC TOTAL	**1**	**0**	**0**	**0**	**1**	**0**

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MedDRA version:	MedDRA 18.1	**Age group:**	ALL

	Single active constituent		Multiple active constituent		Total unique reports*	
Reaction Name	**All**	**Fatal**	**All**	**Fatal**	**All**	**Fatal**
SOC						
HLT						
PT						
Eye disorders						
Lacrimation disorders						
Dry eye	1	0	0	0	1	0
Lacrimation increased	1	0	0	0	1	0
Lid, lash and lacrimal infections, irritations and inflammations						
Eyelid oedema	1	0	0	0	1	0
Ocular infections, inflammations and associated manifestations						
Eye irritation	1	0	0	0	1	0
Pupil disorders						
Pupil fixed	1	0	0	0	1	0
Visual disorders NEC						
Vision blurred	1	0	0	0	1	0
Visual impairment	1	0	0	0	1	0
Eye disorders SOC TOTAL	**7**	**0**	**0**	**0**	**7**	**0**

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MedDRA version:	MedDRA 18.1	**Age group:**	ALL

	Single active constituent		Multiple active constituent		Total unique reports*	
Reaction Name	**All**	**Fatal**	**All**	**Fatal**	**All**	**Fatal**
SOC						
HLT						
PT						
Gastrointestinal disorders						
Diarrhoea (excl infective)						
Diarrhoea	8	0	0	0	8	0
Flatulence, bloating and distension						
Abdominal distension	1	0	0	0	1	0
Gastrointestinal and abdominal pains (excl oral and throat)						
Abdominal pain	8	0	0	0	8	0
Abdominal pain upper	5	0	0	0	5	0
Gastrointestinal necrosis and gangrene (excl gangrenous hernia)						
Gastrointestinal necrosis	1	0	0	0	1	0
Intestinal haemorrhages						
Rectal haemorrhage	1	0	0	0	1	0
Nausea and vomiting symptoms						
Nausea	4	0	0	0	4	0
Vomiting	15	0	0	0	15	0
Vomiting projectile	1	0	0	0	1	0
Non-site specific gastrointestinal haemorrhages						
Gastrointestinal haemorrhage	1	0	0	0	1	0
Haematemesis	1	0	0	0	1	0
Oral soft tissue signs and symptoms						
Oral discomfort	1	0	0	0	1	0
Oral soft tissue swelling and oedema						
Lip swelling	1	0	0	0	1	0
Gastrointestinal disorders SOC TOTAL	**48**	**0**	**0**	**0**	**48**	**0**

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	Single active constituent		Multiple active constituent		Total unique reports*	
Reaction Name	**All**	**Fatal**	**All**	**Fatal**	**All**	**Fatal**
SOC						
HLT						
PT						
General disorders						
Asthenic conditions						
Fatigue	1	0	0	0	1	0
Malaise	1	0	0	0	1	0
Death and sudden death						
Sudden death	2	2	0	0	2	2
Febrile disorders						
Pyrexia	1	0	0	0	1	0
Feelings and sensations NEC						
Chills	1	0	0	0	1	0
General signs and symptoms NEC						
Condition aggravated	1	0	0	0	1	0
Influenza like illness	1	0	0	0	1	0
Interactions						
Drug interaction	3	0	0	0	3	0
Potentiating drug interaction	1	1	0	0	1	1
Oedema NEC						
Face oedema	1	0	0	0	1	0
Pain and discomfort NEC						
Chest pain	2	0	0	0	2	0
Discomfort	1	0	0	0	1	0
Pain	1	0	0	0	1	0
Therapeutic and nontherapeutic responses						
Drug ineffective	2	0	0	0	2	0
Withdrawal and rebound effects						
Drug withdrawal syndrome	5	0	0	0	5	0
General disorders SOC TOTAL	**24**	**3**	**0**	**0**	**24**	**3**

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	Single active constituent		Multiple active constituent		Total unique reports*	
Reaction Name	**All**	**Fatal**	**All**	**Fatal**	**All**	**Fatal**
SOC						
HLT						
PT						
Hepatic disorders						
Hepatic enzymes and function abnormalities						
Hepatic function abnormal	2	0	0	0	2	0
Hepatobiliary signs and symptoms						
Hepatomegaly	1	0	0	0	1	0
Hepatocellular damage and hepatitis NEC						
Hepatocellular injury	1	0	0	0	1	0
Hepatic disorders SOC TOTAL	**4**	**0**	**0**	**0**	**4**	**0**

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Drug name:	NALTREXONE	**Report type:**	Spontaneous
Report run date:	12-Mar-2016	**Report origin:**	UNITED KINGDOM
Data lock date:	11-Mar-2016 19:00:08	**Route of admin:**	ALL
Period covered:	01-Jul-1963 to 11-Mar-2016	**Reporter type:**	ALL
Earliest reaction date:	15-Aug-1988	**Reaction:**	ALL
MedDRA version:	MedDRA 18.1	**Age group:**	ALL

	Single active constituent		Multiple active constituent		Total unique reports*	
Reaction Name	**All**	**Fatal**	**All**	**Fatal**	**All**	**Fatal**
SOC						
HLT						
PT						
Immune system disorders						
Allergic conditions NEC						
Hypersensitivity	2	0	0	0	2	0
Immune system disorders SOC TOTAL	**2**	**0**	**0**	**0**	**2**	**0**

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MedDRA version:	MedDRA 18.1	**Age group:**	ALL

	Single active constituent		Multiple active constituent		Total unique reports*	
Reaction Name	**All**	**Fatal**	**All**	**Fatal**	**All**	**Fatal**
SOC						
HLT						
PT						
Infections						
Abdominal and gastrointestinal infections						
Peritonitis	1	0	0	0	1	0
Breast infections						
Mastitis	1	0	0	0	1	0
Sepsis, bacteraemia, viraemia and fungaemia NEC						
Sepsis	2	0	0	0	2	0
Viral infections NEC						
Post viral fatigue syndrome	1	0	0	0	1	0
Infections SOC TOTAL	**5**	**0**	**0**	**0**	**5**	**0**

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MedDRA version:	MedDRA 18.1	**Age group:**	ALL

	Single active constituent		Multiple active constituent		Total unique reports*	
Reaction Name	**All**	**Fatal**	**All**	**Fatal**	**All**	**Fatal**
SOC						
HLT						
PT						
Injuries						
Limb fractures and dislocations						
Wrist fracture	1	0	0	0	1	0
Maladministrations						
Accidental overdose	1	1	0	0	1	1
Medication errors NEC						
Medication error	1	0	0	0	1	0
Site specific injuries NEC						
Mouth injury	1	0	0	0	1	0
Injuries SOC TOTAL	**4**	**1**	**0**	**0**	**4**	**1**

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MedDRA version:	MedDRA 18.1	**Age group:**	ALL

	Single active constituent		Multiple active constituent		Total unique reports*	
Reaction Name	**All**	**Fatal**	**All**	**Fatal**	**All**	**Fatal**
SOC						
HLT						
PT						
Investigations						
Heart rate and pulse investigations						
Heart rate increased	1	0	0	0	1	0
Liver function analyses						
Alanine aminotransferase increased	2	0	0	0	2	0
Gamma-glutamyltransferase increased	3	0	0	0	3	0
Hepatic enzyme increased	1	0	0	0	1	0
Liver function test abnormal	5	0	0	0	5	0
Physical examination procedures and organ system status						
Weight decreased	1	0	0	0	1	0
Protein analyses NEC						
Globulins increased	1	0	0	0	1	0
Protein total increased	1	0	0	0	1	0
Renal function analyses						
Blood creatinine increased	1	0	0	0	1	0
Investigations SOC TOTAL	**16**	**0**	**0**	**0**	**16**	**0**

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	Single active constituent		Multiple active constituent		Total unique reports*	
Reaction Name	**All**	**Fatal**	**All**	**Fatal**	**All**	**Fatal**
SOC						
HLT						
PT						
Metabolic disorders						
Calcium metabolism disorders						
Hypercalcaemia	2	0	0	0	2	0
Elevated cholesterol						
Hypercholesterolaemia	1	0	0	0	1	0
Elevated triglycerides						
Hypertriglyceridaemia	1	0	0	0	1	0
Total fluid volume decreased						
Dehydration	2	0	0	0	2	0
Metabolic disorders SOC TOTAL	**6**	**0**	**0**	**0**	**6**	**0**

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MedDRA version:	MedDRA 18.1	**Age group:**	ALL

	Single active constituent		Multiple active constituent		Total unique reports*	
Reaction Name	**All**	**Fatal**	**All**	**Fatal**	**All**	**Fatal**
SOC						
HLT						
PT						
Muscle & tissue disorders						
Joint related signs and symptoms						
Arthralgia	3	0	0	0	3	0
Muscle pains						
Myalgia	1	0	0	0	1	0
Muscle related signs and symptoms NEC						
Muscle spasms	2	0	0	0	2	0
Muscle twitching	3	0	0	0	3	0
Musculoskeletal and connective tissue pain and discomfort						
Back pain	1	0	0	0	1	0
Pain in extremity	1	0	0	0	1	0
Myopathies						
Rhabdomyolysis	1	0	0	0	1	0
Spondyloarthropathies						
Spondylitis	1	0	0	0	1	0
Muscle & tissue disorders SOC TOTAL	**13**	**0**	**0**	**0**	**13**	**0**

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MedDRA version:	MedDRA 18.1	**Age group:**	ALL

	Single active constituent		Multiple active constituent		Total unique reports*	
Reaction Name	**All**	**Fatal**	**All**	**Fatal**	**All**	**Fatal**
SOC						
HLT						
PT						
Neoplasms						
Neoplasms unspecified malignancy and site unspecified NEC						
Abdominal neoplasm	1	0	0	0	1	0
Neoplasms SOC TOTAL	**1**	**0**	**0**	**0**	**1**	**0**

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MedDRA version:	MedDRA 18.1	**Age group:**	ALL

	Single active constituent		Multiple active constituent		Total unique reports*	
Reaction Name	**All**	**Fatal**	**All**	**Fatal**	**All**	**Fatal**
SOC						
HLT						
PT						
Nervous system disorders						
Absence seizures						
Petit mal epilepsy	1	0	0	0	1	0
Central nervous system haemorrhages and cerebrovascular accidents						
Cerebral haemorrhage	1	1	0	0	1	1
Subarachnoid haemorrhage	1	0	0	0	1	0
Coordination and balance disturbances						
Balance disorder	1	0	0	0	1	0
Coordination abnormal	1	0	0	0	1	0
Disturbances in consciousness NEC						
Apallic syndrome	1	0	0	0	1	0
Loss of consciousness	2	0	0	0	2	0
Dyskinesias and movement disorders NEC						
Dyskinesia	2	0	0	0	2	0
Dystonias						
Dystonia	1	0	0	0	1	0
Headaches NEC						
Headache	5	0	0	0	5	0
Sinus headache	1	0	0	0	1	0
Increased intracranial pressure disorders						
Intracranial pressure increased	1	0	0	0	1	0
Neurological signs and symptoms NEC						
Dizziness	3	0	0	0	3	0
Paraesthesias and dysaesthesias						
Burning sensation	1	0	0	0	1	0
Hypoaesthesia	1	0	0	0	1	0
Paraesthesia	1	0	0	0	1	0
Seizures and seizure disorders NEC						
Epilepsy	1	0	0	0	1	0
Seizure	3	0	0	0	3	0
Sensory abnormalities NEC						
Sensory disturbance	1	0	0	0	1	0
Tremor (excl congenital)						
Tremor	3	0	0	0	3	0
Nervous system disorders SOC TOTAL	**32**	**1**	**0**	**0**	**32**	**1**

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Reaction Name	Single active constituent		Multiple active constituent		Total unique reports*	
	All	Fatal	All	Fatal	All	Fatal
SOC						
HLT						
PT						
Psychiatric disorders						
Abnormal behaviour NEC						
Abnormal behaviour	2	0	0	0	2	0
Anxiety symptoms						
Agitation	5	0	0	0	5	0
Behaviour and socialisation disturbances						
Aggression	1	0	0	0	1	0
Paranoia	1	0	0	0	1	0
Confusion and disorientation						
Confusional state	6	0	0	0	6	0
Disorientation	1	0	0	0	1	0
Decreased physical activity levels						
Catatonia	2	0	0	0	2	0
Delusional symptoms						
Delusion	1	0	0	0	1	0
Depressive disorders						
Depression	1	0	0	0	1	0
Disturbances in initiating and maintaining sleep						
Insomnia	2	0	0	0	2	0
Increased physical activity levels						
Restlessness	1	0	0	0	1	0
Perception disturbances						
Hallucination	1	0	0	0	1	0
Hallucination, auditory	1	0	0	0	1	0
Hallucination, visual	1	0	0	0	1	0
Hallucinations, mixed	2	0	0	0	2	0
Psychotic disorder NEC						
Acute psychosis	1	0	0	0	1	0
Psychotic disorder	3	0	0	0	3	0
Sexual desire disorders						
Loss of libido	1	0	0	0	1	0
Speech articulation and rhythm disturbances						
Screaming	1	0	0	0	1	0
Substance-related disorders						
Withdrawal syndrome	2	0	0	0	2	0
Suicidal and self-injurious behaviour						
Completed suicide	2	2	0	0	2	2
Suicidal ideation	1	0	0	0	1	0
Suicide attempt	1	0	0	0	1	0
Thinking disturbances						
Thinking abnormal	1	0	0	0	1	0
Psychiatric disorders SOC TOTAL	**41**	**2**	**0**	**0**	**41**	**2**

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MedDRA version:	MedDRA 18.1	**Age group:**	ALL

	Single active constituent		Multiple active constituent		Total unique reports*	
Reaction Name	**All**	**Fatal**	**All**	**Fatal**	**All**	**Fatal**
SOC						
HLT						
PT						
Renal & urinary disorders						
Bladder and urethral symptoms						
Incontinence	1	0	0	0	1	0
Renal failure and impairment						
Acute kidney injury	1	0	0	0	1	0
Anuria	1	0	0	0	1	0
Oliguria	1	0	0	0	1	0
Renal impairment	1	0	0	0	1	0
Urinary abnormalities						
Chromaturia	1	0	0	0	1	0
Urinary tract signs and symptoms NEC						
Renal pain	1	0	0	0	1	0
Renal & urinary disorders SOC TOTAL	**7**	**0**	**0**	**0**	**7**	**0**

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	Single active constituent		Multiple active constituent		Total unique reports*	
Reaction Name	**All**	**Fatal**	**All**	**Fatal**	**All**	**Fatal**
SOC						
HLT						
PT						
Reproductive & breast disorders						
Erection and ejaculation conditions and disorders						
Ejaculation disorder	1	0	0	0	1	0
Reproductive & breast disorders SOC TOTAL	**1**	**0**	**0**	**0**	**1**	**0**

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	Single active constituent		Multiple active constituent		Total unique reports*	
Reaction Name	**All**	**Fatal**	**All**	**Fatal**	**All**	**Fatal**
SOC						
HLT						
PT						
Respiratory disorders						
Breathing abnormalities						
Dyspnoea	3	0	0	0	3	0
Dyspnoea exertional	1	0	0	0	1	0
Pharyngeal disorders (excl infections and neoplasms)						
Pharyngeal oedema	1	0	0	0	1	0
Respiratory tract disorders NEC						
Aspiration	1	1	0	0	1	1
Upper respiratory tract signs and symptoms						
Sneezing	1	0	0	0	1	0
Respiratory disorders SOC TOTAL	**7**	**1**	**0**	**0**	**7**	**1**

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	Single active constituent		Multiple active constituent		Total unique reports*	
Reaction Name	**All**	**Fatal**	**All**	**Fatal**	**All**	**Fatal**
SOC						
HLT						
PT						
Skin disorders						
Angioedemas						
Swelling face	1	0	0	0	1	0
Apocrine and eccrine gland disorders						
Hyperhidrosis	6	0	0	0	6	0
Bullous conditions						
Blister	1	0	0	0	1	0
Erythema multiforme	1	0	0	0	1	0
Dermatitis and eczema						
Eczema	1	0	0	0	1	0
Dermatitis ascribed to specific agent						
Drug eruption	1	0	0	0	1	0
Photosensitivity and photodermatosis conditions						
Photosensitivity reaction	2	0	0	0	2	0
Pruritus NEC						
Pruritus	2	0	0	0	2	0
Rashes, eruptions and exanthems NEC						
Rash	1	0	0	0	1	0
Rash macular	1	0	0	0	1	0
Urticarias						
Idiopathic urticaria	1	0	0	0	1	0
Skin disorders SOC TOTAL	**18**	**0**	**0**	**0**	**18**	**0**

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	Single active constituent		Multiple active constituent		Total unique reports*	
Reaction Name	**All**	**Fatal**	**All**	**Fatal**	**All**	**Fatal**
SOC						
HLT						
PT						
Surgical & medical procedures						
Therapeutic procedures NEC						
Surgery	1	0	0	0	1	0
Surgical & medical procedures SOC TOTAL	**1**	**0**	**0**	**0**	**1**	**0**

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	Single active constituent		Multiple active constituent		Total unique reports*	
Reaction Name	**All**	**Fatal**	**All**	**Fatal**	**All**	**Fatal**
SOC						
HLT						
PT						
Vascular disorders						
Circulatory collapse and shock						
Circulatory collapse	1	0	0	0	1	0
Non-site specific embolism and thrombosis						
Thrombosis	1	0	0	0	1	0
Peripheral embolism and thrombosis						
Deep vein thrombosis	1	0	0	0	1	0
Vascular hypertensive disorders NEC						
Hypertension	1	0	0	0	1	0
Vascular disorders SOC TOTAL	**4**	**0**	**0**	**0**	**4**	**0**

TOTAL NUMBER OF REACTIONS	**248**	**9**	**0**	**0**	**248**	**9**

TOTAL NUMBER OF FATAL ADR REPORTS*		**9**		**0**		**9***
TOTAL NUMBER OF ADR REPORTS*	**88**		**0**		**88***	

_____

[…]
[…]
Subject: Notice Number: NOT-NS-16-024

Below is my submission for Notice Number: NOT-NS-16-024.

----- Forwarded Message -----
From: "Nath, Avindra (NIH/NINDS) [E]" […]
[…]
Sent: Friday, May 20, 2016 12:04 PM
Subject: RE: SEIDS intramural study

Thank you for the excellent suggestions.

Avi

Avindra Nath MD

Chief, Section of Infections of the Nervous System

Clinical Director, NINDS, National Institutes of Health

Bldg 10/ 7C-103

10 Center Drive

Bethesda, MD 20892

[…]

[…]

[…]
Sent: Friday, May 20, 2016 7:42 AM
To: Nath, Avindra (NIH/NINDS) [E]
Subject: SEIDS intramural study

Hello Dr. Nath,

I recently heard about the new Intramural study you are doing on systemic exertion intolerance disease syndrome and wanted to offer some suggestions in an area which I think would be fruitful. My background is as a chiropractor who has been disabled with SEIDS since 2008.

I believe one pathway for developing the disease is from a little known gram negative bacteria called Bartonella Like organism. In 2008, shortly before developing SEIDS I was bitten by a flea from a feral cat. The bite yielded a raised purple papule. The BLO organism appears to be resistant to multiple antibiotics. According to physicians who treat it, the clinical presentation is very similar to bartonella however it yields negative on labs.

Next I was infected by Epstein Barr virus. It initially presented with tender swollen lymph nodes and fatigue but then developed a very strange fasciculation in multiple muscles of my face and upper arms which lasted several weeks then stopped. However then I developed cold skin, depressed body temperature and chronic headache.

My course of infection was as follows:

1. Patient receives a scatch, bite or insect bite from a BLO infected cat.
2. There is an exposure to EBV.
3. BLO inhibits apoptosis by upregulating the NF-kB inflammatory pathway in blood vessels and nervous tissue and macrophage generation of antibodies.
4. EBV inhibits apoptosis through the same pathway as well as the PI-3/AK-t pathway and by blocking antibody attachment to EBV infected tissue.

This pathophysiology explains why SEIDS has been so hard to delineate, it is a superinfection between two commensural organisms, one virus and one gram negative bacteria. As the dual infection becomes established, mitochondria are maintained in a state of partial apoptosis where they are unable to effectively generate ATP from the Kreb's cycle and must resort to glycolysis only.

Treatment should be geared towards: killing the BLO, restoring immunocompetency and apoptosis, lowering the EBV count and regenerating damaged tissue.

[...]
[...]
Subject: Fwd: For the attention of Dr Vicky Whittemore

Dear Dr Whittemore,
I was delighted to speak to you at the Invest in ME conference the other week.

I mentioned my concerns about attitudes towards children and current research projects involving children with ME in the UK, and offered to send you the talk I gave in Belfast last week.

I have put it online here - http://voicesfromtheshadowsfilm.co.uk/2016/presentation-for-belfast-6th-june-2016/

because there are some short video clips.

I very much hope you may have time to read it.

Thank you so much for the work you are doing to help us and for coming over to the UK to tell us about it - and to listen.

'Voices from the Shadows' film at

http://voicesfromtheshadowsfilm.co.uk

[...]

[…]
Subject: ME/CFS research plea

Hello Vicky

I am the Mother to a 48 year daughter who has been disabled for 25 years with ME/CFS.

She saw 22 doctors before she was diagnosed.

She is housebound and lately more bedbound than ever.

It breaks my heart that this illness is so neglected for research and a potential treatment and cure.

How can our supportive groups get more attention placed on this heart breaking disease?

We recently had worldwide protests in 12 cities to bring awareness to this need.

Here is the site used for the rally.

http://millionsmissing.meaction.net/

We contacted our congress men and the CDC.

We know the zika virus is getting all the funding now but surely there could be some economic balance offered to this need.

We also met with Dr Jennifer McQuisten at the CDC.

I have requested that the CDC use my daughter for any housebound ME/CFS study.

Again thank you for your time and advice.

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Subject: LDN and Myalgic Encephalomyelitis

Good Morning,

I am a British UK resident and understand that the USA National Institute of Health grants funds for public research into ME/CFS and that you have put out a Request for Information: Soliciting Input for New Research Strategies for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS). I have personal experience of suffering from severe ME from 2003 to 2012 and although I believe I continue to have the disease, I am able to overcome the dreadful symptoms by taking Low Dose Naltrexone (LDN).
My story is as follows:

During 2003 I succumbed to what I learned over subsequent years to be Myalgic Encephalomyelitis. At the time, I had no idea what I was suffering from and received no help whatsoever from my GP, who diagnosed depression and prescribed anti-depressants, which I took for a very short time; the only other treatment

offered was referral to our local mental health centre for CBT and then, presumably, GET, which I resisted. I was left to cope with the illness on my own, searching for diagnoses and 'cures'. Over the years, I tried several so-called therapies and visited a number of doctors with varying qualifications offering assorted procedures and regimes; none of these routes produced any improvement and consequently I was house-bound for almost nine years, 60% of that period bedridden.

Early in 2009 I heard about LDN (through an article in the Herald Scotland) which intrigued me, but I spent a further three years investigating and deliberating over whether this was the right route for me – or merely 'fools' gold' to which ME sufferers have been historically susceptible. In January 2012 I took the plunge and started the medication; it took a few months to fully take effect, but I have hardly looked back since, although with increasing age (I shall be 75 in October) if I do too much, I occasionally suffer some symptoms, but these are manageable with rest.

Since taking LDN daily my health has improved dramatically. Only a few months after starting LDN I was able to take on a follow-on Hearing Dog, equivalent to the USA Hearing Ear, a process which takes a substantial amount of energy. I now volunteer for the charity as a speaker, am an active member of our local U3A as well as caring for my husband who has been losing his sight over the past two or three years and is now registered severely sight-impaired (blind). I am a grandmother to three children and now able to help with school runs and emergency childcare. I could have done ***none*** of these things without my daily dose of LDN. Once again, I am enjoying my life to the full!
I hope my experiences will be of value to your research.

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Subject: Information regarding ME/CFS

Dear Trans-NIH ME/CFS Working Group,

As an MIT student, I believe in empirical evidence. I love numbers, graphs, predictive models, and the (generally) undeniable truths produced by statistically significant quantities of processed data. When there exists a seemingly infinite number of diseases to treat and an unfortunately finite amount of money and resources that we can spend on research to help those afflicted, it's important that we choose where we spend this money wisely. And perhaps just as important, we must spend this money fairly -- something that the medical community has refused to do for ME/CFS since it was "discovered" due to stigmatization against the afflicted, who many believed were depressed, mentally ill, or even lazy.

I'm sure that by now you've gotten countless emails why ME/CFS deserved more funding. Recent advocates have been demanding an increase from the laughably low amount of $6 million to $250 million (although this still puts it below the "fair funding" amount, based on an estimation of US disability years vs funding). And there arguments are not only convincing, but also factually sound. From the widespread prevalence of ME throughout the United States that keeps individuals out of the workforce, to the small epidemic outbreaks that can devastate afflicted communities, funding research to cure ME/CFS is a sound investment that will not only save lives, but also give back to our economy.

For once, though, I don't want to just talk about numbers and empirical evidence. I can't say anything that the doctors and researchers and advocacy organizations haven't already. What I can talk about, however, is the people that are affected by this disease. I can talk about how what your committee decides, and how

the direction that the NIH takes regarding ME/CFS, can help those who are afflicted by it. The obstacles that we have to face as an ME/CFS community only start with lack of funding. The real core of the issue is that there has been a remarkable lack of compassion for those suffering from it.

I can't blame everyone for not knowing what this disease can do to someone. I didn't know what it could do to someone either. When my brother decided to take the rest of his semester off at Stanford because he was "feeling tired", I assumed that it was because of stress, that it was self-induced, and that he would ultimately take a few month break and then be better. Even when time did nothing to improve his health, I believed the countless doctors that I drove him to see, who all told us that he had a psychiatric illness of one form or another. (Even when one of them diagnosed him with manic depressive disorder, despite the fact that he's the most level-headed human being I've ever met.) I didn't support him like I should have. I didn't understand. How can I blame the NIH, the doctors, and the people that told us that it was all in his head when I even allowed myself to believe it?

The answer is that I don't. I can't blame them for not knowing then. ME/CFS has been an unrecognized disease until very recently. No individual is to blame for not taking initiative with this disease when they didn't even know that it existed. However, now that it has come into the spotlight thanks to the tireless dedication of ME advocates, there are no more excuses for turning our backs on this disease.

I came to understand how serious this disease truly was when I watched my brother turn from a beautiful, optimistic, and incredibly intelligent human being into someone that can barely open his eyes, drinks all of his food, and only leaves the room to be wheelchaired to the car and taken to doctors appointments. I haven't talked to him in over half a year because he is literally to sick to talk. Not everyone has someone in their life as severely affected to open their eyes to what ME/CFS is. But everyone is affected by it. With at least 1,000,000 US citizens that have it, it's almost definite that you, someone in your family, or someone that you know is affected-- and they might not even know it.

Research is the priority to improve these patients lives and one day help them to recover. However, research is not the only solution to implement. We need to support these individuals. We need to stop acting like ME/CFS doesn't exist, and come out with a strong, public stance on fighting this terrible disease. We need to acknowledge our past ignorance, and more importantly declare our intention to support these people in the future.

We need to educate doctors so that they are able to correctly diagnose patients, and we need to educate the public so that they no longer view this disease as the wrongdoing of the patient, but rather for the debilitating ailment that it is.

I don't know whether it's too late for my brother yet, but I know that we can help to improve and save the lives of millions of others across the globe if we resist the inertia that we have on a path of ignorance, and instead step forward, take charge, and tackle this disease from both a medical and societal standpoint.

I look forward to seeing the plan that you put into action, and hope to see the NIH continue make the world a better place, one cured disease at a time.

[...]
[...]

Subject: Notice NOT-NS-16-024 Request for input for ME/CFS research Request for Information -Input for new research strategies for ME/CFS. Notice NOT-NS-16-024

Emerging Needs and Opportunities:

- Investigate energy production systems/mitochondrial dysfunction at the molecular level utilizing metabolomics technology/research.

- Prioritize development of biomarkers and diagnostic tools utilizing epigenomics, metabolomics, genomics, and proteomics strategies.

- Coordinate research with ME/CFS researchers and clinicians regarding existing work for biomarkers discovery and therapeutic interventions.

- Address importance/validity of 2day cardio-pulmonary exercise test (CPET), which objectively measures the metabolic dysfunction and post-exertional malaise/debilitation, which is one of the hallmarks of ME/CFS.

Challenges /Barriers:

Failure to reach consensus on case definition, which also affects research outcomes.

Lack of funding/awareness for this debilitating illness.

Misinformation to public and health care personnel regarding what ME/CFS really is.

Collaboration of NIH with ME/CFS researchers and clinicians.

Thank you for considering my responses. Further research into this illness is imperative due to 17 billion dollars lost in productivity, in addition to all the patients and families suffering from this illness, which is so misunderstood and often dismissed by the medical profession due to misinformation and lack of funding/research. And presently, no cure or therapeutics specific for this illness.

[…]
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Subject: ME/CFS funding- HELP ME AND MILLIONS SUFFERING

[…] I suffered from Chronic Fatigue Syndrome for 6 years of my childhood and am currently home from college on medical leave now due to a bad relapse. I have had to give up so much including school, sports, and time with family because of this illness and I struggle so much day to day with this terrible disease. There are some days that I struggle to even make it out of bed or care for myself. So many people suffer from this disease, yet it remains very misunderstood and lacks so much funding for research to find a cure.

Please help me and the millions suffering from CFS/ME by providing the necessary funds for more research.

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Subject: ME CFS AND LDN

Hi there, I use LDN for my ME CFS, And just read you are after people to pass comments on how they get on with it. If I can help let me know. Thanks

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Subject: Response to request for public input for future direction of ME/CFS research.

Dear NIH:

As a ME/CFS sufferer, I implore you to budget more funds for this life-destroying disease. The number of people with ME/CFS is under-estimated as it often takes many years and many doctors to get a diagnosis. For me it took 9 years and I had to travel over 100 miles after I was repeatedly misdiagnosed and had exhausted all local doctors. Actually, there are approximately 2.5 million people in the US with ME/CFS. That's many more than some other diseases that get well funded from the NIH. MS has about 400,000 people diagnosed and it receives much more funding. Even the CDC acknowledges 1,000,000 patients diagnosed with ME/CFS.

Before we can even begin finding treatments, we need to the develop accepted biomarkers and diagnostic tests. I know that there are challenges and barriers to progress in research on ME/CFS. We know the two major barriers in identifying ME/CFS biomarkers are 1.) variation in how patients are effected in terms of symptoms and disease progression and 2.) the lack of quantitative tools to specifically classify patients and examine the molecular immune underpinnings of the disease. We need to identify gene expression, protein or metabolite signatures to correctly diagnose ME/CFS and distinguish it from other chronic conditions.

Additionally, we need to conduct epidemiological studies, including incidence and prevalence, risk factors, geographical distribution and potential healthcare disparities. Despite differences in presentation of some symptoms, there are many commonalities.

And we need to examine existing drug therapies for fibromyalgia, MS, and other pain related conditions for effectiveness in ME/CFS as well as to incorporate NIH Institutes and Centers not presently represented into the Trans-NIH ME/CFS Working Group to learn from other disciplines and diseases.
We implore you to please pay attention to us.

We are literally dying slowly and painfully, physically, psychologically, and emotionally, all while being ignored. We need to mount an effort equal to that which brought HIV/AIDS under control. Doctors who work in this field (and there are very few) say if they had to choose between having HIV/AIDS or ME/CFS, they would choose HIV/AIDS.

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Subject: Ldn and ME

Yes, I have had a severe case of ME for 29 years with lots of neurological and cNs impairment.

I started on LDN about a year ago, and I have found long standing pain in my body disappear. Love LDN. Great for the fibromyalgia and arthritis in my body too. no help or hindrance to my sleep/insomnia. Buoy for pain, outstanding. waiting to see if my immune system gets stronger over a few years.

I know it was the LDN because I stopped it for about 2 weeks and the pain returned. When I started it up again the pain disappeared within about 2 weeks.

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Subject: Research - ME/CFS

Please please please why don't you add Fibromyalgia (LDN) to your research? Fibromyalgia sufferers are the poor relations of research and thousands suffer misery daily from this insidious, life-sucking 'syndrome'. I have been taking LDN for my Fibromyalgia for four months (I have to buy it privately, because most doctors are uneducated about it and usually won't prescribe it - and 'big pharma' won't undertake research on it because it is not a 'sexy' syndrome, and there is hardly any profit in it for them) - the LDN has given me my life back! In fact almost every Fibro sufferer who struggles hard enough to gain access to LDN sees improvement in their symptoms.
Please do something to help us too!

[…]
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Subject: LDN for ME/CFS

Hi, Its early days in my use of LDN as I have only got up to 2mg in liquid drops as I am very sensitive to medication of any kind. I ordered LDN from a pharmacy in Israel after reading about the use of the drug for CFS and Thyroid antibodies which I have. The difference in my health has improved greatly since using LDN, I have more energy and can think a lot clearer with a lot less headaches. LDN has made my life a lot better.

Keep up the good work with your research because the NHS in the UK is letting a lot of people down.

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[…]
Subject: NOT-NS-16-024;

To: The Trans-National Institutes of Health (NIH) ME/CFS Working Group

Re: Response to Notice NOT-NS-16-024; Request for Information: Soliciting Input for New Research Strategies for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)

Dear Working Group:

The following is my response to NOT-NS-16-024; Request for Information: Soliciting Input for New Research Strategies for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS).

Emerging needs and opportunities that should be considered as new ME/CFS research strategies are developed:

I don't KNOW what needs to be done. I just know that presently, the diagnosis and treatment is sorely lacking and we are ALL losing out on that.

Personally, I am (still using present tense but have been unable to practice for 2 years) a primary care physician assistant who prior to my "syndrome" had climbed Mt. Kilimanjaro, gone to the Base Camp of Amtrak. I did sprint triathlons and obstacle races through the woods and mud. I trekked to Mt. Everest for my 50th birthday, and was on a 100 mile trek in the Alps when I became ill. After that, climbing the stairs would become difficult at times.

Like others, it took awhile to get a correct diagnosis and I was told by at least 3 "specialists" that it was all "psychiatric". Luckily I had a lot of support and love, but last year my husband and I did the POTS (postural orthostatic tachycardia syndrome) walk in Boston for the MIT student who jumped off an airport parking garage because she could no longer live with it.

I currently am in the care of some of the best physicians in the world for these problems, but I HAVE HAD to be the one to drive trying new things to actually IMPROVE instead of just treat the symptoms. I am lucky because of my background and a VERY supportive primary care MD. Because of this, I am more functional, but am not contributing to society like I had as a working PA. I also volunteered for local, State and National Medical Corps and did a medical mission to the Dominican Republic where 3 of us saw 1500 people in a week.

Now, if I am able to make it to a family get together it is a win though I always have to leave early and often end up having to recover in bed the next day. I have built up exercise and ride several days a week (if feeling well), but can no longer ride in the woods because I have had Lyme 2 times in the past 4 months.

Oh ya, it looks like a virus "kicked" all of this off for me wiping out my entire immune system and making it so any testing done to see if I had any infections would come up negative EVEN IF I HAD THEM. I have to insert 4 needles into my abdomen every week and I have a pump that slowly injects 120 cc's of immune globulin (antibodies from about 1000 different people). That's what it took 3 years to finally get someone to treat the virus I had. I kept listing ALL my problems and that ebstein Barr could cause them all AND that my son had had mono 1 month prior to me developing Guillia Barre (the start of my saga which was partial paralysis from waist down and having to drag myself off the Alps for 4 hours then spend 10 days alone not speaking the language while they waited to see if I would need to go on a respirator). My immunologist FINALLY got everyone to understand that I wouldn't show if I EBV or not so I went on an antiviral for 6 months which helped! (All my research and prodding). I also initiated two other novel treatments that are helping and have been embraced by my specialists.

I WANT TO WORK AGAIN.... I WANT TO CLIMB MOUNTAINS AGAIN.... I WANT HOPE...

Thank you for your consideration and your service.

[...]
[...]

Subject: LDN

To whom it may concern,

I have been taking LDN for ME/CFS and it has been helpful in mitigating the debilitating effects of this illness. It allows me to be functional whereas I otherwise could not be. Please consider more research into LDN.

[…]
[…]
Subject: Response to Notice NOT-NS-16-024; Request for Information: Soliciting Input for New Research Strategies for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)

To: The Trans-National Institutes of Health (NIH) ME/CFS Working Group

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Emerging needs and opportunities that should be considered as new ME/CFS research strategies are developed:

Getting the information circulated to the medical field as well as the public. My child has seen several doctors and therapists.

One neurologist dismissed the severity of her current condition and diagnosis of ME/CFS. She went so far as to call it 'simply life-altering' when Make-A-Wish called for her input.

For years leading up to our daughter's diagnosis her symptoms were dismissed by doctors and school individuals.

Thankfully she had one PT therapist who recognized there was something yet to be diagnosed and cautioned us about continuing PT.

Her pediatrician never gave up on her either.

So out of the many, many doctors & therapists she has seen, my daughter has been blessed with 2 good medical professionals.

That doesn't say much when we live in one of the best places for children's medical needs.

She went to Boston Children's and was told "you'll grow out of I" - when she was having trouble getting around the classroom and falling into things.

She saw a top neurologist at MassGeneral who said our daughter's head seemed too big. I will say the Dr. didn't have my daughter's records with her for review either. She blamed us but I knew her staff had received them already - they had asked me specific questions about the files sent.

My story with uneducated doctors goes on but these are just two examples of the ridiculous treatment kids get in 'the best hospitals'.

Educate the medical field and the public. Being dismissed by a doctor is unacceptable.

Thank you for your consideration and your service.

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Subject: re: Your inspiring talk in London on Friday!

Dear Dr Whittemore,

It was a real pleasure to listen to your inspiring Keynote Address in London on Friday. You invited information on ME/CFS research priorities, so I take the liberty of sending my views as a ME/CFS patient of more than 10 years. As I mentioned over lunch, I have attended these conferences for several years. What always strikes me is the dearth of **high quality epidemiological studies on ME/CFS**. I am thinking of studies of the calibre of Prof Walter Willett's nurses studies, and capable of being published in journals such as the New England Journal of Medicine.

I believe that such studies on ME/CFS could give excellent insights into risk factors and into potentially beneficial interventions. As Prof Davis said on Friday, understanding is not prerequisite for effective treatment!

I hope that you find this suggestion useful. Meanwhile best wishes for the National Institute of Neurological Disorders and Stroke and keep up the good work!

[…]
Subject: Additional thoughts for understanding and curing ME/CFS

Other thoughts on ME/CFS:

If my child was in Africa, the course is compatible with western african sleeping sickness.

My understanding is that Dr. John Chia has cured some patients with:
Equilibrant, Inosine, and Epivir.

Please add studying these treatments to the list of treatments to study in curing this horrid life threatening disease.

[…]
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Subject: Request for information answers

To whom it may concern:

· **Emerging needs and opportunities that should be considered as new ME/CFS research strategies are developed**.

The 2016 technology needs to be used on patients with ME. Metabolomics, personalized medicine, microbiome, brain imaging, big data, micro-RNA etc

The technology is here, but what is lacking is funding and dedication.
Other diseases need to be compared, for instance, compare post ebola patient's immune system, neurological symptoms with post viral ME/cfs

· **Challenges or barriers to progress in research on ME/CFS**.

The biggest challenge is bias, stigma and discrimination that patients encounter at all levels of governments, health care and society. From grant reviewers, to biased bad apple in a research group, to british psychiatrist spreading misinformation and publish horrible science in reputable journals. For 30 years now, patients have carried the burden of bias, stigma and discrimination.

Another challenge is case definition. Post exertional relapse needs to be mandatory. A minimum of Canadian consensus criteria needs to be used. The most recent SEID definition should not be used in research.

Another challenge, the sickest patients cannot get to a doctor office or fly across the country for research. By studying the patients who can walk in and travel for a doctor appointment, you may miss important datasets.

No one is experienced at NIH to diagnose a ME patient. There are huge concerns that some in your team may be biased and slanted. NIH must consider the expertise of the few physicians who have strictly seen patients with ME: Dr Klimas, Dr Montoya, dr Peterson, Dr Kogelnik, and the like.

The elephant in the room: the continuing belief that has been passed on to younger generations of researchers that researching ME would be a career suicide.

Another challenge: funding. We need hundreds of millions, not peanuts, to find the exact problem, and to develop therapeutics. And to achieve that, Congress must believe it is worthy enough to fund research. NIH must make ME research a priority

Lastly, this disease doesn't belong to any medical specialty. This causes huge problems in streamlining a disease, and in getting clinical trials which are accessible for all around the country.

· Gaps and opportunities across the research continuum from basic through clinical studies.

The gaps in research are too numerous to write. We need basic research to find biomarkers, mechanism of disease. Clue here would be immunologic, neurology.

Low natural killer cell function is as close to biomarker as possible. RNASE-L abnormalities need to be confirmed. Brain inflammation, microglia activation are interesting leads.

Clinical trials are desperately needed. Ampligen work for some people. RItuximab. Could there be other money clonal antibodies that could be helpful? How about chemo agents like methothrexate or cyclophosphamide? How about Vistide and Valcyte, or even Brincidofovir for those with elevated HHV-6 titers/ CMV titers?

Nobody has researched why patients with ME have sensitivity to epinephrine, in my case i relapse badly if epinephrin is given in local freezing at the dentist.

There needs to be a study on auto-antibodies. Muscarinic and adrenergic receptors antibodies as per the german study, which needs replicating.

So much work needs to be done.

Thank you for reading and request for information. Patients need to be included.

[...]
[...]
Subject: Areas of ME/CFS research that need attention

Gaps and opportunities in ME/CFS research

The biggest gap in research I can see is that people like me, who have been ill with ME/CFS more than 50 years, are being ignored. Much can be learned from us, but other than the 10+ study Fred Friedberg and several of us did 20 years ago, no one is paying attention. It is all very well to start looking at people ill for five years, but it will take another 55 years of following them to learn what could be learned from the history of people like me. We'll be dead and all that info will be lost for half a century. Since no one has helped me much in 59 years of suffering, I don't think anyone ever will. Things are getting too bad.

However, it would be worth it if other people could be prevented from suffering like this by learning from my and other's cases. We were prevented from publishing an important result due to space constraints. However, we found that the 200+ patients ill more than 10 years had a significant change in symptoms as the illness progresses. The illness became more neurological over time. That is being ignored. As an author of the study, I didn't participate in it. But I designed a lot of the questions. The the results we got agreed with my own experience. More neurological and neuromuscular and less fever, etc.

The second serious omission is the lack of a brain bank. I really wish I could donate my brain after death so sometime in the next 100 years someone could learn about the damage this illness does over the decades. Since people don't study us when we are alive, at least they could learn from us after death. But that isn't possible right now. I first became ill after the 1957 flu shortly before my 7th birthday. I had to seek help (but didn't get any) from a neurologist by my 40th birthday because my neurocognitive and neuromuscular problems were getting so bad. Things have only gotten worse in the last 25 years. I'm hardly

alone! Someone needs to pay attention or all of this suffering will be for nothing. All that could be learned from us long-term sufferers will be lost until another 55 years goes by. Please don't let it be the case!

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Subject: Input on ME/CFS research

Dear NIH

Thank you for asking for input on ME/CFS research.
This is a few thoughts.

1) Multiply the biomedical research by a 100 times to find a cure please! We want to be active and useful again! Waited too long.
2) Diastolic dysfunction and reduced cardiac output found by Dr Cheney and others must be looked at. Many ME-patients feel the basic problem is very connected to an inflammation in their heart area.
3) Also.
How reduced is the blood volume?
How does the reduced blood volume and circulation affect different organs?
Do the ME sufferer need a higher concentration of minerals and vitamins in the blood to support the organs?
4) Different sub groups. How is ME changing over time. Risk of relapses. This will clear up a lot of misunderstandings of ME.

[…]
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Subject: RFI: Ampligen research needed

RFI response: Research Needs/Opportunities ME/CFS

NIH should fund and direct a Phase IV clinical trial of Ampligen for the treatment of ME/CFS.

ME/CFS is a severely debilitating, chronic and complex disease. Considered a public health crisis, it is a critical unmet medical need with a severe lack of funding; we recommend a Phase IV study be conducted by the NIH granted under a conditional approval by the FDA and in collaboration with the support of the sponsor. The recommendation fulfills NIH/FDA's goal to speed new treatments to patients announced in 2010*.

o A description of the need or opportunity
Currently there is no approved drug therapies for ME/CFS, however Ampligen provides a most unique opportunity to advance a treatment, further understand the disease and open the regulatory doors for other pharmaceutical companies to pursue drug development. No other therapy has advanced this far in the FDA pipeline. New drug therapies entering the pipeline may take another decade before approval. FDA regulations permit conditional approval of drugs and their collaborative initiative with NIH offers the pathway conduct the study.

o A scientific rationale and potential health impact
Ampligen has completed Phase II and Phase III double blind/placebo controlled studies and has been providing benefit to patients for over 20 years. The FDA advisory committee voted it safe for approval. Drugs with significantly less dosing and with significantly higher adverse events have been approved for use. ME/CFS experts agree that a conditional approval of Ampligen is warranted and could improve the lives of 25-40% of the ME/CFS population.
o Any anticipated challenges that may arise
A concern over wide spread use in the marketplace; recommendation is that a risk mitigation program be established that requires the physician be educated on how to diagnose the disease, treat the disease and properly administer Ampligen; require the patient be educated on the drug and the dispensing pharmacist must check that the doctor and the patient have fulfilled on these requirements prior to releasing the drug.
o Appropriate benchmarks for evaluating progress
ME/CFS experts be included in the conduct of the Phase IV trial and all parties agree upon the measurements and the study must comply with FDA requirements.
* Challenges or barriers to ME/CFS research
Lack of understanding by the health agencies and the healthcare community.
* Gaps and opportunities in research
Funding needed to conduct appropriate level research.
*https://www.nih.gov/news-events/news-releases/nih-fda-announce-collaborative-initiative-fast-track-innovations-public

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Subject**:** RFI response: Research Needs/Opportunities ME/CFS

I have a sister who has suffered from CFS/ME for 28 years. She made some gain in the late nineties with ampligen under Dr Salvato, and again under Dr Peterson in 2002. She would like to try ampligen again. Thanks you for your time and the survey.

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• A description of the need or opportunity Currently there is no approved drug therapies for ME/CFS, however Ampligen provides a most unique opportunity to advance a treatment, further understand the disease and open the regulatory doors for other pharmaceutical companies to pursue drug development. No other therapy has advanced this far in the FDA pipeline. New drug therapies entering the pipeline may take another decade before approval. FDA regulations permit conditional approval of drugs and their collaborative initiative with NIH offers the pathway conduct the study.

• A scientific rationale and potential health impact
Ampligen has completed Phase II and Phase III double blind/placebo controlled studies and has been providing benefit to patients for over 20 years. The FDA advisory committee voted it safe for approval. Drugs with significantly less dosing and with significantly higher adverse events have been approved for use. ME/CFS experts agree that a conditional approval of Ampligen is warranted and could improve the lives of 25-40% of the ME/CFS population.

• Any anticipated challenges that may arise
A concern over wide spread use in the marketplace; recommendation is that a risk mitigation program be established that requires the physician be educated on how to diagnose the disease, treat the disease and properly administer Ampligen; require the patient be educated on the drug and the dispensing pharmacist must check that the doctor and the patient have fulfilled on these requirements prior to releasing the drug.

• Appropriate benchmarks for evaluating progress
ME/CFS experts be included in the conduct of the Phase IV trial and all parties agree upon the measurements and the study must comply with FDA requirements.

• Challenges or barriers to ME/CFS research
Lack of understanding by the health agencies and the healthcare community.

• Gaps and opportunities in research
Funding needed to conduct appropriate level research.

[…]
[…]
Subject: RFI for ME/CFS

Challenges to progress in research:

Funding has been extremely limited despite reputable and experienced researchers requesting funds, Funding is needed for:

1. Basic research in biomarkers, subgroups, metabiome, microbiomes, immunity and treatments
2. Training for medical students and practising doctors.

In addition, accept CFSAC recommendation of one of three (3) Canadian definitions for research. Use fast-track status or conditional approval for Ampligen (phase 4).

WE NEED A SENSE OF URGENCY. I HAVE BEEN SICK FOR 28 YEARS.

[…]
[…]
Subject: Three suggestions regarding ME/CFS research

Hello,
Thank you for requesting input regarding ME/CFS research. I have suffered from a relatively moderate form of ME/CFS for more than five years, and, as an anthropologist, I also have experience performing public-health research. I have read the abstract and, in many cases, the entire text of every research article that I could find on this disease published over the past two years.

I have three comments:

1) Research reports that show the measured values of individual cases should be the default. Averages of key values are interesting, but we need to identify categorical differences rather than ones of degree, and these are hard to discern with summary statistics.

2) More attention should be paid to the timing of symptoms. This must be an avenue to understanding the processes driving the disease. Why does PEM start after a delay and peak after 36-48 hours? This seems like an utterly basic question that affects everyone who has the disease.
PEM for me is a constellation of symptoms. Most of those symptoms can arise almost instantaneously in a situation that's highly stressful emotionally or when I have a particular type of bowel movement. In contrast, they arise daily 45 minutes after breakfast. But one symptom - trouble expanding my lungs - only follows two days after exercise (along with the other symptoms). Why such differences in timing and composition? I think the answer must provide a clue to the mechanisms leading to the symptoms.
3) Recent research at Yale on Ketone BHB as an inherent anti-inflammatory mechanism might provide a path to reducing symptoms (http://www.ncbi.nlm.nih.gov/pubmed/25686106).

"The researchers described how the compound β-hydroxybutyrate (BHB) directly inhibits NLRP3, which is part of a complex set of proteins called the inflammasome. ... BHB is a metabolite produced by the body in response to fasting, high-intensity exercise, caloric restriction, or consumption of the low-carbohydrate ketogenic diet."

The researchers are interested in finding applications for this research: "The goal is to get other scientists interested so that they can also study BHB in specific diseases."

This research caught my eye because of two experiences, one for fasting and the other for intense exercise:

- **Fasting:** My daughter's severe case of mono cleared up instantly when she stopped eating and drinking and had to go to urgent care for dehydration. Once they put fluids back in her, she was completely cured.
- **Extreme exercise:** Ordinarily I would suffer horribly from PEM a couple of days after a lengthy bike ride. However, on an unusually long ride I hit the marathoner's 'wall,' to the point that, shaking and barely able to pedal, I feared collapsing and possibly dying. But I didn't suffer any PEM afterward.

[...]
[...]
Subject: The Irregular Periodicty of MECFS: A seriously ignored confounding issue in present day reseach

https://grants.nih.gov/grants/guide/notice-files/NOT-NS-16-024.html

MECFS is an idiopathic disease of irregular periodic prostration

I was Director of Disease Control of San Francisco in 1984 when I was personally struck with what turned out to be MECFS. From my own personal experience and that of others that I have followed I have found that the irregular periodicity of the disease is one of the most misunderstood and ignored aspects of MECFS and may be the prime reason for our lack of progress in determining the underlying pathophysiology of this disease.

I am referring to the periodic changes that are seen in many patients, from absolute prostration to the complete opposite, the total disappearance of all clinical symptoms. This stage of quiescence may last,

hours, days, months or even years, before the symptoms again reoccur with the full severity that was originally experienced.

I can tell you the time within minutes when I was first struck with this disease. For a long time it seemed as if I had a bad flu. But this flu didn't go away for a number of years and I was eventually diagnosed with MECFS. In the intervening years since my diagnosis, I have been seen by multitudes of medical specialists and have had too many tests all of which were all negative except for some changes in the Killer t cells. But that is it. Even the most skeptical of the medical practitioners I consulted have agreed with the diagnosis.

Over the past 30 years, my illness has waxed and waned and not in a subtle away. It is almost as if there is an on and off switch, and yet I have not been able to correlate it with anything. Exertion plays a role only during the active phase. Then any movement is difficult and leaves me even more fatigued.

The remission phases have been varied in timing but not in character. At times, I seem to be completely better. So much so that for years I thought I was "cured" This quiescent phase can last for days, weeks, months and even years. During these times, I felt as good as I ever did. Even close family, who didn't see me when I was in the attack phase, had difficulty believing that there anything was wrong with me. But then, when the active phase returned, they had no doubt. All they had to do was look at me and they knew I was seriously ill. Often, when I would take trips with people who didn't know me well, I would seem perfectly normal; then, suddenly, it was obvious to them that something had changed and there was something seriously wrong with me.

When I saw clinicians during a remission phase in the early years this was especially problematic since I was almost embarrassed to tell them what was wrong, it seems so far fetched. I was sometimes lumped with those who had a somatization problems at best, and was malingering at worst. However, today it is clear what I have. A physiological disease of unknown cause that comes and goes as it pleases.

I have examined most surveys of MECFS and they don't take this phenomenon fully into consideration. Questions regarding the presence or absence of symptoms (and functionality) often have a checklist that seeks to determine how the patient feels today. Sometimes they ask about the last few days or even the last year, but this is not done in a way that examines the dramatic longitudinal variability of this disease. They assume a constancy that is not present. At best they assume a slight variation but not the extreme total disappearance of clinical symptoms. This may be resulting in data that is at best confusing. and at worst misleading.

The problem is even more serious in studies that are trying to determine the pathophysiology of this illness. While many studies might assume a certain rhythm of the disease process, I am not aware of any that take into account the irregular periodic interplay between the total prostration followed by complete disappearance of symptoms, over and over again.

The sampling of patients in all studies must take into account the phase of the pathophysiology they are experiencing. The lack of attention to this phenomenon is a serious problem with much of the research in MECFS. (I am not aware of any study that seriously examines this issue) The irregular periodic relapsing nature of MECFS has not been taken into full consideration.

I am not certain if this is general characteristic of every long-term patient with MECFS if followed long enough, however, I do know that it is an important characteristic of an at least a large subset of those with this disease and that it needs further attention if we are to ever determine it's basic pathophysiology.

[…]
[…]

NIH Request for Information
Dear Dr. Vicky Whittemore
In regards to

· Emerging needs and opportunities that should be considered as new ME/CFS research strategies are developed.

· Challenges or barriers to progress in research on ME/CFS.

· Gaps and opportunities across the research continuum from basic through clinical studies.

I have the following recommendations to NIH

- The new efforts of the NIH to research ME / CFS or SEID are much appreciated by the patient community. The disease has been neglected for over 20 years and this lack of research funding in the USA and worldwide has had devastating consequences for millions of people. The NIH research funding needs to be expanded in financial terms up to $300 million per year for 5 – 7 years, and in scope to encompass the existing biomarkers and further validation of them and a more intensive development of the structures of causation (plural). The figure of $300 million per year is a reasonable amount when one considers the high number of people with ME and FM (and closely related diseases GWI and Chronic Lyme) of 0.42 to 1 % of the US population, over half of whom are undiagnosed, and the large losses to the American economy, estimated at over $50 billion per year, every year. And the weakening of the American people which has adverse consequences in terms of national security, and the defence of the US nation. Certainly, it would be justifiable to use portions of the US defence budget to research this disease in collaboration with NIH with a view to protecting the health of the nation and it's national security.

  The NIH could better leverage its financial resources and achieve better quality results by funding the OMF in California and other private research bodies listed on www.me-ireland.com/research2.htm which have developed a special expertise in researching ME / CFS. These research bodies have some of the best scientific researchers in the world, including 3 Nobel laureates and globally acclaimed scientists in the fields of virology, immunology, genetics, proteomics, and mitochondria / metabolomics. There would be wider benefits for all neuro immune illnesses, neurological illnesses, and autoimmune illnesses in terms of greater understandings of the dynamics of these related illnesses, including chronic infection and immune system evasion mechanisms by pathogens, and of chronic immune reactions and dysfunctions and tissue and cell destruction and mitochondria abnormalities. The figure of $300 million would be excellent value for money, and would provide a large continuing payback to the US economy, industries, government and people over time. Its important for the NIH to acknowledge that there are some biomarkers for ME / CFS, see www.me-ireland.com/structure.htm#8 and these have been confirmed by scientific research and the clinical experience of medical doctors. These need to be used in scientific research trials by the NIH and others to identify ME / CFS patients, and investigated further down to the genetic and molecular levels and biological network pathways to decipher the exact structures of causation. Focussing on structures of causation emanating from

chronic infections of the brain, nervous system, mitochondria, muscles, glands, veins, heart, joints, organs, b cells, other immune cells and accompanying immune dysfunctions, tissue destruction, and mitochondria abnormalities, will provide the coherent structure for fully understanding ME / CFS. Further refinements and enhancements of diagnostics technologies, including new innovations such as Lipkin's recent one at Columbia University and others such as those in Germany will need to be utilised and deployed within trials, hospitals and clinics to improve time, cost, sensitivity, specificity and accuracy. Some ideas on this are presented on www.me-ireland.com/diag/2.htm and www.me-ireland.com/diag/lyme.htm

I would like to draw your attention to research by the OMF in California which has three Nobel prize laureates and other top scientists involved in research into ME / CFS. Their mitochondria and metabolomic findings point to pathological processes which are systemic and persistent over time. They correspond to and align with similar mitochondria findings in the past, see www.me-ireland.com/scientific.htm#bio . All of these findings appear to back up the Rituximab trials in Norway, the EBV and autoimmune findings of Pender et al. and other scientific findings over several years and decades, see www.me-ireland.com/scientific.htm#bio .These all indicate chronic pathogen(s) infections of the nervous system and brain and the mitochondria primarily and also infections of the muscles, the glands, the veins, the heart, the joints and other organs. In most cases these pathogens are undiagnosed and/or involve reactivated latent infections. In many cases doctors neglect to test for these infections or their health systems lack the technologies to do so. In Britain, doctors are banned from testing for these infections under the NICE guidelines which were written by psychiatrists for the sole benefit of psychiatrists. The inevitable result of this in Britain is more unnecessary patient deaths and much unnecessary suffering. Basically it's illegal profiteering from patient neglect, suffering and deaths.

Rituximab has continued to fascinate the scientific and medical communities worldwide since 2011. Nobody ever asks why Rituximab works in ME / CFS ? destroying populations of B cells achieves what exactly ? and why does the illness return once Rituximab is discontinued and B cell populations grow again ?

Pender et al and Dr. Lerner (RIP) believe that EBV is capable of living inside B cells and instigating autoimmune reactions. And instigating EBV migration to other body parts, eg. nervous system, brain, vagus nerve, spleen, thyroid, liver etc. and causing infection and inflammation there. And that its ability to transform from an active state to a latent state, its various strains, and its ability to hide inside human cells, enables EBV to evade the immune system. And like several other pathogens, EBV can also manipulate cytokine networks to facilitate it's own survival. If EBV can live inside B cells, it should be able to live inside the cells and tissues of organs and joints instigating possible autoimmune reactions. Furthermore, EBV can adversely affect the mitochondria, destroying them and their ability to function. This makes sense, and explains why Rituximab works in ME in the context of reducing infected B cells. The increased energy levels in patients proceeds from the elimination of the pathogen and restoration of mitochondria health. I have explored this and related issues on www.me-ireland.com/right.htm#bcell Other viruses including gamma retroviruses, enteroviruses, herpes, and mycoplasma have been found in subgroups and are capable of hiding in cells, have active and latent forms, and have the ability to evade the immune system and are playing a role in the illness.

While there is an obsession with finding one virus or one pathogen to explain ME, the scientific research findings strongly suggest that several undiagnosed pathogens are involved and I would emphasise undiagnosed in the context doctors are health system are (i) ignorant of ME / CFS and

thus refuse to carry out appropriate tests (ii) lack the technology to carry accurate, sensitive, specific, and effective diagnostic tests. Undiagnosed bacteria and virus infections over many years can inflict severe damage on body systems, and significant illness and debility. Some research listings below point to pathogens as being important in the illness.

www.me-ireland.com/scientific/6.htm
http://www.me-ireland.com/scientific/8.htm

The findings and beliefs of the early pioneers in ME / CFS research and treatment such as Dr. Ramsay, Dr. Acheson, Dr. Richardson, Dr. Sigardssun, Dr. Dowsett, Dr. Shelokov will be proven true in the sense that chronic (undiagnosed) pathogens and accompanying immune dysfunctions are playing a central role in the illness, though differentiated slightly by the existence of subgroups.

As regards effective treatments which can be deployed immediately to save lives, we need some perspective on this matter. ME / CFS has the hallmarks of a plague, and shares many characteristics with plagues in the past, though it kills at a slower rate. ME / CFS has been compared to AIDS by Dr. Nancy Klimas and others in the field and they are correct in this assertion. This further confirms the role of pathogens in ME / CFS. The perspective, we will analyse is The Spanish Influenza of 1918 – 1921 which was the worst plague to afflict humanity. Medical doctors and medicine was completely powerless against the virus. Doctors died, professors (of medicine) died, nurses died, scientists died, and many highly educated and knowledgeable people died from this virus. Yet a few doctors in a certain region of the USA confirmed that a herb called 'Lomatium' used by the American Indians completely cured Spanish Influenza. It saved the lives of many Indians and a few (open minded) white people who took large amounts of the cooked herb over a period of weeks. This greatly surprised doctors and scientists at the time. The patients didn't have time to wait years and decades for 'research' to deliver a cure. This a very important point, dying patients do not have time to wait. When patients are dying it is important to deploy high quality knowledge based solutions, whether they are orthodox or unorthodox or have been used successfully for hundreds / thousands of years. Observing this particular herb lomatium in the modern context, one sees that it possesses dozens of anti viral chemicals, and it is in effect a medicine, so it should not have been surprising to see that it worked during the Spanish Influenza. Though it was and still is not called a "medicine". One should not automatically presume ignorance on the part of native cultures or the natural kingdom which possesses vast amounts of medicinal plant chemicals.

And the use of psychiatrists would have been as useless during the Spanish Influenza as it is today for dealing with plagues. Psychiatry has always been useless, ineffective and wasteful of time, money and resources during the plagues of the 20th century and other plagues going back to the 'Black Death' of the 14th century. (Though some determined psychiatrists will always try to defraud their way to alleged 'cures')

The lesson for science and medicine here is an important one, which needs to be learned, namely that many herbs contain hundreds of anti viral and anti bacteria chemicals which when combined together are more potent than current medicines. They attack different areas, receptors, membranes and pathways of viruses and bacteria. These plant defence mechanisms have evolved over millions of years of plants successfully fighting viruses and bacteria. It is impossible for pathogens to become resistant to hundreds or thousands of plant chemicals at the same time. Combining herbs increases the total number of beneficial plant chemicals. Some medical drugs have been developed from plants, though they usually rely on one or two plant chemicals, which leave them susceptible to resistance by germs. It would be far better to use hundreds of plant chemicals

to destroy pathogens and eliminate all possibility of germ resistance. This has become very important in the age of antibiotic resistance and anti viral resistance by germs, and this is discussed in the context of natural solutions on www.me-ireland.com

How to proceed ?

(i) The NIH could better leverage its financial resources and achieve better quality results by funding the OMF in California and other private research bodies listed on www.me-ireland.com/research2.htm which have developed a special expertise in researching ME / CFS. These research bodies have some of the best scientific researchers in the world, including 3 Nobel laureates and globally acclaimed scientists in the fields of virology, immunology, genetics, proteomics, and mitochondria / metabolomics. For example, the NIH could give a $10 million annual grant to the OMF over 5 years, totalling $50 million would provide the means to conduct large trials using severely ill patients and provide fresh new nights into the biomarkers and structures of causation, and the development of more effective medicines and innovative medical technologies. Distributing millions of dollars of NIH funds to Rituximab trials in Norway, Britain and the USA and to ongoing immune, mitochondria and pathogen research in Australia, USA, Japan, Britain and other countries would corroborate these findings and deepen the existing knowledge, adding to existing treatments to attain highly accurate, precise, subgrouped treatments.

(ii) draw in other top researchers into the field. This will involve the NIH canvassing for researchers in American Universities and private research bodies, research networks and collaborations between academica and the private sector, the defence industry and pharmaceutical companies. Offers of grants for research, new opportunities for existing and new scientific researchers to build a national and international reputation, offering for graduate, PHd and post doctoral students and other incentives could be offered by the NIH.

(iii) The issue of what can be done today, this week and in the immediate future to save the lives of sick and dying patients is top priority and of first importance. Saving lives lies at the very core of medicine and doctor's lives. Let us all proceed immediately with what we know about ME and CFS and make use of the biomarkers immediately, a good diagnostic checklist and treatment checklist is available at www.me-ireland.com/structure.htm#8 . This provides an ordered and structured means to treat patients. The use of certain medicines and of specific herbs with specific anti viral, anti bacteria and anti parasite actions, and which have been used by native cultures for hundreds or thousands of years is also recommended as an addition to standard medicine and also in cases where standard medicine has no solutions at present. Continuous scientific research findings could feed into this process to inform and constantly update the treatments given to ME and CFS patients. In terms of diagnostics and treatments action is required now today, this week, the immediate future, as waiting around for several more years and decades for research to possibly deliver is not an option when patients are dying.

These recommendations can also be viewed online at www.me-ireland.com/nih-research.htm.

[...]
[...]
Subject: LDN

I am submitting information about my experience with LDN as prescribed for ME. I first tried LDN as prescribed by my then neurologist who had diagnosed me with MS in 2010. It reduced muscle and nerve pain. When the neurologist changed his mind and said I didn't have MS, he wasn't sure what I had, he stopped the LDN.

Last year, after receiving the diagnosis of ME, my PCP prescribed LDN, 50 mg, but I was to take only half, 25 mg, one per day.. Again, it was helpful with muscle and nerve pain, which has over the course of this illness, which has progressed, and pain intensified. I took the 25 mg dose until about a month ago when I found, soon after taking the pill, I experienced severe stomach pains. I had been having some abdominal distress for a few weeks, prior to this happening. I tried the same dose 3 times, with the same results, except each time the stomach pains increased, lasting for up to three hours. Of course, I then stopped taking LDN.

I have an appointment with my PCP this month and am going to request the tiny doses, 0.5 mg - 4.5 mg. I do understand that it may take trying different doses to see what works. I do want to give LDN anther try as I found it helpful in the past. Nothing else reduced the pain and was without side effects for me.

[…]
[…]
Subject: ME/CFS

Thank you for seeking further information about ME/CFS. We have waited a long time for this!

I've had ME since around 1987 and for the most part I am housebound with occasional times outside for a few hours which I often pay for with relapses of symptoms a day or so later. Not a fun way to live….

When I first became ill, I had been very healthy for many years. I kept a vegetarian diet, did yoga and meditation daily and all was well with my world, until it wasn't and I could hardly do any of that anymore.

The things that have helped me the most are pacing, seeing Dr Derek Enlander in New York City who was the first doctor I met who really knew what ME/CFS was all about. (he has much experience treating ME and would be a good resource for NIH). After an extensive physical, including a cardiac ultrasound, and other tests along with many, many, lab tests he recommended weekly Hepapressin combination injections which he developed and which are still helping me many years later. Later I added LDN Low Dose Naltrexone and I take many supplements, eat organic food and exercise when I can. I also find that my autonomic nervous system is effected and I have POTS and Endocrine symptoms (low thyroid and adrenal cortisol)

My regular GP says he "doesn't believe in ME/CFS" which may be fine for him, but I have been sick with it for over thirty years and I believe in it!

Ideally we would know what causes ME and drop the CFS altogether. ME is definitely a neurological problem which I experience as inflammation in my spine and brain, along with swelling of lymph nodes especially along my throat and jaw, vertigo, nausea and terrible fatigue that makes everything, and I mean everything, an effort.

To me, there has been a lot of research done and a lot of bio-markers discovered over the years yet to this day we hear there aren't any. It seems to me that the whole knowledge base about ME goes round and round and ends up nowhere as if something or someone blocks any forward progress again and again. Reminds me of a dog chasing it's own tail.

Needless to say, for those of us whose lives are drastically effected by ME this lack of understanding and progress is devastating. Still we live and so we hope. Once again we hope but it gets harder and harder the longer we live without help.

Please hear our cries and help us while we still have life to live. Many have died and more are getting sick, please do whatever is needed to determine causation and treatment for the millions of us, including children, who are waiting so long.

[…]
[…]
Subject: more immediate concern?

Hello,

I do appreciate the opportunity to express my observations about ME and CFS research. While filling out a survey that identified a grand canyon of issues, I wondered HOW the NIH might begin to prioritize the work ahead. Where can you find millions of dollars?

Perhaps the suggestion to create a new institute for complex neuro immune illness is a possibility, but I have concerns about how NEUROIMMUNE is defined.

Years ago, the CDC, in one of the 5 year plans, wrote that early onset of diseases the elderly is and area of CFS study. I am 66. I have been ill since 1980. I am among the large population of patients whose onset was decades ago. We lose someone each month and that is only among my circle of patients. This is part of natural progression.

Autopsy protocol. At what point is an autopsy protocol developed? Who does this? When my son died, I frantically emailed Dr. Reeves at the CDC where a biobank WAS to be set up, but it was not and he had no ideas about an autopsy protocol. Since 2005, people have contacted me about "donating their body to science".

It doesn't work that way. I understand the immense cost of autopsy procedures. […] tissue blocks are stored at the Neuroimmune Institute at the University of Nevada - Reno campus. His was sudden death so an autopsy was performed, but the pathologist had no interest in ME and CFS, despite's finding of the viral myocarditis with fibrosis. I wanted to know if he could ID the virus, but now I understand why he could not. I do think he could have held onto the 5 heart blocks. They were lost.

Do you understand that we feel our lives will be cut short and if able to donate blood, tissue, some part of our body, we have contributed SOMETHING when years ill have taken so much from us and we had little to give?

[…]
[…]
Subject: LDN grants for research

I have been taking LDN since 2005, since when I have had no further attacks of Multiple Sclerosis. I did a rough study on myself just during the month prior to starting LDN and once on it. I created a simple scale that to note daily my symptoms: fatigue, bladder control, stability, falls, cramps, etc. I noted 1-5 daily for a month with 5 being a really good score. Once on the LDN I continued the same notations but expanded my scale to 10 with 10 being "as prior to MS". The results were terrific without my overall average was between 3-4 and once on the LDN 6-7.

There is little scientific about my little study, but it can point to the need to fund quality scientific research. This drug has given me much better control of my life.

[…]
[…]
Subject: ME/CFS and LDN

"Request for Information: Soliciting Input for New Research Strategies for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)"

I have chronic fatigue as a consequence of other illness including hypothyroidism and gluten ataxia. The most helpful drug that I have found is Naltrexone at low dose - usually between 0.5 and 1.0 ml per day. This is very effective in making me feel more energetic.

I would be happy to tell you more of my experience as a patient if you wish to contact me, or to use this information in any way, apart from using my full name.

[…]
[…]
Subject: The successful use of LDN alone for CFS

Dear NIH ME/CFS Working Group:

[…]

I have devoted the past fifteen years to trying to get the attention of both the medical field and the general public about a crucial discovery by a brilliant friend of mine, who was also a medical specialist. Along with my son, we have posted a website that gives all of the details about it; please see: **www.ldninfo.org**.

In the 1980s, my friend Bernard Bihari, MD (now deceased; Harvard Med, NIH, Columbia U.) discovered that just one-tenth dose or less of the FDA-approved oral medication naltrexone (FDA-approved at 50 mg daily for heroin addiction) had the remarkably beneficial effect of normalizing any weak or dysfunctional immune system, with no significant side effects and with no toxicity.

LDN's mechanism relates to the small dosage (3mg to 4.5mg qhs) of naltrexone used; thus blocking one's narcotic receptors for just a few hours. Those receptors, importantly, are also one's endorphin receptors. The blockade induces a doubling or tripling of one's endorphin production; and the endorphins apparently

are the major normalizers/upregulators of one's immune system. Although the blockade from the low dosage ends after just a few hours, the increased level of endorphins lasts all day long. Once normalized, the immune system will not attack "self"!

In Bihari's long private practice, low dose naltrexone (LDN) demonstrated its ability to halt any further progression not only of HIV infections but also of *any* autoimmune disorders (including fibromyalgia and ME/CFS). In addition, about 50% of patients with advanced cancers demonstrated a halt in further disease. In later years, a neurologist discovered that families who utilized LDN for children with autism spectrum disorder were delighted to see real improvements in about 75% of the children. In addition, LDN can halt the progression of Parkinson disease and of ALS or PLS.

Because the original naltrexone has been off-patent for many years and is produced as a very inexpensive generic drug by several companies, nobody can get a financial return on the expenditures needed to obtain FDA approval for LDN's special uses. **Therefore, without the potential for profits, no pharmaceutical company has shown any interest in pursuing LDN.** Certainly, neither my family nor I have any financial interest in LDN.

However, the fact is that LDN is an excellent therapy for dealing with ME/CFS or, indeed, with any autoimmune disease. On my website, one can read the abstracts of various clinical trials of LDN, which were all done at outstanding medical centers. The largest , at Penn State, was a Phase II trial for Crohn's disease, which showed excellent results. All of the research studies are invariably positive, showing LDN to be both safe and effective [on the website's homepage, just click on *Research Trials of LDN*].

