THIRTY YEARS OF DISDAIN
How HHS Buried M.E.

By
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This document has been superseded by an updated version that contains key events through December 2015.

The updated document is available at http://bit.ly/The_Burial_of_ME_Background.

A condensed version is available at http://bit.ly/The_Burial_of_ME_Summary.

What I would most like to see is that fatigue is not abandoned as a subject for careful consideration because of further failures of CFS case definitions or frustrations arising out of shrill pressures to justify an entity of dubious validity.[1]

—Stephen Straus of the NIH (~1994)

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Preface

The February 2015 Institute of Medicine report on ME/CFS and the draft December 2014 Pathways to Prevention ME/CFS report confirmed what patients have long known. For the last thirty years, the government, academic institutes, and medical societies that drive biomedical research and deliver clinical care in the U.S. have at best ignored myalgic encephalomyelitis (ME) and, at worst, led the charge that turned ME into a pariah.

Fixing this problem is going to require sweeping changes in every aspect of HHS's policies and actions toward this disease. But HHS is not going to make the magnitude of changes needed unless pressured to do so by those outside of HHS, particularly the media, the public and Congress.

Long-time advocates know the story of what has happened to ME over thirty years. But for the media and Congress, and for anyone new to this disease, the story is difficult to understand because it is fragmented and obscured by misinformation and the irreconcilable mish-mash of labels, definitions, and disease theories. Our objective in creating this document was to compile one view of this story into a detailed, fully referenced resource. The focus of this document is on the policy decisions and political and social forces that have held ME hostage, with a primary focus on the U.S. and on the time period from the mid 1980s through the end of 2014. Recent events, such as the release of the 2015 Institute of Medicine report on this disease,[2] are covered only briefly. The scientific aspects are discussed primarily in the context of the patients' experience of the disease.

This document uses the term "ME" because the World Health Organization established this name. Just as importantly, the term "ME" is used to clearly distinguish between the neuroimmune disease seen since the 1930s and the collection of non-specific "CFS" definitions that are focused on medically unexplained chronic fatigue. As the IOM report clearly stated, "a diagnosis of CFS is not equivalent to a diagnosis of ME." The objective is to avoid the semantic confusion that has resulted from the interchangeable use of "CFS", "ME/CFS", "CFS/ME", and "ME."

This document is long and is intended primarily as a background reference. The table of contents provides an overview. Shorter, targeted pieces are being created to approach the media and congressional leaders; this document will provide backup where needed.

This document is posted online as a pre-release at (http://bit.ly/The_Burial_of_ME). Important events may have been unintentionally misinterpreted or missed, particularly if supporting resources were not identified. Significant errors or omissions, ideally with supporting references, can be emailed to medimmock@gmail.com. The final version will incorporate corrections.

We wrote this document with the intention of getting the story out and encourage others to use it if it helps your efforts. Feel free to link to the document, print for personal use or quote as long as you cite the authors, the title, the version date (May 2015) and the link. Many of the references cited in this document are available online and can be quoted directly. As this document will change, we ask that you link to it rather than posting elsewhere.

We especially wish to thank the many advocates whose decades of tireless advocacy, writings and personal emails have provided the background and insight into the history of this disease and the politics surrounding it.

Mary Dimmock and Matthew Lazell-Fairman

Introduction

In 2013, I lost a dear friend who died after an extended battle with stage 4 cancer. She fought this battle with courage and a will to win, secure in the knowledge that she had the full support of friends and family and the best that experts in cancer research and clinical care could provide. Armed with tissue studies and genomics, they selected the therapies most likely to control her particular form of cancer. They carefully listened to her descriptions of the symptoms she was experiencing and prescribed a range of treatments to give her relief. They embraced her with empathy and caring when nothing worked. For cancer patients, at least for those with insurance, the cancer medical system is a highly specialized—and in my friend's experience, compassionate—army ready to take on the enemies that have invaded your body. Even when the cancer ultimately wins, as it did with my friend, this is first-class medicine borne of decades of first-class research.

I am grateful for the care that my friend received and for the extra months of life that we were able to share. And I am heartbroken to have lost her. But the experience has underscored the abysmal medical care available for my 27-year-old son.

Five years ago, my son came down with myalgic encephalomyelitis (ME), a neuroimmune disease that has caused a level of debility, suffering, and dysfunction similar to what my friend endured in the last month of her life. Yet, my son's experience with the medical system stands in stark, unfathomable contrast to my friend's experience. Virtually no research is being done on ME, let alone the kind of sophisticated research being done in cancer. No disease-modifying drugs have been approved, and few drugs are capable of lightening the impact of the range of symptoms from which patients suffer. Few doctors even believe that ME is real and organic, much less understand how to treat it.

Doctors have told my son he is just depressed, that he needs to exercise and that he just "wants" to get onto disability, as though that is preferable to the vibrant life he has lost. One doctor admitted she didn't "understand all those tests" that an ME expert had performed, but nonetheless felt educated enough to state that he was suffering from a "spiritual crisis" as a result of being on the "wrong life-path." And worse, even as supportive as my son's family and friends are, many have not understood the seriousness of the disease and have suggested that perhaps he just has a form of narcolepsy, needs electroshock therapy, should take up meditation, or maybe just needs to eat better.

Like my son, ME patients live in a world that is the medical equivalent of the most squalid slum in the poorest country on earth. This medical wasteland has been created by thirty years of misguided U.S. government public health policies toward ME, sloppy and purposely broad disease case definitions (the formal description of the disease), a cognitive bias that has resulted in an emphasis on perceived psychological issues, paltry research funding, misguided epidemiological studies, miseducation of the medical community, and a systematic disregard of both ME patients and ME experts that has virtually ensured that the situation will never change. This wasteland has caused world-class researchers to be unable or unwilling to conduct the research needed to understand the pathologies of ME, develop diagnostic tools, and identify desperately needed treatments. It has caused clinicians to think that ME is some kind of non-specific chronic fatigue, most likely a result of an underlying psychological problem and treatable by talk therapy and exercise. It has left patients to rot, with no medical care and a life-threatening dose of medical-provider induced trauma so severe that patients gamble their lives by avoiding seeing a doctor, even when they are experiencing severe chest pain or other acute medical emergency.[3]

The contrast between the medical wasteland that ME patients face and the first-class medical care that my friend experienced could not be more drastic, especially for those who cannot access the handful of ME experts and do not have insurance or family support. As two Norwegian oncologists who also treat ME patients noted in a comparison of this field to cancer, "the contrast in attitude, investments, research and understanding of disease mechanisms in ME / CFS [sic] are striking."[4] The terrible irony is that my son and other ME patients will only ever access the kind of first-class medical care that my friend received if they develop cancer or heart disease, diseases that studies have suggested are the long-term consequence of having ME.[5]

The harsh reality is that, given HHS's continued neglect, my son will die before he gets better. I am crushed when I think about the terrible suffering and loss that my now 27-year-old son will have to endure for the rest of his life. But I scream, knowing that my son is paying this terrible price because the U.S. government has so badly bungled this ME crisis since before my son was even born.

My son's story—and the story of all ME patients—is about the ugly side of medical care and public health policy in this country: the personal agendas and politics, the sloppy science, the lack of caring, the neglect and arrogance, and the outright refusal to listen to patients and their doctors. It is the story of what happens to a disease exiled outside of the research institutes, academic centers, and medical specialties that drive biomedical innovation and delivery of health care in this country. As the IOM report demonstrates, it is the story of a federal response so flawed that it failed to achieve a single meaningful outcome in thirty years, sentencing my son and all ME patients to lives of terrible debility and stigma, while saddling our country with a huge economic burden.

It is scientifically and morally unacceptable that up to one million disabled Americans have been mistreated, disbelieved and discarded in this way for three decades. This must stop. HHS must accept its responsibility to address this crisis and must implement sweeping changes in its policies, actions, leadership, and commitment to this disease. Band-aids and small changes masquerading as a response are not acceptable. The medical community must learn about the disease and provide the kind of medical care that these patients desperately need and deserve. Our congressional leaders must implement the oversight needed to ensure that HHS makes forward progress. And all of us must start anew and rebuild this story so that ME patients can finally escape this living hell.

Mary Dimmock

1. The Patients' Experience of ME

Since very early on in my illness, when it truly sank in that I was 'incurable,' I knew that I felt so bad that without the 'realistic hope' that I would get better, I could not live indefinitely in this state. That was over 19 years ago, and I haven't experienced a day yet which I would be willing to spend decades living life knowing the next day would be the same forever.

— Eric Moore (ME patient for almost 20 years, died by suicide in 2011)[6]

In the years since my son became sick with myalgic encephalomyelitis in 2010, I have watched this disease rip his life to shreds. A life of joy and promise shattered in the blink of an eye, the wreckage spread across the months, years and likely eventually decades, unless there is a shift in the politics and public policy surrounding this disease.

He is not alone. While the true prevalence of ME is unknown because of problems with epidemiological studies discussed later, the most commonly cited estimated are about one million patients in the United States, with an estimated seventeen million patients worldwide. I have had the opportunity to talk to many patients with myalgic encephalomyelitis. Some of them are less severely ill, some more severely ill. But they all have heartrending stories of misery, despair, broken trusts, and shattered lives.

Health care providers treating both ME patients and AIDS patients have observed that ME patients face the rest of their lives in daily suffering that is as incomprehensibly terrible each day as what AIDS patients experience in the last two months of their lives.[7] And yet, in spite of how sick they are, ME patients can expect to be ridiculed and mistreated by their physician, marginalized and abandoned by their family and friends, and left on the brink of utter financial ruin—all because the rest of us have not believed that they are really sick.

Faced with the twin swords of extreme debilitation and widespread disbelief, patients too often commit suicide—not because they are depressed, but because their hope has been worn so threadbare from the struggle to live that they can no longer bear the magnitude of suffering and disdain that ME imposes for the miserly amounts of joy that it reluctantly concedes.

Before my son developed ME, I could not have imagined that a crisis of such magnitude and gravity could go unnoticed for decades. But after seeing what has happened to ME for the last thirty years, I've come to understand that it was noticed. Then it was buried.

Life in Bloom

My son, Matthew, was always determined to take on challenges beyond his years. When he was 12, he declared that he wanted to learn to skydive and was heartbroken to learn that safety regulations dictated that he wait until he turned 18. When I asked why he was so disappointed, he said that he couldn't bear to think he might reach the end of his life and discover that he had missed his chance to experience the world. He went skydiving on his eighteenth birthday.

That type of quiet determination and hunger for experience defined my son. It drove him to study in Vietnam during college and to devote himself to academics, achieving high honors and departmental awards. It led his advisor to say that he had one of the most incisive and analytical minds of any student that she had ever taught. It drove him to backpack across Asia for five

months after graduation, where he climbed mountains in Tibet, explored China and India, road a motorcycle across Thailand, went scuba diving in Indonesia, and, in Seoul, met the young British woman he would later marry.

He returned from Asia excited to embark on a career and graduate school. But he also returned with an undetected intestinal pathogen called giardia. Suddenly, while being treated for giardia, he awoke one morning feeling like he had been hit by a bus, and he immediately knew that something was drastically wrong with his body.

What he didn't yet know, and wouldn't know for nearly a year, was that he had developed ME. He didn't yet know that his chance to experience the world was gone, just ten short years after I laughed at the simple naïveté of a child worried that he would run out of time.

Myalgic Encephalomyelitis: Disease biology and characteristics

Myalgic encephalomyelitis is a complex disease characterized by profound exhaustion, disordered sleep, joint and muscle pain, memory impairment and disorientation, and an array of other symptoms reflecting dysfunctions across multiple body systems—most notably, the neurological, immunological, and energy metabolism systems, along with the autonomic nervous system which controls functions like heart rate and blood pressure.[8] The hallmark symptom of ME is post-exertional malaise (PEM, also called "post-exertional neuroimmune exhaustion" or "PENE"),[9] a severe worsening of all symptoms, often referred to as a "crash," following even trivial amounts of mental or physical activity.[10]

Myalgic encephalomyelitis has occurred in cluster outbreaks throughout the twentieth century, but it can also occur sporadically, in isolated cases, as it did with my son. Based on the clusters, ME appears to have an infectious aspect. Yet, while ME exists in families, the transmission to family members and partners is relatively low, suggesting that additional factors, such as genetics or environmental factors or the microbiome, may also be involved. While onset can be gradual, it more typically begins suddenly following an acute infectious trigger. ME is often described as the worst flu imaginable. But in the case of ME, the flu-like feeling never ends, leaving ME patients with a unique "energy-brain-pain" triad accompanied by a range of other crushing symptoms.[11]

Patients wake up every morning feeling like they have been beaten up, unrefreshed as if they haven't slept in days. They experience a level of exhaustion that the rest of us (and ME patients themselves prior to becoming sick) have never before felt. Depending on the particular case, ME patients may have severe pain in every region of their bodies and may suffer constant headaches or sore throats. Their memory is shot; their ability to read and write is severely impaired; and they may be disoriented and confused, much like the symptoms seen in patients with untreated AIDS dementia complex or those suffering paraneoplastic syndromes. ME patients have spells of dizziness or vertigo, their hearts rocketing forward with little exertion or even just a change in position. Their eyes may burn, especially in response to even minimal activity, and their vision may worsen. Their previously reliable guts may be in turmoil. Many develop new sensitivities to food, light, noise, and chemicals (akin to the hydrophobia of a rabies patient, or the photophobia in encephalitis or meningitis). Patients can experience ataxia (lack of voluntary coordination of muscle movements) and fasciculations (muscle twitches). And if ME patients try to do even minimal activities—as little as brushing teeth or using the bathroom for the more severely ill patients—all of their symptoms become much worse, sentencing them to their beds for days or even weeks, in that protracted purgatory known as "PEM."

The most severely ill ME patients may never leave their beds, imprisoned in darkened, muffled worlds. In the words of one group of severely ill patients describing the extent of their limitations:

> Some of us are using every available drop of energy just to survive the day--to chew the food that is spoon-fed to us and to use the toilet, commode, or bedpan, with assistance. If we have additional strength, it must go to other basic ADLs, such as bathing and brushing our teeth.[12]

In addition, the neurological symptoms noted in other patients—such as the sensory sensitivity to light, noise and touch, the ataxia, and the pain— can become overwhelming and all consuming. Those who are lucky have family members who provide the round-the-clock, hands-on care that these patients require. Others end up in institutions.

I know that this range of symptoms sounds too fantastical to be real. But try to imagine the worst flu imaginable and you get a glimpse of what even a moderately ill ME patient feels like every day, month after month and year after year. There are no words to adequately convey what the most severely ill ME patients experience.

As noted in a February 2015 report by the Institute of Medicine, there is a "paucity of research" and "remarkably little research funding" with limited studies outside of psychology and psychiatry.[13] Because of the lack of research funding and an excessive focus on psychological issues, too little research has investigated the underlying biological impairment associated with the range of symptoms seen in ME. But enough biomedical research has been done to substantiate the patients' experience and to demonstrate the widespread multi-system impairment underlying the patients' reported symptoms.

