A response to the draft report from the P2P panel on ME/CFS

I am using the SECOND VERSION of the draft report.

First, I want to thank and congratulate you for having taken some important and long overdue steps towards recognizing the reality and biological origins of ME/CFS.

You recognize that there is good evidence for many neurocognitive dysfunctions–found in fMRI and PET imaging, and also "strong evidence indicates immunologic and inflammatory pathologies, neurotransmitter signaling disruption, microbiome perturbation, and metabolic or mitochondrial abnormalities." (82-86). You could add to that Autonomic Nervous System problems, signs of probable Autoimmunity, cardiovascular dysfunctions, and several more. You also state clearly that "Although psychological repercussions (e.g. depression) often follow ME/CFS, this is not a psychological disease in etiology" (92-3). A key statement, thank you for having made it so clearly.

I also thank you for your recognition that there has been–and unfortunately continues to be–among many medical professionals a denigrating attitude, which we hope better education in the realities of the disease, which is one of your targets too, will slowly disperse. Unfortunately, the NIH and CDC have been major contributors to this sad state.

You also recognize that the multiplicity of definitions has been a major problem, and your recommendation that Oxford definition be retired (365) is very welcome news–a brave, clear and helpful statement. We hope that it will be acted upon, since the explicit inclusion of patients with depression has helped confuse and suppress the clear evidence of the biological origins of ME/CFS, which you have recognized. The Fukuda definition suffers from some of the same defects, and retiring that too would be helpful.

These statements form a solid and well directed foundation, but unfortunately I think your recommendations for treatment and research are less successful, and a primary cause for that is the simple fact that you do not know enough about the disease, the research that has been done, and the treatments that have been explored. You are writing from an inevitably inadequate knowledge of the research, social and political history behind this sad state. This is not your fault–it is the fault of the NIH in setting up the parameters of this profoundly unworkable Workshop, against which many of us protested, though we were neither heard nor replied to. You were expected to decide upon the basis of an almost absurd AHRQ review that "excluded" over 1,000 studies, and "included" I believe 78, excluding in the process many of the most promise-filled studies done so far. You were then exposed to some experts, but they could not cover much of the ground that needed to be covered in order for you to have a comprehensive grasp of where we stand today. You were asked to do the impossible, and not surprisingly I am not always happy with your analysis or conclusions, though I believe you acted with the best intentions.

One major point that will keep being repeated in my comments is that many of the good

things you recommend have repeatedly been explicitly refused by either NIH or CDC, and many of us doubt that the underlying negative view of us and our disease held in those bureaucracies will change easily until/ unless there are major changes in the staffing. That will colour some of my remarks, which will attempt to follow the structure of the draft report.

Introduction.
Mostly good suggestions, though I have a few comments:

6) "greater than $billion"–best estimates are much higher, closer to $17b-$29b.

10-11); " the research and medical community has frustrated its constituents"–I would distinguish between the research community, which has in my view been doing its best with what little funding it has managed to obtain, and the medical community at large, which has mostly accepted the diminished view propagated and defended for 30 years by CDC and NIH (see Hilary Johnson's "Osler's Web" and the letter from Steven Straus to Fukuda congratulating him on his new definition, and expressing the hope that CFS would soon disappear in the flood of general fatigue studies.

27) "We critically reviewed the scientific literature"–I fear you were able to do no more than sample it, with many of the most promising small studies hidden from you view–for instance, the Mella and Fluge Rituximab study, which though admittedly very small pointed clearly towards an autoimmune component, a view which has been strengthened by more recent work.

Incidence and prevalence
Mostly relevant and true, but:

52) " a research focus on men"–incorrect (see 88-89–"Caucasian, middle-aged women), though there are two studies underway that do focus on men–the possible differences between the forms the disease takes in men and women is a topic in need of work, as is the possibly different form it may take in the young and the elderly, though there is a brief essay on the latter from Julia Newton's team.

58-59) "Fatigue has been the defining focus of recent research, but many other symptoms need to be explored, primarily neurocognitive deficit...., post-exertion malaise, and pain." The causes of our particular form of fatigue needs more work–we know mitochondrial dysfunction, including problems with ATP production, associated probably with the recently discovered shift in our muscle fibers from slow twitch to fast twitch, ROS and lactic acid build up and slow clearance (glutathione), are all parts of it. But what triggers this? And I would add to the list cardiovascular problems like Orthostatic Intolerance (almost universal, overlapping with POTS) and Autonomic problems; some good work has been done, but we need more before reaching clear conclusions.

65-68) "lazy, deconditioned, and disability seeking...disdain, suspicion, and disrespect." This is largely because of the deliberate, orchestrated work by a group of psychiatrists both

in the UK and the US to push us into the arms of "somatoform" diagnosis, which becomes all the more threatening with the arrival of DSM-V. This has been furthered by the fact that much of the research funded by CDC and NIH in the past has been based on the "biopsychosocial" model, which in practice drops the "bio" part with the imposition of the phrase "medically unexplained symptoms." This has had a devastating effect on the availability of serious biological research funding, and on treatment.