Of interest, by going to http://bit.ly/1CwDELn, you can both see and hear about the results of LDN on ME/CFS from a woman who had been very seriously debilitated. She stood and spoke at our April 2006 Low Dose Naltrexone Conference in Bethesda, Maryland, and she was strong enough to run the conference herself! I am hoping you will pursue the use of LDN for CFS. Because of Big Pharma's inattention and it's singularly greedy focus on profits only, this very important medication has remained out of the hands of countless patients for whom it would be life-changing.

LDN is quite rewarding to use. Among my entire immediate family and many friends and myself, both young and old, all of whom have been using LDN preventively for many years, our average annual number of URI's has declined by some 85%!

Please feel free to call me with any questions about LDN.

Please see Attachment: An online dialog from Feb. 2016 that contains many personal reports re: use of LDN for CFS.

Health Rising
HOME

About ME/CFS

The NIH Clinical Center Study for Chronic Fatigue Syndrome (ME/CFS): the Good, the Bad and the Just Plain Weird
The NIH Clinical Center Study for Chronic Fatigue Syndrome (ME/CFS): the Good, the Bad and the Just Plain Weird
Poll: Should ME/CFS Research Studies Include People with ME/CFS and Depression?

Low Dose Naltrexone Drug Combination Proposed for Chronic Fatigue Syndrome (ME/CFS)

by Cort Johnson | Feb 4, 2016
| Homepage
95 comments (*beginning a few pages down*)
Low Dose Naltrexone Drug Combinatio*n Proposed for Chronic Fatigue Syndrome (ME/CFS)*
+100%-
*In 2011 the CFIDS Association (now the Solve ME/CFS Ini*tiative) engaged a "drug repositioning" company called Biovista to search through thousands *of drugs to find a new approach to ME/CFS.*
(Clarification: I got the $250,000 number cited in the email blast and Facebook post regarding Laura Hillenbrand's donation for this study from a Wall Street Journal article. It turns out the article was inaccurate; the CAA didn't spend nearly that much money on this study.)
search for drugs for ME/CFS
Biovista threw information on ME/CFS into its huge database to look for new drug possibilities for the *disease.*
Biovista's algorithm identified "every known gene, pathway, disease, anatomical location, cell structure and other component of potential drugs, including why and how they succeeded or failed, as well as potential side effects and drug/drug interactions". They threw that with every bit of information on ME/CFS symptoms, pathophysiology and treatment into one pot.
Biovista's searches had previously identified two possible new drugs for progressive multiple sclerosis as well as drugs for brain cancer, thyroid cancer and melanoma. In 2012 the firm boasted a 70 percent success rate in finding drugs that turned out to be efficacious in diseases.
It was exciting stuff and a good gamble.
Surely as Biovista ploughed through thousands of drugs something interesting would pop up. The list, after all, of drugs that had been repurposed for radically different uses was impressive. Antidepressants were helping with pain, Viagra – originally produced to reduce hypertension – was producing uplifting results in men, and thalidomide which caused horrible birth defects was helping people with multiple myeloma bone cancer.
In 2012 the Solve ME/CFS Initiative announced that a new drug combination had been found, and that Biovista would attempt to find partners to finance drug trials. Three years later, (no drug trials in sight) and the Solve ME/CFS Initiative's contractual obligations of secrecy over, the SMCI announced the results.
Biovista's Drug Combo for Chronic Fatigue Syndrome (ME/CFS)

Biovista stated its platform enabled it to find "non-obvious correlations between drugs, molecular targets, pathways, adverse events and diseases." Unfortunately the two drugs it came up with – low dose naltrexone and trazodone – ended up looking pretty obvious. That wasn't necessarily the case in 2011, however, when Biovista's search started.
Only one small study on low dose naltrexone in FM had been done by then and LDN was probably not used much in ME/CFS. Trazodone was probably used more but only one study – involving a mouse model of ME/CFS – had been done on it.
Join Health Rising's ME/CFS, FM and Chronic Pain Forums!
ForumsShare your pain, make friends, find new treatment options, check out recovery stories and more in the Health Rising ME/CFS, FM and Chronic Pain Forums here
questioning woman
LDN and trazodone – not quite the result we'd hoped for.
Still, Biovista didn't provide the out of box drug combination that made us think of ME/CFS in new ways.
Nor did we get a drug trial.

The result was a not a total loss, though. For one thing it focused on low dose naltrexone, a much understudied drug with a lot of promise but not a lot of funding. (This finding is good for LDN.) Plus, both drugs may be targeting a part of the body that could, if the research underway is successful, become very prominent in this disease over the next couple of years.

Low Dose Naltrexone – Glial Cell Inhibitor #1

Naltrexone is an opioid receptor antagonist that's used in opioid withdrawal. Besides blocking opioid receptors it has the nice side-effect of increasing levels of the feel-good chemical endorphin.
The low dose form of naltrexone (LDN), on the other hand, is believed to reduce inflammation by blocking TLR4 receptors on the microglia. It's important to note that LDN has been proposed to be useful in many diseases but most reports are anecdotal and few studies have been done. Much remains to be learned about this intriguing compound.

Low Dose Naltrexone (LDN) Fibromyalgia and Chronic Fatigue Syndrome Resource Center
The fact that LDN popped out of Biovista's search suggests, however, that Jarred Younger may be on the right track with his focus on microglial inhibitors for ME/CFS. (Younger is currently testing dozens of potential microglial inhibitors, including LDN, in his University of Alabama at Birmingham lab . Go here you're interested in participating in a study.)

Trazodone – Glial Cell Inhibitor #2

Trazodone is not your average antidepressant. Structurally very different from other antidepressants, this triazolopyridine derivative has complex effects on serotonin not seen in other antidepressants. It also reduces sympathetic nervous system activity and has some anti-histamine effects.
Sleep Aid

trazodone ME/CFS
Trazodone – not your average antidepressant – can be useful in low doses with sleep.
Trazodone is probably also used more as a sleep aid than as an antidepressant in chronic fatigue syndrome. (As with LDN, lower doses than usual are used to improve sleep.) It's one of the few drugs (Zyrem is another) able to reduce the activity of the alpha waves known to hamper sleep in fibromyalgia.
Learn more about Trazodone and ME/CFS and FM
A 2011 open-label FM study found that Trazodone significantly improved sleep quality, duration and efficiency. The authors called the increase in sleep quality 'striking'. Another 2011 fibromyalgia trial study found that Trazodone in combination with Lyrica (pregbalin) improved pain, anxiety and morning stiffness.
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The IACFS/ME Treatment Primer reported that Trazodone might be able to maintain its effects over time better than any other sleep drug. Dr. Bell and Dr. Lapp both promoted Trazodone use, with Dr. Bell stated Trazodone was one his favorite sleep medications for sleep.
Neuroinflammation Reducer

A 2015 study suggested that Trazodone may be producing its effects in depression by reducing neuroinflammation. Neuroinflammation is common not just in neurodegenerative diseases like Parkinson's, Alzheimer's and multiple sclerosis but in depression as well.
In a mouse study Trazodone upregulated levels of BDNF – a brain growth factor. . BDNF appears to play a critical role in pain sensitization and neuroplasticity. BDNF levels appear to be high in FM but low in ME/CFS.

Trazodone prevented glial cells called astrocytes from spewing out pro-inflammatory cytokines when confronted with an inflammatory stressor. If Younger and Miller are right about microglial cells over-reacting to small amount of inflammation, a drug like Trazodone could be beneficial.
Breaking the BDNF Blues: Dr. Courtney Craig D.C. on Natural Ways to Raise BDNF Levels in Chronic Fatigue Syndrome
Trazodone also appears to effect astrocyte metabolism as well. The glia cells in the brains of mice respond to inflammatory triggers by pumping out lactate – a substance found elevated in the brains of ME/CFS patients. When given 72 hours prior to an inflammatory insult Trazodone enhanced lactate release. (Lactate may be produced in response to stress/pathogens but the substance itself is believed to have neuroprotective effects.)
One of drug repurposing's lessons is the different effects drugs can have in the body. Antidepressants are just antidepressants anymore. The same drugs that relieve depression can relieve pain in people who are not depressed.
Nor is depression a purely psychological disorder either. A significant subset of people with depression are believed to have inflammation driven depression. Given the possible immune involvement in ME/CFS and FM, it's possible that much of the depression is, in fact, immune based. If that's true then perhaps two treatments targeting the microglial could be effective both in depressed and non-depressed ME/CFS patients.
Unfortunately we don't know why Biovista's results plucked out these two possible glial cell inhibiting treatment. (Biovista did not return queries.) They may synergize in ways we can't imagine.
Conclusion

These kinds of exploratory studies are always risky. In this case the results did not fulfill the promise of the study. Even the President of the Solve ME/CFS Initiative, Carol Head, called the results of the Biovista experiment underwhelming.
(The Biovista study was also supposed to help identify biomarkers. If it did that information has not been released.)
LDN trazodone drug combination
If neuroinflammation is found in ME/CFS the two drug combination might be an option for a treatment trial
The study wasn't entirely unsuccessful, though. The results teamed together two drugs that may target a hot topic in ME/CFS – glia cells in the central nervous system.
Although Biovista failed to get a clinical trial going, if imaging studies over the next year or two find evidence of neuroinflammation we may have a drug combo backed by solid evidence that the NIH could use to get a study underway. A successful LDN/trazodone study demonstrating improvement which was correlated with reductions in neuroinflammation wouldn't be the answer to ME/CFS, but it could be a good first step.

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95 Comments

[…] on February 4, 2016 at 1:22 pm
LDN at 4.5 has made the pain change from an 8 to a 2, dome days a 1 for my teenage daughter diagnosed with CFS
Reply

[…] on February 4, 2016 at 1:38 pm
I have been taking a low dose of naltrexone for about three months now. It does seem to reduce the frequency of pain, for which I am thankful. On the other hand, unpleasant dreams and night sweats are a

side effect for me. I stopped taking it for a couple of weeks to check out this correlation and it is empirically true.
Reply

[…] on February 4, 2016 at 2:53 pm
For those of you on LDN, who, please is prescribing this for you?
The CFS specialists I have contacted do not prescribe it.
Specific clinicians, specialities and names would be helpful.
Thank you, each.
Reply

[…] on February 4, 2016 at 3:12 pm
Hi […], I got a prescription for LDN from my CFS doctor. He didn't suggest it, because he thought it was just for FM, but he wrote the prescription. He is Dr. Barry Elson at Northampton Wellness Associates in Northampton, MA. He's not perfect, but he is very nice and knows a lot about CFS and FM and has been treating these chronic illnesses for decades. He does a lot of testing and treating, but I have to prompt him to keep trying things for me.

[…] on February 4, 2016 at 3:16 pm
[…], the other thing about Dr. Elson is that he practices integrative medicine, meaning he does a lot with nutritional supplements, with less emphasis on drugs though he prescribes those, too. And he has an IV department. People come to his clinic from all over New England to get IV treatments for various things.

[…] on February 4, 2016 at 3:56 pm
I have been taking LDN for a couple years now. I am using it to control my autoimmune diseases which it is doing quite well. It isn't curing my CFS or FM but my quality of life is much better.
There are some things CFS patients need to know aobut LDN. AS it moves the upregulated TH2 immune system pathway back towards a more balanced state between TH1 and TH2, if you have candida it can become much worse and can even interfer with the LDN. You need to be ready to treat for candida when that happens or better yet, treat candida before or when you start LDN. If LDN was working and then it stops, first look at possible candida infection as the cause. Also the sleep issues in CFS can become even more of a problem with LDN. There is an LDN group on Yahoo that offers alot of really good information as well as some too generalized or bad information so be careful. Using LDN on CFS or Fibro patients requires more knowledge. My PCP has learned to start these patients at much lower doses of LDN and increase the dose more slowly. In my experience, the Yahoo LDN group as a whole doesnt have the right knowledge to advise CFS/FM patients about LDN and some of members blame the patients when they have problems with LDN. But the goup can offer a list of treating physicians and a list of pharmacies to compound the LDN or where to get it without a script. And they offer information and a perspective that I hadn't found elsewhere. I have used information from the group to educate my doctors on LDN. On thir advise, I finally started taking LDN in the morning to correct sleep problems compounded by LDN. I was surprised but morning dosing is working for me.
A side note, I wonder if this company was going to a combo approach because while LDN is off patent, a combo could be patented.
To find local doctors using LDN, you can try calling your local compounding pharmacy to ask if they make LDN and if yes, what doctors are prescribing it.

[…] on February 4, 2016 at 4:33 pm
I order mine online from a pharmacy based in Israel that also donates to LDN research.

I have a rheumatologist who gave me an rx for it, but my sister and a friend with RA have doctors who refuse. ldnscience.org has the info.

[…] on February 4, 2016 at 5:18 pm
Any doctor can prescribe LDN. Start with only a tiny amount!

[…] on February 4, 2016 at 6:49 pm
[…] I have been seeing Dr. Irma Rey In Kendall Florida since 2011 at Nova Southeastern University,Institute for Neuro-Immune Medicine. She is an awesome doctor. She started me on LDN 1mg. going up slowly per 1/2 a mg. and I am currently at 3.4 mg. She also has me taking a anti-depressant, Remron or generic is Mirtazapine also low dose 7 mg. at night as a sleep aid.[…]

Cort Johnson on February 4, 2016 at 7:07 pm
I believe LDN Research Trust has a list of physicians who will prescribe. Also check out the resource page on Health Rising mentioned in the blog. Lots of stuff on there.

[…] on February 4, 2016 at 7:43 pm
Start here http://www.ldnresearchtrust.org/LDN_Prescribing_Doctors-OLD
If you can't find a doctor in your area to prescribe this is an option, albeit an expensive on for a lot of people. https://ldndoctor.com

[…] on February 4, 2016 at 11:23 pm
I have been taking 4.5mg Naltrexone at night before bed for about three years now. I am treated through Holtorf Medical Group in Torrance, CA. The physician I see there presently is Dr. Wayne Wightman, however all the docs there treat CFS and FM patients. I live in South Dakota, and was very surprised that my health insurance actually covers the full cost of the drug!

Cort Johnson on February 5, 2016 at 12:03 am
I'm astonished as well. How the heck did that happen? :)

[…] on February 6, 2016 at 1:33 am
Ihave been on LDN 4 mg first year now 8 mg oo. My Rheumatology (FM) doc manages for me. Stops the painful inflammational deep pain Of al four extremities from top to end of phalangies. Still have joint pain osteo and brainy fog and Dysautonomia. Having k née surgery Feb 15 . Home this makes a big fifference

[…] on February 8, 2016 at 4:05 am
[…] –
Skip's Pharmacy is a compounding pharmacist. You can order on line & they will ship to you. Skip is highly educated with LDN and they DO return phone calls! He is highly recommended in the LDN community and I highly recommend him as well. You get a script from your doctor, mail, fax or upload the script & email it to them. They will get back to you and get your script off to you. Prices are great, if I recall it was about $25 per month. Here is the contact info…
21000 Boca Rio Rd
Suite A-29
Boca Raton, Florida
33433
561-218-0111
800-553-7429
Fax: 561-218-8873

[…] on February 8, 2016 at 4:08 am
Also, they have a FB page and their website is, http://www.skipspharmacy.com/

[…] on February 4, 2016 at 8:50 pm
Take it in the morning.
Reply

[…] on February 4, 2016 at 1:43 pm
Does trazodone have a withdrawal syndrome?
What low dose have people found most effective?
Reply

[…] on February 4, 2016 at 2:11 pm
I started at 50 mg and went up to 100mg, which I've taken for years, maybe 15. I believe the antidepressant dose is 3-400 mg. I've gone off if trazadone several times over the years with no noticeable withdrawal symptoms, other than more problems sleeping.
Reply

[…] on February 4, 2016 at 3:48 pm
[…] – I have been taking trazadone for about 10 years. I take 150 mg at night. I used to take it every night because the fear of not sleeping was so great but now I have gotten in the habit of not taking it if I am adequately tired/sleepy. i have no withdrawal effects (unlike Nortriptyline, which I take for Fibromyalgia, which leaves me feeling like I was kicked in the head by a mule if I skip one night) and sometimes I go a month without taking any. I was in Dr. Younger's study on low dose naltrexone and I KNEW the second day that I was receiving the drug not placebo. It was the first weekend that I had gotten up off the couch in years. I had to stop taking it when I had surgery and I was really hurting during that time.
Reply

[…] on February 4, 2016 at 1:43 pm
So what kind of "study" was done? Did they actually combine the drugs in some sort of way and give them in a trial such as the Ritalin + Immune Stimulant trial done by Bateman etc?
Reply

Cort Johnson on February 4, 2016 at 3:21 pm
No study – It was big data mining project using computer algorhithms to come up with what appeared to be the best match. I imagine that Biovista came up with a bunch of candidates and they thought this was the best one.
Reply

[…] on February 4, 2016 at 1:55 pm
LDN made me so nauseous. I really wish it worked for me but I had to stop. I even started on a very low dose. I hope it can help some people.
Reply

[…] on February 4, 2016 at 2:45 pm
Not that most people with CFS are drinking but make sure you are not consuming alcohol in any form as there have been reports in patient forums of vomiting in some people when the two are combined. You

might also try a different compounding pharmacy as different ones can use different fillers and/or try a lower dose to start (as little as 0.5mg for ME/CFS patients).
Reply

[…] on February 5, 2016 at 7:46 pm
I too had stomach problems but I knew the ldn was working so I asked my naturopath if I could have it made in gelatin sublingual form called a troche. It worked like a charm and I am delighted with the results.
Reply

[…] on February 4, 2016 at 2:01 pm
I have tried LDN myself (@3.5 mg doses and 5mg dosages). There does seem to be an awesome effect with either dose for my various "pains". However, I (have, and will continually) propose to concentrate all efforts on ridding the body of latest residing pathogens: Lyme bacteria and all Herpes viruses!!! Then let's talk on fixing other things…
Reply

[…] on February 4, 2016 at 2:43 pm
For […] can you please comment on your efforts to rid the body of Lyme, Bartonella possibly, and Herpes viruses? what treatment are you using? is it helping? do you think that this is the main cause of all of the symptoms of ME/CFS. I was biten by a tick 2 years ago and my health has never been the same. neurological symptoms and cardio muscle weakness. sleep disturbance, etc I often wonder what is really wrong with my health and what treatment I should be pursuing. Thanks
Reply

[…] on February 4, 2016 at 6:08 pm
LDN is believed to have anti-viral properties. Celebrex, too.
Reply

[…] on February 4, 2016 at 2:36 pm
From my own research & experience, I discovered that apparently LDN can't work as well as it should if the patient has any underlying undiagnosed or untreated, infections (ie. viral, bacterial, fungal, parasitic, whatever). I tried LDN a few years ago having been prescribed 4.5 mg has (at bedtime). For about 3-4 months, I felt like a whole new person & had my lofe back but sadly after awhile, it failed to help anymore at all & I found myself back at square one in pain, no energy & unable to sleep:-(I've never tried Trazasone but recently have found Nabilone (synthetic THC) @ 1 mg taken between 5-6 pm is helping to reduce my overall daily pain as it's helping me to finally get some decent sleep. My pain level, as it is for many similarly afflicted, is always higher when I don't sleep.
Reply

[…] on February 4, 2016 at 7:24 pm
[…] I have had the same experience with LDN. The first five months of taking LDN I felt like a teenager – a lot of energy, no pain and no brain fog but then no energy and poor stamina returned to the same low level I had before LDN.
Like you I'm still taking it if I stopped I believe I would be back in bed most of the time. I sure would like to know why it stopped working.
I take trazodone 50mg for sleep and it has been a life saver I get a solid 8 hours of sleep.
Reply

[…] on February 5, 2016 at 6:11 am

Thanks for the good info. Cort and thanks to all who commented.
[…], during the time you "felt like a teenager," did you increase your activity? (Dumb question?)
I love having more energy, on those rare occasions that I do–but no matter how well I'm feeling, if I overdo, I always pay for it.
Did you "overdo" while taking the LDN?

[…] on February 4, 2016 at 2:40 pm
I so wanted LDN to work for me, but side effects were too scary. I started out on 3 mg. The next morning I was on top of the world – felt like a million bucks even though I could hardly sleep. The second night I woke up at 3 a.m. feeling as if my chest were EXPLODING. It was alarming, but the weird feeling went away after a half an hour. A couple of weeks later I tried a much, much lower dose – 0.5 mg. No endorphin high the next day, but I got chest pain. I've gotten this peculiar kind of "atypical angina" after taking other meds – Armour thyroid, Cytomel, 5-HTP, tyrosine, Ioderol, Lugol's solution – all stuff that makes me feel better. No one has ever offered me a theory about what's going on with me. I think that feel-good neurotransmitters might be causing cardiac vasoconstriction. Has anyone else gotten this side effect from LDN?
Reply

[…] on February 4, 2016 at 6:11 pm
I have used LDN for about 1 year now… It really helped with my FMS, took pain level down about 60%. If you are starting it, start very slow, at maybe 0.5mg and then increase weekly by about 0.5mg at a time. Top dose for FMS is usually 4.5mg. If you are having vivid dreams, you need to decrease the dose by one degree until that goes away. Too many people are starting on too high a dose… drs are not well enough educated. Also, some do better with taking it in the morning, I do. Doesn't have to be taken at night.
Reply

Cort Johnson on February 4, 2016 at 7:03 pm
Right – the word on LDN used to be that it had to be taken at night to take advantage of the opioid blocking and the endorphrin kick in I believe but that's apparently not true at all. There are some things I can't take at night – like Kombucha – which leads to waking up and being unable to sleep – in contrast to just waking up multiple times – which I can handle during the day.

[…] on February 4, 2016 at 2:40 pm
Has anyone else had stomach problems when taking Trazadone? Stomach pain and nausea slowly crept up and got worse and worse and I had to stop taking it after 3 weeks even though I was on a low dose.
I've taken LDN for 3 years – I tolerate it well. I don't know how much it helps now, as I continue to decline, but I keep taking it assuming I would be worse off pain and sleep wise without it.
Thanks for the report Cort. I must admit I find it quite disappointing. But glad to hear what really happened with all of that.
Reply

[…] on February 4, 2016 at 7:49 pm
I had Trazodone Mylan described by doctor, immediately had stomach pain, nausea and suicidal thoughts. after swimming through those bad side effects for 3 weeks, I finally experienced some nights with 7hrs of sleep for 3 months, then had to go fm 50 mg to 100 mg for about a year. But from day 1 I felt very 'drugged' all day, no nice feeling. And the insomnia nights were never completely gone and came back. still at least once or twice a week; tried several doses but the side effects didn't really improve 'quality'cof life. I stopped taking it.
Reply

[…] on February 4, 2016 at 2:45 pm
I have been taking 4.5 mg LDN at bedtime for 32 months. It may be helping. I still have quite a bit of pain. When first starting, I titrated up at 1.5 mg increments. I think it is worth trying.
I tried Trazadone for sleep. One 50 mg tablet did not work. I tried 1.5 tablets (75 mg). Here are my notes on the bottle: Woke several time during night; Woke with very tight muscles and tight jaw; Vision is very blurry in AM; DON'T USE ANY MORE!
I agree with […]. These diseases are being caused by infectious pathogens, and these pathogens need to be destroyed.
Reply

[…] on February 4, 2016 at 3:05 pm
Does anyone know how LDN would affect medical marijuana use?
Reply

[…] on February 4, 2016 at 7:00 pm
My understanding is LDN and marijuana can be taken together. The only drug that should not be used with LDN is opiates.
Reply

[…] on February 4, 2016 at 3:07 pm
I tried LDN at a dose of 1.5 mg. I took it only one night. It made my pain skyrocket, made me dizzy, and caused heart palpatations. Felt I was way overmedicated.
Reply

Cort Johnson on February 4, 2016 at 7:06 pm
I would go lower – .5mgs ? At the last LDN conference I was really struck by the wide variety of responses to doses. Some people who have horrible responses at a higher dose at first can actually work themselves up to from and benefit from that dose if they go really slowly. It's weird how the body works…
Reply

[…] on February 4, 2016 at 3:29 pm
I've been on LDN for a couple years. I've started out at a very low dose (0.2 mg) and am now at 0.8 mg/day. Yes, it does cause some nausea but the benefit of reduced pain has been worth it. When I feel nauseated, I drink a little ginger ale, and it goes away.
Reply

[…] on February 4, 2016 at 3:48 pm
I have tried LDN for over a year and it didn't seem to make any difference at all.
Reply

[…] on February 4, 2016 at 5:50 pm
[…], that's a bummer. As I understand it, LDN is supposed to retune your immune system away from autoimmune reactions toward fighting infections. Maybe it would help if you increased the dose.
Reply

[…] on February 4, 2016 at 3:53 pm
I have tried Trazadone also without help for sleep. Instead I became very swollen with blurred vision and felt more sick with heart palpitations. I tried several dosages for 2 months as prescribed without success

I do know several people trying LDN with great success but you cannot take it with any other pain medicine or alcohol as Cort said. Most patients start in very small amounts such as .05 or even liquid. There are several Facebook groups where people discuss their use of LDN.
Reply

[…] on February 4, 2016 at 8:54 pm
One of the Facebook groups is called Got Endorphins.
Reply

[…] on February 4, 2016 at 4:00 pm
I was on it for over a year and felt no effect, good or bad. I've just stopped.
Reply

[…] on February 4, 2016 at 4:42 pm
I would like to find a specialist in ME/CFS in the Naples, FL or Ft. Myers area. If anyone knows of a doc who is really well-studied in the complications of CFS, that's who I need. I am a write and researcher on the subject of pain management, and have a wonderful PM doc here in Naples, but he's not into really digging in and doing testing, etc. Thanks, […]
Reply

[…] on February 5, 2016 at 5:54 am
[…],
I have gone to Dr. Jeffrey Dach in Davie, FL. His website is JeffreyDachMD.com. He works in integrative medicine and did extensive testing to sort out my situation. He was the doctor who first suggested LDN to me. I started with an office visit and then followed up long distance, coordinating care with my family doctor. Good luck!
Reply

[…] on February 5, 2016 at 6:47 am
I used to live in that area. I see Dr. Irma Rey at Nova Southeastern in Ft. Lauderdale. Very knowledgeable and does extensive testing.
Reply

[…] on February 4, 2016 at 7:40 pm
Hi Cort, Thank you for writing about Biovista's drug repurposing project that was one of 5 grants made by the CAA in 2012. You can read about it here: http://solvecfs.org/breaking-ground/.
I'd like to make a few clarifications. As noted above, Biovista wasn't "engaged", they submitted an application to a competitive grant process. There application scored well and the grant was awarded. Grantees adhere to the organizations grant policies (grants are quite different from contracts).
The grants made by the CAA were intended as seed funding for projects that were riskier or had little to no preliminary data. It was a great mechanism for enticing new scientists into ME/CFS research. The fact that Biovista's bioinformatic platform identified 2 drugs that are used (off-label) in ME/CFS was actually quite exciting!
We also conducted survey of treatments used by ME/CFS clinical experts. Their responses indicated that LDN and trazadone were effective in treating ME/CFS symptoms. This was important because it validated what Biovista's bioinformatic platform found! A paper describing this survey was just published (http://www.tandfonline.com/doi/full/10.1080/21641846.2015.1126025).
Biovista prepared an Investigational New Drug application and met with the FDA to discuss the combination and the study design requirements. This FDA meeting occurred on the heels of the 2013 FDA Patient-

focused drug initiative meeting – where ME/CFS was the first workshop held by the FDA. The FDA was helpful and interested in doing what they could to make ME/CFS clinical trials happen. It was now up to Biovista to raise the funds to conduct this trial.
I don't have to tell you that raising the $2 million to conduct a 150 person randomized controlled clinical trial is no cake walk. Since the combination has been disclosed it less attractive to potential private and pharmaceutical funders.
It could potentially be funded by NIH. Drs. Deftereos and Persidis remain committed to using their repurposing platform to identify drugs that can be used for ME/CFS treatment and I am hopeful that we will find funding to pursue further repurposed drug clinical trials.
Your analysis of the mechanisms of action of trazadone and LDN are spot on. It is entirely plausible that when combined the mechanisms of these 2 drugs would target sleep, pain and immune modulation. This is why a controlled clinical trial for this combination was and still is important. And we all know that ME/CFS clinical trials and treatments are desperately needed.
In closing, far from underwhelming, Biovista's identification of this novel drug combination demonstrates that targeted treatments are within reach for ME/CFS and every effort should be made to ensure studies like this and clinical trials occur.
Reply

Cort Johnson on February 4, 2016 at 8:01 pm
Two million dollars – ouch!
I think this – along with Ampligen and Rituximab trials – would be a great way for the NIH to demonstrate its new found commitment to ME/CFS.
Thanks for filling in some of the blanks. It was good to hear that the FDA was enthusiastic about a trial like this. Somehow a way has to be found to assist diseases like ME/CFS in which the pharmaceutical companies show little interest. Ditto with drugs like LDN which show real promise in helping people but which big pharma is just not interested. If the NIH and FDA is really serious about doing everything they can to help everybody who is ill these challenges need to be addressed.
Reply

[…] on February 4, 2016 at 7:52 pm
Hi […],
I'm on the Cape but will note down Elson. (Thought of driving there for MJ but they never have any cbd strains). Virtually no mainstream doctor will prescribe LDN in my experience so I got it from India and Israel for my FM. Unfortunately at night I had two terrifying nightmares and when I switched to AM use, going up from .5 to 2.5 gradually with no benefit, I suddenly experienced unbelievable intensification of my FM pain in areas not activated for decades. Went back to "normal" pain in several days after I discontinued. There is an LDN cheerleader group on Facebook that reco's it for everyone for everything.
Reply

[…] on February 4, 2016 at 9:01 pm
Hi […], LDN seems to be very tricky. Dr. Elson is not great at micromanaging doses based on side effects. He will prescribe, but it's not one of his main things. There are other practitioners in his clinic – Elson now works only two days a week. Dr. Lynch is full time and has been there a long time. I hear that he is very smart. And there are a couple of nurse practitioners. Check out the website for Northampton Wellness Associates.
Reply

[…] on February 4, 2016 at 9:30 pm

Thanks, […], will check it out, but I do wish I had tried LDN again at much slower dose increase before my FM pain accelerated, would be tricky to manage with Tramadol and now Lyrica…too many variables!

[…] on February 5, 2016 at 6:41 am
[…], I hear you about the problem of too many variables. It makes the whole thing confusing. But I was impressed with Dr. Jacob Teitelbaum's philosophy – he thinks that you have to hit everything at once. For example, he thinks that for sleep it works better to take very small doses of a lot of soporific herbs rather than putting all your eggs in one basket.

[…] on February 5, 2016 at 9:39 am
I was not impressed with his book. Does not jibe with my scientific background. Up late this AM after first 50 mg Lyrica (not cheap), pretty dopey and headache. we'll see.

[…] on February 5, 2016 at 10:54 am
[…] – In case you are not aware…
If you need financial assistance with paying for meds in the US, go to pparx.org and follow the prompts. Some meds are available for free …sponsored by the pharmaceutical company.
One of mine is sent to my doctor on a quarterly basis and I just go & pick them up.

[…] on February 5, 2016 at 3:27 pm
Thanks, […], nice of you to post that, will tell some people I know. I actually have very good insurance and money is not an issue at the moment. I was just struck by a thirty buck co-payment for a month of 50 mg t.i.d. Lyrica, suggesting to me it is pretty expensive med without insurance or with weaker insurance. I had two wake up calls about meds this week. The pain doc told me no opiates (have never tried) anymore until I have failed a bunch of FM meds, they have tightened up the protocol with all of the ODs and people with real need are going to have to jump through hoops. The second moment was after I handed my scrip to the pharmacy and the tech said " let's see if your insurer will pay for it." That's when I realized that the people controlling our medical care are not our doctors, nor even the Feds, but the drug companies. I have read that Obamacare passed only because Obama caved to Big Parma about not negotiating prices. Reportedly, the aide who wrote most of the legislation later left and went to went for a major drug company I won't mention.
Not to hijack the thread…I don't want to get my hopes up but Lyrica, despite doping me up today for a few AM hours, also made me feel more normal painwise, even awful neuro pain, than I have in two years, astounding, held my AM Tramadol unti 2 PM. I don't see how anyone can take this during the day so I'm going to open the capsule and weigh out half of the 20 mg and take tomorrow in a trial, assuming I again make it to 2 PM if I take at midnite. I also slept through three nightly 2.5 mg Ambien dosages, also astounding. Maybe this is something Big Pharma got right for me. I have had initial positive stuff before with stuff that did not continue or had adverse effects but we'll see.
A book I reco everyone here read is Cure: A Journey into the Science of Mind over Body by Jo Marchant. This is a cutting edge book by a good scientist, both with research and anecdotes that provide actionable info. What color meds work best, can a placebo work even if you know it's a placebo, etc. I'm going to try to use classical conditioning to see if I can use a placebo to extend my Lyrica benefits, if I find it works, or strong pain meds, if I end up on them. Good science, I'm a psychologist with good research background and speculated about some of this stuff in my head the last few years but this is convincing me to try it.

[…] on February 7, 2016 at 5:32 pm
Just fyi…my 30 day Lyrica copay is $100. A 90 day supply is $250. I have "good" insurance and my husband even works for a large retail pharmacy chain!

[…] on February 8, 2016 at 8:33 am
Eek, […]! I hope it works well for you! Day four…it's not going to be anyone's favorite med, if they can do it, is it! I hope the woman doing the trial with the improved version finds it loses a few side effects and ups the positive effects.

[…] on February 8, 2016 at 8:57 am
Wow! The price. Here is a clear example that Big Pharma will make more money on a symptom-treating medication than on a cure.

[…] on February 4, 2016 at 8:38 pm
There is a Facebook Group called "Low Dose Naltrexone (LDN) for Fibromyalgia and (CFS) Fatigue" that has a lot of info. It's more of an informational type of group vs a chat group. In their files they have a list of doctors that they have been compiling that will write a prescription for LDN.
I was on LDN and it did great for my Fibro. But I had to go off of it because it didn't help the pain from the many herniated discs that I have. (It wasn't intended to work on back pain). I started at 1.5 mg and didn't do as well after increasing to 3 mg. The correct dose for each person tends to vary. The best thing to do is start at a low dose. Unlike most drugs, this one doesn't work better as you increase the dose. Increasing the dose is rather intended to find out which dosage works best for you.
Reply

[…] on February 4, 2016 at 8:51 pm
I have taken Trazedone 50 for many years for sleep. When I thought it wasn't working well anymore it was upped to 100mg, Nothing happened – couldn't sleep. So I went off of it for awhile and I slept. When I started back up (because I couldn't sleep again), I went on 50mg and slept like a baby. Now if it stops working, I cut it in half and try that and it works the same. Or I go off for two to three nights and it will start working again. My point is that more may not be better, and it does cause a hangover.
I am encouraged by this article today, but because I have several pain problems I am on high doses of Oxycodone and Fentanyl. I wonder how it would work to go off those and try LDN. I wonder if it would be enough pain meds for me. Have to ask the PM doc but this is very interesting. I also take 800mg Ibuprofen every six hours and it helps me tremendously. Without the meds I wouldn't be able to function at all. With them I get enough relief to be at home, but with the progression of RA and possible Lupus, DDD and ME/CFS, I still can't go out and do anything reliably. All I need is an electric wheelchair in order to get some freedom. I have to sell my electric tricycle first. Bummer because I can ride it at times. Ok, rambling because I am tired. Good to read all these comments after a great and encouraging article!
[…]
Reply

Cort Johnson on February 4, 2016 at 9:16 pm
I love it when less is more :)
Reply

[…] on February 4, 2016 at 10:50 pm
Cort: I just looked at my comment and I have no idea where the word (my moniker) "[…]" came from. Where do I go to change that? Thanks- […]

[…] on February 5, 2016 at 11:06 am
[…] – I'm on the same pain meds that you are on. Scroll up to read my comment. LDN worked for Fibro but not herniated disc pain. In the FB group that I mentioned there should also be a Youtube video available to learn more on how LDN works with Fibro. You can try it, everyone is different but I also know how difficult it

is to wean off of these meds. I'm now weaning off of Fentanyl. And I know how difficult it can be to get these meds. (I don't, but some people do). If these issues could potentially be a problem for you I would reconsider trying it. To avoid waking up in pain at an 8 or 9, I don't sleep for more than 3 consecutive hours at a time. It's not ideal but it works for me.
Reply

[…] on February 5, 2016 at 1:07 pm
Thanks, […]. I am just being curious for people in general I guess. I have no intention to changing my meds right now.
Thanks for the response.

[…] on February 7, 2016 at 2:55 pm
[…], What jumped out at me was where you wrote "…with the progression of RA and possible Lupus…" I needed to encourage you of something that helped me press on. Mindset is very important and when my doctor said to me one time, "Well, your issues are just the PROGRESSION of the disease…" I really reacted!! They DON'T KNOW that the disease has to progress because they don't know everything that causes it and what can reverse it! My mindset is to HALT or REVERSE it- not monitor it's progression as they have been taught.
YOU are on your own most of the time in finding the latest information or protocol. That is unless you can spend unlimited $$ on the few medical professionals that will be able to help because none of them take insurance and also charge $$ because they can. I have found the occasional doctor that is in the system that helps as long as I do my own footwork.
So much starts in the gut. Taking Ibuprofen and other NSAIDs in really bad for the gut lining which will make it worse in the long run. We need to restore and heal that. DIET is everything- nightshades, lectins (NOT just GLUTEN) cause the inflammation. Take a good quality Curcumin (Turmeric extract)- amazing anti-inflammatory! Use ginger supplements.
Do research on your blood type foods (D'Adamo). Dr. Stephen Gundry has done NEW research. Google him. Get you genome done through 23andme BUT have it analyzed by another online source (because 23andme is really pathetic at doing so). I like Promethease, Nutrahacker, D'Adamo's Swami…
If you have not tried LDN, I would encourage you to do so. Just be aware that the way it is formulated (fillers used) and the reputation of the compounding pharmacy is very important. I have taken it since 2010.
It has helped me so much with RA, Lupus, pain- even my Hashimotos BUT I have had bumps in the road recently in my dosage…It has helped my thyroid normalize so much that it went too high on the meds I was taking and I have had to cut them by 1/3…
I have been using different things over the years. I am going to try Trazadone again with this new info here…I remember over 20 years ago, a doctor prescribed Trazadone for sleep, suggesting it would help my Fibromyalgia symptoms. I don't know the dose strength of the tablet but it was way too strong, making it hard to wake up fully. I kept cutting the tablet until I was taking a speck- maybe an 1/8th or less. When I found the right dose, It helped me sleep so well and so fast! At the small dose, I could wake up refreshed. My doctor laughed at the dose BUT he told me I was very sensitive to medications and that I should note that for the future. Those of us with these conditions are the "canaries in the coal mines"- it's a toxic world but our bodies are on our side trying to manage and adjust to the onslaught- have the mind set that your body is NOT attacking itself, it is just trying to find homeostasis- sometimes that causes problems that we need to help with. All I write here is to encourage you so please don't think it is a lecture- I am on the same journey. Please don't give up because you are an encourager too! <3 Best!
Reply

[…] on February 8, 2016 at 6:21 am

[…], you have a wealth of information! And I like your attitude about assuming that you will reverse the illness. About HRT I forgot to give you links last night. About the safety of using hormones cyclically, google Danish study cyclic HRT and you will get a bunch of hits. And about my psychiatrist's approach to HRT, he got a lot of it from going to seminars given by a Dr. Neal Rouzier who has a website – http://www.hormonedoc.com. I found a series of videos he gave about how HRT done right is safer than no HRT.
I agree that getting well is a do-it-yourself project. I happen to have a doctor who has been treating CFS/ME and fibro for decades and he does take insurance. But I still have to do the research and suggest things to him. Then he says OK.
I agree about diet. Pain when almost all away when I gave up gluten and dairy. Then I found that oats, quinoa, and corn gave me inflammatory symptoms, too. I just tested allergic to beans – if I don't eat beans, does that mean I'm getting rid of lectins? Nightshades – maybe they should be the next thing to drop. NSAIDS are bad for leaky gut – I used to take them all the time. I can't take curcumin – it gives me joint pain for some weird reason.
I did 23 and Me on my doctor's advice and got the data to Genetic Genie – confusing. I'll look into the other outfits you suggested for interpretation of results. I wish that I hadn't had such scary reactions to LDN – I avoid drugs that give me chest pain.
The latest thing I'm exploring is whether I have a genetic variation that makes it hard for my body to clear mold biotoxins and whether I might have Chronic Inflammatory Response Syndrome – CIRS. There is a Dr. Ritchie Shoemaker who discovered this syndrome which sounds a bit like CFS/ME. Last week I had 6 blood tests to check myself out for this. This problem has a quick and easy fix! A quick fix would be fantastic.
Thanks for your encouraging words, […]! We all need encouragement.

[…] on February 4, 2016 at 10:06 pm
Naltrexone (I hope that's right damn SPELLCHECKER keeps changing it) and this is probably redundant not low dose. Are we freaking Americans so afraid someone might get better and live a happy life? Or does the medical community need that much cash. But this drug has treated Canadians with Fibromyalgia successfully for years, because I checked into and found out I would need to have a Canadian daddy and could only get prescribed 3 months at a time. Too cold in Canada. We are so developmentally challenged in the greatest nation and it isn't just the Bible belt where I live. It's the DC Beltway! I would love to have the Congress tested since you can't sell Marijuana for profit or grow it, especially without a DEA permit, and seeds are illegal to sell in the U.S. I guess you go to DC and they give out complimentary joints on your motel and hotel pillows and in bowls in Bars instead of Pretzels. Or maybe it's like on Cops and it's just laying on the ground. Hypocrites. You should have seen what I wrote to Georgia Legislators when I was asked if I felt my condition was left out and why? If you cannot understand Perocet and oxycontin are more addictive in treating pain then Medical Marijuana, but you afraid because then you may lose control of Marijuana as one of your arguments. Do you not know Percocet and oxycontin have been lost control of, too. Are still more addictive, and less effective? Are we dealing with knuckle draggers? I did not vote for these people. It's been a very stressful day. And I am sick of the shit. We have played this game for decades. No stingy funding. Laughable care. Russian roulette prescriptions.Low dose is not enough, sorry if Canadians get the pill and are doing great, we American s will, too!
Reply

Cort Johnson on February 5, 2016 at 7:52 am
Minx on the Health Rising Forums just reported that it really matters what time she takes LDN
http://www.cortjohnson.org/forums/threads/ldn-low-dose-naltrexone-whats-the-latest.2873/#post-10413
When I tried it last year i was taking it at 8 a.m. (no sleep if I take it at night). This time I have experimented. I took it at 4 a.m. 6 a.m even 5 a.m. But the perfect time for me is 5:20-5:30 am. The difference in how I feel is huge.

Even if I don't get back to sleep, which I usually don't, I'm awake and up by 7:30. I used to lay in bed in a coma and have to drag myself out. I couldn't function for hours.
I have more energy, mentally and physically. My pain has decreased a huge amount. Inflammation in my brain and lungs are down. Fog is better. It's pretty incredible.
I have to be careful. If I overdo it I can feel things flare, brain fog gets worse, pain gets worse, I get wiped. Yesterday I had to go out at 9 a.m. I was gone 1 1/2 hours and spent the day on the phone, copying, faxing and dealing with a huge problem. I expected to be bad today. I wasn't. I'll see how tomorrow is.
Understand, I'm not going to run laps or even go shopping. But for me, this is pretty big.
Reply

[…] on February 8, 2016 at 9:33 am
I take LDN at bedtime. It's supposed to work by blocking your opioid receptors for two to three hours per night, thereby causing your body to make more endorphins. Normally, your body would re-absorb the endorphins.
I started at 1.5 mg for three to four weeks in June 2013. I had 1.5 mg capsules compounded at a local pharmacy.
At first, I had some startling reactions like a new type of wakefulness and vivid nightmares; a definite impact on the brain. But after three or so days, those calmed down.
I increased the dose by 1.5 mg, and stayed on that for three or four weeks. Then I added a third 1.5 mg capsule, making the total 4.5 mg recommended by my doctor. 100 capsules @ 4.5 mg cost about $80.
Reply

[…] on February 8, 2016 at 10:45 am
In one sense, it would be worth a higher price if Big Pharma would actually do big dosing studies for our conditions, variable as individual responses are. My two terrifying LDN nightmares were of dying in a car crash and another situation I have forgotten, game enders for me for evening dosing. When I switched to AM, as I noted, my fibro pains went off the chart. I don't know what could make me do another trial, a whole lot of great data maybe.

[…] on February 5, 2016 at 8:18 am
I started LDN a year ago. 4.5 mg made me too nauseated and caused insomnia, so I dropped down to 2.25 and it's taken me a year to titrate up to 4.5, upping the dose every 90 days. I do get a little nausea and slight insomnia for about a week, but then I'm fine. I've found that LDN has increased my stamina. I rarely get tired any more, so now my main issue is fibro pain.
Reply

[…] on February 5, 2016 at 8:51 am
That's so great. Which country are you in if you don't mind telling? I am taking just cannabis oil without THC and that's no real help with pain, like chronic pain, but has cleared nerve pain, insomnia, nausea 80%, IBS70%, and most everything but chronic pain and energy is not consistent, but have weird POTS, probably low blood volume, but live in Georgia, U.S., and Doctor, started looking November for someone who has even heard of that test near, still no answer.
Reply

[…] on February 5, 2016 at 9:30 am
You know after reading all the warnings, that it has been available since 1985, that it's linked to so many "quirks" I already have. I can see why I was never sent tilting after that Wind Mill. So happy for the rest of you that you have found your relief till science catches up with the causation to this madness. I need just simple and natural, and the older drugs just work better, and the fewer the better, though minimal relief,

the side effects are just down right deadly at times. But as I have said again and again, all us Immunologicals are warehouse under a few simple Names, might as well describe us: Sony, Panasonic, Vivatar, GE, Samsung, Sharp, LG, Vizio. But if I went into Best Buy and said I need to replace my Samsung and that's all the information I had. I would get a whole lot of different and diverse products. That's the way we are and different parts relieve. We are on different paths of our pathogens. We are at different stages. And we are all important, worthy and worth being fixed as well as be willed according to our individuality. We need our own specialist for our specifics, whatever we have. Whoever's brave enough to admit we are more than a sum of symptoms, but individuals.
Reply

[…] on February 5, 2016 at 1:36 pm
I tried taking a very small dose of LDN (1.5mg) after reading about how much it seemed to help others with ME/CFS & FMS. I was disappointed because it made me not sleep, at all. I took it for two nights, but I just couldn't forego sleep for the third night. Sleep is so important to me and so fragile, I can't take a medication that interferes with it, even for a few nights. Thanks for the info on trazodone. I may see if my GP will let me try that.
Reply

[…] on February 5, 2016 at 2:23 pm
About 18 years ago I was put on Trazadone to help me sleep. It left me in a state almost of hallucination. (In the UK the only ME 'treatment' was Cognitive Behaviour Therapies. I had to see a psychiatrist first to determine if I was depressed. He considered me to be depressed and put me on Prozac. A month later he doubled the dose. A month later I complained of poor sleep so he halved it and added in Trazodone. After a few nights on Trazadone I cut it out completely and also stopped the Prozac. No side effects. My next visit to the psychiatrist I told him I was feeling great and he admitted I was the best he'd seen me – and then I told him I'd cut out all medication. Of course he could not deny my improvement but could not accept that perhaps I had never been depressed in the first place and it is just that the ME is worse at certain times of the year and he had seen me at my worst.)
A few years later I took part in a trial at a local hospital where the test drug was a breakdown product of Trazadone. My first experience was with the placebo. The second was the drug – and it was obvious! I could not even raise an arm. Afterwards I could not walk a straight line down the corridor to the taxi but had to be helped by a nurse. The doctor in charge gave me her phone number to call if I needed her at night. (I think I should probably have been put in hospital rather than sent home alone.) I did not sleep all night but also could hardly move. The nurse told me that everyone who had ME reacted badly whereas the control patients had no reaction. (I gathered that the idea was that it could be used as a diagnostic tool for ME. However, I have never been able to find out anything about the research.)
I have always said I would avoid Trazadone after that, but perhaps the problem was the quantity, not the drug itself.
Reply

[…] on February 5, 2016 at 4:07 pm
Oh my! That's the same "paralyzed but unable to sleep" reaction I had to Xyrem. It was horrible. Maybe I won't run right out and see if my doc will give me trazodone….
Reply

[…] on February 5, 2016 at 5:24 pm
I have been diagnosed with CFS but have no pain or fibro. My doctor says that LDN is good for pain, and since I don't have any, I don't need it. What are your thoughts? Thank you for replying.
Reply

[…] on February 9, 2016 at 6:16 am
I would suggest to go back & read all of Cort's posts on the subject. And watch the video on how LDN works with your body. LDN is said to work with improving your immune system. I would think that should be very appealing for anyone with CFS. The nice thing is if it doesn't work you can simply stop & it's affordable.
Reply

[…] on February 5, 2016 at 6:30 pm
I started taking LDN 18 months ago when it was prescribed as a mild prokinetic for SIBO. I believe it works by decreasing gut inflammation. I started at 0.5mg and upped it very slowly over a year to 4.5mg. Honestly I'm not sure if it helps my SIBO directly but it totally zapped my fibromyalgia muscle pain! I barely have any bodily inflammation anymore. I plan to take LDN for the long-run if it keeps working its magic. It hasn't helped my brain fog and low mental stamina as much, so somehow it doesn't seem to quell the inflammation in my brain as obviously as it is in my body. Fortunately other things are helping me there. As I continue to unwind the tangled web, LDN has become one of a handful of potent solutions for me.
Reply

[…] on February 5, 2016 at 6:36 pm
That's very good. Probably a subset of LDN responders. Or maybe a subset of non-responders…
Reply

[…] on February 5, 2016 at 6:44 pm
Indeed, […]. One big thing I've learned on this journey is how differently we all respond to different therapies. There are many more things I've tried that haven't worked than have, even though they work wonders for others. The art is in the experimenting! n=1

[…] on February 6, 2016 at 4:34 pm
I want a drug that is proven, in CFS, to reduce exhaustion and brain fog.
I don't need its pain relief capabilities; I have that under control 'Feel good' is nice, but without dealing with the brain fog, it's an illusion. And the extreme fatigue needs addressing. Period.
Does LDN do that? I can never get an answer.
I'm interested, at this point, ONLY in that (and that it not make anything else, like sleep, worse).
Reply

[…] on February 6, 2016 at 6:09 pm
[…], I think we'd all like all like a drug that would reliably reduce extreme fatigue and brain fog for everyone with CFS. I think maybe it doesn't exist yet. Like you, I have the pain aspect under control more or less. Years ago some part of my body hurt all the time. When I went gluten free and then dairy free, the persistent inflammations went away. The other thing that helped a lot with pain was magnesium – taking pills didn't do it so I had to get magnesium shots every 3 weeks, which chased away my painful restless leg problem and the other aches and pains all over. But when I got rid of pain, fatigue took its place! Not fair.
A comment about sleep: I have been leery of taking meds like trazadone, so I've developed a concoction that works for me most of the time. My sleep medicine doctor told me that the most effective thing for postmenopausal women is hormone replacement. When I increased my dose of estradiol and of natural progesterone (200 mg 25 nights a month), I finally got good sleep for about 7 hours most of the time. In addition I take some calming amino acids – theanine, taurine, and glycine and 3 mg of sublingual melatonin before bed.
Reply

[…] on February 7, 2016 at 3:18 pm
[…], Please tell me more about the estradiol and of natural progesterone. Is the 200mg a combined dose? Compounded?
I wish to resume my bioidenticals again as I feel I was better off. Please mention any links to info where I can find more info.
Your other suggestions are also helpful. Thank you!

[…] on February 7, 2016 at 9:27 pm
[…], I take a generic estradiol patch that I change twice a week. The dose is .075 mg. My health fell apart when my gynecologist reduced the dose to 0.05. Finally my PCP increased the dose back up and the hot flashes that had been waking me up 3 or 4 times a night went away. I think the patch is much safer than the pill – much lower dose and it doesn't do a first pass through the liver. I saw a study that found that taking HRT cyclicly is much safer than if it's daily, so I take a three day break once a month.
The progesterone I use is bio-identical natural progesterone. I had been taking one 100 mg pill 12 days a week. Then I went to an integrative medicine psychiatrist (not because I was having psychiatric problems) and he upped the dose to 200 mg 25 days out of 28. This made it much easier for me to go back to sleep if I woke up briefly. My PCP is horrified by this – she blames my fatigue on the progesterone because it can make you sleepy. The psychiatrist says that natural progesterone protects against breast cancer. At first I was taking the brand name Prometrium, but then it went generic. Now I've switched to one 100 mg pill and 100 mg of compounded bio-identical progesterone in a topical cream that I get from Life Extension. Since it doesn't do a first pass through the liver, it provides a bigger actual dose. Also the psychiatrist says that the transdermal hormone will make me less sleepy. If I'm really in need of a good night's sleep, I'll take 300 mg of progesterone and sometimes I get a night when I don't awaken.
Another doctor prescribed a cream form of an alternative estrogen called estriol. It's supposed to be safer, but it's much weaker and I started to get way too many hot flashes and awakenings so I gave up on that. Also I was supposed to apply it twice a day over a lot of skin, but not before a shower. Too much trouble.
I hope this is info is helpful, […]. My HRT meds are my favorite meds. Sleep is so precious. One more thing – I think the progesterone makes me feel calm and relaxed. I had a couple of horrific eye surgeries last year and I didn't freak out at all – just did what I had to do without worrying. This psychiatrist prescribes HRT because he finds that it helps people feel better psychologically.

[…] on February 7, 2016 at 4:13 pm
[…],
Sleep is adequate, and I'm far enough past menopause that I have no problems there.
I overreact to almost all medications, and would never take hormones – with all their side effects – because the likelihood of help is small compared to the likelihood of problems.
I can't afford the time it takes to try out new medicines – it stops my writing flat any time there is a problem. And that's the only thing I have left of myself.
So I keep reading these things. I think we're not going to get anywhere until they figure out how this illness works. I want to know – and then to have someone target the disease specifically.
For heavens' sake – they got a vaccine for Ebola in record time! HIV/AIDS is no longer a death sentence. And they can't even figure out what's wrong with us, agree, and find a cure?
I don't want half measures and comfort measures and pat-on-the-head measures. I want results.
Glad the hormones work for you.

[…] on February 7, 2016 at 9:35 pm
[…], I'm glad you sleep OK. That's huge. And I hear your frustration. I hope they figure out what's causing CFS and how to fix it, but meanwhile I'm up for anything that helps somewhat. I'm frightened of most meds, but I take a lot of supplements, each of which helps a little bit in some area of distress. The thing that's

giving me the most noticeable help these days is hyperbaric oxygen treatments. I feel better after an hour breathing 100% oxygen under the pressure of 1.3 atmospheres for an hour. I'm thinking of renting a chamber to use at home because I feel so much worse on the weekends when I don't do it. Money and trouble! But some relief. Let's keep our fingers crossed about the medicos coming up with a treatment that actually works!

[…] on February 7, 2016 at 3:10 pm
There is no magic bullet to eliminate/ reduce exhaustion and brain fog. There are many reasons and variables involved.
If you mean "proven" as in FDA and clinical trials, you won't get those for LDN (which is Low Dose Naltrexone) because it will not make BigPharma any profits so there is not incentive.
Pain is an indicator of something not right in your body. You also say you have the pain "under control", but not what you do to control it. Have you decided that you cannot eliminate it without a drug ? There is much you can do for yourself but it requires you to not totally put your life in the hands and control of the pharmaceutical world…
Reply

[…] on February 8, 2016 at 4:23 am
[…] – I think we'd all like a specific protocol to follow for any of our symptoms. Each one of us with CFS and/or Fibro have a lot of primary symptoms that are very similar but at the same time there aren't two people with the same exact symptoms as I'm sure you are aware. To add to that the majority of us have additional illnesses. For me, I heavily research each experience (med/supplement/avoidance of foods, etc) that is of interest to me. If the symptoms, results and expense of trying it is within my reach I take the risk of trying it. Each one works differently on everyone. With all the variables it is very difficult to get a direct answer on how it will work for you. I will tell you that I am not a patient person by any means and I'd love for a direct answer for any of this. I've been sick with EBV/CFS/Fibro for nearly 30 years. I've tried many things. My symptoms have also changed over the years. And if I do find something that helps with a specific symptom, another symptom will become my worst symptom. I hope you can find something to help.
Reply

[…] on February 7, 2016 at 11:00 pm
After getting diagnosed with metastatic thyroid cancer, on top of my severe me/cfs at age 25 I nearly lost all hope of ever improving. However, I remembered something in my medicine cabinet, LDN. I had taken it one night during my first six months with cfs and it made my symptoms worse so I didn't pursue. I decided to try after a thyroidectomy made my fatigue paralyzing. I can't believe how much it has helped me. I've been able to leave the house everyday and even exercise mildly! (Ex Hour on a horse). This was completely impossible before LDN. I still have cfs but it's a 5 not a 10. It's a miracle for me. And just in case your wondering, my cfs doctors (dr Levine) and oncologists do not believe my fatigue is due to cancer. Thyroid cancer is almost always asymptomatic:)
Reply

[…] on February 8, 2016 at 1:49 pm
So weird to read this now! I was just prescribed Trazodone last week for sleep and have been feeling much better. I wasn't sure if it was because the sleep was much improved (I had a sleep study done once and there were not major issues) or perhaps that a subtle underlying depression was resolved. I ended up doing some research and found this study: http://www.ncbi.nlm.nih.gov/pubmed/25911310 which I was going to show my doctor, and incidentally, was also going to email Cort about it. Ah well, my work here was done for me lol.
Reply

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Subject: ME/CFS research

Hi

I have uploaded a document to my web site giving details of what I think systains ME/CFS and I include a method of treating that condition (Metabolic Damage). If clinical trials are being set up this would be an ideal opportunity to confirm my method of treatment.

This is the link to my web page
http://www.lougogan.com/health/how-to-correct-hypo-metabolic-damage.php

The medication is safe but the timeline for the treatment (full cure) is approx
4 years. BUT the method of treatment could be shown to be correct even before the full treatment ends - approx 8 months.

Any further questions etc ....

[…]
[…]
Subject: NIH RFI ME/CFS

Dear NIH:

Please fast track both research and treatments for ME/CFS. My once brilliant son and Stanford student […] has been ill for 2.5 years. He is now bedridden with encephalopathy-sleeping 23/24 hours per day, severe hyperacusis, extreme photophobia, and likely bulbar palsy-drinking all nutrition through a straw for the past 6 months. He is still "there." He wrote on a piece of paper to me one day: ?Ampligen ?Rituxan ?plasmapheresis.

As a physician, I knew nothing of this disease until my son unfortunately developed this disease. What I have learned simply leaves me stunned at the history of this disease and neglect of these patients. To become afflicted with this disease in the past decades is to have 3rd world medicine in the richest nation on earth.

We have millions missing their lives-patients and caregivers. NIH scientists: Please look at the forest rather than the trees. **Generously fund Ron Davis and Ian Lipkin.** These are brilliant proven successful researchers that are highly motivated to understand and find cures for this disease. Without fast tracking, […] could easily die of this disease, adding his name to the obituaries like outstanding […] (Harvey Mudd graduate) or […] (MIT and Stanford graduate).

Dramatically and swiftly increase funding and physician education. This is decades overdue.

Next, **immediately change the name to the historical name Myalgic Encephalomyelitis (WHO 1969).** The barriers are too great to surmount the negative emotional reaction and stigma that accompanies the name CFS. Call it ME, present the biologic pathophysiology known, and interested researchers aren't associated with "CFS."

Use only the CCC or ICC for selecting patients. The other criteria do not exclude other diagnoses.

Look at the big picture and fast track the research. Go with those who have outstanding proven track records. They know the technical details of what needs to be researched far better than I. Trust them. They

are motivated to solve this problem and help these patients. I don't want my son […] to die, so please don't leave researchers like **Davis and Lipkin** poorly funded. **They are our greatest HOPE.**

Include **intracellular bacterial pathogens** like Mycoplasma and Bartonella in the list of potential pathogens. (The only herpes titer that my son has is HHV-6 and it is not high. His Bartonella titer is high). Stay open minded to infectious (viral, bacterial, parasitic,etc) and autoimmune etiologies.

Next, fast track listing every treatment ME physicians have successfully used on long term ME patients that have been cured. I personally know 2 people that underwent experimental treatments after 10 years of the disease and were cured. Include: long term antivirals, long term antibiotics, Vitamin C, glutathione, hyperbaric oxygen, GcMAF, Coenzyme 10, IVIG, ?ozone. **Study less risky medications along with the powerful, potentially dangerous treatments.** Consider roxithromycin which has both anti-infective and anti-inflammatory effects (See Broderick's research with regards to IL-6 and IL-8). One Australian reportedly was cured with long term roxithromycin. We need trials with less risky treatments also like ?roxithromycin, Imunovir, LDN and dextromethorphan, antivirals, antibiotics, and the other treatments that helped patients listed above. Is there any role for plasmapheresis?

Pool the knowledge of the prominent physicians that see lots of ME patients.

Capture the knowledge of those who have cared for these patients for decades. Lerner is now deceased, and most of those with decades of experience are near the end of their careers/lives (Bell, Cheney, Peterson, Komaroff, etc).

Can you name another life threatening disease that patients can't find a doctor that knows much about the disease—especially a physician that is covered under an insurance plan? Or that families have to spend their little spare time raising research funding, doing advocacy and writing letters because the situation is so dire?

Please minimize the bureaucracy and fast track treatments and cures. **I don't want my son […] to die.**

These attachments/links put a human perspective and suffering to your research efforts:
[…] obituary
[….] photo before illness and one year into illness
[…] letter to Senators January 2015
Stanford Daily article
[…] photo two years into illness
[…] letter to a Senator
Washington Post Davis
Washington Post Vastag

[…] obituary ME/CFS

[…] photo me/cfs advocacy.jpg

Dear Senator by […]

Stanford Daily Article Chronic Fatigue Syndrome

[…].JPG

[…] letter to Senator office "X"

Washington Post and Davis article fall 2015

Washington Post and Vastag

[…]
[…]
Subject: CFS Research

To Whom It May Concern,

I am a physician with a wife and daughter with CFS. They have seen multiple physicians and have been devastated by this poorly understood and inadequately researched disease.

They have been treated by Dr. Jose Montoya at Stanford and have improved by taking Colchicine and Valgancyclovir.

I was top of my class at Dartmouth Medical School and completed two residencies and a fellowship at the Massachusetts General Hospital and have been frustrated at the profound lack of insight in this illness.

Physicians are minimally exposed to CFS in medical school and it is treated with cynicism and skepticism throughout our training. It is essential that the NIH increase their meager funding to help research on CFS.

[…]
[…]
Subject: LDN

Good Afternoon,

I am writing with information as to my experience as a fibromyalgia patient who is taking LDN.

I have been taking LDN for a month now and my pain is better controlled than when I was taking Norco. I have FMS, back pain (sciatica, 3 pinched nerves, spinal stenosis, and some bulging discs), I also have bursitis of the left hip that my nurse practitioner had ordered an MRI for because she thought I would have to have the bursa surgically removed.

After 2 weeks of taking LDN, my hip pain was GONE and I cancelled my MRI.

My fibro pain is much better controlled. Prior to LDN my pain ranged anywhere between a 6-9/10. Now its only 3-4/10 and sometimes even less than that.

Feel free to contact me with any questions. I will be happy to help as I am an RN and prior to losing my career I was a nursing instructor, so I know how valuable having feedback and input is for research purposes.

[...]
[...]

Hello, I am responding to the Request for Information: Soliciting Input for New Research Strategies for ME/CFS.

As an ME/CFS patient I want to thank you for the investigative research you are doing and the outreach to patient groups in the form of webinars and calls for information. The most frustrating thing about this disease is how little we know about it, and I can't tell you how much I appreciate the work you are doing.

My perspective is one of a former CFS-denier. I was very active -- running, swimming, hiking, running triathlons, volunteering at Habitat, and coaching a running program for elementary school girls (Girls On The Run). And I believed that what most CFS and Fibro patients needed was to jut get outside and walk more. After all, I was actually not any good at the sports I was doing (a very slow runner, etc), but kept doing them anyway because they were fun and for the social aspect.

But then I became ill in March of 2014, and after attempting to 'will' my way back into health, finally had to face the reality that something is, in fact, terribly wrong with my body, and no-one seems to be able to figure out what that is.

However, my background is also from a technical world, majoring in CS and working on Software Development teams. The last few years before I became ill were spent testing software, which lends itself to a unique perspective on the disease I'm living with. My job was to take a problem, systematically narrow down the possible variables, determine the exact cause and nature of the problem, and then figure out how to fix it (or work around it).

In the absence of a better diagnosis, or a definitive treatment plan for my condition, I have been applying the same principles, with the primary goal of being able to explain, to the best of my ability, exactly what is going on.

I've found a number of 'weird', 'random' things, which I hope might be helpful as you create a plan of attack for defining and understanding this illness --
- I experience three main sets of symptoms:
-- Those that happen in a flare
-- Those I live with every day
-- Those that occur when I become overheated or attempt too much physical exercise
- I have been able to bring the flares under control with celiac-level avoidance of gluten and dairy. *I realize how controversial food sensitivity is.* However, I am fairly confident of the circumstances which confirm this -- among other evidence: even trace amounts (even in 'blind' conditions, where I accidentally encounter it) trigger a flare involving a terrible migraine headache. I've tested negative for Celiac, but have been following the research into Zonulin, hoping it might provide some answers one day.

- My GI issues seem to improve by taking Zyrtec regularly
- Severe leg pain (in thighs, which occur during a flare) seems to improve with Claritin
- When I become overheated or overly tired, I experience an increase in nerve pain on my right side, and terrible leg pain (both legs) at night. More troubling, however, is the terrible effect on cognitive functioning and motor coordination. While my thinking processes are always diminished from what they were before I became ill, there is a threshold of physical activity that, once crossed, becomes frightening.
-- Approaching the threshold, I experience one or two smaller "brain fog"-type moments: forgetting where I was driving to, or putting clothes away in the wrong place. If I push through and try to keep going, I quickly move into what feels like a dementia-level impairment which makes it unsafe to drive or operate a stove. (Unable to figure out what side of the road to drive on, unsure how to turn the stove on or off, severe motor coordination issues...).
-- Through a tracking system I developed, I was able to determine the exact threshold where these issues occur. I began it as an experiment to see how many goals I could reach each week, but it turns out that the results are incredibly consistent.
--- Using a step counter: at 2,000-3,000 steps in one day, I experience severe leg pain and other physical issues
--- At 3,000 steps my cognitive functioning starts to go, and at 3,500 it becomes a severe, frightening, impairment
--- Tracking it a different way, I've found that the total amount of light-to-moderate physical activity (cooking, errands, housework) must be limited to an average 2.5 hours per day
- There is a specific day in March of 2014 when it was clear that something was wrong. However, looking back, it is also clear that I was not well for some time, and that over the course of many months there were physical issues that put 'dings' into the underlying illness until it got to the point that my body gave in and said "no mas".
-- I would caution the temptation to declare a single event -- physical, illness, emotional, stressful, or otherwise -- as the 'cause' of CFS. I now recognize that I had been ill for a very long time, but dismissing symptoms which I now experience in a more severe form. The incidents that occurred leading up to March of that year (eg: surgery for wisdom teeth the previous December) were putting fuel on the fire, but the problem was already there. In fact, there are actually a fourth set of symptoms -- ones that were happening leading up to March of 2014, but changed after that month.
There are many other pieces to this, effecting my entire body -- from hair loss, to skin changes, to balance and motor coordination, to GI issues.... Some occur every day, while others only creep up during a flare. It is a confusing and frustrating disease, and while I continue to learn how to manage it better, the great hope is that someone will be able to put the pieces together and explain the mechanism that is causing all of this.

As a patient, my thoughts include:
- Granting study participants access to their data. This is an ambitious research project, requiring a big commitment from patients. Partnering with them by allowing them to take home results from testing would go a long way in attracting patients.
- Thinking outside-the-box when it comes to research goals. A biological marker and better understanding of the physical mechanisms is top priority, but a good secondary one would be to come away with a better definition of the symptoms and life-altering nature of an illness. (It goes far beyond "fatigue". And perhaps even a better set of diagnostic, evaluation, and treatment tools available. If doctors could understand the multi-systemic nature of this disease, and if patients could be given tools to better describe and summarize their symptoms... it would still be a step in the right direction.

I encourage you in your research, and will be following it closely. And, if possible, would like to volunteer for the study when the time comes. I have quite a lot of information about my personal journey through this

illness, and have been able to mark a number of contributing elements to it. I'm happy to answer questions if you have any.

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Subject: ME/CFS RFI response

Response to RFI re ME/CFS

Dear NIH,

This response to your RFI comes from an 83 year old retired McGill Prof of Literature who moved to Victoria, BC in 2006, succumbed to ME in 2007, and has been sick ever since. I have been active in the local support group in recent years, and have been following both the politics and the research fairly closely.

May I begin by a general comment stemming from your specifying 3 questions; I would ask you to not try too hard to control all elements. Your organization has an unhappy and long history of ignoring or trying to minimize our disease, and you do not have any well recognized experts with a lot of experience or deep knowledge of a very complex disease. I would ask you to be more open to input from, and collaboration with, external experts. I see this is beginning, with the appointment of Ian Lipkin to a role in the new internal research project, and I hope this is a sign of a growing shift. But there have been comments from within your ranks that one of your motives has been to protect us from "bad doctors," and I trust that is not now a part of the NIH project.

A "Emerging needs and opportunities" and "gaps and opportunities." I have lumped these two categories togethe.

1) further intensive investigation of the possible differences between the disease as it appears in men and women; medicine is beginning to realize that in many diseases, such as heart disease, there are substantial differences between the sexes, and particularly in view of the strong predilection of ME for females, while also choosing a substantial number of males (myself included), this may become an important parameter. There are a few bits and pieces here and there, but the topic is still radically underexplored.
The same is true in respect to age, though here there are a few interesting papers–Julia Newton has a short piece on how ME manifests in the old (fatigue and OI–fits me!), and Mady Hornig has a good essay on changes in the disease over time. But there is still much to learn about the possible differences in ME when it hits the young and the old–most studies have most of their patients in the 30-50 bracket, more or less, and with 75-80% of women. These differences may become even more important when it comes to possible treatments.
2) the sex ratio, and the recent results from the Rituximab studies, point strongly towards an important autoimmune component, and there have been several small studies confirming this. It is time for a full-scale inquiry, which may also open up further avenues towards treatment.
3) the role of mitochondrial dysfunction. There are now some papers on this, and Sarah Myhill in the UK has been pursuing this path for some years. Now Ron Davis and the mito expert Naviau have made a preliminary comment that mito dysfunction may be at the root of the disease.
They may or may not be able to clinch this, but I think they deserve funding from you, though Ron Davis reports having had a research proposal turned down because it "lacked a hypothesis." I think that there is room at this relatively early stage for research aimed primarily at creating a large body of data, which can

then be mined for a variety of possibly relevant anomalies, and this appears to be one. Serendipity rewards good and prepared minds.

4) some exploration of possible environmental triggers. There has been a lot of not always conclusive focus on viruses, and other pathogens, and some focus on genetics, but as in the case of cancer I suspect that that will prove less than conclusive, though of course it will always have some relevancy. There is some evidence (the Countess of Mar in UK is quite clear that chemicals used in sheep dipping triggered her own case) that pesticides and other noxious chemicals may play a role.

Encourage by the recent publication of some results (more are to come) from that large US study on the effects of RF (cell phones, WiFi, "smart" meters, etc etc), making it quite clear that there are impacts on biological tissue, including mitochondrial function, and helped by recent research by such as Paul Héroux at McGill and Martin Pall, retired Professor Emeritus at Washington, who wrote a once famous book "Explaining Unexplained Diseases" that dealt with ME, I think it would be helpful to investigate seriously the possible role of this increasingly invasive energy in triggering ME among other diseases involving mitochondria and neural degeneration. I write this in part because it seems to me the most likely trigger for my own case, which hit unusually late at age 74, with no obvious viral attack, but also because there is now increasing evidence.

There are doubtless other possible environmental triggers that should be investigated, and combined with this should be some detailed epidemiological studies. For instance, has the incidence been rising, or has it kept steady? If there are environmental triggers that appear relevant, do any mesh closely with an increase/decrease in numbers? There does, for instance, appear to be a disturbingly close relationship between the alarming rise in ASD and the number of required vaccinations in the US (there are several good academic studies tracing this); is there anything comparable with ME/CFS? I shall add here that my suggestion to explore the possible role of RF could certainly not explain the whole issue, or one would have a delayed exponential effect, which I do not think is happening. But do we really know? This question is of course heavily impacted by the effect of having had for years multiple definitions giving vastly different estimates of the numbers affected. One more reason for choosing and sticking to one as long as possible. So...

5) agree on a definition, in the full realization that it may have to be amended later. The appeal by researchers and advocates to adopt the CCD was ignored–maybe now it could be agreed upon? The Oxford should be retired and all studies based on it too–as that AHQ metareview acknowledged, such studies probably skew the overall picture–but they did not exclude them, and it is time this part of the picture was cleaned and clarified. It has been shown repeatedly that use of the Fukuda, or the CDC revision of it, produce very large numbers, which drown out information about people who really have ME/CFS. Leonard Jason has shown that unexpectedly the International definition also includes people who do not really belong.