Neurological Dysfunction

One of the areas studied in ME is neurological dysfunction. In a 2011 review, Dr. Anthony Komaroff, a Harvard University researcher-clinician who has studied and treated this disease since the 1980s, described the evidence that demonstrated reduction in gray matter volume, reduction in blood flow in the brain, increases in brain lactate levels, changes on MRI and EEG, evidence of autonomic dysfunction, and the presence of abnormal proteins in the spinal fluid.[14] Dr. Gudrun Lange, a clinical neuropsychologist currently at Rutgers Medical School, demonstrated changes in information processing, particularly slowed processing speed, deficits in attention, and limited working memory, all of which explain patients' reports of mental confusion and poor memory.[15]

A series of studies released in 2014 further support this picture of neurological impairment. In one small study, Japanese researchers used PET scans to demonstrate neuroinflammation in widespread areas of the brain, which it found to be associated with the severity of cognitive dysfunction.[16] Dr. Jose Montoya and Dr. Michael Zeineh of Stanford demonstrated brain abnormalities that included reduction in white matter and abnormalities in the right arcuate fasciculus, a tract that connects the frontal lobe and temporal lobe.[17] These abnormalities were correlated with disease severity. Dr. Mark Zinn and Dr. Marcie Zinn, also of Stanford, demonstrated a disruption of information transfer across cortical (brain) networks, a finding that also correlated with symptom severity.[18]

Speaking to the Zinns' study at the 2014 IACFS/ME conference, Dr. Komaroff said that these changes demonstrate brain dysregulation and are "the sorts of things that you see in a whole host of well-documented neurologic diseases."[19]

In Dr. Komaroff's 2011 review, he also described dysfunction in the autonomic nervous system, particularly orthostatic intolerance in which blood pressure and heart rate regulation is not working properly in ME patients and thus does not respond appropriately to standing or even sitting upright.[20] One form of this dysfunction is postural orthostatic tachycardia syndrome in which standing results in a large increase in heart rate. Patients can also experience neurally mediated hypotension in which the blood pressure drops.[21] Other changes include heart rate variability and reduced plasma volume, for which some patients are able to access treatment with IV saline.

Immunological Dysfunction

Researchers have long identified evidence of immunological dysfunction as well. In his 2011 review and in a 2014 Internal Medicine Grand Rounds at Stanford,[22] Komaroff noted the consistent reports of immunologic findings identified by researchers over the last twenty-five years. These abnormalities include increased numbers of activated CD8 cytotoxic T cells, lowered functioning of natural killer cells that are involved in defending against viruses and malignancies, an activation of the system typically involved in defense against RNA viral infections and an increase in the levels of pro-inflammatory cytokines. As reported by Komaroff at the 2014 Grand Rounds at Stanford, Montoya's 2014 study demonstrated that fifteen of these pro-inflammatory cytokines "distinguishes cases from controls, or correlated with symptom intensity or both." In a 1999 study, famed HIV and SARS researcher, Dr. Ian Lipkin of Columbia University, reported evidence of polyclonal B cell activation.[23] In 2013, Lipkin discussed "evidence of ongoing stimulus to the immune system [. . .] that may well account for many of the symptoms associated with the disease."[24] In 2015, Dr. Mady Hornig of Columbia University reported that the immune profile varied with disease duration with those with less than three years duration showing an activation of pro- and anti-inflammatory cytokines that wasn't present in longer disease duration, suggesting that the immune response wasn't static over time and possibly indicating that the stimulation seen in the first three years leads to an exhaustion of the immune system later on.[25]

Given that ME often has a sudden onset triggered by a full-body infection, researchers have looked for the singular etiological pathogen (e.g.. viruses or bacteria) causing this disease. Lab tests often show high levels of common viruses, such as HHV-6, CMV and EBV[26] and yet, treatment with antivirals has not always improved patient symptoms. Dr. Martin Lerner, an infectious disease specialist who treats ME patients, has suggested that the conflicting response could be due to failure to match treatment to the patients' specific viral load.[27] At this time, while a specific etiological pathogen has not been identified to date, the possibility of a single etiological pathogen being the cause or acting as a cofactor has not been ruled out. In a March 2015 news report, Dr. Ian Lipkin of Columbia University and a co-author on the Hornig paper cited above, stated, "We think this is likely an infectious disorder, something that triggers an abnormality of the immune system which then results in all these problems."[28]

A second explanation is that the triggering pathogen sets off widespread disruption of key neurological and immunological regulatory processes,[29] and it is this widespread dysfunction that drives the disease. Supporting this theory are the 2006 findings of the Dubbo Infections Outcome study in Australia, which found a similar rate of post-infectious debilitation regardless of whether the case was triggered by EBV, Ross-River virus or Coxiella burneti.[30] Such immune dysfunction could result in the reactivation of viruses, which would lead to high viral loads. In the 2014 Internal Medicine Grand Rounds at Stanford, Komaroff stated that "many of the agents that have been linked to the illness… [cannot] be fully eradicated by the immune system and virtually all of

them infect the central nervous system."[31] He suggested that this could reflect chronic low-grade encephalitis, a suggestion he said was supported by the Japanese PET study, discussed above, which "demonstrated increased activation of glial cells." Glial cells are found in the brain and part of their role is to destroy pathogens there.

A third explanation was discovered accidentally after ME symptoms were reduced in an ME patient treated for B-cell lymphoma with Rituxan. This result suggests either an autoimmune process or that an as-yet-undetected virus residing in the B cells is at the root of this disease.[32]

Some have suggested that environmental toxins and/or toxic mold could be playing a role, and patients have reported improvement from mold-avoidance practices.[33] But as yet, no formal studies have explored the role of these factors in ME.

The real possibility exists that some combination of continued pathogen assault, neuroimmune dysregulation, and autoimmune response is happening and that it may change over the course of the disease. These could be influenced by such factors as the patient's genetics, the severity of illness, and the nature of the initial onslaught. Regardless of the ultimate cause, evidence suggests an impaired immune system incapable of managing the various assaults that a healthy immune system would easily manage, allowing various common viruses, such as EBV and HHV-6, to reactivate opportunistically.

Energy Metabolism Dysfunction

Equally intriguing are the studies investigating the abnormal energy production associated with the symptom of PEM. As early as 1977, Dr. Melvin Ramsay, a consulting physician at Royal Free Hospital where an early ME outbreak occurred, suggested, "the illness may accompany the more common viral infections and that the unique fatigue pattern may be due to mitochondrial damage."[34] Mitochondria are the structures in every cell in the body responsible for producing the energy needed by that cell. This finding was reinforced in a 1984 study where Dr. D.L. Arnold showed abnormal muscle acidosis upon exercise in ME patients, which he felt could represent excessive lactic acid formation indicative of a disorder of metabolic regulation.[35] In a 1992 study, R. Wong examined the response to exercise and found lowered levels of intracellular ATP (used for energy in the body) that suggested a defect in oxidative metabolism that could "contribute to the reduced physical endurance" of patients.[36]

In the 2000s, Dr. Chris Snell, retired University of the Pacific professor of Health and Exercise and Sports Science and Ms. Staci Stevens of the Workwell Foundation pioneered the use of the widely accepted cardiopulmonary exercise test (CPET), performed on two sequential days. This 2-day CPET test objectively demonstrates that ME patients shift from producing energy aerobically to the much less efficient anaerobic energy system at an abnormally low heart rate,[37] an effect that was even more severe on the second day of the two-day test. This worsening on the second day reflects the patients' experience of the symptom of PEM. It also objectively differentiates ME patients from patients with deconditioning, depression, and a number of other chronic illnesses,[38] who do not experience the increased impairment on the second day.

The choice in energy production that the body must make, as Dr. Paul Cheney, ME clinician and researcher, has reportedly stated, is "between lower energy and life versus higher energy and toxins and death."[39] In my son's case, the heart rate at which he switched into anaerobic mode on the second day of his CPET test was lower than the heart rate he can experience just from standing up because of his autonomic dysfunction. Put another way, the simple act of standing up can cause

ME patients to start producing energy anaerobically, which explains why so many ME patients spend their days lying flat in a too-often futile attempt to avoid exacerbation of all their symptoms.

Other studies have further demonstrated the biological abnormalities associated with energy production in this illness. In a 2009 study, Dr. Sarah Myhill, a U.K. physician who treats ME patients, demonstrated a very significant correlation between "the degree of mitochondrial dysfunction and the severity of illness," using biochemical tests of mitochondrial function of the neutrophils of the immune system.[40] In a 2013 study, Professor Julia Newton, of Newcastle University, demonstrated "compromised skeletal muscle response to exercise, with CFS patients generating higher levels of acid within their muscle".[41] Her team also confirmed that those patients with "the skeletal muscle abnormality were significantly more likely to have concurrent impaired cardiac energetics." In a small 2015 study, Newton studied cultured muscle cells in-vitro and demonstrated that these patients experience "impaired activation of AMPK, impaired stimulation of glucose uptake and diminished release of IL6" which "points to a genetic/epigenetic mechanism."[42]

In a 2005 study, Dr. Gwen Kennedy, Of Ninewells Hospital and Medical School in Dundee Scotland, reported that patients had significantly increased markers of oxidative stress, such as isoprostanes, which the authors stated was the gold standard for oxidative stress at the time.[43] As summarized by other researchers[44] and reported by Komaroff at the 2014 Internal Medicine Grand Rounds at Stanford,[45] oxidative stress and nitrosative stress can be triggered by inflammation and can damage the mitochondrial membrane, leading to the impairment in energy metabolism noted by Snell.

This abnormal response to activity is so significant that some researchers have used it to probe other facets of the disease. In a 2010 study, Drs. Alan and Kathleen Light, both of the Department of Anesthesiology at the University of Utah, demonstrated an abnormal expression of sensory, adrenergic and immune genes following an exercise challenge,[46] an effect that was not significant prior to the exercise challenge. The sensory genes examined were those that could detect metabolites produced by muscle contraction and can signal physical fatigue and muscle pain. Adrenergic genes are involved in the portion of the autonomic system called the sympathetic nervous system, which is responsible for boosting heart rate and blood pressure. [47] Such changes in the expression of sensory, adrenergic, and immune genes reflect the kinds of symptoms reported by patients.

Given that PEM is associated with mental as well as physical activity and given the rate of consumption of energy by the brain, it is not surprising that in a 2013 study, University of Adelaide Ph.D. candidate, Susan Cockshell, found that even mental activity can lead to a substantially delayed recovery compared to controls.[48]

Contrary to the perception implied by the name, this post-exertional exacerbation of all symptoms follows even minimal mental or physical activity and does not require exertion the way that healthy people think about it. For the sickest ME patients, even the most essential activities of daily living are too much. This exacerbation and the associated energy metabolism impairment are so distinctive that the disease diagnostic definitions authored by disease experts and preferred by patients—the 2003 "ME/CFS: Clinical Working Case Definition, Diagnostic and Treatment Protocols" (commonly referred to as the Canadian Consensus Criteria or CCC)[49] and the 2011 "Myalgic Encephalomyelitis: International Consensus Criteria" (commonly referred to as the ME-ICC)[50]—require post-exertional exacerbation of symptoms as a defining symptom. The Canadian Consensus Criteria calls the symptom "PEM," which it describes as "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." The ME International Consensus Criteria calls the symptom post-exertional neuroimmune exhaustion (PENE), which it describes as the "pathological inability to produce sufficient energy on demand with prominent symptoms primarily in the neuroimmune regions." Both definitions describe a pathologically long period of recovery that can last more than 24 hours.

Regardless of the term used, the impact on patients is best seen through the words of an ME patient as reported by ME patient and lawyer Jennifer Spotila in a series of articles on PEM for the CFIDS Association:

> Muscle wilting meltdown, air gulping short of oxygen feeling, brain blood vessels flayed on a laundry line in the wind, metal rods in the back of head . . . someone crushing your ribcage, limbs giving out, mesh bag constricting head,. . . increased gravity feeling, being pushed backward into bed, temple-to-temple headache, weak arms as if bound down by stretchy ropes, eyes and brain blanking with a kind of pulse through the head…[51]

This is far different from what those of us who are healthy or even sick with another chronic illness think of as fatigue. As author and ME patient Laura Hillenbrand expressed it, "This illness is to fatigue what a nuclear bomb is to a match. It's an absurd mischaracterization."[52]

Demographics, Prognosis, Functional Impact and Economic Impact

Because of the issues with how ME has been characterized, it is difficult to make definitive statements about the demographics and prognosis of ME. But the best information available gives the following picture: ME affects an estimated one million Americans (Appendix 2)[53] and seventeen million worldwide. Like many autoimmune diseases, this disease is more common in women, but it affects all ages, races, and sexes and can affect multiple members (siblings, parents, or children) of the same family. Ten percent of patients are children, some as young as five.[54] ME patients can be as functionally impaired as patients with congestive heart failure, multiple sclerosis, and end-stage renal disease.[55] A researcher has said that patients can have a level of impairment that is so severe that if they were heart transplant patients, they would be ineligible for a transplant because they would not survive.[56]

This degree of functional impairment leaves an estimated 35 to 69 percent of patients unable to work,[57] with one survey reporting that as many as 87 percent[58] were unable to work; those few patients who are able to work spend the rest of their time recovering from the effort. An estimated 25 percent of patients are bedridden, housebound, or wheelchair-dependent, with up to 60 percent bedridden on their worst days.[59] The sickest patients never leave their beds, living in a dark world where all light and sound must be filtered out in a hopeless attempt to avoid exacerbating their symptoms.[60] There are no approved treatments and relatively little that can be done to relieve the symptoms. Recovery is rare, typically estimated at 5-10 percent,[61] and the limited information available suggests that patents may die up to 25 years prematurely from cancer, cardiovascular disease, or suicide.[62] The Chronic Fatigue Initiative, a $10 million initiative funded by the Hutchins family to study potential causes of the disease,[63] reported that of 59 deaths in a small survey of 960 people, 38 percent died of cancer, 19 percent of cardiovascular disease and 19 percent were due to suicide.[64]

The best estimate of the yearly economic impact that this disease imposes on patients and on the U.S. economy is an astronomical $19-24 billion in lost productivity and direct medical costs.[65] The lost productivity costs are unexpectedly high in ME, compared to other chronic diseases, because so many patients are unable to work for so many years.[66] And yet, even this huge number is an underestimate of the true fiscal impact of ME because medical and insurance guidelines and policies typically cover only a few tests and even fewer treatments. Furthermore, this estimate doesn't account for the cost associated with the increased likelihood of cancer and cardiovascular disease for which these patients are at risk. Patients lucky enough to have the financial resources, may have additional tests and experimental therapies that can be tried, although these can cost thousands or tens of thousands of dollars a year out of pocket and have no guarantee of success.

But these are just faceless descriptions and statistics that fail to convey the totality of ME, described by some patients as a one-way ticket to hell. The only way to fully understand the reality of this disease is to see it through the eyes of its victims.