Fostering innovative research

76-77); "minimal progress has been made to improve the state of the science....". That is not accurate. We have had some good science on the dysfunctions in the immune system, the autonomic nervous system, on brain and cognitive issues, and others. It is true that it has not yet gelled into a clear and comprehensive overview, but progress has been made in spite of the outrageously low contribution of funding from the NIH. You go on to list some of those successes in (82-86).

92-101) I find this not quite clear. You begin with a good, clear statement-"although psychological repercussions (e.g. depression) often follow ME/CFS, this is not a psychological disease in etiology." There is, as you say, overlap with other conditions, but that is not quite the same as naming them as "comorbidities" in all cases. Having ME can certainly cause some anxiety and depression, but are those truly "comorbidities" or consequences? My experience, and that of a good many others (I have been a board member of the local support group for several years now) is that they are more often consequences–and that is rather different.

104-107) One of many places where you discuss the problem of definitions. You note a "consistent constellation of symptoms: fatigue, post-exetional malaise, neurocognitive deficits and pain." This is true, and I would add two more to that "core" list–Orthostatic Intolerance (not universal, but very frequent) and sleep disturbance (virtually universal). I would also add that Dr. Unger of the CDC has been flatly unwilling to accept PEM as a necessary symptom, despite the extraordinarily high rate in all of the CDC's multi-center study. I would add that this "core" is not purely arbitrary–though ME is unquestionably a variable and difficult to define disease, I do not believe it is infinitely so–Mella and Fluge comment in their Rituximab trial that among those who responded, "all symptoms improved" in step, which they interpreted, correctly I hope, as a sign that they had hit a central mechanism. And a study from Julia Newton's team found an "association" (their word–they were being careful) between build up of lactic acid in muscles, brain hypofusion, and the Autonomic Nervous System. Fatigue, PEM, and "brain fog" are related, though just how has not yet been clarified. We have many symptoms, but they cannot be shuffled into an infinite variety of structures. There are some potentially describable processes going on here.

110) "Clinical trials require large investments of time and energy, and may be associated with other harms..."–not sure of your direction here–are these reasons for not conducting such trials? You seem to negate that with the next sentences, but doubt lingers..

113-116) “CBT and GET demonstrate measurable improvement, but this has not translated to improvements in quality of life. Thus, they should not be a primary treatment strategy and should be used as a component of mutimodal therapy.” Here I disagree on several fronts. First, if you remove those trials that used the Oxford definition, which include the large and notoriously defective and deceptive PACE trial, there is very little substantial evidence for benefit from either CBT or GET, and considerable evidence of sometimes serious harm from GET. If you recall, at the end of Chris Snell’s presentation he put on the screen two quotes from the manual used in PACE, which made it clear that the CBT version used there depended on persuading the patients that they did not have a serious disease, and so need not fear harm from GET. This is, as you yourselves note at several points, quite wrong. There are other passages in which you offer an unclear picture of how you respond to GET–in (135-138) you state that “In many cases [of exercise programs] lack of instructions or guidance for including graded exercise therapy often causes additional suffering, creating fear of harm from a comprehensive self-management program that may include some physical activity (e.g. mild stretching).” I do not know whether this means that GET would be OK if properly guided, or whether it means that GET triggers an unhealthy fear of all exercise, even the mildest form. My own view is clear–GET does more harm than good, but careful paced exercise can do some good, though it must be paced by the patient her/himself, preferably with both guidance and the use of a Heart Rate Monitor, as described by Nancy Klimas and Connie Sol. But GET is deadly to those with ME–and so is complete inactivity. The path between these is tricky and unsure, but many of us can do a little more than “mild stretching” without triggering PEM.

This is one of four spots in the draft where you refer to “multimodal therapy,” though one of these only points without naming (303-305)-“We believe ME/CFS is a distinct disease that requires a multidisciplinary care team (e.g. physicians, nurses, case managers, social workers, psychologists) to optimize care.” Elsewhere (350) you refer to it as a “future treatment” that should be evaluated, and as a therapy for which there is a “specific role” (371). I make two points: multimodal therapy is a direct derivative from CBT and is closely related to it, and was tried for five years in Sweden, and found not functional–it has since been replaced by clinics run by teams of specialists, which I think is much more effective–the Centers of Excellence which were closed by HHS afer a few years. I think they should be the wave of the future, as a mode of combining research with treatment, and in fact this model, more or less, is behind such new programs as that at Stanford, in Ohio by the Lights and Bateman, and by Kogelnik at the Open Medicine Istutute. This seems to me the best path to improvement. Multimodal therapy is already a past failure that should not be repeated.