B "Challenges or barriers to progress in research on ME/CFS".

1) Painfully obvious is the absence of adequate funding from the NIH. No elaboration needed, other than to point out that this has been remarked upon by many, including the Evidence Based review that fed the P2P process. It continues today, as marked by Jennie Spotila's RFA count. A couple of internally generated grants do not compensate–see initial comments suggesting that you should not attempt too much to control the whole research process.

2) The recent NIH rejection of at least two grant applications from highly qualified and experienced researchers point to grave deficiencies in the grant review process currently in place. Ian Lipkin reported that his had been turned down by a reviewer who believed that ME was a psychological problem. That degree of ignorance is intolerable in one chosen to do that job. Ron Davis has reported that his application was turned down for its lack of a clear hypothesis. As argued above, I think there must be room at this stage of research for work designed to produce a large data base that can then be mined for specific issues

that appear. It seems that their data may already have produced such an issue–the centrality of mitochondrial dysfunction.

I could also suggest that subjecting researchers of the stature and record of these two to review is really an insult; my feeling, and I write as an experienced academic from another field, is that beyond a certain point the notion of "peer review" should be replaced by making space for any qualified readers to respond to the work published. In spite of what the public has been led to think, "peer review" has too often resulted in the repression of new ideas by old established ones. Obviously as a publicly funded organisation you would be required to exercise some supervision over the grant–to ensure that it is not spent on holidays in Hawaii–but beyond that I think that researchers of real calibre should not be asked to waste much of their time writing overly detailed applications, which might overcommit them to predetermined ends that might well have to be changed as results began to flow in.

1) there still seems to be a reluctance on the part of NIH to fully engage the patient/advocate/researcher communities. We are much encouraged by the apparent major shift in attitude, perhaps especially evident in Vicky Whittemore's comments, and her appearance at the conference in England. This reinforces hopeful feelings. But there are still signs that disturb–and please remember that the hijacking of this disease by the psychiatry has a long and painful history, and some of us have long memories.
For instance–the new internal NIH study, impressive though it seems to be, has a couple of oddities attached to it.
One is the initial statement that both Fukuda/CDC and Canadian Concensus definitions would be used, though all subjects would fit the CCD. I fail utterly to understand this; it is pretty clear that the CDC ropes in many more than does the CCD, so what happens? 100 subjects get through the CDC screen, and then are whittled down to 40 when passed through the CCD? Then why bother with the CDC at all? I do not understand, but is it a reluctance to fully make the shift to accepting the CDC as the standard until research shows that it in turn needs revision?
The choice of Brian Walitt as Lead Clinical Investigator is a real problem as far as I and most of us are concerned. We have received reassurances that are essentially meaningless in the face of his well documented opinions. Some of the other "associate investigators" are also open to question: Dr. Leorey Saligan has written "the unnecessary increase of attention to the symptom in catastrophizers may influence the person's motivation to perform activities of daily living, making catastrophizing as an ideal behavioural marker for central fatigue." This really is offensive nonsense; we don't "catastrophize," we remember what happened last time when we overstepped some invisible boundary.
And now you have given a large grant to Fred Friedberg to enable the participants to become MORE aware of internal events such as "heart rate variability" in order to possibly enable us to minimize our reactions to "prevent or reduce relapse by adjusting...activity patterns in advance." Unfortunately, major life events have a nasty habit of coming unannounced, and of course they can worsen any chronic disease, including ours.
Despite verbal reassurances, I still harbour an uneasy feeling that the doctrines of Steven Strauss and others are still at play within the NIH. I wish to emphasize that the first priorities for funding should be given to studies aiming to uncover the basic etiology–or etiologies–of this disease, and use that knowledge to discover at least moderately effective therapies.
2) the absence of usable biomarkers is still a major barrier to progress, though there are now probably enough laboratory tests to serve the purpose for research. I wish to differ with the hopes expressed by some that the 2 day VO2 Max test be used–it is simply too damaging to moderately or severely ill patients. I do suspect that enough markers have now been uncovered that a careful choice of a few could do the job, if a careful search were made assessing the competence of say 4 or 5 acting in concert, beginning with the well established incompetency of our NK cells. This has fair specificity, but poor selectivity–we do not "own"

this anomaly. But maybe this could be paired with one or two anomalies that rated high in selectivity, but not so high in specificity. Might it be possible to use two or three such tests to form a workable biomarker?

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Subject: LDN for CFS caused by oxidative stress from hereditary hemachromatosis

I was taking up to 40 mg of hydrocordone per day plus diclophenic. I had intractable pain in my lumbar and lower extremity's. I landed in the hospital with pulmonary embolisms originating from my left foot. It was ridiculous to take medication at that level to allow me to walk with for 10 minutes before the pain returned.

Due to lack of insurance, limited intervention was prescribed by my providers.

I purchased naltrexone as I took control of my health direction from my hospital bed. After a two-week washout from prescribed painkillers, I ramped up over a six-week period to 4.5 mg of naltrexone daily... LDN therapeutic level. I feel much better and can walk up to an hour without significant pain.

I still suffer from episodes where I ate to the bone. I believe CPPD crystal deposition trigger some of the joint pain, but it wouldn't account for bone pain.

Due to existing damage and the propensity for iron overload to create oxidative stress, I will likely be at the 4.5 mg per day for the rest of my life. At only $.20 per day, I do not understand why LDN fails to gain traction as a primary treatment modality.

Multiple groups promote LDN for the relief of pain. The Cleveland Clinic is successfully treating patients with chronic pain. I shudder imagining what my life would be like without LDN. A prime challenge to me is whether I can procure another reputable supply of Naltrexone. Given current track record with opioids and addiction/death, I am beyond words medication commonly used for opioid and alcohol cessation is kept from me. Why force me to the streets?

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Subject: Input for New Research Strategies for ME/CFS

Dear Trans-National Institutes of Health (NIH) ME/CFS Working Group Members,

Thank you for your Request for Information: Soliciting Input for New Research Strategies for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS), Notice Number: NOT-NS-16-024.

Before I list particular recommendations, I'd like to tell you a bit about myself. I was diagnosed with ME-CFS in 2010, was declared disabled by the SSA in 2012, and have been essentially mostly bedbound and housebound for the 5 years. Prior to this, I graduated in the top 1% of my high school class of 500, then earned my BA in Sociocultural Anthropology from Harvard, and later an MA from Antioch University while also working full time for the local public health department. I then taught graduate and undergraduate courses. I enjoyed my intellectual life very much. I was also physically and socially active. All of those are relegated to my past.

Due to ME-CFS, I suffer from a myriad of physical and cognitive symptoms, and I am unable to carry out routine life activities that normal people do not give a second thought to. I have lost the ability to read academic and scientific articles, and I am unable to prepare a well-researched and well-organized list of suggestions, as I would have in the past.
However. I will touch on a few points.

First, I believe that one main opportunity is educating physicians and physicians in training on the current state of ME-CFS research and its clear evidence of a biophysical cause. Diagnosis and care is lagging far behind, and many physicians still maintain the outmoded belief that it is a psychosomatic illness, if they think of it at all. Still others dismiss patient reports of fatigue out of hand. This means that possibly thousands of patients are undiagnosed and suffering.

Second, it is essential to find biomarkers, and to adequately fund this research, with $250 million yearly made immediately available. Ideally, numerous centers would be set up across the country--perhaps in partnership with university medical centers--in order to collect specimens, with a focus on the most ill, those who are bedbound and housebound.
Additionally, biomarker research that has already taken place should be evaluated, so that time isn't lost reinventing the wheel; and world-class virus and other biomarker researchers, such as Ian Lipkin and Maddy Hornig at the Columbia School of Public Health, and ME-CFS clinical experts such as Lucinda Bateman at the Bateman Horne Center for ME/CFS and Fibromyalga, should be included at a high, decision-making in the planning and implementation.

Also, it may be advisable to conduct significant research on several treatments that seem to have a mildly ameliorative effect on symptoms, such as LDN (low dose nalrexone) and IV saline infusions, and if they prove to have a measurable and significant positive effect, to educate physicians about these treatments and add information about their viability to any of your organization's public pages about ME/CFS.

Thank you for your consideration.

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Subject: ME research strategy

This will be less developed than I would like to make it due to my own health limitations. I have had ME since 1998. Currently I'm at housebound level. I read ME research as it is published and I am excited by the prospect of adequate funding for ME studies.

Emerging needs and opportunities that should be considered as new ME/CFS research strategies are developed:

I'm noticing greater collaboration and converging themes from international ME researchers. There's an important opportunity to build on this. For example, multisite studies or replications. Themes seem to involve B cell issues (and related rituximab treatment and auto antibodies), the microbiome and metabolics. It would be useful to study all of these in the same well-defined patient group.

Challenges or barriers to progress in research on ME/CFS:

Previous research has been very hard to compare due to confused case definitions and methodological issues. For example, the recent systematic review of drug therapies (Collatz et al 2016) found that, although there were some significant outcomes, the results of the studies are limited to their respective cohorts and can't be applied to other groups of people with ME (pwme). Depressingly for us this meant they could not recommend any treatment due to these problems with past research. They suggest this can be overcome by

1) using clearly defined, standardised diagnostic criteria such as ICC
2) standardising questionnaires and scales so that they are sensitive, specific and comparable in meta analysis
3) reaching consensus on how to measure the effectiveness of treatment in ME
I would add that objective measures should be included wherever possible, not just subjective scales which can be interpreted differently by different patients and researchers (this might include common technology such as a sports watch recording heart rate, sleep and steps).

Heated debate around the labels of ME and CFS causes problems for patients and researchers. These terms are used differently around the world. The label SEID doesn't seem to work for most patients and hasn't become popular. I wonder if it could help to drop the CFS term, take up a strict ICC criteria for research, but then also acknowledge those who don't quite meet ICC as still physically ill but with Atypical ME (when working I saw this strategy used for other conditions)? Or a concerted effort to subgroup according to biomarkers could lead to specific, new labels which move away from negative past association with CFS.

Gaps and opportunities across the research continuum from basic through clinical studies.
There's a lot of gaps in ME research, so I'm finding it hard to summarise here. A key starting point is people with Severe ME. Although Severe ME patients are hard to access the data will be much richer.

In addition to really getting to grips with aetiology and biomarkers longer term, we need some quick results on therapeutic interventions (even if the mechanism of action isn't well understood). I am interested in Jared Younger's current research into Gulf War Illness using 9 supplements which are easily available. Some quick turn around research like this into ME would be much appreciated. Some of us have been ill for decades with virtually no treatment. We don't all have another 5 years to wait.

Also, once we are diagnosed with ME it is common for new symptoms to be dismissed as part of the ME and not treated. I recently had this experience with a 11 hour paralysis outside of my previous experience of 18 years with ME. I missed a comorbid POTS diagnosis and treatment for 16 years for this reason. Research to clarify which symptoms are exclusively ME and which associated (already treatable) co-morbidities could be valuable.

I contributed 2 research ideas to the Norwegian Research Council request for patient input when I was doing better. It will save me some energy to copy those here:

1) **"Extended Family Extensive Medical History and Genome Analysis in Families with Multiple ME Patients**
In what area do we need new research into CFS / ME ?

There is already good evidence of a genetic predisposition to ME, with a hereditability estimate of around 50% (2nd World Conf). There is also evidence of mitochondria dysfunction, cardiovascular and autonomic impairments (which can have a hereditability element). It would be useful to do in-depth medical history and extended pedigree research on case study families where more than one person has had ME, taking a

broad view of different health conditions. Depending on resources, this would include Genome Wide Association or a focus on areas such as mitochondrial DNA, immune function, MTHFR gene mutation and conditions related to dysautonomia such as Ehlers-Danos Syndrome. How do family members' symptoms of other illnesses relate to recent genetic ME research? For example, hablogroup H has been associated with Post Exertional Malaise; J with joint pain and U with less bloating in ME (Billing-Ross et al 2016). Do family members experience these symptoms in the absence of meeting ME diagnosis criteria?

What specific issues should be investigated further ?
It would be interesting to find out if genetic variations related to ME can be expressed as different conditions in other family members, or as variations which would not be severe enough for diagnosis. This idea is inspired by a paper posthumously analysing the medical history of Charles Darwin's family (Hayman, 2013). Many of his relatives suffered chronic illness but in different forms (including the appearance of ME/CFS). This paper speculates a specific A3243G mtDNA mutation caused the different symptoms. What is more interesting for ME research is that "the detailed, lifetime history of his illness and those of family members shows us the range of symptoms that may occur with the one mtDNA abnormality".

Any research on participants with ME should also include careful recording of length of illness, apparent triggers, severity, the nature of symptoms and other co-morbidities for use as further comparison or subgrouping.

Why is this important for this population ?

This could be an important element of identifying hereditary causal factors, which in turn could identify effective treatment. It may also be possible to identify differences in relation to triggers. In relatives who have similar mutations, but do not develop ME, what life experiences have been different for these individuals? In particular, what has their experience of infectious disease been? Does anything appear to be protective against ME, despite having a genetic predisposition? This could be useful for younger relatives who are at risk of ME.

If the families do not demonstrate clean Mendelian segregation patterns, does this suggest the possibility of multiple underlying genes requiring further research?

Why is this important and useful for therapists (health) ?

If family members have genetic mutations in common, but different expressions of illness, it may be that existing treatments for their other conditions are beneficial to ME patients with this specific variation. Information about patient reaction to drugs may also come out of this research (for example the families may be more often poor metabolizers). There may be useful preventative precautions for other family members, or treatment that could be taken early if relatives show initial symptoms.
It could lead to useful subgrouping, as patients with different mutations are likely to need different treatment. For future patients, with the same mutation as those studied, it would not be necessary to analyse their extended family tree to get the relevant information.

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2)**Glucose Metabolism Dysfunction and Personalised Nutrition in ME**
In what area do we need new research into CFS / ME ?

Anecdotally many people with ME complain of issues to do with sugar, but are not usually diabetic. Some people cut down portions of carbohydrates and others cut out refined sugar. One study found that a low sugar diet was not significantly different from a healthy eating control diet, contrary to patient perception (Hobday et al, 2008).

However, in a recent study people with CFS were shown to have elevated glucose levels, there appeared to be an inhibition of glycolysis (Armstrong, 2015). Another recent study, found striking biochemical differences in skeletal muscle cultures, including a lack of increase in glucose uptake following 16 hours of stimulation (in contrast to control cultures) despite remaining responsive to insulin (Brown et al, 2015).

Is there an unusual metabolic problem with glucose in ME? For example, greater fluctuation than normally seen, apart from in diabetics? Can this be managed with any efficiency at the diet level or is it a more fundamental metabolic problem?

What specific issues should be investigated further ?

A study similar in design to the Zeevi general population study in Israel that had nearly 1000 participants could be useful (Zeevi et al, 2015). That study had 2 phases. Firstly they constantly measured blood glucose levels via a glucometer placed under the skin and recorded sleep and activity using an activity wristband (eg a fitbit). Participants recorded further information in real time about their food, mood and exercise regimes on an app. Obviously a ME study would add in symptom scales into this too and detailed information on activity would be essential. They also took a stool sample for microbiome information.

The Israeli team then created ‘good’ diets that prevented blood sugar spikes based on data from the 1st phase of the study (results were surprisingly individual). They found that not only did blood sugar respond as predicted but that the ‘good’ diet was associated with positive microbiome changes too. Can this diet information be applied in ME too and used as a 2nd phase?

Why is this important for this population ?

Energy metabolism dysfunction is a likely problem in ME and deserves further investigation. The 1st phase of this research can contribute valuable data about glucose metabolism in ME. The 2nd phase may provide an evidence informed approach to managing diet. Even if diet changes are not substantial enough to correct potential problems at the level of ATP production, is it beneficial for patients to keep glucose levels more consistent? In the absence of substantial research, patients find it hard to interpret information about diet and information is shared at an anecdotal level.

In the Zeevi study they found surprising levels of individual difference in blood sugar reaction to food. For example, some people have a healthy reaction if foods include fat whereas for others this makes no difference. People's response to food was also linked to their gut bacteria composition. There was a benefit to individualising diet advice. Can this general population data be useful for people with ME?
Why is this important and useful for therapists (health) ?

Further information about patients' glucose metabolism would be useful for medics. At the moment glucose issues in ME are rarely acknowledged in primary care, once diabetes has been ruled out. It maybe, depending on results, that treatment for other conditions could be used once the nature of the problem is known. This approach is also very likely to steer nutritionists to improved dietary advice for patients.

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Thank you for investing in ME research I believe that this can be solved.

[…]
[…]

To Whom It May Concern:

I have found pain relief from LDN--low dose Naltrexone. It is not an opioid so I'm glad to take LDN for OA pain instead of opiates.

[…]
[…]
Subject**:** CFS

After being a victim in a domestic violence head strike, I having a valid restraining order in effect, almost dying from my brain trauma, then being accused of the attack as being my fault, my adrenal gland has never been the same.

Then I witnessed a murder. The nurse I was seeing said the body pain's I have are all in my head, and wanted me to take Lyrica. Then the new's is out about Lyrica and making your brain cell's die. I have denerative disc diease proof. I also showed through all of my year's of blood test's for my thyroid ,etc that I have never abused my opiate pain medication !!

It's not fair if we the none abuse's don't recieve help. But all other drug user's get help !! Meth , marijuwauna, crack, alcoholic's .

They all get help, but we in chronic pain suffer.

[…]
[…]
Subject: RFI: ME/CFS

I am a patient who has had ME/CFS for over 14 years. Two years after I got sick, on March 1, 2002, both of my young sons, then ages 6 and 10, also got ME/CFS. After 10 years, one of them (whose ME/CFS was always milder) was completely recovered, but the older son, now 22, still has ME/CFS, as do I.

There is an urgent need for treatments to be officially approved in the US for ME/CFS. Having a technical background myself (ChE), I have devoted much of the past 14 years to researching and trying treatments. Although nothing so far helps a lot, we have found quite a few treatments that each help a little, and those add up to greatly improved quality of life and ability to function. Both my son and I are far more functional than most people with ME/CFS because of these treatments, though we are both still clearly disabled by the illness and must live our lives as defined by restrictions & limitations.

I also manage several online and in-person groups for parents whose kids have ME/CFS and so have collected information on treatments from them, as well. Many of their children are housebound or bedridden by this debilitating disease. **There is a serious lack - and an urgent need - for more research into treatments for children with ME/CFS.** There has never even been an ME/CFS population study of children & teens conducted.

There are millions of Americans - including many, many children and teens - suffering from ME/CFS in the US…and not a single approved treatment.

All of the treatments that have helped my son and I are currently available in the US, and many of them are off-label uses of existing medications. Research is needed to quickly assess the effectiveness of these already existing treatments in order to approve them and make them available to more people. Currently, most of these treatments are either not known by most doctors or doctors are hesitant to prescribe the drugs off-label. We have been fortunate to be able to travel to see ME/CFS experts, but that is not possible for most patients. We are also fortunate to have a primary care physician who understands ME/CFS and was willing to listen when I brought her information, so some of these treatments were prescribed by her. Most SHOULD be readily available through primary care physicians - they are only lacking the knowledge.

ALL of these simple and inexpensive treatments should be made available to ALL patients (and doctors should be trained in their use for treating ME/CFS) - I am including links to more information:

- **Correcting the sleep dysfunction** characteristic of ME/CFS **using low-doses of tricyclic antidepressants at bedtime to help increase serotonin and/or dopamine**, as a healthy body would

naturally. This has worked remarkably well for my son and I, providing deep, normal sleep every night for over 10 years now. https://web.archive.org/web/20011201183549/http://www.cfids.org/archives/2001rr/2001-rr3-article01.asp

- **Treating Orthostatic Intolerance with a variety of medications, including (Florinef), midodrine, and various beta blockers at low doses**. Note that different people respond differently to beta blockers, so any study on using them for OI should 1) start with an extremely low dose - even 1/2 or 1/4 of the lowest dose available, and 2) allow for patients in the study to try a variety of types and doses (trial and error) to find the one that works best for them. Keeping the dose low helps to prevent additional fatigue from the medication. When given the opportunity to use trial and error to try different types and doses of beta blockers, ME/CFS patients are almost always successful in finding one that helps them. http://www.dysautonomiainternational.org/pdf/RoweOIsummary.pdf
- **Treat immune dysfunction**. Immune dysfunction is at the heart of ME/CFS and is the root of many (perhaps all) of its resulting symptoms. **Normalizing the immune system** can therefore help to improve all symptoms. Two treatments that have worked very well for us and contributed a great deal to our improvement over the years are **inosine (available as a supplement in the US) and low-dose naltrexone (LDN), which uses a tiny dose (1 mg - 4.5 mg) of an already long-approved drug, naltrexone**. Both of these help to normalize the immune system in ME/CFS but - again - dosing is critical as most ME/CFS patients over-respond to medications. Though LDN is typically thought of with 3 mg or 4.5 mg as ideal doses, many people with ME/CFS do better with only 1 mg or 1.5 mg. Inosine must be used according to a complicated dosing schedule in order for it to remain effective. Dozens & dozens of studies on LDN for immune disorders (but none yet for ME/CFS): http://www.ldnresearchtrust.org/Clinical-trials-studies More info on LDN & how it works: https://www.ldnscience.org/ Inosine - note that this article refers to the name brand Imunovir, sold in Europe & Canada, but we have found the generic inosine supplement to work exactly the same for us: http://www.anapsid.org/cnd/drugs/isoprinosine.html http://www.anapsid.org/cnd/diagnosis/cheneyis.html
- **Treat underlying infections**. Perhaps the most important step in improving or even recovering from ME/CFS but one that most doctors do not understand or know about. The immune dysfunction of ME/CFS causes reactivation of latent infections, so these should be treated aggressively with antivirals or antibiotics. **Common culprits in ME/CFS include mono (EBV), HHV-6, CMV, enteroviruses, Lyme disease and other tick-borne infections**. My own son has 3 different tick infections and has improved greatly with treatment for those. If someone with ME/CFS has high levels of EBV or contracts mono for the first time (as is true of many teen ME/CFS patients), most doctors only know the standard protocol - no treatment and wait for it to pass. But people with ME/CFS - especially children and teens - stand to improve significantly and perhaps even recover with aggressive antiviral treatment using Valtrex or Famvir. Dr. Martin Lerner pioneered much of the existing research into treating underlying infections in ME/CFS with great success: http://www.hhs.gov/advcomcfs/meetings/presentations/presentation_10122010_martinlerner.pdf http://www.ncbi.nlm.nih.gov/pubmed/23080504
- **Address methylation**. For most ME/CFS patients, their methylation cycle is severely dysfunctional, causing problems with energy production, adrenal function, and detox pathways. This last one is probably at least partially responsible for the fact that so many ME/CFS patients can not tolerate even small doses of medications. Often, **methylation can be addressed very simply (and cheaply) with B12 folate (specific types) supplementation and results in significant improvement**. This was key in my own son's improvement. Dr. Amy Yasko in the UK has written extensively about this: http://www.dramyyasko.com/our-unique-approach/methylation-cycle/ Here in the US, Rich Van Konyenburg (sadly, now deceased) also did some important work in methylation, including a

simplified protocol for ME/CFS
patients: http://www.prohealth.com/library/showArticle.cfm?libid=17178&site=articles

For more information on all of these treatment approaches and how they have worked effectively for my son and I, see this blog post I wrote: http://livewithcfs.blogspot.com/2015/08/effective-treatments-for-mecfs.html

All of these areas need attention from NIH - to further research the effectiveness of these treatments for ME/CFS (again, keeping in mind that doses must be VERY low for most ME/CFS patients), and even more importantly, to help educate mainstream doctors about the use of these simple treatments to help improve functionality and quality of life in their ME/CFS patients. Right now, the education and information sharing is happening almost exclusively among patients, with almost no knowledge among most doctors of how to treat ME/CFS - even the simplest of facts, like that Orthostatic Intolerance is an integral part of ME/CFS and is easy to treat.

There is also a significant need for continuing **new research into ways to diagnose ME/CFS, its causes and exact physiology, and more effective treatments**. One particular area of current interest is the **use of Rituximab for ME/CFS**. To date, the only studies that have been done have been in Norway (one is planned in the UK), but the results from Norway have been very promising, with 60% of ME/CFS patients improving significantly or even recovering in multiple studies. The US needs to get moving and do its own patient-based studies to move this research along further and fully investigate any dangers or downsides.

Challenges:

ME/CFS has some significant challenges that have gotten in the way of effective research in the past and could make further research useless if ignored:

- ME/CFS is a multi-system disease that affects almost every part of the body. The traditional approach of trying to squeeze it into one single category or medical specialty doesn't work.
- ME/CFS patients tend to over-respond to "normal" doses of medication or supplements (see notes above re: beta blockers and LDN). Studies that use a single standardized dose to test a treatment are bound to fail. ME/CFS patients need a period of trial and error, starting with the tiniest dose available (often needing to cut pills in halves or even quarters or use a liquid) and only increasing dose as tolerated. Clinical studies should be set up with this understanding.
- ME/CFS is heterogenous. Different patients have different primary symptoms and respond differently to treatments. Again, allowing for some trial and error in clinical studies would help tremendously, and standardized dosing is certain to fail.

Ultimately, the goal for ME/CFS research should be not just finding treatments that help to improve symptoms a little bit but finding the cause of ME/CFS and a cure so that patients no longer need to live with a lifelong sentence of disability and limitations.

[...]
[...]
Subject: RFI response: Research Needs/Opportunities ME/CFS

NIH should fund and direct a Phase IV clinical trial of Ampligen for treatment of ME/CFS.

ME/CFS is a severely debilitating, chronic and complex disease. Considered a public health crisis, it is a critical unmet need with a severe lack of funding; we recommend a Phase IV study be conducted by the NIH granted under a conditional approval by the FDA and in collaboration with the support of the sponsor. The recommendation fulfills NIH/FDA's goal to speed new treatments to patients announced in 2010*

- A description of the need or opportunity Currently there is no approved drug therapies for ME/CFS, however Ampligen provides a most unique opportunity to advance a treatment, further understand the disease and open the regulatory doors for other pharmaceutical companies to pursue drug development. No other therapy has advanced this far in the FDA pipeline. New drug therapies entering the pipeline may take another decade before approval. FDA regulations permit conditional approval of drugs and their collaborative initiative with NIH offers the pathway to conduct the study.
- A scientific rationale and potential health impact
- Ampligen has completed Phase II and Phase III double blind/placebo controlled studies and has been providing benefit to patients for over 20 years. The FDA advisory committee voted it safe for approval. Drugs with significantly less dosing and with significantly higher adverse events have been approved for use. ME/CFS experts agree that a conditional approval of Ampligen is warented and could improve the lives of 25-40% of the ME/CFS population.
- Any Anticipated challenges that may arise A concern over wide spread use in the marketplace; recommendation is that a risk mitigation program be established that requires the physician on how to diagnose the disease and properly administer Ampligen; require the patient be educated on the drug and the dispensing pharmacist must check that the doctor and the patient have fulfilled on these requirements prior to releasing the drug.
- Appropriate benchmarks for evaluating progress ME/CFS experts be included in the conduct of the Phase IV trial and all parties agree upon the measurements and the study must comply with FDA requirements.
- Challenges and barriers to ME/CFS research Lack of understanding by the health agencies and the healthcare community.
- Gaps and opportunities in research

Funding needed to conduct appropriate level research

[...]
[...]
Subject: LDN for ME/CFS

I am a chronic fatigue patient, ill for 30 months. I started LDN six months ago. It has reduced my pain by about 85% and enabled me to get out of bed daily, although not yet out of the house. Please investigate this drug for future approval in treating chronic fatigue. I feel it could help so many people who are suffering great pain every day.

[...]
[...]

[...]

I am a survivor of the "original CFS cohort", which started up in Incline Village.
I literally started this famous syndrome by telling researchers they need to look into the mold that was making us ill.

None of them ever did. All CFS researchers chased viruses instead.

I am an Incline Village survivor and original prototype for Holmes et al "Chronic Fatigue Syndrome"
No CFS researcher of any type ever looked into our outbreak, our illness, and our evidence.

As a prototype for this syndrome, it is not my job to beg the CDC/NIH or "CFS researchers to do so.
Do your job. Look into the reason why there is a "Chronic Fatigue Syndrome", or flush your "researcher credentials" down the toilet, for you have abandoned the methods of science.

https://www.survivingmold.com/community/[...]

[...]
[...]
Subject: ME/CFS research

Dear Group Members,

I am a 38 year old woman diagnosed with CFS in 2012, and a third generation sufferer of this devastating illness afflicting women in my family. I am a college graduate that held my last job for almost 9 years, and a fiercely independent person. Due to CFS I lost my job after a year spent fighting tooth and nail to drag myself to work every morning, where inevitably I became too exhausted to sit, and would drag myself home only an hour or two later to lie in bed for the rest of the day. At the worst points of my illness I have been unable to feed and care for myself, and have spent many days in the dark of my bed, unable to tolerate lights and sounds from the outside world. I have difficulty with speech and memory often, and am no longer able to read more than a few paragraphs due to cognitive symptoms. Despite visiting many doctors, having a never ending stream of tests, physical therapy, acupuncture, chiropractics, injections, supplements, and medications, I am not well or even improved after 4 years. I have spent thousands on credit, desperate to recover despite my lack of income, only to find myself buried under the weight of debt in addition to my illness. I have been denied disability because my tests are "normal" and there is no measuring the total exhaustion I feel most hours of nearly every day. I have appealed the ruling, and pray that my marriage can survive the strain of my total lack of income, severe dependency, and general lack of physical contribution to our household. Thank you in advance for your time reading this, and for considering the toll this illness has on its sufferers, who have spent long years in the darkness of misunderstanding and inadequate treatment. Below are my suggestions for research.

-I believe that it is important to understand the ways CFS patients differ in response to exertion compared to healthy individuals. I also believe it is insulting to recommend graded exercise therapy or other physical activity to a sufferer of CFS unless there are treatments that allow a return to normal energy levels. Exercise as treatment for CFS implies that we patients are to blame in some way, or that our aversion to activity is laziness. Nothing is further from the truth, and I do not believe this logic to be applied to other serious diseases, and therefore should not be applied to CFS.

-I feel that one of the largest barriers to getting quality care is the ongoing assumption that a patients psychology is somehow involved in this type of illness. It would be naive to dismiss the power of ones

mental health on the physical, but it is not at the root of this disease, and the experience of being invalidated through every stage of care because this illness is not yet understood is the worst thing for the psychology of us patients. Also, I believe that there is still significant gender bias at work in the medical profession. A large majority of CFS patients are female, and many doctors in my experience still seem to view us through the skewed lens of past misconceptions about our mental frailty and tendency towards hysteria. It is a real bias, and should be addressed with physicians so improvement can begin.

-Inpatient treatment facilities should exist for those severely ill and bed bound with this disease. It is incapacitating to many people who are unable to work or care for themselves. It seems an insurmountable obstacle that those of us who can barely walk, converse, drive, or afford help should have to wait years for any relief. I dread doctors visits, feeling unable at times to make even the phone call, knowing I will have to shower, dress, arrange transportation, wait for hours, struggle to communicate how truly awful I feel every day as a blank faced Dr. Looks at me and puzzles over my clean lab results. Then to know I will have to make it to another lab or test, try new medications, and possibly wait several months in agony just to have no results or hope feels inhumane. If inpatient treatment was an option, lab work,IV therapies, and other care providers in one place would potentially eliminate years of visits that are burdensome and if effective treatments were identified, potentially mitigate the extreme cost of lost wages and other ill effects of struggling just to survive each day.

-Identify some standard protocol of lab work and other tests that could definitively diagnose and identify areas for treatment. Right now I feel it has taken years for my large collection of doctors to cycle through basic to complex lab work and other tests. Why is CFS the term here in the US but ME seems to be used in other countries? If they have tests for ME that show something is amiss, could we make it standard in the us? It is so difficult to "prove" CFS for purposes of diagnosis and disability assistance, and it is an unfair burden to patients in very real physical stress.

-I would like to know if there is a genetic link as 3generations of women in my family have this illness. Could it be a viral infection passed from the mother to child? Or genetic defect? If so, what triggers it to become activated to cause full blown disease after years of apparent health?

-Finally, I believe that more resources available to patients quicker would ease some of the suffering and burden involved in having CFS. Until it is cured, it should be seen as a diagnosis on par with other serious diseases such as the AIDS virus, and recognized by our disability system as such. Making available help around the home, transportation, childcare, and financial assistance would lessen the blow and maintain families who otherwise would be under great strain to care for us patients. I would love to be less of a burden to my loved ones, and it would help me enormously to feel less dependent.

Thank you for your time and for your wisdom in helping the chronically ill affected by this, you have the ability to change many lives by addressing this.

[...]
[...]
Subject: NIH request for patient input

Dear Ladies and Gentlemen of the Trans – NIH Working Group:

The ME/CFS community is undoubtedly giving you many excellent suggestions for research priorities for ME

and CFS which you'd be wise to take under consideration. But before you even consider research priorities, you have a more basic task to accomplish. You need to show that NIH is, at long last, trustworthy.

Bluntly, that is an uphill task. If that sounds harsh, it is because it is – but it is a situation of the NIH's own making.

Even though the community hopes the tide has finally changed, it also remains skeptical. For three decades, HHS and NIH have failed to help, and have often harmed, the CFS and ME community. There has been significant malfeasance (which Webster's defines as "illegal or dishonest activity especially by a public official"). While the CDC has earned the lion's share of dishonor, and while NIH has sidestepped legal censure, the agency's hands are far from clean. There are examples going back to the earliest days of recognition of this disease but just the length of time this illness, which strikes males and females of any age, was left to rot in the "Office of Women's Health" (an office without a clear line of funding and no other "assigned" illnesses, including those of female genitalia) proves the point.

Many are glad that NINDS has finally "accepted" this disease into its institute. Most know better than to believe it will change things until they actually see NINDS acting with the same respect towards ME as it does towards Parkinson's and stroke. Given that we've already been told there is no funding plan for at least two more budget cycles, forgive us if we don't hold our breathe. I won't actually be *excited* until I see NINDS (or any other NIH division) actually doing research the community values – I've seen too much poor research over the years. NIH and its institutes are held in high esteem worldwide yet they have failed this community profoundly.

The agency's years of open contempt and its lack of urgency (despite innumerable excellent CFSAC recommendations) have already cost a million or more Americans the bulk of their lives, not to mention literally billions of income-producing hours. An announcement alone isn't going to nullify that, nor will a few token grants. It is not just time to fund this illness commensurate with its incredible toll, it is time to make up for lost time. While it may not be entirely fair that the burden of decades of neglect and open contempt is now on your shoulders to remedy, that is part of your job.

What can this committee do to regain the squandered trust?

1. Use what you've already been given.

CFSAC, and CFSCC before it, has written excellent, expert recommendations for more than two decades. These are clear and specific recommendations that were carefully written and documented. The number acted upon is nearly nil. In one real sense, you have no need of this request for community input: research priorities and rationales have been regularly handed to HSS/NIH on a silver platter approximately twice a year for decades. In the process of fact checking this document, I came across the 1997 testimony/requests by Mary Schweitzer and *every single point she made then is <u>still</u> an active request,* with (perhaps) the sole exception of the question of whether this could be infectious at some point in the disease's progression.[i] So pick a list, any list, and you will already have a good starting place. The recommendations are nearly unchanged, which speaks volumes about why patients are so mistrustful.

2. Listen to what the community, the advocates, and the experts say.

There is one recommendation that, in particular, is a glaring need. The request to adopt the Canadian Consensus Criteria as a working definition has been specifically made over and over. The IOM ME/CFS contract was a blatant attempt at an end-run around patients, advocates, and experts when they united in

2013 to specifically demand this via letter and petitions. IOM's lack of success in superseding that definition is evident in Dr. Whittemore's 5/26/16 presentation to NINDS, where she replied to the question of whether there were "very well-defined criteria at this point" by saying, "That's a very good question, and no, there are not." Millions of patients and the overwhelming majority of experts would strongly disagree. And while some patients prefer the CCC and others the 2011 revision called the International Consensus Criteria, the overwhelming majority prefer *either one* over every other existing definition.

Is the U.S. government really so petty that the word "Canadian" continues to be a stumbling block to getting American the answers they deserve? Who cares who wrote it if it is the best at defining patients! Whether or not HHS or any sub-agency likes it, CCC (not IOM) *is* the current gold standard and research based on it *is* producing results. There is no need of debate about definitions at this point – absolutely none. Adoption of the CCC (or, alternatively the ICC) by the US Government, especially the medical research arm of the US Government, is a decade overdue. The use of either of these definitions needs to be a baseline of every NIH-approved study until such time as another definition can be clearly proved to be superior. Bluntly stated, patients demand and deserve nothing less.

There are too few research dollars and too many years wasted to subject patients to yet another multi-year attempt unlikely to end in a better definition. *If* there is no biomarker in the future, and *if* there is substantial new knowledge, and *if* the NIH displays a good comprehension of that knowledge, *then and only then* with there be even the hint of an excuse to waste more of patients' lives and more research funding to replace an expert definition that the governmental bureaucracy "doesn't like." *Until such time, STOP wasting our lives and get on with research!* The continued intransience only makes the NIH look foolishly stubborn.

3. Actively seek out your critics.

Just as it did in the early AIDS years, the NIH must go out of its way to solicit input from people who have been, and continue to be, highly critical of it. No doubt it will be highly uncomfortable for officials and highly-educated researchers to be challenged by "mere" patients yet we are a resource that NIH absolutely must not continue to squander.

The internet and computational power makes direct patient input a possibility in a way that was impossible during the AIDS crisis. Many highly knowledgeable patients want a say and the NIH needs to take full advantage of that. There are also highly knowledgeable patients who refuse to participate. Why? Bluntly, people are tired of "research" that only muddies the waters. They have watched NIH's actions make their lives harder rather than easier. Some of them have previously believed NIH's promises only to have their hard-won contributions, often "bought" with weeks or months of exacerbated symptoms, go absolutely nowhere. Others have seen the pattern and refuse to likewise be patsies. It is your job, and yours alone, to convince them that this time Lucy won't move the football.
Why deal with troublesome patients at all? First, NIH's decades-long neglect means patients have earned a say, a price paid for in advance with their lives. Second, many of them are opinion makers in the community, the very people needed to persuade the participation of solid research cohorts. Third, they deserve respect as highly knowledgeable experts: NIH's lack of action left many with little choice but to earn MD-PhD's at U of HK (University of Hard Knocks) – and not a few hold degrees from traditional venues as well. And finally, because NIH has so willfully remained ignorant for so long, the agency needs them to jumpstart its research with requests such as this so that another generation is not lost.

In the past year, NIH officials have met with those who are the least confrontational within the community. Recently, the conversation was opened up to numerous advocacy groups, including a few which were openly critical. Now NIH needs to actively engage those who remain highly critical. Find out *why* patients reject NIH's ideas… and then act on that knowledge. These represent pitfalls that can be avoided. Is it "fair" to ask a scientific agency to pursue sceptics? No, it is not … until you consider NIH's poor history with this disease.

This public call is a good first step… provided NIH clearly acknowledges *and acts* upon this input. If the NIH chooses to ignore patient suggestions – either the ones submitted in response to this request or to those otherwise sought out – we deserve a convincing reason why. "Because I said so" is a refrain only fit for children. We are owed a thoughtful response and we are scientifically sophisticated enough to spot BS when we see it. Mind you, I'm not saying patients' opinions should automatically overrule the staff's ideas of "good science" but that the NIH *no longer has the option* to simply pretend it didn't hear. Make no mistake, NIH is being watched and lip service isn't going to go unnoticed. If NIH is seen to disregard this input, it will be worse than if patients hadn't been asked at all.

4. Put your money where your mouth is.

This community has heard "new leaf" speeches before – and we have seen nothing come of it. It is why we won't believe these speeches until we actually see the kind of investment we deserve spent on research which had a real chance of changing the paradigm.

Some of us have been essentially told that budgetary increases should be "incremental." Surely, NIH scientists must be math whizzes if they can get "incremental change" to result in real funding when starting from near zero. This new "concerted effort" was announced 9 months ago and, as of this date, ta dah, the grand total amount designated for ME/CFS RFA to date is… $0,000,000,000.00 out of the full RFA total of $2,114,715,000 (October 2015 to date). That is anything but reassuring. We understand ramp up time – we also understand NIH has had 30+ years to ramp up, and approximately 18 months since preliminary findings of both IOM and P2P were made known. The excuse is embarrassingly threadbare.

The NIH needs to make a major investment now, not in 3 or more budget cycles. It also needs to listen to the community about where to put money. The agency had a perfect opportunity invest in a bold idea put forth by a dream team of new researchers that incorporated what patients have long clamored for (right definition, right cohort, and right scale of vision). Instead, the twin proposals were rebuffed with "criticisms" that displayed a complete lack of comprehension. Bluntly put, NIH goofed – big time – by not funding the Open Medicine Foundation's Big Data study. The reasons cited it the rejection were patently ridiculous.

Just to jog the readers' memories, this was a preliminary (not final) proposal for a "big data" study to search for biomarkers exclusively in the most extremely ill population of this disease (with appropriate controls), patients who were so extremely medically fragile that they would be unable to tolerate invasive testing (such as a spinal tap) and who had such profound neurological issues that many have lost the ability to speak or respond. This study was to be overseen by a dream team of Stanford and Harvard stars, including not one but three Nobel Prize laureates. The rejection letter from the committee was cringe-worthy if you believe the NIH's current PR of a serious commitment to ME/CFS research. It said:

- they [the committee] were not sure the study fell within NINDS because there was "no mention of collection of CSF or of analysis of cognitive…function," (aside from the fragility and obvious

neurological problems of the patients, *neurologic* dysfunction is a defining component of this disease even in mild patients)

- that authors should "narrow the focus of the application to focus on the very ill population,"
- that there was a "lack of clear hypotheses" (the concept formulating/refining hypotheses *based on data* was taught in my *grade school* science class, for heaven's sake, and the premise that there will be some physical abnormality (s) in near-comatose patients is hardly a stretch) and "lack of detail" (the concept of preliminary seems to have eluded the committee, even though the extremely high caliber of both researchers and overseeing committee could obviously be counted upon to realize the need of, then to provide, details of rigorous experiments)
- and finally, stating that "large biomarker study is needed in ME /CFS/SEID, but…" (But what!?! Wait until patients find a better team? Until yet more patients die?) They go on to say the proposal should "spell[s] out what NIH would like to fund" (when, in fact, NIH had/has no idea what to fund and this is exactly the type of project which *potentially would set the very research priorities needed)*.

The entire community was aghast at the idiocy of the twin refusals to entertain this massive opportunity with such a research team. The community is still aghast. From all appearances, this was, "No," for the sake of no. For the NIH to say, as it has, that the lack of funding is because it does not get meritorious proposals is insulting when a request of this caliber is dismissed out of hand. One can only wonder what other potentially groundbreaking studies NIH has summarily dismissed over the years. Waiting for research to pan out is one thing; Waiting for Godot is quite another.
[A quote from Act I of Becket's play seems especially fitting here: "ESTRAGON: (*feebly*). Help me! VLADIMIR: It hurts? ESTRAGON: (*angrily*). Hurts! He wants to know if it hurts! VLADIMIR: (*angrily*). No one ever suffers but you. I don't count. I'd like to hear what you'd say if you had what I have. ESTRAGON: It hurts? VLADIMIR**:** (*angrily*). Hurts! He wants to know if it hurts!" – So, since you asked, NIH, yes. It hurts both physically and existentially.]

This is undoubtedly not the only worthy project put forward last year but it is representative of the mindless obstructionism this disease has long suffered under. No research is a sure bet but this proposal was/is easily the most promising and original research this illness has ever seen. It is exactly the kind of research this request for commentary is inquiring about. An about-turn on funding on this project would go a very long way towards building a bridge between the NIH and the community, towards actually showing agency actually intends to fund studies that could make progress happen. That would mean the NIH would need to reach out to OMF and ask for another proposal. Yes, yes, I understand "that's not how it's done" – so, 30 years of neglect *IS* "how it's done"? It is past time the "rules" bent the patients' way for a change!
I will point out something else. It was said by Cheryl Kitt at the 8/18/15 CFSAC meeting that this field lacks research dollars because it lacks quality research proposals (and presumably quality researchers). Not so. When researchers of the caliber of Davis and Lipkin have to resort to crowd-funding of their high-quality research, that isn't "lack of quality proposals," it is a lack of money and NIH interest. This lack of funds means only a small number of highly dedicated researchers have been willing and able to scratch out a career investigating this disease. Most chose to scrabble because they had a loved one affected, the rest because they are true scientists and doctors who were both intrigued and in a position to put pursue answers on behalf of their patients. Given the huge college debt most doctors leave school with today, very few will have that option even if they sincerely wish dedicate their lives to this disease. The majority of researchers who have given their professional lives to this disease are, after 30 years, reaching/have reached the end of their professional lives. Unless there is an immediate, sizable, and consistent commitment openly made to this disease, the generational handoff of knowledge will be missed.

- And it isn't only researchers who are poised to go MIA. Our clinicians are also aging out. There are already so few that most have waitlists years long. If medical students do not learn the basics of this disease (which the CDC has, to date, failed to insure) and if our clinicians/researchers do not immediately begin to train the next generation, millions more patients will go undiagnosed and untreated for the foreseeable future, on top of the millions already aging with this illness. How can NIH justify an entire program for rare, one-off diseases – and nothing for a disease far more common than multiple sclerosis?

  I recognize that all the above forms a harsh indictment of the NIH. But is it really too harsh when patients' reality is to regularly open their Facebook feeds to find that yet another has died young from cancer or heart disease, or has given up in the face of this disease's face of unending agony (both literal and figurative) and committed suicide? Is it too much to ask that prevalence data, 30 years in, not have a delta of as many as 3 million patients? Is it too much to expect that patients need not plaintively beg others for names of doctors within a few hundred miles of them who are not openly hostile? NIH bears a significant part of the blame for every one of these truths. Maybe this request for participation really does mark a change of heart. I hope that these bald truths motivate this committee to act to restore the integrity that NIH was once known for. Then the work can at last begin in earnest.

  In closing, allow me to answer your questions regarding the needs and opportunities in ME/CFS Research:
  - What is the need or opportunity? The need is a clear, steady, and robust funding stream paired with robust cohort selection based on the gold standard definition(s) of CCC and/or ICC. This funding must be large enough for multiple, broad-scaled studies each year. Nothing less than this will attract and hold new researchers, especially of the caliber this patient population deserves after so many years.
    It is time that NIH stops blaming the lack of research on anything by their lack of support. The early days of AIDS shows that, yes, money does result in an explosion of research even when that research potentially exposes researchers to unknown, lethal pathogens. Recent Ebola research reiterates that fact. Our history, on the other hand, shows that a lack of money make a field "career poison."
  - What is the scientific rationale and potential health impact?
    First, the health impact cannot be understated. Patients are first profoundly disabled by this illness and then die years younger than their peers.
    Second, as if this were not enough, this has the scientific potential to elucidate the mitochondrial workings of the cells in the same way as HIV elucidated the immune systems workings. That said, just as it would be unethical to use HIV/AIDS research solely to benefit others with immune dysfunctions, so it is equally unethical to use ME and/or CFS solely to benefit those with mitochondrial dysfunctions (much less garden variety "tiredness).
  - What anticipated challenges may arise? What challenges or barriers to ME/CFS research can be foreseen? Based on past history, the primary challenge will be NIH's own incalcitrant behaviors in the face of Congressional, CFSAC, advocate and even scientific pressures. It is time to end this nonsense, once and for all.
  - What are appropriate benchmarks for evaluating progress? This is simple: funding commensurate with disease burden and prevalence; the adoption of either (or both) CCC or ICC as the official minimum requirement for cohort selection.
  - Finally, what gaps and opportunities in are there in research? As mentioned above, the priorities of 20 years ago remain the priorities of today. The most glaring lacuna is biomarkers, followed closely by effective treatment. There are, to my knowledge, no

studies of the natural course of the disease, especially none that are longitudinal. But the real answer is that the gaps and opportunities will quickly become apparent if there is sufficient funding to motivate new researchers, especially young new researchers, to seek niches of study. It is time, gentlemen.

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http://www.cfids-me.org/cfscc/cfsccs97.html

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Subject: ME/CFS RFI - Pediatric

Dear Sir or Madam:

My daughter was finally diagnosed with ME/CFS after almost five months of deteriorating health that prompted consultations with multiple physician specialists both in the community and at academic and teaching medical centers. My daughter was 17 at the time; she went from being a star athlete with great grades to being unable to sit up for most of the day, fainting, weakness, losing weight, and experiencing dizziness. She saw her pediatrician, a pulmonologist, cardiologist, infectious disease specialist, and rheumatologist. We were repeatedly told that "there was nothing wrong with her", she was "anorexic", and she was "depressed" and "anxious".

I am grateful that my sister, who is a nurse who has had ME/CFS for six years, recognized her symptoms as being consistent with ME/CFS. We brought my daughter to my sister's rheumatologist, who practices at NYU Medical Center. He took a detailed history and conducted a thorough physical examination, and diagnosed her with ME/CFS. He immediately started her on Plaquenil. My daughter continued to deteriorate for another month, to the point where we had to bathe and feed her. She was in bed all day and slept for at least 20 hours each day. She looked severely ill, and people who saw her all said that she belonged in the hospital. As you can imagine, this was a very frightening time for my family. After she had been on Plaquenil for two months, she started to improve, and by four months on Plaquenil she had improved enough to start home tutoring. She has gained the twenty pounds that she had lost during this illness, and she is now able to be up for most of the day with several naps interspersed.
As I write this letter, my daughter's friends are recovering from the Senior Prom that they went to last night and they are preparing for their high school graduation this Saturday. My daughter is not well enough to attend either of these events. Although I mourn the senior year that was denied her, I am grateful that she has improved significantly, and we are hopeful that she will make a full recovery from this dreadful disease. I realize how fortunate we have been to see a rheumatologist who understands this disease and is willing to treat it with medications.

I urge your committee to prioritize Pediatric ME/CFS. That so many children and families are being devastated by this illness is unconscionable. The mainstream medical community has summarily dismissed this disease as "not a real disease" and not worthy of consideration or treatment. The educational community follows the lead of physicians, and these children are often shunned and stigmatized. Sick pediatric patients should not be subjected to doctor visit after doctor visit by physicians who are uneducated and ignorant about this disease. The psychological toll of these doctor visits is enormous on the patient and the family. Having witnessed this on numerous occasions, I can attest to the deleterious impact it has had on my daughter. I find it ironic that physicians and other health care providers must go

through annual training to recognize child abuse, yet there are no standards for physicians to meet regarding identifying, diagnosing, and treating this disease.

Emerging Need:

- Educate pediatricians and other health care providers treating children to recognize and be knowledgeable about ME/CFS
- Require accredited medical and nursing schools to include ME/CFS in their curriculum
- Develop geographical Pediatric ME/CFS referral program so that patients can receive treatment from knowledgeable physicians
- Spearhead data collection of pediatric cases
- Prioritize pediatric ME/CFS for clinical research
- Identify currently available drugs that may have utility in treating pediatric ME/CFS (such as Plaquenil which has helped my daughter)

In closing, I would ask that you evaluate the priorities as if you had a child with this disease. Time is critical, as these children are losing their childhood to the ravages of this disease. They are being denied their right to become functioning and contributing citizens because the scientific and medical community has not considered their disease to be important. Vice-President Biden's son had cancer, so now the nation is behind the Moonshot to find a cure. My child has ME/CFS. Who is behind her Moonshot?

Thank you for your consideration. Please feel free to contact me if I can be of further assistance.

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Subject: ME/CFS RFI Response

Hello,

I have suffered from ME/CFS for 17 years. The following is my response to the RFI.

Emerging needs and opportunities:

1. Biomarker discovery including testing already existing samples.
2. Confirm the utility of two-day VO2max cardiopulmonary exercise testing (CPET).
3. Study metabolomics findings with genetic results.
4. Thoroughly investigate changes in the gastrointestinal microbiome in ME/CFS.
5. Address the of burden of disease.

Challenges and barriers to progress:

1. Case definition consensus.
2. More resources and heightened urgency.
3. There are very few ME/CFS researchers in training.

Gaps and opportunities across the research spectrum:

1. Strategic on going research plan.
2. Clinical trials including Ampligen and Rituximab.

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Subject: Health Care Professional and Patient Response to RFI

Dear Sir or Madam:

Thank you for the invitation to provide my perspective on issues that the Working Group is considering for ME/CFS. I have worked in the healthcare and pharmaceutical industry for over thirty years. I have been afflicted with ME/CFS for over six years. My ME/CFS onset was sudden, and occurred exactly three hours after my second radiation therapy treatment for noninvasive, Stage 0 breast cancer. I was told that radiation therapy might cause fatigue that would last several weeks. I was never told that radiation therapy could "trigger" a disease that would leave me totally debilitated and bedridden for two years, followed by additional years of disability and frail health which continue to this day. I lost my career, my job, my health insurance, and my financial stability due to this disease that the oncology community completely ignores and sweeps under the rug. I received no treatment for this disease from my treatment team at one of the world's leading cancer centers and my symptoms were routinely attributed to "anxiety" or "depression", despite my denials of such.

I consider myself lucky that my primary care physician referred me to a rheumatologist after my severe fatigue had persisted longer than six months. My rheumatologist believes that my immune system is "hyperactive" and he has prescribed medications that "tamp down" my immune system. I have improved significantly on these medications that are widely used in the treatment of rheumatoid arthritis and lupus. The mechanism of action of these drugs is similar to drugs such as cyclophosphamide and rituximab that have demonstrated promising activity in treating ME/CFS. The drugs that I take are oral, generic, and widely available throughout the world. They have been used for decades and have well characterized safety profiles. I have been on these drugs for approximately four years. Interestingly, on several occasions I have had to temporarily discontinue the drugs due to unrelated infections. In all instances when I discontinued the drugs, my ME/CFS symptoms came raging back rendering me completely bedridden. Upon re-starting the drugs, my condition did not improve until I had been on the drugs for six weeks or more, which is consistent with the mechanism of action and timing for peak activity of these drugs.

I am on the following drug regimen:

Plaquenil (hydroxychloroquine) 200 mg twice a day
Doxycycline 100 mg once a day
Imuran (azathioprine) 50 mg twice a day

Plaquenil is an immune modulator. Doxycycline is an antibiotic that has anti-inflammatory and immune activity. Imuran is an immune suppressant. All of these drugs have been used in various auto-immune disorders such as lupus and rheumatoid arthritis.

Based on my personal experience, I would like to make several suggestions for the committee's consideration:

Emerging Needs

Quantify the incidence and prevalence of ME/CFS in patients who have received treatment for cancer.

Focusing on patients who are considered cancer "disease free" following cancer treatment would eliminate the confounding effects of cancer disease burden on the development of fatigue

Both chemotherapy and radiation therapy have been reported to cause ME/CFS

Educate the oncology provider and patient community about this devastating complication of cancer treatment

Encourage and incentivize the oncology community to conduct basic scientific and clinical research in post-treatment ME/CFS that goes beyond psychotherapy and exercise regimens

Emerging Opportunity:

Explore the feasibility of conducting clinical trials with the immune drugs that are commonly used for other auto-immune diseases such as Plaquenil, Doxycycline, and Imuran

Delineate scientific rationale for using these drugs

Stratify patients according to the cause of ME/CFS, more specifically patients with an infectious component vs. patients without an infectious component
Consider a trial design where patients act as their own controls by switching placebo for active drug intermittently

I urge the group to seriously consider starting clinical trials with currently available immune medications. I am living proof that these drugs do have a place in the treatment of ME/CFS. The fact that these drugs are already on the market means that years can be taken off the timeline to get an FDA approval for the treatment of ME/CFS. We patients have waited too long for an effective treatment for this disease.

Thank you for your consideration. Please feel free to contact me if I can be of further assistance.

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Subject: CFIDS research

I have been a ME/ CFIDS patient for 23 years. I feel more research needs to be directed to the possibility that these symptoms could be attributed to a hormone allergy within my own body. An allergy to adrenal, sexual or thyroid hormones could be the cause of my symptoms. As I get closer to 50 and menopause is approaching I find myself finally feeling a bit better. I am guessing that is because my hormone levels are dropping. Hormone allergy is a recognized disease but finding a viable cure/solution is not easy. I propose that hormone allergy be studied as a cause for CFIDS and that new solutions to this allergy be found. thank you

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Subject: CORRECTED - Comment to ME CFS NIH RFI

[…] - ME patient advocate

For the past three decades, ME stakeholders including patients, advocates, medical experts and CFSAC members have given countless recommendations as to what should be studied to enable scientific progress for the disease. This was done in the form of working groups, CFSAC meetings, written and oral communications from patients, advocates and medical professionals.

None of these recommendations were acted upon. Instead, we have seen the creation of yet more NIH working groups. So now, yet again, we are being asked for our input. In all honesty, the time for more words is long over. While NIH is busy talking more and more brave ME patients are dying prematurely from this disease and new patients are being diagnosed every day. **The urgency is dire – we need action now!**

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Emerging needs and opportunities that should be considered as new ME/CFS research strategies are developed.

Replications of past significant studies. There are over five thousand peer reviewed scientific studies that have been published in journals on ME. They have not had a major impact because most were small due to funding restrictions and in need of large scale replications. These include studies showing disruption of the immune system and neurological deficits. Biomarker studies such as two-day CPET exercise testing. low NK cell function and Rnase-L enzyme dysfunction. These studies need to be replicated in a grand scale.

Studying patients from the Lake Tahoe, Nevada outbreak. These patients were at ground zero. After all, it was following this outbreak that this disease was re-defined and re-named. Since then, because of the poor name and criteria, the patient cohort has become muddied and have included many who do not suffer from ME.

Pharmaceutical studies on currently used treatments. These include Ampligen, Rituximab, low dose low dose Naltexone (LDN), anti-virals and IVIG therapy.

Challenges or barriers to progress in research on ME/CFS.

Lack of NIH funding. This is and has been the greatest barrier in meaningful research for this disease. It has resulted in few and especially small scale studies without any replications. We need an increase of **$243,000,000** just to get us on par with similarly burdened diseases. This is not taking into account that our need is even greater than those other diseases since we currently have no officially accepted biomarkers nor any FDA approved treatments. Without an increase of this scale, we have no hope of advancing science to the level that is needed to bring hope for a treatment or cure to ME patients.

Use of the wrong cohort. Using the government constructed criteria such as Oxford, Reeves and Fukuda has been an impediment to scientific advances. These criteria are overly broad and include people who do not have the ME. They include patients that actually suffer from other illness or patients who just suffer from 'fatigue'. We have strict criteria developed by our international ME experts, the CCC and ICC – we should use them.

Studies based on psychiatric and somatization theories. Studies based on these misguided theories are not only a waste of time and money, they have been the cause of harm to patients. Some have been permanently damaged based on these studies. (PACE). See above for what should be studied.

Rejection by NIH of applications for impactful biomedical studies. Among many other respectful ME experts, scientific giants such as Dr. Lipkin and Dr. Davis have had their proposals rejected. The NIH employees who evaluate study proposals for research in ME are not knowledgeable about the disease and therefore are not capable to make a fair and accurate decision on which study proposals to accept. ME experts should be evaluating these applications

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Subject: Use of LDN for ME/CFS

I have used LDN for well year a year now- as part of my protocol to help ease the symptoms of ME.

I believe LDN has helped to slow down the progression of this illness but it is by no means a cure. I am still debilitated and if I have any attempt at normal life I relapse into malaise and fatigue. I am housebound for much of the time.

I would be happy to answer any questions.

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Subject: Study effects of MECFS

It would be good to do a study of people with MECFS to have a cohort of patients and controls and give them CPET evaluations and NEUROPSYCH evaluations. There is a paucity of info on the disabling effects of MECFS patients. This would be an important study.

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Subject: Low dose Naltrexone 4.5 mg four your MS study

I am 52. I became ill at age 39. I was bedridden with CFS, FIBROMYALGIA, EHLERS-DANLOS, and a 15mm pineal cyst.

I spent horrid decades on opiod pain meds. I truly wanted to kill myself.

In 2015 I was given Low Dose Naltrexone. My world changed. I am back to normal.

When I read it also helps with MS, I tried to tell each of my doctors and sickly friends to PLEASE try it.

Please include LOW DOSE NALTREXONE 4.5mg/day in your study for both MS and CFS.

The pharmaceutical companies are fighting hard to launch smear campaigns, and spread false info on dangers. The more recognition this molecule gets, the more money they lose.

It is gonna be a war. I've seen silly things with many patients pushing some wacky treatment, but I've never seen a substance with so many DOCTORS pushing for its use. This is big.

[...]
[...]
Subject: area of research in ME/CFS

Mast cell activation disorder is found in ME/CFS, fibromyalgia, diabetes. Irritable bowel and obesity. What could be triggering the mast cells to activate and medications to stop the degranulation of the mast cells would be a good area to study.

[...]
[...]
Subject: Two Simple Steps to Solve CFS & ME. 1) Halt HIV Spending. 2) Fund Gulf War Syndrome. Problem Solved.

1.1.1 HIV-NEGATIVE AIDS SPREADS TO CHINA. -- WhiteOutPress (05/17/16):

1.1.2 "May 17, 2016. China (ONN) Three years ago, Whiteout Press published an explosive report about a mysterious illness unofficially called HIV-Negative AIDS.

1.1.3 Thanks to the activism of one of our readers who is afflicted with the disease, thousands of Americans have stepped forward to count themselves among the infected. Even with undeniable evidence, medical professionals deny the condition exists. Now, the disease that doesn't officially exist has spread to China."

1.1.4 READ MORE: http://whiteoutpress.com/articles/2016/q2/hiv-negative-aids-spreads-china/

1.1.5 or simply google "NON HIV AIDS"

[...]
[...]
Subject: IRT RFI ME CFS

Hello,

Attached please find a response the NIH Request for Information, NOT-NS-16-024, concerning a plan for ME/CFS research.

Thank you,

Friday, June 24, 2016

To: Vicky Holets Whittemore, Ph.D.
Chair, Trans-NIH ME/CFS Working Group
[...]
Subj: Response to National Institutes of Health Request for Information NOT-NS-16-024

Dr. Whittemore,

The RFI asked responders to identify c*hallenges or barriers to progress* in ME/CFS research. Of the many such challenges, I would like to focus on two. One is the apparent lack of enthusiasm for studying it, both at the NIH and in the broader research community. The other is how to conceptualize ME/CFS; in other words, what kind of problem is it? I will address these two challenges, then the research opportunities that may surmount them.

As patients have been told, no one at the NIH is "interested" in ME/CFS research. Certainly, no one is interested in a vaguely-defined disorder apparently lacking in pathology, biomarkers, consensus case definition, or a clearly identifiable patient population. Indeed, few would be interested in such a disorder, except perhaps those who witness the functional devastation it causes.

However, the statement that no one is interested is an equivocation. In the work of those few who study it, ME/CFS leaves clues in areas in which the NIH already show an interest. These include immune abnormalities; autonomic dysfunction; disturbances in the brain; and mitochondrial dysfunction. Therefore, in the absence of a clear and comprehensive ME/CFS research agenda, the logical course of action is to integrate study of ME/CFS into overlapping NIH-sponsored work. If the NIH cannot bring interest to an ME/CFS research program, then we can bring ME/CFS to NIH's areas of interest.

The second challenge is that no one, interested or not, knows exactly how to study ME/CFS, or where it belongs in the sphere of medical inquiry. Historically, research into ME/CFS has been locked into what I would term a false dichotomy: namely, that the disease origin is psychogenic; or that the disease origin is infectious. Even today, the NIH intramural study of ME/CFS is predicated on clear signs of an infectious onset. Why? What is the basis for this assumption? After repeated failures to link ME/CFS both to existing viruses and to non-existent retroviruses, why is the infectious assumption being carried forward as if nothing had happened prior? Meanwhile the psychogenic model flatly fails to explain such biological evidence as has been found.

One disease model has not been pursued seriously at all: an autoimmune model. We lack the evidence today to say ME/CFS is autoimmune; however, we have ample negative evidence to say the model has not been rigorously pursued by anyone. Whether the model is

borne out by evidence or not, an NIH research program proceeding on a hypothesis of autoimmunity could very well advance scientific knowledge and public health.

A model for autoimmune inquiry already exists. Josep Dalmau identified Autoimmune Encephalitis (AE) barely a decade ago (Dalmau, 2007). In this disease, the immune system does not attack the brain generally, but only a specific class of receptor, most famously the NMDA receptor. (Other receptors are known to be targeted; still more have yet to be investigated.)

In signs and symptoms, AE manifests both neurologically and psychiatrically. Once identified, it is treatable with existing immune therapies, including rituximab. I have seen no broad studies on the prevalence and incidence of AE. So having found this disease that straddles neurology and psychiatry, we have limited understanding of where the border between the two fields is. NINDS and NIMH may wish to explore that question.

Traditionally, neurological disease is identified by pathology, but what is the clearly visible pathology of AE? In AE even the most advanced imagery available typically shows nothing at all. Dalmau originally found the disease through painstaking immuno-histochemistry on rat brains. The commercially available antibody blood test for the anti-NMDA form is a chief diagnostic tool. If NIBIB wants an imagery challenge, it can figure out how to see AE on scans, and possibly ME/CFS as well.

Recently, investigators found receptor problems in ME/CFS (Loebel, 2016). This is in the same population that seems to respond to rituximab. So at first blush, AE would appear to have a lot in common with ME/CFS. Studying them together might very well advance understanding of both.

Other areas of NIH study and sponsorship seem to lend themselves to including ME/CFS patients and samples:

Mitochondrial dysfunction and its role in cardiac failure is the central focus of research at the NHLBI (Ping, 2015). Meanwhile, mitochondrial dysfunction has been examined in ME/CFS, albeit inconclusively (Billing-Ross, 2016). ME/CFS patients and samples could be folded into the NHLBI existing plan and work.

Chikungunya is a virus already linked with Mitochondrial Anti-Viral Signaling (MAVS) problems (Schilte, 2010). I submit to you, that no virus, including Zika, can be fully understood until its interaction with mitochondria-driven innate immunity is more fully understood. Zika research is now funded, and its mitochondrial and immune aspects could easily overlap with ME/CFS research.

Ultimately, if the NIH cannot agree upon and implement a comprehensive ME/CFS research program, then they needn't have one. Instead, take as many ME/CFS patients and samples as can be made available, and spread them across any and all existing research agendas that seem remotely applicable. Those programs listed above are suggestions, and hardly all-inclusive. This could be done in a way that minimize the cost and inconvenience to

the host programs, and maximizes the exposure of new models and methods of inquiry to ME/CFS and its many scientific gaps and problems.

Whatever path the NIH follow, they will have to spend money, and they will have to try. Who knows? Someone may find something "interesting".

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Subject: Request for Information: Soliciting Input for New Research Strategies for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS), Notice Number: NOT-NS-16-024.

Please see attachment. Thank you.

June 23, 2016

Dear Trans-National Institutes of Health (NIH) ME/CFS Working Group Members,

Thank you for your Request for Information: Soliciting Input for New Research Strategies for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS), Notice Number: NOT-NS-16-024.

Before I start, I'd like to acknowledge the untimely death of M.E. patient and advocate Jodi Bassett, founder of the Hummingbirds' Foundation for M.E., who died at home, surrounded by her family on June 11, 2016, at the age of 40.

As I am a severe ME/CFS patient and one of the Millions Missing, I'd like to start by introducing myself since who I am is inseparable from how I expect to be treated as a human being and what I expect from health care as a citizen of the United States. I have been taken out of too much already; I won't be taken out of my letter too. If medicine is to treat patients, our stories must be heard, honored and counted; not cast aside as a nuisance to the practice of medicine. In part, it is because we are not deemed competent to bear witness to our own experiences that we are therefore left to suffer in isolation in a hell on earth. I have been ill since May 1983, when at the age of 17, while a junior in high school, I had mono and a severe strep throat at the same time. I gave up all of my favorite activities; including riding and showing my dearly loved horse, working on the farm where she was boarded, working as a summer camp counselor at this farm and seeing my friends there. I rested and concentrated on high school and was able to finish high school but only because I finished a semester early. I never regained my health, and at age 18, I was bedridden with daily migraines, vomiting and many other symptoms. I was so ill, I was afraid I was going to die. "Fatigue" was never a word that I would have thought to use to describe what I felt and endured. At this time, I was diagnosed with migraine, hypoglycemia and mitral valve prolapse. During the next 12 years, some of the time I was bedridden, some of the time I was house confined, some of the time I tried to work part or full-time, and/or I attended college either part or full-time. The last time I worked at a job, I was 24 years old and had to stop for good after adult chicken pox. I was also married during some of this time and we owned a house. Eventually, I lost my marriage and my home. After ten years, at age 27, I was finally diagnosed with CFS; for which I was told most people get better over time. I was also diagnosed with fibromyalgia, irritable bowel syndrome, multiple chemical sensitivities and numerous allergies to dusts, molds, tree pollens, grass pollens, weed pollens, dander from various animals and many foods. I was never cautioned about exertion and I engaged in a horrendous push-crash cycle not understanding that I was still doing too much. Only lengthy periods of chronic migraines would bring me to complete inactivity. I eventually finished my college degree, studying from home and with minimal in person attendance through an off-campus, accredited college program just before my 29th birthday. I was accepted to graduate school in the same off-campus, accredited program but after extensions to complete my work and medical leave, I finally had to withdraw for good. I had been in and out of college so many times that I nearly paid for two degrees just to complete one. At the time I withdrew from graduate school, I didn't even understand my own undergraduate work anymore. I spent my 30s mostly house confined and most of my 40s to the present bedbound. I am now 50. I am 5' 5" tall, I weigh 98 lbs., I look sick and my eyes show the pain and shock that I've endured all of these years. I have been sick and without appropriate medical care for 33 years.

I am not communicating now because I am able. On the contrary, interacting with other people; having thoughts and language and conversations in any kind of active way in my brain, as opposed to passively skimming written information that I'm allowed to forget; on certain levels, as I read it, literally makes me sick with migraines, vertigo and other symptoms and incapacitates me. Pieces of thoughts and memories and conversations spin around in my head; like my head is a blender, never letting me rest. It even affects my sleep and dreams as my mind is constantly trying to assemble the spinning fragments in the blender to make coherent whole meanings and memories. It's an amnesiac blender, constantly turning, trying to coalesce thoughts, memories, conversations and

meaning in a waking-sleeping-spinning-timeless-time of constant sickness. It would never occur to me to call this "fog". It feels torturous to be writing this now. It will be worse when I'm done and it will spin in my head more and I'll remember less. It is an act of faith to write this and let it go, as the reader will understand it better than I will. All I know is that it is true when it comes out of me and it's something that I'll stand behind and then it's gone from me.

Since last summer, during the sweltering heat of August, when a week and a half of construction disrupted my sleeping and resting and ability to run air conditioning during the days; due to the fumes from the construction, I've taken the hardest hit I've ever taken and have declined into especially more severe vertigo, orthostatic intolerance, cognitive difficulties, exhaustion and sound sensitivity. I feel as though I am continually falling; getting closer and closer to death and that I have lost the strength to keep quiet; as though I must scream to hear my own voice again and remember my soul. Consider this letter my scream, before I go missing again; away from too many thoughts and words in order to take care of myself. Consider this letter a scream that I want heard in case I never return. Consider this letter a scream from all the generations that came before me and all that they had to endure so that I could even exist; screaming for my well-being now, so that I may live in my time. I have some Blackfoot ancestry on my mother's father's side of the family. My great grandmother; on my mother's side of the family, died giving birth to my grandmother. My great grandmother; on my father's side of the family, was able to come to America as a teenager from Poland and to create a new life and a family for herself here. Her brother; who stayed in Poland, was shot and killed by a Nazi soldier while he was out gathering firewood. I'm an only child and I was never well enough to have children. I haven't been well enough to trace my family tree and I'm missing branches I'll never create in my family tree because of the politics of this disease. Consider this letter a scream from the children I'll never have and from their children and their children and their children and so on through the future generations that will never exist. No more generations should be lost to the politics of this disease; which are the politics of torture and of genocide.

These are my recommendations:

1. A meaningful, explicit, official government apology for decades of the malpractice of politics, narcissism, sexism and cookbook medicine, replacing respectful, intelligent, compassionate listening to patients and quality care. From the government, to top medical institutions, educational institutions, journals, textbooks, hospitals, doctors offices… there is absolutely no excuse whatsoever for the mistreatment that patients have been subjected to. If a child or spouse living in a household were physically abused by being denied help to get required medical care, financially abandoned when care could be afforded, further violated by being told that they weren't actually ill and threatened by the knowledge that to speak up could make things worse for them, it would be considered criminal. Why is it alright when governments and doctors commit these crimes? Without a meaningful, explicit, official government apology and immediate correction of inaccurate, abusive, malpractice-worthy material, along with a substantially corrected accurate narrative, I don't see how things can change at the accelerated pace that desperately needs to happen; a pace that will quickly shift decades' worth of untruths. **Patients deserve the true PACE - Public Apology Correcting Errors.** The government then has to pull up on the old boot straps and get to work creating an extensive, accelerated, collaborative, biomedical research effort that in itself sends a very strong, new, correct message about this disease.