Life Destroyed

In the months after May 19, 2010, the day Matthew woke up with ME, he could feel himself growing sicker with each passing day as he desperately tried to understand the deluge of unimaginable symptoms that were overpowering him. Every morning, no matter how much he slept, he would wake feeling like he hadn't slept in three days after having run a marathon while extremely hung over and severely sick with the flu. He had constant headaches, dizziness, burning eyes, sensitivities to light and sound, and severe cognitive issues that left him struggling to perform even the simplest parts of his job as a paralegal for the Federal Trade Commission in Washington, D.C. When he closed his eyes to rest during quiet moments at work, he became disoriented and felt as though the room was spinning. He found that increasingly small amounts of activity would land him in a post-exertional crash. Eight months into his illness, he had become so sick that when he stopped into a museum to rest after a long day at work, he became so disoriented and confused that he stumbled from room to room to room, unable to find his way out.

This 23-year-old man, who had managed to navigate solo across the panoramic breadth of Asia, was hopelessly lost in the local museum. Like so many ME patients before him, he was trapped in a labyrinthine nightmare, overcome with sudden confusion, unable to navigate familiar surroundings, and decimated by abrupt, obliterating physical debility. His world had become truly horrifying.

When he first went to doctors in search of answers, he found sympathy and was reassured that the problem would be solved—until all the standard tests came back negative. Then, in the blink of an eye, respectful and productive relationships with doctors turned sour. Over the next year, in a hundred different ways, doctors either suggested that his symptoms were not actually debilitating or that he must be depressed, was suffering from a spiritual crisis, or was just deconditioned. At times, the change in the doctor's behavior was so abrupt and their suggestions so ludicrous that he didn't know whether to laugh or to cry. Frustrated and browbeaten, he sought support from family and friends. Many echoed his doctors' sentiments, believing that if the problem was not immediately apparent, then it was in his head. Others trivialized his health problems with suggestions that he needed to rest more, eat organic and meditate. One recommended that he consider electroshock therapy. Early on, when he first began to realize that he had ME, his father told him, "Oh, I think I had that once. I was really exhausted at work. I stopped working so much, changed my diet, began to exercise, and felt better." Meanwhile, my son's life was crumbling around him.

Matthew kept fighting, kept trying to push through in spite of his increasing debility. But within a year, he was no longer able to work and was seldom able to leave the house. He found that he had become so sensitive to light and sound that if he went to stores and restaurants, watched television or even just listened to the music that he loved, he would trigger a crash that would increase his pain and suffering to unbearable levels for long stretches of time. He was unable to comprehend even short articles, let alone the kinds of books and ideas that had enthralled him in college. Like all ME patients, he learned that he had to obey the rigid, yet capricious limits that ME dictates. He darkened the windows of his bedroom, restricted himself to simple audiobooks, and even began to shower sitting down in a hopeless gambit to avoid the crashes that would magnify his pain and suffering. To conserve enough energy to go to a quiet restaurant with his wife for their first anniversary, he had to lay flat for three days before and again after, doing nothing more than listening to audio books.

Like most ME patients, Matthew has experienced some fluctuations in his level of debility. At his worst, he became so cognitively challenged that he was unable to make sense out of a single written sentence and his thoughts were strangled before he could turn them into sentences. He was physically unable to walk more than 250-300 steps a day or watch a short video on the small screen of his computer, without suffering PEM for days. On days like that, he would lie in bed in the dark for the entire day, unable to do anything, lightheaded, and zoned out. As his fried brain tried to recover, his head ached horribly, his eyes burned like fire pits, his muscles were sore and weak and his every experience of reality was mediated by pain and incomprehensible fatigue.

Matthew is not alone. Many ME patients experience Matthew's level of debility or worse. In a New Zealand study released in 2014, Dr. Don Baken, a clinical psychologist at the School of Psychology at Massey University, reported that ME patients have a very low quality of life, with "scores in the bottom ten percent of the population for measures such as NIH's PROMIS physical health scale (a measure of physical quality of life)" and went on to state that ME patients had worse scores than patients with Parkinson's and Multiple Sclerosis.[67] In a recent talk, Dr. Lucinda Bateman discussed vitality scores, part of the SF-36 health survey tool that measures functioning across a number of major areas, such as physical, emotional, and social function. She stated that SF-36 vitality scores for this disease had lower scores than other diseases such as stage 3 congestive heart failure, rheumatoid arthritis, major depression and chronic hepatitis C without cirrhosis.[68]

And yet, in spite of how sick Matthew has been, he is not as severely sick as some ME patients, who must preserve all of their energy for activities of daily living such as toileting, bathing, and eating and who may even need help with those most basic activities. Some never leave their beds and may be exquisitely sensitive to any light, noise, or even touch.

One such patient is Sophia Mirza, a U.K. patient who first became ill in 1998, after a trip to Africa in which she contracted malaria.[69] She appeared to recover, but then became ill again the following year. By the end of that year, she was so ill that she was largely bedridden, sentenced to a darkened, muffled room. She was increasingly sensitive to chemicals, unable to read or write, or even listen to the radio, constantly suffering from pain. Her situation worsened after she was involuntarily committed to a psychiatric facility in 2003, which according to her mother, "devastated her fragile health." She died shortly after in 2005 at age 32. According to Louette Harding of the Daily Mail, the neuropathologist said that her spinal cord was inflamed. The post-mortem pathology report found dorsal root ganglionitis (inflammation of dorsal root ganglion at the entry point to the spinal column) and stated that the cause of death was acute renal failure, resulting from "CFS."[70]

Another severely ill patient was Lynn Gilderdale, who became ill at 14 after receiving the Bacillus Calmette–Guérin vaccine. Like Sophia, she was confined to her bed, could not tolerate light or sound and suffered from recurring infections. She was unable to move her legs, swallow, feed herself, chew her own food, or speak. As Caroline Gammel of the Telegraph said in a 2010 article about Lynn, "Her life became ruled by the tubes running down her nose, into her chest and inner thigh, the tubes that fed her and that were a constant reminder that she would never again live a normal life." Yet, as obviously sick as Lynn was, she and her mother endured the disbelief that ME patients universally face. When Lynn first became ill, according to her mother, "All we got was accusations that she was pretending" or that she had school phobia. Unable to continue, Lynn talked to her parents about committing suicide, a conversation once unimaginable to me as a mother but now all too familiar. With the support of her mother, Lynn committed suicide at age 31. Lynn's mother was charged with attempted murder but was eventually cleared.[71]

Linda Crowhurst is a severely ill U.K. patient who has been sick for 20 years. Linda experiences extreme sensory sensitivity, paralysis and whole-body pain that can drown the spirit as the body tries to cope with the magnitude of it.[72] Linda also experiences periods of paralysis and extreme sensory sensitivity that she has described as:

> Broken ability to move, to speak, to reach out, to do anything at all, no matter how small or seemingly insignificant, even scratch your face or move your finger, blink your eye or swallow. Let alone touch, hold, call out, explain, tolerate, bear physical contact or even presence in the room.
>
> Every noise, already a torment, slices through you, causing internal mayhem, every exposure to light, which hurt indescribably before you were paralysed, burns you inexplicably deep inside your head. Every movement near or past you is like a slap, a push, a confusion, a shake to your whole system. Every exposure to perfume a mind - numbing, nauseating, gut hitting, head banging experience.[73]

Being so severely ill and living in the U.K. where ME is treated as a psychological illness, Linda has virtually no hope of getting any care beyond the constant care that her husband provides. Matthew is luckier, in part because he is able to travel to a doctor and in part because he has had the resources to access what biomedical care is available. In the last year, Matthew had some small improvement as a result of being on the experimental therapy, Rituxan, which has allowed him to do three or four hours of activity two days in a row as long as he rests with little activity for the next 2-3 days. This has allowed him to occasionally go to stores and quiet restaurants without experiencing severe post-exertional crashes. He was even able to go on a hot air balloon ride once. The difference in his quality of life now compared to the weeks and months that he spent chained to his bed is significant. Yet, even with this improvement, he is still very ill by the standards of those of us who are healthy. He still spends a significant portion of even his "active" days lying flat listening to audiobooks. The out-of-state trip to the doctor twice a year is still punishing, and he still has severe cognitive issues that have left him unable to read or write.

But it's important to put Matthew's improvement, as small as it is, in context. Some patients are so severely ill that they cannot travel to see a doctor. Even when they can travel, there are no approved treatments. Very few patients have access to disease experts or experimental therapies like Rituxan, which can cost $40-60K a year out of pocket with no guarantee that these treatments will help. And even when there is improvement, that improvement can be fragile, mysteriously disappearing at any time, and is rarely enough to allow patients to resume their lives and go back

to work. In Matthew's case, he recently relapsed for a few months likely due to a gastrointestinal complication, losing some of the improvement he had gained on Rituxan. All ME patients live with the terrifying knowledge that at any point, they can be sent hurtling deeper into the hell hole of their disease, never knowing what triggered the relapse, how long it will last, or how much sicker they will be.

A Living Hell

For ME patients, the physical limitations and suffering imposed by the disease are compounded by the tremendous emotional and financial burdens that come with any severely debilitating and chronic disease. For Matthew, as for many ME patients, this has been soul crushing. Almost overnight, his sense of boundless opportunity, his hunger for experience, and joy of life were crushed, replaced by a never-ending sickness that for much of the last five years has rigidly dictated the boundaries of his life. Isolated by sickness, he has had to watch as his friendships withered and his extended family faded away. He has had to let go of his dream of having a career and giving back to his community, of experiencing the joys of childbirth and first birthdays, graduations, and grandchildren.

But worse, he has to face a world in which he is so sick that much of life's simplest pleasures are off limits. He has had to grapple with how to carve meaning out of what little life is left to him. Were Matthew less devastatingly ill, he would find solace in reading books, listening to music, or even just sitting outside and lying in the grass or listening to crickets on a summer night. But, when a layer of pain, suffering, and debilitation permeates every moment of your life, you find that it is difficult to appreciate even the simplest moments that you once cherished. It is a mark of how blunted Matthew's life has been at times that when asked how to fill such a brutally empty life without suffering post-exertional crashes, his doctor suggested taking care of a houseplant. One severely ill ME patient spent her days watching a snail in a terrarium.[74]

Matthew is not unique.

In a 1997 article examining quality of life in Holmes defined patients, Dr. Jill Anderson of the University of Illinois at Chicago Medical Center examined four dimensions of quality of life —health and functioning, social and economic, psychological/spiritual, and family—and found that patients with this disease had a significantly lower overall quality of life than other chronic diseases, particularly in the domains of health and functioning, social and economic, psychological/spiritual.[75] Anderson stated that these patients experienced "profound and multiple losses, including the loss of jobs, relationships, financial security, future plans, daily routines, hobbies, stamina and spontaneity, and even their sense of self because of CFS," further explaining that some patients had reduced their activity to the most basic needs. As one patient told Anderson, "It's changed absolutely everything I do: what I eat, where I live. It's stopped my life. My whole perception of life, which took 30 years to put together, is totally gone."

This is what ME does to even moderately ill ME patients. This sense of vulnerability and tenuousness, the damage to one's esteem, the sense of worthlessness and the loss of all hope for a future worth living can be overwhelming for all ME patients.

Obviously, while the impact of ME on patients is particularly severe, ME is not the only disease to impose such physical suffering and emotional and financial devastation. ME is not the only disease for which there are no treatments and where there is no hope of a cure.

But what makes ME especially cruel is the added layer of deeply corrosive stigma thrown at patients when they seek out support from the medical community, family, and friends. Patients have broadly reported widespread disbelief, dismissal, and outright abuse at the hands of the medical community. The raw fact is that patients are blamed by a world that thinks they are malingers, depressed, or attention seeking. This is not just an issue of mistreatment at the hands of doctors, as noted above. In a blog highlighting the stigma that patients experience, advocate Craig Maupin described one patient whose family gave up on her and felt that "if she didn't have a blood test to confirm her health problems, she had disgraced them."[76] In the Obama-Biden Transition Report on this disease, patient advocate Dr. Mary Schweitzer and others stated that ME patients are "cast out by spouses or parents, scolded and disdained by siblings, and even abandoned by their churches."[77]

These are not just stories from patients; researchers have also documented the disbelief and stigma that patients experience.[78] As Dr. Anderson noted, a 1991 study by Komaroff had found that 33 percent of patients "reported strained relationships with family, friends, and coworkers due to disbelief or poor acceptance of their illness."[79] In Baken's 2014 study of ME patients in New Zealand, discussed above, he found that only 15 percent of patients "said they never felt blamed for their disease."[80] Pia Asbring, of Karolinska Institute in Stockholm, Sweden, found that patients "are characterised by the physicians as ambitious, active, illness focused, demanding and medicalising."[81] Dr. Leonard Jason of DePaul University has compared the stigma experienced by these patients to that seen by lepers in earlier centuries.[82]

No one suggested to my friend with cancer that she would have a poorer prognosis if she persisted in thinking she had an organic disease or that she should go to talk therapy to reverse those "false illness beliefs" that were supposedly keeping her sick. No one blamed her for getting cancer to begin with or for then failing to recover. Yet, this is exactly the kind of muddled thinking that ME patients face every day.

At all levels, this stigmatization crushes patients and leaves them even more emotionally isolated than they already are physically. When a horrible disease has ripped your life to shreds, isolated you from your family and friends, destroyed your career, left you destitute, and clinging to a life you no longer have; it is deeply demoralizing and heartbreaking to have to fight off suggestions—as so many ME patients do—that you just want to be on disability or that you could overcome your ill health with right thinking and exercise. I have watched this creeping demoralization[83] in my son and other patients, who have been belittled by doctors and marginalized by callous comments from insensitive or misunderstanding family members and friends.

This deadly combination—physical suffering, loss of function, loss of all that gives life meaning, the stigma and especially the loss of all hope—is why suicide is so prevalent in the ME community.

In a vain attempt to get staff at the U.S. Department of Health and Human Services (the U.S. governmental agency responsible for responding to diseases) to understand the reality of ME, my son once wrote the following:

> I had always seen suicide as an act of escape. But now, having lived this disease, I have realized that suicide can also be an act of courage and a manifestation of love for life untrammeled, a manifestation so deep that death is preferred to living without any of life's pleasures. In this respect, suicide is not an escape, but an act of creation and self-definition for someone who has lost all control and all manner of expression, whose fate is decided by forces they are powerless

> to influence. If I have arrived at this understanding, it is not because I do not enjoy life or because I cannot find my place in the world, but because I love life too much to bear living without the things that make life worthwhile.[84]

As author Norman Cousins once said, "Death is not the greatest loss in life. The greatest loss is what dies inside while still alive."