Presentation and diagnosis of ME/CFS in the clinic

Many sympathetic points; your comments on self-management (130-134) are well taken, though there are many supports for this on the web already. But it would be very helpful if primary physicians knew this stuff.

Tools, measures and subsets

143-5); “There is little understanding of the inciting event or the cellular and molecular mechanisms...”. Only partly true–researchers like Julia Newton and team in Newcastle and

the Lights in Iowa have been making progress on this front.

149-150); "interdisciplinary collaboration"–potentially very useful–and already being applied at Stanford, etc. But one must be careful–it would be helpful to have researchers investigate fundamental pathways common to other diseases like ASD, Parkinsons, Guillaume-Barre (you recommend this 205-208), and I agree but on the other hand one can get the blind men and the elephant syndrome–bits and pieces that don't add up to an elephant. And there is nothing in the past behaviour of the NIH that would make us happy with the notion (208-210) that this effort should be led by "Additional NIH Institutes and Centers."

163-165) all this would be very helpful.

166-7); I don't think this is accurate–we know the symptoms that really diminish our lives, and some of the research does aim at those.

175)–gene-environmental intereaction: very important –there are many anecdotal accounts of ME following vaccinations, and Martin Pall (Prof. Emeritus of Washington State U, Medical Biology) has recently pointed a stern finger at the huge increase in Radio Frequency emissions, which are the most likely culprit in my own case. There would be strong industry resistance to such enquiry, but I think it must be pursued. Martha Herbert has a strong section in BioInitiative 2012 on the disturbing parallels between known metabolic dysfunctions in ASD children and known effects of non-thermal radiation. The dysfunctions she lists largely duplicate dysfunctions found in ME/CFS–there seem to be basic pathways in common. The Open Medicine Institute aleady includes ASD within its scope.

Directions and Recommendations

First, another statement that I question: (180)-"nothing has improved the lives of the patients. Overall, there has been a failure to implement what we already know...." This is only partially accurate. Antivirals have improved and even recovered a few select patients under the care of Lerner and Peterson. Ampligen, though once again rejected by FDA, has significantly improved the lives of some of those able to access it. Rituximab has radically improved the lives of a significant fraction (67%) of those in the very small trial by Mella and Fluge. The improvement was only temporary in most, though not all, cases. This trial brought the issue of autoimmunity in ME to the fore, and though doubtless not the final solution, needs to be followed up by large trials. A couple are now getting under way, but NIH has declined to assist with a grant.

202) "Assemble a team of stakeholders (e.g. patients, clinicians, researchers, federal agencies) to reach concensus on the definition and parameters of ME/CFS. A national and international research network should be developed to clarify the case definition...." In effect the 50 researchers and 175 advocates asked that the Canadian Concensus (which included international names) be accepted until the time came for improvements; HHS rebuffed this approach. You must be aware that this act aroused a good deal of anger and

disappointment in the community.

212) This is one of several places where you recommend "bench-to-bedside to policy" research (another is 187) and I support this strongly. The projects outlined in (259-266) are all valuable, but have already been worked on by researchers like Nancy Klimas and Mary Fletcher and the Lights and others. Their work needs to be continued until a clear overall picture appears, of course, and I believe that they are being funded by NIH–hurray!

271-275); "Patients often choose ...non-pharmacological and alternative medicine because effective treatment is not available.... Studies investigating homeopathy, non-pharmacological, complementary, and alternative medicine treatments are needed." Apart from homeopathy, for which I see little viability, this is a good suggestion. But you should know that FDA is currently trying hard to bring supplements, which many of us do use, under its control, and is explicitly trying to establish that any research done on a supplement automatically makes that supplement into a "drug," that would then have to undergo the arduous, ultra-expensive process of FDA approval, like any other drug. Again, you seem to be working against the whole HHS, and I have grave doubts that you will win.

212-219) "Create new knowledge"; once more you recommend cooperation between multiple NIH Institutes and Centers and others to "coordinate research efforts to promote efficiency and effectiveness, while using public/private partnerships to leverage and catalyze the use of existing NIH infrastructure and dollars." Cooperation and efficiency seem to be the things that NIH is weakest in. I fear this may be another doomed suggestion.

234-6); Microbiome–yes indeed, but Ian Lipkin's grant request to do just that, with the best equipped lab for the job, was turned down last year by NIH, apparently by having been sent to a reviewer who held to the "psych" view of the disease–a fact which must, or should, have been known to whoever sent it that way (from 34 years spent in academia, I can testify that "peer review" can be a good way to suppress new approaches).

244-248) "more trials, previously collected research data should be analyzed ..."–I hope this does not point to more EBM style reviews–the EBM movement is now under serious review in England, led by smart people like Trisha Greenhalgh, as its serious defects and limitations become ever more visible–as in the AHRQ which concealed more than it revealed to you.