Furthermore, an apology is crucial to shift things as quickly as possible so that patients can get an early diagnosis, appropriate care and societal understanding so that their lives aren't destroyed because they did too much or did the wrong things. Patients should not be blamed for having a disease. Children need to have their needs understand and appropriate accommodations made for their educations. College students and workers also need to understand their limitations and have the appropriate accommodations. More severely disabled people need to be able to get the disability benefits that they are entitled to without further harm to themselves.

I personally had family who financially supported me for about 2 decades and helped me try everything I could to get better. My family spent their savings on me. My parents were never able to retire to Florida like they had planned and they live very minimally now. Think about my parents the next time you get to take a vacation or go out to eat. I finally had to apply for disability about a decade ago. It was a three year fight to get benefits which greatly harmed me even more. I now live on less than half the minimum wage for my state and my case is presently under review again. My parents are both elderly now and when they are gone I won't have any family members to take care of me. I have no idea where I will live or what will happen to me. You owe my family an apology.

2. Immediate appropriate funding for disease burden which is at least 250 million dollars a year, plus the decades of unethical and criminal missing funding. This is the richest country on earth. There is absolutely no excuse for the unconscionable inhumanity of not funding this disease, leaving patients in a state of perpetual suffering and furthermore, draining hardworking families of all their savings in desperate attempts to help their loved ones.

3. **Triage. Triage. Triage.** I don't know how such a basic idea can get so lost. The most severe patients who are not well enough to leave their homes without further torment and harm must be immediately found, expertly cared for, expertly monitored and expertly researched from their homes. It is depraved to let these people suffer with no appropriate care for years and decades. Leaving patients to death and to suicide is a crime against humanity. I also shudder to even think about the homeless people with this disease. Severe patients need traveling expert doctors to provide care, traveling health care workers with oversight from expert doctors to also provide care, collect samples for lab work, etc. and severe patients need traveling expert researchers. The able bodied should be going to the severely disabled, not the other way around. Existing technology and technology that could be created must be put to use for patients to get care. This can involve simple technology, more complex technology and technology that may be briefly used and then passed on to another patient through mail exchange. Things like sleep, heart function, orthostatic intolerance, cognitive function, pain, exhaustion etc. could be tracked to help patients by providing things like CPAP machines and appropriate medications as well as for research purposes and for the purposes of documenting disability so that patients can receive the benefits that they are entitled to. Also, expert doctors providing outreach are extremely important to act as advocates for patients in emergency situations. The most fragile part of the ME/CFS population must be identified and served. If this part of the ME/CFS population is too ill to leave their homes now, that will still be the case if/when biomarkers and treatments become available. If medicine is supposed to first do no harm, patients shouldn't be harmed because they can't get care. They also shouldn't be harmed for weeks, or months, or permanently because they were over-exerted trying to get care. Once the most severe patients are taken care of, this type of care could extend out to a greater population of ME/CFS patients whose needs are not being met. **Triage.**

Please see the following:

> Telemedicine or home visits for those unable to participate in clinical trials/treatment in person and outreach to underserved communities are needed. New technologies to address underserved populations and unmet needs (e.g., mobile technology, online tracking tools) should be developed and employed to measure progress and to enable communication, especially for those who are not served in the clinic setting. (NIH Pathways To Prevention Workshop: Advancing the Research on ME/CFS, page 13).

The most severe patients need to be researched and they need the best research. Therefore, I want to stress the importance of the work of Ron Davis, Ph.D. at Stanford University and the Open Medicine Foundation along with his team of exemplary researchers, including 3 Nobel Laureates, internationally recognized researchers and expert clinician researchers Dr. David Bell, M.D. and Dr. Paul Cheney M.D., Ph.D. Their work must be fully funded now and continually funded to expand. More top biomedical researchers must be found and funded to study severe patients. The sickest patients must be helped and researched first. **Triage.**

My last medical care was only out of great desperation and it required an ambulance and the ER as I thought that I was having a heart attack; which I probably would have tried to ride out at home, as I had done this before with heart trouble, but I was also having great difficulty breathing and became desperate for air. The ambulance picked me up around sunrise. They just wanted to get me to the hospital and in the ER they just wanted to run their tests on me. The fact that I am a bedridden ME/CFS patient went willfully unacknowledged and my ME/CFS uncared for. At the hospital, they monitored my heart all day and I had lab work, chest X-rays and an echocardiogram. For my breathing, a respiratory specialist came to see me and after being given an inhaler to use my breathing was much better. I had been up struggling the entire night before and had barely eaten or had enough to drink the day before. All day in the hospital, I was not allowed to drink or eat or given an IV even though I'm hypoglycemic, terribly needed fluids and had a horrendous migraine. My concerns we not addressed and my questions went unanswered. When they released me, they gave me a partially used inhaler to take home. For my heart, I was told to take daily, high doses of Ibuprofen for pericarditis. When I arrived home, my migraine was as bad as it could be, I was vomiting the water I was trying to drink; so I still wasn't getting fluids and couldn't eat. I was also terribly weakened from the ordeal and from having not slept the night before. I struggled to stay awake until the vomiting stopped and I could get some fluids into me and a little protein that I had to digest in my sleep. The rest of my nourishment and fluids had to wait until I woke up in the struggle of the next day of further escalating symptoms, migraines and spinning fragments of memory endlessly flying through my head. The pericarditis made it too painful to lay flat, so two wedges and some pillows to stack were purchased for me. My ER records were sent to my doctor who was supposed to write me a prescription for my inhaler since ERs don't write or refill prescriptions but he wouldn't write it without seeing me. I was too sick to see him and went without an inhaler when mine ran out. I was left struggling to breathe, sleeping wedged upright, having chest pain, migraines and collapsed with many symptoms, some of which I previously hadn't had, escalating my disease. Paying corporeally for corporeal care is an immoral currency.

4. Extensive, accelerated, collaborative, biomedical effort. You have the IOM and P2P reports, the CFSAC recommendations and other relevant recommendations and demands. Vicky Whittemore, Ph.D. has just attended the IIME conference. Get to work and include patient input. We need collaboration among all top biomedical researchers and expert clinicians seriously researching this devastating biomedical disease and sharing data. We need incentives for new researchers,

treatments and many regional Centers of Excellence. I believe that researchers and doctors should be using the Canadian Consensus Criteria. I believe that part of the reason doctors don't believe that we are truly ill is because they are using poor criteria in a superficial and partial way. If doctors can't listen to their patients, use intelligence, compassion and substantive criteria to diagnose patients while engaging with their patients to try to alleviate their suffering, than they shouldn't be practicing medicine. Doctors inappropriately misdiagnosing ME/CFS as a way to not treat patients need to be reprimanded for their malpractice. Professionals need to do their jobs or be fired and replaced with competent individuals. Patient's lives are more important than politics or researcher's agendas, reputations and/or egos.

I had been missing from interacting in the ME/CFS online community; since it began, until February of this year, when I think I finally just snapped as the burden of quiet and silence is so great and the representation of severe patients so lacking. I'm trying to save myself and others whose desperate screams no one hears before I go silent again. What I have written here, is in part the compilation of several things that I wrote online and information I included in my disability review. Therefore, it can be thought of that this letter took me almost 5 months to write and has caused me countless days with a worsening of: cognition, migraines, pain, severe vertigo, photophobia, sound sensitivity, motion sensitivity, orthostatic intolerance, heart pounding, breathing difficulty, coughing, nausea, digestion problems, sweats, chills, sleep reversal, sleeplessness, racing, exhaustion that gets so severe I have to press a button on a horn to get someone to come and hand me my water that sits on a table next to my bed, or to come on their own to check on me and make sure I remember to drink and that I'm eating the food that was left for me, and more…. This isn't "malaise", it's more like obliteration! Remember, only a small percentage of the patients with this disease are even diagnosed and of those that are diagnosed, the sickest among us aren't ever heard from. The sickest patients need to be held up the highest and taken care of first. Find us now. Take care of us in our homes now. Monitor us from our homes now. Research us now.
We can't wait. **Triage.** Thank you.

[…]
[…]
Subject: Response to NIH RFI ME/CFS - Notice Number: NOT-NS-16-024

Attached is a response to the NIH RFI - Notice Number: NOT-NS-16-024
Thank you for this opportunity to provide input.

Response to Notice Number: NOT-NS-16-024

Request for Information: Soliciting Input for New Research Strategies for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

Information Requested

Through the RFI, the Trans-NIH ME/CFS Working Group invites input from researchers, health care providers, patient advocates and health advocacy organizations, scientific or professional organizations, Federal agencies, and other interested parties. Organizations are strongly encouraged to submit a single response that reflects the views of their organization and membership as a whole.

Please provide your perspective on the following issues as they relate to the Working Group's planning efforts:

Emerging needs and opportunities that should be considered as new ME/CFS research strategies are developed.

- Need: Validation and replications of many promising studies whose findings may have already identified biomarkers and/or significantly moved the field forward but can't be used or built upon, YET, because they have not been replicated or validated YET.

  It may be most efficient, economical and effective to do the study design at NIH in collaboration with AHRQ and include all elements needed for validation, and then put out an RFA or RFQ (seeking qualified vendors) to replicate or validate. Is this possible? As the P2P demonstrated, many of the most important research efforts failed to qualify (because of the lack of replication and validation) while some very old, incorrect and damaging studies made the cut. This is crazy, wasteful and very destructive to people living with the disease. It's a job that needs to get done.

  Opportunity: Since the initial research has already been done, it only requires validation – not starting from scratch. Also, since the research has already been done and paid for, it would be a shame to let the money spent on the research go to waste, not to get one's monies worth.

- Need: Identify Biomarkers for easier, clearer and more timely diagnosis.

  Provides evidence to skeptics that ME/CFS is a real disease, clarifies what the disease is to those who are misinformed and increases interest in the disease from all sectors, researchers, clinicians and the general public, which in turn can increase funding, research and better support systems for patients and their caregivers.

  More people will be diagnosed and diagnosed sooner and more confidently. It's estimated that only 85-90% of people living with the disease have received a diagnosis, and, for those who have one, it takes an average to 2 ½ years and/or 20 doctors to obtain that diagnosis. Given this is not a newly discovered disease, those numbers are jaw-dropping.

- Opportunity: Connecting existing dots and understanding how the interconnected nature of outstanding needs can reveal and lead to sensible priorities and research targets.

For example: A research study by Ian Lipkin and Maddie Hornig found reason to believe there may be at least two stages of the disease; 1) an initial three-year period of an upregulated immune system followed by 2) a chronically weakened immune system. If validated, it could point research toward intercepting the disease in the first three years, which may stop a chronic or permanent phase two.

"Stuck in High Gear

The study supports the idea that ME/CFS may reflect an infectious "hit-and-run" event. Patients often report getting sick, sometimes from something as common as infectious mononucleosis (Epstein-Barr virus), and never fully recover. The new research suggests that these infections throw a wrench in the immune system's ability to quiet itself after the acute infection, to return to a homeostatic balance; the immune response becomes like a car stuck in high gear. "It appears that ME/CFS patients are flush with cytokines until around the three-year mark, at which point the immune system shows evidence of exhaustion and cytokine levels drop," says Dr. Hornig. "Early diagnosis may provide unique opportunities for treatment that likely differ from those that would be appropriate in later phases of the illness."

https://www.mailman.columbia.edu/public-health-now/news/scientists-discover-robust-evidence-chronic-fatigue-syndrome-biological

Dot connecting. However, if it takes 10-15% of the people living with the disease 2 ½ years to get a diagnosis and 85-90% don't get a diagnosis, it's sadly unlikely patients would be diagnosed in time to benefit from an early intervention treatment, if/when treatment is developed.

Early intervention requires early diagnosis and effective medical treatment.

- Need: Given limited resources, treatments toward a cure should be given priority over research on practices designed to alleviate or accommodate symptoms.

  If we get a tooth ache, we don't go to a pain specialist to learn how to better cope and accommodate pain. We go to the dentist to get a root canal and crown. How does it make sense to (try to) treat symptoms forever (chronic) and not seek to find the source of the pain and ways to fix the problem forever? The patient and caregiver community want the ME/CFS equivalent of a dentist – We don't have one, and we need one.

- Need – DRUG TREATMENT clinical trials to create new and approve existing drugs for ME/CFS. Examples: Ampligen, Rituximab.

  1) Unless approved for use for ME/CFS, the full costs come out of patients pockets, which is unstainable for the vast majority of patients. - Rituximab.

2) Some drugs cannot be obtained and used in America, such as Ampligen.
3) An effective drug provides a great opportunity to better understand the natures of the disease. The drug points the way to the problem it's treating.

Challenges or barriers to progress in research on ME/CFS

Not having a home in and full commitment of an NIH Institute, Center or Office, puts ME/CFS in a "homeless" disease category.

That results in the lack of a long term (or permanent) commitment, ownership of and responsibility for the disease by an NIH Institute, Center or Office. This results in the disease not being included in things such as the development of an NIH 5-year strategic plan, inclusion in big data and disease burden calculations and a part of an annual budget plan.

Like all homeless, whatever is provided them is seen as "taking away" funding from other diseases and institute budgets rather than it being one of all diseases and equal to all diseases – a family member, one who belongs.

Lack of funding and research opportunities targeted specifically for ME/CFS that encompasses the whole of ME/CFS disease.

Gaps and opportunities across the research continuum from basic through clinical studies.

No comment.

When commenting on a research need or scientific opportunity, The Working Group suggests that your comments contain the following for our full consideration:

- Description of the need or opportunity
- Scientific rationale and potential public health impact
- Anticipated challenges that will need to be addressed
- Appropriate benchmarks for evaluating progress.
- For this RFI, the NIBIB is interested in the ideas for the development of new imaging and bioengineering technologies that could have the potential for a significant impact on ME/CFS research.

The Trans-NIH ME/CFS Working Group also welcomes your general comments.

[…]
[…]
Subject: NOT-NS-16-024 - Comments of […] to National Institutes of Health Re NIH Request for Information (RFI): Soliciting Input for New Research strategies for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

(ME/CFS) Number

Dear NIH:

Please find attached and pasted the Comments of […] to National Institutes of Health Re NIH Request for Information (RFI): Soliciting Input for New Research strategies for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) NOT-NS-16-024.

June 24, 2016

COMMENTS OF […] to National Institutes of Health Re NIH Request for Information (RFI): Soliciting Input for New Research strategies for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) Number: NOT-NS-16-024 (Release Date: May 24, 2016 / Response Date: June 24, 2016)

Submitted via email at MECFSRFI@mail.nih.gov

Dear NIH:

Stakeholders in this area may broadly be broken down into the following six groups: (1) Public health policy makers; (2) Scientific and academic institutions; (3) Specific research groups; (4) Clinicians (internists and specialists); (5) Patient advocacy groups; and (6) Individual patients.

These Comments essentially propose three primary ways to serve the convergent interests of all stakeholders: (1) Utility of ME/SEID for devising new research models and broadened interdisciplinary collaboration. (2) Adoption of ME/SEID as the operative concept. (3) Upgrading of survey instruments.

Emerging needs and opportunities that should be considered as new ME/CFS research strategies are developed.

Need and Opportunity

Need

What the NIH here designates as ME/CFS appears to be one of the most multisystem, multi-system disorders about. Prior efforts to understand it have led to a plethora of different, often morphing, names, case definitions and diagnostic criteria.

Is Myalgic Encephalomyelitis (ME), Chronic Fatigue Syndrome (CFS), and Systemic Exertion Intolerance Disease (SEID) one and the same condition? The truth is, nobody really knows. And, until recently, the field has been a muddled mess.

Nevertheless, the strongest evidence supports viewing this disorder as a discrete multisystem, multi-symptom spectrum illness that results from a dysfunctional reaction to an immune assault that, in turn sets off an injurious cascade of interactions and feedback loops. We also know the condition is highly fluctuant.

How to promote investigative efforts that add clarity to this complex disorder, and not just more confusion?

Until the disorder is better elucidated, it should be viewed as ME/SEID, i.e., as a spectrum incorporating both ME and SEID. CFS is an outmoded overly vague definition which should be phased out. (The rationale is discussed later.)

A primary and urgent need is for the NIH to strongly advocate the use – in both clinical and research forums – of upgraded survey instruments that will more precisely delineate all commonly identified symptoms. Research based on poorly delineated symptoms and inadequately characterized cohort groups is of limited value.

Opportunity

The problems that have posed such a challenge are precisely the ones which present an extraordinary opportunity.

Multisystem, multi-symptom illnesses are the very diseases which hold the greatest potential to unlock the clues to a vast array of other conditions.

The illness is fascinating and supremely well suited for facilitating the breakdown of traditional disease boundaries. The multisystemic and dysfunctional cascade aspects of the disease should encourage a much needed interdisciplinary approach. It should also attract researchers in emerging disciplines such as symptoms biology (complex interactions and network theory); symptomatology (identifying symptom links and aggregates); epigenetics (investigating gene expression caused by mechanisms rather than DNA); psychoneuroimmunology (focusing on mechanisms underlying brain-to-immune crosstalk); and other emerging fields.

The long-standing lack of proper professional attention ironically allows a rare opening for consideration of entirely new models of investigative approach. This is because there is less professional thought entrenchment and hypothesis orthodoxy to be a “drag” on creative thought.

Further, these opportunities come at a time of expanding computational power and reformulations of approach in other complex fields like climate science. For decades, many have urged more collaboration between the life and physical sciences, engineering, the humanities and economics. There may be no condition with more potential for exploration of novel multi-disciplinary approaches than ME/SEID.

Scientific Rationale and Potential Public Health Impact

The scientific rationale for the SEID construct is well described in the 2015 Institute of Medicine (IOM) report. The IOM report has hopefully cleared away a lot of the debris which has long cluttered the literature. The core symptoms promulgated in the IOM report – whether or not they represent the crux of the illness – have strong evidence behind them and represent a reasonable platform on which to build.

The IOM also rightly noted that a streamlined set of central or characteristic symptoms will make it easier for clinicians to recognize and accurately diagnose patients in a timely manner. However advancement of

scientific knowledge and patient care mandate a far more in-depth and detailed understanding of this condition.

Many experts and patient groups have emphasized the utility of the 2003 Canadian Consensus Criteria (CCC) and the 2011 International Consensus Criteria (ICC). Both do a good job – in different ways – of articulating a paradigm and describing the unique experience of ME. Publicizing and utilizing the Carruthers criteria can greatly facilitate elucidation of the illness and help ultimately clarify whether SEID may be validated as a preliminary diagnostic schema.

Thus the combined ME/SEID working definition would incorporate both the believed core scaffolding of the illness and prominent details which distinguish it from other chronic multi-symptom conditions with complex patterns of disability.[1]

Vastly improved survey instruments and data collection is needed to map out the disorder with precision. Without far more questions being asked, and data reliably compiled and maintained, this newly cleared field will just become a slightly reoriented morass. No stakeholder interest is served by that advent.

Most critically, from a public health standpoint, the believed trigger of the illness in acute onset cases should *always* be identified. This is an imperative for flagging emerging epidemic outbreaks caused by specific pathogens.[2]

Trigger identification also presents an important opportunity to advance knowledge about potentially dangerous chemicals and environmental conditions. While etiological investigations have focused predominantly on viral and other pathogenic infections, toxins have also been identified as triggers. Toxic insult is notably implicated in Gulf War Illness and the so-called "Chernobyl AIDS" syndrome, conditions strikingly similar to – and arguably a variant of – ME/SEID. Pathophysiology likely varies because of (a) the nature of the initial triggering agent, (b) population heterogeneity, and (c) the number, dynamics and ambit of the cascade of dysfunctional neurological, immune, endocrine, autonomic, cardiovascular, and gastrointestinal cycles involved. Individuals who develop ME/SEID as a result of chemical or low level radioactivity exposure, may be the proverbial canaries in the coal mine who can flag broader population health risks.[3]

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[1] The 1994 Fukuda CFS definition was intended as a starting point. The Fukuda authors specifically noted that the complexities of the syndrome and the methodological problems "indicate the need for a comprehensive, systematic, and integrated approach to the evaluation, classification, and study of persons with this condition and other fatiguing illnesses." Yet Fukuda ended up calcified for two decades as a CDC definition impeding both research and clinical evaluation. As many have noted, misdirection has emanated from nomenclature unduly focusing on fatigue, which is simply a single symptom of a complex multisystem illness. Continuing use of the CFS nomenclature is likely to perpetrated misunderstanding and research disinterest. However a name change to ME/SEID without a corresponding delineation of the full spectrum and pattern of the disorder will be of limited value.

[2] The increasing likelihood of vector transmitted illnesses with climate change may increase prevalence of ME/SEID and might present large enough populations for quality prospective studies.

[3] The reasoning regarding vector initiated ME/SEID would apply to toxic exposures. Pre-existing populations with known chronic radionuclide and lead exposures exist: Native American communities, communities around nuclear

Surveys should also seek to ascertain whether multiple cumulative infections, exposures, or injuries may be complicit in either initiating ME/SEID or affecting its severity. If this is indeed a maladaptive host response disease, allostatic load possibilities should be explored.

Prospective studies would also be enabled by trigger tracking.

Both enhanced scientific understanding and public health considerations *mandate* creation of a registry that – at a minimum – identifies the geographic residence and occupational exposure history of the patient.

Better recognition of the illness in its complex form will also drastically reduce the cost and suffering burden of patients who are now kicked from specialist to specialist, overtested and improperly medicated for other conditions. For individuals who experience sudden onset following a flu-like infection and then demonstrate the extensive highly-eccentric symptom clusters well described by Carruthers, diagnosis could be readily made by any knowledgeable physician.[4]

From a public health point of view, this raises the possibility of arresting – and even reversing – the disease process at the prodromal stage, when fewer symptoms may be present. Again, this mandates substantially improved recognition on the part of medical professionals of the precipitating factors and red flag symptoms at the very early stage of the disorder, before the full cascade of dysfunction cycles has erupted.

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power plants, and Flint, Michigan. These provide prime laboratories for exploring how chronic exposures to chemicals with known neurotoxic and immune effects may give rise to illnesses like ME/SEID (and not limited to ME) with multiple system, multiple system presentations. This is an area of prime import to public health and has received precious little government-supported research attention. Data compilation and analysis would also elucidate oncology, as environmental exposures are strongly implicated in the etiology of cancer.

[4] By way of example, consider the following two theoretical patients:

One is a long sedentary 60 year old who reports gradually developing chronic problems with concentration, tension headaches, tender lymph nodes, and joint pain; with all of the symptoms being fairly moderate and consistent.

The other is a highly active athletic 24 year old graduate student in robust health who is suddenly stricken – following a flu-like virus – with over a dozen never before experienced debilitating symptoms, including: a prolonged sense of energy loss following physical and/or cognitive exertion (PEM); severe sleep disturbance; rapid muscular fatigability and muscle pain while exercising; a drastic reduction in the ability to multi-task; difficulty with word retrieval; dyslexia; photophobia; IBS; hypersensitivity to chemicals; loss of adaptability to changes in ambient temperature; orthostatic intolerance; heart palpitations; and Reynaud's Syndrome. The symptoms are wildly fluctuant. Some are severe. Every time the symptoms abate, he eagerly returns to his prior busy schedule. Yet virtually every time he pushes himself beyond his subjective sense of capability, the young man becomes utterly depleted. The experience is something he can only describe using the term "crashing." The student's level of activity and productivity is reduced dramatically to about 30% of his pre-illness onset level.

As things now stand, both of these patients can be lumped together in the same purportedly "well defined" research cohort if the CFS definition is incorporated. From a research guidance perspective, this is simply absurd.

Aggressive early intervention is a low hanging fruit, and may involve something as simple as pharmaceutical support to alleviate sleep disruption and strong guidance on pacing.

The idea of children, adolescents and young adults being effectively sentenced to a lifelong illness that might be avoided simply by more informed pediatricians and internists who provide good counsel seems particularly compelling.

Anticipated Challenges that Will Need to Be Addressed

Creation of strong, thorough and functionally effective survey instruments is a major challenge – but one which is a predicate to informed research and absolutely necessary to understanding of the mechanisms which underpin and promulgate this disorder.

In its September 2013 "The Voice of the Patient" report, the FDA noted its ME/CFS workshop and survey identified over 50 symptoms. Depending upon how they are broken down, the CCC and ICC definitions identify some 26-40 symptoms. Prior to the 1994 Fukuda CFS definition, Nancy Klimas and colleagues proffered a list of over 30 symptoms in sample cohort using Holmes, 1988 selection criteria.

Although specific symptoms vary, pattern presentations, system interaction dynamics, and the avalanching of symptoms following similar aggravating factors distinguish ME (and presumably SEID) from other conditions.

However many of the most repeatedly identified symptoms remain very poorly delineated. These broadly include autonomic, cardiovascular, endocrine, neurological and cognitive irregularities. A more specific list would include: post-exertional exhaustion; severe sleep dysfunction; fluctuant working memory and visuo-spatial deficits; word retrieval aphasia; dyslexia; handwriting problems; pronounced clumsiness; slowed information processing; inability to multitask or maintain task focus when subjected to external stimuli; chronic pharyngitis; susceptibility to infection; chemical hypersensitivity; sensory dysfunction; vision problems; sensory hypersensitivity; overload susceptibility; muscle and joint pain; muscle weakness and susceptibility to injury; heart palpitation episodes; Raynaud's syndrome; migraines or tension headaches; psychomotor problems; orthostatic abnormalities; a drastically reduced ability to tolerate heat …. the list could go on. Each of these warrants exposition.

Significantly, detail needs to be added to the picture even with respect to the symptoms which have received the most focused attention to date: fatigue and post-exertional malaise (PEM – which might better be described as PED – post-exertion depletion). Fatigue manifesting as severe mental or physical exhaustion differs from somnolence or lack of motivation. A substantial body of patient description and gray literature suggests that fatigue in this illness presents in at least four distinct ways. The first is in a remitting-relapsing fatigue similar to the "sickness behavior" response to infection. The second is a significant reduction in general stamina. The third has yet to be adequately characterized, but appears to be a maladaptive stress response. And the fourth is invariably described by patients themselves as the experience of "crashing."

Crashing is arguably the most provocative of the above litany. It has been described as a sudden, precipitous loss of energy and disintegration of cognitive function. It is often reported to be accompanied by reduced neurological control (clumsiness); a heightened and extreme sensitivity to light, sound, and motion; a sudden-onset pressure headache; palpitations; and an extreme urge to lie down. Do most patients experience crashing in the same way? If so, that would surely suggest cerebral hypoperfusion.

Survey instruments need also to include open-ended avenues of inquiry to allow for the possibility that some crucial symptoms – and possibly key disease mechanisms – are being missed. There is, for example, indication that ocular and dermatological problems may be common, but remain virtually uninvestigated. Some current questionnaires list photophobia, but none in common use inquire about floaters or excessive eye dryness. Similarly, while some surveys list "rashes," they invariably fail to ask about skin fragility, dermatitis, and itching. Yet such eye and skin problems point to accelerated cellular aging, mast cell activation, and inflammation – all potential indications of autoimmune disease.

Appropriate Benchmarks for Evaluating Progress

Avenues must be created to enable patients to become collaborators, particularly with respect to delineation of illness presentation, therapeutic preferences, disease management, and outcome measures. Scientists may have considerable scientific expertise, but they often bring biases to the table and lack in-depth knowledge of their subjects.

Human beings are not mice. They do not live in a lab. They have personal histories, life experience, priorities and needs often overlooked by investigators. Those differences need to be recognized and better explored. Not only would researchers gain invaluable information about their subjects, but research design and priority settings could be improved to create larger cohorts and more sophisticated benchmark schemes. For example, patients who are unwilling or unable to travel to major medical center settings could help researchers design methods which collect data via internet applications or which pool data from multiple primary care tests. This could reduce the confounding factor of patient exhaustion involved in evaluations which require travel and large time commitment.

Imaging and Bioengineering Technologies that Could Have Potential for Significant Impact

Patient health and well-being should not be compromised in the name of science. Studies which involve introduction of radioactive agents should be conducted only when such investigations are made for concomitant, reasonably necessary medical purposes.

Non-invasive studies examining the specific dysfunctions - such as autonomic response - should be expanded beyond traditional testing modes and recalibrated for more applicability to the type of presentations involved in this particular disorder (which may be more subtle than POTS). Innovative and novel methods need to be designed to investigate symptoms like "crashing" or post-exertional malaise

(PEM), which are prominent features of this disorder, are triggered variously by mental and physical exertion, and have irregular patterns of appearance.

Investigations should prioritize low-impact, low risk, and non-time consuming testing methods in view of the negative impact of onerous testing regimes in this population. Investigation should be expanded to look at low-hanging physiological fruit like fingernails, hair, and bodily fluids. More ophthalmological data should be obtained, as this could be compiled from ordinary yearly eye doctor visits. Information such as inflammatory processes can be deduced in this simple, low cost way.

Conclusion

The dual task of advancing highly specialized, rigorous research and capturing "outside the box" transformative approaches is a tough one, particularly given financial constraints. The solution lies in designing structures which facilitate broad thinking, easy information sharing, and cross-pollination from groups which have been so-far quite exiled from the process. Much of value may be obtained with limited expense. For example, modern communication technology can be readily harnessed for web-based, phone-linked formats which enable informal input from policy experts, health care workers, educators, and patients.

Important contributions can be made not just by people with information, but by people posing novel questions.

This is a unique moment of opportunity in biomedical research. But unless better mechanisms are set up for acquisition, organization, and easy access of data, frankly, a lot of money and effort is going to be wasted.

Computer science, of course, enables massive acquisition of information and opens venues for dynamic and flexible forms of inquiry. Multiple algorithms can data mine narratives, organize information, and pick out patterns which human beings (constrained by time, patience and eye strain) cannot. Data can be broken down into tiny bits and stored. Assumptions underlying research investigations can be identified and kept accessible. We no longer need to rely on findings based on destroyed records or mountains of paperwork sitting in a warehouse. We no longer need be perplexed by hypotheses based on premises that should have gone the way of the dinosaur.

We're in a new age but doctors, medical centers, and research groups are still using highly simplistic investigative instruments (like short paper surveys) which fail to capture crucial data. Right now there is not much incentive for them to do otherwise. The NIH needs to push folks into the 21st Century.

A point of emphasis here is that many excellent detail-oriented research groups continue to be hampered by poor data acquisition and maintenance on the part of primary care doctors. How can a well characterized cohort be selected from a poorly characterized pool?

Collaborative efforts are a major theme. However there has been – and continues to be – little institutional guidance from the NIH as to how productive interaction between different groups may be efficiently achieved.

In addition, while rigor and reproducibility are laudable goals, creativity and new hypothesis generation also need to be encouraged.

Improvement of NIH (and its sundry agency) web pages should be elevated as a priority. Much of the information is over-generalized. It is especially difficult and frustrating for doctors and researchers to get a handle on new developments in fields outside their own sphere of expertise.

These comments represent my personal opinion, and do not represent any position held by any organization with which I am affiliated. However, I work in the environmental and energy public policy arena and have spent considerable time investigating illness patterns related to environmental toxic exposure. I am also the author of the first peer-reviewed journal study analyzing application of the Americans With Disabilities Act.

[…]
[…]
Subject: New Research Strategies for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)

Hello

I suffer from ME/CFS for over 20 years. Eight years ago I found out about Low Dose Naltrexone (LDN) and asked my Doctor to prescribe it for me. I get it from a compounding pharmacy and it costs me $82 for 90 days supply.

Before LDN I was fatigued all the time and in severe pain, especially in my legs and my back. Six months after starting to take LDN I realised that I was just not fatigued all the time but someone who got tired easily. This was a huge difference for me. Also I was no longer in pain in my legs or back unless I overdo things. I understand that you are considering funding some trials and I do believe that a trial with LDN for ME/CFS would be enormously helpful. Not many Doctors know of its existence and it is often difficult to get them to write a prescription because they do not understand how LDN works for people with ME/CFS.

[…]
[…]
Subject: RFI: Myalgic Encephalomyelitis/CFS

To: The Trans-National Institutes of Health (NIH) ME/CFS Working Group
Re: Response to Notice NOT-NS-16-024; Request for Information: Soliciting Input for New Research Strategies for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)

Dear Working Group:

The following is my response to Soliciting Input for New Research Strategies for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS).

Emerging needs and opportunities that should be considered as new ME/CFS research strategies are developed:

1. Investigate energy production and recovery mechanisms.
2. Confirm the utility of two-day VO2max cardiopulmonary exercise testing (CPET).
3. Analyze existing samples for biomarker discovery.
4. Undertake a deep dive for biomarker discovery.
5. Conduct an accelerated longitudinal study to elucidate the natural history of ME/CFS.
6. Address the questions of burden of disease and undiagnosed ME/CFS patients.
7. Invest in development and validation of outcomes measures.
8. Fund systems biology and computational biology approaches to pathophysiology.
9. Leverage wearable devices to objectively measure function.

Challenges or barriers to progress in research on ME/CFS:

1. The failure to reach consensus on case definition is a steep barrier to progress across the ME/CFS landscape.
2. More resources and heightened urgency are required to address this public health crisis.
3. ME/CFS patients, researchers and clinicians are not involved in NIH's efforts in a sustained and meaningful way.
4. There are very few ME/CFS researchers in training.
5. Methodological flaws make it challenging to interpret the evidence base.

Gaps and opportunities across the research continuum from basic through clinical studies:

1. ME/CFS research requires a coordinated, strategic plan.
2. Clinical trials and pediatric research are significant gaps in the current approach to ME/CFS research.

Thank you for your consideration and your service.

[…]
[…]
Subject: ME/CFS

To: The Trans-National Institutes of Health (NIH) ME/CFS Working Group

Re: Response to Notice NOT-NS-16-024; Request for Information: Soliciting Input for New Research Strategies for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)

Dear Working Group:

The following is my response to NOT-NS-16-024; Request for Information: Soliciting Input for New Research Strategies for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS). Please excuse the fact that I am too sick to go into detail regarding each recommendation. Be assured I am a long-time patient and that I have a quite thorough knowledge of the history of ME including how it has been dealt with by NIH (for a non-employee of NIH) and I have carefully considered my responses and I strenuously urge you to seriously consider and to implement them.

Emerging Needs and Opportunities:
- None identified as such

Challenges and Barriers to Progress (in descending order):

- The Canadian Consensus Criteria ("CCC") and International Consensus Criteria ("CCC") should be used in all NIH studies (alongside the Centers for Disease Control ("CDC") Fukuda CFS Case Definition ("Fukuda"), just for purpose of reference to past studies, almost all of which have used Fukuda, with the understanding that Fukuda is not a valid definition).

- Misinformation disseminated by NIH and CDC including on their websites.

- Failure to have experts (clinical, research and patient) in the disease deciding all aspects of the how ME('cfs') is dealt with by the public health service including NIH. For NIH this includes these experts being involved in drafting and implementing a strategic plan, making grant funding decisions and drafting information distributed by NIH on the disease, including on the NIH website.

- Funding of unhelpful or harmful studies (studies that don't add much to the knowledge base or are actually pseudo-science) by NIH including psychological and psychiatric studies (including Cognitive Behavioral Therapy and Graded Exercise Therapy studies), studies by biased researchers (e.g. Suzanne Vernon) and studies using invalid definitions of the disease such as CDC Fukuda and CDC Reeves while failing to use valid definitions, namely CCC and ICC.

- Use of the misleading term "CFS," as opposed to the valid, longstanding nomenclature "ME."

- Gross lack of funding (and sense of urgency).

Gaps and Opportunities:

- Full funding of all of Prof. Ronald Davis' work at Stanford University and Open Medicine Foundation.
- Full funding of all Dr. Ian Lipkin's' work at Columbia.
- Need a coordinated strategic research plan drafted by clinical, research and patient experts.
- Biomarkers research
- Neuro-inflammation research

Thank you for your consideration and your service.

[...]

[...]

Subject: survey response

Thank you for the opportunity to respond to the NIH RFI for input for new research strategies for ME.
Some of the issues that need to be addressed are:
Emerging Needs and Opportunities

Develop outcome measures that are meaningful to patients.

Validate biomarkers.

Study the validity of the 2 day CPET test with gas exchange as a test identifying ME. Following on that, and given that undertaking a 2-day test is problematic for many patients, are there tests (gene expression, cytokine activity etc) that can be administered after a one day test to identify ME patients (so that they don't have to endure a 2-day test).

What does the impaired energy production and impaired recovery from exertion (cognitive or physical) tell us about patients and how does that compare to other diseases and healthy controls? Keeping in mind that PEM (post-exertional malaise) is NOT fatigue, a few questions might be:

Is the definition of post-exertional malaise consistent across illnesses?
If there are multiple definitions, how do they differ and what are their common features?
Who generated the definition(s)?
Are there question/concerns among clinicians/patients about the definitions?
How is PEM measured for each illness?
Who developed and or validated the tools for each illness? Are they generally accepted or are there questions about the thoroughness and/or validity of the tools?
Do each of the illnesses that have PEM have
physical and cognitive triggers,
physical and cognitive symptoms as part of PEM?
In ME, is cognitively induced PEM more/less severe than physically induced PEM or the same in duration/frequency/severity as physically induced PEM?
Are an individual's symptoms of cognitively induced PEM the same as their symptoms of physically induced PEM?How does cognitively induced PEM differ from physically induced PEM in ME and other illnesses?What is the duration of PEM in each?
What is the severity of PEM in each?
What is the timing of PEM onset – rapid/delayed? What are the implications (duration, severity, etc) of rapid or delayed PEM onset/
Are there preventive measures to avoid PEM in each illness? How successful are they?
Are there treatments for PEM in other illnesses and if so, how effective are they for each symptom and illness?
How does PEM in other illnesses compare to PEM in ME in terms of duration, frequency, severity, symptom?
In ME and other illnesses, are there some symptoms that are unique to PEM?
Does patient experience of and management of PEM change over the course of the illness and if so, what impacts that change?
Do PEM symptoms change over the course of illness? If so, why and how?
In patients with sudden vs gradual disease onset, is there a difference in the symptoms and severity of PEM?

Are there unique characteristics of families with multiple patients? A few questions additional questions might be:

Is symptom severity and frequency of one family member an indicator of duration and or severity for other family members?
Does severity vary within families? If so, in what ways?
Does onset (gradual, sudden) vary within families? If so, why?

Undertake a longitudinal study of carefully characterized patients. A few questions might be:

How does disease change over time?
Are there symptoms that are specific to onset?
Are there symptoms indicative of later course of illness?
Are there symptoms that indicate prognosis?

Does onset (gradual, sudden) or symptom severity indicate prognosis?
Do symptoms frequency and severity give indications of the course of the disease?
If sore throat/swollen lymph nodes etc are not a consistent symptom in young people but they occur or develop later in illness, is this an indication of severity and or duration of disease?

The need is urgent. Patients have been held in limbo for decades and desperately need and want to return to productive lives! Please join us in this urgency.

Challenges and Barriers

There is definitely a need for greatly increased resources both in terms of funding and in terms of numbers and age of researchers.

The lack of clarity on research definition has resulted in overly broad definitions which has muddled the evidence base. Flawed methodology in studies hasn't helped either.

Currently there is no clear strategy or plan for ME research.

Gaps and Opportunities

The SOK (2011), NIH P2P (2014) and the IOM (2015) reports each noted the paucity of research on pediatric patients. It is imperative that pediatric ME patients be clearly identified and studied.

The symptom overlap between concussion (and post-concussion syndrome) with ME symptoms calls out for investigation and capitalizing on initiatives devoted to concussion and the brain. The symptom overlap is not just cognitive symptoms but physical symptoms as well.

The CDE project must be developed based on ME, not on patients meeting Fukuda or Oxford.

Use the NIH Graduate Partnership Program (and other mechanisms) to expand the physican and researcher knowledge base about ME with an aim to increase the number of physicians capable of appropriately treating this disease and researchers investigating it.

[…]
[…]
Subject**:** ME

I have chronic fatigue.

I had open abdominal surgery in September 2014.

Followed by wound infection.

Followed by food intolerance and severe diarrhoea for three weeks, resulting in the loss of 2 stone in weight.

I thought the fatigue that followed was because of the lack of nutrition and weight loss. My sleep became sleep day..awake night.
Intestinal disturbances continued, however are managed by daily eating slow moving food first and only then allowing myself to eat any fibre e.g. Fruit.

I had no idea what cfs was nor that I might have it.

I recognised that physical, emotional or cognitive activities created a fatigue similar to what I would previously experienced when I had gone for a very long fast walk or a very vigorous cycle or had been studying for my degree for days at a time.

I also noticed if I got excited or surprised or laughed heartily and unexpectedly. .I would have a very sudden drop in energy. .actually passing out, momentarily, on a few occasions.

I have a theory, a lay person's unsupported theory..yet a theory all the same.

I believe this is a ?prehistoric primitive reaction by the human herd animal to what would have been a catastrophic event, leading to certain death, when there was no medicine available.

The injury/infection/trauma would have killed the human herd animal in the past. So there may be a built in trigger to ensure the fatally injured human animal is the one that cannot run away when the herd/group is being hunted. Protecting the group by sacrificing an individual that will die anyway.
I don't have any more energy to go into more detail about my numerous symptoms in order to support this 'theory', but it makes sense to me. .but..I do have moderate/severe cfs..so sense is an infrequent visitor these days..

Good luck with your research.

Thank you for doing this.

My life is lost to this illness. .without your help.

[…]
[…]
Subject: research suggestion

I have big problems with hypovolumic hypertension. Hypovolumia seems to be a problem with those with CFS. Some even get litters of IV saline regularly. The high blood pressure has created problems for me with having had a stoke, procedures declined and big doses of hypertensive medication.
I would love to see some good data on the problem.

[…]
[….]
Subject: ME/CFS PLEASE HELP ME

My name is […]. I am 21 years old and have been suffering from Chronic Fatigue Syndrome for 2 years. I have had to leave my university and return home to be taken care of. I am bedridden and too sick to leave the house. I was a very productive and active person and it took away my life. I have been receiving treatment from Dr. Jose Montoya at Stanford University via phone calls. VALCYTE and COLCHICINE improved my health dramatically but I have since relapsed and my symptoms have returned. The doctors

and researchers at Stanford desperately need the funding to conduct lifesaving research on the effect of anti-viral and anti- inflammatory treatments.
Information on ME/CFS needs to be spread throughout the world and taught in all medical schools curriculum.

From all of the patients suffering from ME/CFS, please help us by providing the necessary funds to conduct this research.

[…]
[…]
Subject: NOT-NS-16-024

DEAR MEMBERS OF THE TRANS-NIH ME/CFS WORKING GROUP,

HERE ARE OUR COMMENTS ON YOUR RFI, PLEASE SEE ATTACHED FILES (SAME CONTENT IN TWO DIFFERENT FORMATS, FOR YOUR CONVENIENCE).

KIND REGARDS,

Response to Notice NOT-NS-16-024; Request for Information: Soliciting Input for New Research Strategies for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)

Dear members of the Trans-NIH ME/CFS Working Group,

We are very grateful for the initiative and for this opportunity to offer input.

Here are our comments on your Request for Information.

Earlier recommendations from CFSAC, IOM and P2P

Many well-founded recommendations regarding ME/CFS have been directed to the NIH over the years by the DHHS Chronic Fatigue Syndrome Advisory Committee. Surprisingly, very few, if any, of these recommendations have been acted upon. We would suggest the NIH revisit these recommendations and let them direct your future work in this area.

The Institute of Medicine's report on ME/CFS as well as the NIH P2P report also contain a number of very useful recommendations. Some of these will be re-iterated in our own response below.

Funding and Program Investments Commensurate with the Disease Burden

The NIH must dedicate funding for biomedical ME/CFS research and program investments for ME/CFS commensurate with the disease burden (the number of patients affected, illness severity and societal costs) and with comparable disorders, and they must do this without continued delay, as patients have already been waiting more than three decades.

This would mean a raise from $5 million to $100-270 million per year.

A sequence of RFAs is essential, multiple RFAs over several years, starting this year (2016). Dedicated funding over several years is necessary to convince researchers that NIH is serious about its focus on ME/CFS and to attract new researchers to the field. As long as the perception lingers that NIH does not really want to invest in this disease, we will not see research move forward with any increased speed.

We need the first RFA to be this year. The dire situation for ME/CFS patients needs to be addressed with great urgency.

The lack of NIH funding for ME/CFS research is at the heart of all the problems the field is facing. If any progress is to be possible at all, this needs to be remedied immediately. Year after year, ME/CFS has been kept among the bottom 15 among the circa 230 disease categories on the NIH's list of funding levels[i]. By any comparison, the field receives far too little for any meaningful research to be possible.

ME/CFS receives around 20 or 30 times less funding than comparable diseases such as Parkinson's, MS, epilepsy or RA. In total per year, the NIH allots around $140 million to Parkinson's disease, $115 for MS and $130 million to epilepsy. It is completely out of step that ME/CFS is allotted a meagre $5 million — meaning it receives 20 times less than these comparable diseases.

Per person afflicted, it compares even worse. According to the Fair Allocations In Research Foundation in 2013 cancer research received $4,400 in funding per cancer patient. Parkinson's patients receive $221 yearly, MS patients $287. ME/CFS patients receive $5 per person afflicted per year. Again, totally out of range – ME/CFS receives 50-60 times less funding per person per year than comparable diseases. Hence, it could be said that it takes at least 20--60 years to get 1 year's worth of ME/CFS research done. What MS researchers get done in a year, we have to wait decades for.

At this pace, many years of many lives will go by before disease mechanisms, biomarkers and treatment are finally unveiled for ME/CFS. On the other hand, if ME/CFS was granted a level of funding on par with other high--impact diseases, we could quickly see very promising progress.

There has been no lack of promising leads and exciting possibilities (abnormalities in the immune system, the brain, the metabolic system, the possible autoimmune factor, etc., etc.). But these successful initial small studies are almost never followed by larger confirmatory studies, due to lack of funding and rejected applications. It's no surprise, then, that many researchers have chosen a different, more lucrative and rewarding, career path.

Sometimes we hear that 'there has been no proof of a biomedical cause for ME/CFS' and 'in spite of decades of research, there is no cure for ME/CFS'. We should perhaps answer: 'First, let's spend as

much money on biomedical research for ME/CFS as we do with other diseases, for a decade or two. Then, let's resume this discussion.'

As you understand, this deplorable dearth of funding must change. Increased investment on the part of the NIH for ME/CFS biomedical research is absolutely necessary if ME/CFS patients are to have a chance of one day getting better and returning to functional lives.

RFAs for ME/CFS have been called for by numerous parties numerous times over the past decade, by the IACFS/ME[ii], members of Congress[iii] and the HHS's own advisory committee, the CFSAC[iv] [v] [vi] [vii]. In 2005, a RFA for ME/CFS was issued, so it is clear that this is a viable action, but since then the NIH and the HHS have remained inactive. In 2011, the NIH held a State of the Knowledge Workshop on ME/CFS, and the medical community expected that it be followed by a RFA, but were disappointed (and confused, since there really seemed to be no follow-up at all regarding the SOK Workshop).

If we are to see any progress in this field, it is vital that your foremost recommendation is for the NIH to increase funding levels for biomedical ME/CFS research to $100-270 million per year, by producing multiple RFAs over several years. Without such a recommendation, I doubt that it will be possible for any of your current recommendations to ever be carried out.

PEM, not 'fatigue'

Characterization and evaluation of the hallmark symptom post-exertional malaise (PEM) in carefully designed high-quality studies with large cohorts is absolutely essential.

We would like to address the important issue that fatigue is often misleadingly stated to be the most important and/or characteristic symptom of ME/CFS, whereas in fact leading experts agree that the actual cardinal symptom of ME/CFS is post-exertional malaise (PEM), also called post-exertional relapse, post-exertional amplification of symptoms or post-exertional crash.

'Fatigue' completely fails to capture the essence of this complex condition. Reducing a complex multisystemic illness such as ME/CFS to just one single diffuse symptom that can also be found in a myriad of other illnesses, that can't even be measured objectively, is unacceptable. Focusing on fatigue alone may identify some ME/CFS cases, but may also capture many individuals who do not have ME/CFS.

The failure to differentiate between patients with the symptom of subjective unexplained fatigue on the one hand, and objective immunological, neurological and metabolic dysfunction on the other, has made interpretation of the current evidence base hugely problematic. When you can't even be sure of what illness each study has investigated, how could then you draw any relevant conclusions at all?

Recognizing PEM as the distinguishing symptom is key to improving both the research field and clinical care for ME/CFS patients.

The fact that PEM, not fatigue, is the cardinal symptom of ME/CFS is also clear in the Canadian Consensus Criteria (CCC)[viii], where PEM is a mandatory symptom:

> Post-Exertional Malaise: “There is an inappropriate loss of physical and mental stamina, rapid muscular and cognitive fatigability, post exertional malaise and/or fatigue and/or pain and a tendency for other associated symptoms within the patient’s cluster of symptoms to worsen. There is a pathologically slow recovery period — usually 24 hours or longer.”

The CCC has become the preferred definition for most of the international experts in the field (both clinicians and researchers), not least due to this very fact; that it requires PEM for a diagnosis of ME/CFS to be made. Research (Jason et al[ix] [x] [xi] [xii], Marshall-Gradisnik et al[xiii] [xiv] [xv]) has shown that the CCC, the ICC and other definitions where PEM is mandatory capture a smaller, more severely ill, more disabled and more homogenous patient group.

We will discuss the issue of research criteria below, under the next heading.

The Primer for Clinical Practitioners[xvi] published by the professional organization International Association for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (IACFS/ME)[xvii], and written to complement the CCC, explains that post-exertional malaise is ”the key feature” of the illness:

> The key feature of the syndrome, post-exertional malaise, is the exacerbation of symptoms following minimal physical or mental activity, which can persist for hours, days or even weeks.[…]
>
> 5:4 Fatigue and Post-exertional Malaise
> Patients with ME/CFS experience abnormal fatigue that is both more intense and qualitatively different from normal tiredness. The fatigue in ME/CFS may take several different forms: post-exertional fatigue (abnormal exhaustion or muscle weakness following minor physical or cognitive activity), persistent flu-like feelings, brain fog (mental exhaustion from everyday cognitive effort), and wired fatigue (feeling over-stimulated when very tired).
>
> The type of fatigue that is a core feature of ME/CFS is post-exertional malaise (PEM). PEM is the exacerbation of fatigue and other symptoms (e.g., cognitive difficulties, sore throat, insomnia) following minimal physical or mental activity that can persist for hours, days or even weeks. PEM may be related to abnormal energy metabolism.

The Myalgic Encephalomyelitis: International Consensus Criteria (ICC)[xviii] use the term ”post exertional autoimmune exhaustion (PENE)” to describe a post-exertional exacerbation of symptoms, and explains that it is a ”cardinal feature” of the illness:

> A. Postexertional neuroimmune exhaustion (PENEpen’-e): Compulsory
>
> This cardinal feature is a pathological inability to produce sufficient energy on demand with prominent symptomsp rimarily in the neuroimmune regions. Characteristics are as follows:

1. Marked, rapid physical and/or cognitive fatigability in response to exertion,which may be minimal such as activities of daily living or simple mental tasks, can be debilitating and cause a relapse.
2. Postexertional symptom exacerbation: e.g. acute flu-like symptoms, pain and worsening of other symptoms.
3. Postexertional exhaustion may occur immediately after activity or be delayed by hours or days.
4. Recovery period is prolonged, usually taking 24 h or longer. A relapse can last days,weeks or longer.
5. Low threshold of physical and mental fatigability (lack of stamina) results in a substantial reduction in pre-illness activity level.

The Institute of Medicine's report on ME/CFS[xix] states that "Several studies have found that PEM best distinguishes ME/CFS from idiopathic chronic fatigue":

POST-EXERTIONAL MALAISE (PEM)

Description of PEM in ME/CFS

PEM is an exacerbation of some or all of an individual's ME/CFS symptoms that occurs after physical or cognitive exertion and leads to a reduction in functional ability (Carruthers et al., 2003). As described by patients and supported by research, PEM is more than fatigue following a stressor. Patients may describe it as a post-exertional "crash," "exhaustion," "flare-up," "collapse," "debility," or "setback."2 PEM exacerbates a patient's baseline symptoms and, in addition to fatigue and functional impairment (Peterson et al., 1994), may result in flu-like symptoms (e.g., sore throat, tender lymph nodes, feverishness) (VanNess et al., 2010); pain (e.g., headaches, generalized muscle/joint aches) (Meeus et al., 2014; Van Oosterwijck et al., 2010); cognitive dysfunction (e.g., difficulty with comprehension, impaired short-term memory, prolonged processing time) (LaManca et al., 1998; Ocon et al., 2012; VanNess et al., 2010); nausea/gastrointestinal discomfort; weakness/instability; light-headedness/vertigo; sensory changes (e.g., tingling skin, increased sensitivity to noise) (VanNess et al., 2010); depression/anxiety; sleep disturbances (e.g., trouble falling or staying asleep, hypersomnia, unrefreshing sleep) (Davenport et al., 2011a); and difficulty recovering capacity after physical exertion (Davenport et al., 2011a,b). In some cases, patients experience new symptoms as part of the PEM response.[…] The types and thresholds of triggers of PEM, its onset, and its duration may vary among individuals and over the course of illness. […]

PEM as a Characteristic Symptom of ME/CFS

The existence of PEM can help physicians confirm a diagnosis of ME/CFS earlier rather than only after extensive exclusion of other conditions. Several studies have found that PEM best distinguishes ME/CFS from idiopathic chronic fatigue (Baraniuk et al., 2013; Jason et

> al., 2002a) and may help distinguish it from other fatiguing conditions with a lower frequency of PEM, such as multiple sclerosis and major depressive disorder (Hawk
>
> et al., 2006a; Komaroff et al., 1996b). Further, PEM may be an important prognostic indicator because its continued presence or increased duration predicts a poorer outcome for ME/CFS patients (Taylor et al., 2002).

The Institute of Medicine's report guide for clinicians[xx] states that ”There is sufficient evidence that PEM is a primary feature that helps distinguish ME/CFS (SEID) from other conditions.”

> "Post-exertional malaise (PEM)
> PEM is worsening of a patient’s symptoms and function after exposure to physical or cognitive stressors that were normally tolerated before disease onset. Subjective reports of PEM and prolonged recovery are supported by objective evidence in the scientific literature, including failure to normally reproduce exercise test results (2-day cardiopulmonary exercise test) and impaired cognitive function after exertion. There is sufficient evidence that PEM is a primary feature that helps distinguish ME/CFS (SEID) from other conditions."

Also see the letter written to DHHS by 50 leading ME/CFS experts[xxi] where the authors state that PEM is a hallmark symptom of the disease and should be mandatory in the definition/criteria. Quote:

> “the symptom of post-exertional malaise (PEM), which researchers, clinicians, and patients consider a hallmark of the disease”

An important note on PEM in the severely ill: It is absolutely crucial to be aware that mere biomechanical strain can cause PEM. Please refer to Dr Peter Rowe's webinar ”Inducing Post-Exertional Malaise in ME/CFS: A Look at the Research Evidence (2015)”[xxii] for details, in particular where he describes what happens after e.g. ”passive” activation of muscles (for example when a physiotherapists lifts and/or moves the limbs of the patient) at 44:45 minutes in.

Research Criteria

The failure to reach consensus on research criteria is a steep barrier to progress across the ME/CFS landscape. A single set of universally accepted research criteria is needed to conduct reproducible research and appropriate treatment strategies.

Until a consensus can be agreed upon, or new research criteria is developed, NIH should request that researchers use the Canadian Consensus Criteria (Carruthers, 2003), which is the research criteria recommended by the International Association for CFS/ME and the DHHS CFS Advisory Committee.

It is of utmost importance that future research is based on criteria where PEM is a required symptom.

The CCC has already become the preferred definition for most of the international experts in the field (both clinicians and researchers), not least due to the fact that it requires PEM. Research (Jason et al, Marshall-Gradisnik et al) has shown that the CCC, the ICC and other definitions where PEM is mandatory capture a smaller, more severely ill, more disabled and more homogenous patient group.

See "An Open Letter to the Honorable Kathleen Sebelius, U.S. Secretary of Health and Human Services", written by 50 expert biomedical ME/CFS researchers and clinicians[xxiii].

> The CCC was developed by an international group of researchers and clinicians with significant expertise in ME research and treatment, and was published in a peer-reviewed journal in 2003 (Carruthers et al, Journal of Chronic Fatigue Syndrome, 2003). Unlike the Fukuda definition, the more up-to-date CCC incorporates the extensive scientific knowledge gained from decades of research. For example, the CCC requires the symptom of post-exertional malaise (PEM), which researchers, clinicians, and patients consider a hallmark of the disease, and which is not a mandatory symptom under the Fukuda definition. The CCC was endorsed in the Primer for Clinical Practitioners published by the International Association of Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (IACFSME). This organization is the major international professional organization concerned with research and patient care in ME/CFS.
>
> The expert biomedical community will continue to refine and update the case definition as scientific knowledge advances; for example, this may include consideration of the 2011 ME International Consensus Criteria (Carruthers et al, Journal of Internal Medicine, 2011). As leading researchers and clinicians in the field, however, we are in agreement that there is sufficient evidence and experience to adopt the CCC now for research and clinical purposes, and that failure to do so will significantly impede research and harm patient care. This step will facilitate our efforts to define the biomarkers, which will be used to further refine the case definition in the future.
>
> We strongly urge the Department of Health and Human Services (HHS) to follow our lead by using the CCC as the sole case definition for ME/CFS in all of the Department's activities related to this disease.

Disparate criteria create great risk of harm

The P2P Panel recommended that the Oxford definition be retired. We agree and strongly urge NIH, CDC and all others to immediately cease using all overly broad 'fatigue' centered criteria, e.g. Oxford, Fukuda and Reeves.

Although dedicated expert researchers and clinicians have identified parameters for defining ME/CFS, those parameters have not been universally adopted. As a result, studies of ME/CFS are fraught with methodological problems, preventing a clear understanding of who is affected by the disease.

There is currently a vast number of wildly disparate and arbitrarily used case definitions and critera for ME and CFS research and diagnostic purposes. A substantial body of evidence shows that these

definitions do not all represent the same disease and that there are significant differences in patient populations, making some of these definitions highly unreliable and inaccurate.

Needlessly to say, this is extremely problematic, not least because evidence reviews and suchlike usually don't acknowledge the differences, nor the consequent problems and risks, and therefore often present their findings in such a way that the uninformed reader is led to believe that their conclusions are applicable to all patients meeting any CFS or ME definition regardless of the research criteria used in a particular study. Sadly, this is true for even the most reputable ones, such as for example Cochrane and the Agency for Healthcare Research and Quality (AHRQ), as well as the information and educational material currently provided by the CDC, MedScape, Up To Date, Kaiser etc.

This cannot be overstated: it is unscientific, illogical and creates undue risk of harm to lump disparate patients together without regard to substantive differences in their underlying pathologies and conditions.

Subgrouping

We belive possible subgroups is a critical issue that must be taken into careful consideration at all times, including treatment trials, and especially seeing that there currently is no consensus on research criteria.

The following are examples of factors relevant for subgrouping:

- Differences in biological pathologies
- Duration of illness
- Symptom clusters
- Level of severity
- Acute vs gradual onset
- Infectious vs non-infectious onset
- Triggers
- Pathogens
- Single vs cluster outbreaks
- Fluctuating pattern vs progressive decline
- Increased susceptibility to infection vs decreased susceptibility to infection since onset of ME/CFS

Replication and validation of existing biomedical studies

There has been no lack of promising leads and exciting possibilities (abnormalities in the immune system, the brain, the metabolic system, the possible autoimmune factor, etc., etc.). But these successful initial small studies are almost never followed by larger confirmatory studies, due to lack of funding and rejected applications.

Here are some of the most intriguing findings that need to be replicated, in carefully designed well-controlled studies with good methodology and much larger cohorts.

Further research into PEM

Further research into the physiological underpinnings of PEM is essential and urgently needed.

Please refer to the following article for a list of most of the published abnormal responses to exercise:
Twisk and Geraghty. Deviant Cellular and Physiological Responses to Exercise in Myalgic Encephalomyelitis and Chronic Fatigue Syndrome. J J Physiology. 2015, 1(2): 007

http://www.jacobspublishers.com/images/Physiology/J_J_Physiology_1_2_007.pdf

Two-day Cardiopulmonary Exercise Testing

Two-day Cardiovascular Exercise Testing (CPET) with gas exchange is an important physiological marker for the cardinal symptom known as post-exertional malaise (PEM), and presents compelling preliminary evidence that a biosignature for ME/CFS has been found.

Well-funded, well-controlled, high quality clinical trials using large sample sizes are now urgently needed in order to validate these findings and stratify subgroups, and to find out whether it is a true biomarker.

Two-day CPET should urgently be further studied as a complement to other diagnostic measures, as an objective method to document and better understand the metabolic, neurologic and autonomic dysfunction of ME/CFS, and as a possible tool for objective physiological outcome measures in clinical trials.

The test-retest stategy (Stevens' Protocol) is crucial in this context. Other forms of single tests and short term testing usually fail to capture the delayed symptom exacerbation following physical activity, and to describe and objectively document the fluctuating nature of ME/CFS.

Please also note that a maximal exercise protocol is required, since submaximal testing isn't fully sufficient in this context.

Also, the NIH and researchers should consider how can this or an equivalent be adapted for severely ill patients, without causing them harm or putting them in danger?

CPET is already widely recognized as an accurate, reliable and reproducible way to measure the cardiovascular, pulmonary and metabolic responses at rest and during exercise, as an objective tool for disability evaluation and other medico-legal assessments, as well as a way to determine which system limits function.

The IOM report accepted the two-day CPET and stated "One way to demonstrate this delayed lack of recovery in patients with ME/CFS is to perform two cardiopulmonary exercise tests separated by 24 hours." The IOM included CPET in its list of tools that could be used to assess PEM, stating the

2-day test would "demonstrate marked inability to reproduce maximal or anaerobic threshold measures on the second day."

According to a 2010 presentation by Dr. Chris Snell at CFSAC[xxiv], CPET is considered the gold standard for assessing functional capacity for a number of diseases and by a number of medical societies - e.g. American Heart Association, American Medical Association, to name a few. Also by the U.S. Social Security Administration, who accepts the two-day CPET as objective proof of disability in ME.

See the studies listed below:

Keller BA1, Pryor JL, Giloteaux L.. (2014) Inability of myalgic encephalomyelitis/chronic fatigue syndrome patients to reproduce VO2-peak indicates functional impairment. J Transl Med. 2014 Apr 23;12:104. doi: 10.1186/1479-5876-12-104.

http://www.ncbi.nlm.nih.gov/pubmed/24755065

Christopher R. Snell, Staci R. Stevens, Todd E. Davenport, J. Mark Van Ness. (2013). Discriminative Validity of Metabolic and Workload Measurements to Identify Individuals With Chronic Fatigue Syndrome. Physical Therapy Jun 2013, DOI: 10.2522/ptj.20110368 DOI: 10.2522/ptj.20110368.

http://ptjournal.apta.org/content/early/2013/06/26/ptj.20110368.full.pdf+html

Vermeulen R. (2010) Patients with chronic fatigue syndrome performed worse than controls in a controlled repeated exercise study despite a normal oxidative phosphorylation capacity. Journal of Translational Medicine20108:93. DOI: 10.1186/1479-5876-8-93.
http://translational-medicine.biomedcentral.com/articles/10.1186/1479-5876-8-93

VanNess M. (2007) Diminished Cardiopulmonary Capacity During Post-Exertional Malaise. Journal of Chronic Fatigue Syndrome Volume 14, Issue 2, 2007 pages 77-85. DOI: 10.1300/J092v14n02_07
http://www.tandfonline.com/doi/abs/10.1300/J092v14n02_07

VanNess M. (2010) Postexertional malaise in women with chronic fatigue syndrome. J Womens Health (Larchmt). 2010 Feb;19(2):239-44. doi: 10.1089/jwh.2009.1507.
http://www.ncbi.nlm.nih.gov/pubmed/20095909

Gene expression alterations

Researchers have found differing gene expression alterations following exercise in ME/CFS patients, which need larger replication studies. See the studies listed below:

Light AR, Bateman L, Jo D, Hughen RW, Vanhaitsma TA, White AT, Light KC. (2012) Gene expression alterations at baseline and following moderate exercise in patients with Chronic Fatigue Syndrome and Fibromyalgia Syndrome. J Intern Med. 271:64-81. http://doi.org/10.1111/j.1365-2796.2011.02405.x

http://www.ncbi.nlm.nih.gov/pubmed/21615807

http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2796.2011.02405.x/abstract

White, A. T., Light, A. R., Hughen, R. W., VanHaitsma, T. A., & Light, K. C. (2012). Differences in metabolite-detecting, adrenergic, and immune gene expression following moderate exercise in chronic fatigue syndrome, multiple sclerosis and healthy controls. Psychosomatic Medicine, 74(1), 46–54. http://doi.org/10.1097/PSY.0b013e31824152ed
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3256093/

White AT, Light AR, Hughen RW, Bateman L, Martins TB, Hill HR, Light KC. (2010) Severity of symptom flare after moderate exercise is linked to cytokine activity in chronic fatigue syndrome. Psychophysiology. 47:615-24.

http://onlinelibrary.wiley.com/doi/10.1111/j.1469-8986.2010.00978.x/abstract

Light A. (2009) Moderate Exercise Increases Expression for Sensory, Adrenergic, and Immune Genes in Chronic Fatigue Syndrome Patients But Not in Normal Subjects. The Journal of Pain October 2009Volume 10, Issue 10, Pages 1099–1112. DOI: http://dx.doi.org/10.1016/j.jpain.2009.06.003

http://www.jpain.org/article/S1526-5900%2809%2900574-4/fulltext

Other important studies that need to be replicated and expanded

Rituximab
Fluge Ø and Mella O. B-lymphocyte Depletion Using Rituximab in Chronic Fatigue Syndrome/ Myalgic Encephalopathy (CFS/ME). A Randomized Phase-III Study. (RituxME).
https://clinicaltrials.gov/ct2/show/NCT02229942

Fluge Ø, Mella O et al. (2015) B-Lymphocyte Depletion in Myalgic Encephalopathy/ Chronic Fatigue Syndrome. An Open-Label Phase II Study with Rituximab Maintenance Treatment. PLoS One. 2015 Jul 1;10(7):e0129898. doi: 10.1371/journal.pone.0129898. eCollection 2015.
http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0129898

Fluge Ø, Mella O et al. (2011) Benefit from B-lymphocyte depletion using the anti-CD20 antibody rituximab in chronic fatigue syndrome. A double-blind and placebo-controlled study. PLoS One. 2011;6(10):e26358. doi: 10.1371/journal.pone.0026358. Epub 2011 Oct 19.
http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0026358

Fluge Ø, Mella O. (2009) Clinical impact of B-cell depletion with the anti-CD20 antibody rituximab in chronic fatigue syndrome: a preliminary case series. BMC Neurol. 2009 Jul 1;9:28. doi: 10.1186/1471-2377-9-28.
http://bmcneurol.biomedcentral.com/articles/10.1186/1471-2377-9-28

Studies indicating abnormal NK cell function in ME/CFS
The Institute of Medicine's report on ME/CFS states: ”One of the most consistent findings in ME/CFS subjects is poor NK cell function.” But study results vary and further investigation and large-scale replication is necessary.

Please see the following examples of NK cell studies:

Klimas, N. G., Salvato, F. R., Morgan, R., & Fletcher, M. A. (1990). Immunologic abnormalities in chronic fatigue syndrome. *Journal of Clinical Microbiology*, *28*(6), 1403–1410.
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC267940/

Fletcher, M. A., X. R. Zeng, K. Maher, S. Levis, B. Hurwitz, M. Antoni, G. Broderick, and N. G. Klimas. (2010) Biomarkers in chronic fatigue syndrome: Evaluation of natural killer cell function and dipeptidyl peptidase IV/CD26. PLoS ONE 5(5):e1081
http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0010817

Brenu, E. W., M. L. van Driel, D. R. Staines, K. J. Ashton, S. B. Ramos, J. Keane, N. G. Klimas, and S. M. Marshall-Gradisnik. (2011) Immunological abnormalities as potential biomarkers in chronic fatigue syndrome/myalgic encephalomyelitis. Journal of Translational Medicine 9:81
http://translational-medicine.biomedcentral.com/articles/10.1186/1479-5876-9-81

Brenu, E. W., M. L. van Driel, D. R. Staines, K. J. Ashton, S. L. Hardcastle, J. Keane, L. Tajouri, D. Peterson, S. B. Ramos, and S. M. Marshall-Gradisnik. (2012) Longitudinal investigation of natural killer cells and cytokines in chronic fatigue syndrome/myalgic encephalomyelitis. Journal of Translational Medicine. 10:88.
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3464733/

Ampligen (Rintatolimod)

Large-scale RCTs investigating whether the drug Ampligen is effective in a sub-group of ME/CFS patients. Ampligen has shown promise and could bring relief to patients soon. Therefore NIH-sponsored trials should be carried out in the near future, this should not wait until the intra-NIH study reaches its final stage.

Strayer DR, Carter WA, Brodsky I, Cheney P, Peterson D, Salvato P, et al. (1994) A controlled clinical trial with a specifically configured RNA drug, poly(I).poly(C12U), in chronic fatigue syndrome. Clin Infect Dis. 1994;18 Suppl 1:S88-95.
http://cid.oxfordjournals.org/content/18/Supplement_1/S88.long

Strayer DR, Carter WA, Stouch BC, Stevens SR, Bateman L, Cimoch PJ, et al; (2012) Chronic Fatigue Syndrome AMP-516 Study Group. A double-blind, placebo-controlled, randomized, clinical trial of the TLR-3 agonist rintatolimod in severe cases of chronic fatigue syndrome. PLoS One. 2012;7:e31334. doi:10.1371/journal.pone.0031334
http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0031334

Neuroinflammation

Yasuhito Nakatomi et al. Neuroinflammation in Patients with Chronic Fatigue Syndrome/Myalgic Encephalomyelitis: An 11C-(R)-PK11195 PET Study
J Nucl Med June 1, 2014 jnumed.113.131045
http://jnm.snmjournals.org/content/early/2014/03/21/jnumed.113.131045.abstract

Distinct cerebrospinal fluid proteomes

Schutzer SE, Angel TE, Liu T, Schepmoes AA, Clauss TR, Adkins JN, et al. (2011) Distinct Cerebrospinal Fluid Proteomes Differentiate Post-Treatment Lyme Disease from Chronic Fatigue Syndrome. PLoS ONE 6(2): e17287. doi:10.1371/journal.pone.0017287
http://journals.plos.org/plosone/article?id=10.1371%2Fjournal.pone.0017287

Brainstem perfusion is impaired

Brainstem perfusion is impaired in chronic fatigue syndrome. DC Costa, C Tannock and J Brostoff. Quarterly Journal of Medicine December 1995:88:767-773)

Further investigation into whether autoantibodies are involved in ME/CFS
Replication and expansion of the following:

Nishikai M. (2007) [Antinuclear antibodies in patients with chronic fatigue syndrome]. Nihon Rinsho. 2007 Jun;65(6):1067-70.
http://www.ncbi.nlm.nih.gov/pubmed/17561698

Loebel M. (2016) Antibodies to β adrenergic and muscarinic cholinergic receptors in patients with Chronic Fatigue Syndrome. Brain, Behavior, and Immunity Volume 52, February 2016, Pages 32–39.
http://www.sciencedirect.com/science/article/pii/S0889159115300209

Elfaitori A et al. (2013) Epitopes of Microbial and Human Heat Shock Protein 60 and Their Recognition in Myalgic Encephalomyelitis. http://dx.doi.org/10.1371/journal.pone.0081155
http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0081155

Are ion channels implicated in ME/CFS?