This disease is especially hard on those who are ill as children and adolescents, patients like Lynn Gilderdale as well as two young brothers I know who became ill in their early teens and are still sick eight years later. My son became ill after the tentative years of adolescence. He had already graduated from a university, had proved himself academically and found his voice, had travelled the world, made great friends, and had found his soulmate. Cruelly, ME patients falling ill as children and adolescents miss all of these milestones. There may not ever be a first love, a first job, a first time driving a car or the excitement of high school and college graduation. There may never be a chance to just hang out with friends. All of those formative moments that help to define us, that help adult ME patients find meaning in lives stunted by disease and give them the resources to withstand the relentless stigmatization and suffering, have been stolen from young and adolescent ME patients.

Even worse, being children, adolescents are particularly vulnerable to the often-incredulous reactions from school systems. As Lynn Gilderdale's parents found, schools tell parents that their children are just school-phobic, despite how inconsistent this may be with the patient's academic history.[85] One parent was told that her previously "straight-A" student was a "defiant, cheating liar."[86] Other parents have reported having medical neglect or medical child abuse complaints lodged against them, with a few even being accused of Munchausen by Proxy for supposedly exaggerating their child's illness.[87] Ryan Baldwin, sick with ME since the age of 11, is one example of this. Ryan's parents were charged with medical neglect, and Ryan was removed from his home in 2009. He was not returned to his parents for a year.[88]

Matthew is lucky to have both enough physical capacity and the financial resources to allow him to gain access to one of the very few ME experts across the country. Many patients do not have the insurance or else are too severely sick to make the trip. For many ME patients, the quality of clinical care is so astonishingly abysmal that patients hope to at least find a doctor who doesn't outright reject them. And even if they find a sympathetic local doctor who is willing to work with them, insurance may not cover the tests or recommended treatments. As a result, few have access to the kinds of treatments that have given Matthew even the small improvements in quality of life that he has seen.

But above all else, Matthew is lucky to have the unfailing support of his wife. Too many patients have been abandoned or are poorly supported by their families, sadly because family members either do not believe that their loved one is really sick or they cannot deal with the reality of this disease. For patients who only have Social Security Disability Insurance (SSDI) or, even worse, Supplemental Security Income (SSI), abandonment can leave patients in utter poverty. Such abandonment amplifies the stress of an already difficult existence and shatters a patient's last bastion of emotional, financial, and caregiving support.

Summary

Early in my career in pharmaceuticals, I had a colleague who suddenly became ill with what I have

since come to realize was ME. Her illness was unnamed, bizarre, difficult to understand, and ultimately easy to dismiss as not real and not serious. From the perspective of an outsider, her illness just didn't seem to have the gravitas of the "real" diseases that my colleagues and I were investigating in our work. But like those lost languages for which there is no Rosetta stone, the problem is one of translation when our only languages are health, the typical aches and pains of age or the better-known diseases, such as cancer, which have instant credibility. We struggle to imagine the tortured landscape created by ME and to escape the strongbox of our own perceptions long enough to allow the reality of these patients to intrude into our daily lives.

The harsh reality is that Matthew, like other ME patients, will likely live the rest of his life shackled inside the prison of his body until this disease ultimately kills him. It has been heartbreaking to watch the promise of my son's vibrant and spirited future turn into this soul-crushing existence that is so unrelentingly harsh and circumscribed, so brutal, so sequestered, so ruinous to his psyche, and filled with so little hope that I don't know how he manages to keep going.

But worse than the heartbreak, it has been profoundly disturbing and surreal to watch as the world around my son not only dismisses his disease but ridicules and even brutalizes him for believing that his disease is serious and organic. It has been profoundly disturbing to realize that his situation is a direct result of the misguided policies and actions taken by U.S. Dept. of Health and Human Services for over thirty years that have effectively obfuscated ME inside of an unscientific collection of medically unexplained fatiguing illnesses called "chronic fatigue syndrome."

2. What is Chronic Fatigue Syndrome?

"There has been a creeping movement to include other types of medical conditions under the rubric of CFS…This serves to broaden the scope of the clinical entity to the point at which it is no longer definable."

Dr. H. James Wedner
Clinician and researcher at a 1993 scientific conference[89]

The term "chronic fatigue syndrome" has created a medical Rashomon effect of biologically unrelated diseases and conditions that have little more in common than the fact that CFS patients suffer from some form of "medically unexplained chronic fatigue."

What do I mean by this? When some doctors use the term "CFS", they are using it as a synonym for ME with its demonstrated neurological, immunological, and energy production dysfunction and hallmark symptoms such as post-exertional malaise or PEM, a debilitating symptom triggered by even trivial levels of mental of physical activity. (See the chapter "What is ME?" for more information.) For these doctors, this disease is best described by disease definitions, such as the 2003 Canadian Consensus Criteria, that require PEM, unrefreshing sleep, and neurocognitive dysfunction. Because these definitions more accurately describe ME, they are able to distinguish ME from other unrelated causes of fatigue such as deconditioning and depression.

But for other researchers and clinicians, the term "CFS," refers to a condition that they believe is the result of a maladaptive avoidance of activity, a kinesiophobia which is driven by temperament or personal choice and which has resulted in deconditioning. Some believe the patient is suffering from maladaptive coping (e.g. escape-avoidance behaviors) a full-blown personality disorder, an excessive concern with one's health and bodily symptoms or a form of depression. Still others are referring to an umbrella collection of medically unexplained fatiguing illnesses, which by definition is vague and meaningless.

The clinicians and researchers who advance these psychological and fatigue-centered ideas typically use overly broad "CFS" definitions, notably the 1991 Oxford Definition,[90] the 1994 Fukuda definition[91] and, historically, the 2005 Empirical (Reeves) definition.[92] The last two of these were created by the Centers for Disease Control and Prevention (CDC). All three of these CFS definitions focus on chronic fatigue that is not explained by other *medical* causes, do not require that patients have any of the hallmark symptoms of ME, and only exclude certain forms of primary psychiatric illness (e.g. Fukuda excludes schizophrenia and major depressive disorder with psychotic or melancholic features but not anxiety disorders or other forms of depression.) As a result of such vague and overly broad definitions, CFS has become a man-made wastebin of disparate conditions that share nothing more than the symptom of debilitating, chronic fatigue for which no medical explanation has yet been found.

One does not have to be a Nobel laureate to recognize that these diverse "CFS" definitions (Appendix 1) cannot possibly encompass just a single disease or even a group of related diseases. It's just as obvious that these overly broad "CFS" definitions do not describe ME because they fail to require the specific biological abnormalities of ME, such as orthostatic intolerance or PEM and its associated energy metabolism dysfunction—symptoms that are mandatory in the Canadian Consensus Criteria and the ME International Consensus Criteria. As a result, Fukuda, Oxford, and Empirical encompass many patients who do not have ME.

So what precisely is "CFS" then? "CFS" is a political creation driven by political agendas combined with a remarkable level of scientific sloppiness and a strong cognitive bias that this disease must be a psychological problem simply because the medical cause is *not yet* known. For the past thirty years, powerful forces have ignored the biological reality of ME and instead morphed "CFS" into a vague condition of medically unexplained fatigue strongly associated with psychological illness.

The result of these actions has been an unfathomable level of confusion about the nature of ME. It has also focused government funding and priorities on the ill-defined "CFS," which has stymied research into ME, stalled ME drug development, resulted in erroneous and harmful ME medical education, driven researchers away from the field, and confused doctors and the public at large on the nature of ME. This terribly debilitating disease has been effectively buried in a scientific quagmire of irreconcilable definitions and disease theories, all masquerading under the name "CFS".

In 1993, before Fukuda and the Empirical definitions were even created, Dr. H. James Wedner, professor of Immunology and Allergy at Washington University, warned that CFS had become indefinable.[93] Twenty-one years later, the situation is much worse. As long as this definitional chaos continues, ME will remain forever medically unexplained, held hostage by the bad science and politics of "CFS."

The Birth and Evolution of CFS

Discovering Myalgic Encephalomyelitis *(1934 to the mid 1980s)*

Myalgic encephalomyelitis is not a new disease. Throughout the twentieth century, a number of documented outbreaks and sporadic cases of ME occurred across the globe. Some of the recorded outbreaks occurred in Los Angeles in 1934; Iceland in 1946; Florida, Maryland, Alaska, and London (England) in the 1950s; and Texas, Scotland, Switzerland, and another in England in the 1960s and 1970s.[94] The outbreak in London was at the Royal Free Hospital in 1955 and forced the closure of the hospital for over two months. Almost 300 members of the staff fell victim, about half of them nurses. Over 200 had to be hospitalized and 40 percent of these stayed in the hospital for more than a month.[95] While the outbreaks suggest a possible involvement of an infectious agent (or possibly a shared environmental factor), ME does not appear to be easily transmitted to family members by typical routes of transmission.[96]

Following the Royal Free Hospital outbreak, the name "myalgic encephalomyelitis" first appeared in a 1956 *Lancet* editorial,[97] published anonymously but attributed to Sir Donald Acheson. The word "benign" was reportedly included because, at that time, the disease was not thought to lead to death. Reports and reviews of various outbreaks and sporadic cases of ME appeared in the scientific literature and described the key features of the disease, including a 1959 article by Dr. E.D. Acheson, of State University of New York, College of Medicine of New York, that reviewed 14 epidemics.[98] In 1959, Dr. Donald Henderson (epidemiologist at Centers for Disease Control and Prevention) and Dr. Alexis Shelokov (from the National Institute of Allergy and Infectious Diseases at the National Institute of Health) summarized twenty-three outbreaks of the disease occurring in different parts of the world. These outbreaks had been given a variety of labels, such as "Iceland disease," "ME," and "atypical polio" among others.[99]

Using the term "epidemic neuromyasthenia," Henderson and Shelokov described a condition characterized by fatigability, sore throat as an early (prodromal) symptom, headaches and other pains, protracted debility, and a greater prevalence in females. They concluded that the differences

across the epidemics were minor and that these outbreaks likely shared a similar "nosologic, if not etiologic, association."

In 1969, the World Health Organization officially recognized the term "benign myalgic encephalomyelitis" and classified it as a neurological disease in the *International Classification of Diseases (ICD)*.[100] In 1978, the Royal Society of Medicine held a symposium to discuss the disease and plan future research directions.[101] As reported in a lead editorial in the British Medical Journal, attendees discussed the variety of physical findings associated with the disease, described the characteristic exhaustion following any effort and the muscle fatigability. They agreed on the term "myalgic encephalomyelitis" (acknowledging there was nothing benign about the disease and that other terms were not appropriate), stated that there were both epidemic and sporadic cases and reiterated that ME is a distinct nosological organic entity, not a psychological illness. They concluded that outbreaks were still occurring, that future outbreaks "should be studied by a collaborative team of neurologists, epidemiologists, virologists, and immunologists" and that those findings would have relevance for "other neurological disorders, including multiple sclerosis."

In 1986, Dr. Melvin Ramsay, consultant physician in infectious diseases at Royal Free Hospital, established the first case definition for myalgic encephalomyelitis, in which he described the essential features of cognitive impairment and also delayed recovery following mental or physical exertion.[102] Ramsay suggested that the disease was likely associated with the "abnormal immunological response" to a pathogen. In a latter monograph, he described the "unique pattern of muscle fatigability" after even trivial effort as a "sheet anchor" that was required for an ME diagnosis and that separated it from other forms of post-viral fatigue.[103]

The importance of the muscle fatigability noted at the 1978 Royal Society of Medicine conference was bolstered experimentally by Dr. D. L. Arnold's 1984 study (noted above) that reported abnormal acidosis from exercise. Arnold postulated that this could "represent excessive lactic acid formation resulting from a disorder of metabolic regulation."[104] This was one of the earliest studies noting the physiological basis of the muscle fatigability that is associated with PEM. These findings are reflected in current research into the ME patient's abnormal biological response to exertion by researchers such as Dr. Christopher Snell and Professor Julia Newton.[105]

Dismissing Myalgic Encephalomyelitis *(mid 1980s)*

But then, starting in 1984, the same year as Arnold's study was published, two more outbreaks of ME occurred in the United States. One was in Incline Village, Nevada and the other in Lyndonville, New York. It was those outbreaks and the subsequent attention by the Centers for Disease Control and Prevention (CDC) and the National Institutes of Health (NIH) that triggered the tortured twisting of the definition of myalgic encephalomyelitis into a vaguely defined syndrome of medically unexplained chronic fatigue inextricably associated with psychiatric illness.

The story of what happened in Incline Village and Lyndonville has been documented extensively in a number of early reports,[106] including a late 1980s' *Nightline* story,[107] a 1990 *Newsweek* article,[108] a series of 1993 videos by the CFIDS Foundation,[109] a 1996 *Primetime Live* investigative report,[110] and Hilary Johnson's 1996 book *Osler's Web.*[111]

In the fall of 1984, Incline Village clinicians Dr. Paul Cheney and Dr. Daniel Peterson began seeing patients with a severe flu-like illness, marked by dramatic and unusual cognitive dysfunction and crippling exhaustion. Yet, the patients didn't get well as they normally would have following a flu. According to the numerous reports cited above, Drs. Cheney and Peterson repeatedly begged the

CDC to investigate the illness[112] because it was afflicting more and more people, seemingly spreading in Incline Village and the neighboring towns. They also noticed it occurring in clusters, such as a group of teachers at a certain school, a group of casino workers and a local girl's basketball team. Finally, one year later, the CDC sent two epidemiologists, Dr. Jon Kaplan and Dr. Gary Holmes, to Incline Village. According to *PrimeTime Live*,[113] the two investigators "looked at charts and test results, took some blood samples and headed back to CDC without a word." Hilary Johnson told *PrimeTime Live* that the attitudes behind the scenes at the CDC reflected Dr. Kaplan's attitude: "complete and utter ridicule" of the disease.[114]

At the same time as the outbreak in Incline Village, Dr. David Bell of Lyndonville, New York, was also dealing with an outbreak of ME. Like Cheney and Peterson, he also called on the CDC to investigate the unusual combination of symptoms of an illness that he did not recognize. (Although ME had been seen for decades, it was not commonly known or taught in medical schools). According to *PrimeTime Live*,[115] not only did the CDC not respond, it didn't even tell Bell that a similar outbreak was happening in Nevada.[116] This author did not locate a clear explanation of why the CDC failed to respond to Bell's request.

Lacking support from the CDC, Peterson and Cheney tried to do what they could for their patients. This included ordering MRI brain scans, which they paid for out of their own pockets. A neuroradiologist told the two doctors that the scans looked like those of AIDS patients,[117] which led Cheney and Peterson to question whether the illness involved immunodeficiency or general immune dysfunction. But in May of 1986, the CDC issued a report on the Incline Village outbreak,[118] referring to it as "a syndrome of chronic fatigue". In the 1996 *PrimeTime Live* program, Cheney said of the 1986 CDC report "the overall message, the tone of the paper, was that this [disease] did not appear to be anything at all."[119]

Some researchers, including Dr. Stephen Straus of the National Institute of Allergy and Infectious Diseases (NIAID) at the NIH, investigated a potential connection between this disease and Epstein Barr Virus (EBV), a herpes virus. This theory stemmed from patients' higher EBV titers (a measure of immune system response to the virus) and that the disease sometimes follows a bout of mononucleosis, a disease usually caused by EBV. Based on that theory, Straus conducted a clinical trial assessing the effectiveness of Acyclovir, a drug used to treat herpes viruses. The patients who fulfilled the Holmes criteria (described below), met study criteria for levels of EBV antibodies that would indicate the potential for responsiveness to treatment and had no other medical explanation for their fatigue.