277-282) "while including the patient's voice through patient reported outcomes." So far, the NIH has not been responding positively to patient input, and in the present situation I would be very uneasy about an "ME/CFS methodological workgroup." You go on to say "A community based participatory research approach is needed to increase patient involvement in determining priorities for research and care." In fact the NIH has been rejecting patient input consistently this year; maybe you can help change that?

288-290) "Although ME/CFS is not a psychiatric disease, exploring psychiatric comorbidities such as depression, anxiety and fear is critical to improve quality of life." There seems a real lack of decisive clarity in your view on this psych thing. I am not at all

convinced that these feelings are truly comorbidities and not natural results of having a chronic and disabling disease. Nearly all the patients I have met as VP and as a Director of the local support group, would lead me to believe that most would give all the psych help they could possibly receive in exchange for a modest improvement in their physical status–that would be the biggest boost to their psyches that most could imagine. That should remain the focus of attempts to help.

Provide training and education

Education for physicians is very important indeed–to make a course on ME and FM and other "mystery" diseases a regular part of the curriculum at all medical schools is one of the most potentially game-changing things that NIH could do for us. But then you spoil it by revealing that what you really have in mind is "multimodal" or CBT stuff–"a multidisciplinary team (e.g. physicians, nurses, case managers, social workers, psychologists) to optimize care." This is not what we would like to see taught as treatment in such courses. A revival of Centers of Excellence, or whatever you want to call them, would be more useful, a centre where I could be seen by a cardiologist who understood me and my problems with chest pain and orthostatic intolerance, by an immunologist who could work with my immune problems, by a neurologist who understood my autonomic dysfunctions, etc. etc. I would have nothing to say to, or hope for from, a psych. I know how to take care of myself as best I can. Those having real problems keeping themselves afloat financially would probably do better with a lawyer who could help them get or improve their Disability.

316) "Patients-in addition to medical therapies they are receiving, patients must become active participants in their overall treatment." I think that most of us are doing pretty well considering the total lack of help that medical profession as a whole is giving us.
We are for the most part as active as it is safe for us to be, and often more.

Finding new funding resources–and a couple of final comments

First reponse–the real problem is getting NIH to give our researchers funding appropriate to the seriousness and numbers involved in our disease. So far they have given us absurdly low funding, and have even been convicted of having disobeyed Congress by spending money that we should have received on other things. Before searching for "new" funding resources, you need to persuade NIH to move us up to an appropriate level. A request for an ROI was denied this year. So please start there!

385) "federal departments, advocacy groups, and industry work together in public-private partnerships to help advance research." NIH should lead the way here in funding fundamental research, like helping to fund the multi-center Rituximab study. When there is enough large-scale and well-focused work done on us, industry will become interested. But since they are purely profit driven, not until then. We know that Abbott, for instance, is potentially interested, but they are waiting until the situation clarifies. Can we blame them? It is all, or nearly all, up to NIH to do its mandated job–unless enough people with money and relatives sick with ME get angry enough to both increase their already generous funding to organizations such as the Open Medicine Foundation and Stanford, and simultaneously put enough pressure on Congress to trigger real action.

You focus on “partnerships across institutions to advance the research”–this is already happening, Simmaron connecting with an Australian group, Jason working on one paper with Julia Newton of Newcastle, England, and so on. I think connecting committees and programs across the multitude of such in the various branches of HHS is doomed to failure–the lack of coordination is already very visible.

Despite your recognition that ME/CFS is “not a psychological disease,” the primary recommendation you seem to make is for the inclusion of some form of CBT and GET (the support for which largely vanishes if trials based on the Oxford are removed from consideration–which means in part the removal of patients suffering primarily from depression). You focus on the umbrella of “multimodal therapy,” which is firmly based on and descended from CBT, and was tried for five years in Sweden and then abandoned for lack of success in favour of a center focused on biomedical specialists and knowledgeable physicians, with a minimal supporting staff of one nurse. I think you should examine this recommendation further–repeating an already failed experiment is not a good idea.

380) perhaps related to this therapy modality is your reference to “patient-centered homes for people with ME/CFS”. I have no idea what this might mean, but it sounds potentially scary–we are all acutely aware of the fate of poor Karina, still virtually imprisoned in a psychiatric hospital in Denmark, being given heaven knows what drugs, apparently in very bad shape, and sequestered from parents and friends. I am sure this is not what you intend, but what do you mean by this phrase?

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PS. hope you will forgive a certain asperity in some of my remarks–they are aimed at the HHS and particularly at NIH as a whole rather than at your panel, but since for the time being you are acting within NIH, there may be some overspill.

I am also aware that this draft was written very quickly, presumably under pressure–and so are my present remarks. So I apologize for any errors or misunderstanding of what you intended.

Chris Heppner