Marshall-Gradisnik S. (2016) Natural killer cells and single nucleotide polymorphisms of specific ion channels and receptor genes in myalgic encephalomyelitis/chronic fatigue syndrome. Dove Press: The application of Clinical Genetics Volume 2016:9 Pages 39—47. DOI
https://dx.doi.org/10.2147/TACG.S99405
https://www.dovepress.com/articles.php?article_id=26236

Nguyen T. (2016) Novel identification and characterisation of Transient receptor potential melastatin 3 ion channels on Natural Killer cells and B lymphocytes: effects on cell signalling in Chronic fatigue syndrome/Myalgic encephalomyelitis patients. Biological Research201649:27. DOI: 10.1186/s40659-016-0087-2
https://biolres.biomedcentral.com/articles/10.1186/s40659-016-0087-2

Marshall-Gradisnik S. (2016) Genotype Frequencies of Transient Receptor Potential Melastatin M3 Ion Channels and Acetylcholine Muscarinic M3 Receptor Gene Polymorphisms in Chronic Fatigue Syndrome/Myalgic Encephalomyelitis Patients. Immunology and Immunogenetics Insights 2016:8 1-2. DOI: 10.4137/III.S37042
http://www.la-press.com/genotype-frequencies-of-transient-receptor-potential-melastatin-m3-ion-article-a5387-abstract?article_id=5387

Marshall-Gradismik S. (2015) Examination of Single Nucleotide Polymorphisms (SNPs) in Transient Receptor Potential (TRP) Ion Channels in Chronic Fatigue Syndrome Patients. Immunology and Immunogenetics Insights 2015:7 1-6. DOI: 10.4137/III.S25147. http://www.la-press.com/examination-of-single-nucleotide-polymorphisms-snps-in-transient-recep-article-a4824

The microglia activation hypothesis proposed by Jarred Younger
Younger J. (2014) The use of low-dose naltrexone (LDN) as a novel anti-inflammatory treatment for chronic pain. Clin Rheumatol. 2014; 33(4): 451–459. doi: 10.1007/s10067-014-2517-2 http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3962576/

https://selfhacked.com/2016/03/29/dr-jared-younger-cutting-edge-research-on-cfs-neuroinflammation-pain-and-fatigue/

The vagus nerve infection hypothesis proposed by Michael VanElzakker
VanElzakker B. (2013) Chronic fatigue syndrome from vagus nerve infection: A psychoneuroimmunological hypothesis. Medical Hypotheses Volume 81, Issue 3, September 2013, Pages 414–423. oi:10.1016/j.mehy.2013.05.034
http://www.sciencedirect.com/science/article/pii/S0306987713002752

Loss of capacity to recover from acidosis on repeat exercise in CFS
Jones DE. (2011). Loss Of Capacity To Recover From Acidosis On Repeat Exercise In Chronic Fatigue Syndrome A Case Control Study. European Journal of Clinical Investigation 2011 DOI: 10.1111/j.1365-2362.2011.02567.x
http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2362.2011.02567.x/abstract

Abnormalities in pH handling by peripheral muscle and potential regulation by the autonomic nervous system in CFS
Jones DE. (2010) Abnormalities in pH handling by peripheral muscle and potential regulation by the autonomic nervous system in chronic fatigue syndrome. J Intern Med. 2010 Apr;267(4):394-401. doi: 10.1111/j.1365-2796.2009.02160.x
http://www.ncbi.nlm.nih.gov/pubmed/20433583

Jones DE. (2011) Loss of capacity to recover from acidosis on repeat exercise in chronic fatigue syndrome: a case–control study. European Journal of Clinical Investigation Volume 42, Issue 2, pages 186–194, February 2012. DOI: 10.1111/j.1365-2362.2011.02567.x.
http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2362.2011.02567.x/abstract

A comprehensive biomedical research program

There's a great need for a massive and comprehensive, multi-faceted biomedical research program including (but not restricted to) research on the immune system, metabolites, proteomics, genomics, epigenetics, bioenergetics, B cell function, gut microbiome, systems biology, microRNAs, gene

expression profiling, genome wide association studies, neuroendocrine signalling, biochemical pathways, roles of pathogenic agents, neuroimaging, immune-brain communication, virological studies, personalized medicine, vagus nerve infection etc.

We believe it is important to encourage both hypothesis-generating and hypothesis-driven investigations.

Bioenergetics
We believe bioenergetics, the field of science that describes the underlying biochemical activities of energy production needed for all physiological and cognitive activities, is highly relevant in ME/CFS research at the cellular level, and might be a key to understanding the pathophysiology of energy metabolism defects, mitochondrial dysfunction, faulty recovery mechanisms, nutrient sensing and signalling, hormonal regulation, the metabolic basis of energy production etc. Also, it might help identify specific biomarkers for diagnosis and clues for potential therapeutic interventions.

Dr Ron Davis at CFS Research Center at Stanford
Definitely worth a mention in this context is Dr Ron Davis[xxv] [xxvi] [xxvii] at CFS Research Center[xxviii] at Stanford. His Severely Ill Big Data study[xxix] and the Expanded ME/CFS Metabolomics study[xxx] in collaboration with Dr Robert Naviaux are of particular interest, and represent our idea of an excellent role model. We would love to see him and his team get all the funding and any other kind of support they may need from the NIH.

A possible autoimmune connection
We would like to see a thorough full scale investigation of autoimmune possibilities or autoimmune-like activity (that isn't necessarily caused by autoantibodies, but could be caused by e.g. cell receptors that are abnormal by frequency, function, type or structure).

Highly intriguing in this context, of course, are the studies by Dr Øistein Fluge and Dr Olav Mella at Haukeland University Hospital in Bergen, Norway: the Rituximab and Cyclophosphamid (B cell depletion) trials, as well as all the sub studies on endothelial functioning, exercise testing, gastrointestinal functioning, genetics, flow-mediated dilation and skin microcirculation etc. The NIH should consider in what ways they can support Fluge & Mella's current work as well as any future projects based upon new clues that are discovered along the way.

The intestinal microbiome
Another team of researchers well-deserving of a mention here are Dr Ian Lipkin and Dr Mady Hornig at the Columbia University Center for Infection and Immunity, Mailman School of Public Health, New York.. We believe their approach to exploring the intestinal microbiome is very exciting and has great potential.

What do the researchers want?

We asked one of the published biomedical ME/CFS researchers currently working in the field here in Sweden. These are the things he feels are important to focus on:

- Systematic studies of different patients' health history, including which infections the patient has undergone before the onset of ME / CFS
- Epidemiological studies
- Comparing PEM occuring in PBC (primary biliary cirrhosis) with PEM in ME/CFS
- Studies of antibodies to mitochondrial components and to mitochondrial function in ME/CFS
- Changed content of immune proteins a few years after the onset of ME/CFS
- NK cell activity as a potential biomarker
- Studies on specific brain findings need to be replicated and expanded
- A larger Rituximab trial
- Heritability, and how often are spouses affected?
- Continued studies on IBS, changes in the gut flora and micro leakage in ME/CFS
- Studies on autoreactive B cells in ME/CFS in relation to the gut flora
- Comparative studies of different ME/CFS definitions

Biomarkers and diagnostic tests

The importance of biomarkers cannot be overstated. Not only in a medical context, but also as a crucial step towards overcoming stigma, bias and discrimination.

Larger, definitive studies on diagnostic biomarkers are urgently required.

Objectively measurable outcomes

It is absolutely essential that this is made a priority. NIH must invest, without delay, in development and validation of objective outcomes measures.

A central problem in clinical trials in the ME/CFS field has been the complete lack of objectively measurable outcomes. This (in combination with other methodological problems) has allowed for studies which proclaim to demonstrate effectiveness of a certain psychosocial or cognitive-behavioural treatment modality, but in fact at best probably only show placebo effect improvements.

It is absolutely necessary that future treatment trials include objective measures of effectiveness, such as actigraphy, long-term actometer data, exercise testing e.g. two-day CPET according to Stevens' Protocol (when appropriate), employment data, disability payments data, tilt table testing, quantitative EEG, PET scans, validated tests for cognitive functioning, gene expression, immunological, autoantibody and cytokine profiles etc.

Also, it is crucial that the total amount of activities and other factors that involve exertion — both physical and mental, perhaps even environmental ones such as e.g. extreme temperatures — are considered as a whole, as measuring just one specific type of activity can often be very misleading (one type of activity can often be increased at the expense of other activities and straining factors). Long-term follow-up is essential in this aspect as well.

Centers of Excellence

NIH must fund and establish 5-10 Centres of Excellence for expert clinical care, biomedical research and clinical trials, all combined under one roof. These Centers should also participate in the creation of Common Data Elements and the Data Coordinating Center.

This is absolutely vital for future progress of the ME/CFS field, and has been requested many times by the CFS Advisory Committee[xxxi xxxii xxxiii xxxiv xxxv xxxvi].

Pharmacological treatments

There are currently no FDA-approved drug therapies for ME/CFS; this gap should be specifically addressed.

Clinical trials of Rituximab and other promising pharmaceuticals are needed, such as Ampligen, Low Dose Naltroxen, anti-virals (e.g. Valcyte) and cytokine inhibitors.

Many people with ME/CFS are experiencing symptom relief thanks to vitamin B12 injections (often but not always combined with folate). However, it's often very difficult for patients to get access to this kind of treatment because of the current lack of scientific evidence.

The same could be said about saline infusions (please refer to te work of Dr David Bell) and intravenous immunoglobulin therapy (IVIG).

The NIH and researchers should consider what drugs previously targeted only for autoimmune, neurodegenerative, viral and retroviral diseases could be examined for their effectiveness in patients with ME/CFS.

Again, taking possible subgroups into account is absolutely crucial. If a small proportion of patients are helped by a specific treatment, it is necessary to try to find out why and how, instead of just dismissing the treatment outcomes altogether.

Longitudinal study

There is a need for an accelerated longitudinal study to elucidate the natural history of ME/CFS.

I.e. To answer the questions:

- How is ME/CFS changing over time?

and

- What about the risk of relapses for people who are supposedly recovered or in remission?

Distinct plasma immune signatures in ME/CFS are present early in the course of illness, but differ in long-term patients and such differences could be investigated further. For example the following

research found differences in short and long-term patients:

Distinct plasma immune signatures in ME/CFS are present early in the course of illness

Mady Hornig, José G. Montoya, Nancy G. Klimas, Susan Levine, Donna Felsenstein, Lucinda Bateman, Daniel L. Peterson, C. Gunnar Gottschalk, Andrew F. Schultz, Xiaoyu Che, Meredith L. Eddy, Anthony L. Komaroff, W. Ian Lipkin

Science Advances 27 Feb 2015 : e1400121
http://advances.sciencemag.org/content/1/1/e1400121

Cytokine network analysis of cerebrospinal fluid in ME/CFS
M Hornig, G Gottschalk, D L Peterson, K K Knox, A F Schultz, M L Eddy, X Che and W I Lipkin
Molecular Psychiatry 21, 261-269 (February 2016)
http://www.nature.com/mp/journal/v21/n2/full/mp201529a.html

The severely ill

The situation is absolutely desperate for the approximately 25% who are severely ill, who aren't able to leave their house or their bed. It's extremely difficult to get access to home visits by competent doctors and/or home-based medical care, so there's a large group of immensely sick people who are totally abandoned by the health care system.

It is absolutely crucial that the severely ill patients – those who are housebound or bedbound – must be included. Patients must be at the center of the research efforts, and this must include the severely ill. There has to be a way to make it possible for them to access medical care and to participate in clinical trials.

Dr Ron Davis' Severely Ill Big Data study is a great example of how it can be done, proof that it can indeed be done. The NIH should consider what it can learn from his approach, and how can it further develop it.

It is hugely important to acknowledge that so far the most severely affected patients have been — and still are — very unlikely to participate in studies. Most studies completely lack data on severe cases of ME/CFS. This is an immense problem that has to be taken into consideration when trying to interpret the evidence base.

The P2P report made several valuable suggestions:

- Use telemedicine or home visits for those unable to participate in clinical trials/treatment in person.
- Develop and employ new technologies to address underserved populations and unmet needs (mobile technology, etc) to measure progress and enable communication.
- Improve quality of care by learning from palliative care.

Also, we believe that the severely ill patients should be allowed access to experimental treatments on compassionate use and named-patient basis, in the same way that patients living with other similarly disabling illnesses are.

Most importantly, these patients are at an exponentially higher risk for great and irreverisble harm when subjected to medical neglect or inappropriate treatments.

Pediatric Research

Pediatric biomedical research is a significant gap in the current approach to ME/CFS research.

Prognosis is often said to be much better for children than for adults, but many children are ill for a long time, often very ill for a very long time. Why is that? What aspects affect the prognosis (acute vs gradual onset, type of trigger, subgroup, symptom clusters, severity, severity during the first 5 years, degree of PEM, frequent over-exertion, genetics..?) How common is it that children are ill for longer than 5 years? Longer than 25 years? What proportion of children with ME/CFS become severely affected long-term? How is their illness changing over time?

Parents and caregivers of children with ME/CFS often report that ME/CFS isn't taken seriously by most doctors, that they tend to shrug it off saying things like "they are young, it will pass". Sadly, the doctors are all too often wrong about that. According to the lived experience of many parents, leaving children with ME/CFS without adequate medical care and/or practical help (e.g. teaching the children and the adults around them the importance of Pacing, making reasonable adjustments regarding their schooling etc) greatly increases the risk of them becoming ill long-term.

Could it be that the prognosis for children actually isn't as good as currently claimed, or do they become long-term sufferers because they aren't receiving adequate help? Do children really have a better chance of recovering than adults do?

Is it possible that the methodology and outcome measures used by the biopsychosocial proponents in many of these kinds of studies tend to be misleading? For example, children are often great at adapting to their illness, easily making adjustments in order to live a "normal" life. Could it be that after a while these adjustments become so natural to them that they aren't even aware of them any longer, and therefore report that they "feel better" and are "less impared", that their symtoms have "improved"?

A lot of abuse towards children and young people with ME/CFS are based on this unproven expectation, that they are "supposed to recover" within 3-5 years. This expectation is a problem not only medically, but also in regards to health insurance, in dealing with schools and other authorities etc.

It is also necessary to investigate heritability and familial associations. E.g. do symptoms differ between children and adults, and if so in what way?

Allergies and food intolerances should be investigated as well[xxxvii].

Pacing

The results from patient surveys repeatedly and consistently show that Pacing, also known as the Energy Envelope Theory approach, is the most effective, safe, acceptable and preferred form of activity management for people with ME/CFS. Please see the following survey:

ME Association's report on the acceptability, efficacy and safety of CBT, GET and Pacing as interventions used as management strategies for ME/CFS.
http://www.meassociation.org.uk/2015/05/23959/

Please see the following articles for an in-depth explanation of Pacing:

Jason, L. A., Brown, M., Brown, A., Evans, M., Flores, S., Grant-Holler, E., & Sunnquist, M. (2013). Energy conservation/envelope theory interventions. Fatigue: Biomedicine, Health & Behavior, 1(1-2), 27–42. **http://doi.org/10.1080/21641846.2012.733602**
http://www.tandfonline.com/doi/abs/10.1080/21641846.2012.733602#.V2mlS6Katj8

Goudsmit EM, Nijis J, Jason LA, et al. Pacing as a Strategy to improve energy management in myalgic encephalomyelitis/chronic fatigue syndrome:a consensus document. (2012) Disabil Rehavil; 2012 34 (13): 1140-7.
http://www.tandfonline.com/doi/abs/10.3109/09638288.2011.635746

We would love to see the NIH, through its research efforts, make sure that the safety and widespread acceptability of pacing within the patient community is accurately reflected in the scientific literature as well as in all ME/CFS information and educational materials, clinical guidelines etc.

However, please note that the term pacing is not used consistently in the medical literature and sometimes overlaps with graded exercise therapy. We here refer to a method that advices patients to pace or "spread out" activities so that ongoing exertion remains below the threshold of post-exertional symptom flare-ups (IACFS/ME Primer for Clinical Practicioners). The method should be applied individually in a flexible manner, and not follow a rigid scheme with an established baseline as for example the adaptive pacing therapy used in the much-critizised PACE study.

Please also note that similar sounding concepts such as "graded pacing", "pacing up", "activity pacing"and "time/quota/etc contingent pacing" are much closer to graded exercies therapy in their setup, and therefore very different from the method we refer to here.

Blood volume and circulatory impairment

Diastolic dysfunction and reduced cardiac output[xxxviii] [xxxix] must be looked at.

Also, to investigate: how reduced is the blood volume? Why? How does the reduced blood volume and circulation affect different organs?

And, do the ME/CFS sufferer need a higher concentration of minerals and vitamins in the blood to support the organs?

Comparisons with infectious disease emergencies

We recommend making comparisons with post-infectious states in high-profile diseases such as Ebola and Zika virus. I.e. to explore what similarities and differences there are between the "post-viral fatigue" that has been reported among Ebola and Zika patients, compared to that of ME/CFS patients. For example, would it be possible to add ME/CFS patients as a control group in post-infectuous studies on Ebola and Zika?

Cluster outbreaks

We believe there is a lot to learn from cluster outbreaks.

Please see Dr Rosemary Underhill's A Neglected Subgroup of Patients with ME/CFS (CFSAC testimony 3 Oct, 2012):
http://www.hhs.gov/advcomcfs/meetings/presentations/underhill_rosemary_100312.pdf

Neurocognitive deficit and orthostatic intolerance

Many small but promising studies have explored these major symptoms, but they need to be explored further:

- Neurocognitive deficit ("brain fog") [xl] [xli] [xlii] [xliii] [xliv]
- Orthostatic intolerance [xlv]

Post-mortem studies and tissue bank

Post-mortem studies are essential to elucidate the disease mechanisms in ME/CFS. A post-mortem tissue bank should be established by the NIH.

The following studies explore some intriguing research potential of post-mortem studies and the feasibility of setting up a post-mortem tissue bank.

O'Donovan D, Harrower T, Cader S, Findley L, Shepherd C, Chaudhuri A. International Science Symposium 3-4 – Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) Queensland,

Australia: Population Health and Neuroimmunology Unit, Bond University; 2010. Pathology of Chronic Fatigue Syndrome: Pilot Study of four autopsy cases.

http://www.meassociation.org.uk/research2015/current-research2015/pathology-of-cfs205/

Nacul L, O'Donovan DG, Lacerda EM, et al. Considerations in establishing a post-mortem brain and tissue bank for the study of myalgic encephalomyelitis/chronic fatigue syndrome: a proposed protocol. BMC Research Notes. 2014;7:370. doi:10.1186/1756-0500-7-370.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4076507/

Collaboration and converging themes

There is already great collaboration and converging themes happening among international ME/CFS researchers. There's an important opportunity to build on this, for example through multi-site studies and replications of promising biomedical pilot studies, as well as partnering with and supporting existing international ME/CFS expert biomedical research organizations and networks such as the International Association for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (IACFS/ME) and the European ME Research Group (EMERG).

Biobank

We believe a biobank would be an invaluable resource, and would like to see it happen as soon as possible.

We also believe it is important to leverage existing registries.

The metadata will be crucial, and is at this point in time (due to the current lack of validated biomarkers) heavily dependent on the development of other aspects, such as finding a consensus regarding research criteria, subgrouping etc.

The P2P Panel made a recommendation: Establish a central archive of de-identified data and tissue samples from prior and ongoing studies to enable data and sample sharing.

CFSAC made additional recommendations in their comments on the P2P report draft:

> *Addition Requested: (after Line 234) "The NIH should adapt the architecture of the National Autism Research Database (NDAR) to setup and provide ongoing support for a data and bio-bank sharing platform for ME/CFS research. This platform should allow for both phenotype and biologic data."*
>
> Rationale: The National Autism Research Database (NDAR) is an NIH-funded research data repository that aims to accelerate progress in autism spectrum disorders (ASD) research through data sharing, data harmonization, and the reporting of research results. NDAR also serves as a scientific community platform and portal to multiple other research repositories, allowing for aggregation and secondary analysis of data. NDAR is an extensible, scalable

informatics platform for ASD relevant data at all levels of biological and behavioral organization (molecules, genes, neural tissue, behavioral, social and environmental interactions) and for all data types (text, numeric, image, time series, etc.). NDAR was developed to “share data” across the entire ASD field and to facilitate collaboration across laboratories, as well as interconnectivity with other informatics platforms. A similar database is needed to advance ME/CFS research.

Common Data Elements and a data coordinating center

Common data elements and a central data repository, a data coordinating center, are much needed, especially given that ME/CFS specialists and researchers are scattered across the country (and the world) with limited systematization of data collection.

The P2P Panel also recommended this: develop large datasets using bioinformatics techniques and store in a central, publicly accessible database.

Patients must be at the center of all research efforts

Patients must be at the center of the research efforts. Their engagement is critical. NIH must incorporate public input in a meaningful way in planning and executing ME/CFS research initiatives. So far NIH has not engaged or involved stakeholders in a substantive nor adequate way.

From now on, we expect the NIH to commit to increased transparency and accountability, to actively engage patients and the biomedical expert community in every ME/CFS study from the moment of its inception, and to make expansive participation and collaboration a priority. Ideally, there should be established and accessible ways of two-way communication and input throughout the entire process. This includes the planning and implementation of the design, recruitment, trial, analysis, study outcome, peer-reviewed publication, as well as the dissemination and publicity.

It is absolutely critical that NIH consider the range of views among patients, advocates, clinicians and researchers – and meaningfully incorporate that input also into designing RFAs, studies, data elements, and future initiatives.

Adverse effects, harms

The issue of harms associated with the so called biopsychosocial model and its interventions such as Cognitive Behavioral Therapy (CBT) and Graded Exercise Therapy (GET) has to be addressed.

At this stage it would be a mistake and a huge waste of resources to spend precious research dollars on behavioral treatment modalities, alternative or complementary medicine, or multimodal treatment, when there is such a dire need for biomedical ME/CFS research. Biomedical research has to be the only priority for now.

ME/CFS patients are frequently wrongly treated with psychiatric and other inappropriate drugs that may cause harm. A very large number of patients worldwide have been caused harm, often irreversibly, by GET.

The educational material and guidelines currently offered by for example the Centers for Disease Control, MedScape, the Mayo Clinic, Kaiser, Up To Date and the British National Health Service sadly underplay or completely ignore the serious risk of harm for ME/CFS patients who are being prescribed exercise, despite the large amount of existing biomedical evidence that clearly show that the vast majority of people with ME/CFS are physically and biologically incapable of exercising without incurring harm.

Please see the article "Reporting of Harms Associated with Graded Exercise Therapy and Cognitive Behavioural Therapy in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome"[xlvi], especially Table 1 and Table 2, pages 105-110.

From the article:

> "High rates of adverse reactions following GA/GE [i.e. graded activity/graded exercise therapies] programs have consistently been reported in large patient surveys in various countries over the last two decades (see Table 1) (75, 77-85). Participants in these surveys were asked about the effect of GET [graded exercise therapy] and a myriad of treatment and management strategies on their health. The data has been pooled in Table 2, with the mean of worsening for GET/GAT and CBT respectively amounting to 51.24% (range: 28.1-82%) and 19.91% (7.1-38%) of subjects. The percentages of subjects adversely affected in Table 2 are not low; in comparison, an average of 2.58% (of 5894) subjects reported that "pacing" worsened their health."

Patient organizations around the world continually report on the harm caused to ME/CFS patients by graded exercise therapy and similar exercise programs. Please see ME Association's 2015 report on the acceptability, efficacy and safety of CBT, exercise therapy and Pacing as interventions used as management strategies for ME/CFS[xlvii]. In their survey of 1,428 people with ME/CFS, 73 per cent reported that CBT had no effect on symptoms while 74 per cent reported that graded exercise therapy had made their condition worse.

Public health recommendations around the world have been strongly influenced by the PACE trial. However, no objectively measurable improvement has been demonstrated in the PACE trial, nor in other CBT and GET studies. In fact, most of these studies do not even include any objective outcomes at all.

We strongly urge you to read Prof David Tuller's series of articles "Trial by Error" on the PACE trial, and the subsequent worldwide call to release the PACE trial data for an independent review.
http://www.virology.ws/mecfs/

Please also see The Centre for Welfare Reform's report "In the Expectation of Recovery".
http://www.centreforwelfarereform.org/news/misleading-mability-cuts/00270.html

Anther valuable read on methodological problems is Rebecca Goldin's "PACE: The research that sparked a patient rebellion and challenged medicine", published by the American Statistical Association. http://www.stats.org/pace-research-sparked-patient-rebellion-challenged-medicine/

There's also a petition, currently signed by more than 12 000 people, demanding that "Misleading PACE claims should be retracted", asking for the raw data to be released for an independent review. http://www.stats.org/pace-research-sparked-patient-rebellion-challenged-medicine/

Finally, may we please direct your attention to this open letter to The Lancet, written by a large group of scientists, which calls for an independent evaluation of the PACE trial data: http://www.virology.ws/2016/02/10/open-letter-lancet-again/

Other kinds of harms

The Institute of Medicine's report on ME/CFS describes at length the stigma, bias and discrimination people with ME/CFS are historically and currently suffering. This cannot be overstated. Public education, medical training and investment in research can help reverse this prejudice.

Challenges and barriers to ME/CFS research

Besides the ones already mentioned earlier in this document, some of the main challenges and barriers to ME/CFS research we have identified are:

- Lack of public awareness
- Lack of awareness and decent training among doctors
- Lack of awareness among scientists
- Difficulty to attract new researchers
- Psychosomatic model leads to misinformation, bias and harm
- Severe patients are not represented in research
- Lack of harms reporting
- Insufficient availability of raw, anonymized data (open to all who ask)
- Lack of patient involvement in research design
- No universally accepted or standard research criteria
- Insufficient expert (researchers, clinicians, advocates, patients) participation in the design of research and programs
- The name Chronic Fatigue Syndrome

There has to be a sense of urgency

We want to see the NIH move much more quickly and with a greater recognition of the urgent need for progress from now on. Much more resources and a heightened urgency are required to address this public health crisis. The patient community has already waited more than thirty years with no

treatments, and there's no time to lose. How much more suffering, how many more will have to die before things start to change for the better?

Many thanks for taking these comments into consideration.

Signed

[…], ME/CFS advocate suffering from ME since 2004, bedridden/housebound

[…], suffering from ME triggered by a throat infection in 1989

[…], ME/CFS advocate, ill with ME

[…], ill with ME since 2005

[…], ME patient for more than 20 years

[…], daughter is suffering from ME

[…], close friend of a severely ill ME sufferer

[…]

[…], ME for 10 years, severely ill for the last 3.5 years and housebound

[…], ME for 17 years, diagnosed 7 years ago

[…], ill with ME for 32 years, diagnosed 2 years ago

[…], ME for 14 years

[…], ME since 2011

[…], had to fight for 12 years in order to get a correct diagnosis

[…], ill with ME for 18 years, diagnosed 4 years ago, housebound

[…], was Director of Development, ME for two years, diagnosed 8 months ago, housebound

[…], ill with ME for 8 years, diagnosed 4 years ago

[…], was a journalist, suffering from ME since 2000, diagnosed in 2009

[…], ME since October 1, 1994 after strep throat, diagnosed 1-2 years later

[…], suffering from ME for a very long time, misdiagnosed for a very long time, correct diagnosis in 2005

[…], ill with ME for 14 years

[…], trained nurse, ill with ME for at least 15 years, diagnosed after 8 years, mainly homebound

[…], ME since 1994, diagnosed in 2002, daughter has ME

[…], ill with ME for 14 years

[…], fell ill with ME after pneumonia 10 years ago

[…], IT consultant, fell ill with ME after an infection 11 years ago and got much worse after a chlamydia pneumoniae infection

[…], ME triggered by anaesthetic 27 years ago, mother has ME too

[…], was IT consultant, have been suffering from ME for 11 years

[…], ME/CFS advocate suffering from progressive ME since 2012

[…], ME triggered by prolonged glandular fever in 1995, diagnosed in 2015

[…], was web designer, fell ill 2009, bedridden since 2011, diagnosed in 2012

[…], ME for 20 years, daughter has very severe ME

[…], was designer/seamstress, ME for 40 years, severely ill since 2013, bed/housebound

[…]

[…], ME triggered by pneumonia

[…], family member has ME

[…], ill with ME, disability pensioner at the age of 38

[…], ME for 34 years, diagnosed in 2009

[…], ME triggered by a sinus infection in 2001

[…], suffering from ME since 2012

[…], ME for three years, triggered by pregnancy

[…], gradual onset ME, numerous infections, much worse the last 5 years due to exercise

[…], qualified speech therapist, ill with ME for more than 20 years, diagnosed in 2014, got much worse in 2006

[…], was a teacher, ill with ME for 4 years

[…], suffering from ME since 1983

[...], suffering from ME since the 1990s

[…], autoimmune ME/CFS for 25 years

[…], registered nurse, ME for 11 years triggered by a flu, severe deterioration after back surgery and exercise

i http://report.nih.gov/categorical_spending.aspx (Click on the year (top row) to sort the funding by decreasing amounts.)

ii http://www.iacfsme.org/LinkClick.aspx?fileticket=tnCp3meyVmU%3d&tabid=36

iii **https://dl.dropboxusercontent.com/u/57025850/Congressional%20letter%20-%20Dr.%20Collins%20-%20March%202014.pdf**

iv http://www.hhs.gov/advcomcfs/recommendations/06142014.html

v http://www.hhs.gov/advcomcfs/recommendations/10032012.html

vi https://wayback.archive-it.org/3919/20140324192811/http://www.hhs.gov/advcomcfs/recommendations/11092011.html

vii http://www.hhs.gov/advcomcfs/recommendations/2015-08-18-19-recommendations.pdf

viii Carruthers BM, Jain AK, De Meirleir KL, Peterson DL, Klimas NG, Lemer AM, Bested AC, Flor-Henry P, Joshi P, Powles ACP, Sherkey JA, van de Sande MI. Myalgic encephalomyelitis/chronic fatigue syndrome: Clinical working case definition, diagnostic and treatment protocols (Canadian case definition) Journal of Chronic Fatigue Syndrome. 2003;11(1):7–115. https://med.stanford.edu/content/dam/sm/chronicfatigue/documents/overview/CanadianCriteriaCFS2003.pdf

ix Jason LA, Brown A, Clyne E, Bartgis L, Evans M, Brown M. Contrasting case definitions for chronic fatigue syndrome, myalgic encephalomyelitis/chronic fatigue syndrome and myalgic encephalomyelitis. Evaluation and the Health Professions. 2012A;35(3):280–304. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3658447/

x Jason LA, Brown A, Evans M, Sunnquist M, Newton JL. Contrasting chronic fatigue syndrome versus myalgic encephalomyelitis/chronic fatigue syndrome. Fatigue. 2013A;1(3):168–183. Doi: 10.1080/21641846.2013.774556 http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3728084/

xi Jason LA, Sunnquist M, Brown A, Evans M, Newton JL. Are myalgic encephalomyelitis and chronic fatigue syndrome different illnesses? A preliminary analysis. J Health Psychol. 2016 Jan;21(1):3-15. doi: 10.1177/1359105313520335. Epub 2014 Feb 7. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4125561/

xii Brown AA, Jason LA, Evans MA, Flores S. Contrasting case definitions: The ME international consensus criteria vs. the Fukuda et al. CFS criteria. North American Journal of Psychology. 2013b;15(1):103–120. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4215640/

xiii Johnston, S. C., Brenu, E. W., Hardcastle, S. L., Huth, T. K., Staines, D. R., & Marshall-Gradisnik, S. M. (2014). A comparison of health status in patients meeting alternative definitions for

chronic fatigue syndrome/myalgic encephalomyelitis. Health and Quality of Life Outcomes, 12, 64. http://doi.org/10.1186/1477-7525-12-64 http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4008489/

xiv Brenu, E., Johnston, S., Hardcastle, S., Huth, T., Fuller, K., Ramos, S., Marshall-Gradisnik, S. (2013). Immune Abnormalities in Patients Meeting New Diagnostic Criteria for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis. Journal of Molecular Biomarkers & Diagnosis, 4(3), 1–6. Doi: 10.4172/2155-9929.1000152 http://www.omicsonline.org/immune-abnormalities-in-patients-meeting-new-diagnostic-criteria-for-chronic-fatigue-syndromemyalgic-encephalomyelitis-2155-9929.1000152.php?aid=20654

xv Hardcastle SL, Brenu EW, Johnston S, Staines D & Marshall-Gradisnik S (2014): Severity Scales for Use in Primary Health Care to Assess Chronic Fatigue Syndrome/Myalgic Encephalomyelitis, Health Care for Women International, DOI: 10.1080/07399332.2014.962139 http://www.tandfonline.com/doi/full/10.1080/07399332.2014.962139

xvi International Association for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis: Chronic Fatigue Syndrome/Myalgic Encephalomyelitis – Primer for Clinical Practitioners, 2014 Edition http://iacfsme.org/portals/0/pdf/Primer_Post_2014_conference.pdf

xvii International Association for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis http://iacfsme.org/

xiiii Carruthers et al (2011), Myalgic encephalomyelitis: International Consensus Criteria. Journal of Internal Medicine, 270: 327–338. doi: 10.1111/j.1365-2796.2011.02428.x http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2796.2011.02428.x/abstract

xix Institute of Medicine/The National Academies of Sciences. Beyond myalgic encephalomyelitis/chronic fatigue syndrome: Redefining an illness. Washington, DC: National Academies Pr; 2015. http://iom.nationalacademies.org/Reports/2015/ME-CFS.aspx

xx Institute of Medicine/The National Academies of Sciences. Beyond myalgic encephalomyelitis/chronic fatigue syndrome: Redefining an illness. Report guide for clinicians. http://www.iom.edu/mecfs

xxi https://dl.dropboxusercontent.com/u/89158245/Case%20Definition%20Letter%20final%2010-25-13.pdf

xxii Peter Rowe MD. Inducing Post-Exertional Malaise in ME/CFS: A Look at the Research Evidence. Solve ME/CFS Initiative Webinar July 16, 2015. https://www.youtube.com/watch?v=ux93w7yGQ5g

xxiii https://dl.dropboxusercontent.com/u/89158245/Case%20Definition%20Letter%20final%2010-25-13.pdf

xxiv http://www.hhs.gov/advcomcfs/meetings/presentations/presentation_10132010_snell-stevens.pdf

xxv Stanford Medicine: The puzzle solver – A researcher changes course to help his son http://stanmed.stanford.edu/2016spring/the-puzzle-solver.html

xxvi Palo Alto Online: Invisible Illness - Stories of Chronic Fatigue Syndrome https://www.youtube.com/watch?v=9_HwOUiImvw

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[…]
[…]
Subject: ME/CFS - diagnostic testing - Vicky Whittemore - MicroRNA (miRNA) - mass spectrometry

Vicky, you asked for emailed suggestions re ME/CFS at the 2016 Invest in ME conference in London, see below some thoughts re diagnostic testing.

My daughter has severe fatigue, disturbance in day/night (circadian) rhythm etc which among other things has affected her ability to attend university. However, while this is similar to symptoms of ME/CFS we have not had a diagnosis established on a biochemical basis, hence my email.

MicroRNA (miRNA)

Olta, I was interested in your recent talk at the Invest in ME Conference in London and looked briefly at your paper re miRNA biomarkers in fibromyalgia. As stated in your paper validation in larger study groups is required before the results can be transferred to the clinic.

I understand that James Baraniuk has been working on a NINDS funded study (signed off by Vicky) looking at miRNA in ME/CFS patients.

Vicky, my understanding is that these studies identify potential miRNA biomarkers which may provide the basis for a diagnostic test for ME/CFS and fibromyalgia. Presumably there are readily available diagnostic kits i.e. to measure miRNA biomarkers in blood samples. However, validation in larger study groups is required before the results can be transferred to the clinic.

Mass Spectrometry

If I understand correctly, Ron Davis highlighted potential biomarkers [and deficiencies e.g. biotin & tryptophan (circadian rhythm)] in ME/CFS in his talk at the 2016 Invest in ME conference in London. These potential biomarkers/deficiencies were identified using mass spectrometry (LC-MSMS). Mass spectrometry is used routinely in statutory (Government) food safety monitoring programs e.g. of antibiotic levels in food. The cost of routine mass spectrometry testing is Northern Ireland is approximately £200 per sample (conversation with Government laboratory testing food samples as part of the EC statutory program).

Vicky, US Government FDA laboratories in Washington routinely use mass spectrometry (LC-MSMS) testing in their food safety monitoring programs e.g. of antibiotic levels and can advise on costs of analysing routine samples. However, initially detailed research programs are required to identify potential biomarkers in ME/CFS i.e. using mass spectrometry. James Baraniuk was of course one of the first to publish on the use of mass spectrometry in ME/CFS (in 2004 - NIH funded study) and others have carried out further research Jonas Bergquist (see DVD of the 2015 Invest in ME conference), Ron Davis (2016 Invest in ME conference) and Maureen Hanson (2016 Invest in ME conference). Once biomarkers have been identified ***the cost of routine mass spectrometry testing would presumably be similar to the current cost of testing food samples using mass spectrometry (approximately £200?) and be less than/similar to the cost of an MRI scan***.

[…]:
Olta – […] James Baraniuk – […] Ron Davis – […] Maureen Hanson – […] Jonas Bergquist – […]

[…]
[…]
Subject: Input for New Research Strategies for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)

Description of the need or opportunity [reduced steroid hormone synthesis and cholesterol metabolism in ME/CFS]

Some people with ME/CFS exhibit signs of impaired cholesterol metabolism and decreased levels of pregnenolone (see below*). Measurement of steroid hormone may provide an insight into the disease mechanism and opportunities to treat ME/CFS. You may wish to discuss this with Professor Jonas Bergquist Uppsala University (this email has also been sent to Professor Bergquist) as I seem to recall that he was interested in measuring steroid hormones in people with ME/CFS.

Scientific rationale

The following extract from the Follow ME in Denmark website sets out rationale for measuring steroid hormone synthesis and cholesterol metabolism in ME/CFS.

*From http://followmeindenmark.blogspot.co.uk/search?updated-min=2016-01-01T00:00:00-08:00&updated-max=2017-01-01T00:00:00-08:00&max-results=6

"*When disease occurs epigenetic changes - including DNA methylation. Different genes will be expressed differently and some of the body's cells will be changed processes. If a given DNA methylation feed through to every cell in the body? Want an altered DNA methylation in brain cells also reflected in the immune system's T-cells? It has a group of researchers studied. Rats were applied chronic neuropathic pain through nerve damage. This resulted in changes in DNA methylation in both brain cells and in T cells. DNA methylation patterns were not identical in the two kinds of cells, but showed 72% agreement. By using 11 of such epigenetic changes from T-cells, one can separate the rats with neuropathic pain from Checking the rats. (Ref 1) A study of T-cells from CFS patients have shown DNA.metylering modified in a number of genes. (Ref 2) The most substantial change was in the gene NINJ2. It is the gene for the protein ninjurin 2 (ninjurin is shortened from nerve injury induced). It is an adhesion protein in Schwann cells which are found in the peripheral nervous system (PNS). Reflecting this change in DNA methylation that PNS involved in ME disease mechanism? The gene for thioredoxinreductase1 - TXNRD1- had also changed DNA.methylering. This enzyme plays a role in the redox status of the cell and protects against oxidative stress. These thiolredox processes involved in the regulation of TRP ion channels, which may be relevant in relation to the latest ME research that points to an involvement of trps in the disease mechanism. There was also demonstrated altered DNA methylation of the gene DGKQ. It is the gene for diacylglycerol kinase, theta (DGK-theta). Can this change also penetrate into cells from binyrene? It would be interesting to study because reduced expression of DGK-theta reduces steroid hormone synthesis and cholesterol metabolism. I have seen individual analysis data from the ME patients who exhibit signs of impaired cholesterol metabolism and decreased levels of pregnenolone.*

references:
1.Gregoire et al: Broad and highly Organized changes in DNA methylation in the prefrontal cortex and T cells in a model of chronic neurppathic pain in rats. University of Montreal.
2.Brenu et al: Methylation profile of CD4 + T cells in CFS / ME. J Clin Immunol Cell 5, 228th"

Potential public health impact

Measuring steroid hormone synthesis and cholesterol metabolism may provide the basis for the development of a diagnostic test and treatment i.e. to address impaired cholesterol metabolism and decreased levels of pregnenolone.

Anticipated challenges that will need to be addressed

Specialist input [e.g. from scientists such as Jonas Bergquist] would be required to identify potential tests and target molecules. Measurement of low levels of hormones may require the use of specialist mass spectrometry equipment.

Appropriate benchmarks for evaluating progress

Evaluation of the progress would be based on completion of key stages e.g.: select management board, identification of potential tests, biomarkers and detection levels [in relation to steroid hormone synthesis and cholesterol metabolism], selection and recruitment of test and control groups possibly including genetic testing (see research from Griffith University re TRPM3 gene), selection of group to carry out clinical

evaluation of patients and controls, protocols developed re (blood) sampling, selection of clinical group to carry out blood sampling, selection of group to carry out steroid hormone synthesis and cholesterol metabolism testing (including quality control by independent laboratory), study write up by suitable qualified personnel and publication of study. NIH has commissioned and carried out similar studies; therefore, NIH is familiar with the evaluation process.

For this RFI, the NIBIB is interested in the ideas for the development of new imaging and bioengineering technologies that could have the potential for a significant impact on ME/CFS research.
Development/validation of methods to measure steroid hormone synthesis and cholesterol metabolism presumably using mass spectrometry and the application of genetics testing e.g. of TRPM3 (Griffith University).

Happy to discuss

[…]
[…]
Subject: Input for New Research Strategies for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)

Description of the need or opportunity [diagnostic testing using MicroRNA]

Studies have shown that MicroRNA testing of blood samples could be used to diagnose ME/CFS.
Scientific rationale

The following studies have shown that MicroRNA testing of blood samples could be used to diagnose ME/CFS:

James Baraniuk has identified potential MicroRNA biomarkers which could be used to diagnose ME/CFS [NINDS funded study (signed off by Vicky Whittemore) completed in 2016];

Australian researchers at Griffith University have (to my knowledge) patented a diagnostic test for ME/CFS based on MicroRNA biomarkers;

Elisa.Oltra – fibromyalgia study has identified potential MicroRNA biomarkers which could be used to diagnose fibromyalgia. Fibromyalgia has similar clinical symptoms to ME/CFS. MicroRNA testing would therefore appear to be able to separate patients with ME/CFS from those with fibromyalgia;

Potential public health impact

Currently there is no diagnostic test, based on biochemical markers, for ME/CFS. The development of a test, based on biochemical markers, for ME/CFS would assist doctors to arrive at an accurate diagnose and avoid inappropriate treatments. In the longer term, it will aid research into potential treatments.

Anticipated challenges that will need to be addressed

The potential MicroRNA biomarkers identified in the studies referred to above would need to be validation in larger study groups before the results can be transferred to the clinic.

Appropriate benchmarks for evaluating progress

Evaluation of the progress would be based on completion of key stages e.g.: select management board, identification of potential MicroRNA biomarkers and detection levels, selection and recruitment of test and control groups possibly including genetic testing (see research from Griffith University re TRPM3 gene), selection of group to carry out clinical evaluation of patients and controls, protocols developed re (blood) sampling, selection of clinical group to carry out blood sampling, selection of group to carry out MicroRNA testing (including quality control by independent laboratory), study write up by suitable qualified personnel and publication of study. NIH has commissioned the initial research (e.g. Baraniuk study) and carried out similar clinical evaluations; therefore, NIH is familiar with the evaluation process.
For this RFI, the NIBIB is interested in the ideas for the development of new imaging and bioengineering technologies that could have the potential for a significant impact on ME/CFS research.
MicroRNA testing as outlined above, the application of genetics testing e.g. of TRPM3 (Griffith University) and also mass spectrometry testing (see below).
Description of the need or opportunity [diagnostic testing using Mass Spectrometry]

Studies have shown that mass spectrometry testing could be used to diagnose ME/CFS.

Scientific rationale

The following studies have shown that mass spectrometry testing could be used to diagnose ME/CFS: study titled "A chronic fatigue syndrome – related proteome in human cerebrospinal fluid" by James Baraniuk et al – published in 2005 – funded by the National Institutes of Health;

study titled "Distinct Cerebrospinal Fluid Proteomes Differentiate Post-Treatment Lyme Disease from Chronic Fatigue Syndrome" – by Steven E. Schutzer et al published in 2011 – funded by the National Institutes of Health;

Jonas Bergquist (who is one of the authors of the Schutzer study); data presented at the 2015 Invest in ME conference which has not yet been published [see conference DVD];

The above studies used cerebrospinal fluid study; therefore, further studies would be required to try to convert these into a blood test.

In terms of blood biomarkers Ron Davis (Stanford University) and Maureen Hanson (Cornell University), working independent, have both identified potential biomarkers in blood samples (using mass spectrometry) which could potentially be used to diagnose ME/CFS. Data presented at the 2016 Invest in ME conference which has not yet been published (Vicky Whittemore attended this conference).

Potential public health impact

See comments above re MicroRNA testing.

Anticipated challenges that will need to be addressed

The potential protein biomarkers identified in studies which used cerebrospinal fluid may not be present at detectable levels in blood samples (correspondence with Jonas Bergquist). Taking cerebrospinal fluid samples from patients may not be acceptable due to the invasive nature of the procedure. However, the work carried out by Ron Davis and Maureen Hanson identified potential protein biomarkers in blood samples i.e. demonstrates that it may be possible to develop a clinical mass spectrometry test based on blood samples.

A detailed study of potential biomarkers in blood samples is required i.e. based on the studies referred to above; this is likely to be expensive. However, once biomarkers in blood (or siliva or urine) are identified then the cost of routine testing is likely to be similar to the cost of routine testing of food samples using mass spectrometry (approximately £200 in Government laboratories in Northern Ireland – FDA can advise on cost in America).

Appropriate benchmarks for evaluating progress

See comments above re MicroRNA testing. The key difference is that US Government laboratories already use mass spectrometry and can advise, possibly the FDA could provide an independent expert (mass spectrometrist) to sit on the project management board. Another issue is that some of the data referred to above (Bergquist, Davis and Hanson) has not yet been published.

For this RFI, the NIBIB is interested in the ideas for the development of new imaging and bioengineering technologies that could have the potential for a significant impact on ME/CFS research.

See comments above re MicroRNA testing.

Description of the need or opportunity [autoimmunity]

Some people with ME/CFS appear to have an autoimmune disease since they improve when treated with rituximab.

Scientific rationale

Data presented at the 2016 Invest in ME Conference in London showed that rituximab worked in autoimmune diseases but did not work in non-autoimmune diseases. Some people with ME/CFS improve after treatment with rituximab. Therefore, it appears that, these people are suffering from an autoimmune disease.

See DVD of the conference i.e. presentation by researchers from University of London. Vicki Whittlemore attended the conference. The Norwegian rituximab study, and the proposal that improvement after treatment is evidence of autoimmunity, has also been set out in other publications.
If there are autoimmune forms of ME/CFS then understanding these will provide insight into the disease mechanism i.e. in non-autoimmune cases. E.g. treatment using immunosuppressents may result in the levels of biomarkers returning to normal levels thereby indicating that these (biomarkers) are good indicators of disease/normal state and can potentially be applied to the evaluation of potential treatments in non-autoimmune cases.

Potential public health impact

If there are autoimmune forms of ME/CFS then a systematic search for the autoantibodies would provide the basis for the development of a diagnostic test (for the identified autoantibodies) and treatment using currently available immunosuppressants. In the longer term less harmful drugs could be used to switch off the disease.

Anticipated challenges that will need to be addressed

Identifying autoantibodies is a significant challenge. However, review of similar (successful) research may provide the basis for a strategy. E.g. previous research on NMDAR encephalitis and antibody-associated limbic encephalitis (contact Angela Vincent Oxford University). Mass spectrometry testing may indicate the effect of the disease e.g. low/high levels of particular metabolites ("downstream effect"); which may indicate what the autoimmune antibodies are targeting ("upstream cause") – would this also apply to MicroRNA testing? Testing with another immune-suppressant may provide further evidence that particular cases are autoimmune.

Appropriate benchmarks for evaluating progress
See comments above re MicroRNA and mass spectrometry testing. In terms of independent expertise, an immunologist would presumably be required to sit on the project management board.

For this RFI, the NIBIB is interested in the ideas for the development of new imaging and bioengineering technologies that could have the potential for a significant impact on ME/CFS research.
See comments above re MicroRNA testing.

[…]
[…]
Subject: ME/CFS and Low Dose Naltrexone

Hi,

Heard that you are requesting grants for studies in ME/CFS and medications that have helped me personally.

I would love to see you do a study on Low Dose Naltrexone. I was bedridden for 2 years and going downhill in a fast fashion. I hated my life and the pain. Narcotics took some of it away, but over time, I had to increase my dose over and over again. And they continued to have numerous side effects that needed medication to counteract them.

I went to 5 doctors to ask them to prescribe it. Not one of them would! Not one! So, I followed the footsteps of many others and ordered the pills on-line and made my own mix. The first day after taking it was a miracle. I was off my narcotics and in a lot of pain. However, I woke up with some energy and a lot less pain. It was like a miracle for me.

I have been using it for 8 years now and finally have an Rx. But not without a lot of pleading. That was so disappointing. Now, 8 years later, we have an international list of doctors that will prescribe it. I continue to educate any new doctor I have about it and on-line assist many people on how they can not have to feel so much pain and get some energy back.

I will never stop taking it. I got off 13 medications taking it. I was still on my antidepressant, but recently weaned off of those as well.

I think everyone should have access to this drug because it keeps the immune system healthy. I know someone with HIV/AIDS that has been on it over 20 years. He is very healthy and runs his own pharmacy. He is living life to the fullest!

I later learned that I had Lyme Disease. I know it helps with that too. Not enough, but the boost is worth it to me!

I hope you will consider studying this wonderful drug which has saved so many. There are lots of websites with information.

www.LowDoseNaltrexone.org
www.LDNResearchTrust.org

On Facebook, there are lots of groups - my favorite is Got Endorphins.

If you would like more information, don't hesitate to contact me. I am a HUGE advocate for this drug because it is keeping me out of bed! That was a horrible place. I still have other problems, but LDN keeps me going.

[...]
[...]
Subject: ME/CFS funding priorities

Hey, I can't even get basic care! The infectious disease doctor I was referred to refused to see me solely on the grounds I have CFS. And my new primary care nurse practitioner (no docs available here in Lane County, OR) refused to give me any tests, treatments or referrals for my illness. She even refused to do a pre-auth on a protocol that her predecessor had prescribed for me. That's zip, zero, nada while I slowly slip into oblivion. So yeah, we need basic funding for research and all that. But we also need a PR campaign to educate medical practitioners and the public about what we already know. And to tell them, This Is Serious. Perhaps even penalties for denial of treatment specifically aimed at deniers of ME/CFS.

[...]
[...]
Subject: ME/CFS Request for Information

To Whom It May Concern:

Thank you for considering my comments to help guide the Working Group's planning efforts.

CHALLENGES TO PROGRESS IN RESEARCH ON ME/CFS

1. UNKNOWN ETIOLOGY OF DISEASE
Time and money is being spent to research drug and psychological treatment options for ME/CFS patients without first knowing the etiology of disease. More resources should urgently go to funding biomedical research that will identify the etiology first, and then identify evidence-based treatments. As a metaphor, how could the war on cancer be effective if researchers focused all their energy on finding drugs to treat symptoms of the patient's illness without first finding the cancer, and identifying the type of cancer? ME/CFS needs to be taken seriously as a severe, life-altering disease with a discoverable cause.

2. NON-INCLUSIVITY OF THE SICKEST PATIENTS
The sickest patients are often unaware of or are too sick to participate in clinical trials. Therefore, the sickest patients may not be included in research, and researchers may miss valuable information about the nature of the disease.

Thought should be given to methods of clinical trial design that would be inclusive of the sickest patients (e.g. home visits by an RN to collect samples of blood, stool, urine, etc.)
Non-inclusivity of the sickest patients is just one problem that may have contributed to troubling claims about effectiveness of treatments for ME/CFS. For example, the claim that that exercise therapy and CBT are treatments for ME/CFS. Exercise therapy is not an option for patients that are bedbound because they can't move their muscles. CBT is not a viable option for patients who are too weak to project their voices, read, or listen to someone talking.

3. BROAD DEFINITION AND PROBLEMS WITH STRATIFICATION
The definition of ME/CFS is so broad that it can fit a patient population that is somewhat sick to completely disabled. Regardless of whether research is aimed at understanding mechanisms of disease or treatment options, studies MUST BE DESIGNED TO STRATIFY PATIENTS according to their severity as well as unique symptom criteria, past medical history, disease onset, etc. It is not adequate to simply say "all patients met the criteria".

4. CLINICAL TRIALS MAY LACK ADEQUATE POWER
Clinical trials may lack power. Academic multicenter collaborations need to be encouraged and funded. Particularly as it pertains to the sickest patients, we need adequate numbers of subjects.

5. LACK OF FUNDING IS A BARRIER TO DISCOVERY

OPPORTUNITIES ACROSS THE RESEARCH CONTINUUM

As it relates to ME/CFS, there are likely to be major potential opportunities in the following fields:
Infectious disease
Biochemistry
Immunology
Genetics and epigenetics
Microbiome studies
Patient history analysis, with attention to history of antibiotic use (including fluoroquinolones and bactericidal antibiotics with documented risks of mitochondrial damage) in ME/CFS patients prior to development of disease

[…]
[…]
Subject: Response to Trans-NIH ME/CFS Working group RFI

The Trans-NIH Working RFI has asked for suggestions to help identify research areas and topics to be included in strategies to advance research efforts on ME/CFS. Last month a journal editorial did exactly that. It was written by Professor Jonathan Edwards (who pioneered rituximab therapy for rheumatoid arthritis) along with three patients and a carer. We are the authors of this and believe our editorial will be of interest to the Trans-NIH working group.

The biological challenge of myalgic encephalomyelitis/chronic fatigue syndrome: a solvable problem - Fatigue: Biomedicine, Health & Behavior - Volume 4, Issue 2

It highlights some of the most promising research to date, outlines several broad theoretical models that could explain the disease and suggests practical steps to move research forward. These steps include both specific areas to target (such as brain imaging) and changes in how research is done (such as international cohorts/biobanks, replication, and stress-testing (exercise or mental challenge).

We hope the ideas we lay out in the editorial will be helpful to the Trans-NIH Working Group.

[…]
[…]
Subject: NiH Request for information. ME/CFS Auto forwarded by a Rule

I welcome new research but have concerns that may affect its validity and usefulness. I also hope that concerns will be taken into account at this stage, not just glossed over.

1. The nature of ME needs to be understood. eg PEM. Any research that isn't repeated after 24-72 hours is of no use. . Activity the week before also needs to be recorded. We rest in advance of important events.

See http://www.ncbi.nlm.nih.gov/pubmed/23813081 “Follow-up classification analysis differentiated between groups with an overall accuracy of 95.1%.” on the second day, with no significant difference on the first day.

2. The appointment of Walitt is concerning, even though Dr Nath has seniority.
Particularly concerning is his role in the selection of participants, perhaps the most important job in establishing the validity of the research.

He could well discredit the whole project. Lessons need to be learned from the PACE trial now under investigation. The same people will be scrutinising your findings.

His doesn't have the qualifications or any evidence to back up his confident assertion that it is a “psychosomatic experience,” part of the “range of normal,” rather than an abnormal disease state; a way of “dealing with the difficulties of just being a human.”

Is someone so easily satisfied and so sure of his case suitable for a role requiring impartiality? It should not be an exercise in proving prejudices.

Also, he doesn't state his beliefs on your page or the link to his bio. He has stated he believes patients should be allowed to think you believe their faulty beliefs.

You state you will be selecting participants from “established clinics”. What is the model they work by? Who refers them? If it is psychological then the findings will be biased.

Another concern is that the IOM survey refers to 117 pieces of research. Some very good, eg brain imaging, mitochondria, but underfunded. Imhope they will be followed up rather than starting from scratch.

Can I also add that any abusive responses will be from trolls whose sole aim is to disrupt and destroy. ME groups have to block such people from their sites. They do not represent us.

Thank you for your consideration.

[…]
[…]
Subject: Re: LDN

I have had ME/CFS for 16 years and recently attempted LDN, starting at 1.5 mg at night. I began rather quickly having severe intestinal cramping and stomach pain, and although I cut the dosage down to .5, I still had gastrointestinal issues. After my experience, I found that a very small percentage of people who commented on forums about LDN also had the same problems with cramping. I hope this is somehow helpful.

[…]
[…]
Subject: FEEDBAC for: Request for Information: Soliciting Input for New Research Strategies for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)

ME/CFS relapses and remits in some patients. Some go into what may be remission and very few actually recover (although I do not believe the ever return to 100% if in fact they actually did have ME/CFS.)

When a patient is in a state of remit or remission then they can exercise which is good health maintenance for anyone. Muscle tone, weight maintenance, etc. However, they must not get their heart rate up as doing this puts the patient at risk of relapse.

Exercise will NOT help the patient treat their ME/CFS and the patient MUST BE IN REMIT OR REMISSION to exercise at all (never getting their heart rate up). This is a very delicate decision on the part of the doctor and the patient because if the patient is not in a true Remit or Remission state then they will cause more physical damage and send the patient into the disease further with no possible chance of Remit or

Remission ever again or gain back the point they were at before the exercise and may become bed or wheel chair bound due to exercise.

[…]
[…]
RE: Request for Information: Soliciting Input for New Research Strategies for ME/CFS

Please find attached my four (4) page statement regarding new research strategies for ME/CFS.
TO: Trans-NIH ME/CFS Working Group

NOTICE NUMBER: NOT-NS-16-024

FROM: […]

DATE: June 22, 2016

RE: Request for Information: Soliciting Input for New Research Strategies for Myalgic Encephalomyelitis / Chronic Fatigue Syndrome (ME/CFS)

My interest in submitting the following comments for your consideration is the fact that my adult daughter has been severely ill with ME/CFS since October 31, 2005.

My daughter and the other 836,000 to 2.5 million Americans who suffer on a daily basis from ME deserve a serious attempt by NIH to find a cure.

I do not have a medical or science background but I would like to offer the following observations.

EMERGING NEEDS AND OPPORTUNITIES THAT SHOULD BE CONSIDERED AS NEW ME/CFS RESEARCH STRATEGIES ARE DEVELOPED:

1. From my daughter's personal experience, I believe it is important to understand the benefits of immunoglobulin infusions (IVIG) in treating ME/CFS.

My daughter has had 6 ½ to 7 ½ hour infusions every 3 or 4 weeks for several years which have provided a significantly improved level of function. Since immunoglobulin infusions are not FDA approved and are being used "off-label" we have had significant problems obtaining insurance coverage.

NIH studies into the effectiveness of immunoglobulin infusions as a treatment may provide an understanding of ME/CFS and make IVIG more widely available through FDA approval and insurance coverage as a treatment option.

The Institute of Medicine (IOM) 2015 report states, "Rowe (1997) conducted a randomized placebo-controlled trial of IVIG in 71 Australian adolescents with ME/CFS. There was a significant improvement in overall function at 6-month follow-up in those who had received IVIG in a dose of 1 gram/kg (max 60 grams) monthly for 3 months. Cell-mediated immunity was abnormal in 52 percent of ME/CFS participants at baseline. Given the scientific strength of the randomized controlled trial design, the larger sample size, and the reported benefit of IVIG for pediatric ME/CFS patients, further investigation of IVIG in the pediatric ME/CFS population is warranted." (2015 IOM report, p. 195)

2. Please review and consider the recommendations of both the Institute of Medicine (IOM) 2015 report and the NIH Pathways to Prevention (P2P) 2015 report.

Both the IOM report and the NIH P2P report identified the critical need to increase medical research to cure ME/CFS.

As stated in the IOM report "… the committee was struck by the relative paucity of research on ME/CFS conducted to date in many areas related to this disorder. Remarkably little research funding has been made available to study the etiology, pathophysiology, and effective treatment of this disease, especially given the number of people afflicted. Thus, the committee was unable to define subgroups of patients or even to clearly define the natural history of the disease. More research is essential." (p. 225)

The IOM report further states, "(f)inding the cause of and cure for ME/CFS may require research that enlists a homogeneous sample of patients from which important subsets can be identified in terms of disease symptomatology, responses to physical and cognitive stressors, brain imaging, the microbiome, virology, immune function, and gene expression. Integrative approaches using systems biology may be useful in unraveling illness triggers. Studies aimed at assessing the natural history of the disease and its temporal characteristics (onset, duration, severity, recovery, and functional deficits) are essential for better understanding of ME/CFS and also are important to further refine the diagnostic criteria proposed in this report" (p. 225)

The IOM report recommends that "(i)dentification of a set of distinctive biomarkers for this disorder should also be a priority." (p. 223)

As a non–scientist I am not commenting on many of the NIH P2P report recommendations. However, the following action items identified in the NIH P2P report occur to me as being important:

A. Develop biomarkers and diagnostic tests (p.10).

B. Create opportunities and encourage junior and new researchers into the cause and cure of ME/CFS (p. 10).

C. Investigate the intestinal microbiome and the effect of the environment and microbiome on ME/CFS (p.11).

D. Examine drug therapies for fibromyalgia and other pain-related conditions for effectiveness in ME/CFS (p.11).

E. Leverage existing registries (p. 11).

F. Develop large datasets using bioinformatics techniques and store in a central publicly accessible database (p.11).

G. Increase patient involvement in determining priorities for research and care (p. 13).

H. Leverage the power of other NIH longitudinal studies to better understand ME/CFS (p. 13).

I. Ensure professional licensing and accreditation agencies use a curriculum that facilitates ME/CFS knowledge acquisition (p. 14).

J. Create a network of collaborative centers working across institutions and disciplines, including clinical, biological, and social science (p. 15).

K. Establish a central archive of de-identified data and tissue samples from prior and ongoing studies to enable sample sharing (p. 15).

L. Utilize the NIH Clinical Center for clinical trials and fast-track testing of new therapies (p. 15).

M. NIH and FDA convene a meeting on the state of ME/CFS treatment (p. 16).

N. Translate best practices to primary care clinicians (p. 17).

3. Develop therapeutic treatments.

4. Consult with and expand through NIH infrastructure and NIH funding the research being conducted by ME/CFS physicians / researchers including, but not limited to, Lucinda Bateman, MD, Bateman Horne Center; Ronald Davis, Ph.D., Stanford University; Nancy Klimas, MD, Nova Southeastern University; Andreas Kogelnik, MD, Ph.D., Open Medicine Institute; Ian Lipkin, MD and Mady Hornig, MD, Columbia University; Jose Montoya, MD, Stanford University; Daniel Peterson, MD, Simmaron Research; and Peter Rowe, MD, Johns Hopkins University.

5. Recognizing the severity of this disease, I fervently hope that NIH leadership will inform the research community of the critical need to find a cure and actively solicit those researchers that need to be involved.

6. ME needs to be associated with a major NIH Institute that fosters biomedical research. I believe that the National Institute of Neurological Disorders and Stroke (NINDS) or the National Institute of Allergy and Infectious Disease (NIAID) are most appropriate.

It is my understanding that without a “home institute” it is difficult to find personnel at NIH to advocate for Requests for Applications (RFA) and Centers of Excellence (COE). Both are needed.

CHALLENGES OR BARRIERS TO PROGRESS IN RESEARCH ON ME/CFS:

1. Develop a national and international research network to clarify the case definition. (NIH P2P Report p. 9)

2. Two major factors in the lack of progress in finding treatments and a cure over the past thirty (30) years have been:

A. the lack of urgency by NIH leadership to solve this public health crisis, and

B. the minimal number of dollars allocated by NIH to ME medical research.

NIH leadership must recognize and correct both mistakes.

Significant NIH funding for biomedical research into the cause and cure of ME is essential. ME biomedical research must be funded in an amount that achieves research funding parity with other illnesses of similar severity and disability.

3. Educate medical students and practicing physicians about ME/CFS.

4. Encourage clinicians to specialize in the treatment of ME. With 836,000 to 2.5 million Americans suffering from this devastating disease, far too few physicians are qualified or have an interest in treating ME.

5. Create Centers of Excellence throughout the country where ME patients can obtain appropriate treatment and “bed to bench” research can be conducted.

6. Educate and encourage both established medical researchers and those in training to understand the dire need to solve ME/CFS.

GAPS AND OPPORTUNITIES ACROSS THE RESEARCH CONTINUUM FROM BASIC THROUGH CLINICAL STUDIES:

1. Increase research into pediatric ME/CFS. As stated in the 2015 IOM report, “(w)hen evaluating the available research to develop its findings, conclusions, and recommendations on pediatric ME/CFS, the committee was struck by the paucity of research conducted to date in this population.” (p.183)

2. Some endeavors are best accomplished through the collective resources of the Federal government. ME research belongs, I believe, in this category.

NIH must be pro-active in solving the ME public health crisis.

NIH must assume the overall responsibility to develop a coordinated, strategic plan for ME/CFS research.

In addition, NIH must actively recruit and adequately fund the best current and the most promising future ME/CFS researchers.

[…]
[…]
Subject: RFI NOT-NS-16-024 Response: Please Fund Ampligen Clinical Trial

The attached response to RFI NOT-NS-16-024 is respectfully submitted on behalf of 7 ME/CFS organizations and over 100 patients and caregivers requesting that NIH fund a late-stage clinical trial of Ampligen and other potential treatments immediately.

The attachment provides discussion supporting this request, including an appeal by ME/CFS experts and samples of testimonials from patients.

Thank you for your work to speed ME/CFS research.

Response to Notice Number: NOT-NS-16-024

Request for Information: Soliciting Input for New Research Strategies for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

NIH should immediately fund a small, well-powered clinical trial to demonstrate efficacy of Ampligen for treatment of ME/CFS patients or a subset thereof, soliciting applications in 2016 from clinicians experienced in treating patients with Ampligen. The trial should be double-blind, placebo-controlled, demonstrating efficacy and characterizing responders.

Additionally, NIH should solicit applications for new clinical trials of promising medications for treatment of ME/CFS, such as rituximab, anti-virals, monoclonal antibodies, and cross-purposed treatments from similar diseases like Multiple Sclerosis.

Supporting discussion:

ME/CFS affects 850,000-2.5 million Americans, according to the Institute of Medicine (2015).

There are no FDA-approved medicines for patients with ME/CFS. ME/CFS is as debilitating as end-stage renal failure, late stage HIV, and COPD, among other disabling diseases. In 2015, NIH's Pathways to Prevention Panel and the Institute of Medicine reports both stressed the urgent need for medical research that can lead to treatments for patients. The FDA issued Industry Guidance in 2014 stating: "CFS/ME is a serious disease and there is unmet medical need in the treatment of CFS/ME."

Only one medication, Ampligen, has completed a Phase III placebo-controlled trial under an FDA application for treatment of ME/CFS in 30 years. Ampligen has been used to treat ME/CFS patients for 25 years under FDA-approved clinical trials. More than 90,000 doses have been administered safely to hundreds of ME/CFS patients over 25 years. In December 2012, the FDA Advisory Committee voted that data submitted under its New Drug Application demonstrated that Ampligen was safe for ME/CFS patients.

An NIH-funded clinical trial will unlock private pharmaceutical industry investment in ME/CFS. The pharmaceutical industry has witnessed the only ME/CFS treatment to reach Phase III trials languish and fail to obtain FDA approval for 25 years. Until the first medication is approved by the FDA for treatment of ME/CFS, industry will not invest significant funding in medical treatments to fill the serious unmet need in this disease. NIH officials including NIH Director Francis Collins have repeatedly stated they wish to increase investment in ME/CFS research and treatment. NIH funding of a clinical trial has the power to spur private dollars roughly 20-50 times an NIH investment, and is among most leverage-able public investment options available today.

The only medication that could reach FDA approval within 3 years is Ampligen. Without independent support for a confirmatory clinical trial, the small pharmaceutical company which has financed 25 years of FDA-approved clinical trials of Ampligen in this disease will fail, and with it a medication that has been safe and effective for a subset of patients will disappear. This crisis is immediate, and action by NIH and FDA is required to encourage industry to step up to the plate.

NIH is currently funding clinical trials for other serious diseases. NIH funds clinical trials throughout the Institutes to further scientific understanding, fill knowledge gaps, and spur private

industry investment in treatments for serious diseases such as Myasthenia Gravis, Parkinson's, cancer, Systemic Lupus, Multiple Sclerosis, Rheumatoid Arthritis, Inflammatory Bowel Disease, and many others.

Expert design: It is essential that an Ampligen clinical trial at this stage be well-designed by experts in the disease and especially by clinicians with diagnostic expertise and experience treating ME/CFS patients with Ampligen. Such diagnostic expertise is critical in a disease with multiple definitions and a broad spectrum of symptoms. There is an unprecedented opportunity to utilize a well-designed Ampligen trial to characterize responders and identify immunological impairment in ME/CFS or a well-defined subset.

Personal Suffering: Most importantly, the personal anguish of patients with ME/CFS who have no access to treatments is compelling and well documented. Independent panels (NIH P2P, FDA Voices of the Patient, and IOM) have underscored the urgency of bringing evidence-based treatments to those who suffer. Patients cannot wait until 2018 to see progress on clinical trials, as outlined on the Trans-NIH Working Group's timeline. Serious study of treatments by the world's leading research institutes must come immediately to break down the barriers that prevent evidence based treatments from being available to suffering patients.

Among the signatories to this RFI Response are:

- A mother whose seriously-ill son gave up in the despair of having no treatments and no hope for treatments.
- One of the first ME/CFS patients to have access to Ampligen, a woman who has been on and off Ampligen treatments for 19 years.
- A father who moved his family twice to Reno, Nevada to participate in the Ampligen clinical trial, who is unable to help raise his sons without it.

Attached is a sampling of 800 email testimonies appealing to the FDA to approve Ampligen in 2012, by patients who had an opportunity to participate in an Ampligen clinical trial and many more who urgently need and hope for a treatment to try under the care of their physicians.

Also attached is a 2015 letter by leading ME/CFS clinicians and experts urging the federal government to move toward approval of Ampligen.

Respectfully submitted,

Courtney and Robert Miller obtained Pres. Obama's promise to elevate ME/CFS

Billie Moore, Advocacy Chair, New Jersey ME/CFS Association, Florham, NJ

Solve ME/CFS Initiative, Los Angeles, CA, national association

Health Rising, online patient community, Cort Johnson, ill 36 yrs,

Massachusetts CFIDS/ME & FM AssociationQuincy, MA

Pandora Org, Inc., Traverse City, MI, Lori Chapo-Kroger, RN

ProHealth, online patient community
Wisconsin ME and CFS Association, Inc., Patricia Fero, MEPD, President

[…], Nevada, ill 30 years

[…] – Diagnosed 2005, Race to Solve ME/CFS

[…], I've been on Ampligen for a total of about 1 1/2 years

[…] patient on Ampligen

[…], on Ampligen 2 years

[…]: I would be more than willing to sign anything that might get us Ampligen that is covered by insurance. I have been on this since 2010 and it has pretty much been the thing that has kept me going. It has also the reason that I did not take a dirt nap when that coxackie virus would not let go. I worry about when the new prices go into effect. What will I do and how will I make decisions based on that?

[…], on Ampligen since 2012, ill 25 years.

[…], Partner to […] on Ampligen

[…], parents of […] on Ampligen since 2012

[…], patient

[…], mother of patient, CT

[…], patient

[…], Waltham, MA, friend of patient on Ampligen

[…], friend of patient on Ampligen

[…], friend of patient on Ampligen

[…], Associate Editor, Journal Psychological Trauma: Theory, Research, Practice, and Policy; Past Chair, Committee on Ethnic Minority Affairs (CEMA), American Psychological Association

[…], friend of patient on Ampligen

[…], Washington D.C.

[…], Ill for 35 years, Illinois

[…]

[…], participated in Phase-lll trials back in 2001-2002, but was on placebo most of time. Would take it today if it was approved.

[…]: I was on Ampligen for about 11 years. Prior to taking Ampligen, I would wake up every morning afraid to move my pain wracked body, even to do the most basic things such as getting to the bathroom, pouring a glass of water or changing position. My fatigue made it impossible to have a conversation, make a meal or watch television. My favorite hobbies such as reading or music could not be tolerated. I slept or was confined to a dark room due to light sensitivities. My cognitive function was too impaired to undertake mental tasks. I was unable to bathe or dress by myself. Showers were a nightmare and fatigued me for several days. Following my first year of Ampligen I was fully able to care for my grooming and eating needs. More of my family could visit as my brain didn't shut down due to multiple conversations due to extreme noise sensitivity. Ultimately I was able to again drive a car and complete a few errands. I will be forever grateful for the years of improvement I received from my twice weekly doses of Ampligen.

[…], Ampligen recipient for 2.5 years.

[…], Sick ten years, on Ampligen for a year but could no longer afford it. I was seventy percent better and could have gone back to work. Three weeks off Ampligen and I relapsed completely.....

[…], on Ampligen 18 months beginning l997, 18 months beginning 2001, 12 months beginning 2010 for a total of 4 years off and on.

[…], Portland, Oregon. I've had ME/CFS for 22 years, from age 17 'til now, age 39. (yep, that's more than half my life). I was actually lucky enough to be a part of phase II (open label) Ampligen tests conducted by Dr. Peterson in Incline Village, NV in the past. I am now 39 years old. I was sucked down the rabbit hole of ME/CFS in 1995, when I was only 17 years old. That's 22 years lost to this — although Ampligen did give me an amazing 5 year remission from 2001 to 2006, before I relapsed again. The way things have deteriorated for me the past ten years, I'd love to have the chance to try Ampligen again. Certainly many many more people should have access to this medication, and for that to happen the studies need to happen, they need to be funded, and they need to start ASAP. FDA approval for Ampligen would bring a tidal wave of positive potential to our forgotten community, and hopefully motivate other drug companies and institutions to expand research into treatment for ME/CFS. I've lost more than half of my life to this disease so far. I recognize a real treatment, to say nothing of a cure, may not happen in my lifetime — though I certainly hope it does. What I'm trying to say is that research has this wonderful side effect of bringing us some much needed hope. It makes us feel less forgotten by the world. Ampligen certainly warrants further study — it exists now; we know about it. I've seen it help me and I've seen it help others. It's time to fund more studies so it can finally win FDA approval.

[…]. I have been ill with ME for 19 years. I live in Victoria, Australia. I would very much like to join the Ampligen letter. I was on a trial of Ampligen in 2004-5 and went from being four years bedridden to walking around again and re-enrolling at university. Since the trial ended, I have gradually declined and have spent many years trying to get on Ampligen again.