But using both patient-reported outcomes and objective immunological markers, the study failed to show a difference in efficacy between placebo and treated patients. In the study publication, Straus concluded that "affect plays an important role in the perception of illness severity," stating that the observed clinical improvement was due to "either spontaneous remission of the syndrome or a placebo effect" and further stated that "subjective improvement correlated with various measures of mood."[120] In other words, from his perspective, these patients were not sick but rather just moody.

Dr. Judith Richman, of the Department of Psychiatry at the University of Illinois, discussed how the failure of the Acyclovir study to demonstrate a link to a viral etiology coincided with "substantial shift in the dominant research paradigm."[121] According to Richman, this shift resulted in an increased focus on psychological and psychosocial factors, pursued by researchers who viewed this disease "as a flight into the sick role in order to escape from cultural expectations." She further pointed out how such views took on a decidedly gender-based view of this disease by focusing on

the "problematic cultural expectations for women's social role functioning that led women to unconsciously seek refuge in the sick role."

Certainly, Straus helped spark the psychologicalization of this disease in his own expressions of bias. In a circa 1987 *Nightline* interview, he stated, "From my own research, I know that this disorder is so subjective that patients will commonly feel better no matter what you give them."[122] Following Straus's logic, the *Nightline* reporter suggested a possible cause during his interview of Hilary Johnson: "if the power of the human spirit can make these people better, then maybe it was the power of the human spirit that got them sick in the first place."[123]

Then, in a 1988 *New York Times* article, Straus is quoted as saying that these patients were "psychologically different long before they developed the syndrome." He described them as anxious, depressed and neurotic on the one hand or driven and under undue stress from busy lives on the other.[124] In a 1988 study, Straus noted that the disease affected mostly educated adult white women, which he postulated could be due to a selection bias driven by those who could afford treatment or else some "unique constitutional frailty of such individuals."[125] He went on to conclude, "A less casual appraisal, however, often uncovers histories of unachievable ambition, poor coping skills, and somatic complaints." It should be noted that Straus's "appraisal," in its "casual" deviation from objective science, quickly put patients between a rock and a hard place: having to prove they did not have "unachievable ambition" but also that they did not suffer from neuroticism or from the "fear of movement" that a group of British psychologists were beginning to promote at about this time. Such a claim promotes a cause that is not supported by any hard evidence.

As Richman pointed out, the dominant paradigm that emerged was increasingly at odds with the perspectives provided by patients and the small group of clinicians and researchers who continued to study and treat this disease as a biomedical disease.

The Birth of Chronic Fatigue Syndrome and the Holmes Definition *(late 1980s)*

A 1987 *JAMA* article by Dr. Gary Holmes indicates that the CDC was aware of the earlier outbreaks going back to the 1930s[126] yet it does not appear that CDC staff followed up on that literature or the work going on in Europe. Then, in 1988, the CDC published the Holmes definition[127] and established the trivializing name "chronic fatigue syndrome." Dr. Vincent Racaniello, Professor of Microbiology and Immunology at Mt. Sinai School of Medicine is quoted in a 2011 article by journalist David Tuller as saying that CDC's choice for naming the disease came from an intent to discourage "unproven assumptions about viral origins."[128]

The Holmes definition was the first of a series of CFS definitions focused on medically unexplained chronic fatigue as the primary symptom. Minor symptoms included any eight choices out of a list of non-specific symptoms such as weakness, malaise, a mild fever (less than 101.5 F, also described as a subjective fever), decreased memory, confusion, and sleep disturbance. The Holmes definition was intended to be a restrictive case definition to make it easier for researchers to identify associations. Thus, people would not receive a diagnosis of CFS according to Holmes if they had any of a long list of "exclusionary" diseases, such as a history of or a new onset of psychiatric disease. Because of the restricted criteria, but also because of methodological issues associated with how the early "CFS" prevalence studies were conducted, prevalence was initially estimated at 0.0073 percent of the population, a rate equal to 23,000 patients if applied to the total 2012 U.S. census of 314 million (Appendix 2). This prevalence rate was very low compared to later estimates.[129]

Inexplicably, given their knowledge of the disease and their role in bringing it to the attention of the CDC, Cheney, Peterson, and Bell were not listed as authors on the Holmes definition. Two physicians with extensive ME experience, NIH's Shelokov (one of the authors of the 1959 review of ME outbreaks) and an ME physician from England, Dr. J. Gordon Parrish, were on the CDC-sponsored panel that worked on the development of Holmes.[130] But Shelokov and Parrish reportedly "refused to sign the final document and withdrew from the panel because the proposed definition and new name were too different from the ME with which they were so familiar."[131] Of the sixteen final authors, it is unclear if the others had any experience treating ME patients, with the notable exception of Dr. Anthony Komaroff, the Boston researcher and clinician who had been involved in studies on Incline Village patients and who had also studied and treated ME patients in the Boston area. In fact, Komaroff had conducted a SPECT scan study on ME patients that showed neurological changes similar to the AIDS dementia complex patients and different from patients with depression.[132]

But in practice, as researchers used the Holmes definition over the coming years, they soon determined that patients who met the Holmes CFS criteria were indistinguishable from patients with non-specific chronic fatigue. They also determined that eight or more minor symptoms combined with non-specific symptoms increased the likelihood that individuals with psychiatric problems would be misdiagnosed with CFS.[133]

The Growing Focus on Psychological Issues

At least by the late 1980s and early 1990s, the published literature showed that scientists were acutely aware of the range of specific multi-system pathologies involved in ME and were reporting on a variety of immune abnormalities, neurological issues, and findings that indicated viral involvement.[134] For instance, according to a 2011 article by journalist Tuller, a Harvard-led research team reported in the 1992 *Annals of Internal Medicine* that the Incline Village patients had "abnormal MRI brain scans, significant alterations in white blood cell counts and functioning, and signs of active infection with a recently discovered pathogen, HHV-6." In the study report, Dr. Debra Buchwald, of the University of Washington and lead author, stated, "Neurologic symptoms, MRI findings, and lymphocyte phenotyping studies suggest that the patients may have been experiencing a chronic, immunologically mediated inflammatory process of the central nervous system."[135] It's worth noting that in this same timeframe, HIV/AIDS researchers were investigating the possibility that this pathogen, HHV-6, was a potential co-factor involved in driving the pathogenesis of HIV/AIDS.[136]

But as pointed out by Tuller, Dr. William Reeves, head of CDC's CFS program from 1989 to 2010, rejected the findings of the Buchwald study in a letter to the Annals. Reeves concluded, "The disease that Buchwald and co-workers described is not the chronic fatigue syndrome or any other clinical entity."[137] According to the *PrimeTime Live* report on the Incline Village outbreak, Reeves stated: "One, there is no viral cause for this problem. Two, there are no immune system abnormalities in patients with chronic fatigue. And three, there are no clusters." When the interviewer then asked him what had happened in Incline Village, he replied, "That was hysteria."[138] That response speaks volumes about the gulf in understanding between the CDC on the one hand and the clinicians and researchers studying and treating ME patients on the other. And while the CDC no longer states that what happened in Incline Village was hysteria, the CDC still maintains that it has not been able to confirm the occurrence of any outbreaks, as it did when it rejected the 2012 recommendation by the CFS Advisory Committee (CFSAC, responsible for advising HHS on this disease) to allocate funds to study patients from past cluster outbreaks.[139]

CDC has not been alone in recasting this disease as a psychological problem. As early as 1970, Dr. A.W. Beard and Dr. Colin McEvedy, both of the Department of Psychological Medicine at Middlesex Hospital in London, had set that tone when they reanalyzed case notes from the Royal Free Hospital outbreak and decided, reportedly without seeing any patients,[140] that the outbreak was "epidemic hysteria."[141] This reinterpretation was broadly rejected at the time by those physicians who had actually treated Royal Free patients.[142] In a separate article, Beard and McEvedy examined the 14 outbreaks reported in Acheson's 1959 review and decided that the epidemics were the result of either mass hysteria and/or an "altered medical perception of the community," in which doctors exhibited a preoccupation on these patients.[143] Beard and McEvedy recommended the name "myalgia nervosa."

In 1991, Toronto Hospital's Dr. Susan Abbey and Dr. Paul E. Garfinkel, a psychiatrist at the University of Toronto, stated a similar position to that of Beard and McEvedy. They argued that "chronic fatigue syndrome will meet the same fate as neurasthenia—a decline in social value as it is demonstrated that the majority of its sufferers are experiencing primary psychiatric disorders or psychophysiological reactions."[144] Neurasthenia was a nineteenth century concept originally described as an organic disease but which over time was often viewed as an emotional distress postulated to be due to the stresses of dealing with modern civilization. As discussed by Dr. Judith Richman, Drs. N. Ware and A. Kleinmen, both of Harvard Medical School, embraced similar views for CFS but added a gender slant: "'Liberated' by feminism to enter previously all-male occupations, women in the 1970s found themselves exhorted to 'have it all' by combining a demanding career with a rich and fulfilling family life. This meant juggling a number of incompatible identities."[145]

Such psychologicalization of medically unexplained disease and/or attributing women's health issues to psychological processes is not unique to this disease. As noted by Dr. Judith Richman, multiple sclerosis, another disease that affects primarily women, was originally believed to be "caused by stress linked with oedipal fixations" and associated with an "MS-prone personality."[146] Other examples of such psychologicalization are discussed further below and in each case, were only rejected once evidence disproved them.

In the case of ME and the group of disparate conditions labeled "CFS," it was a group of British psychiatrists who have pushed this psychological conceptualization the farthest.[147] In 1989, Professor Simon Wessely, currently at Kings College in London, stated that the symptoms of the disease are "perpetuated by a cycle of inactivity and deterioration in exercise tolerance… and is compounded by the depressive illness that is often part of the syndrome."[148] He further stated, "Cognitive behavioural therapy (CBT)…helps the patient understand how genuine symptoms arise from the frequent combination of physical inactivity and depression."

In a highly cited 1989 article, Wessely stated that CFS patients more closely resembled patients with psychiatric disorders than patients with neuromuscular disorders associated with peripheral fatigue.[149] Then in 1990, he compared the current outbreaks of ME to neurasthenia, which he viewed as a "culturally sanctioned expression of distress."[150] Also in 1990, Wessely said that patients developed "chronic activity avoidance" as a maladaptive response to an acute illness and it was this activity avoidance behavior that resulted in fatigue, deconditioning, and the other symptoms of "CFS".[151]

Again, one has to question how patients with so-called "unachievable ambition" might also suffer from the unquenchable desire to avoid activity. These allegations squarely placed patients in a

conundrum of having to prove they were seeking a perfect "Goldilocks zone" of not being pathologically ambitious, yet never being slothful.

This theory of "CFS," which is often referred to as the "biopsychosocial model" for CFS, the "fear avoidance" model or the "activity avoidance" model, draws on psychiatrist Dr. George Engel's biopsychosocial approach.[152] He emphasized reducing mind-body dualism by considering the role of the psychological and social factors in human disease and also focused on the importance of treating the whole patient. Social and psychological factors undoubtedly play a role in human disease. But there is a vast difference between a humane understanding that heart disease might be aggravated by stress or lead to secondary depression and the idea that a contrived behavioral trait or a maladaptive personality is the sole determinant keeping an ME patient sick. A 2005 *Psychology Today* article said "With diseases like chronic fatigue syndrome and fibromyalgia, what you believe about your illness influences how sick you become." In his response to the article, Jason stated, "Stress is also a contributor to such "biological" disorders as cancer, hypertension, heart attacks, etc. But we don't tell people with heart disease that they are overachievers and, therefore, personally blame them for their illness."[153]

In the hands of those who promote the "biopsychosocial model" for CFS,[154] the factors related to disease risk, causation, and persistence are almost entirely devoid of consideration of the biological pathologies (abnormalities) beyond acknowledging that an infection *might* have initially triggered the disease. This "biopsychosocial model" for CFS, still in active use today,[155] fails to account for existing research demonstrating the biological pathology of ME.[156] As a result, the studies that have pursued the "biopsychosocial model" for CFS have had a laser focus on psychological and behavioral disease theories and treatments. Those treatments include a form of CBT, designed to change the patient's "false illness beliefs," and graded exercise treatment (GET), designed to reverse the presumed deconditioning felt to be causing disease symptoms.[157]

A closely related psychological theory holds that CFS is a somatic (somatoform) disorder in which a patient has an excessive focus on his bodily symptoms and excessive concern over his health.[158] But regardless of the specifics of the particular theory, when CFS is seen through such a psychological lens, it becomes a disease of faulty behavior and thinking. The faulty biology is denied or ignored as irrelevant.[159]

In this book, these psychologically centered theories are collectively referred to as the "psychosocial model" of CFS because, in applying Engel's biopsychosocial model to this disease, its proponents have cynically excised the role of biology.

Many of the psychosocial studies have been performed in England and a few other European countries and have used the Oxford criteria. This includes the well-funded £5 million 2011 PACE trial, which found that CBT and GET could result in "recovery" by mediating "fear avoidance" and were more effective than the usual care provided by specialists or by activity pacing, the patient-preferred approach to managing the disease.[160] However, the PACE trial findings are highly disputed for a number of methodological reasons.[161] One of the most significant is the use of overly broad selection criteria like Oxford, which result in cohorts of patients with a range of medically unexplained fatiguing conditions. PACE claimed that it found the same result for other definitions but it used modified and non-standard versions of those definitions. Another significant concern is the reliance on subjective measures and the failure to demonstrate clinically meaningful objective improvement.[162] Such an approach can result in biased results in unblinded studies like PACE. Other methodological concerns include the post-hoc decision to drop most of the objective measures and to change the definition of recovery. As a result of this change, patients could be

designated as "recovered," and yet have a greater level of disability than that required for admittance into the trial. Finally, the PACE trial failed to adequately report harms in the trial. This is a critical failure because patient surveys have long reported that patients experience harms from CBT and GET. As noted by ME patient and advocate Tom Kindlon, 51 percent of survey respondents reported that GET worsened their health while 20 percent said that CBT worsened their health.[163] The level of harm reported was significantly greater for one of the surveys conducted in severely ill patients—82 percent of respondents reported harm due to GET.

But in addition to the methodological issues of a given trial, it is also important to question the scientific validity of the underlying psychosocial model. What scientific proof has been provided for this model? And is it scientifically reasonable to expect that fear-avoidance and deconditioning treatments would be effective in a disease characterized by the kind of profound neurological, immunological, autonomic, and energy production dysfunction seen in ME? This is a particularly important question because studies based on the psychological model have likely included patients who may not have ME.