[…] I have been severely affected for over thirty years and now worsening. Housebound and largely bed bound. A tested and approved drug urgently needed and well worth trying. I fear for the future otherwise.

[…], 23 years disabled by ME/CFS, in New York State

[…], 10 yrs sick

[…], niece of patient on Ampligen

[…], friend of patient on Ampligen

[…], friend of patient on Ampligen since 2012.

[…], patient on Ampligen 4 1/2 years from 2012 to March 2016. Also participated in the 516 study in 1999-2000.

[…], I have been ill with ME/CFS for 23 years and I live in Gastonia, NC. I am currently taking a break from Ampligen after having been on it for 1 1/2 years for the second time. Both times it has helped improve my stamina, cognitive and physical energy and strength PTL!

[…], a former adult nurse practitioner living in Wisconsin. I have been ill since 2006 and disabled since 2009.

[…], friend of patient on Ampligen

[…], friend of patient on Ampligen

[…], friend of patient on Ampligen

[…], friend of patient on Ampligen

[…]: I enthusiastically recommend the continued work by the NIH to fund a clinical trial of Ampligen.

[…], friend of patient on Ampligen

[…] Diagnosed 25 years ago, Still awaiting Ampligen Approval...

[…], California, age 54, sick 28 yrs, participant in 516 Ampligen trial

[…]. I have been sick for 15 years. I live in Jacksonville, NC

[…], Sick for 25 years, Washington State

[…], ill 24 years

[…]

[…]. I am from California and I have been ill for 21 years.

[…], 19 years ill, North Carolina

[…], 8 years seriously ill, 18 moderately ill, Florida

[…], Ph.D. candidate, Columbia University, Ill with ME since 2006

[…], We have both been ill since 2000.

[…], diagnosed 18 months ago, California

[…], ill 3 years

[…]New England, I have been sick for 33 years. I got sick at age 17; in May 1983, when I had mono and a severe strep throat. I'm presently bedridden and have been for about decade.

[…], TN, 15 years ill

[…], I have been ill with ME for 35 years. I live in Virginia

[…]. I have been I'll with ME/CFIDS for over 20 years.

[…], ME/CFS 20 years, CA

[…], Maryland, I've been ill with ME for 7 years

[…], ill 15 years, California

[…], 20 years, Washington State

[…], Sick since 2009, South Carolina

[…], I've been sick with CFS almost 20 years, as well as Fibro for close to 8 years following the laparoscopic surgery to remove my gallbladder.

[…], ill 5 yrs 7 months, California

[…], VA, 6 years ill

[…], ill 29 years, Oklahoma

[…]

[…], Louisiana, 8 years ill

[…], Fresno, California, Years Ill: 5

[…], Diagnosed 2007 - sick since 2003, Reno, NV

[…], Years ill: 33

[…], 44 years ill with cfs/me, Charleston, SC

[…], Delaware, 48 years with cfs, developed following the 1968 flu pandemic, progressively worsened with each succeeding case of the flu, have been unable to work at all for 25 years. I lost a whole life, but society lost too because once upon a distant time I was a smart, well educated professional who had a lot to contribute. This has been a genuine waste and a torturous nightmare that no one else should ever have to experience.

[…], Ill with ME/CFS over 30 years, Utah

[…], 31.5 years (Incline Village), California

[…], 8.5 years ill.

[…], Sick for 32 years, California

[…], sick since 2003, CT

[…], M.E. for 34 years, Colorado

[…], 21 years ill, Colorado

[…], 17 years ill, Texas

[…] sick for 5 years from NY. Hope they fund Ampligen.

[…], Portland OR, ill since March 1989, I am unable to work and am largely housebound

[…], 3 years diagnosed / 13 years ill, Maryland

[…], Sick with ME/CFS for 17 years, Washington State

[…], I have been ill with M.E. for 38 years (since 1978). It took 37 years to be diagnosed correctly even though I never gave up seeking a diagnosis. I traveled across the United States and was examined by physicians at The Mayo Clinic, Massachusetts General Hospital, University of California San Francisco, and Stanford, to name a few. I live in California and have been home-bound (except for medical appointments) since 2009. I don't have more time to waste waiting for help - now is the time for our Government to act responsibly and with urgency to start helping ME patients. Please do not ask us to wait any longer.

[…], 10 yrs ill, Chicago, Illinois

[…], ILL 2 years, TX

[…]. I have been ill with ME/CFS for 16 years. Currently, I am primarily housebound with this devastating illness. I have a strong immune component and have tried innumerable methods to improve, including IVIG every 21 days, with minimum benefit. Please add my name to the NIH request to fund a clinical trial with Ampligen!

[…], 14 years ill with ME/CFS, California

[…], Fort Myers, FL, I've been ill 27 years

[…], 12 years ill, Washington state

[…], 11+ years ill with CFS, fell ill in 2005—diagnosed in 2015

[…], Sick since 2012, Sweden

[…], Ill since 1983, Ontario

[…], Ill since 1997, Ontario

[…], Ottawa, Ontario, I have been sick & disabled with M.E. since 1989, 27 yrs.

[…], ill 7 years, from Burnaby BC, Canada

[…], 30 year patient, UK

[…], Very ill after throat infection in 1989. Got gradually better during 5 yrs. I had a bad relapse last year. Can be slightly active for 4-5 h per day.

[…], I have been sick - combination of gradual and acute onset since 1985. Full blown ME by early 1991. I live in BC, Canada.

EXHIBIT 1: 2015 Letter from ME/CFS Experts re Ampligen

Date: June 5, 2015

To: White House, HHS, Senate HELP Committee and House Energy Commerce Sub- Committee on Health, Drs. Woodcock, Chowdhury and Maynard

From: Clinicians and Biomedical Experts in ME/CFS

Re: Request FDA Facilitate 2-day Meeting for Treatment of ME/CFS

As clinicians and biomedical experts in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS), our goal for over the last four plus decades has been to advance the care and treatment of those patients suffering from this devastating illness. Critical in their care and treatment is access to approved treatments.

Recently the Institute of Medicine (IOM) released a report, *"Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness"* [(1)] stating ME/CFS is a legitimate, serious and complex systemic disease that dramatically limits the activities of affected individuals. This disease is characterized by profound fatigue, cognitive dysfunction, sleep abnormalities, autonomic manifestations, pain, and other symptoms that are made worse by exertion of any sort. ME/CFS can severely impair patients' ability to conduct their normal lives. The report states there may be as many as 2.5 million Americans affected at a cost upwards of $24 billion per year. This report is an example of a significant number of strides which have been made in our field; yet there are still no FDA approved treatments for this disease.

We are requesting your support to compel the FDA to facilitate a process with the sole purpose of providing conditional approval for the drug Ampligen®. We recommend a two day, facilitated process to examine how to address scientific and medical concerns of the FDA. We are in consensus in this request and commit to provide our time and expertise to this process along with the sponsor, Hemispherx Biopharma.

Ampligen is the only drug in the pipeline and has been evaluated in Phase II and III clinical trials in ME/CFS over the last two decades. Since 1997, it has been provided under an open label treatment protocol. To date hundreds of patients have been infused with more that 90,000 of doses of Ampligen and there are patients who have received more than 1500 doses over 12 years and remain on the drug.

Ampligen is a broad spectrum antiviral and immune modulator which has demonstrated that it provides substantial improvement in this patient population. In a 2012 peer reviewed article in PLOS ONE [(2)], the conclusion was Ampligen [rintatolimod] produced objective improvement in Exercise Tolerance and a reduction in ME/CFS related concomitant medication usage as well as other secondary outcomes. Experts have provided public testimony that approximately 25-40% of the patients, who are able to access the drug, have shown improvement in their daily function. At the 2012 FDA Advisory Committee Meeting, the committee voted 8 to 5 that the safety profile of Ampligen was adequate for the approval for the treatment of

CFS. We know CFS is heterogeneous. We know there are those individuals with CFS who benefit from Ampligen.

So why has the drug not been approved? This is an extremely complex chronic illness and this disease has long been poorly understood by the scientific, medical and regulatory communities. The movement of Ampligen through five separate divisions of the FDA demonstrates the lack of understanding of the illness and of the drug's benefits and risks. At a meeting of experts and patients with the FDA in March of 2014, FDA still mischaracterized CFS symptoms as adverse events.

FDA has been given the authority to provide access to promising treatments to patients with serious and life threatening diseases; specifically when there is a large unmet medical need. For example, two obesity drugs were denied approval [(3)] then through a collaborate process with the FDA, the drugs were granted approval with conditions. During the meetings, the experts were able to demonstrate a clearer understanding of the risk/benefit ratio and impact on quality of life of these patients. The FDA recognized the need, understood the risk/benefit and realized there was still more to learn. We believe the approval of the obesity drugs with conditions is a good model for the approval of Ampligen for ME/CFS with conditions.

With our medical and research expertise in this disease, our clinical trial experience and understanding of Ampligen, we will work collaboratively with the FDA to outline a path to approval with conditions that will answer any unresolved concerns. We will assist in the development of an appropriate REMS program to advance physician education and ensure proper administration of the drug.

We applaud the efforts by both the House and the Senate on their work to advance biomedical innovation, however, the patients cannot afford to have another decade pass. Currently, the quality of life of patients with ME/CFS can simply be measured in years of life lost – with no hope of recovery. If you review the thousands of testimonies provided to the Dept. of Health and Human Services, you would easily find these two phrases repeated over and over again, "*I have lost my life to this disease and I have tried everything*". We request that you assist us in creating a collaborative pathway and allow access to treatment for those suffering this devastating illness.

Sincerely,

Dharam V. Ablashi, DVN, MS, Dip Bact.
Scientific Director of HHV 6 Foundation
Co-Founder of IACFS/ME
Santa Barbara, CA

Lucinda Bateman, MD
Clinician and Researcher
Fatigue Consultation Clinic
Salt Lake City, UT

Laura Black, MD
Physician
Hunter-Hopkins Center
Charlotte, NC

Derek Enlander, MD
Clinician and Researcher
ME/CFS Center
Faculty, Mt. Sinai Medical School
New York, NY

Kenneth J. Friedman, PhD
Associate Professor of Pharmacology and Physiology (retired)
Board Member and Treasurer, IACFSME
Fort Lauderdale, FL

Maureen Hanson, PhD
Researcher, Liberty Hyde Bailey Professor
Department of Molecular Biology and Genetics
Cornell University
Ithaca, NY

Leonard A. Jason, PhD
Professor of Psychology
Director, Center for Community Research
DePaul University
Chicago, IL

Nancy Klimas, MD
Clinician and Researcher
Director, Institute for Neuro Immune Medicine
Nova Southeastern University
Fort Lauderdale, FL

Andreas M. Kogelnik, MD, PhD
Clinician and Researcher
Director, Open Medicine Institute
Mountain View, CA

Charles Lapp, MD
Clinician and Researcher
Hunter Hopkins Center
Charlotte, NC

Gailen D. Marshall, Jr., MD, PhD, FACP, DFACCI FAAAAI
Department of Medicine
The University of Mississippi Medical Center
Jackson, MS

Daniel Peterson, MD
Clinician and Researcher
Founder/President, Sierra Internal Medicine
Incline Village, NV

Dr. Richard Podell, MD MPH
Clinician and Researcher

Podell Medical Practice
Somerset, NJ

Dr. William Mitchell, MD, PhD
Professor of Pathology, Microbiology and Immunology
Vanderbilt University Medical Center
Board of Directors, Hemispherx Biopharma
Nashville, TN

Connie Sol, PhDc
Clinical Exercise Physiologist
Institute for Neuro Immune Medicine
Nova Southeastern University
Ft. Lauderdale, FL

J. Mark VanNess, PhD
Professor of Health, Exercise Science and Bioengineering
University of the Pacific
Stockton, CA
Researcher, The Workwell Foundation
Ripon, CA

(1) http://www.iom.edu/Reports/2015/ME-CFS.aspx
(2) http://www.plosone.org/article/authors/info%3Adoi%2F10.1371%2Fjournal.pone.0031334
(3) http://www.nejm.org/doi/full/10.1056/NEJMp1211277

EXHIBIT 2: 2013 Petition to approve Ampligen

http://www.ipetitions.com/petition/ampligen/

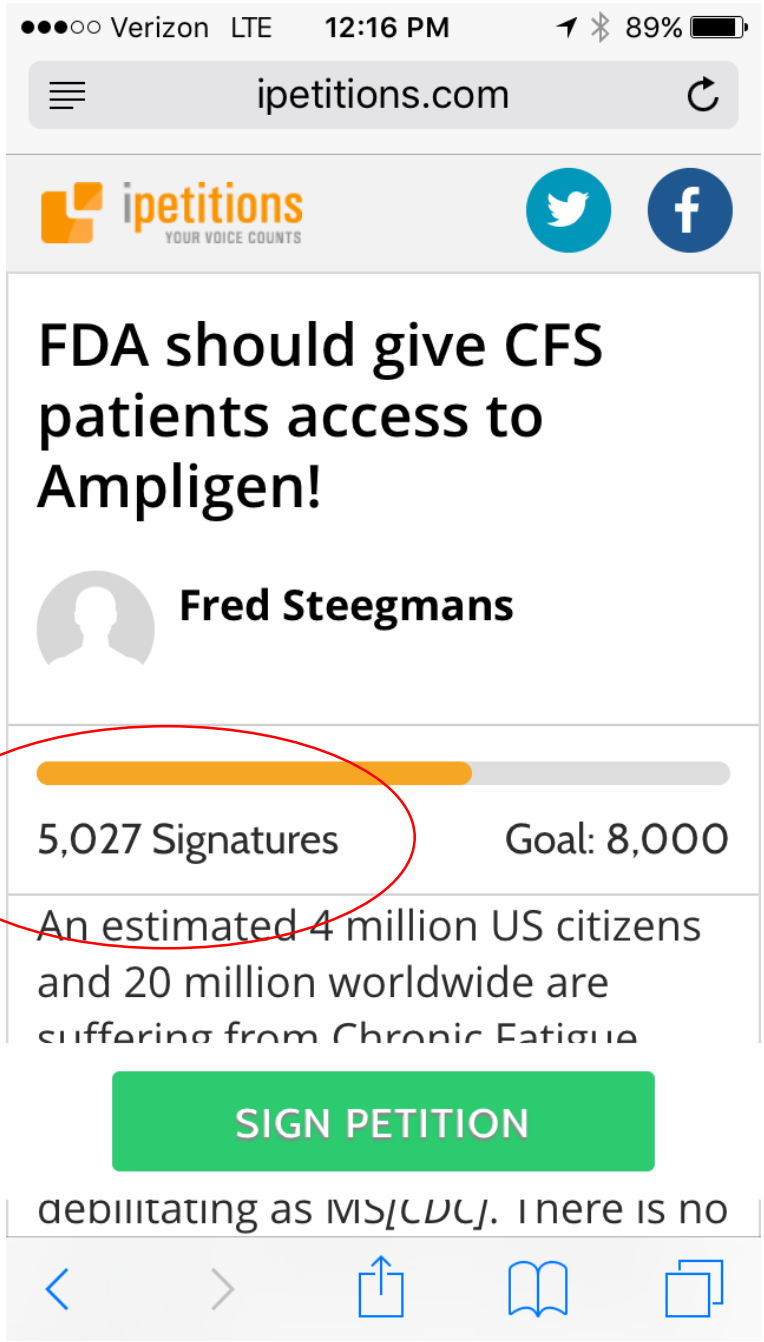

EXHIBIT 3: Excerpt from 800 testimonies submitted to FDA in 2012

[…]
To: aac@fda.hhs.gov
Subject: Treatment for Chronic Fatigue Syndrome - Ampligen

Date: Mon, 3 Dec 2012 11:42:08 -0600

To the Advisory Committee Reviewing Ampligen:

My name is […] and I have had ME/CFS since the early 1980's, following a series of upper respiratory infections and two abdominal surgeries for endometriosis.

In the beginning, my disease followed a relapsing and remitting pattern. During this time, I could maintain my job (iunior high science teacher and later secretary general for my religious community), but there were periods when I was completely knocked out for weeks at a time with a flu-like illness. I would slowly recover and then resume my employment. But even in the better periods, my energy was never comparable to those around me, and I always experienced joint and muscle pain. At times, the muscles in my arms and legs would give out on me. I also frequently suffered from incapacitating migraine headaches. I knew the disparaging reputation "chronic fatigue syndrome" had, and so I kept it as secret and as hidden as I could, and tried to pass for normal and well.

This went on for many years.

Then, in January of 1996, I had back surgery for a herniated disc pressing on a nerve. I was never the same afterwards. The ME/CFS had become constant and severe. It was incapacitating, never-ending, and could no longer be hidden. In August of that year I experienced a "shift" in my brain. Besides being constantly dizzy, I began having whirling vertigo attacks that would come on suddenly and cause me to drop to the ground, no matter where I was, to ride them out. I could no longer drive. My depth perception was off, and I would bump into things. My hands would often not be able to hold on to things and I would drop them. I could not tolerate noise and movement around me. My brain became overloaded from external stimuli. When people tried to talk to me in a noisy environment, such as a cafeteria, I could not understand what they were saying to me. I could no longer comprehend what I was trying to read. I lived in a fog and with severe fatigue. During this time I was a secretary in the medical staff office of a hospital. I tried desperately to hold on to my employment. I transferred to a secretarial position in the hospital's parish nursing department, where the duties would be a little less demanding. Even then, I had to go from an 8 hour day to a 6 hour day to a 4 hour day to per diem status. Eventually I quite my job and returned home to our community's central convent.

I have since educated myself about ME/CFS and the best way to live with it. I am under the care of holistic practitioners, including a neurophysiologist whose QEEG has shown that my brain was 90% impaired with slow wave brain activity, the result of a metabolic encephalopathy she sees in ME/CFS patients. I have had to make major adjustments in the way I live. I have had to face the stigma, misunderstanding, and derision from those around me. A MAJOR educational campaign regarding the true nature of ME/CFS, not only to the medical profession but also the general public, is greatly needed, and long overdue. Much work needs to be done to correct the misperceptions about this disease that are so greatly entrenched in peoples' minds, the result of many things, including the trivializing, totally inadequate, and irresponsible name given to it -- chronic fatigue syndrome, often shortened to chronic fatigue, which translates into "tired," "whiny," "lazy" and/or depressed.

My days now are much different. I have learned the safe boundaries of my energy envelope. If I stay within them, I attain a better quality of life in that the intensity of my symptoms are reduced. The size of my energy envelope, however, is quite small. There is no way that I can keep to the regular schedule and activities expected of a nun. My limited schedule is carefully planned out by the day, week, and month, as I pace out basic activities of daily living and medical protocols. That

is about alii can accomplish without triggering the post-exertional malaise which is the hallmark of this disease. Even my interactions with the other Sisters, my family, and friends has to be limited. I am basically homebound, going out only for medical appointments, and sometimes even having to cancel them. At time has gone on, I have developed cardiac problems and collagenous colitis.

I have tried many medications and supplements with only minimal improvement, if any. It is hardly necessary to say that good biomedical research is needed to uncover the pathophysiology of this disease. Unfortunately, ME/CFS has been at the bottom of the list of diseases funded by the NIH. Historically, the CDC has had their own problems regarding this disease. The ME/CFS community is so hoping for better responses from all involved and responsible for the health of this nation, and is encouraged by the recent efforts of the FDA. Thank you for listing ME/CFS as a "serious and/or lifethreatening disease." Just giving it that status has helped.
Blessings on all your efforts.
Sincerely,
[…]

Hello,
My name is […]. I am board certified and residency trained in Emergency Medicine. In the summer of 2009 I worked part time in Urgent Care in Manitowoc, WI. I enjoyed robust health, and was able to run a 10K race, and hike up five different 14,000 foot peaks in Colorado. On September 12th, 2009 I contracted a seemingly benign viral illness from my son. He recovered in 5 days. I did not. My symptoms included tremulous fatigue, documented low grade fevers, headaches, both vascular and later tension type, myalgias, malaise, tinnitus, muscle twitching and cognitive symptoms including an inability to concentrate, and pronounced memory impairment, and I couldn't stand up without getting severe lightheadedness. I was hospitalized twice and all my doctors could say was that I had a viral infection. I had immunology and infectious disease consultations, as well as 2 lumbar punctures, a total body SPECT scan, an MRI of the head, and multiple CT scans, all of which ruled out other pathology. On October 21, 2009 I had a total T cell count of342. My CD4 count was only 216. My CD8 count was 106.
I worsened clinically, and became housebound for 3 months. It was all I could do to get out of bed and walk to the kitchen, let alone try to walk to the mailbox.

Since I couldn't fmd a doctor who would treat me with any medication or treatment, I put myself on Valtrex, based on Dr. A. Martin Lerners pioneering work with its use in CFS. It did help somewhat in reducing my oral ulcers, but my severe CFS symptoms remained. I tried multiple other dietary supplements without change. In February, my postural lightheadedness resolved, and I boarded a plane to see CPS expert Dr. Dan Peterson in April of 2010. He was very thorough in testing, and told me I had a classic case of ME/CFS. Lab work revealed a low white blood cell count, lymphocytopenia, and intermittent monocytosis, elevated RNase activity, and extremely low NK cell number and function, and EBV reactivation. My desire was to stay home in Wisconsin if possible, so I could see my 12 year old son grow up. 56 We tried a multitude of treatments, including testosterone supplementation for low T, which did give me slightly more energy, antibiotic therapy for leaky gut, which did not result in any amelioration of my symptoms, and Valcyte and Vistide, both of which had to be stopped due to toxicity. Furthermore, clinically, I was beset by 6 basal cell carcinomas on my skin in one year. I could actually watch them grow from week to week and after removal I would get another crop which would grow rapidly. I am a physician, and I knew that this wasn't normal, and Dr. Peterson and I both knew that I had impaired immunosurveillance, which is one of the characteristics of low NK cell number and function. So in order to improve my clinical status and not wanting to risk an internal malignancy such as non-Hodgkins lymphoma, I made the decision to opt for enrollment in the Ampligen 511 cost recovery trial. I started the drug in June of this year.

There is no doubt in my mind as a clinician that the drug is bioactive, as it did worsen my tinnitus and left me tired, and at times gave me muscle aches and headaches, but I never had to skip a dose and did not experience anything but mild side effects. Month by month my ME/CFS symptoms lessened and I have increased energy.

I have been able to decrease naps from 5 times per week to once-twice weekly.
I first started walking, then hiking, and am now able to hike up mountain peaks again, as well as kayak, mountain bike and ski.

I am in the process of preparing to work part time within the next 6 months.

Please look at the spreadsheet of my lab values. No treatment interventions changed my T cell subsets until Ampligen, and with Ampligen:
My Total T cell count improved from 667 to 1426.
My CD4 count improved from 380 to 792.
My NK cell count improved from 36 to 68.

I am amazed at the degree of subjective and objective improvements with this drug, and I look forward to more of the same over the coming months. It is my strong recommendation that Ampligen be approved, because I believe that literally tens, if not hundreds of thousands of patients could benefit. It has a very favorable safety profile, and in my case clearly the clinical benefits were great.

[…]
Treatment for Chronic Fatigue Syndrome - Ampligen
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[…]
To: "AAC@fda.hhs.gov" <AAC@fda.hhs.gov>
[…]
Tue, Dec 4,2012 at 7:01 PM

To The Advisory Committee Reviewing Ampligen:

My name is […]. I have had CFS for more than 19 years. Before I became ill I had a life that was very active and rewarding. I was a new wife and a young mom of a newborn. I had a wonderful job as an Occupational Therapist at a State Psychiatric Hospital. I was creative, intuitive, and very good at my job because of my bubbly personality and energy level. I use to go home to quilt, paint, and bake. I use to go hiking when ever I could. I loved to ride my bike with my son in his baby seat. I use to go shopping in malls, and mow my lawn. I actually use to help my husband on the weekend with our landscaping buisness. I was able to take home the bacon and fry it up too. I use to remodel houses, doing heavy lifting and being able to raise my hands over my head to use a hammer. I was able to go to Church and sell woodcrafts at craft shows on the weekend. I thought I was on top of the world and I was so active, fulfilled, and productive. My life since having CFS has been a Lifetime movie. It is all about Dr. appt.'s and blood draws and laying on the couch watching my 3 children become teenagers. I have been through 2 divorces because it is hard to understand not being able to do things when you want. I have to adjust priorities and make hard choices about using my energy to help my kids with their homework or clean the toilets because I could only do one thing a day. I had to move near my parents and have them help take care ofl me and my house. They had to help do all the things around the house because 1 was to stubburn to let them raise my kids

without my involvement, but that left me drained once they left for school. It is unimaginable, to have your baby cry at night, and not have the strength to lift them out of the crib. I know how horrible it feels to use all your energy for one day on just taking a shower and having to sleep the rest of the day, to exhausted to get even get dressed. I know that there are medicines out there waiting for us. I was on Valcyte with Dr. Lerner and I got better. I was able to be a single mom of middle schooler and go back to work part time. I was able to start camping, and hiking again. I had energy to work on my house and garden. I started dating and meet a wonderful man and we fell in love. My live was not normal, but with pacing it was wonderful to be alive again. OtT the medicine, due to other health issues, I am not as well. I am able to struggle at work for 2 days a week, but I would not give it up because it makes me feel alive. I am able to go to my daughter's basketball games, but I have to wear ear plugs. I have to explain over and over again why I can't be counted on, I have to explain that I am not really stupid, I just can't think when I get tired, or even talk. I have to explain, I am not mad, but when I am tired my face droops and I look anger y. Do you have any idea how much energy it takes to smile? There is so much more I want to say, stuff that is stuck in my head, but it is a bad day and I can not get stuff out right. One word sums it up, Frustrating. I am an intelligent, active, bubbly, zestful person inside the body of a a 44 year old shell. After 3 decades, We Need treatment. We deserve treatment and the ability to access it. Just like AZT for AIDS or Chemo for Cancer or Tysarbri for MS or Benlysta for Lupus. We are not second class patients. Reality of CFS, it is Serious and Life Threatening. According to CDC studies, CFS is comparable to MS, AIDS, Lupus, Rheumatoid Arthritis, Heart Disease, Renal Failure, COPD and Chemotherapy. *CFS/ME* effects every moment of my life. We've seen and heard of patients responding to Ampligen. Give patients Hope by approving Ampligen. We want our lives back.

Thank you,
[...]

[...]

[...]
December 6, 2012
[...]

I am registered to speak at the Open Public Hearing (OPH) segment of the December 20, 2012 meeting of the Arthritis Advisory Committee at which the committee will discuss new drug application (NDA) 22151, rintatolimod injection (proposed trade name AMPLIGEN) submitted by Hemispherx Biopharma, Inc. for the treatment of patients with chronic fatigue syndrome. Thank you for this opportu~ity to tell of personal experience with Ampligen. Please pass these comments on to the committee members.

In 1994, I was in training to hike the Grand Canyon for my fortieth birthday. I developed an acute viral infection with high fever, severe muscle aches, nausea and vomiting . Five days later, I was admitted with bilateral pneumonia. My life filled with bicycling, gardening, attending family functions changed forever. I was unofficially diagnosed with CFS/ME by an internal medicine resident in 1997. I was able to keep my

urological practice viable with modifications. Fall of 1998, I developed pneumonia in a matter of 12 hours to a severity of hypoxic brain injury.

CFS/ME was going to kill me if I did not get a diagnosis and a treatment. I met Dr. Daniel Peterson, was diagnosed with CFS/ME as well as a immunoglobulin deficiency (IGG and IGA). I was started on Gammagard and made some progress to better health until 2001. After several surgeries, I had come to the point of doing something radical or go on disability.

Doing something radical was to start on Ampligen on the cost recovery program. By the time I started Ampligen January 2002, I needed help to pack my suitcase and could not walk the jet bridge to the plane. I started feeling better and was able to start commuting back to Sioux Falls from Incline Village, NV, to continue my urology practice. My labs normalized and I could now keep up with my 80-year old mother. I went on a drug "holiday" April 1 2004 but within six months, my labs reverted to pre-ampligen levels and my energy levels were not as good. I restarted Ampligen and everything turned around. I had another 5 month "holiday" but my NK cell lysis bottomed out. Ampligen has given me my life and I do not regret the millions of airline miles flown, holidays away from family, etc.

I have had a few reactions to Ampligen including a period last year of cytokine-storm symptoms. Another time, I had a full bottle of 400 mg (back when 400 mg bottles were available) infiltrate into my right breast when the portacath became disconnected from the port site. The possibility of a mastectomy was mentioned. I had muscle aches and fever the first 48 hours, followed by a burn-type local reaction to the skin involving my whole right breast. The site was very painful. I was treated with Aloederm local application, topical lidocaine, and time. "All tissue return to normal over a two week period" . Local Infiltrates are also painful and the patients have found arnica cream or aloe, immediate ice to the site, and elevation helps.

I think there needs to be some qualifications for physicians prescribing Ampligen. After 11 years of getting Ampligen twice a week, I have seen the dramatic changes in patients. I think about how Dr. Peterson picks what patients go on Ampligen and which patients get other treatments. An algorithm could be used as well as a timeline of when to try to discontinue "drug-holiday".

I am alive today because of Ampligen. There is absolutely no doubt. There are side effects to all drugs but the benefits for me far outweigh the minimal side effects. I would plead with this panel to recommend approval of Ampligen to the FDA. After 3 decades of CFS/ME, we (patients and physicians) need a treatment approved. We deserve treatment and the ability to access it. Just like AZT for AIDS or chemotherapy for cancer or Tysarbri for MS or Benlysta for Lupus. We should not be discriminated against because the world of medicine and the government can't explain the cause of CFS/ME. CFS/ME is serious and life threatening. According to CDC studies, CFS is comparable to MS, AIDS, Lupus, Rheumatoid Arthritis, Heart Disease, Renal Failure, COPD and Chemotherapy. CFS/ME effects every moment of my life. I have seen and heard of patients responding to

Ampligen first hand. Give patients hope by recommending approval of Ampligen. All CFS/ME patients want their lives back.

It is my life that you have in your hands. I do not want to go back to the time that I did not have Ampligen in my treatment plan.

Thank you.

[…]

Fw: Treatment for Chronic Fatigue Syndrome - Ampligen

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[…]
Thu, Dec 6,2012 at 12:51 PM
----- Forwarded Message -----
[…]
To: "AAC@fda.hhs.gov" <AAC@fda.hhs.gov>
Sent: Thursday, December 6,2012 1:49 PM
Subject: Treatment for Chronic Fatigue Syndrome - Ampligen

To The Advisory Committee Reviewing Ampligen

I am […]of Tucson, AZ. Ihave had CFS for over 21 years. I had a productive and satisfying life before becoming ill. Iworked as a CPA and enjoyed the many outdoor activities that Arizona provides. Ihad friends and an enjoyable social life. Since becoming ill, my world has shrunk mostly to my home and looking for an effective treatment for any of my health problems. Idon't socialize any longer because Iam very susceptible to common viruses, which sap what little energy Ihave and worsen other symptoms of my *illness.*

Those of us with *ME/CFS* desperately need help. We have waited so long to be taken seriously. If studies indicate that Ampligen may be of help with this illness, please aprove it for treatment of *ME/CFS.* Even if it is not everything that one would hope for in a treatment, we have to start somewhere and we are willing to take appropriate risks to find effective treatments. Please help us if you can.

Sincerely,
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Gmail - Treatment for Chronic Fatigue Syndrome - Ampligen Page 1 of 1
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Treatment for Chronic Fatigue Syndrome - Ampligen

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To The Advisory Committee Reviewing Ampligen:

My name is […], my sister […]has had CFS for more than 10 years. Before she became ill she had a life that was full of hopes and dreams. She had a successful career and enjoyed many of life's simple pleasures that a healthy person does. Things that when you are healthy would never cross your mind as debilitating.

Since her illness, she has trouble even getting out of bed for the day. Everyday activities have become chores. For example, I went shopping with her once at a local electronics store and one of the employees brought her a chair to sit in while we were waiting in line. He could tell that she was about to collapse waiting in line! When my sister comes to stay with me, she can't take a show in the guest bathroom because she can't stand long enough. She has to take a show in my master bathroom because there is a seat in that shower stall. These are just are just two examples of how her everyday activities are curtailed by CFS.

Please help my sister. Her pain needs to be validated and TREATED. Give her the treatment she deserves and that will help her. After 3 decades, We Need treatment. She deserves treatment and the ability to access it. Just like *AIT* for AIDS or Chemo for Cancer or Tysarbri for MS orBenlysta for Lupus. She is not a second class patient. Reality of CFS,it is Serious and Life Threatening. According to CDC studies, CFS is comparable to MS, AIDS, Lupus, Rheumatoid Arthritis, Heart Disease, Renal Failure, COPD and Chemotherapy. *CFS/ME* effects every moment of her life. We've seen and heard of patients responding to Ampligen. Give patients Hope by approving Ampligen. She deserves and wants her life back.

Thank you,
[…]

Treatment for Chronic Fatigue Syndrome - Ampligen

[…]
To: AAC@fda.hhs.gov

To The Advisory Committee Reviewing Ampligen:
Tue, Dec 4,2012 at 6:30 PM

My name is […]and I have had ME/CFS for more than 9 years.

Before I became ill I led a full and active life .. I married in my early 20's and worked my way up the corporate ladder to Vice President for a real estate syndication firm. In the years that followed I established my own management company, raised a family, did volunteer work, and managed a social life as well. In 2003 I came down with a "flu" that was worse than anything experienced before. It took an act of will to move, to hold my head up, and even to speak. While being driven to the ER I wondered if I was going into a coma. Although I recovered enough to return to work, in the months and years that followed my health declined as I pushed and crashed, went from doctor to doctor, and was continually misdiagnosed. Eventually I was so disabled that I had no choice but to sell the business I had worked so hard to build. I am now unable to work. I am not the wife and mother I want to be, and I have no social life. I live each and every day with pain, sensory overload, shortness of breath, nominal aphasia and other neurocognitive symptoms, increasing allergies, GI problems, chemical sensitivities, vertigo, nausea and many other symptoms. This year I was diagnosed with Common Variable Immunodeficiency as well.

I have spoken with several patients who have responded very well to Ampligen. It seems to be a viable option for patients who are suffering so seriously with no where to turn.

Please give our community a viable treatment option - please approve Ampligen now.

Thank you,
[…]

Please Approve Ampligen!

[…]

[…]
To: "AAC@fda.hhs.gov" <AAC@fda.hhs.gov>
[…]
Tue, Dec 4, 2012 at 1:37 PM

To the Advisory Committee Reviewing Ampligen:

I have had ME/CFS for over 28 years. The hallmark features of the illness have been crushing fatigue and post-exertional relapse ifl use too much energy. The relapse is a complete "crash" with no energy, "burning" muscles, and inflammation in and around the brain stem. It can last one to four days. Over the years, my energy level has averaged 10-15 percent of what it once was. Other symptoms have included sore throat, swollen lymph nodes, sleep disturbances, night sweats, IBS, and cognitive difficulties, like problems with memory and processing new information.

Prior to the illness, I was a public school teacher, took care of my family, volunteered in the community, socialized with friends, traveled and pursued hobbies. Since acquiring the illness, I have been largely housebound, I cannot work, I struggle to do light housework, and I socialize very infrequently. My illness has created hardships for my family.

The one million ME/CFS Americans with *ME/CFS* desperately need treatment! Dr. Jose Montoya of Stanford has likened *ME/CFS* to "another form of death." The FDA considers it "serious and life-threatening." *ME/CFS* patients, like patients with AIDS, MS, cancer, lupus, and other serious illnesses, need effective treatment. It has been heartening to hear of patients with *ME/CFS* dramatically improving on Ampligen!

Please approve Ampligen! Give patients access to this drug that has worked well for many *ME/CFS* patients! We desperately want to become healthy, productive citizens once again! Thank you very much for your attention to this important matter!

Sincerely,
[…]

Treatment for Chronic Fatigue Syndrome - Ampligen

[…]
To: AAC@fda.hhs.gov
[…]

Helio,

Wed, Dec 5, 2012 at 7:56 AM

Approval for Ampligen it absolutely critical for ME/CFS patients. Right now we have nothing, and there is little prospect for that changing if the FDA continues to sit on its hands.

I have been ill for more than nine years. Over that time I have been examined by more doctors than I can shake a stick at. Half of them tell me they can't help me and they don't know who can. The other half tell me I'm not ill - I just need exercise and psychotherapy. Meanwhile I continue to get sicker and sicker.

I used to have a life. Now I typically spend 20 hours a day lying down or propped up on the couch. Some days I can barely get to the toilet and make toast and coffee. Instead of writing computer telephony software and building the hardware to run it, I mostly listen to the radio. I can no longer cut firewood, plant a garden, restore cars, go backpacking,

skiing, play saxophone in community bands, travel to visit my mother, or even drive. The illness has financially shattered me. My only source of income is food stamps. I have been struggling to get Social Security Disability for five years; I will finally have a hearing before an Administrative Law Judge early next year. I am presently attempting to get through the arduous bankruptcy process. I can no longer even buy car insurance or repair my 20 year old truck. If something breaks, it has to stay broken. The roof on my 25 year old trailer house leaks; a tarp is presently keeping most of the water out. The oven quit working; I can't replace it. I can't pay this year's property taxes, which makes my home subject to seizure for taxes. I have to beg for rides to the grocery store. I have to beg for firewood from my neighbors, as I am no longer well enough even to dumpster dive for pallets and scrap wood, which I did three years ago. I am sick of living on my knees, begging for crumbs, in the richest society on the planet.

I have been abandoned by most friends and family, and by society at large. The social service agencies that claim to exist to help poor people prefer to use their resources to deny services. My medical records are full of unhelpful statements like, "patient is seeking attention", "exaggerates symptoms", "drug addict", "insists disability would solve all his problems". I don't care about the possible risks of Ampligen. My life is already destroyed, I am on the path to being bedbound; how can Ampligen make it worse? I don't want to die yet. I want my life back, but if society refuses to help, and the illness continues to worsen, there is only one alternative. Please stop fiddling. Don't wait another 20 years to approve this drug. Do it now. Make sure people like me have access to it. Make sure the doctors start prescribing it. You know it's the right thing to do.

[...]

Treatment for Chronic Fatigue Syndrome - Ampligen

[...]
To: AAC@fda.hhs.gov
[...]
Sat, Dec 8,2012 at 9:35 AM

To the Advisory Committee reviewing Ampligen:

My name is [...]and I have had Chronic Fatigue (Immune Disorder) Syndrome for 35 years. had a healthy childhood, but have been ill since the 1980s. I managed to finish high school despite missing 3 months out of every 9 due to a constant flu state. Sometimes it was better and I could manage to get to school but after a couple of weeks, the exhaustion would become overwhelming and I would be asleep for a couple days. I did well in school, earned some awards and participated in the Academic Decathalon. Although it took 9 years, I graduated from college. I would work for awhile, then take some classes. This illness forced me to live in a frustrating push/crash cycle that was ultimately destructive to my health. Every crash resulted in another immune system failure - severe allergies, death of my thyroid (Hashimoto's), adrenal fatigue, irritable bowel syndrome and finally fibromyalgia, which rendered me completely unable to work in 1998.

After 3 decades, we deserve to have the only CFS treatment, Ampligen, to be approved for use. In the same time frame, AIDS has had all kinds of treatments approved and AZT was the one that proved most useful. Ampligen has the same potential. While CFS/CFIDS doesn't kill us, it renders us completely useless and wishing we would die. I would REALLY like to return to the world of the WORKING, instead of being condemned to interminable days bedridden, dependent on government assistance and a burden on my society and family.

CFS/CFIDS is not some yuppy disease that only high strung women get and can be dismissed as such. The misery is real, unwanted and impacts the seemingly trivial aspects of daily life. CDC studies have found that it is as devastating as MS, AIDS, Lupus, Rheumatoid Arthritis, Heart Disease, Renal Failure (treated), COPD and even Chemotherapy.

I have heard about the wonders of Ampligen in the experimental treatment of CFS/CFIDS for MANY years. I would like the opportunity to see if it works for me. Thousand of other sufferers, who aren't well enough to write, desperately want the chance to try Ampligen, the ONLY CFS/CFIDS treatment discovered since the Tahoe outbreak in the 1980s. Many of those outbreak victims have taken their lives because they lost hope of ever getting better. Please, give the rest of us hope of getting better. This disease is a horrible prison and Ampligen has improved the lives of those lucky enough to have been administered it.

Thank you for your serious consideration of this matter.
Sincerely,
[...]

To: AAC@fda.hhs.gov
Subject: Treatment for ME/CFS-Ampligen
[…]
December 4, 2012

To the Advisory Committee Reviewing Ampligen:

My name is […]. I have had Myalgic Encephalomyelitis otherwise known as Chronic Fatigue Syndrome for 27+ years. It struck me at the age of 24 just as my career as a teacher was getting started. I am presently 51 years old. I was working as a high school teacher teaching English to mainstream students and English as a Second Language to newcomers who were eager to learn our language and our ways. I have always worked at high poverty schools because I felt it was my calling. I loved it because I felt I could help turn their lives around by assisting them to access good educations and, in turn, aid them in plan for their post-secondary futures.

Although I am American, I grew up overseas and lived in Latin America learning Portuguese when I was 5 years of age and Spanish when I was 10. When I graduated, I returned to the U.S. to attend university. I had seen so much *poverty* and misery growing up that it affected my career choice. I wanted to help kids pull themselves out of the misery of poverty in my own country because, afterall, we live in a country of opportunity. I wanted my struggling students to have choice in their lives. Moving up the ranks economically was very difficult to do in those other countries where I had spent my formative years. Their societal structure was such that what you were born into was your lot in life. I found this concept very difficult to accept as a child and inspired me to help change lives by being an educator.

Luckily, I have been able to have a career up until now. I have been able to go back to university and receive my masters in counseling and have worked as one for 21 years. I even returned to university to work on my administrative credential and was thinking about earning a doctorate. This disease stomped on my dream and brought me to my knees midway through this process. In other words, I fell very ill. I have not been well enough to return to my coveted studies.

My natural state is to be in perpetual motion and I used to be very active. I have always loved dancinq, kayaking, jogging, playing tennis, basketball, hiking and many other physical activities. I have also enjoyed travelling all over the world. Growing up in Latin America inspired me to see the rest of the world. I have always loved to entertain by hosting parties and cooking. I was very active at work and had won several awards in my teaching career. In contrast, presently, it's a great day if I can make it to the grocery store, church or a social event where I just sit and visit for a moment.

When this illness hit, it devastated me and changed my life forever. When I would get flare ups, I would be off work for at least 6 months on bed rest. I would make it back to work, but then it would take a good two or three years to recover. I would never fully recover because the disease was constantly nipping at my heels and the post-exertional malaise would send me to bed for weeks at a time. I would drag myself to work and continue to try to be productive. After those two or three years, I would still have to be careful in what I could do. My immune system was shot and I would pick up every cold and flu I seemingly came into contact with. I kept persevering. I decided after 6 years of teaching to switch careers into that of being a school counselor.

Though counseling students was still very demanding, it continued to give me contact with the student population whom I loved so much. I was able to help my students without all the correcting and prepping that you must do with teaching and that I couldn't sustain energy-wise anymore. Switching jobs to counseling gave me more of an opportunity to rest at home after work hours.

Through all these years of battling this debilitating disease, I have not had much medical care. What I did receive was minimal. The attitudes I have encountered from medical personnel have been nightmarish. I have had many doctors not believe I was ill; they felt I was malingering, and/or that I was depressed. I had one doctor go as far as tell me that I was depressed, I needed to get married and that nothing was wrong with me. When I told him he was wrong and that I was ill, he became enraged pointed to his framed certificate on the wall furiously and said he was board certified at Stanford University. The other doctors who were kinder and would listen to my litany of symptoms would say, "Just rest." I didn't want to "just rest"! I needed a cure. Through the years, I have resorted to many alternative methods such as accupunture, chiropractic care, and naturopathic doctors because at least they offered some relief and some sort of treatment.

I am married, but I have missed out on the opportunity to have children. Both my husband and I couldn't imagine raising children since I could hardly take care of myself due to my disease. This has been a full time proposition for both he and 1. It will be a regret of mine forever that this disease took away the possiblity of a family because my body couldn't handle it.

I have gotten progressively worse as I have aged. I had Kaiser Permanente for 18 years, and they had no treatment for me. The only thing they would give me was vitamin 8-12 shots to help my energy a little. Five years ago I had a flare up from which I haven't bounced back. I had been noticing more difficulty in my cognitive processing (short term memory issues, problem solving and doing math) increasing frequency of post-exertional malaise, and a weakening immune system (bout with pneumonia that laid me out for 2 months). I was doing much more resting on the weekends and after work. I was unable to go on field trips with my students to vist college campuses, for example, because I COUldn'twalk more than ten minutes at a time. In November of 2011, my body crashed and I was flat on my back. I have not been able to work since then. Thankfully, I was able to cet onto mv husband's Insurance and off Kaiser Permanente HMO insurance and am currently being actually treated now by Dr. Daniel Peterson of Incline Village, Nevada. I have been seeing him for almost a year now and started Ampligen in April, 2012.

I have made it my life's work to fight for others. I have offered tools and resources to hopefully help my students be who they are meant to be in life and not live the life they were born into. As I stated previously, this is the land of opportunity. I feel like others and myself who have this disease *have* not been treated as though we live in the land of opportunity. We have been abandoned and left by the roadside of life. I feel like Dr. Peterson has been a Godsend because up to now, no one has been fighting for me for 27 years. Our society and medical establishment has not been educated on this disease. No one wants to acknowledge it's existence and its devastating *affects* on our lives and livelihoods and those of our families. Why can't we approve Ampligen and finally legitimize this disease?

I am in a battle with my income protection insurance, The Standard, because they don't believe I'm ill, so they won't help me with my income. I pay them monthly for this income protection, but they refuse to pay and have denied my claim. Thankfully, my school district approved my catastrophic leave application having commenced in my October paycheck, two months ago, and are paying my

salary for the rest of the school year, but this runs out in May. Then, what will I do if I can't get back to work or need a little more time to get well? I lose my job and I have no income. I am the main breadwinner in my family. We have so much to lose, and I have worked so hard my whole life!

After all these years, I feel so lucky to have the opportunity to receive Ampligen. The problem is my husband has to take off of work two times a week to drive me to my Ampligen infusion. We also have to travel 250 miles roundtrip each time we do so. The cost of Ampligen is so very high because it hasn't been approved. I'm not sure how we make it each month economically, but by the' grace of God, and with the help of family we do. Sometimes my parents will drive me, elderly though they are, if the weather conditions are okay. Presently, the weather is snowy through the Sierras and I will not permit them to drive me. Thus, my husband has to take off work twice a week to do so.

If Ampligen were approved by the FDA, I could access this medication locally and my insurance would pay for it. I wouldn't be able to afford this treatment in the future if Ampligen weren't approved and if I lost my job. It's just too costly. Dr. Peterson says I am making good progress as he reviews my blood work frequently since being on Ampligen. I can feel the positive *affects* as well. I am hopeful and praying that I can return to the work that I love before I lose my job. Please approve this medication thus making it available to the million plus Americans suffering from this life altering disease. Everyone deserves treatment and the ability to access it! The reality of Myalgic Encephalomyelitis/Chronic Fatigue is that is serious and life threatening. I had one of my good friends, [...], die from this disease this year on July 21, V 2012. She wanted so much to be well, go back to work, and be a part of life again. This disease is so isolating and riddled with suffering. She had gone through so much and seemed to be doing better when she inexplicably died in her sleep. She was not *receiving* Ampligen. I am so sad that she could not see the day when a treatment would be made *available* to her and so many others.

Please legitimize my life and *everyone* else who is touched by this disease by approving Ampligen. According to CDC studies, this disease is comparable to MS, AIDS, Lupus, Rheumatoid Arthritis, Heart Disease, Renal Failure, COPD, and Chemotherapy. ME/CFS affects every moment of every day, week, month and year of my life and those in my circle of family and friends. I *have* responded well to Ampligen and many others have too! Please *give* us all hope by doing the right thing and approving this important medication. Iwant my life back. Everyone with this nightmare of a disease wants their life back.

Most Sincerely,
[...]

[...]
Subject: Request for Information

Dear Sir/Madam,

I'd like to thank you, as a housebound ME/CFS patient of 30 years, for your RFI on ME/CFS.
Given the urgency of the situation - millions sick, many for decades, many severely disabled, some dead or dying - I'd like the NIH to fund the research of Dr. Ronald W. Davis at Stanford University.

Dr. Davis has said publicly that he was twice turned down by the NIH for grants on his groundbreaking ME/CFS "big data" work on the molecular biology of the disease because the grant reviewers believed that he should have had a hypothesis.

I was a university-based research epidemiologist and in much research, yes, of course you'd want a hypothesis - but not at the discovery stage. And because so little work has been done on ME/CFS at the point, we're at the discovery stage.

As Dr. Davis has said, "When we launched the Human Genome Project, we did not have a hypothesis. It was incredibly successful, and it's totally revolutionizing medicine right now."
I beg the NIH to revisit this poor reviewing decision, with a view to fast-tracking and fully funding this research. Preliminary results are already very exciting:

http://www.meaction.net/2016/06/04/ron-davis-errors-metabolism/

I'd also like to see the NIH look at the quality of its review process for ME/CFS research so that future high-quality submissions are not rejected for similarly inappropriate reasons.

People with ME/CFS have grown old in their beds. Please act with the urgency that the situation demands and fund this work.

[…]
Subject: response to RFI regarding ME/CFS

Thank you for requesting this information.

Response to the NIH Request for Information: Soliciting Input for New Research Strategies for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome, May 24, 2016.

- **Emerging needs and opportunities that should be considered as new ME/CFS research strategies are developed.**

> **"CFS/ME is a serious disease and there is unmet medical need in the treatment of CFS/ME." [highlighting added]**

Over two million people in the U.S. alone are estimated to have ME/CFS. It seems to be alone among all diseases with this number of patients in having no FDA approved treatments. As it is a very serious, multi-system disease which causes unimaginable suffering, drug trials are critically needed. **This is not an emerging need; it is one that has unfortunately existed for 30 years. But it is a critical need.** Even one approved drug will give patients some possible relief from their loss of lives, figuratively and sometimes literally. It will also give them hope - hope that they are not forgotten after all; that there might be more drugs approved within the foreseeable future; and simply, a reason to keep on living.

This is hardly the first time that it has been suggested that drugs for the disease are desperately needed. The purpose of the 2013 FDA Drug Development Workshop (2 days) was exactly that. Unfortunately, no drug companies were invited beyond those who had representatives on the panels.

Shortly thereafter, A *Guidance for Industry* was created, which stated that "CFS/ME is a serious disease and there is unmet medical need in the treatment of CFS/ME. There are FDA programs intended to help ensure that therapies for serious conditions are approved and available to patients as soon as it can be concluded that the benefits of a therapy outweigh its risks."[5]

Unfortunately, this document also made this shocking statement: "Currently, there is no single case definition or set of criteria that is uniformly recognized as the standard for diagnosing patients with the disease. At this time, the FDA does not recognize any particular disease definition, nomenclature, or diagnostic criteria for CFS/ME as the most appropriate for use in clinical trials of new drug products. **Consequently, any case definition or criteria for CFS/ME can be used to define the patient population**."[6] **This approach invites invalid results and unrepeatable outcomes. There is a need for a clear research definition that will guide drug companies in their planning of trials for drugs or other treatments for ME/CFS.** Currently the Canadian Consensus Criteria are used for much ME/CFS research. **The 2013 Guidance document should be updated to reflect this and should remove the statement quoted.**

What can be done right now? There is one drug in the pipeline at the FDA which awaits one more clinical trial before it can be fully approved (it has met the requirement for safety). This drug is Ampligen, which for a variety of reasons has been in the FDA pipeline for 25 years. One patient, whose testimony is appended, has been on and off the drug, in trials, for **19 years!**[7] As was said at the FDA 2012 Advisory Committee hearing by a panelist who has ME/CFS, the side effects mentioned in the prior testing of Ampligen ***are not as bad as the effects of the disease itself***. Hundreds of patients have found it to be effective. At least one physician who administers Ampligen as part of a continuing trial (Dr. Dan Peterson, Simmaron Institute, Reno, Nevada) believes he has criteria for determining the subset of patients in whom will Ampligen work.

It is well known that there are a multitude of drugs which have been approved by the FDA which have worse safety and efficacy records than Ampligen, which has been proven to be safe by the 2012 Federal Advisory Committee. And there are many diseases which have drugs approved regularly which have far fewer patients, and/or the drugs are merely supplemental to many other drugs approved for the diseases targeted***. ME/CFS has no approved treatments.***

Ampligen needs to be given conditional approval and simultaneously be subject to a Phase IV clinical trial conducted by the NIH with ME/CFS expert involvement in the design, analysis and written conclusions in order to prove efficacy. Ampligen has been tested for many years and is the only drug anywhere near approval for use for ME/CFS.

In addition, there are other avenues which must be pursued to encourage even more drug companies, universities, and research facilities to submit requests for grants for trials into possible ME/CFS treatments. A number of drugs are used off label by expert clinicians in treating ME/CFS. The FDA and the NIH should

[5] Guidance for Industry Chronic Fatigue Syndrome/ Myalgic Encephalomyelitis: Developing Drug Products for Treatment, Draft Guidance; U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), March 2014, Clinical/Medical
[6] Ibid, p. 3
[7] Statement by this person is appended.

work with the experts in identifying the most promising of these and notify the companies that make such drugs that there is a need for some of their drugs for ME/CFS.

- **Challenges or barriers to progress in research on ME/CFS.**

The greatest barrier to progress in research on ME/CFS is the lack of money committed to such research over the last 25 years by the HHS, particularly the NIH. The piddling amount now committed ($6 million a year) is totally inadequate. There is also a lack of urgency within the HHS to find causes and treatments for ME/CFS. To stimulate research by medical researchers as well as pharmaceutical companies, **Requests for Applications for grants should be announced in 2016, not in the undefined future. These RFAs should total a significant amount of money.** It has often been stated by the NIH that more money has not been granted for ME/CFS research because there are not enough researchers applying. This is neither an encouraging approach nor true. Providing multi-million dollar research grants will stimulate interest to a degree never seen before for this disease. Much research in the last 20 years has been not instituted, or dropped after initial trials, or been discouraged or turned down by the NIH or university medical approval offices because there has been essentially no funding – no support – from the federal government for research into this disease. **To repeat, multi-millions are needed**. Dr. Jose Montoya, ME/CFS expert clinician and researcher at Stanford University, called for a federal commitment of $100 million. The patient community is asking for much more - $250 million yearly in NIH grants, commensurate with the burden of disease on the patients and their families and the U.S. economy.

In summary,

- **ME/CFS patients desperately need FDA approved treatments.**
- **The NIH should create a clinical trial immediately for Ampligen, with ME/CFS expert involvement from beginning to end.**
- **The NIH should encourage the companies that are using approved drugs off label for ME/CFS to apply for grants for trials for these drugs for ME/CFS.**
- **There is a monumental need for much more federal commitment, in the form of grant money, to stimulate research into this disease.**

Respectfully submitted,

[…]NJM/CFSA Advocacy Chair

[…]writer of the statement below.

The following is a statement of an ME/CFS patient who started with Ampligen treatment 19 years ago. This statement illustrates perfectly the benefits of Ampligen to those who have been on it and have been helped so tremendously, and also the outlook of those who cannot get similar relief. **People have died in the years since Ampligen was disapproved by the FDA in 2009 and 2012, by extreme sickness from ME/CFS and from suicide from having no hope that Ampligen or any other drug would be approved in their foreseeable future. As the writer says, this situation is unconscionable.**

I have been on a clinical trial of Ampligen on the cost-recovery AMP-511 safety protocol study for 19 years. For the 11 years prior to starting on treatment I had been very ill, having suddenly gotten the flu in September of 1986. I had to get around using an electric cart because of having constant infections and troubles with my immune and energy systems that were wiped out at the time of sudden onset of the viral illness. My original lab tests showed positive ANA (antinuclear antibodies), white spots in my brain on my MRI, abnormal EMG (electromyography), as well as being unable to walk and use my muscles. I could not sleep and had immense all-over body pain where the muscles connect to the bone. I had to quit working because I was a typist and could no longer lift my arms up to the keyboard, could not remember where the keys were, and could not even transfer phone calls to the correct person when they transferred me to another department. My brain suddenly did not respond to my desire to keep track of daily schedules, and I had severe headaches. I could only walk 4 minutes on the treadmill, and my VO2max score (a measure of energy) was only 15, lower than the legal disability for heart disease. I could not stand without fainting.

All of that changed when I began Ampligen therapy. I was extremely grateful for the opportunity to have medicine and I got well like there was no tomorrow.

> **My treadmill test went from 4 minutes to 19 minutes and my VO2 max improved to 35. My oxygen exchange rate improved to that of normal. My natural killer (NK) cells that help the body fight disease were at a low level of 2 and rose to upwards of 50 on Ampligen therapy. My labs improved by Ampligen's having raised my natural killer (NK) cell function from 2 to 50,**

eradicating the 5 chronic active viruses in my blood and spinal fluid. That increased my oxygen capacity to my now being at 117% of normal, meaning I am able to exercise and walk up to 2 miles when previously able to walk only 20 feet. My quality of life has risen, my social life has expanded, my ability to be up and out of bed, off the sofa and participate in society by volunteering at a medical nonprofit, by driving myself and other patients to their appointments, by walking my dog, by hosting lunches and dinners, by attending church and Bible studies, by watching the news, by typing, and overall expanding my energy envelope.

I was continuously on Ampligen for 8 years. I went off it and subsequently got ill all over again, and was back to being bedridden and housebound with severe headaches and using my walker to get around. I would wake up and not know where I was, what day it was, and had trouble watching TV and certainly was not able to type. Words were hard to find and I had trouble expressing myself with language. I had trouble reading. Due to the extreme swelling and inflammation in my brain from the cytokines and virus in my spinal fluid, shown by the PET scans and SPECT scans (brain scans), I had reduced blood flow in my brain which resulted in loss of some hearing and vision. I lost nine teeth due to bone infections and got two partial dentures in order to eat. I got gastroparesis in the tummy and at times had four months where I could only tolerate liquid nutrition. The nerves died in the gut as well. Honestly, if it was not for my faith in God, I would have given up as life was intolerable in many ways.

In 2011 I went back on Ampligen and again have been on it continuously for another 5 years and achieved the same level of

wellness as when previously on the medicine. During all of this time I have been a patient advocate, fighting for the approval of Ampligen, and now I volunteer at a medical non-profit in order to further the work of science and research and the education on ME/CFS. My heart is completely hurt every single day as I look around at the gift that it is to be well and to have been given the chance to get well. That chance is not available to the upwards of 2 million patients, and it is NOT RIGHT that there is a medicine out there, stuck in clinical trials and not being approved.

In fact, since the FDA Advisory committee meeting in December of 2012, there has been no visible movement by the FDA to provide therapy and medicine to the patients that are waiting. I have to bounce by those patients every time I dose medicine at the doctor's office, and they wonder why THEY do not have the same chance at wellness as I do. Try sitting next to somebody in the waiting room who has all of my same symptoms that I USED to have and give an explanation for how I am now doing. I end up hiding and being embarrassed to have had the chance, and what can I tell them that will make them feel one bit better that they do not have access to a medicine that has helped me this much???? Those same patients have been sick as long as me, 30 years, many of them, since the original outbreak at Lake Tahoe in the 1980's. They are still bedbound, unable to enjoy the social activities that I do, unable to marry, have children, work and provide for themselves, unable to host the lunches and dinners that I do, unable to walk, unable to feel the breeze hit their face while riding a bike, unable to walk the shores of beautiful Lake Tahoe and no prospect of anything changing in the future. Many have lost hope, and I personally know 6 patients that have taken their life because the suffering is intolerable.

This situation is UNCONSCIONABLE!!! I cannot sit by any longer and watch others while living with the guilt of why I was chosen to get well. Twice! It is a lovely gift that I thank God for every day, but I just cannot stop fighting for the rights of other patients to have the same chances I have had.

Please grant immediate Conditional Approval to Ampligen and help my friends and all the other more than two million patients get well! This drug works!

[...]
Subject: The Trans-NIH ME/CFS Working Group also welcomes your general comments.

The first thing is to validate / replicate the 2 day cpet study (I think is called the exercise one). Here is my reasoning: This study is accepted by disability and all industry. This will give us 100% of plp w real ME + will fix the gap so while the patient gets better can get some income. So we address a biomarker (can be combined w immune tests), a disability acceptable tool, and an objective / measurable evaluation tool for future treatment (how effective it is) / studies. I am convinced this is where we need to start.

2) We should join forces with Dr Grubb on OI. There are effective treatments that can get people out of bed immediately. Long out there drugs that work today (when the prescriber knows what it is doing). So see if betablockers(case by case), Calcium Channel Blockers (case by case), Vassoconstrictors (case by case), Vassodilators (case by case)..... This is cheap, fast and effective treatment we can have studies up and running fast and with good immediate results (per soubgroup).

3) Validate GET w the 2 day CEPT study (once this is validated).
4) Try MS and RA drugs for CFS.

[...]
Subject: Response to request for information NOT-NS-16-024 Auto forwarded by a Rule

With the goal of developing a research strategy for ME/CFS, there are several critical needs that must be addressed by the NIH:

1) Identify and use accurate research criteria, clinical case definitions, and objective measures.
Rationale:
As the US Institute of Medicine noted in their report 'Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness', a diagnosis of CFS is not equivalent to a diagnosis of ME.[1]

The NIH must recognize that by researching 'ME/CFS', they are committing themselves to studying (at least) two separate disease states, not one. Any research done on these diseases must take into account the various different descriptions and case definitions available for both ME and CFS. The differences must be understood by those undertaking the study and appropriate criteria and measures must be used. The disease entity first described in the 1950s as myalgic encephalomyelitis is distinct from the syndrome created in 1988 by the US Centers for Disease Control.

For better or for worse, the CDC has created a syndrome, CFS, that millions of people fall under. Not all of these people will also fall under criteria that defines ME but this chronic fatigue group should not be left behind in research. It is crucial however that these two groups are not combined in research.

There is no scientific evidence available that demonstrates that ME and CFS are the same entity. There is however evidence[2] that demonstrates that they are different, and these differences must be acknowledged and addressed before research work can go forward.

It is also important that objective measures be used whenever possible in the study of ME. While the primary symptom of CFS is fatigue (which cannot be objectively measured,) the primary symptom of ME is abnormal muscle fatigability with delayed recovery.[3] This can be shown objectively[4] with minimal danger to the patient, and it goes along with other objective findings such as abnormal muscle lactate production and clearance.[5] There is also a high incidence of autonomic dysfunction in patients with ME and these findings can also be objectively measured with relative safety. These are all important biomarkers that correspond directly to the symptoms of ME. Going forward, no research on ME should use fatigue as a measure, as it is not a required or even significant symptom of the disease.

2) Acknowledge and utilize the existing epidemiological and virological evidence base for myalgic encephalomyelitis
Rationale:
While largely ignored in the US research arena, there is considerable evidence from multiple investigators all over the world over several decades that link the onset and perpetuation of ME with a specific viral agent, the enterovirus.

When preparing a literature review for the 2015 NIH 'Pathways to Prevention report' on ME/CFS, the US Agency for Healthcare Research and Quality made the bizarre decision to cut off their literature search at 1988 to coincide with the creation of the first CFS definition. This left five decades worth of published evidence on ME unreviewed. Had they reviewed the literature prior to 1988 for example, they would have seen four separate instances where an enterovirus was linked to endemic or epidemic ME cases.[6-9] They would have noted that the characteristics of the prodromal infection that normally triggers ME are highly compatible with an enteroviral cause and are not compatible with a retroviral or herpesvirus cause as has often been claimed.

Among all of the pathogens suspected of being involved in ME, the evidence for the enterovirus is the strongest. Enteroviral genomic material has been isolated from the muscles of ME patients and is correlated with the abnormal lactate response to exertion.[10] Isolation of the same viral strain has been performed on patients over several years, demonstrating the ability for the virus to persist.[11] Enteroviral antigen has been isolated from the blood of patients and its presence or absence corresponds with relapse and remission.[12] Three separate postmortem studies on deceased ME patients have demonstrated the presence of virus in the brain, heart, and muscles.[13-15] Long term enteroviral persistence has been demonstrated in the gastrointestinal tract of ME patients.[16] A longitudinal study of patients presenting to the hospital with acute enterovirus infection showed that a percentage of these patients will go on to

develop ME and viral persistence.[17] Several cohort studies have shown a high incidence of abnormal viral serology for various enterovirus serotypes, with clear evidence of viral persistence.[18,19]

It is very important that the NIH utilize all existing evidence available for ME, especially that which was generated before 1988 or was generated in another country such as the United Kingdom. A lot of work has already been done and the NIH could use this work to build a strong foundation for further research on ME.

This is information that could be put to use immediately. For example, enterovirus serology should be performed on patients in the upcoming NIH post-infectious ME/CFS study, but no plans to do so have been made public at the time of writing. I'm not sure how else to view this, other than a massive failure to acknowledge and embrace the existing validated medical literature on ME.
3) Regarding the NIBIB's interest in imaging, it would be important for them to acknowledge the evidence produced using various imaging technologies to show abnormalities in ME, such as SPECT[20], PET[21], MRI[22], voxel-based morphometry with MRI[23], and qEEG[24]. It is important to note that many of the abnormalities shown by these imaging techniques are localized to the brainstem. This existing evidence should be reviewed and used to guide further brain imaging studies in ME patients.

Thank you for your consideration,

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[…]
Future Direction of CFS/ME Research

Thank you for inviting suggestions from the public on the future direction of ME/CFS research. This opportunity is very much appreciated. I am writing as an ME/CFS patient and advocate.

I have a few suggestions to make:

1) Over the years, and especially recently, there have been numerous studies with interesting results which require replication - and in some cases, larger studies - to validate the findings. But all too often such replication is never attempted. Patients find this very frustrating. It would be very useful (to say the least) if some of the future studies could build on this previous work. I am thinking especially of recent studies which have reported possible biomarkers. Here are some of them:

COLUMBIA UNIVERSITY
https://www.mailman.columbia.edu/public-health-now/news/scientists-discover-robust-evidence-chronic-fatigue-syndrome-biological

UNIVERSITY OF ALBERTA (Edmonton, Canada)
Full report: http://bmcimmunol.biomedcentral.com/…/10…./s12865-016-0142-3

ST. GEORGE'S UNIVERSITY OF LONDON,
Full report: http://journals.plos.org/plosone/article…

NATIONAL CENTRE FOR NEUROIMMUNOLOGY & EMERGING DISEASES (NCNED)
At GRIFFITH UNIVERSITY, QUEENSLAND, AUSTRALIA

https://app.secure.griffith.edu.au/news/2016/03/01/screening-test-for-chronic-fatigue-syndrome-on-its-way/

2) Considerable confusion has been caused by the large number of differing diagnostic criteria which have been used in ME/CFS research, making both comparisons and progress difficult. For example, the recent systematic review of drug therapies (Collatz et al 2016) found that, although there were some significant outcomes, the results of the studies were limited to their respective cohorts and could not be applied to other groups of people with ME. It is therefore vital to standardise such criteria. Many existing criteria (such as the popular Fukuda definition) are widely acknowledged to be too broad and include patients who do not have ME/CFS. The stricter Canadian Criteria have long been suggested as the ideal standard by patients. Questionnaires and outcome measures should also be standardised, otherwise money is being wasted on studies that are of little practical use.

3) Even using the Canadian criteria, it seems likely from previous research that there will be sub-groups within the definition. This is an important issue which has to be borne in mind. Indeed, in view of the heterogeneous nature of the condition, with symptoms varying substantially from patient to patient, it seems likely that the individualised medicine made possible by recent advances in genomics and supercomputing may be ideal for use in ME/CFS, an example being Prof Ron Davis' current big data study.

4) It is vital that severely affected patients should not be excluded from studies (as has been the case in the past). Most of these patients are currently left in a terrible situation without any medical help.

5) Existing drugs including anti-virals such as valacyclovir and also low dose naltrexone (LDN) are currently being used successfully for ME/CFS by some specialist doctors. Further research into such strategies could possibly make treatment available on a relatively short timescale which would be much appreciated by patients after all the years of little being offered them. Here as a relevant link re anti-virals: http://hhv-6foundation.org/news/cfs-patients-with-cihhv-6-may-benefit-from-antiviral-treatment

Thank you for reading this and for the work you are doing to advance research into this condition.

[…]
Subject: CFS research

I've suffered with chronic fatigue all my life. In my 40's I was diagnosed with fibromyalgia. I am now in my 60's and have chronic daily diarrhea, migraines, pulmonary embolisms, shortness of breath, just diagnosed with mitochondrial oxidative myopathy, and many other symptoms.

I would appreciate some research done along the lines of the following:

Role of genetics
Testing for mitochondrial disorders

Treatments for CFS INCLUDING supplements Treatments for mitochondrial disorders INCLUDING supplements Testing for coagulation problems before suffering embolisms

I understand that some of these tests may exist, and if they do, Doctors should be allowed and instructed in using all tests available for preventive care. It seems like a blood test would be more cost effective than hospital stays for embolisms, migraine/TIA, and removal of organs because of mitochondrial myopathies (if, in fact, that is the cause). At 5 yrs I lost my tonsils. At 14 I lost my appendix. At 55 I lost my gall bladder. At 62 I lost part of my thyroid. At 63 I had masses of pulmonary embolisms twice within a year. At my age I don't expect a miracle, but for future generations, I feel it is essential to focus on saving the human bodies from disease. Thus far, it seems the blame for illness has been put on the patient. People have been relying on their physicians to help them. Since the embolisms I had gained 25 lbs. I have tried exercise, which is extremely difficult in my condition, but I push through it when I can. I tried weight watchers, but could not keep up due to chronic diarrhea, brain fog, and fatigue. I have cut calories, cut sugar, cut carbs, cut fat, increased vegetables and fruit, been on innumerable diets, eat mostly organic, with no weight loss. Is the reason medication? Is it my supplement cocktail? Is it the oxidative myopathy? I do not want to be fat. I'm uncomfortable and its "unhealthy". My doctors have no answers, except do the best you can. Not good enough.

Thank you for reading, if you made it this far. I do hope you will consider some of these issues for research funding. Thank you.

[…]
Subject: "Request for Information: Soliciting Input for New Research Strategies for Myalgic Encephalomyelitis

Dear NIH,

LOW DOSE NALTREXONE, VALTREX, IMMUNOVIR & IV IgG….

I will explain the difference these 4 drugs made in my life. There is a need for clinical trials for all of them so as to become effective treatments for ME/CFS.

I became sick in 2002. I became fully disabled in 2006 without a correct diagnosis. January 2011 after a SPECT brain scan a correct diagnosis was made. I met […]in August 2011 and she recommended experimental drugs, which ALL worked at allowing me to block further decline from ME/CFS. Since the diagnosis was 9 years too late, substantial irreversible damage has occurred and left me permanently disabled. I am a 53 year old single mom and ex athlete and stockbroker who also served in public office. I currently am […]of the ME/CFS Safe Exercise Team on facebook, a closed group of about 50 members.

Within 6 weeks of being placed on 2 grams of VALTREX daily, my brain fog reduced and the noises and light sensitives drastically reduced. Within 4 months of being on LDN, my pain that was at a suicidal high level reduced to a tolerable level and even periods with no pain at all. My balance to be able to walk and not fall over came back and now I actually exercise at a low safe level but still find myself often house bound or on the couch, but I have a life.

I had to have a 2nd heart surgery and was forced off of my cocktail mix. I was warned I would relapse but I pretended I was cured in my mind and accepted that risk. I made it 10 months off of my 3 drug cocktail mix when I experienced the worse relapse ever to 100% couch bound.

I reloaded LDN and Immunovir along with a safe exercise program on my back for not more than 3 minutes at a time and a capped heart rate of 110. A few months later IV IgG was added instead of the Valtrex. I remain at a 6 on a scale of 10, when for years I was a 3. 6 provides me with a quality of life I had not had and allows me to care better for myself and my child instead of my child caring for me!
IgG is expensive and LDN and Immunovir is dirt cheap. So it makes easy sense for a study to be done for the latter two drugs.

[…]
Subject: Re: ME/CFS and LDN

Hi […]:
In response to your outreach: Yes, I have CFS and have been taking LDN since February of this year. I am 61 years old. Am also dealing with recurring stage IV colorectal cancer and started the LDN primarily for that and noticed a decrease in CFS symptoms. I wish you the best and thank you from the bottom of my heart for the work you do on behalf of LDN.

[…]
Subject: MECFS RFI New Research Strategies

Attached is my response to your RFI issued on May 24, 2016.

To: The Trans-National Institutes of Health (NIH) ME/CFS Working Group

Re: Response to Notice NOT-NS-16-024; Request for Information: Soliciting Input for New Research Strategies for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)

I am […] from Massachusetts and an MECFS patient for 31 years. I was primarily bed and house bound from 1985-1990, ages 32-37, the prime of my career and life. I lived with and suffered from over 75 symptoms that I personally documented, because there was no real support from the traditional medical community. From 1990-2006, I very slowly regained fragments of my health through alternative and complimentary approaches to healing. Nearly all help I received was out of pocket expenses.

In 2004, I was introduced to yet another “alternative”, by 2005, I was noticing significant (to me) and consistent improvements. In early 2005, I decided to engage with this program by totally changing what I ate. By 2006, I was able to board a plane to California to go learn more for 6 days. This was like climbing Mt. Everest for me and I returned with knowledge that I believe could help many with this illness. It is not a silver bullet but the quality of my life has improved by leaps and bounds compared to what I was dealing with: And it is based in sound science not theory.

I would like to see an alternative and complimentary approach to research for MECFS incorporated into your “New Research Strategies” based on the science I have learned. I have documented much of my recovery process.

I believe that with the support of NIH and other government agencies, we could cause improvement that could be studied by our researchers that would lead us much closer to resolving the MECFS puzzle.

I have run out of money to continue my progress, but with research focusing on this approach, I feel real progress can be made and validated.

The approach that I am writing about is based on the research of Robert O. Young, PhD and the science behind his pH Miracle program. NOT ALL pH/ALKALINE Programs are the same and some are truly harmful based on assumption and incorrect conjecture, not real science.

What is needed:

1. An environment of full support for this program
2. Lab tests to follow the progress using reference ranges that reflect the alkaline design of the inner terrain
3. Nutritional Microscopy Sessions to track progress at the cellular level
4. Medical oversight by physicians willing to explore and blend their current knowledge with this protocol

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[…]
Subject: MECFSRFI 06242016

MECFSRFI@mail.nih.gov

To: The Trans-National Institutes of Health (NIH) ME/CFS Working Group

Re: Response to Notice NOT-NS-16-024; Request for Information: Soliciting Input for New Research Strategies for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)

Dear Working Group:

The following is my response to NOT-NS-16-024; Request for Information: Soliciting Input for New Research Strategies for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS).

I am not a researcher or clinician, so my ideas may not be as fully developed, supported and documented as you would like, but please give them some consideration anyway. Perhaps someone else has had the same ideas but expressed them better.

Emerging needs and opportunities that should be considered as new ME/CFS research strategies are developed:

Synergy between the NIH's intramural study and Dr. Ron Davis's ME/CFS Severely Ill-BIG DATA Study (Open Medicine Foundation). In the NIH study, numerous "samples" will be collected from 40 well-characterized moderately ill ME/CFS patients and 40 controls. A variety of sophisticated tests will be run on these samples. In the Severely Ill Big Data study, numerous samples will be collected from a comparable number of well-characterized but severely ill patients and controls, and again, a variety of sophisticated tests will be run on these samples. Why not exchange whatever samples can be shipped so that at least some of the same tests can be run on both moderately ill and severely ill patients? This may be a once-in-a-lifetime opportunity and to let it pass for lack of funding to carry it out, or because of bureaucratic restrictions (Dr. Davis' study is privately funded), would be both wasteful and shameful. Please figure out a way to make this

happen, either now or in the near future (if samples can be frozen and used later, and the tests would still be valid).

Challenges or barriers to progress in research on ME/CFS:

The main barrier in my opinion is the lack of understanding and respect that this disease has been accorded in the past. Clinicians and researchers will not pursue studies on a disease that is blamed on the patient's attitude. Interest and participation in ME/CFS activities and treatment of patients with ME/CFS has been viewed as a "career-ender." Most medical students and residents are not taught about ME/CFS. Some major medical journals will not consider publishing papers on ME/CFS. Funding for research on ME/CFS has been miniscule. This has been a self-reinforcing cycle. ***The only way to break out of this is a determined and very public shift in attitude toward the disease*** (for which the groundwork has been laid by the IOM and P2P reports) ***supported by a large increase in funding for research***. If there is money, researchers and deans of medical schools will follow the dollars.

Gaps and opportunities across the research continuum from basic through clinical studies:

One very obvious opportunity to fill gaps is to create a network of Centers of Excellence for ME/CFS, as recommended by the Chronic Fatigue Syndrome Advisory Committee (CFSAC) at the May 17-18, 2016, meeting. A very well researched and supported proposal was presented there, so I will not repeat the main points.

[…] (but writing as an individual); we would very much like to see one of these Centers in Massachusetts, or at least in New England. Boston is a medical mecca for every other disease and a wasteland for ME/CFS (but also consider central MA/UMass Medical School and CT/Yale-New Haven as locations). There are a few researchers who are directly involved ME/CFS, but also a large number of excellent researchers who are investigating aspects of illness which are related. We have many ME/CFS patients here who could be recruited for studies, and we sorely lack access to good clinical care throughout Massachusetts and New England. We have many research hospitals and a number of medical schools who would most likely be interested if there is start-up money available. Our Association would be available to help in whatever way possible, particularly with outreach to patients.

Thank you for your consideration and your service.

[…]
Subject: survey response

Thank you for taking the time to help us with this huge issue of the disease ME/CFS. As a patient in response to your request for information, I think the best thing for me to do is share my own personal story and struggles that I have dealt with because of this disease. I am confident you will be able to see the things that need to be prioritized... intense widespread medical community education and communication, plus public awareness and education with extensive positive media coverage emphasizing the physiological reality and seriousness of this devastating disease. And the need for people to know the truth about the false stigma that everyone believes, but is NOT correct. We are legitimately SICK and we deserve respect, support and help! But, most importantly, the overwhelming need for proper research and funding.

I have attached some documents that I have put together slowly over the past few years for various reasons. I hope they will be helpful. I would also be happy to answer any questions you may have.

Thanks again!!

I pushed myself for at least 2 years trying to work a full time job, telling myself my health issues were 'in my head' because I wanted to be normal, while my body was continuing to break down. I finally had to quit 3yrs ago (May 2013) because my health had steadily declined and I literally felt like I was pushing myself to death, but I was still in denial until about November 2013. I was previously a Business Office Manager making $16 an hour. I have since lost my house I lived in for 20yrs and my new car. I had a 740 credit score and now I am filing bankruptcy. It took me 3yrs to get my disability. Plus I lost most of my "friends". I have been snubbed, looked down on condescendingly, and been called crazy. I have been to over 20 doctors, including going to KU Med Center and Mayo Clinic. BUT…by doing online research and asking questions (which took me 2yrs because of my illness and cognitive issues) I ended up going to Dr. Kaufman at Open Medicine Clinic in California. The doc knew what to look for, did tons of blood work and is treating my deficiencies... high ammonia, histamine, and viral counts, low NK cells, hormones, Vit D, and potassium. He also put me on low dose naltrexone. My medications cost me $400 when I only get $850 for disability. Plus, because many treatments for my disease are considered experimental, my insurances won't pay for them. I had to pay $2000 for 2 blood tests and I have to pay $450 for a doctor consult. Plus we have had to pay numerous travel expenses. My husband works two jobs and has ended up in the hospital twice himself because of it. It is difficult enough having to deal with constantly feeling ill, but then there is the added of stress of not being able to get proper medical attention or even understanding, people not believing you, and having almost no support with anything at all. Try to imagine how would you feel if you KNEW something was physically wrong with you but no one could help? And how would you feel if you had a serious disease, but instead of getting sympathy you get ignored or even scoffed at? This disease is real. It is hell.

Life with ME/CFS by […]

So sad that I have to be willing to pay to gain understanding.

So sad that I see sympathy for hurting animals but none for me.

So sad that people are willing to help a stranger but not a friend.

So sad that pennies can be dropped in "help me" jars at convenience stores but I'm just ignored.

So sad that this disease has such a false stigma that people don't even want to be associated with me.

So sad that there is such a waste of life and no one seems to care.

SHAMEFUL and SINFUL that people aren't even willing to listen or learn.

12/2002 Unusual dizzy spell at Sunset, my job was to assist in nurses office, doctor diagnosed ear infection but not sure if I was actually seen, no pain and relieved with antibiotics

2003 Fatigue, food sensitivity begins right after the dizzy spell incident

4/2003 strep infection

2004-2008 Mold exposure

7/2004 tooth infection

11/2004 Root Canal, epinephrine sensitivity, slept for 2 days

2005 Candle sensitivity begins

-----Fatigue/unusual illness issue begins, affected by anything causing weakness, especially hormones

11/2005 reaction to Omnicef

12/2007 noticeable increase in fatigue, started going to bed at least 2hrs earlier

1/2007 -3/2007 Mold in house

2/2007 Reaction to erythromycin, major drop in sodium, hospitalized

~Since approximately 2007 I have been on occasional daily doxycycline, also numerous other times for skin and sinus infections

2010 -2013 fatigue and symptoms extremely noticeable and steadily worsening, mentioned in work evaluation in 2011, should not have been working after approximately Spring 2012, couldn't get through the day without naps, several schedule adjustments and use of sick time, many times fell asleep right when I got home, and sometimes went to bed at 6pm (incident falling asleep in my car at work and not being able to drive home, April 2012), many times my family would have to

come get me because I couldn't drive, felt completely drained by about 3pm even with naps and asked to have schedule changed early 2013 but was refused by new supervisor

11/2009 to present Dr. Morgan, gynecologist, Salina KS, uterine fibroids

2/2012-6/2012 Dr. Gomendoza, endocrinologist, Wichita KS, extensive blood work, dexamethasone suppression test

5/2012 Dr. Isaac, neurologist, Hutchinson KS, Electromyography showed muscle weakness, I was ill that day, referred to KU Med Center

12/2012- 5/2013 KU Med Center, Kansas City KS, several trips, narcolepsy/hypersomnia diagnosis, doc just wanted to continue trying different meds and I kept having reactions to each

Early 2013 trip to ER when ill, blood pressure 225/150

9/2013 to present Drastic increase in all symptoms, loss of job, pursuing diagnosis and disability, loss of home and good credit

11/2013 – 3/2014 ~3 trips to Mayo Clinic, Rochester MN, numerous docs seen and tests done, hypersensitivity diagnosis, CFS & fibromyalgia diagnosis, they wanted to push exercise and CBT, which I had already been doing for years but continued to worsen

First part of 2015 Periods of being bedbound

I continued to see my GP through all this but no doc was truly able to help until I met Dr. Kaufman. Dr. Gomendoza actually refused me services in late 2015. I only needed him to order a test that Dr. Kaufman had requested for me to have done locally so I wouldn't have to travel back to California. I had also sent Dr. Gomendoza my lab results so he could see my abnormalities, but he still refused.

3/2015 to present Dr. Kaufman, ME/CFS/SEID specialist, Mountain View CA, intestinal malabsorption (SIBO), blood results show low natural killer cells, viruses present, gene mutations, abnormal hormone and vitamin levels, past Epstein Barr infection …all factors that are studied in ME/CFS/SEID

Present… I am slightly improved and able to function better. At least I am only bedbound occasionally as long as I pace myself properly. But some things make me extremely ill, like weather changes in Kansas, or increased allergens or illness. When

a cold front comes thru I can be in bed for 3 days with even more extreme fatigue, dizziness, pressure headache, weakness and shaky. And my physiological abnormalities still persist even with treatment. I have low NK cells, high immunoglobulin E, histamine, ammonia and viral counts, low hormones and vitamins, and persistent recurring infections such as SIBO, sinus and skin infections.

Prescription~

Linzess 290mg x2 daily

Valacyclovir HCL 1gram x2 daily

Lisinopril 10mg, 1 daily

Singulair 10mg, 1daily

Advair 1 inhalation, 1 daily

Lactulose 15 ml x1 daily

Pyridostigmine BR 60mg x3 daily

Proair inhaler 90mcg as needed

Naltrexone 4.5mg daily

Dexamethasone .5mg daily

Hydrocortisone 5mg x3 daily

Hydrochlorothiazide 25mg daily

Phentermine 18.75mg daily

Xifaxan 550mg x3 daily

Flagyl 500mg x3 daily

Non-prescription~

ImmunoProRx 1-2 scoops daily

Zantac 150mg x2 daily

Allegra 180mg, 1 daily

Zyrtec 10mg, 1 daily

Flonase 1 spray each nostril, 1 daily

NeuroProtek x 5 daily

Iberogast 20 drops x3 daily

Milk of Magnesia 8 Tbsp x1 daily

Fiber Choice

Acidophilus 20mg, 1 daily

DHEA 25mg, 1 daily

Methyl B12 5000 micrograms

Methyl Folic Acid 15mg

Vit D 2000 IU

Vitamin & Fish oil

Potassium

Tylenol 500 mg as needed

Ibuprofen as needed

Correctol as needed

[…]
Subject: My Response to NIH RFI

Dear Trans-National Institutes of Health (NIH) ME/CFS Working Group:

For background on my responses to your request for information in NOT-NS-16-024, please read this 2014 letter to the Institute of Medicine: http://paradigmchange.me/wp/severe/ Signed by nine severely ill ME patients, the letter lays out the needs and requests of severe patients.

Emerging needs and opportunities that should be considered as new ME/CFS research strategies are developed:

I call on NIH to study the sickest ME patients, those who are bedbound and unable to carry out basic activities of daily living such as walking to the toilet, bathing, dressing, and even feeding themselves. For too long, we have been excluded from research studies because of ignorance, bias, and a refusal to accommodate our physical limitations. The Open Medicine Foundation's current study of the severely ill is the first of its kind. (Notably, NIH twice refused to fund the OMF's grant applications.)
We should be included in all research studies, and at least half of all studies should focus entirely on the severely ill.
Excluding the sickest patients from studies is like completely ignoring Stage 4 cancer patients while studying only Stage 1 cancer patients. All scientists studying human disease deserve subjects with the most pronounced pathologies.

Challenges or barriers to progress in research on ME/CFS:

Barriers include ignoring severely ill ME patients; pretending we don't exist; falsely claiming psychiatric etiologies of our disabilities; claiming NIH is incapable of sending phlebotomists into patients' bedrooms; and lumping us, via vague case definitions, with people who are virtually indistinguishable from healthy controls and the mentally ill.

For a mere $7 million—a small fraction of what it spends each year on multiple sclerosis—NIH could study 100 bedbound ME patients across the US, collecting massive amounts of data, as the OMF is doing.

Any bedbound survivors of the Lyndonville and Lake Tahoe 1980s epidemics would make especially good subjects.

Please note that severe patients cannot participate in any type of exercise testing.

Gaps and opportunities across the research continuum from basic through clinical studies:

Dr. Francis Collins has a wonderful opportunity to step forward and end bias toward severely ill ME patients. Because of false beliefs among doctors and the general public, we with severe ME struggle to get medical care, government benefits, services like homecare, and respect from our families and friends.

Dismissed as lazy or head cases, bedbound ME patients are among the most maligned segments of American society.

I call on Dr. Collins to hold a press conference devoted to severe ME patients, using Whitney Dafoe as a case study. Unable to eat, Dafoe has been on total parenteral nutrition for years. The "CFS" construct has so trivialized my illness that most doctors are shocked to learn that up to 25% of patients are bedbound.

At this press conference, I also ask Dr. Collins to explain why NIH has allotted just $5 or $6 million per year to research such a disabling illness—less funding than hay fever receives—for the past thirty years.

[…]
Subject: Response to Notice # NOT-NS-16-024; Request for Information: Soliciting Input for New Research Strategies for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)

To: The Trans-National Institutes of Health (NIH) ME/CFS Working Group

Re: Response to Notice NOT-NS-16-024; Request for Information: Soliciting Input for New Research Strategies for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)

Dear Working Group:

The following is my response to NOT-NS-16-024; Request for Information: Soliciting Input for New Research Strategies for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS). Please excuse the fact that I am too sick to go into detail regarding each recommendation. Be assured I am a long-time patient and that I have a quite thorough knowledge of the history of ME including how it has been dealt with by NIH (for a non-employee of NIH) and I have carefully considered my responses and I strenuously urge you to seriously consider and to implement them.

Emerging Needs and Opportunities:
- None identified as such

Challenges and Barriers to Progress (in descending order):
- The Canadian Consensus Criteria ("CCC") and International Consensus Criteria ("CCC") should be used in all NIH studies (alongside the Centers for Disease Control ("CDC") Fukuda CFS Case Definition ("Fukuda"), just for purpose of reference to past studies, almost all of which have used Fukuda, with the understanding that Fukuda is not a valid definition).

- Misinformation disseminated by NIH and CDC including on their websites.

- Failure to have experts (clinical, research and patient) in the disease deciding all aspects of the how ME('cfs') is dealt with by the public health service including NIH. For NIH this includes these experts being involved in drafting and implementing a strategic plan, making grant funding decisions and drafting information distributed by NIH on the disease, including on the NIH website.

- Funding of unhelpful or harmful studies (studies that don't add much to the knowledge base or are actually pseudo-science) by NIH including psychological and psychiatric studies (including Cognitive Behavioral Therapy and Graded Exercise Therapy studies), studies by biased researchers (e.g. Suzanne Vernon) and studies using invalid definitions of the disease such as CDC Fukuda and CDC Reeves while failing to use valid definitions, namely CCC and ICC.

- Use of the misleading term "CFS," as opposed to the valid, longstanding nomenclature "ME."

- Gross lack of funding (and sense of urgency).

Gaps and Opportunities:
- Full funding of all of Prof. Ronald Davis' work at Stanford University and Open Medicine Foundation.
- Need a coordinated strategic research plan drafted by clinical, research and patient experts.
- Biomarkers research
- Neuro-inflammation research

[…]
Subject: MECFSRFI

To the Working Group:

We are the parents and caregivers of our 27 year old son who is housebound because of ME/CFS.
Our son is a graduate of Stanford University, has studied at Oxford University, and was attending law school at the University of California, Davis when he became ill. He was also a triathlete.
He was on a career path to law enforcement/public safety, where he would have been a major contributor to the well-being of our society. He contracted a flu-like illness, has never recovered, and his health has continued to decline.

As you know, research in this field has been shockingly limited. But what if the world's greatest virus hunter and his team at a prestigious Ivy League University were interested in using their expertise to solve this disease? THEY ARE. Ian Lipkin and the team at Columbia's Center for Infection and Immunity have said that they can solve ME/CFS within 3-5 years given appropriate funding. This would miraculously improve a great many lives. PLEASE FULLY FUND Lipkin, Hornig studies at CII.
ME/CFS research should be funded at a level commensurate with disease burden. At a very minimum, $250 million dollars toward understanding causation and developing treatments is desperately and immediately needed.

[…]
Subject: Response to Notice NOT-NS-16-024

To: The Trans-National Institutes of Health (NIH) ME/CFS Working Group
Re: Response to Notice NOT-NS-16-024; Request for Information: Soliciting Input for New Research Strategies for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)

To Our Working Group:

Following is my long response to **NOT-NS-16-024; Request for Information: Soliciting Input for New Research Strategies for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)**. I am too ill and brain fogged to edit my work and the deadline for this is tomorrow. If there isn't time to read it, my main requests are numbered and emboldened. There is also an asterisked note at the bottom about a 15 part article I'd like everyone to read at some point when you have time. It is long, but well written and an important look at what can and is happening Don't assume you know all about this already (unless you've read it).

[…]

1) Finding BIOMARKERS or other relatively non-invasive diagnostic tests is my first priority.
I've been ill with ME/CFS for 51 years and believe my son, who lives with us under my care, has it too. I haven't been willing to subject my bright but increasingly disabled 35 year old son, who has been ill for 25 years,* to the serial humiliation I experienced before and after my ME/CFS diagnosis until a) definitive relatively non-invasive biomarkers are found, b) adequate treatment with minimal side effects, and c) appropriate education of all practitioners are in place.

[…]

Epilepsia. 2011 Jan 26. doi: 10.1111/j.1528-1167.2010.02927.x. [Epub ahead of print]
Comorbidities of epilepsy: Results from the Epilepsy Comorbidities and Health (EPIC) Survey.
Ottman R, Lipton RB, Ettinger AB, Cramer JA, Reed ML, Morrison A, Wan GJ.

Purpose: To estimate the prevalence of neuropsychiatric and pain disorders in adults with epilepsy in the United States. Methods: In 2008, an 11-item survey including validated questions to screen for a lifetime history of epilepsy was mailed to 340,000 households from two national panels selected to be generally representative of the noninstitutionalized U.S. population. Information on epilepsy and other disorders was collected from 172,959 respondents aged 18 or older. Propensity scoring was used to match respondents with and without epilepsy on baseline characteristics and risk factors for epilepsy. Prevalence ratios (PRs) of comorbidities in respondents with epilepsy were calculated using log-binomial generalized linear models.

Comorbidities were categorized as neuropsychiatric (anxiety, depression, bipolar disorder, **attention-deficit/hyperactivity disorder,** sleep disorder/apnea, and movement disorder/tremor), pain (migraine headache, chronic pain, **fibromyalgia,** neuropathic pain), and other (asthma, diabetes, and high blood pressure).

Key Findings: **Respondents with self-reported epilepsy were more likely (p < 0.001) than those without epilepsy to report all six neuropsychiatric disorders (PR from 1.27-2.39), all four pain disorders (PR 1.36-1.96), and asthma (PR 1.25)**.

Significance: Neuropsychiatric conditions and pain disorder comorbidities were reported more often in individuals with self-reported epilepsy than in those without epilepsy. Identification of these conditions is an important consideration in the clinical management of epilepsy.

Wiley Periodicals, Inc. 2011 International League Against Epilepsy.
PMID: 21269285 [PubMed - as supplied by publisher]

[…]

2) Fund ME/CFS research by Dr. Michael B. Bracken Ph.D., MPH FACE Yale School of Public Health. Let him know such work might be funded, or contact him directly for help. I don't know whether he's aware of our disease at all.
I watched Dr. Bracken's NIH Robert S. Gordon Lecture: "Biomedical research: increasing value, reducing waste" https://videocast.nih.gov/summary.asp?Live=18959&bhcp=1 on April 20, 2016 on the NIH website and was struck by how important his input might be if the PACE study's methodology (or better still, ALL studies based on the bias that our illness is psychosomatic, leading to CBT and GET recommendations which have harmed so many of us) were examined by him and/or his department and reported on generally - to the NIH, the *Lancet* (which has published his work) and any other journals as a perfect storm of harm to our entire ME/CFS population.

[…]

I thought of emailing Dr Bracken directly […]as his interests http://publichealth.yale.edu/people/michael_bracken.profile seem to encompass our situation, especially now that we've been moved out of the Office on Women's Health. The PACE study is still being

reported as real news and I haven't seen any retraction or response from the *Lancet*. Anything that might further validate the questions David Tuller raised might help us. An expert's assertion, publicized, might mitigate the harm we're still being dealt which has already replaced 2015's IOM and P2P news in the minds of many.

3) Education Education Education - NOTE: NINDS needs to list our illness in their Disorder Index.
Are you aware that NO version of our illness is currently listed under the alphabetical listing of disorders (Disorder Index) at the NIH's National Institute of Neurological Disorders and Stroke website? http://www.ninds.nih.gov . Nothing for ME, ME/CFS, CFS, CFS/ME Chronic Fatigue Syndrome, CFIDS or SEID. ...NOTHING...

[...]

4) Could NINDS agree to become a resource for us? for our doctors? for training professional practitioners and therapists still in school? for continuing (regularly updated) education for the already practicing in all medical, dental and healing arts fields? There are reasonable self-protective explanations for waiting to get officially diagnosed until something useful will come of having a diagnosis that won't just alienate our practitioners. It would be good for NINDS to know how many of us there truly are, but until more practitioners are adequately educated, it is not in our interest to pursue a dx. Once there's a test that will prove to practitioners we're not all wing-nuts, we might be more willing to be exposed and counted. It is also not in our interest to rely on Big Pharma to find and market cures once diagnostic criteria are established, I'm far from certain we can or should trust these companies to act responsibly. We are not adequately protected.* (please see paragraph below my signature)

[...]

Thank you for your consideration and willingness to allow input from patients. If you skipped most of it, that's OK. If you didn't, I salute you. If one person reads it, that's great. It is tremendously important to us to have our experience respected after so many years of being discounted and ignored. Sometimes that gets us stirred beyond reason and we want to tell you everything we can think of that might add breadth to your understanding of what we face every day. We don't get out much. Do save the article I mention below for when you have time. It's important.

*There was a beautifully researched 15 part article by Steven Brill published last year as part of the *Highline* (Miracle Industry) series of the *Huffington Post* called "America's Most Admired Lawbreaker" (Johnson & Johnson) http://highline.huffingtonpost.com/miracleindustry/americas-most-admired-lawbreaker This was as shattering an exposé as Wendell Potter's book *Deadly Spin* about common for-profit Health Insurance Companies practices at the time. Potter had been a VP at Cigna. His testimony before Congress may have helped pass the ACA. I believe the full Brill article should be required reading for everyone at the NIH and publicized widely in our country describing J&J's (and by extrapolation other for-profit Big Pharma) marketing (off label) of Risperdal® (risperidone) while under patent to children and elders and the minimal effect on them of their loss in court that showed how little they value the lives and health of their consumers and how small an impact their loss in court had on their bottom line - "just the cost of doing business".

I believe the work to find a cure for us needs to be started by non-profit and government sponsored researchers, once criteria can be agreed upon.

[…]
Subject: LDN Works Well for My CFS/ME

I've had CFS/ME for 35 years and MS was added to my diagnosis 13 years ago. I've been on 4.5 mg. LDN for 6 months and it's helped me immensely.

My energy and strength are much better, my cognition and mood are improved, and my insomnia is much improved. My balance and coordination are also much better. Because of LDN I was able to get off the 20 mg. of Ambien I was taking and will soon be completely off an immune-suppressing drug I was on. I couldn't do without LDN.

[…]
Subject: Comments on NIH research on ME/CFS

I have already sent in my formal comments, but I forgot to add the most important one!

Every year, CFSAC creates a list of recommendations for the Secretary of HHS. I know that they go to a lot of trouble to do this. Most of these are very good recommendations. Please go back and compile them and take them into consideration. Thank you.

[…]

[…]

These are the corrected comments - I added number 6, because I think it is important.

————————

Re: Notice Number: NOT-NS-16-024

1. It is critical that we find a way to diagnose the 850,000 Americans with ME/CFS who have no diagnosis today.

In 1988, after a series of cluster outbreaks across the nation, US experts attended a meeting put together by NIH and CDC to give a name to the disease that had been called CEBV. They chose "chronic fatigue syndrome," or CFS.

That was nearly 30 years ago. In the intervening time, CDC has so misjudged the prevalence, severity, and urgency of the need to understand and control this disease, that today, with a national prevalence of at least 1 million adult Americans, CDC admits that only 15% of patients even have a diagnosis.

That tells me that the decision to focus on "fatigue" was a disaster. And I wonder where the other 850,000 Americans are. Since this is an equal opportunity disease - but that's not true of those who are diagnosed - the population of undiagnosed patients with this disease is going to be skewed towards people of color, and I also suspect people of lower income. They are suffering alone.

2. We need to go back and investigate the phenomenon of cluster outbreaks.

Once EBV was dismissed as a possible cause of this disease (prematurely, as it turns out), all interest in the possibility of cluster outbreaks disappeared. Yet many patients experienced this disease in what appears to have been a cluster outbreak. CDC and NIH responded to the experience of patients by saying (to me, personally), these were not outbreaks of disease - they were outbreaks of diagnosis. It was the belief of Drs. Straus and Reeves that since this was obviously not a disease that was in any way contagious (decided in Washington and Atlanta, without really studying patients or statistics), then the evidence of outbreaks must be cases where patients found a friendly doctor willing to confirm their belief that they had a "real" illness.

That goes against the evidence.

More important, where we are today, I believe there has been a new set of cluster outbreaks. Why? Because I have been contacted by patients for twenty years, and starting around 2010, I began to be contacted by young people in their 20s and 30s and the parents of teenagers. They had become sick SINCE 2010. If there is indeed a new set of cluster outbreaks, let me suggest that we start to get control of it by looking at cases of EBV and asking for evidence of the long-run health of patients.

3. We need biomarkers now.

Both items 1 and 2 are direct consequences of the absence of biomarkers. It is hard to find out how many people have this disease when you are reduced to questionnaires. It is hard to find out whether there are cluster outbreaks (or outbreaks of diagnosis) without biomarkers.

I have had specialists who have been using biomarkers for two decades. I see no reason to have to start from scratch. We will at least catch a significant subset of patients. NIH needs to look at natural killer cell function as both a marker showing THAT you have The Disease, and also a marker of the SEVERITY of The Disease.

The 37kDa Rnase-L was a useful biomarker for some specialists until we lost the ability to send blood to Belgium. A new lab was started in the US, but the group it was connected to had problems and it closed. The patent was owned by Temple University, but they have said they do not care if they are reimbursed - anyone may use it.

Dr. Robert Suhadolnik, now deceased, did a study in the 1990s of 100 patients from the Incline Village cluster outbreak, 100 patients with fibromyalgia but no symptoms of CFS (Fukuda 1994), 100 patients with major melancholic depression (at the urging of Dr. Straus), and 100 controls. 98 of the 100 patients from Incline Village had the defective protein. Only 2-3% in each of the other three groups did. That is profound, but it was ignored.

In the meantime, Drs. Catherine Bisbal and Luc Montaigner tested patients with PVFS in France and Belgium, and had similar results. This is even more fascinating given that Dr. Suhadolnik was using an electron microscope, but Drs. Bisbal and Montaigner weighed the protein (hence the name 37kDa Rnase-L).

So two different sets of researchers, on two different continents, using two different methods, found the same thing. The researchers switched blinded samples and got them all right. So I think the 37kDa Rnase-L biomarker is worthy of consideration of an important characteristic of at least a subset of patients.

So many different specialists have worked with cytokine profiles that I can't even list them all here. But abnormal cytokine profiles are another area for biomarkers.

As I write, biomarkers are being proposed by researchers from Griffith University in Australia to Stanford and Columbia Universities, to the Simmaron Foundation in Incline Village, NV, the NOVA clinic in Davie, FL, and many more. We need a systematic way to look at the existing evidence and start using biomarkers to find at least a subset of patients.

4. We need treatments now.

Ampligen is already available and it has been shown to lead to dramatic improvements in 30-40% of patients. I am one of them. We ask that NIH help us get this drug provisionally approved. The company does not have the money to do another large double-blind study. I would contribute my own money towards such an effort. In the meantime, the drug needs to be made more available because of the severe geographic restrictions it puts on those patients (such as myself) who would be vegetables without it.

Rituximab needs to be researched. It has shown promise in Norway.

Patients have improved on gamma globulin and on antivirals, specifically Valcyte and Vistide.

We need to find other drugs to repurpose. I believe there also needs to be a push to develop more antivirals, period, and more pharmaceuticals targeted to the immune system.

5. We need to pay more attention to viruses.

From the first diagnosis of atypical polio in 1934 (which became Myalgic Encephalomyelitis in the British Commonwealth nations and Epidemic Neuromyesthenia in the US in the 1950s, CEBV in the 1980s, and then CFS in 1988), the evidence has strongly suggested that the disease is connected to a virus. Which virus? If you don't test people, how do you know? Now that there are better methods for finding viruses, we need an all-out push to find the viruses behind cases of ME/CFS in the United States. (In my own case, both HHV-6A and CMV were in my spinal fluid in 2009, during a 2-year period when I could not get Ampligen.)

The earliest viruses suggested were those in the polio family, now called enteroviruses. Coxsackie B was considered a prime candidate for the culprit in the UK (before the psychiatrists got involved), and it has also been found in patients in the US. I also know patients whose illness began with an episode of adenovirus infection.

However, in the US, the viruses most commonly found are EBV (particularly at the start) [HHV-4], CMV [HHV-5], HHV-6A, HHV-6B, and HHV-7.

6. Pay attention to 12 years of CFSAC recommendations.

Every year, CFSAC creates a list of recommendations for the Secretary of HHS. I know that they go to a lot of trouble to do this. Most of these are very good recommendations. Please go back and compile them and take them into consideration.

7. Don't start from scratch. Use existing research.

Let me suggest the numerous websites that I referenced in my May 12 blog, "ME is not a mysterious disease." It would take too much space to write it all down here now!

http://slightlyalive.blogspot.com/2016/05/for-may-12-2016-me-is-not-mysterious.html

———————————————————

This spring I lost 3 good friends whom I had known for 20 years as fellow patients with this disease. One had been sick for 32 years; another died at 40 from breast cancer because her ME-battered body could not take the necessary chemotherapy regimen; one died in the hospital of pneumonia, again because his body was so weakened. I look at a new generation of patients who got this disease as teenagers and wonder - will they still have it in their 40s, as is true for many patients I know? Are they doomed? Please stop this rolling epidemic now, because more and more people have it every time there are a series of outbreaks.

I thank you for the opportunity to comment, and I am hopeful that with the will to do so, NIH can stop this unending tragedy.

[…]
Subject: RE: Notice Number: NOT-NS-16-024 - Soliciting Input for New Research Strategies for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)

- Re: Request for Information: **Soliciting Input for New Research Strategies for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)**
- Notice Number: **NOT-NS-16-024**

Hello:

1. **Disease definition**: Use either the International Consensus Criteria or the Canadian Consensus Criteria.
2. Retire all usage of the CDC criteria including Oxford, Fukuda, and Reeves.
3. Study patients with severe and very severe ME/CFS
4. Study patients who have had ME/CFS for more than five (5-10) years.
5. NIH must partner openly and transparently with stakeholders
6. Conduct a comprehensive, "Big Data" analysis on severely ill ME/CFS patients with the goal of finding sensitive and distinctive molecular biomarker(s). The molecular biomarkers that reflect the symptom mechanism are expected to be strongest in the approximately 25% of ME/CFS patients who have a severe form of the disease and are home-bound or bedbound.
7. Identify biomarkers that may be found in the blood, saliva, sweat, urine and feces.
8. Look for diagnostic biomarker(s) in the DNA, RNA, proteins, carbohydrates or metabolites, and from an associated microbe in or on the body.
9. Examine biomarkers that go up or down with symptom severity to provide targets for treatment trials.
10. Conduct comprehensive/extensive testing of severely ill patients. By thoroughly checking blood, urine, and other body products, look for biological abnormalities that could explain the debilitating symptoms.
11. **Research Tests**
    a. RNA Gene Expression – PBMCs
    b. RNA Gene Expression – NKs
    c. RNA Gene Expression – Monocytes
    d. RNA Gene Expression – T-Cells
    e. RNA Gene Expression – B-Cells
    f. RNA Gene Expression – Macrophages
    g. RNA Gene Expression – Dendritic Cells

h. MicroRNA in Plasma
i. Proteomics
j. Cell-Free DNA
k. Whole Genome Sequencing
l. Whole Exome Genome Sequencing
m. Mitochondrial Genome Sequencing
n. Mitochondrial DNA/Nuclear DNA Radio
o. HLA DNA Sequencing
p. WBC density
q. Autoantibody panel
r. T-cell Repertoire DNA Sequencing-Stanford
s. T-cell Repertoire DNA Sequencing-Sequenta
t. CyTOF Standard Panel
u. CyTOF Additional Panels
v. Pan Viral Panel
w. Serum Cytokines
x. Ceres Nano Lyme
y. Microbiome – stool
z. Metabolomics – stool
aa. Metabolomics – plasma
bb. Metabolomics – urine
cc. Heavy Metals – blood
dd. Heavy Metals – urine
ee. Mycotoxins by Magarray

12. Clinical Testing

a. Acylcarnitines
b. Ammonia
c. Bartonella extended cx
d. Biotin (Vitamin B7)
e. CBC (Complete Blood Count)
f. Chemistry Comprehensive Panel
g. Creatine Kinase
h. Copper
i. C- Reactive Protein
j. Cysteine
k. Folate
l. FSH (Follicle-Stimulating Hormone)
m. LH (Luteinizing Hormone)
n. Estrogen
o. HbA1C (Hemoglobin A1c)
p. Homocysteine
q. IgG Subsets
r. Lactate
s. Lyme Serology with reflex Western Blot
Lymphocyte Subsets
t. MMA (Methylmalonic Acid)
u. MTHFR Mutations (Methylenetetrahydrofolate)
v. Natural Killer Cell (Count & Function)
w. Organic Acids – urine

x. Pyruvate
y. Serotonin
z. Testosterone
aa. Thyroid Panel
bb. Uric Acid
cc. Vasopressin/ADH
dd. Viral Digital PCR
ee. Viral Serologies:
i. EBV EA (Epstein Barr Virus EA)
ii. EBV NA (Epstein Barr Virus NA)
iii. EBV VCA (Epstein Barr Virus VCA)
iv. CMV (Cytomegalovirus)
v. HHV-6 (Human Herpesvirus 6)
vi. Parvovirus
vii. HHV-7 (Human Herpes Virus 7)
viii. HSV1&2 (Herpes Simplex 1 & 2)
ff. Vitamin B12 (Cobalamin)
gg. Vitamin D25 OH

13. Other Testing/Monitoring

a. Extended EEG
b. Sleep monitoring
c. Fitbit
d. Cognitive Testing
e. Questionnaires – SF36, PROMIS

14. Analysis:

a. Conduct extensive bioinformatics analyses on the data sets. Search for the best combination to generate a diagnostic biomarker set. Because of the large data sets, false discovery is of serious concern. Evaluate the diagnostic molecular biomarker set on different patients with and without ME/CFS to determine sensitivity and specificity.

b. Another problem is the possibility that ME/CFS is heterogeneous, and no biomarker set can be found. Attempt to cluster the patient population into groups and search for a biomarker set in each group. The Immune repertoire of all immune cells may be a useful data set to achieve biological meaningful clustering. It is possible that the repertoire will reflect the initiating event. This approach has been successful for other diseases.

15. Final notes:

a. Please fund the research of Dr. Ronald W. Davis, director of the Stanford Genome Technology Center! Patients are acutely aware that NIH has not funded his research and we patients are deeply and justifiably angry with NIH and HHS about this.

b. We need treatments NOW. I have been ill with ME/CFS for 38 years and home-bound for more than 9 years. NIH and HHS must act with **URGENCY** and **RESPECT** for patients. Employees at NIH and HHS have all the time in the world. ME/CFS patients have lost much of their lives because of decades of deliberate government inaction. Please – help us now.

More notes:

Emerging needs and opportunities:

1. Investigate energy production and recovery mechanisms.
2. Confirm the utility of two-day VO2max cardiopulmonary exercise testing (CPET).

3. Analyze existing samples for biomarker discovery.
4. Undertake a deep dive for biomarker discovery.
5. Conduct an accelerated longitudinal study to elucidate the natural history of ME/CFS.
6. Address the questions of burden of disease and undiagnosed ME/CFS patients.
7. Invest in development and validation of outcomes measures.
8. Fund systems biology and computational biology approaches to pathophysiology.
9. Leverage wearable devices to objectively measure function.

Challenges and barriers to progress:

1. The failure to reach consensus on case definition is a steep barrier to progress across the ME/CFS landscape.
2. More resources and heightened urgency are required to address this public health crisis.
3. ME/CFS patients, researchers and clinicians are not involved in NIH's efforts in a sustained and meaningful way.
4. There are very few ME/CFS researchers in training.
5. Methodological flaws make it challenging to interpret the evidence base.

Gaps and opportunities across the research spectrum:

1. ME/CFS research requires a coordinated, strategic plan.
2. Clinical trials and pediatric research are significant gaps in the current approach to ME/CFS research.

If you have the ability to submit responses to NIH, I strongly encourage you to do so. One of the worst outcomes would be if NIH gets very few responses to this RFI. That could reinforce the view that there are just not that many people interested in ME/CFS research. So if you can send even one specific answer to NIH, I hope you will!

===

Advancing the Research on ME/CFS Action Items Identified in the P2P Panel's Final Report: June 16, 2015
Note: These action items were derived from the P2P Final Report, and are listed in the order they appear in the report. The items have been edited to use active language.

- Shift research priorities to basic science and mechanistic work that will contribute to biomarker and therapeutics discovery (p. 8).
- Answer questions about the pathogenesis of ME/CFS, including roles of pathogenic agents, genetics, and symptom pathways (p. 8).
- Assemble a team of stakeholders (patients, clinicians, researchers, federal agencies) to reach consensus on the definition and parameters of ME/CFS (p. 9).
- Develop a national and international research network to clarify the case definition and advance the field (p. 9).
- Incorporate NIH Institutes and Centers not presently represented into the Trans-NIH ME/CFS Working Group to learn from other disciplines and diseases (p. 9).
- Invest in bench-to-bedside research (p. 10).
- Prioritize the development of biomarkers and diagnostic tests (p. 10).
- Create opportunities for junior and new investigators (p. 10).
- Coordinate research efforts to promote efficiency and effectiveness (p. 10).
- Use public/private partnerships to leverage existing NIH infrastructure and dollars (p. 10).
- Develop valid prognostic tests to guide treatment strategies using genomic, epigenomics, proteomic, and metabolomic strategies to identify critical biomarkers (p. 10).
- Identify gene expression, protein or metabolite signatures to correctly diagnose ME/CFS and distinguish it from other chronic condition (p. 10).

- Stratify patients using physiologic measures, pathophysiology, genome-wide association studies and phenotyping (p. 10).
- Study fMRI and imaging technologies as diagnostic tools and to better understand neurologic dysfunction in ME/CFS (p. 11).
- Link biological samples and de-identified survey data in a registry/repository (p. 11).
- Explore the intestinal microbiome and the effect of the environment and microbiome on ME/CFS (p. 11).
- Conduct epidemiological studies, including incidence and prevalence, risk factors, geographical distribution and potential healthcare disparities (p. 11).
- Analyze previously collected research data to inform trial development and design (p. 11).
- Examine drug therapies for fibromyalgia and other pain-related conditions for effectiveness in ME/CFS (p. 11).
- Leverage existing registries (p. 11).
- Develop diagnostic and prognostic algorithms to identify who will develop ME/CFS after infectious or other triggers (p. 11).
- Conduct "omics"-based drug repurposing and neurobiology studies (p. 11).
- Develop large datasets using bioinformatics techniques and store in a central, publicly accessible database (p. 11).
- Use a systems-level approach to understand how immunologic, neurologic, and metagenomic factors may contribute to ME/CFS (p. 12).
- Define and characterize immunologic mechanisms and pathways associated with disease progression (p. 12).
- Conduct longitudinal studies to explore the possibility of a progressive immune exhaustion or dysfunction (p. 12).
- Study gene expression in identical twins to identify gene expression biomarkers (p. 12).
- Use male and female models to explore the role of gender, X-chromosome genes, and hormones in developing ME/CFS (p. 12).
- Explore how patients' background medications affect function and outcomes (p. 12).
- Encourage studies investigating homeopathy, non-pharmalogic, complementary, and alternative medicine treatments, and biopsychosocial parameters, function, and quality of life (QOL) (p. 12).
- Improve measures to identify ME/CFS while including the patient's voice in patient-reported outcomes (p. 13).
- Develop an ME/CFS methodological workgroup at NIH (p. 13).
- Increase patient involvement in determining priorities for research and care (p. 13).
- Use already well-validated measures such as PROMIS and CESD (p. 13).
- Use a battery of simplified measures (p. 13).
- Leverage the power of other NIH longitudinal studies to better understand ME/CFS (p. 13).
- Use telemedicine or home visits for those unable to participate in clinical trials/treatment in person (p. 13).
- Develop and employ new technologies to address underserved populations and unmet needs (mobile technology, etc) to measure progress and enable communication (p. 13).
- Ensure professional licensing and accreditation agencies use a curriculum that facilitates ME/CFS knowledge acquisition (p. 14).
- Engage with Health Resources and Services Administration (HRSA) to facilitate training (p. 14).
- Facilitate a public-private partnership with professional societies and patient organizations to train and fund health care professionals (p. 14).

- Partner across institutions to advance research and develop new scientists (p. 14).
- Develop a cadre of junior investigators, including women and minorities, using new collaborative models, investigator-initiated studies, career development, and small grant mechanisms (p. 14).
- Create efficiency and co-fund research to promote diversity in the pipeline, eliminate disparities, and enhance the quality of the science (p. 14).
- Create a network of collaborative centers working across institutions and disciplines, including clinical, biological, and social sciences (p. 15).
- Charge the centers to determine biomarkers for diagnosis and prognosis, epidemiology, functional status and disability, patient-centered QOL outcomes, cost-effectiveness of treatment studies, role of co-morbidities, and characterize control and recovered populations (p. 15).
- Establish a central archive of de-identified data and tissue samples from prior and ongoing studies to enable data and sample sharing (p. 15).
- Create a website for patient and clinician educational materials, as well as clinical trial information (p. 15).
- Utilize the NIH Clinical Center for clinical trials and fast-track testing of new therapies (p. 15).
- Improve quality of care by learning from palliative care (p. 15).
- Examine role of self-management techniques as part of a comprehensive treatment plan during and after clinical interventions (p. 16).
- Evaluate multifaceted therapies focused on biomedical and supportive care (p. 16).
- Conduct comparative effectiveness research (p. 16).
- NIH and FDA convene a meeting on the state of ME/CFS treatment (p. 16).
- Retire the Oxford definition (p. 16).
- ME/CFS community to agree upon a single case definition (p. 16).
- Patients, clinicians, and researchers agree on a definition for meaningful recovery (p. 16).
- Use new avenues to fund research (p. 17).
- Develop demonstration projects with CMS and PCORI for patient-centered medical homes for people with ME/CFS, using a comparative effectiveness research framework to determine best evidence-based practices (p. 17).
- Translate best practices to primary care clinicians (p. 17).
- Create quality metrics and a standard of care in collaboration with federal agencies and professional societies (p. 17).
- Form private-public partnerships between federal departments, advocacy groups, and industry (p. 17).
- Monitor progress by convening another ME/CFS Expert Panel in five years (p. 17).
- Federal agencies, clinicians, patients and advocates should consider the IOM and P2P reports together to move the science forward (p. 18).

Thank you.

[…]
Subject: response to RFI

Dear Working Group Members:

I am a 64 year old ME/CFS patient who has been ill for 48 years. My mother, although never officially diagnosed with ME/CFS, was also ill, possibly as early as her teens in the 1940s. I am sorry to say that I am not well enough, or knowledgeable enough, to respond in as much detail as you request, but I will attempt to make a few points.

Pediatric research should be a priority.

But please address also the needs of geriatric ME/CFS patients. If participation on online patient forums is any indication, the elderly and near-elderly population of patients is large. Many of these people have been ill for decades. Is the disease progressive? What palliative care and social support can be offered to them?

Longitudinal studies would be good.

Why in some households are multiple people ill, usually blood relatives but sometimes unrelated members?

ME/CFS patients who are parents have often reported on patient forums that they have autistic children. Also some ME/CFS patients report having grown up with autistic parents (my own father I believe had Asperger's). Research the connection between ME/CFS and autism.
The narrative of this illness has almost entirely been told by affluent, well-educated white patients. More research needs to be done to identify the incidence of illness among the poor and minorities and to address how to help them.

I understand, of course, that basic work such as agreement on a research diagnostic definition and identifying a biomarker or biomarkers has yet to be done and that the federal government must allocate much more money for research, a fair amount, enough to catch up, reparations.
Thank you for offering this opportunity to speak. Thank you for the work you do.

[…]
Subject: RE: Notice Number: NOT-NS-16-024 - Soliciting Input for New Research Strategies for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)

- Re: Request for Information: **Soliciting Input for New Research Strategies for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)**
- Notice Number: **NOT-NS-16-024**

Dear NIH Staff,
I offer the following suggestions for research topics aimed at studying ME/CFS. As the spouse of a ME/CFS patient, I am keenly interested in seeing research advances that will bring better understanding of this disease and lead to effective treatments.
Please consider the following research topics and suggestions:

1. **Disease definition**: Use either the International Consensus Criteria or the Canadian Consensus Criteria.
2. Retire all usage of the CDC criteria including Oxford, Fukuda, and Reeves.
3. Study patients with severe and very severe ME/CFS
4. Study patients who have had ME/CFS for more than five (5-10) years.
5. NIH must partner openly and transparently with stakeholders
6. Conduct a comprehensive, “Big Data” analysis on severely ill ME/CFS patients with the goal of finding sensitive and distinctive molecular biomarker(s). The molecular biomarkers that reflect the

symptom mechanism are expected to be strongest in the approximately 25% of ME/CFS patients who have a severe form of the disease and are home-bound or bedbound.

7. Identify biomarkers that may be found in the blood, saliva, sweat, urine and feces.

8. Look for diagnostic biomarker(s) in the DNA, RNA, proteins, carbohydrates or metabolites, and from an associated microbe in or on the body.

9. Examine biomarkers that go up or down with symptom severity to provide targets for treatment trials.

10. Conduct comprehensive/extensive testing of severely ill patients. By thoroughly checking blood, urine, and other body products, look for biological abnormalities that could explain the debilitating symptoms.

11. Research Tests

a. RNA Gene Expression – PBMCs
b. RNA Gene Expression – NKs
c. RNA Gene Expression – Monocytes
d. RNA Gene Expression – T-Cells
e. RNA Gene Expression – B-Cells
f. RNA Gene Expression – Macrophages
g. RNA Gene Expression – Dendritic Cells
h. MicroRNA in Plasma
i. Proteomics
j. Cell-Free DNA
k. Whole Genome Sequencing
l. Whole Exome Genome Sequencing
m. Mitochondrial Genome Sequencing
n. Mitochondrial DNA/Nuclear DNA Radio
o. HLA DNA Sequencing
p. WBC density
q. Autoantibody panel
r. T-cell Repertoire DNA Sequencing-Stanford
s. T-cell Repertoire DNA Sequencing-Sequenta
t. CyTOF Standard Panel
u. CyTOF Additional Panels
v. Pan Viral Panel
w. Serum Cytokines
x. Ceres Nano Lyme
y. Microbiome – stool
z. Metabolomics – stool
aa. Metabolomics – plasma
bb. Metabolomics – urine
cc. Heavy Metals – blood
dd. Heavy Metals – urine
ee. Mycotoxins by Magarray

12. Clinical Testing

a. Acylcarnitines
b. Ammonia
c. Bartonella extended cx
d. Biotin (Vitamin B7)
e. CBC (Complete Blood Count)
f. Chemistry Comprehensive Panel

g. Creatine Kinase
h. Copper
i. C- Reactive Protein
j. Cysteine
k. Folate
l. FSH (Follicle-Stimulating Hormone)
m. LH (Luteinizing Hormone)
n. Estrogen
o. HbA1C (Hemoglobin A1c)
p. Homocysteine
q. IgG Subsets
r. Lactate
s. Lyme Serology with reflex Western Blot
Lymphocyte Subsets
t. MMA (Methylmalonic Acid)
u. MTHFR Mutations (Methylenetetrahydrofolate)
v. Natural Killer Cell (Count & Function)
w. Organic Acids – urine
x. Pyruvate
y. Serotonin
z. Testosterone
aa. Thyroid Panel
bb. Uric Acid
cc. Vasopressin/ADH
dd. Viral Digital PCR
ee. Viral Serologies:
i. EBV EA (Epstein Barr Virus EA)
ii. EBV NA (Epstein Barr Virus NA)
iii. EBV VCA (Epstein Barr Virus VCA)
iv. CMV (Cytomegalovirus)
v. HHV-6 (Human Herpesvirus 6)
vi. Parvovirus
vii. HHV-7 (Human Herpes Virus 7)
viii. HSV1&2 (Herpes Simplex 1 & 2)
ff. Vitamin B12 (Cobalamin)
gg. Vitamin D25 OH

13. Other Testing/Monitoring

a. Extended EEG
b. Sleep monitoring
c. Fitbit
d. Cognitive Testing
e. Questionnaires – SF36, PROMIS

14. Analysis:

a. Conduct extensive bioinformatics analyses on the data sets. Search for the best combination to generate a diagnostic biomarker set. Because of the large data sets, false discovery is of serious concern. Evaluate the diagnostic molecular biomarker set on different patients with and without ME/CFS to determine sensitivity and specificity.

b. Another problem is the possibility that ME/CFS is heterogeneous, and no biomarker set can be found. Attempt to cluster the patient population into groups and search for a

biomarker set in each group. The Immune repertoire of all immune cells may be a useful data set to achieve biological meaningful clustering. It is possible that the repertoire will reflect the initiating event. This approach has been successful for other diseases.

15. Final notes:

a. Please fund the research of Dr. Ronald W. Davis, director of the Stanford Genome Technology Center! Patients are acutely aware that NIH has not funded his research and we patients are deeply and justifiably angry with NIH and HHS about this.

b. We need treatments NOW. My wife has been ill with ME/CFS for 38 years and home-bound for more than 9 years. NIH and HHS must act with **URGENCY** and **RESPECT** for patients. Please – help us now.

More notes:

Emerging needs and opportunities:

1. Investigate energy production and recovery mechanisms.
2. Confirm the utility of two-day VO2max cardiopulmonary exercise testing (CPET).
3. Analyze existing samples for biomarker discovery.
4. Undertake a deep dive for biomarker discovery.
5. Conduct an accelerated longitudinal study to elucidate the natural history of ME/CFS.
6. Address the questions of burden of disease and undiagnosed ME/CFS patients.
7. Invest in development and validation of outcomes measures.
8. Fund systems biology and computational biology approaches to pathophysiology.
9. Leverage wearable devices to objectively measure function.

Challenges and barriers to progress:

1. The failure to reach consensus on case definition is a steep barrier to progress across the ME/CFS landscape.
2. More resources and heightened urgency are required to address this public health crisis.
3. ME/CFS patients, researchers and clinicians are not involved in NIH's efforts in a sustained and meaningful way.
4. There are very few ME/CFS researchers in training.
5. Methodological flaws make it challenging to interpret the evidence base.

Gaps and opportunities across the research spectrum:

1. ME/CFS research requires a coordinated, strategic plan.
2. Clinical trials and pediatric research are significant gaps in the current approach to ME/CFS research.

If you have the ability to submit responses to NIH, I strongly encourage you to do so. One of the worst outcomes would be if NIH gets very few responses to this RFI. That could reinforce the view that there are just not that many people interested in ME/CFS research. So if you can send even one specific answer to NIH, I hope you will!

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Advancing the Research on ME/CFS Action Items Identified in the P2P Panel's Final Report: June 16, 2015
Note: These action items were derived from the P2P Final Report, and are listed in the order they appear in the report. The items have been edited to use active language.

- Shift research priorities to basic science and mechanistic work that will contribute to biomarker and therapeutics discovery (p. 8).

- Answer questions about the pathogenesis of ME/CFS, including roles of pathogenic agents, genetics, and symptom pathways (p. 8).
- Assemble a team of stakeholders (patients, clinicians, researchers, federal agencies) to reach consensus on the definition and parameters of ME/CFS (p. 9).
- Develop a national and international research network to clarify the case definition and advance the field (p. 9).
- Incorporate NIH Institutes and Centers not presently represented into the Trans-NIH ME/CFS Working Group to learn from other disciplines and diseases (p. 9).
- Invest in bench-to-bedside research (p. 10).
- Prioritize the development of biomarkers and diagnostic tests (p. 10).
- Create opportunities for junior and new investigators (p. 10).
- Coordinate research efforts to promote efficiency and effectiveness (p. 10).
- Use public/private partnerships to leverage existing NIH infrastructure and dollars (p. 10).
- Develop valid prognostic tests to guide treatment strategies using genomic, epigenomics, proteomic, and metabolomic strategies to identify critical biomarkers (p. 10).
- Identify gene expression, protein or metabolite signatures to correctly diagnose ME/CFS and distinguish it from other chronic condition (p. 10).
- Stratify patients using physiologic measures, pathophysiology, genome-wide association studies and phenotyping (p. 10).
- Study fMRI and imaging technologies as diagnostic tools and to better understand neurologic dysfunction in ME/CFS (p. 11).
- Link biological samples and de-identified survey data in a registry/repository (p. 11).
- Explore the intestinal microbiome and the effect of the environment and microbiome on ME/CFS (p. 11).
- Conduct epidemiological studies, including incidence and prevalence, risk factors, geographical distribution and potential healthcare disparities (p. 11).
- Analyze previously collected research data to inform trial development and design (p. 11).
- Examine drug therapies for fibromyalgia and other pain-related conditions for effectiveness in ME/CFS (p. 11).
- Leverage existing registries (p. 11).
- Develop diagnostic and prognostic algorithms to identify who will develop ME/CFS after infectious or other triggers (p. 11).
- Conduct "omics"-based drug repurposing and neurobiology studies (p. 11).
- Develop large datasets using bioinformatics techniques and store in a central, publicly accessible database (p. 11).
- Use a systems-level approach to understand how immunologic, neurologic, and metagenomic factors may contribute to ME/CFS (p. 12).
- Define and characterize immunologic mechanisms and pathways associated with disease progression (p. 12).
- Conduct longitudinal studies to explore the possibility of a progressive immune exhaustion or dysfunction (p. 12).
- Study gene expression in identical twins to identify gene expression biomarkers (p. 12).
- Use male and female models to explore the role of gender, X-chromosome genes, and hormones in developing ME/CFS (p. 12).
- Explore how patients' background medications affect function and outcomes (p. 12).
- Encourage studies investigating homeopathy, non-pharmalogic, complementary, and alternative medicine treatments, and biopsychosocial parameters, function, and quality of life (QOL) (p. 12).

- Improve measures to identify ME/CFS while including the patient's voice in patient-reported outcomes (p. 13).
- Develop an ME/CFS methodological workgroup at NIH (p. 13).
- Increase patient involvement in determining priorities for research and care (p. 13).
- Use already well-validated measures such as PROMIS and CESD (p. 13).
- Use a battery of simplified measures (p. 13).
- Leverage the power of other NIH longitudinal studies to better understand ME/CFS (p. 13).
- Use telemedicine or home visits for those unable to participate in clinical trials/treatment in person (p. 13).
- Develop and employ new technologies to address underserved populations and unmet needs (mobile technology, etc) to measure progress and enable communication (p. 13).
- Ensure professional licensing and accreditation agencies use a curriculum that facilitates ME/CFS knowledge acquisition (p. 14).
- Engage with Health Resources and Services Administration (HRSA) to facilitate training (p. 14).
- Facilitate a public-private partnership with professional societies and patient organizations to train and fund health care professionals (p. 14).
- Partner across institutions to advance research and develop new scientists (p. 14).
- Develop a cadre of junior investigators, including women and minorities, using new collaborative models, investigator-initiated studies, career development, and small grant mechanisms (p. 14).
- Create efficiency and co-fund research to promote diversity in the pipeline, eliminate disparities, and enhance the quality of the science (p. 14).
- Create a network of collaborative centers working across institutions and disciplines, including clinical, biological, and social sciences (p. 15).
- Charge the centers to determine biomarkers for diagnosis and prognosis, epidemiology, functional status and disability, patient-centered QOL outcomes, cost-effectiveness of treatment studies, role of co-morbidities, and characterize control and recovered populations (p. 15).
- Establish a central archive of de-identified data and tissue samples from prior and ongoing studies to enable data and sample sharing (p. 15).
- Create a website for patient and clinician educational materials, as well as clinical trial information (p. 15).
- Utilize the NIH Clinical Center for clinical trials and fast-track testing of new therapies (p. 15).
- Improve quality of care by learning from palliative care (p. 15).
- Examine role of self-management techniques as part of a comprehensive treatment plan during and after clinical interventions (p. 16).
- Evaluate multifaceted therapies focused on biomedical and supportive care (p. 16).
- Conduct comparative effectiveness research (p. 16).
- NIH and FDA convene a meeting on the state of ME/CFS treatment (p. 16).
- Retire the Oxford definition (p. 16).
- ME/CFS community to agree upon a single case definition (p. 16).
- Patients, clinicians, and researchers agree on a definition for meaningful recovery (p. 16).
- Use new avenues to fund research (p. 17).
- Develop demonstration projects with CMS and PCORI for patient-centered medical homes for people with ME/CFS, using a comparative effectiveness research framework to determine best evidence-based practices (p. 17).

- Translate best practices to primary care clinicians (p. 17).
- Create quality metrics and a standard of care in collaboration with federal agencies and professional societies (p. 17).
- Form private-public partnerships between federal departments, advocacy groups, and industry (p. 17).
- Monitor progress by convening another ME/CFS Expert Panel in five years (p. 17).
- Federal agencies, clinicians, patients and advocates should consider the IOM and P2P reports together to move the science forward (p. 18).

[…]
Subject: Spotila Response to RFI 062116

Attached please find my response to your Request for Information NOT-NS-16-024

To: Trans-NIH ME/CFS Working Group

From: […]

Date: June 21, 2016

Re: Response to Request for Information, NOT-NS-16-024

ME/CFS research has long been relegated to scientific backwaters despite the disease's tremendous public health burden, but there are now hopeful signs of movement, including this Request for Information. Other projects include: the ME/CFS Clinical Care Study led by Dr. Avindra Nath; the proposed ME/CFS consortium of research sites and data-management coordinating center; and the NIH and CDC effort to establish common data elements for ME/CFS studies. However, much work remains to be done, and I appreciate that you have sought public input on new strategies and priority setting for ME/CFS research.

In responding to your request, I assume you are already familiar with the 2011 State of the Knowledge Workshop Report,[1] the 2014 systematic evidence review,[2] the 2015 Pathways to Prevention Workshop Report,[3] and the 2015 Institute of Medicine report.[4] I have based my comments on these reports, but have also drawn on my 20-plus years of experience with this disease.

I got sick on October 6, 1994. For most of the last 7,924 days, I have been housebound, and periodically bedridden, due to ME/CFS. However, my opinions about ME/CFS research are informed by more than my own health. I have been an ME/CFS advocate for more than fifteen years. I served on the Board of Directors of The CFIDS Association (now the Solve ME/CFS Initiative) from 2006-2011, and was chairman of the Board in 2008-2009. During my chairmanship, the CFIDS Association strategically refocused its research program, and I also participated in grant review of investigator-initiated proposals. Since 2013, I have been a

participant in FDA's Patient Representative Program and have also been a member of a working group for development of an ME/CFS outcomes measure. This mix of experience has influenced my personal opinion about what is needed to advance ME/CFS research and find effective treatments for patients. I offer the following recommendations in response to your request:

Emerging needs and opportunities:

1. Investigate energy production and recovery mechanisms.
2. Confirm the utility of two-day VO2max cardiopulmonary exercise testing (CPET).
3. Analyze existing samples for biomarker discovery.
4. Undertake a deep dive for biomarker discovery.
5. Conduct an accelerated longitudinal study to elucidate the natural history of ME/CFS.

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[1] National Institutes of Health [NIH], (2011). *State of the Knowledge Workshop: ME/CFS Research, Workshop Report.*

[2] Smith, M. E. B., Nelson H. D., et al. (2014). *Diagnosis and Treatment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. Evidence Report/Technology Assessment No. 219*. (Prepared by the Pacific Northwest Evidence-based Practice Center under Contract No. 290-2012-00014-I.) Agency for Healthcare Research and Quality, Publication No. 15-E001-EF. Rockville, MD:

[3] Green, C., Cowan, P., et al. *Pathways to Prevention Workshop: Advancing the Research on ME/CFS.* Retrieved June 12, 2016, from https://prevention.nih.gov/docs/programs/mecfs/ODP-P2P-MECFS-FinalReport.pdf

[4] Institute of Medicine [IOM]. (2015). *Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness.* Washington, DC: The National Academies Press.

6. Address the questions of burden of disease and undiagnosed ME/CFS patients.
7. Invest in development and validation of outcomes measures.
8. Fund systems biology and computational biology approaches to pathophysiology.
9. Leverage wearable devices to objectively measure function.

Challenges and barriers to progress:

1. The failure to reach consensus on case definition is a steep barrier to progress across the ME/CFS landscape.
2. More resources and heightened urgency are required to address this public health crisis.
3. ME/CFS patients, researchers and clinicians are not involved in NIH's efforts in a sustained and meaningful way.
4. There are very few ME/CFS researchers in training.
5. Methodological flaws make it challenging to interpret the evidence base.

Gaps and opportunities across the research spectrum:

1. ME/CFS research requires a coordinated, strategic plan.
2. Clinical trials and pediatric research are significant gaps in the current approach to ME/CFS research.

Emerging needs and opportunities

There are myriad needs and opportunities for ME/CFS research, although most cannot be considered "emerging." The needs are clear, and have been identified in multiple reports in the last five years.

1. **Investigate energy production and recovery mechanisms.** The IOM's proposed diagnostic criteria require post-exertional malaise, defined as "an exacerbation of some or all of an individual's ME/CFS symptoms that occur after physical or cognitive exertion and leads to a reduction in functional ability."[5] Note that post-exertional malaise (PEM) is much more than the symptom of fatigue.[6] Both the symptom profile and the response to maximal exercise testing point to possible impairments in energy production and recovery mechanisms. Research suggests that the dysfunction is not in muscle fibers themselves, but in other aspects of energy production, perceived exertion, and recovery.[7]

   Investigation of energy production and recovery in ME/CFS may get at the very heart of the disease. The public health relevance of unraveling where these systems are failing would be enormous. Understanding the pathophysiology could potentially identify biomarkers that do not require the risky two-day maximal exercise challenge (see #2). In turn, if we understood the impairments on the molecular level, perhaps we could identify treatments that would significantly improve function and quality of life.

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[5] IOM, 78-86.

[6] Food and Drug Administration [FDA], 2013. *The Voice of the Patient: Chronic Fatigue Syndrome and Myalgic Encephalomyelitis*, Retrieved June 12, 2016, from http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM368806.pdf ()

[7] NIH, 2011, 12.

2. **Confirm the utility of two-day VO2max cardiopulmonary exercise testing (CPET).** Among the many studies finding biomarker abnormalities in ME/CFS patients are the intriguing results of two-day CPET in patients versus controls. ME/CFS patients are unable to reproduce their performance on the second day of the test, and this impairment may be unique among disease groups, including congestive heart failure and multiple sclerosis.[8] Confirmation of this finding would not only give doctors a test for ME/CFS, but it would distinguish ME/CFS from other disease groups that experience fatigue. The AHRQ systematic evidence review stated, "Further studies are needed to determine the utility of 2-day cardiopulmonary exercise testing to identify or monitor symptoms of post-exertional malaise."[9]

While using exercise challenges to induce post-exertional malaise has become widely accepted as necessary in ME/CFS research, the use of the two-day VO2max protocol is not. For example, in discussing the use of an exercise challenge in the NIH Clinical Care Center study, Dr. Avindra Nath said, "I just want to be able to fatigue patients and see that if before and after fatigue, is there a change in the immune profile? . . . And so the test that we have in order to fatigue patients is going to be different."[10] This approach is flawed, in part because it ignores the distinct signature of PEM – an exacerbation of

multiple symptoms after exertion.

However, a key advantage of the two-day VO2max protocol is that there is objective evidence of maximal effort. Once the subject's respiratory exchange ratio exceeds 1.0, maximal effort has been achieved. Some ME/CFS patients may exercise for twenty minutes before reaching that threshold; some may exercise for only five minutes. But by requiring evidence of maximal effort, we ensure that the responses to exercise are comparable. Whether a study examines changes in gene expression or immune profile or the microbiome, use of the maximal challenge means that all subjects reached the same threshold, regardless of how long it took them to get there.

The public health relevance of validating the two-day CPET results, including comparison to other disease groups, is significant. This could be the first objective diagnostic test for the cardinal symptom of PEM, and it would revolutionize diagnosis of ME/CFS. The main challenge is that the test is risky for ME/CFS patients. Patients who have undergone the test experience prolonged periods of PEM, and there is a risk of permanent exacerbation of the disease. The most severely ill patients cannot complete the test at all. However, the potential of an objective test for ME/CFS cannot be overstated.

3. **Analyze existing samples for biomarker discovery.** There are now multiple repositories of blood samples from ME/CFS patients. These samples are a unique and "research ready" resource for discovery research. The P2P report recommended that "A

[8] Keller, B. A., Pryor, J., & Giloteaux, L. (2014). Inability of Myalgic Encephalomyelitis/chronic Fatigue Syndrome Patients to Reproduce VO2peak Indicates Functional Impairment. *J. Transl. Med*. 12(1), 104.

[9] Smith, M. E. B., et al., 90.

[10] MEAction, 2016. Dr. Nath Solve ME/CFS Initiative webinar transcript, 16. Retrieved June 12, 2016 from: http://www.meaction.net/wp-content/uploads/2016/04/Dr-Nath-SMCI-webinar-transcript-reformatted.pdf

priority should be placed on developing biomarkers and diagnostic tests," and that existing registries should be leveraged.[11]

There are many potential targets for biomarker discovery. The P2P report described the breadth of opportunities: "genomic, epigenomic, proteomic, and metabolomic strategies to identify critical biomarkers that will be clinically applicable should be developed.
Gene expression, protein, or metabolite signatures that can correctly diagnose ME/CFS and distinguish it from other chronic conditions while predicting disease severity and clinical outcomes are needed. Determining the most important physiologic measures and pathophysiology, as well as genome-wide association studies and phenotyping, are essential for stratifying patients."[12]

The public health relevance of these existing sample banks is clear. Maximizing this existing resource may help speed discoveries of biomarkers and targeted treatments. The main challenges with these samples are the different selection criteria for subjects, different sample collection methods, and navigation of multiple IRB approvals. However, integration of data from these collections into the proposed central data repository could potentially jumpstart multiple studies. A benchmark should be established for the number of samples analyzed and integrated at the three-year or five-year mark.

4. **Undertake a deep dive for biomarker discovery.** Development of an objective and low burden test for ME/CFS remains a desperate need in the field. Biomarkers will help subtype patients with similar phenotypes. Biomarkers are also needed to understand pathophysiology and objectively measure outcomes. Multiple candidate biomarkers have been identified[13] but none have been validated in a sufficiently large ME/CFS cohort.

Biomarker discovery may take two possible approaches. First, adequately powered studies of well-characterized ME/CFS patients should attempt to validate the existing biomarker candidates. Second, given how little we understand ME/CFS etiology and pathogenesis, we need a large, rigorous fishing expedition to see what we can see.

The NIH Clinical Care Center study will conduct a massive deep dive, and ME/CFS subjects will share the phenotypes of infectious onset and illness duration. However, only 40 ME/CFS subjects will be studied. Other approaches could be used, such as focusing on severely ill subjects or specific types of infectious onset (e.g. gastrointestinal vs. respiratory) or those with phenotypes indicating immune activation vs. immune suppression. A fishing expedition could also focus on specific symptoms, such as investigating neurological abnormalities and inflammation in ME/CFS subjects with cognitive dysfunction. An area that has been completely ignored is the development of sequelae (e.g. lymphoma) in ME/CFS patients, and associated prognostic biomarkers.

Validation of even a single biomarker in ME/CFS would revolutionize both research and clinical care. Previous efforts have failed, and there has been insufficient funding to

[11] Green, C., et al., 10-11.
[12] Green, C., et al., 10-11.
[13] NIH, 2011, 13-14.

follow the leads we have now. The risk of finding nothing in a biomarker fishing expedition is more than outweighed by the potential scientific and public health reward.

5. **Conduct an accelerated longitudinal study to elucidate the natural history of ME/CFS.** There are very few papers on the natural history of ME/CFS, and I am not aware of any large-scale, long-duration longitudinal studies. The Institute of Medicine noted the essential need for natural history studies, both to identify disease characteristics and to further refine diagnostic criteria.[14] The P2P report also recommended longitudinal studies.[15]

An accelerated longitudinal design has several advantages. First, by selecting subjects all along the illness duration continuum, such a study has the potential to identify changes in biomarkers associated with disease progression. In one study, differential analysis of a mixed duration cohort was necessary to detect significant differences in immune functioning.[16] Second, recruitment of subjects in an early phase of illness is difficult given the high rate of under-diagnosis.[17] Prospective studies have the potential to identify early stage illness,[18] but have the disadvantage of the time required to simply identify those subjects who develop ME/CFS. Third, an accelerated longitudinal study can be completed much more quickly across a broader spectrum of patients than a traditional longitudinal design.

6. **Address the questions of burden of disease and undiagnosed ME/CFS patients.** The IOM report estimated that ME/CFS affects between 836,000 and 2.5 million people in the United States.[19] However, many of those patients have not been accurately diagnosed. There is also evidence that patients with other diseases are incorrectly diagnosed with ME/CFS.[20] A major barrier to accurate estimates is the use of multiple case definitions, and the absence of any new epidemiology using the IOM definition.

The burden of disease can only be estimated, given the uncertainty about prevalence and diagnosis, but the estimated price tag is an astronomical $18 to 24 billion dollars a year.[21] ME/CFS was not included in the Global Burden of Disease Study 2010,[22] and no DALY analysis of ME/CFS patients has been undertaken in the United States. However, given

[14] IOM, 225.

[15] Green, C., et al., 8,12.

[16] Hornig, M., Montoya, J., Klimas, N., et al. (2015). Distinct plasma immune signatures in ME/CFS are present early in the course of illness. *Sci Adv*. 1(1). Pii: e1400121.

[17] Jason L. A., Richman J. A., Rademaker A. W., et al. (1999) A community-based study of chronic fatigue syndrome. *Arch Intern Med* 159: 2129-2137.

[18] Hickie, I, Davenport, T, Wakefield, D, et al. (2006). Post-infective and chronic fatigue syndromes precipitated by viral and non-viral pathogens: Prospective cohort study. *BMJ*, 333(7568):575.

[19] IOM, 31.