In a 2003 paper, Dr. Per Dalen, Swedish professor of psychiatry, discussed this issue of presuming a psychological explanation for diseases in which there is not yet a medical explanation.[164] He stated, "the boundaries of the [somatoform disorder] largely coincide with the current limits of received medical knowledge." In other words, somatoform disorder becomes the default explanation when medical science is unable to provide a medical explanation.

As an example of this effect, Dalen cited the disturbances in sensitivity and blood circulation first seen when chain saws were introduced into forest work. Lacking a medical explanation, doctors initially interpreted patient complaints as psychosomatic until vibration-related illnesses became an accepted medical concept. He concluded that "there is no proof that it is justified to apply the label of 'somatization' to such conditions as … chronic fatigue syndrome, multiple chemical sensitivity, and several more illnesses that established medicine has so far failed to explain scientifically."

Yet, such psychological theories toward this disease have achieved significant reach, even today. As an example, a 2012 article on CFS in the journal *Academy of American Family Physicians*, stated:

> "Patients with poor social adjustment, a strong belief in an organic cause for fatigue, or some sort of sickness benefit (i.e., financial incentive) tend to have worse responses to [cognitive behavioral] therapy."[165]

It is true that supportive counseling therapy can help patients cope with any chronic organic disease and deal with the limitations caused by their disease. According to the U.S. National Alliance on Mental Illness, cognitive behavioral therapy is also successfully used for a wide range of mental illnesses—depression, anxiety, personality disorders, substance abuse disorders, and eating disorders to name a few. In those cases, CBT is used to help patients question their misperceptions that are leading to destructive actions.[166] But in the case of ME, the idea that the profound debility of the disease has been caused by an ongoing organic illness has been dismissed in favor of unproven psychological causation. Such a singular, slanted focus on psychological and social problems as the explanation for continued ill health would never be tolerated for other organic diseases such as cancer, multiple sclerosis, heart disease or AIDS. Concluding that there is a psychological pathology in ME, without proof or evidence, has been both a significant impediment to research progress and a source of great stigma and harm for ME patients.

By the early 1990s, such psychological theories had a strong foothold in the study and treatment of this disease. In March 1991, the National Institute of Allergy and Infectious Diseases (NIAID) and the National Institute of Mental Health sponsored a conference,[167,168] with the purpose of reviewing the use of the Holmes criteria, making recommendations for its modification, and discussing approaches to assessing disease severity. While ME clinician Dr. Paul Cheney was listed as a contributor, so were a number of individuals who viewed CFS as a psychological disease, including Dr. Stephen Straus, Dr. Susan Abbey, Professor Simon Wessely, and Dr. Peter Manu, a University of Connecticut researcher.[169] The final report acknowledged the concern that patients with psychiatric illness and other chronic diseases were being misdiagnosed with "CFS" by the broader medical community and that even the experts were applying the Holmes case definition inconsistently. But, remarkably, the report then went on to recommend that the definition be modified, not to make the criteria more restrictive but rather to *exclude fewer patients with psychiatric illnesses*.

Further, betraying the focus on psychological causation, the report advocated for "an integrative approach that gives consideration to issues relating to comorbidity and *possible common pathogenic pathways in patients with CFS and psychic stress*" (emphasis added). The report did recommend stratifying patients with psychiatric illness but in practice that seldom if ever happened. The net effect of these recommendations was to create a catchall disease definition that was destined to include psychiatric illness and that completely failed to parse out ME patients into a more tightly defined research group.

Considering the concern that patients with a psychiatric illness were incorrectly being given a diagnosis of CFS, many will see the recommendation to *exclude fewer* patients with psychiatric illness as inexplicable. But given the contemporaneous statements of conference attendees and others about the supposed connection between this disease and psychiatric disorders, the conference report predictably maintained that this increased psychiatric focus in the definition would "lead to a better understanding of factors underlying CFS." Far from bridging the mind-body dualism, as many might have understood the intent, the report's approach allowed the attendees to effectively morph the concept of this disease to fit their beliefs that the disease is rooted in psychological and behavioral dysfunction. As Dalen described for somatization disorder, this was not a natural disease category but rather a category "pieced together and adapted by moving boundaries and stretching earlier assumptions."[170]

The differences in the scientific paradigm held by those who participated in the 1991 NIH conference and work being done elsewhere at the time are dramatic. For instance, in 1990, an international symposium of ME experts, spearheaded by Dr. John Richardson, an English physician, was held in Cambridge, England. As an outgrowth of that conference, Dr. Byron Hyde and the Nightingale Research Foundation published a compilation of articles representing the breadth of biomedical research and clinical approaches at the time.[171] That book, and the 1990 conference in Cambridge, examined the range of biological dysfunction that ME experts are investigating today: neurological, immunological, cognitive, muscle and exercise, cardiac, gastrointestinal, the role of infection, and the importance of post-exertional fatigability. Those researchers also noted that the disease was being conflated with psychiatric illness and were concerned that this psychological focus could cause important disease factors to be overlooked or could in fact even obscure the very existence of the disease. This turned out to be prophetic given what has happened to ME since.

In the same year as the 1991 NIH conference, the U.S. government also made the decision to categorize CFS as a subtype of "Malaise and Fatigue" in the "Signs And Symptoms" chapter of the

ICD-9-CM, the U.S. version of the *International Classification of Diseases Version 9 (ICD-9)*.[172] The inclusion of CFS in the "Signs and Symptoms" chapter of *ICD-9-CM* further distanced CFS from ME, which the World Health Organization (WHO) had categorized as a neurological illness in 1969. This decision also further reinforced the U.S. government's emerging position that CFS was a non-specific symptom that should not be considered as a distinct clinical entity. In sharp contrast, in 1992, when WHO added the term "CFS" to *ICD-10*, it decided to categorize CFS as a neurological disease and assign it the same code used for ME.[173]

The confusion and ambiguity resulting from the evolution of the CFS definitions were obvious to researchers even at this early point in the history of CFS. In 1993, NIH's Dr. Stephen Straus moderated a discussion at the annual meeting of the Infectious Disease Society of America. One of the speakers, Dr. H. James Wedner, a professor of Immunology and Allergy at Washington University and a clinician who had treated CFS patients, pointedly described how the continued broadening of the case definition was affecting CFS as a clinical entity:

> There has been a creeping movement to include other types of medical conditions under the rubric of CFS. For example, various forms of post-infectious fatigue, fibromyalgia, and non-psychiatric and depressive disorders were permitted by consensus of [the 1991 NIH workshop referenced above]. Somatoform disorders and panic disorder became part of what could be encompassed within the CFS case definition. This serves to *broaden the scope of the clinical entity to the point at which it is no longer definable.* (Emphasis added)[174]

This was a strong indictment that those responsible for CFS within the NIH and the CDC were consciously expanding and reshaping the very meaning of the disease labeled "CFS." Yet, Wedner's concerns did nothing to reign in the "creeping movement" being promoted by key individuals both inside and outside of the U.S. Department of Health and Human Services.

Establishing Oxford and Fukuda *(early 1990s)*

In the early and mid 1990s, a number of new definitions were created for CFS, including the 1990 Australian definition (which was not extensively used),[175] the 1991 Oxford definition[176] and the 1994 Fukuda definition[177] (which replaced the Holmes definition.) The Oxford and Fukuda definitions, still the two most commonly used definitions today, were ostensibly created in part to address the problems in consistent application and cross-study comparability seen in the Holmes definition. But, not surprisingly given the 1991 NIH conference and the reconceptualization of "CFS" as a psychological disease,[178] both Oxford and Fukuda also further broadened the diagnostic criteria by allowing the inclusion of primary psychiatric illness and focusing on the broad and non-specific symptom of medically unexplained chronic fatigue.

The 1991 Oxford definition was developed in the U.K. under the primary influence of a group of British psychiatrists who promoted the psychosocial model of CFS. These included Professor Simon Wessely; Michael Sharpe, professor of Psychiatry, University of Oxford; and Dr. Peter White, of Barts and The London School of Medicine, Queen Mary University of London. The Oxford definition does not require any of ME's hallmark symptoms, such as post-exertional malaise, for a patient to be given a diagnosis of "CFS." Remarkably, Oxford has a stunning absence of any criteria at all, except for six months of debilitating, medically unexplained fatigue, which "affects mental and physical functioning." Oxford specifies that the fatigue *must* be subjective, not physiological. Further, while schizophrenia and manic-depressive illness are excluded, all other forms of primary psychiatric illness are allowed. All "medical conditions known to produce fatigue" are excluded, whether seen at the initial visit or subsequently. (This begs the question of what happens to the

patient's CFS diagnosis if a patient subsequently develops a fatigue-associated condition such as cancer or heart disease, for which these patients are at high risk.)

Oxford does nothing more than describe the non-specific and ill-defined *symptom* of chronic fatigue, a symptom that is associated with many diseases. But by excluding all known medical causes and focusing on medically unexplained fatigue, Oxford virtually guarantees that "CFS" will be interpreted as psychological.

At about the same time and reflecting the positions taken at the 1991 NIH conference, the CDC developed the 1994 Fukuda definition, with input from Oxford authors Professor Sharpe and Professor Wessely.[179] Like Oxford, the Fukuda definition uses an overly broad approach to diagnosing CFS. Fukuda, originally designed for research but used clinically as well, only specifically requires six months of medically unexplained chronic fatigue and then specifies that patients have *any* four of eight other symptoms. Like Oxford, Fukuda does not require hallmark symptoms such as PEM or cognitive dysfunction, while allowing the patient to have most forms of primary psychiatric illness (e.g. allows anxiety disorders, somatoform disorders or other forms of depression;[180] excludes schizophrenia, bipolar illness and major depressive disorder with psychotic or melancholic features).[181] Fukuda excludes patients with any medical condition that could cause fatigue and has dropped the previous requirement for the physical signs that Holmes had required.

Dr. Leonard Jason, of DePaul University and an authority on the CFS and ME definitional issues, has noted that patients with primary depression can easily qualify for a diagnosis of "CFS" because they have fatigue plus four of the Fukuda symptoms even if they do not have a hallmark symptom such as PEM.[182] This is problematic for research and the development of treatments because patients with ME have underlying biological pathologies (abnormalities) that are different from depressed patients, as objectively demonstrated in exercise testing and neurological studies.[183]

The Fukuda definition states that the rationale for inclusion of psychiatric illness is that "such psychiatric conditions are highly prevalent in persons with chronic fatigue and the chronic fatigue syndrome, and the exclusion of persons with these conditions would substantially hinder efforts to clarify *the role that psychiatric disorders have in fatiguing illnesses*" (emphasis added). This statement, combined with the1991 NIH conference report statement about the "overlap with psychic stress" (noted above), betrays a predominate focus on psychological problems. Such a focus would not be tolerated in other serious chronic diseases whose patients can experience reactive depression. Further, when considered in the context of other statements in the definition, it demonstrates that the Fukuda definition was designed to provide a conceptual framework for the study of CFS *and other medically unexplained fatiguing illnesses*[184] in one lumped-together category.

This is significant because, like the Oxford definition, the Fukuda definition was never intended to provide a clear and distinct definition for ME patients. Instead, it mixes ME patients with disparate fatiguing conditions, including primary psychiatric illness. And while the Fukuda definition specifically acknowledges the importance of stratifying patients by factors such as coexisting psychiatric illness, few studies have done that in practice.[185]

Leaving aside the inclusion of primary psychiatric illness, the focus on medically unexplained fatigue as the basis of the clinical entity called "CFS" is suspect: there appears to be no scientific rationale to expect that all types of unexplained fatigue are similar enough to justify grouping together into a single clinical entity or that such unexplained fatigue would be biologically

distinctive from explained fatigue. Yet, in a feat of circular logic, Wessely has suggested exactly that. In a 2009 article, he stated that the fact that CFS is only diagnosed when other active medical or psychiatric conditions are absent implies that "the aetiology of '*unexplained*' CFS is different to that of the '*explained*' fatigue seen in those with a diagnosed medical condition" (emphasis added).[186] To my knowledge, this statement has never been proven with hard biological evidence demonstrating that the nature of fatigue varies simply based on whether it is "explained" or not.

Studies with both Oxford and Fukuda have resulted in significantly higher CFS prevalence estimates than the prevalence of around 23,000 seen with the Holmes definition. In 1997, Wessely estimated Oxford prevalence at 2.2 percent and Fukuda prevalence at 2.6 percent.[187] These rates are equal to 6.9 million and 8.2 million people respectively in the U.S. when applied to the total 2012 U.S. census of 314 million people (Appendix 2). Notably, the rates estimated by Wessely fell to 0.7 percent for Oxford and 0.5 percent for Fukuda when psychiatric illness was excluded, demonstrating that Wessely's application of Oxford and Fukuda have disproportionately included those with psychiatric illnesses. Across researchers and time, estimates of CFS prevalence based on Fukuda studies have ranged from the high of 2.6 percent reported by Wessely down to a low of 0.07 percent with the most frequently accepted prevalence being the 0.42 percent reported in a 1999 study by Jason (Appendix 2).

As Jason has noted, such a wide variance in prevalence is a reflection of the use of overly broad, non-specific definitions, methodological issues in how the studies were executed, including the methods and instruments used to identify CFS patients, and even the researcher's conceptualization of the disease.[188]

In addition to establishing the diagnostic criteria, Fukuda also recommended a minimal set of diagnostic tests, following recommendations made at the 1991 NIH conference. The tests recommended by Fukuda (e.g. complete blood count, a liver function test, urinalysis) are almost invariably normal in ME patients and are intended to be done solely to exclude other diseases, not to help diagnose this disease. The Oxford definition does not make explicit recommendations for testing, but some researchers and clinicians who use the Oxford definition have also promoted a similar reductive testing approach.[189] From one perspective, this recommendation reflects the failure to validate the biomarkers seen in the literature and used by disease experts today, a predictable result of the lack of funding. But it also reflects the unstated position that this disease is psychological and can therefore never be associated with abnormal signs and lab tests; if any abnormal signs or labs *are* found, then a search for the *real* disease should continue. When combined with an overly broad definition that encompasses disparate conditions and the diagnostic reliance on the *absence of evidence* of a known disease, this minimalist testing approach has had the impact of ensuring that the disease would not be taken seriously and that it would remain medically unexplained.

In practice, the Oxford definition has been used most frequently by those who promote the psychosocial model of CFS and/or believe that the disease can be predisposed or perpetuated by neuroticism, a belief that the illness is organic, and membership in a support group.[190] For its part, the Fukuda definition has been used by some of these same researchers but also by those who view CFS as a non-specific umbrella of medically unexplained fatigue or by those investigating ME's immunological, neurological, energy production, and other multisystem dysfunctions. Regardless of which disease theories are being pursued, both the Fukuda and Oxford definitions encompass a range of unrelated conditions[191] as a result of the choice of inclusion and exclusion criteria and the particular researcher's choice of methods and instruments used to determine who has the disease and who does not.

The obvious question is why was this done? Why was "CFS" defined so broadly that it failed to specifically describe ME as a disease and encompassed such diverse and unrelated patient cohorts?