[20] Berger J. R, Pocoski J., Preblick R., & Boklage S. (2013) Fatigue heralding multiple sclerosis. *Multiple Sclerosis Journal* 19(11): 1526-1532.

[21] IOM, 33.

[22] Murray, C., TheoVos, R., Mohsen, N., et al. (2012). Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 380: 2197.

the NIH strategic plan goal of incorporating disease burden into grant decision-making,[23] this work should be done. In addition, identifying the prevalence of true cases will help address the public health emergency of ME/CFS patients who have been misdiagnosed with other diseases or who have completely fallen through the cracks of the healthcare system.

7. **Invest in development and validation of outcomes measures.** Validated outcomes measures are lacking in ME/CFS. The IOM report lists thirty questionnaires and tools for assessing ME/CFS symptoms, but notes that many have not been tested in ME/CFS patients.[24] FDA has not qualified an outcomes measure for ME/CFS clinical trials, and this remains a barrier to drug development. Both the systematic evidence review[25] and the P2P report[26] recommended that a core set of outcomes measures be validated.

There are several benefits to public health if validated outcomes measures are developed. First, clinicians would have tools to help diagnose and manage ME/CFS, particularly if a tool is short and easy to administer in clinical practice. Second, a qualified outcomes measure would encourage investment by pharmaceutical companies in repurposing drugs or developing new ones. Third, validated measures would complement NIH's Common Data Elements project and the proposed ME/CFS research consortium.

8. **Fund systems biology and computational biology approaches to pathophysiology.** The value of a systems biology approach to the pathophysiology of ME/CFS has been recognized for years. In 2011, the NIH State of the Knowledge Workshop included results of studies that found unique systems networking of immunological markers in ME/CFS patients.[27] The P2P report also highlighted the potential for systems biology approaches.[28] These systems and computational approaches are well suited to investigating ME/CFS, given that it is a multi-system disease. Using exercise challenges to provoke PEM, or using a "good day/bad day" design, requires blood sampling at multiple time points. The complexity of immune signaling alone requires a systems and/or computational approach in order to uncover signaling pathways, gene expression changes, etc.

The public health relevance for these approaches is not necessarily an immediate translation from bench to bedside. However, being able to model the abnormalities of multiple systems and the effect of behavior on those systems would advance our knowledge of the pathophysiology of the disease, and could uncover treatment approaches that would otherwise not have been identified. The main challenge to this work is funding. It will be expensive to assemble a sufficiently large, diverse, and well- characterized cohort, and expensive to collect multiple samples from all of them and

[23] National Institutes of Health, (2016). *NIH-Wide Strategic Plan, Fiscal Years 2016-2020*, 30-31. Retrieved June 12, 2016, from https://www.nih.gov/sites/default/files/about-nih/strategic-plan-fy2016-2020-508.pdf
[24] IOM, 269-72.
[25] Smith, M. E. B., et al., 90.
[26] Green, C., et al., 12-13.
[27] NIH, 2011, 9-10.
[28] Green, C., et al., 10.

apply computational methods. However, this is another area that complements the proposed ME/CFS research consortium nicely.

9. **Leverage wearable devices to objectively measure function.** The definition of improvement and recovery in ME/CFS is problematic, especially in the absence of validated biomarkers and outcomes measures. Furthermore, the cognitive dysfunction experienced by many patients can make it difficult to recall whether a symptom has improved or worsened over time, even in response to a specific treatment. Using wearable devices to collect data on measures such as movement, sleep, and heart rate would have value for both clinical care and research studies.[29]

Despite the proliferation of wearable devices, and the ease of collecting and analyzing the resulting data, ME/CFS studies have not begun to tap this potential in study design. For example, the PACE trial is the largest study to date of cognitive behavioral therapy and graded exercise treatment in patients diagnosed with CFS using the Oxford definition.
The study protocol included use of actimeters to measure changes in physical activity of the subjects. However, this measure was dropped from the final analysis with no explanation.[30] Yet it is critical that functionality be objectively measured. In another
study of graded exercise, actimeter data showed that after 10 days, ME/CFS subjects became less active and more symptomatic, suggesting that they had reached a level of exercise intolerance.[31]

It is obvious that focusing on ME/CFS patients' functionality has high public health relevance, both in research and in patient care. Incorporating wearable devices into longitudinal and research studies is also relatively easy. The devices are cheap, easy to wear, and data collection is both easy and customizable.

Challenges and barriers to progress

1. **The failure to reach consensus on case definition is a steep barrier to progress across the ME/CFS landscape**. I'm certain that the Trans-NIH ME/CFS Working Group is well acquainted with the various case definitions used in ME/CFS research and clinical practice. You are also familiar with the methodological and analytical problems caused by the lack of a single, operationalized definition. However, the solution to the current situation goes beyond selecting a single definition.

Generally speaking, the working assumption among many people is that the eight case definitions describe the same population. The paradigm is of one illness characterized by

[29] Smith, M. E. B., et al., 90.

[30] White P. D., Sharpe M. C., Chalder T., et al. (2007). Protocol for the PACE trial: a randomized controlled trial of adaptive pacing, cognitive behavior therapy, and graded exercise, as supplements to standardized specialist medical care versus standardized specialist medical care alone for patients with the chronic fatigue syndrome/myalgic encephalomyelitis or encephalopathy. *BMC Neurol*, 7(1):6.

[31] Black, C. & McCully, K. (2005). Time course of exercise induced alterations in daily activity in chronic fatigue syndrome. *Dynamic Medicine* 4:10.

debilitating fatigue not explained by any of the exclusionary conditions, and accompanied by a shifting list of other symptoms that may or may not be categorized into subtypes.
That is representative of HHS's official view. In describing the CDC multisite study at the FDA's meeting in April 2013 on Drug Development for ME/CFS, Dr. Unger said that CFS or CFS/ME is a generic term, and an "umbrella diagnosis."[32]

However, the disease we described to the FDA in April 2013 is not an umbrella. Patients collectively described symptoms along common themes aligned more closely with the Canadian Consensus Criteria than the Fukuda definition. This more precise view of the disease characterized by PEM, cognitive dysfunction, sleep disturbances, along with immune and autonomic dysfunction represents a discrete entity – distinct from the broader group captured by the Oxford, Fukuda and Reeves definitions. The IOM's clinical case definition for SEID tracks this description closely.

The umbrella or combination approach is emblematic of the mushy thinking that has hindered this field for thirty years. If we fail to acknowledge and grapple with this problem, then we perpetuate that sloppy thinking as well as the detrimental effects on patients. There is a distinct entity, which is referred to as ME/CFS or ME, characterized by PEM, cognitive dysfunction, sleep disturbances, along with immune and autonomic dysfunction. This disease must be the focus of NIH efforts.

The P2P report recommended that NIH: "Assemble a team of stakeholders (e.g., patients, clinicians, researchers, federal agencies) to reach consensus on the definition and parameters of ME/CFS. A national and international research network should be developed to clarify the case definition and to advance the field."[33] This must be done, and done immediately. The Common Data Elements project is not sufficient to address this problem. One must first define the disease before one can identify the common data elements that should be collected in research on the disease. It is past time for NIH to take a clear position on what disease we are studying when we say "ME/CFS."

2. **More resources and heightened urgency are required to address this public health crisis.** ME/CFS is a complex multi-system disease that creates significant disability and harm. Such a complex scientific problem cannot be solved on a pittance of $5 or $6 million a year. Furthermore, despite Dr. Francis Collins's statement that NIH is taking ME/CFS seriously, progress has been painstakingly slow.

Why has NIH failed to invest adequate resources in ME/CFS research? Why has there been no urgency to address the gaps and opportunities in this field? There is no simple answer to those questions. But it begins with an acknowledgement of the damage done to the research field and to patients by NIH's failure to address these issues. ME/CFS has never been a priority to any Institute at NIH. There have been and always will be other public health issues that need urgent attention, including Zika virus, the Cancer

[32] FDA Center for Drug Evaluation and Research, Drug Development for Chronic Fatigue Syndrome and Myalgic Encephalomyelitis: Public Workshop Day Two. (2013, April 26). 227. Retrieved June 12, 2016, from: http://www.fda.gov/downloads/Drugs/NewsEvents/UCM355406.pdf
[33] Green, C., et al., 9.

Moonshot, the Precision Medicine Initiative and others. ME/CFS has been waiting its turn for thirty years, and continues to be passed over. This must change immediately, because ME/CFS is an expensive public health crisis.

3. **ME/CFS patients, researchers and clinicians are not involved in NIH's efforts in a sustained and meaningful way.** At the present time, external stakeholders in ME/CFS research are relegated to very limited opportunities to offer input into NIH's strategy and priority setting. This Request for Information is a refreshing step forward. Typically, the public has been confined to offering public comment on draft reports (such as the P2P panel's report) or brief speaking opportunities at meetings (such as the State of the Knowledge and P2P workshops). This is a completely inadequate level of engagement.

The P2P report acknowledged that "Patients must be at the center of the research efforts, and their engagement is critical . . . Patients must also be involved in determining priorities for research and care."[34] The AHRQ systematic evidence review was also specific on this point: "It is recommended that future studies include the patient and/or advocate voice in the planning and development phases so that future research is relevant and meaningful to those affected by ME/CFS."[35]

NIH's own strategic plan also promises fundamental changes across the Institutes to engage external stakeholders: "Patients, disease advocacy organizations, and community members at the local, state, and federal levels also are playing an increasingly significant role in spurring advances in biomedical research. Consequently, NIH will embrace these and other members of the public as active partners in the research enterprise, with the aim of generating more effective – and more relevant – research outcomes. This will include seeking input from diverse volunteers *at all stages of the research process, from study design to data collection and analysis*."[36] (emphasis added)

By not engaging ME/CFS patients, researchers, and clinicians, NIH is losing the tremendous value that these stakeholders bring to the table. The early missteps in the NIH Clinical Care Study are a prime example: stakeholders would have advised against using the functional movement disorder control group and the Reeves definition. But because stakeholders were not consulted, NIH had to course-correct after the fact. Furthermore, external stakeholders can provide direct input into the symptoms and outcomes that are most meaningful to patients, the most promising scientific leads, and optimal study design. A free exchange of ideas between external stakeholders and internal NIH staff would benefit all parties.

The CFS Advisory Committee has formed a working group to examine how HHS agencies, particularly NIH, can systematically engage external stakeholders in ME/CFS research. However, it may be some months before that working group offers recommendations. This issue is too urgent to wait. I strongly recommend that you take immediate steps to invite stakeholder participation in your meetings. I also recommend

[34] Green, C., et al., 9, 13.
[35] Smith, M. E. B., et al., 90.
[36] NIH (2016). 38-39.

that stakeholders be given a significant and substantive role in determining the future direction of ME/CFS research at NIH, beyond the input you will collect in response to this RFI. What is most needed is integrated, substantive engagement with stakeholders in the planning stages of initiatives. In order for that to be productive, NIH should select patients, clinicians and researchers who are suited to the task of strategic thinking and consensus building. A focused engagement such as that would be complementary to general solicitation of input, such as through this RFI. More than one method of engagement will be needed to bring the most value to NIH's initiatives.

4. **There are very few ME/CFS researchers in training.** Dr. Vicky Whittemore noted during her May 26, 2016 presentation to the NINDS Council that NIH has never received a training grant application in ME/CFS.[37] The researchers and clinicians currently involved are generally older, and will soon be retiring. We face the tremendous risk of reducing the number of scientists just when this field needs them most. There are many reasons for the lack of interest and the failure to train new experts. ME/CFS is a contested illness with a substantial stigma, and is perceived to be damaging to one's career. The lack of funding has also discouraged participation. NIH will need a multi-prong strategy to address this looming knowledge gap, and to facilitate excellence in future ME/CFS research. It is essential that NIH engage with current ME/CFS researchers to support their efforts to develop future experts as well.

5. **Methodological flaws make it challenging to interpret the evidence base.** The AHRQ systematic review criticized ME/CFS studies for having small sample size, short duration and lack of replication.[38] The IOM criticized the field for using healthy controls, instead of patients with other fatiguing illnesses.[39] The P2P report recommended that NIH form a methodological working group.[40] However, it must be recognized that the dearth of funding is the main barrier to larger sample sizes, longer duration, replication attempts and multiple control groups. A methodological working group and the Common Data Elements project are two pieces of the solution, but adequate funding for research will also be necessary to overcome this barrier.

Gaps and opportunities across the research continuum

1. **ME/CFS research requires a coordinated, strategic plan.** The P2P report identified 65 actionable items to help advance ME/CFS research (see Appendix A for this list). That is just the beginning of the list of possible areas of inquiry. Given the lack of funding, many leads have never been followed and intriguing results have not been replicated. Pilot studies do not secure funding to expand subject cohorts. The list goes on and on.

[37] Whittemore Presents ME/CFS Proposal to NIH. Retrieved June 12, 2016, from: http://www.meaction.net/2016/05/27/transcript-of-dr-vicky-whittemores-mecfs-proposal-to-the-nih-council-meeting-26-may-2016/

[38] Smith, M. E. B., et al., 90.

[39] IOM, 225.

[40] Green, C., et al., 13.

There has been very little strategic thinking in the field beyond what a single organization might do for its own operations. No one has articulated the desired end state, and the interim milestones required for progress. No one has determined what must be accomplished in the next five years or ten years in order to reach the desired end state.
Furthermore, there has been no prioritization among the many areas that need attention. Even the P2P Panel did not indicate whether it reported recommendations in priority order. No one is measuring performance beyond gross metrics such as annual spending.

Because ME/CFS has no Institute "home," it is not included in any Institute's strategic plan at this time, nor is it included in NIH's overall strategic plan. Yet there are many NIH initiatives that are well suited for ME/CFS research, such as the BRAIN Initiative and the Precision Medicine Initiative. ME/CFS grant applications would also benefit from the select pay option,[41] if there were any Institute directors inclined to do so.

Now is the time to develop a strategic plan with meaningful, sustained engagement of external stakeholders. A plan must be in place to facilitate progress once the recently announced projects are underway. There should be no delay in undertaking the planning process, and the process will be vastly improved by substantive participation from external stakeholders. The resulting plan can then guide future NIH efforts and funding levels for this disease.

2. **Clinical trials and pediatric research are significant gaps in the current approach to ME/CFS research.** One could argue that there are more gaps in the field of ME/CFS than there are building blocks. Two deserve particular mention.

First, there are virtually no clinical trials, despite the identification of drug repurposing targets. Strategies to support clinical trials are desperately needed and should be implemented.

Second, pediatric studies have been virtually nonexistent. The IOM report states, "When evaluating the available research to develop its findings, conclusions, and recommendations on pediatric ME/CFS, the committee was struck by the paucity of the research conducted to date in this population. For major ME/CFS symptoms such as PEM and sleep disturbances, no more than 10 papers were available on each of these topics."[42] Given the severe impact of ME/CFS on education and development in pediatric patients, and given identified differences between adult and pediatric ME/CFS cases, this is a gap in research that deserves priority.

[41] NIH, (2016).28.
[42] IOM, 183.

Appendix A

Action Items Identified in the P2P Panel's Final Report

These action items were derived from the P2P Final Report, and are listed in the order they appear in the report. The items have been edited to use active language.

1. Shift research priorities to basic science and mechanistic work that will contribute to biomarker and therapeutics discovery (p. 8).
2. Answer questions about the pathogenesis of ME/CFS, including roles of pathogenic agents, genetics, and symptom pathways (p. 8).
3. Assemble a team of stakeholders (patients, clinicians, researchers, federal agencies) to reach consensus on the definition and parameters of ME/CFS (p. 9).
4. Develop a national and international research network to clarify the case definition and advance the field (p. 9).
5. Incorporate NIH Institutes and Centers not presently represented into the Trans-NIH ME/CFS Working Group to learn from other disciplines and diseases (p. 9).
6. Invest in bench-to-bedside research (p. 10).
7. Prioritize the development of biomarkers and diagnostic tests (p. 10).
8. Create opportunities for junior and new investigators (p. 10).
9. Coordinate research efforts to promote efficiency and effectiveness (p. 10).
10. Use public/private partnerships to leverage existing NIH infrastructure and dollars (p. 10).
11. Develop valid prognostic tests to guide treatment strategies using genomic, epigenomics, proteomic, and metabolomic strategies to identify critical biomarkers (p. 10).
12. Identify gene expression, protein or metabolite signatures to correctly diagnose ME/CFS and distinguish it from other chronic condition (p. 10).
13. Stratify patients using physiologic measures, pathophysiology, genome-wide association studies and phenotyping (p. 10).
14. Study fMRI and imaging technologies as diagnostic tools and to better understand neurologic dysfunction in ME/CFS (p. 11).
15. Link biological samples and de-identified survey data in a registry/repository (p. 11).
16. Explore the intestinal microbiome and the effect of the environment and microbiome on ME/CFS (p. 11).
17. Conduct epidemiological studies, including incidence and prevalence, risk factors, geographical distribution and potential healthcare disparities (p. 11).
18. Analyze previously collected research data to inform trial development and design (p. 11).
19. Examine drug therapies for fibromyalgia and other pain-related conditions for effectiveness in ME/CFS (p. 11).
20. Leverage existing registries (p. 11).
21. Develop diagnostic and prognostic algorithms to identify who will develop ME/CFS after infectious or other triggers (p. 11).
22. Conduct "omics"-based drug repurposing and neurobiology studies (p. 11).

23. Develop large datasets using bioinformatics techniques and store in a central, publicly accessible database (p. 11).
24. Use a systems-level approach to understand how immunologic, neurologic, and metagenomic factors may contribute to ME/CFS (p. 12).
25. Define and characterize immunologic mechanisms and pathways associated with disease progression (p. 12).
26. Conduct longitudinal studies to explore the possibility of a progressive immune exhaustion or dysfunction (p. 12).
27. Study gene expression in identical twins to identify gene expression biomarkers (p. 12).
28. Use male and female models to explore the role of gender, X-chromosome genes, and hormones in developing ME/CFS (p. 12).
29. Explore how patients' background medications affect function and outcomes (p. 12).
30. Encourage studies investigating homeopathy, non-pharmacologic, complementary, and alternative medicine treatments, and biopsychosocial parameters, function, and QOL (p. 12).
31. Improve measures to identify ME/CFS while including the patient's voice in patient-reported outcomes (p. 13).
32. Develop an ME/CFS methodological workgroup at NIH (p. 13).
33. Increase patient involvement in determining priorities for research and care (p. 13).
34. Use already well-validated measures such as PROMIS and CESD (p. 13).
35. Explore psychiatric comorbidities to improve QOL (p. 13).
36. Use a battery of simplified measures (p. 13).
37. Leverage the power of other NIH longitudinal studies to better understand ME/CFS (p. 13).
38. Use telemedicine or home visits for those unable to participate in clinical trials/treatment in person (p. 13).
39. Develop and employ new technologies to address underserved populations and unmet needs (mobile technology, etc) to measure progress and enable communication (p. 13).
40. Ensure professional licensing and accreditation agencies use a curriculum that facilitates ME/CFS knowledge acquisition (p. 14).
41. Engage with HRSA to facilitate training (p. 14).
42. Facilitate a public-private partnership with professional societies and patient organizations to train and fund health care professionals (p. 14).
43. Partner across institutions to advance research and develop new scientists (p. 14).
44. Develop a cadre of junior investigators, including women and minorities, using new collaborative models, investigator-initiated studies, career development, and small grant mechanisms (p. 14).
45. Create efficiency and co-fund research to promote diversity in the pipeline, eliminate disparities, and enhance the quality of the science (p. 14).
46. Create a network of collaborative centers working across institutions and disciplines, including clinical, biological, and social sciences (p. 15).
47. Charge the centers to determine biomarkers for diagnosis and prognosis, epidemiology, functional status and disability, patient-centered QOL outcomes, cost-effectiveness of treatment studies, role of comorbidities, and characterize control and recovered populations (p. 15).

48. Establish a central archive of de-identified data and tissue samples from prior and ongoing studies to enable data and sample sharing (p. 15).
49. Create a website for patient and clinician educational materials, as well as clinical trial information (p. 15).
50. Utilize the NIH Clinical Center for clinical trials and fast-track testing of new therapies (p. 15).
51. Improve quality of care by learning from palliative care (p. 15).
52. Examine role of self-management techniques as part of a comprehensive treatment plan during and after clinical interventions (p. 16).
53. Evaluate multifacted therapies focused on biomedical and supportive care (p. 16).
54. Conduct comparative effectiveness research (p. 16).
55. NIH and FDA convene a meeting on the state of ME/CFS treatment (p. 16).
56. Retire the Oxford definition (p. 16).
57. ME/CFS community agree upon a single case definition (p. 16).
58. Patients, clinicians, and researchers agree on a definition for meaningful recovery (p. 16).
59. Use new avenues to fund research (p. 17).
60. Develop demonstration projects with CMS and PCORI for patient-centered medical homes for people with ME/CFS, using a comparative effectiveness research framework to determine best evidence-based practices (p. 17).
61. Translate best practices to primary care clinicians (p. 17).
62. Create quality metrics and a standard of care in collaboration with federal agencies and professional societies (p. 17).
63. Form private-public partnerships between federal departments, advocacy groups, and industry (p. 17).
64. Monitor progress by convening another ME/CFS Expert Panel in five years (p. 17).
65. Federal agencies, clinicians, patients and advocates should consider the IOM and P2P reports together to move the science forward (p. 18).

[…]
Subject: Input: ME/CFS circulatory impairment

An important area of research is circulatory problems in ME.

Here is my proposal:

http://www.meadvocacy.org/circular_impairment
Please read and get back to me.

[…]
Subject: Comments for RFI for ME/CFS

Re: Response to Notice NOT-NS-16-024; Request for Information: Soliciting Input for New Research Strategies for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)

The form of CFS known as myalgic encephalomyelitis as described by the experts in the International Consensus Criteria has been grossly neglected. Thank you for the opportunity to have input into the planning process.

I am 56 and have been ill with ME as described by the ICC/CCC for 26 years. I run a support group, am active in the advocacy community, and have extensive experience after seeing multiple specialists and speaking with hundreds of people who have had similar experiences.

As ME is a multi-system disease, a wide spectrum of avenues needs to be addressed.

I understand and whole heartedly support research to get at the root cause of this illness and those efforts should be fully funded. Increased funding to an organization focused on ME research like Open Medicine Foundation would signal real change at the NIH.

The current reality is there are over 1 million Americans suffering 24/7 with debilitating symptoms which could be alleviated today with proper studies and using information we already have. Disseminating this information to doctors is long overdue.

Those of us on the front lines are aware too many patients are being pushed toward psychiatric care and exercise while the immune dysfunction, exertion intolerance, pain, etc. is neglected. I am focusing my recommendations on using the information we have now that can be leveraged quickly for real change. Because one of the main drawbacks in the past was focusing on "fatigue" patients who do not fit the experts' criteria for ME, I recommend any research be done only on those who fit the International Consensus Criteria and have been ill for 5 or more years.

By using these parameters, there will be a much higher level of confidence that the patients studied are not suffering from anything other than ME. The ICC criteria specifically stipulate the inclusion of post exertional neuro-immune exhaustion (PENE) which is the hallmark of this disease. I have added the 5 year suggestion as the science is now showing that patients in the early years of the disease have differing immune reactions than those who have reached the 5 year mark. I would also add that the five year mark would also rule out those who may have been misdiagnosed as the time factor will likely have led to a proper diagnosis of MS or other illnesses which mimic this disease.

One of the main challenges the NIH faces is the historical bias toward psychosomatic causes for the symptoms we experience. I sincerely hope this RFI is a turning point for eliminating that bias.

ACTIVITY EXACERBATION OF SYMPTOMS (PENE)

- **Description of the need or opportunity**

Because mental and physical activity exacerbates symptoms (immune abnormalities, cognitive issues, pain and the ability to work and do self-care), addressing this symptom is a high priority.
The 2 day CPET studies done by the Workwell Foundation have shown that the aerobic system is significantly impaired and the oxygen exchange system is malfunctioning. (See info at: www.workwellfoundation.org)

Utilizing the results obtained by the studies that have taken place or replicating studies, if necessary, should be a high priority as this information has a huge impact on the patient community.

- **Scientific rationale and potential public health impact**

Information is clearly showing the only way to reduce PENE is to restrict activity in order to stay inside a safe envelope. Maximizing the anaerobic system is crucial to improving patient quality of life. Educating doctors and the general public about this devastating symptom would have a significant positive health impact on patients.

We have repeatedly seen the damage done by doctors and the health communities who have promoted exercise as a treatment. The harm caused by family and friends pushing patients with the expectation that increasing their activity (graded exercise) will "help" has been devastating. Patients, too often, are belittled for taking the rest needed to avoid exacerbation of symptoms. This has led to patients becoming severely disabled and also to suicide because of the lack of understanding and support.

- **Anticipated challenges that will need to be addressed**

The main challenge toward making progress in this area is preconceived misconceptions about the reality of ME. The actions of the NIH and the CDC have made it very clear that they do not understand the full impact of PENE.

NIH studies MUST take PENE into consideration.

CDC MUST educate health care professionals about the dangers involved with patients doing anything aerobic.

PENE can be measured, but the challenge lies with the damage caused from inducing PENE in order to take the measurement. Accepting the reality of PENE is the first step to having a real impact on the patient community.

- **Appropriate benchmarks for evaluating progress.**

Success in this area will be measured by the support patients will receive when the medical establishment is educated about the dangers of aerobic activity.

HEART ISSUES:

- **Description of the need or opportunity**

The significant impact on patients caused by heart issues is described in the article which has previously been sent to the NIH: **Circulatory Impairment in Myalgic Encephalomyelitis: A Preliminary Thesis** by Maryann Spurgin, Ph.D. (http://www.meadvocacy.org/circulatory_impairment). I recommend the research done by Maryann Spurgin be given full consideration for advancing knowledge in this area. As many of us are struggling with orthostatic intolerance and/or POTS-like symptoms, we often find ourselves in the care of a cardiologist who specializes in these symptoms. Unfortunately, these doctors seldom understand the full impact of this disease and are not educated in the post exertional neuro-immune exhaustion (PENE) symptom.

- **Scientific rationale and potential public health impact**

There are many aspects of the heart and circulatory issues that need to be studied. One useful study would be to evaluate the effectiveness of Corlanor. If proven helpful, this medication would have a life changing impact on a significant number of ME patients. (I have no conflict of interest making this recommendation.)

Corlanor (Ivabradine) is a newer medication that many of us are finding effective in alleviating the elevated heart rate issues. Studying the benefits of this medication could lead to significant quality of life improvement for ME sufferers.

- **Anticipated challenges that will need to be addressed**

I would recommend the focus of this research be on those who are low-to-moderate in activity level, as this drug is meant to improve quality of life for those who are able to stand but have difficulty maintaining appropriate heart rate while standing.

Challenges:

1. Every participant would need full screening to look for the heart issues that often accompany ME.
2. PENE could be exacerbated as patients have an improvement in their overall heart rate and POTS/OI symptoms which could lead to increased activity possibly exacerbate the illness, thus leading to further damage of the oxygen exchange system. (I understand the irony of making people feel better could be dangerous to their health.)
3. Medication intolerance is a significant problem with most patients which could lead to exacerbation of illness.
4. Evaluating the baseline by using a 2 day exercise test (see Workwell Foundation data) could lead to exacerbation of illness and permanent deterioration.
5. Cost of this medication could be prohibitive.

- **Appropriate benchmarks for evaluating progress.**

Using information from a 2 day exercise test, I've been monitoring my heart rate in order to appropriately pace my activities. Many stories reach me regarding numerous people with orthostatic intolerance interfering with their daily life, thus leading me to understand the importance of addressing this symptom.

The benchmark I would use would be evaluating this medication (Corlanor) in those who are unable to do activity without exceeding their maximum heart rate. Monitoring would include charting heart rates before and after taking the medication.

Note: I, like many others, am highly intolerant to most medications. The side effects often cause more problems than they solve. Low doses of this medication have been effective in reducing my heart rate issues without compounding other symptoms. I understand other medications often prescribed for POTS cause significant exacerbation of fatigue and other symptoms.

- For this RFI, the NIBIB is interested in the ideas for the development of new imaging and bioengineering technologies that could have the potential for a significant impact on ME/CFS research.

In relation to the dysautonomia heart rate issues, monitoring heart rate issues could be very effective in finding patterns which are indicative of PENE. Many of us who have monitored our heart rates see the difference in HR when we are rested and when we are in PENE. The significant elevation of HR issues when standing during PENE is something that could be used by doctors and researchers to better understand ME.

Contact information for Corlanor at AMGEN 1-800-772-6436 to get specific information.

STUDY EFFECTIVENESS OF LOW DOSE NALTREXONE (LDN):

- **Description of the need or opportunity**

As ME symptoms include immune abnormalities, pain and sleep issues, studying LDN which can have a positive impact on all three of these symptoms could have a significant impact on the affected population.

- **Scientific rationale and potential public health impact**

I and many others with ME, as well as MS, have seen improvement in symptoms using very low doses of naltrexone. I have heard some stories of significant improvement. Personally I use 3.5 mg nightly and have seen a significant improvement in my sleep and a reduction in my pain levels, but there has been no reduction in the symptom of PENE so my activity envelope has not been significantly affected. I have been on this medication for over 2 years and slowly increased from a starting dose of 0.5 mg.

- **Anticipated challenges that will need to be addressed**

This medication does not come in these low doses so they must be compounded. And because many of us have multiple sensitivities to additives, it will be necessary to use minimal added ingredients. Improvements from this medication often take months and the effectiveness is mostly subjective. Although measurements using sleep study analysis would probably be effective as most everyone I have spoken with indicates a change in the sleep pattern.

Measuring pain reduction is subjective, but significant improvement would be clearly evident.
As soon as more of the immune marker abnormalities are pinned down, measuring improvements in immune system could prove whether LDN has a positive effect.

STUDY MULTIPLE CHEMICAL SENSITIVITY and MOLD SENSITIVITY

Many of us are highly sensitive to MSG and other chemicals in food as well as airborne chemicals. This sensitivity could be a major factor in the cognitive issues which have a significant impact on quality of life.

- **Scientific rationale and potential public health impact**

I have seen information indicating the cause for this symptom is a damaged blood brain barrier. Since many of us experience significant reactions in the brain when exposed to chemicals, it makes sense to study this aspect of the disease.

Potential health impact is significant. As many patients are finding themselves having to avoid mold and chemicals, they are left isolated from society in order to maintain control over their environment. Many patients have been forced to move from their homes that have mold or leave environments that have airborne chemicals.

- **Anticipated challenges that will need to be addressed**

One challenge is the lack of understanding medical professionals have about the impact chemicals and mold have on the patient. I have seen very little focus on this problem in the ME research despite the fact it seems to have a high incidence of interfering with normal function.

Testing for chemical and mold reactions means putting patients at high risk for worsening of symptoms.

SOMETHING THAT COULD BE DONE TODAY

The lack of urgency has been appalling. Much of what is needed could be addressed by using the media to explain the true nature of ME as described by the experts who wrote the CCC and ICC. The impact of explaining the devastating nature of coping with this illness which limits day to day activity to a point where many never leave their homes, needs to be made clear to the public so that friends, family, and health care professionals will start treating patients with respect.

In closing, I urge you to consider a multi-prong approach - biomarkers, cause, cure, treatments that are available today, but most importantly, make clear to the public this is a real disease with devastating consequences. Ask for their help to identify possible patients and get patients the care they need by educating medical professionals about the dangers of over-exertion and the importance of addressing immune dysfunction.

[…]
Subject: ME/CFS RFI Submission

My apologies for adding to your workload, but my submission to your Request for Information is below. Thanks!
****
Emerging needs and opportunities:

Need in ME/CFS research has been not only emerging but beating the ever-living sh%# out of patients for decades. Clinicians need tools with which to diagnose and treat patients and currently have NONE.

Think about that: *not a single treatment*. They do not even have the information necessary to not harm their patients! The research community — the apotheosis of which is NIH — has failed *both* clinicians and patients for decades. The level of need is so overwhelming at this point, that it's difficult to know where to start, though diagnosis and treatments should be among the top research priorities for NIH.

While I recognize that NIH does not develop drugs, it does collaborate with outside organizations including drug companies to develop clinical trials, such as is currently being done with Rituxan and Myasthenia Gravis. Given compelling current work on Rituxan and ME/CFS being done in Norway, NIH is in an excellent position to work with organizations and drug companies here in the US to facilitate

clinical trials of Rituxan and ME/CFS modeled on that mentioned above with MG. Ampligen and various anti-virals would also be good candidates in this regard. Drugs for similar diseases such as MS or Lupus may be of promise as well.

Compelling preliminary research with 2-day cardiopulmonary exercise tests suggest an excellent opportunity to attempt large-scale replication of these findings. While it may be of small but minimal therapeutic value, it would have a profound impact on validating the experience of Post-Exertional Malaise that patients have long described for the medical community and contribute to a wider understanding of the phenomenon of PEM which can, in turn, provide a foundation for further research.

We need biomarkers. We've needed them for the last thirty years. There are so many potential biomarkers to choose from: R-nase L, cytokine profiles, NK cell function, qEEG, 2-day CPET. But patients need to be diagnosed so much earlier than they are. Many of us may well have preserved much more functional capacity had we been diagnosed earlier.

The ever-increasing technological sophistication of supercomputers and microchips and their ability to identify complex physiological mechanisms has shown preliminary promise in this field, such as seen in the work of Ron Davis, Gordon Broderick, Ian Lipkin or Jared Younger and NIH would do well to collaborate on much larger scale with such researchers.

Citizen scientists and crowd-sourcing data is an exciting new avenue within medical research. With smart phones, wearable devices such as Fitbits, and third-parties such as uBiome, NIH has a fantastic opportunity to potentially gather large amounts of data quickly and cheaply.

At one time there existed Clinical Care Centers of Excellence for ME/CFS and they were producing some very valuable and innovative research before they were cut. Restoring them would provide both much needed clinical care for a population with few such resources, while at the same time providing the research community with a hub around which to engage in cutting-edge, translational research.

Challenges and barriers to progress:

Biases and stigma which have permeated research institutions, grant-review committees, medical schools, hospitals and clinics, as well as the evidence base leading to a preponderance of poorly-designed and executed behavioral studies devoid of objective measurement of pathology enforcing the incorrect belief that ME/CFS is primarily a mental illness.

LACK OF MONEY AND URGENCY: The biases and stigma have meant this disease has been, for the most part, ignored. It goes without saying that patients have been and continue to suffer in truly appalling conditions as a result of this indifference. As another submission to this RFI put it, "the technology is here, but what is lacking is funding and dedication."

No agreed-upon research definition: One hopes that CDC's multi-center study will soon provide a data-driven picture of what constitutes a typical ME/CFS patient. Until then, the use of the Canadian Consensus Criteria has near universal approval within the ME/CFS community.

Lack of validated biomarkers.

Heterogenous patient populations: Past research has lumped the patient population together rather than teasing out subgroups with often conflicting physiological responses to the underlying disease mechanism. This obviously causes conflicting results that muddies the evidence-base.

Many patients are housebound and simply cannot get to a clinic (myself included). Thus they will need researchers — at the very least, phlebotomists — to go to them.

Lack of integration with outside researchers and clinicians, as well as lack of participation of patients in all stages of NIH efforts on ME/CFS. No decisions about us, without us.

Lack of autopsy studies.

Lack of longitudinal studies.

Dearth of existing research. Thirty years of neglect has meant it is very difficult to know which of the many compelling but small studies to attempt to replicate first.

Few researchers studying ME/CFS.

Gaps and opportunities across the research spectrum:

Everybody with or who researches and/or treats this disease has a pet theory about what causes it and the disagreement within the ME/CFS community about what to focus on can sometimes be vitriolic. So the fact that there is near unanimous agreement that large-scale replication attempts of compelling early research in exercise/metabolic dysfunction as measured by 2-day Cardiopulmonary Exercise Testing should make this a research opportunity of singular importance to any NIH research efforts.

Auto-immunity: Fluge & Mella's work with B-cell depletion therapy has invigorated this field like few areas of research have (the aforementioned 2-day CPET testing being among them). Its value includes not only a potential elucidation of disease mechanism, but also treatments with therapeutic agents already FDA-approved (such as Rituxan, cyclophosphomide, methotrexate, Imdur), meaning patients and clinicians may finally have hope of readily prescribe-able treatment. Fluge & Mella's current hypothesis that there is B-cell-mediated endothelial dysfunction due to problems with Nitric Oxide Synthase has been of special interest to me personally as vasodilation (warm bath, opioids, herbal supplements like niacin, huperzine or vinpocetine) ameliorate my symptoms. Attempts to replicate their work as soon as possible have the potential to bring real relief to patients. Negative results are just as important here, since there is no use wasting years and funds on something that is a lab artifact.
Cellular "Big Data" studies: Given the thousands — if not tens of thousands — of complex cellular processes occurring at any given second in the human body, it makes sense that dysregulation of one of the many complicated cycles involved in these processes could be the mechanism of action in this disease. The ever increasing technological sophistication and power of supercomputers and microchips and technologies currently being developed make the ability to finally understand complex, interlocking cellular systems more possible than ever before. Moreover, wearable devices could provide a lot of data far more quickly than traditional studies.

Subgroups: I respond to vasodilators, my friend Marjorie to vasoconstrictors. Whatever dysregulation is occurring in this disease is obviously causing opposite reactions in patients who likely have the same disease. But instead of teasing out subgroups, past research efforts have lumped everybody together.

Why? This is a glaring gap in the field that should have been sorted out two decades ago when instead it mysteriously moved the other direction.

Microbiome and gut studies: So much compelling research being done in this field right now, including in ME/CFS. Since this is such a hot area of research, it's a great opportunity to leverage that excitement and bring new researchers into the ME/CFS field. Again, on a personal level, the worse my gut symptoms, the more incapacitated I am globally — sensory sensitivities, orthostatic symptoms, pain, sleep, flu-like feeling, etc.

Orthostatic issues: This is a research area that is decades old but about which we still know little. POTS and neurally-mediated hypotension are readily identifiable, but the work of Stewart, et al and others suggests that the orthostatic intolerance occurring in ME/CFS is more subtle and not as easily identifiable with tilt-tables or blood-pressure cuffs. Moreover despite reports of low-blood volume in patients, there is no easy direct way of measuring blood volume, especially at the clinical level. The emergence of technologies like Daxor could help verify initial findings of low-blood volume or even show problems with blood volume regulation in which both hypo and hypervolemia are present in this disease.

Many of the challenges and barriers mentioned above are also major gaps in our understanding of this disease.

[...]
Subject: ME/CFS RFI comments

I am a parent of a 24 yr old female patient and wife of a 67 yr old patient. I know how real this disease is and if anyone knows a patient, they would not question that. From what I've seen and read, it involves immune system and severe energy production problems. The brain and nervous system are effected and symptoms are debilitating. All these areas of study will help ME patients, but also benefit others with illnesses effecting these areas. Extremely little has been done to this point, and there are an estimated 2 million patients or more waiting in the US alone. Trusting their government to do something. We have had to protest to be heard. To be blunt, most doctors are ignorant and totally untrained on ME. They offer no help or referrals. The patients end up doing their own research to find help. This takes years, money and energy they don't have. Then, we've learned that it is still incurable, with no routine tests or approved treatments. We need them! Why is research money is near the bottom? And there's a ridiculous "stigma" to fight, too! Reality: effects of the illness continue and have killed. Many have given up waiting, in pain and isolation and commit suicide. And there will be more. How would you feel if it was your loved one? It could be. These studies must be done.

[...]
Subject: The Trans-National Institutes of Health (NIH) ME/CFS Working Group

To: The Trans-National Institutes of Health (NIH) ME/CFS Working Group

Re: Response to Notice NOT-NS-16-024; Request for Information: Soliciting Input for New Research Strategies for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)

Dear Working Group:

The following is my response to NOT-NS-16-024; Request for Information: Soliciting Input for New Research Strategies for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS).

Emerging needs and opportunities that should be considered as new ME/CFS research strategies are developed:

The effect of Chernobyl incident is coincident with peak ME/CFS outbreak in USA

Challenges or barriers to progress in research on ME/CFS:

Employ Illumina's gene sequencing HiSeq X in exploring the riddle of CFS since it makes the cost more affordable

Gaps and opportunities across the research continuum from basic through clinical studies:

Funding is urgently needed to enable Dr. Ian Lipkin's research to continue on the 'Microbe Discovery Project' (microbediscovery.org) that is underway by private donations that enabled samples to be collected from 100 ME/CFS patients. Additional funding to complete the testing is needed.

Thank you for your consideration and your service.

[...]
Subject: ME/CFS PLEASE HELP ME

My name is [...]. I am 23 years old and have been suffering from Chronic Fatigue Syndrome for 2 years. I have had to leave my university and return home to be taken care of. I am bedridden and too sick to leave the house. I was a very productive and active person and it took away my life. I have been receiving treatment from Dr. Jose Montoya at Stanford University via phone calls. FAMVIR and COLCHICINE improved my health dramatically but I have since relapsed and my symptoms have returned. The doctors and researchers at Stanford desperately need the funding to conduct lifesaving research on the effect of anti-viral and anti- inflammatory treatments.
Information on ME/CFS needs to be spread throughout the world and taught in all medical schools curriculum.

From all of the patients suffering from ME/CFS, please help us by providing the necessary funds to conduct this research.

[...]
Subject: RFI in researching

Hi,

I don't know if this is open to patients or not, and I am too sick to weed through all the info to find out. But I am wondering if you have considered that Fibromyalgia and Chronic Fatigue Syndrome might be tied in to sleep disorders? I have a couple of sleep disorders and have been also dx with CFS and FMS plus Chronic Myofascial Pain Syndrome. I have been on a medication (Xyrem) for the sleep disorders that has helped immensely and almost completely cleared all my pain from the FMS. It is my belief that a lot of those dx with FMS and CFS actually have sleep disorders and that when they do not go into restorative sleep, lactic acid builds up in the muscles and never dissipates, thus leading to the chronic all over body pain and fatigue. Due to FDA interference, and the hoops my doctor has to jump through to prescribe the medicine I have been on, my doctor is now refusing to prescribe it for me anymore. It is the only med that has helped me, even though I've tried dozens of other meds over the last 40 years. I have been on the med for over 8 years and now I am looking at going back to sleeping 18+ hours a day and being in excruciating pain. I am in dire need of someone to advocate for me in finding a new doctor to prescribe this med or help me find something else to take its place. Please HELP ME!

[...]
Subject: input for RFI re ME/CFS Working Group Auto forwarded by a Rule

To: The Trans-National Institutes of Health (NIH) ME/CFS Working Group

Re: Response to Notice NOT-NS-16-024; Request for Information:
Soliciting Input for New Research Strategies for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)

Dear Working Group:

Thank you for your time.

Some suggestions: Research regarding ME/CFS is especially important.
Other suggestions include:

-understanding the cognitive dysfunction associated with the disease.
But there are so many more areas that need investigation, including characterization and evaluation of post-exertional malaise, investigating the possible autoimmune connection, neurological connections.

-Answer questions about the pathogenesis of ME/CFS, including roles of pathogenic agents, genetics.

-Study fMRI and imaging technologies as diagnostic tools and to better understand neurologic dysfunction in ME/CFS

-Explore the intestinal microbiome and the effect of the environment and microbiome on ME/CFS

-Develop diagnostic and prognostic algorithms to identify who will develop ME/CFS after infectious or other triggers

-Conduct longitudinal studies to explore the possibility of a progressive immune exhaustion or dysfunction

-Create a network of collaborative centers working across institutions and disciplines, including clinical, biological, and social sciences

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[...]
Subject: RFI response: Research Needs/Opportunities ME/CFS

NIH should fund and direct a Phase IV clinical trial of Ampligen for the treatment of ME/CFS.

ME/CFS is a severely debilitating, chronic and complex disease. Considered a public health crisis, it is a critical unmet medical need with a severe lack of funding; we recommend a Phase IV study be conducted by the NIH granted under a conditional approval by the FDA and in collaboration with the support of the sponsor. The recommendation fulfills NIH/FDA's goal to speed new treatments to patients announced in 2010*.

• A description of the need or opportunity Currently there is no approved drug therapies for ME/CFS, however Ampligen provides a most unique opportunity to advance a treatment, further understand the disease and open the regulatory doors for other pharmaceutical companies to pursue drug development. No other therapy has advanced this far in the FDA pipeline. New drug therapies entering the pipeline may take another decade before approval. FDA regulations permit conditional approval of drugs and their collaborative initiative with NIH offers the pathway conduct the study.
• A scientific rationale and potential health impact
Ampligen has completed Phase II and Phase III double blind/placebo controlled studies and has been providing benefit to patients for over 20 years. The FDA advisory committee voted it safe for approval. Drugs with significantly less dosing and with significantly higher adverse events have been approved for use. ME/CFS experts agree that a conditional approval of Ampligen is warranted and could improve the lives of 25-40% of the ME/CFS population.
• Any anticipated challenges that may arise
A concern over wide spread use in the marketplace; recommendation is that a risk mitigation program be established that requires the physician be educated on how to diagnose the disease, treat the disease and properly administer Ampligen; require the patient be educated on the drug and the dispensing pharmacist must check that the doctor and the patient have fulfilled on these requirements prior to releasing the drug.
• Appropriate benchmarks for evaluating progress
ME/CFS experts be included in the conduct of the Phase IV trial and all parties agree upon the measurements and the study must comply with FDA requirements.
• Challenges or barriers to ME/CFS research
Lack of understanding by the health agencies and the healthcare community.
• Gaps and opportunities in research

Funding needed to conduct appropriate level research.

https://www.nih.gov/news-events/news-releases/nih-fda-announce-collaborative-initiative-fast-track-innovations-public

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[...]
Subject: Request for Information: Soliciting Input for New Research Strategies for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)

Dear Trans-NIH ME/CFS Working Group and Dr Whittemore,

I'm a Doctor who has been bedridden with severe ME/CFS for a long time after graded exercise therapy caused a severe relapse from which I haven't recovered and I will only get my health and independence back if I get treated with effective medication which isn't available yet as a review of the PACE trial has now clearly shown that CBT and GET are ineffective for this debilitating disease [1].

I am writing to you in relation to your "NOT-NS-16-024: Request for Information: Soliciting Input for New Research Strategies for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)".

I would like to ask you to focus more research into the underlying problems in the severely affected ie viral, Lyme and co-infections like Bartonella etc, metabolic and energy problems, auto antibodies and treatment trials with (for example) Ampligen, antiviral medications, ARV's and medication that works for (other) autoimmune diseases.

The reason to concentrate on the severely affected is the worse the disease the more likely it is that patients have ME and not something else.

I also have a more detailed RESEARCH PROPOSAL and that's why I have taken the Liberty to copy this email to Professor Julia Newton who has done a lot of research on the energy production problems in this disease. She was involved in the paper by Jones et al. [2] and like Lane et al. [3] they demonstrated a left shift in the anaerobic threshold in about 40% of patients.

I have done some research on myself and found a big left shift as well and last year I published a paper about it [4] in which I demonstrate that if I eat less than 3 hours before I just walk to the toilet and back, this left shift will get a lot worse and the same applies to the delay in releasing a second batch of lactic acid after the exercise. Even though walking to the toilet and back is trivial, eating has the same effect as it did in the past when I would go for a long run ie I would need to make sure that I had eaten 3 hours or more before I did go for the Run. If I do that now I have "more power" and less pain afterwards.

In the paper I show that it's very likely that the oxygen uptake into my muscle cells or mitochondria is impeded and my RESEARCH PROPOSAL therefore is the following:
Take 10 to 15 ME/CFS patients with a left shift of the anaerobic threshold and the same number of healthy controls, let them do exercise which they can do which produces a large quantity of lactic acid but doesn't cause a relapse and let them inhale radioactive oxygen to see if the oxygen distribution into the muscles is the same as in the healthy controls to find out if a severely reduced oxygen uptake is the reason for the severe problem with the oxidative phosphorylation hence we have to rely on the glycolysis, produce lots of lactic acid for trivial exercise which results in a left shift.

The reason why I have taken the liberty to include Professor Newton in this email is that she might be interested to do that study and maybe you could then Finance it.
(Due to the severity of my illness I had to use my energy for this email and haven't been able to contact Professor Newton about it. So I do apologize for that).

I didn't attach my article because I wasn't sure if you would open an email from an unknown person with an attachment. The full article is available here:
The Aerobic Energy Production and the Lactic Acid Excretion are both Impeded in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome http://dx.doi.org/10.16966/2379-7150.112

Thank you for your time.

Sincerely,

[…]
{Family Physician}

References

1. Vink M (2016) The PACE Trial Invalidates the Use of Cognitive Behavioral and Graded Exercise Therapy in Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome: A Review. J Neurol Neurobiol 2(3)

2. Jones DE, Hollingsworth KG, Taylor R, Blamire AM, Newton JL (2010) Abnormalities in pH handling by peripheral muscle and potential regulation by the autonomic nervous system in chronic fatigue syndrome. J Intern Med 267: 394–401

3. Lane RJM, Woodrow D, Archard LC., (1994) Lactate responses to exercise in chronic fatigue syndrome. J Neurol Neurosurg Psychiatry 57:662–663.

4. Vink M (2015) The Aerobic Energy Production and the Lactic Acid Excretion are both Impeded in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. J Neurol Neurobiol 1(4)

[…]
Subject: Re: News Update - NIH issues Request for Information on ME/CFS research

Ms Emr and the Trans-NIH working group,

I've identified three issues of overwhelming importance in the public health effort against ME/CFS. They are, in order of importance:

1. educated doctors
2. access to effective medication
3. a biomarker

The recent IOM report noted an 8 year dx rate. That is unacceptable. It's further unacceptable that many of us are disbelieved and frequently abused by those who are paid to listen and understand us. As

a patient with considerable brain fog, I am expected to be informed enough on pharmacological technicalities to spar with nurses, MDs and the rare psychiatrist. I deserve better, and my friends without the appropriate scientific bacground deserve much better.

I am in remission now and that is thanks to my own creative offlabel use of various pharmaceuticals. This is a curable, or at least treatble, illness. Therefore, it is entirely unreasonable that patients should not have access to the drugs that allow them to resume their lives as productive adults. We need to fast-track approval for drugs like ampligen, rituximab, LDN, valtrex and valcyte to be available and recommended, if only experimentally, for adults with ME/cfs. CBT and GET are not a viable substitute, esp considering the significant number of harms they incur.

Finally, due to the immeasurably destructive psychosomatic model, we patients are not often believed when we present to a doctor with our symptoms. Our clean serology reports don't help matters much. In order to convert the disbelievers, we must pour resources into finding a biomarker, and then a causative agent immediately. It is my belief that this is an infectious illness, maybe even a retrovirus, and that we have a simmering, enormous public health problem on our hands.

addendum:

I'd note that any research on the ME/CFS front could result in considerable gains for patients with "postinfectious" lyme and gulf war syndrome as there's evidence to suggest that the same inflammation pathway may be involved. I imagine the same is true vice versa.

[...]
Subject: LDN ME FM

Hello My name is [...]..I live in Canada ..British Columbia. I was contacted by [...]regarding being a patient with FM ME on LDN.

I am in month 11 being on LDN.....I am a patient with ME and FM...and I am also MCS as well as depression anxiety, osteoarthritis, as well as a highly sensitive personality coming from an autistic family but I do not have autism. I am also MTHFR having done the 23 and me genetic saliva test. If I can be of any help please contact me.

[...]
Subject**:** Request for Information

Attachment (at bottom) includes text in microsoft doc.
Text below is pdf

To: The Trans-NIH Working Group
[...]
Re: Request for information
Date: 24th June, 2016

It is impressive and gratifying that this Trans-NIH Working Group is reaching out to a wide and varied range of stakeholders in ME/CFS.

In the main society relies for medical progress on the extensive skills and knowledge of people who have committed their professional lives to biomedical science in order to understand and treat M.E. and other diseases. These have included clinician/researchers and scientists at academic medical centers, at the CDC, as in the stunning Dubbo project, and even scientists on military contracts. And now one looks forward to beginning to access the wealth of America's great national resources at NIH in both personnel and technology.

Yet your interest in reaching beyond these to others in health care, to patient advocates and organizations, to scientists with ad hoc interest in ME/CFS, and to others is to be applauded. Such wide-ranging sources of observations, intuitions and contributions would seem likely to gain ground more rapidly on this terrible, destructive disease which so impoverishes our nation of talent, productivity and wealth. Equally important, the history of science contains many incidents where an odd thought or tidbit of fact from beyond a scientist's usual ken precipitates a proverbial "Eureka!"

I hope that my efforts to contribute can benefit the Working Group's newly energized endeavor, which seems admirable as well as necessary. My background is more in business, where numerous studies from high-powered academicians support the concept that a group can be the most effective and insightful format for making decisions.

My work has always involved intensive research in pursuit of information and insights, and perhaps there is complementarity in that. In the 1970s I worked as a financial journalist and in the 1980s, following an MBA degree, in financial markets as an analyst of energy industries. Certainly the subject matter was very different from what is needed to solve questions pertaining to ME/CFS. However, research in financial analysis or (investigative) journalism does share with biomedical \ science the requirements of persistence, initiative, and inventiveness in pursuit of knowledge. In addition, analysis in both areas involves data and statistics.

It is my aim with this background to make a helpful contribution to the Working Group.

I would caution that one large challenge is that there will be an "elephant in the room" connected with the Working Group endeavors. My experience suggests that the most effective way to deal with such an "elephant" is for everybody to examine it as thoroughly as possible. Each person can bring their own perspective to bear. Inevitably confronting difficult subjects may seem uncomfortable to everybody involved. For this reason the Working Group may sometimes want to invoke two special provisions: 1. Absolute confidentiality and immunity as to content of discussion, though only and specifically in respect of this difficult "elephant" subject matter, and 2.Assistance from an experienced and sensitive facilitator not otherwise involved with NIH. I can make enquiries as to where to best search for such if that is helpful.

I only bring up this “elephant” after due consideration because my best judgment and experience suggest that a subject so long festering is likely to stand in the way of your goals and your best efforts unless it is duly grappled with and wrestled into inconsequence.

The “elephant” would be the long-term and widely institutionalized tradition at NIH and HHS of disinterest in and skepticism about ME/CFS. Realistic treatment options such as Ampligen and Rituximab remain inaccessible because they are ignored as subjects for study. “Good enough” biological markers have served the dozen or so expert physicians available to America’s one million patients, but no funding is available to develop newer science into better biomarkers.

This has not been in the national interest. Some $30 - $50 billion of GDP has been lost annually. This is because, with no effective treatment, roughly 80% of those taken ill by ME/CFS end up too disabled to work or attend school or college; some 50% remain largely housebound and in the range of 20% bedbound. The economic cost misses further societal losses of contributions to family and community. The total national loss is more easily comprehended by reviewing M.E.’s ubiquitous cognitive dysfunction, loss of strength and mobility, and disproportionately long periods of collapse after exertion (PEM.)

In business generally and in academic study study of business “Corporate Culture” is widely regarded as key to success or failure. At this time one of the most important tasks in front of the Working Group is to frame matters and even campaign outright to the end that NIH Corporate Culture develop a positive attitude to ME/CFS.

This is hard work, and demanding of energy. It may need input from top pros in advertising and public relations. A case must be made for the development of a strong push throughout NIH so that the institution becomes broadly committed to development of understanding as to the etiology and the treatment of M.E.

In fact M.E. is an ideal candidate on which to practice the sort of integrated and cross-specialty medicine that is looked to for the future. The immune therapies being developed in cancer research can for the benefit of all specialties be further trialed and modified in work on M.E. -- perhaps with a longer-distant goal of use in MS or Lupus, or others of the myriad immune diseases. M.E. is the perfect candidate for application of precision medicine to mutual benefit. The National Heart, Lung and Blood Institute (NHLBI) is needed to apply cardiac expertise to the M.E. pathologies of early heart failure and POTS. And surely the $3 billion annually assigned to that other disease of immune deficiency, HIV-AIDS, could produce some shared lessons from work on ME/CFS. But none of this can happen without a positive Corporate Culture -- understood, adopted and deeply absorbed throughout NIH, towards beating the disease.

[…]

Subject: things to study - management tools, improving life while waiting for a cure

1. Heart rate-based pacing and activity management program.

Description: The use of continuous heart rate monitoring and heart rate variability measurements, to facilitate the patient, in managing their day to day exertion levels, rest and activities.

In order to provide the patient with objective tools, that will enable the patient, to avoid symptom exacerbation and facilitate stabilisation. To help the patient stay under their anerobic threshold, and to stay within their "energy envelope", in order to minimise pushing and crashing and hence, further deterioration.

2. Heart rate based restorative exercise program (not for the profoundly ill, many of whom, may need to focus on lying extremely still, so as not to exacerbate their symptoms and go over their anaerobic threshold).

The goal is to increase the patient's ability to utilize anaerobic energy systems, by increasing strength and flexibility. Patients use a heart rate monitor to help assess and stay under their anaerobic threshold, while trying to expand their capacity. Patients to avoid aerobic exercise, such as walking, cycling, and all activities that push them over their anaerobic threshold, or cause symptom exacerbation.

1. Food intolerances and FODMAPS. Some patients have found the Royal Prince Alfred Elimination Diet Handbook from the NSW Allergy Clinic has helped the identity and remove foods that they are intolerant to from their diet. Others have found the FODMAPS diet from the Monash University Melbourne, helpful. Investigation into identifying how best to determine which of these and/or other readily available scientific diets suits which subset of patients.

2. Noise sensitivity to be investigated and quantified. Some patients have found constant low level noise eg neighbouring residents TV's to be more harmful than the occasional loud noise. Noise characteristics of the ideal environment to be determined as a step towards, characterising the ideal care environment for a patient with ME.

3. Light sensitivity to be investigate and quantified. Many patients require a dark room, with low lights or torches to be used by carers. Light levels to determined and suitable methods for lighting rooms of people in care to be determined.

4. Hospital and clinic admissions. Recently yet another ME patient has died due to being unable to access medical care for a comorbid condition. Like many ME patients this person was too ill to attend out patient clinics, hospital etc... Investigation into effective ways to provide medical care to all citizens, even those with ME.

[...]
Subject: management tools while we wait for treatment

Dear NIH

Thank you for all the great work you are doing.
I'm writing to suggest an area of research that is ripe, for some quality studies.

The use of continuous heart rate monitoring and heart rate variability, to manageexertion and rest in people with ME/CFS.

Not a cure, of course but a means of immediatel, improving or stabilising our quality of life, while we wait for a cure.

The work of Staci Stevens, Mark VanNess, Alison Bested, Christopher Snell, Nancy Klimas is helping patients worldwide. We eagerly await the videos that they post online, we print off their papers, for out doctors. Their names, are quoted extensively....but we need more, to get their management practices, into mainstream ME/CFS management.

We have a lot of questions: Our doctors and exercise physiologists look at us as if we are nuts, when we describe the effect of exertion on our heart rates..... Yet the same weird heart rate patterns, are shared by many of us. Maybe all of us? Facebook groups consisting of people, pacing with heart rate monitors, may or may not, be representative, of the entire ME/CFS, population.

A study to quantify and illustrate the patterns, so that we can better manage our health is desperately needed.
We have no medical professionals to talk to about these things because they don't listen to us. We shut up, at the first eye roll, the first hint of disbelief. It doesn't take many doctors visits, to realise that as well as losing our active healthy lives, we've lost our credibility. We were working professionals, whose opinions were respected, now we are chronically ill patients, who are suspected of malingering and looking for pity? Sympathy? Benefits? Insurance?
Findings and questions.

Continuous heart rate monitoring
Staying under our anerobic threshold at all times appears much more beneficial than occasional "cheating".
In order, to stay under our anerobic threshold, we need to retire to bed, crawl to the bathroom, use wheelchairs, shower on the floor of the shower, wash the dishes on the floor of the shower, cook on burners placed on the floor...pay someone to clean, precook meals, use pee jars to limit the need for walking to the toilet, keep the room dark. - we can still physically walk, so these measures appear extraordinary and .. absurd. We need research, into this aspect of management. All I can say, is that these extreme measures, have turned my life around. My life was a continuous, slow, deterioration and loss of ability to drive/walk/talk/think. Now I'm to stabilised and a slowly improvimg. 9 months late, I'm still in my bed most of the day, BUT I'm feeling better and able to do a little more- I can now, walk to the bathroom, whenever I want to!! I can write this emai. Albeit over a number of days.
Heart rate based pacing, is working for many of us. It's hard because it is, so, so restrictive and we need to rest, far far more than we ever imagined, was necessary. Improvements, are incredibly slow, but real, OBJECTIVE, measurable.
Heart rate monitoring, also helps the profoundly ill, one bedridden persons findings Heart rate anerobic threshold, exceeded by hearing a person entering the room, someone switching the light on, lifting a fimger - focused on lyimg still NOT moving, over a year of NOT moving, gradually I just naturally did more. My mental focus was to NOT move but as physically, i was more able i foumd i would naturally do more. At no time, did I ever encourage myself, to do more. After a year I was moving around in my bed, helping myself get onto the bedpan. Then I started gentle hand squeezes….after 2 years, I'm still 100% bedridden. However, I've improved, from being spoon fed puréed food- to feeding myself; lying in the dark- to watching the aged care residents, in the courtyard (not for long); not able to be

touched-to having massages (which reduce my constant pain, a little);not able to use the phone- Skype my mother; severely under weight, too looking healthy in the face; from no future, to hope of a life in the real world; severe intense unfathomable pain, to constant but not totally overwhelming pain.
The weird heart rate things, peole with ME/CFS are finding Our heart rate elevates enormously on standing (POTS)- many of our cardiologists, doctors etc expect our tachycardia to be present immediately. They measure our heart rate when we are lying and as soon as we stand- you are ok they say. Hang on the tachycardia starts a few minutes after we stand still…..
After small amounts of physical, exertion, our heart rate rises. Our heart rate, will stay elevated above its normal resting rate, for a few hours after exertion.
If we exert ourselves for longer, we notice that our heart rate plumets down/rises way up. 150 -40…. Is not uncommon. We find a plummeting/spiking heart rate, is an early warning signal, of too much exertion, and will be followed by post exertional debility. (Malaise is not a word that conveys the intensity of the post exertional Neuroimmune exhaustion).
If we ignore the plummeting/ spiking heart rate, and continue exerting ourselves, our heart rate may settle to a nice level, that looks "normal". Our chest, feels slightly tight and constrained, we might feel a wee bit breathless. Our heart rate is in the 60's - so we are good to go? No, this "too good to be true" heart rate. It's actually a sign of, even more over exertion, than a spiking/plumeting, heart rate. The longer we continue exerting ourselves, the more severe the post exertional debility, and the longer the recovery period. A too good to be true, heart rate is easily identifiable- if we rest/lie down, when we suspect our heart rate, is too good to be true, our heart rate will rise and settle at an elevated level. In contrast if our heart rate is genuinely low, we will feel relaxed and on resting our heart rate will drop,to our normal restin baseline.
The stress and exertion, of getting to a doctors office, can set off this too good to be true, heart rate pattern. Here, we are a crazy ME/CFS patient, telling you, our doctor that we have POTS a high resting heart rate…. Only, in your office, our heart rate looks normal, it doesn't rise when we stand, and looks normal.
The day after exertion
The day after, too much exertion our true resting heart rate may actually, be lower than its normal baseline by a couple of beats. This is not a good sign, it is accompanied by a subtle tight chest feeling. Rest is needed. Day 3 and the full post exertional debility, impact will be felt. Resting early, reduces the depth of the crash and the length of the crash. If we rest heavily, over the next 3-4 days, our resting heart rate, slowly reduces, a couple of beats a day, until it's back to baseline. Resting heavily means dark, quiet, flat - meditating or sleeping.
What we notice, is that on the days after, too much exertion, our heart rate is unstable - it rises much more quickly than usual eg walking to the bathroom that we could do and stay under our heart rate cap, becomes impossible to do safely. Slowly over 3-4 days of heavy rest our heart rate becomes more stable, and returns to baseline.
We notice that after exetion our chest heart rate monitors give weird spikes - I don't think my heart is really beating at 400 or 800 bpm and these spikes don't show on my wrist strap monitor. I know I get weird readings when my chest strap hasn't s good connection but I've checked that. When others on Facebook mention the same oddities, I know I'm not crazy. It happens again and again and only when I've over exerted myself. I don't think my heart rate monitor only plays up when I'm over exerted??
Reading/writing/concentrating and our heart rate slowly rises, warning us when we need to rest.
Emotional stress can have as much impact on the heart rate as other exertion. Environmental intolerances affect the heart rate. Notice a heart rate rise, everytime you eat gluten? Heart rate rise on exposure to perfumes? Heart rate can help identify food and environmental intolerances.
Mark VanNess, tells us our heart rate monitor never lies. Sometimes we just can't believe how little exertion will set it off. Mark is right - our HRM never lies.

I recently watched, Mark VanNess's 2016 conference talk, it brought tears to my eyes. For the first time, an expert in exercise physiology, acknowledged the existence of people profoundly ill, with ME/CFS. His video is the first time, I've heard a health professional mention the profoundly ill. The profoundly ill desperately need help. I call on the NIH and the CDC, to include these people in their studies. Is there is a story in their heart rate data? Obviously many of these, people are far too ill to partake in any activity that causes more than a tiny amount of stress.

Heart rate variability

The other tool we are finding really useful is measuring our heart rate variability. It is proving to be really useful. The day after too much exertion, our true resting heart rate might be low, but our heart rate variability, will indicate that our body is stressed and we need to rest. It's often hard to rest, the day after too much exertion, as our bodies feel wired, it's exciting, to feel as if we have got away with, doing something. The HRV data warning us to rest, is really helpful. From experience many of us are finding, that if we listen to our HRV, warnings we will recover faster. The app HRVElite is handy because it's nice and simple- green ok, yellow warning, red danger. The written guidance is not at all relevant to us, but the dial is.

My visit to a cardiologist.

I've asked if I can lie down somewhere instead of sitting when I arrive, told yes. Enter in a wheelchair. At the ultrasound I'm asked if I expected my heart to look normal, I said yes, I didn't think I needed this test dome again but I was told its your standard procedure. Sonographer tells me about the people she sees with really bad hearts who are still walking around, you wouldn't believe, how ill some people are and they come in here unaided. They are lucky, I say. I wasn't expecting that response says her face.

Next I'm checked for POTS- my heart rate doesn't rise imediately on standing and I ask for it to be remeasured, after I've been standing a few minutes. No need you don't have POTS, your heart rate, didn't rise immediately. I lie back down in the waiting room across a few chairs.

Next stop the cardiologist. My wheelchair with its extended legs is at the wrong angle to get through the door, so I get out and manipulate it through. Look at you he says ….in a wheelchair, what can I do? I think you need to see a psychiatrist. Gob smacked I explain that my GP wants to ensure I'm on the best beta blocker for my POTS. He says I don't have POTS but I show him my photos of veneous pooling and my BP and heart rate recordings on standing. He agrees that I have POTS. i list the management measure I take to reduce POtS. Do they help he asks. I don't know I say but they can't hurt.

He tells me about new research using IV saline. I say yes, Vanderbilt University has some studies on it, I say I'm not keen to try it as my daughter who also has the same "MAST cell" subset of ME/CFS, as me tried it and over time reacted to the plastic chemicals in the saline.

You've spent 18 months bed/couch bound you're deconditioned, he says. In part, I say, but this is not, why I am ill, I was really active before getting ill.

I give him my graph of daily exercise against resting heart rate. This graph clearly illustrates that when I severely reduced my exercise and started heavily resting my true resting heart rate dramatically lowered, step wise over 2 weeks. He is surprised. He tells me about a rare disease called post viral fatigue, I excitedly tell him, that is another name for ME/CFS. Oops - I've forgotten I'm the patient, I'm not actually meant to know anything. Have you seen a psychiatrist, he asks again? I wanted to discuss my heart rate findings, I know from my contacts on Facebook, that my weird findings are a common pattern. I don't. I can't face being told for the third time to see a psychiatrist.

I try talking to my exercise physiologist, about my heart rate findings. She talks about heart rate lag and natural delays ….. we are not on the same page. She tells me that heart rate variability, won't be useful in my case because I'm largely bedridden. I say nothing, I can see from her face, there is no point in saying anything. I email, her screen shots of my ridiculously high heart rate spikes from days after I'd exerted myself. She never responds.

My exercise physiologist encourages me to spend some time in the chair, to do some knitting. She means well. I've learnt I need to trust my body. I focus on the words of Alison Bested and tell my brain, that for now my body sets the pace. I've learnt that I can trust my body, to do more once it's able. I don't have to encourage, coerce or tell my body to do anything. I focus on NOT, doing anything and as I'm able, much to my surprise, I just find myself doing more.
I wore an arm brace for a torn ligament. The physiotherapist said wear the brace whenever you feel you need to, but don't force yourself to wear it, she said over time, you will naturally find yourself not wearing the brace.
My experience of ME/CFS is the same as my experience of wearing that arm brace was. I don't need to tell my body to do things, over time as it is well enough, I just naturally do more.
It is the misguided and deeply held belief that ME/CFS is a mental health disorder, that leads to us being coerced, into doing things, we are not well enough to do.
We don't talk to our doctors because they don't listen to us. We don't tell our doctors, the truth because they don't believe us. We lie, agree that we will write a book, because "we are just hanging around" with CFS/ME as my doctor told me. We don't explain that we can't think/write/process/keep a thought in our brain. Our doctor is excited about their idea of how we could fill in our time. We leave them deluded, how can we explain that ME/CFS takes all our energy, that we lie in bed and the day just disappears.
It is only as we recover that the full extent of how ill we were hits us. I feel like sitting in the recliner, I feel like opening the curtains, I feel like getting dressed- I'm recovering.
I'm tell you the things, I can't say to my doctors and exercise physiologist, because if the NIH and the CDC are truely mean what they say when they say they want to help people with ME/CFS, then they need to know the truth.
The pathophysiology will come out of the biomedical research but the management tools are already available.
All that is needed is research into how best use them.
There is also an urgent need to find a less harmful test, than the 2 day CPET test, to measure disability.

[...]
Subject: NIH RFA RE: Myalgic Encephalomyelitis

Dear Dr. Vicky Whittemore,

As a patient I think what we need in short is **more** (a lot more) and specifically more stringent criteria for research (two candidates the Canadian Consensus and International Consensus have already been used in research articles), more funding of all kinds, more clinical resources, and more planning, including probably a central institute of some kind dedicated to researching ME and making recommendations for clinical care.

Consider the science done via the Human Genome Project, or if that is too daunting an Analogy than the epigenetics of fruit flies.

What we need is a coordinated effort, with one or a few people in charge, and patients in some advisory capacity (for example, as a board of directors) that has goals and has funding. If we had a "Manhattan Project for ME" the amount of progress that could be made into even a few years would be incredible.

All this depends however, on a few leaders on the science side who are willing to follow the historical trail of papers on ME research back to the Royal Free outbreak in 1955 and not discard those that conflict with their hypotheses as became fashionable in the early 90s. They will find despite the shoe-string budget there is strong evidence for a "flu-like" illness at onset, blood volume abnormalities in the chronic stage and other intriguing signs low SED rate, and increased Neutrophil apoptosis.

Also because the CDC has no trust among patients the NIH would have to take the lead, perhaps more than is usual with other diseases. The CDC "effort" to understand this illness was lead by the late WC Reeves, who believed it was psychosomatic and created such a faulty definition that anyone who came home from a long day of work (indeed probably many of you) would qualify for. A grossly inappropriate definition which the CDC has been very slow to renounce (to the extent they have).

One thing to realize is that much of the biomedical research has been produced by small groups, often patient funded (for reasons that must be known to you) and exploratory. Using poor definitions (such as the CDC 1994 and the aforementioned even worse CDC 2005) these findings have often been not replicated or simply ignored this must change because there is infact a solid core of biological research on which to build a research effort on.

I would direct you specifically to the database of articles maintained by ME research UK (http://www.meresearch.org.uk/our-research/completed-studies/) among other resources for some of this.

One of the most knowledge patient advocates I know regarding the scientifically and historically important research I know is Maryann Spurgin who I'm sure would be responsive to inquiries from the you or another representative of NIH ([…]).

A well known ME advocate Jodi Bassett just died at the age of 40 and yet there is no federal registry of mortality and other health complications due to ME, though I imagine such a thing would be technologically straightforward and low-cost to set-up.

Related to the complications from this disease for which there is absolutely no "support net" many with ME are too sick to feed themselves and either risk starving to death or become institutionalized when they run out of money to pay for carers or if their family abandons them. I know some of these persons but cannot help them due to being ill with little money myself.

In short I believe several centers of excellence in research and medical care should be established, with a central institute that works, in addition, to coordinate the others. Research data should be shared. A strong definition should be used. Given flu like onset and progressive, deterioration we mostly experience, the concept of stages should also be included in research. A shared research and epidemiological database should be established. And of course all of this will need to be funded.

If ME were funded at the rate of MS an illness it often compared I believe this would cover the costs of the above especially if the NIH, the Congress or whoever is responsible, took into account the lack of funding for the past 30 years to "jumpstart" research especially in the next five years.

Thank you for reading my letter.

I sincerely believe that people with ME are one of the most neglected, or the most, neglected severe and prevalent disease in modern medicine. But there is no reason this need be. ...

[...]