In a letter apparently sent about the time of the 1994 publication of Fukuda and obtained by advocate Craig Maupin through a FOIA, NIH's Dr. Stephen Straus congratulated CDC's Dr. Keiji Fukuda on "his efforts to forge an international consensus that has scientific merit and is *politically acceptable*" (emphasis added). Betraying the unspoken intent behind the Fukuda definition, Dr. Straus made the following points:

> My own sense is that a few years of use [with the Fukuda definition] in the field will once again verify that there is no demonstrable or reproducible differences between individuals who meet the full CFS criteria and those who can be said to suffer Idiopathic Chronic Fatigue. This would beg the question of whether additional revisions to the definition are warranted, or its entire abandonment.
>
> I predict that fatigue itself will remain the subject of considerable interest but *the notion of a discrete form of fatiguing illness will evaporate.* We would, then, be left with Chronic Fatigue that can be distinguished as Idiopathic or Secondary to an identifiable medical or psychiatric disorder. I consider this a desirable outcome.
>
> What I would most like to see is that fatigue is not abandoned as a subject for careful consideration because of further failures of CFS case definitions or frustrations arising out of *shrill pressures to justify an entity of dubious validity such as CFIDS* [CFIDS is Chronic Fatigue and Immune System Dysfunction, an alternative name for CFS]. (Emphasis added)[192]

"The notion of a discrete form of fatiguing illness will evaporate." Indeed. But my son didn't evaporate. ME patients haven't evaporated. They just became invisible, disbelieved and abandoned on the trash heap of our medical system.

Especially when put into the context of Dr. Straus's other statements, can there be any more damning evidence that key leaders within HHS, whether through scientific misunderstanding or conscious intent, had rejected ME as a real disease and were morphing it into a vague condition of medically unexplained chronic fatigue associated with psychological problems?

Institutionalizing the Psychological and Broadening the Scope: The Empirical

In 1996, the recasting of ME as a psychological condition was given further institutional support when the British Joint Working Group of the Royal Colleges of Physicians, Psychiatrists, and General Practitioners issued a report on Chronic Fatigue Syndrome.[193] This report discouraged the use of the term "myalgic encephalomyelitis," which it stated to be originally associated with outbreaks of unexplained neurological symptoms. The authors felt that "encephalomyelitis is a specific pathological process not seen in these patients" and that the diagnosis was being misused. The report also found that 75 percent of patients had psychiatric disorders, recommended cognitive behavioral therapy and graded exercise as treatments and reported a prevalence of one to two percent. This was significantly more than Jason's generally accepted prevalence estimates of 0.42 percent.

A *Lancet* editorial was very critical of this report, stating, "We believe that the report was haphazardly set-up, biased, and inconclusive, and is of little help to patients or their physicians."[194] But not surprisingly, given his long-standing views about the nature of this disease, NIH's Dr. Straus gave a ringing endorsement of the report's recommendation, stating, "The report constitutes, arguably, the finest contemporary position statement in the field, and physicians and patients are well advised to read it." He further endorsed the psychosocial model of CFS and how that approach "stresses the complex interplay of social, behavioural and emotional factors in the presentation and perpetuation of [CFS] symptoms."[195] Notably, Straus didn't even mention the biological factors involved in the "presentation and perpetuation" of this disease.

In his acceptance speech for the 1998 American Association for Chronic Fatigue Syndrome's Rudy Perpich Award,[196] U.S. Assistant Secretary of Health Dr. Phillip Lee strongly disagreed with Dr. Straus's endorsement of the 1996 Royal Colleges Report. He voiced his concern that the psychosocial model of CFS had gone too far in its excessive emphasis on the social, behavioral, and emotional factors to the exclusion of biological factors.[197] He also cited a number of additional concerns, including the categorization of CFS in the U.S. version of the *ICD-9* (*ICD-9-CM*) where CFS had been classified in the "Symptoms" chapter, in contrast to the World Health Organization's classification of "ME" and "CFS" in the neurological chapter.[198] Lee also reminded the audience of what Dr. H. James Wedner had said at the 1993 meeting of the Infectious Disease Society of America: "Chronic fatigue syndrome…is neither a disease nor a syndrome. It is a committee definition." But in spite of his position in the Department of Health and Human Services, Dr. Lee's views apparently did not influence the official policies and actions being taken on this disease by the CDC or the NIH.

In February 2000, NIH held the "Chronic Fatigue Syndrome State-of-the-Science Consultation,"[199] which provided further evidence of NIH's psychological conceptualization of the disease. As stated in the final report, the purpose of the meeting was to "improve the quality, direction and extent of CFS research." These are important goals that require a solid understanding of the current state of science. Yet, as Kim Kenney (McCleary), CEO of CFIDS Association of America at the time, was able to determine, Dr. David Morens, NIH CFS program officer, stated that NIH's initial plan for the conference was for only four attendees: Dr. Stephen Straus, Professor Simon Wessely, Professor Michael Sharpe (in the Departments of Psychiatry and Clinical Neurosciences of the University of Edinburgh at that time), and Dr. Mark Demitrack, a psychiatrist from Eli Lily. At least three of them (Dr. Straus, Professor Wessely, and Professor Sharpe) promoted the biopsychosocial view of the disease.[200] Further, although the CFS Coordinating Committee (CFSCC, the group that advised HHS on CFS at that time) had originally recommended this conference to inform itself on the current state of science,[201] CFSCC was not involved in planning the meeting, and no CFSCC members or other disease experts were initially asked to participate.[202] As a result of vocal patient opposition, three ME clinicians were invited to observe the meeting: Dr. Nancy Klimas Miami was invited to attend at the last minute and NIH also expanded the meeting panel to include 11 participants, none of whom were disease experts.[203]

The report did contain some recommendations for biomedical research, but also demonstrated a continued strong focus on stress and psychological illness. Not surprisingly, given the commitment by some of the attendees to the psychosocial model of CFS, the report stated that "beliefs about illness should be explored as an aspect of CFS," and discussed the use of CBT and exercise as a treatment. The report further emphasized the need to distinguish between predisposing, precipitating, and perpetuating factors; language used in the psychosocial model of CFS. Finally, they stated that the case definition was "highly selected and unrepresentative of the true spectrum

of illness."[204] In other words, Fukuda, the case definition in use at that time, was too narrow and restrictive.

As a result of the widespread controversy surrounding the February 2000 conference, the CFSCC organized a second conference in October 2000,[205] to which they invited a number of well known ME expert clinicians and researchers. Unlike the February conference, this later conference focused on the dysregulation of biological systems—not on the dysregulation of thoughts, beliefs and behaviors. It included discussions on neuroendocrinology, cognition, chronic pain, sleep, immunology, orthostatic intolerance, fatigue, functional status, and disability. Further, while the February 2000 conference report had stated that the case definition was "unrepresentative of the true spectrum of illness," the October 2000 conference report specifically stated the need to further "constrain the diagnostic criteria" (emphasis added). In other words, the attendees at the October 2000 conference believed that the definition, particularly in research, needed to be made more restrictive, not less. But as with Dr. Wedner and Dr. Lee before them, their concerns appeared to have had little influence on the future evolution of the CFS case definition, as it would play out with CDC's expanded Empirical definition.

For historical context, it's important to note that these conferences coincided with the release of the U.S. General Accounting Office (GAO) report in 2000.[206] The GAO report was critical of HHS's handling of CFS, particularly in the lack of coordination between the NIH and the CDC. It exposed the CDC's misuse of $12.9 million in funds earmarked for CFS research and criticized both agencies for disregarding the input of external researchers and advocates in the development of research programs. This last point is well demonstrated in how NIH planned and executed the 2000 NIH workshop.

It is also worth noting that in this same timeframe, the NIH moved the CFS program out of the National Institute of Allergy and Infectious Diseases (NIAID), where it had been placed originally because of the early association with Epstein Barr Virus (a virus that the institute was investigating.) In 1999, the CFS program was first moved to NIH's Office of the Director, reportedly because NIH leaders Dr. Harold Varmus and Dr. Anthony Fauci "recognized that a multidisciplinary and integrated approach encompassing the missions of many NIH ICs [NIH institutes and centers] was necessary to address CFS."[207] Then, in 2001, the NIH's CFS program was moved to NIH's Office of Research on Women's Health (ORWH), reportedly to make it easier to "reach across the institutes."[208]

While it cannot be ascertained for certain that moving CFS to the ORWH was based on the NIH's institutional leanings to a biopsychosocial belief about the disease,[209] it did further marginalize the disease and did little to increase research funding of the disease. If it wasn't assigned an institute home in the NIH, as other diseases were, then who was going to take it seriously, and which institute was going to be responsible for researching it? Whatever the reasons,[210] the impact of this move was that no NIH institute was responsible for researching it or funding research for it. NIH did not appear to be taking the disease seriously.

Because of ambiguities in the Fukuda definition, the CDC held a series of closed workgroup meetings between 2000 and 2002 to discuss the substantial difficulties and inconsistencies in how cases of CFS were being diagnosed.[211] These workgroups also discussed how to uniformly apply standard instruments (largely patient-reported) to measure symptoms including fatigue, how to assess psychiatric comorbidity, and how to identify the dimensions of symptoms in patients with unexplained chronically fatiguing illnesses, including, but not limited to CFS.

The resultant 2003 paper stated that CFS is "defined by unexplained disabling fatigue and a combination of non-specific accompanying symptoms."[212] The paper questioned Fukuda's earlier restrictions on previous major depressive psychiatric illness. It emphasized the non-physical view of the disease, stating that the existence of any physical signs (as opposed to symptoms reported by patients) "should prompt the search for alternative diagnoses." The paper then recommended a set of largely patient-reported instruments to assess the various symptoms of the disease. Finally, foreshadowing the broader scope of disease that would emerge in CDC's Empirical definition, the paper called for empirical studies to "delineate the *different syndromes contained in unexplained fatigue* [emphasis added]."

According to comments made by CDC's Dr. Reeves at a May 2009 CFSAC discussion,[213] the authors of the 2003 Reeves paper did not recommend scales, so the CDC selected the scales that it felt "best represented the type of disability or the type of fatigue" seen in CFS. He also stated that previous episodes of major depressive disorder should not be considered exclusionary as it had been done previously, and he justified the use of certain scales that would preferentially select those with mental illness. Finally, he described the use of an "unwellness" screening strategy, a screen that cast an even wider net than a screen for fatigue. These CDC-selected and CDC-modified instruments and criteria were carried forward into studies that used this new Empirical approach to case selection.

In 2005, the CDC published "Chronic Fatigue Syndrome – A clinically empirical approach to its definition and study," which used these modified scales, the "unwellness" screening strategy and the relaxed exclusion criteria.[214] The study re-examined patients that had come from CDC's Wichita surveillance study,[215] a Fukuda definition study published in 2000. Importantly, the 2005 report found that the diagnosis of CFS in the new study was not consistent with how those same patients had been diagnosed originally. Specifically, using the same criteria as that used in the original study, only about ten percent of the patients were still diagnosed with CFS in 2005.[216] This is a remarkably low number, given that so few ME patients are known to recover.[217] Further, there was also remarkably little agreement (only 25 percent concordance) between the diagnosis of CFS using the Empirical method of identifying cases and the more traditional methods, as pointed out by Dr. Leonard Jason. [218] In short, Fukuda could not be reproducibly applied over time and the Empirical approach and Fukuda did not diagnose the same patients.

Remarkably, the 2005 Reeves study concluded that it had proven that the Empirical approach addressed the lack of reproducibility and consistency seen with Fukuda and that the approach was capable of distinguishing between CFS and chronic fatigue. It didn't appear to question whether the Empirical definition itself could also be flawed. Finally, the report recommended the use of the Empirical approach for both research and for clinical evaluation and follow-up care.

CDC went on to use this "Empirical approach to defining cases of CFS" in other studies. One of these was a prevalence study in Georgia.[219] This study reported a ten-fold increase in the prevalence of CFS over CDC's 2003 Fukuda-based prevalence estimates and a 6-fold increase over Jason's 1999 prevalence estimates. At 2.54 percent in 18-59 year olds, the rate of prevalence seen in the Georgia study was even higher than the 2.2 percent CFS prevalence that Professor Simon Wessely found using the Oxford definition in his 1997 study. Yet, remarkably, in an editorial published concurrently with the 2005 Reeves study, Dr. Peter White, one of the authors of the Oxford definition and a principle investigator on the PACE trial, embraced this increased prevalence and called for broadening CFS even further. He stated:

> Our current criteria for diagnosing CFS are arbitrary, and we need to widen the net to capture *all those people* who become so chronically tired and unwell that they can't live their lives to their full potential [emphasis added].[220]

Similar recommendations for criteria that encompassed broader populations were made in two studies published by CDC staff in 2009.[221] But one of these studies, on which Dr. White was also an author, reported that the factors associated with CFS were obesity, sleep problems, depression, and the multiplicity of symptoms. The disparity between these factors and what other researchers were reporting about the disease calls into question what population was being evaluated in this study.

As Dr. White said, some people are undoubtedly "chronically tired and unwell" for a variety of reasons that may include issues like depression, sleep problems, and obesity. But neither of these studies, nor White's editorial, demonstrated how lumping all these patients together in one undifferentiated group is a scientifically valid way to study the non-specific problem of unwellness. Further, none demonstrated how broadening the CFS criteria even further would advance a specific understanding of ME.

CDC has used the Empirical approach to study more than prevalence; it has also been used to assess what factors, including risk factors, were associated with CFS.[222] In 2007, Jason reviewed the findings of a number of these studies.[223] One of these studies was a 2006 study by Dr. Brian Gurbaxan of the CDC, who reported that depression was the single factor best capable of distinguishing between CFS and controls, but he found little association with 20 biological factors.[224] Jason also reviewed a 2009 study by Dr. Christine Heim of Emory University and CDC's Dr. William Reeves of the CDC that reported that childhood trauma was associated with a 6-fold increased risk of CFS.[225] In 2010, Dr. Urs Nater, of the CDC and Emory University, reported that CFS was associated with an "increased prevalence of maladaptive personality features and personality disorders."[226] In 2012, Nater reported that CFS was associated with maladaptive coping styles.[227]

Of course, the problem with these conclusions and interpretations is that they were based on tautological reasoning: Psychiatric risk factors were found in patient populations that had been expanded to include patients with psychiatric illness.[228] Put another way, if patients with psychiatric issues are merged into a cohort of "CFS" patients because they suffer memory and sleep problems and meet a non-specific CFS definition, then of course the resultant combined patient groups might have higher instances of childhood trauma or maladaptive coping. The inclusion of primary psychiatric illness has skewed the results.

More fundamentally for ME patients, such broadened "CFS" cohorts are not representative of ME patients.

Those outside of the CDC quickly decided that CDC's Empirical approach to diagnosing CFS was deeply flawed. In a 2008 paper evaluating the 2005 Empirical approach,[229] Jason raised concerns about the dramatic increase in prevalence and he also reported that 38 percent of major depressive disorder patients would be misdiagnosed as having CFS using the Empirical definition and methods. Jason also highlighted the fact that changes in the approaches used to assess cases of "CFS" could increase the percentage of "CFS" patients that had other psychiatric or fatiguing conditions, while failing to require that patients had the hallmark symptoms of ME. For example, a person could meet the new criteria even if they only scored lower than the 25th percentile on *just one of any* of the SF-36 scales for a diagnosis of CFS. As a result, patients with impairment on just

the role emotional scale (as might be seen in mental illness), but not on the physical function scale, could be given a diagnosis of CFS.

The impact of such changes on the cohort of people diagnosed with this disease was substantial. For example, Jason noted that the authors of the Reeves 2007 prevalence study had stated that the use of an 'unwellness" screen had resulted in the identification of 13 percent more "CFS" cases, while the use of the new "standardized criteria" had increased the number of cases 300 percent.[230] Jason further noted that the assessment approaches and criteria used in the Empirical definition might lead to the inappropriate conclusion that only "distress and unwellness characterize CFS," a conclusion that would bolster the idea held by some researchers that CFS was a functional somatic syndrome. Jason's point was that, collectively, these factors would result in a broader range of patients, including those with primary psychiatric illness, being given a diagnosis of CFS. It would also result in researchers and clinicians equating CFS to psychiatric illness.

Because of the patient selection problems with the Empirical definition, Jason has questioned the validity of the studies that used this approach. For example, using stricter disease criteria, Jason reported that a history of abuse was not a significant predictor of chronic fatigue syndrome.[231] This is in sharp contrast to Heim's study that reported that it was. Jason did report that a history of child abuse was positively associated with other conditions, such as PTSD and anxiety disorders, that can also have associated fatigue.[232] This finding is important because some patients with PTSD or anxiety disorders could qualify for a "CFS" diagnosis using the Empirical definition, skewing the results of the study.

One source of confusion that needs to be highlighted involves how the 2005 "Empirical approach to the study of CFS" is referenced by the CDC and in the literature. Many outside of the CDC refer to the definition as the Empirical definition or the 2005 Reeves definition. But CDC staff has stated that the 2005 definition is not an empirical definition but is rather just an operationalization of Fukuda.[233] As a result, the CDC appears to prefer to refer to this definition as the Fukuda definition or an operationalization of Fukuda. Some study publications, such as a recent review of prevalence studies by Brurberg, do the same.[234] But given the differences in inclusion and exclusion criteria, the differences in case selection methods highlighted above, and the dramatic increase in prevalence when using the Empirical approach, referring to Empirical as Fukuda only further confounds the already muddled situation. Therefore, for purposes of clarity, this paper uses the name "Empirical definition" to refer to the "Empirical approach to defining cases of CFS" laid out in the 2005 Reeves study.

In spite of the Empirical definition being largely discredited outside of the CDC, some HHS agencies, including at least the CDC and the FDA, still use an upper prevalence limit of four million, a level that can only have been based on the findings of the Empirical study prevalence rate of 2.54 percent.[235] In addition, the CDC has stated on a number of occasions that it has done an analysis that demonstrates that the Empirical definition describes the same set of patients as those selected by the Fukuda-based approach used in earlier Wichita studies in spite of the ten-fold increase in prevalence.[236] But as of the end of 2014, CDC's analysis demonstrating this equivalence has not been published, even though the CDC continues to publish Empirical studies as recently as 2015.[237]

Britain's NICE criteria

During the years when the U.S. was developing and using the 2005 Empirical definition, Britain developed the National Institute for Health and Care Excellence (NICE) Guideline for CFS/ME,[238] which was published in 2007. The NICE Guideline for CFS/ME was based in part on the 2005 York

CFS Evidence Review.[239] The resultant guideline is part diagnostic criteria, but also includes recommendations for management of CFS.

Diagnostically, NICE requires that patients have unexplained fatigue that is persistent, has resulted in a substantial reduction in activity and is characterized by post-exertional malaise. NICE then specifies that patients have *one* additional symptom out of a list of ten non-specific symptoms that are similar to the Fukuda symptom list. It is unclear how NICE defines post-exertional malaise. From a disease management perspective, the NICE guideline endorses graded exercise therapy (GET) and cognitive behavioral therapy (CBT). The NICE guideline's stated rationale for CBT reflects the psychosocial model of CFS. The guideline states that CBT is intended to get the patient to "avoid over-vigilance to symptoms" and to examine the "challenging thoughts and expectations" and "relationship between thoughts, feelings, behaviors, and symptoms" that may affect the person's state of illness. The rationale for GET is to reverse the presumed deconditioning.

It's important to note that the York Evidence Review, upon which the NICE guidelines were based, lumped together the Holmes, Oxford, Fukuda, Dowsett, Australian, London and Canadian definitions as representing the same disease or group of related diseases. This approach, used across many evidence reviews, including a 2014 one by AHRQ, likely encompasses a range of disease populations. That approach calls into question the validity and ethicality of applying the recommendations (particularly the treatment recommendations) based on studies in one definition to all so-called but possibly very different CFS and ME patients. Doing so is especially concerning to ME patients because of their energy production impairment.

As a result of paltry research funding, which has limited the type and size of research studies being performed, some of the most important studies into ME pathology, diagnostics, and treatment fail to be included in evidence reviews because they are small or otherwise fail to meet the criteria.

Normally in Britain, clinical guidelines like those for CFS would be reviewed every two years. But in early 2014, the NICE guideline for CFS/ME was placed on the static list, which means that it will not be reviewed for five years. The rationale for this decision was that NICE was not aware of any upcoming studies that would require an earlier review or call into question the current guideline. Patient groups have broadly objected to this decision, not only because of emerging science, but also because the current recommendations ignored existing biomedical studies and instead focused on psychological and behavioral treatments.[240] Recommendations for such treatments are largely based on Oxford studies, have not been specifically tested in populations selected by ME definitions, and are based on unproven psychological theories of disease persistence.

Resurrecting ME

In contrast to the overly broad "CFS" definitions established since 1988, internationally recognized ME experts have established disease-specific definitions that more closely reflect the descriptions of ME seen in the 1986 Ramsay definition. These ME definitions describe the neurological, immunological, autonomic, and energy production impairment of ME and require hallmark symptoms such as post-exertional malaise, unrefreshing sleep, and cognitive dysfunction.

The first ME definitions created after the 1986 Ramsay Criteria were the 1990 Dowsett criteria[241] and the 1994 London Criteria.[242] The London Criteria were not formally published, and different sources give conflicting information on the official reference, the date published and the authors. The Dowsett and London criteria have not been used extensively (although the PACE trial used a variant of the London criteria as discussed below), and these criteria have been largely supplanted.

The next definition to be created was the 2003 Canadian Consensus Criteria (CCC),[243] authored by a group of ME experts at the request of Health Canada. The CCC shifted from a singular focus on the ubiquitous symptom of fatigue to a focus on the hallmark symptoms of the disease. Unlike the Oxford, Fukuda and Empirical CFS definitions, the Canadian Consensus Criteria requires that patients have the hallmark symptom of post-exertional malaise plus fatigue, unrefreshing sleep, and pain. In addition, patients must also have two or more neurological/cognitive symptoms plus at least one symptom from two of the following categories: autonomic, immunological, and neuroendocrine. Primary psychiatric illness is not allowed although depression is listed as a co-morbid condition. Finally, the CCC established the term "ME/CFS," intending it to be a bridging term until the term "ME" was adopted. With hindsight, many now see that this likely contributed to the definitional confusion.

The requirement for the hallmark criteria of post-exertional malaise and the exclusion of primary psychiatric illness are important differentiators between the CCC on the one hand and the CFS definitions on the other because the latter only exclude certain primary psychiatric illness while allowing others. This exclusion of primary psychiatric illness also differentiates CCC patients from the psychosocial model of CFS. The proponents of the psychosocial model of CFS have stated that as many as 70 percent of CFS patients have evidence of a psychiatric disorder preceding their CFS onset.[244]

The Canadian Consensus Criteria has been used in both clinical care and in research, is widely respected by patients and experts alike, and provides additional information on testing (e.g. tilt table testing and NK cell activity) and differential diagnosis to aid a clinician in diagnosing ME. In addition, the Canadian Consensus Criteria has been used in a prevalence study where Canadian Consensus Criteria prevalence was found to be about 60 percent of that seen for Fukuda CFS.[245] Finally, the Canadian Consensus Criteria has been used as the basis of clinical guidelines published by the International Association for CFS/ME (IACFS/ME), the *CFS/ME: A Primer for Clinical Practitioners.*[246] This primer includes information on both diagnosis and treatment and is in its second edition, published in 2014.

In 2006, Dr. Byron Hyde, an ME clinician, established the Nightingale definition,[247] although the definition has not been broadly disseminated. Two more recent definitions have built on the 2003 CCC. The first of these is a pediatric ME definition published in 2006[248] that also requires post-exertional malaise and other hallmark criteria.

More recently, in 2011, a group of twenty-six ME experts from thirteen countries, with a total of 400 years of ME disease experience, published the ME International Consensus Criteria (ME-ICC).[249] The ME-ICC used the CCC as its basis but dropped the six-month waiting period. Importantly, it also dropped the requirement for fatigue. Instead, the ME-ICC distinguishes between the fatigue seen in other conditions and the fatigability seen in ME.[250] It emphasizes the abnormal response to exertion and the post-exertional exacerbation of all symptoms, which the ME-ICC refers to as post-exertional neuroimmune exhaustion (PENE), but what is known more commonly referred as "post-exertional malaise." The ME-ICC also reintroduces the requirement that the disease result in a 50 percent reduction in premorbid activity, a requirement that had been seen in the Holmes definition. In addition to post-exertional neuroimmune exhaustion, patients must also have neurological symptoms; symptoms reflecting immune, gastrointestinal and genitourinary dysfunction; and a symptom reflecting energy production and transportation impairments, including cardiovascular and respiratory issues.

Like the CCC, the ME-ICC provides information, including objective measures and signs, which help the clinician better understand and diagnose ME. Further, in response to the confusion resulting from overly broad "CFS" definitions and interchangeable names, the ME-ICC adopted the disease name "ME" and called for patients that meet the ME-ICC to be removed from the broader cohort of "CFS" patients. Finally, the ME-ICC has also been used as the basis of a primer, the *Myalgic Encephalomyelitis - Adult and Pediatric: International Consensus Primer for Medical Practitioners*,[251] which was published by many of the authors of the ME-ICC. The ME-ICC has only recently been used in published studies and does not appear to have been used in prevalence studies yet.

Some countries have moved to adopt these criteria. In 2010, the Scottish Public Health Network recommended that the CCC be adopted clinically for the diagnosis of ME because it better reflects the neurological nature of the disease, and it recommended that the NICE criteria be used for CFS.[252] Professor Wessely objected to the recommendation to adopt the Canadian Consensus Criteria for ME, in part because he objected to the inclusion of certain neurological symptoms in the definition and because the report expressed reservations regarding CBT and GET for ME patients.[253] The Public Health Agency of Canada lists the 2003 CCC in the "A to Z" listing of diseases and clinical criteria on its public website.[254] Finally, for its part, the Norwegian Health Directorate circulated a draft recommendation in 2012 that recommended ME-ICC and Fukuda for diagnostic criteria. However, possibly in response to objections from the Norwegian College of General Practice at the time, the Norwegian Health Directorate's current guideline lists both the Canadian Consensus Criteria and Fukuda and supports a more psychosocial approach to management.[255]

It is not just countries. In 2012, Euromut, a Belgian health insurance company, apparently had also endorsed the Canadian Consensus Criteria for the diagnosis of this disease. At this time, Euromut appears to have merged with another company and the reference no longer exists.[256]

But in the United States, Health and Human Services has refused to adopt either the CCC or the ME-ICC, despite repeated calls by experts and advocates to adopt it.

The Problem with the Name

It's not possible to imagine a more trivial and misleading name than "chronic fatigue syndrome," as the name is too easily misunderstood to be simple tiredness. This name has contributed to the extensive stigma and disbelief that patients and their carers encounter because everyone can be tired.

According to advocate Craig Maupin, Dr. Anthony Komaroff (one of the authors of the Holmes definition) noted that this impact was not anticipated when the term "CFS" was first coined. Komaroff stated: "None of the participants in creating the 1988 case definition, and the illness name, ever expressed any concern that the name might appear to trivialize the illness. We simply were insensitive to that possibility, and we were wrong."[257] He went on to note that since fatigue is part of the "universal human experience," many might connect the term "chronic fatigue syndrome" with their own fatigue and tiredness and be left wondering why that is considered a disease.

Dr. Leonard Jason confirmed this reaction in a 2007 study that examined the responses of both medical trainees and college undergraduates to the labels "chronic fatigue syndrome" and "myalgic encephalopathy."[258] Jason found that the participants' perceptions of the illness and its severity was related to the label given to the illness. Participants associated the "myalgic encephalopathy"

label with the poorest prognosis and were more likely to associate it with a physiological rather than a psychological cause.

At the recommendation of the CFS Coordinating Committee (CFSCC), a Name Change Workgroup was organized in 2001 to assess the issues involved in changing the name. The committee recommended the label "neuroendocrineimmune dysfunction syndrome (NDS)" in recognition of the range of systems affected.[259] Because the CFSCC had been disbanded before reviewing the Workgroup recommendations, its replacement, the CFS Advisory Committee (CFSAC), reviewed this recommendation in 2003.[260] At that meeting, CDC's Dr. William Reeves (head of the CDC CFS program at the time) spoke against adopting a new name because, among other things, he said that the term "CFS" was recognized, and that changing the name could set back all the "educational and scientific publication accomplishments." The CFSAC ultimately tabled the name change recommendation, and no further action was taken.

Reeves' concern that a name change would orphan research is still raised by some today. But that concern seems trivial compared to the problems that have resulted from continuing to use the same "CFS" label for definitions as disparate and sometimes non-specific as Oxford, Fukuda, CCC and ME-ICC.

Today, CFS is the official label used by both Fukuda and Oxford. Doctors in the U.S. diagnose CFS even if the patient meets the CCC or ME-ICC criteria.[261] The CCC uses the hybrid term "ME/CFS" and the NICE Guideline uses the term "CFS/ME". But in reality, all of these terms—"CFS", "ME", "CFS/ME" and "ME/CFS" and even just "chronic fatigue"—are being used interchangeably with little regard to the underlying definitions and associated disease theories.

This has created a linguistic babel that thwarts efforts to reach a shared understanding of this disease. It is surreal to watch people communicate past each other, thinking that they are talking about the same disease because they are using the same disease name. But in reality, these definitions encompass a disparate range of diseases and conditions, for which little or no evidence of biological relatedness has been provided.

In February 2015, the Institute of Medicine (IOM), under contract from Health and Human Services, issued new diagnostic criteria and a new name, "systemic exertion intolerance disease" or "SEID."[262] The IOM report called for those patients that met the SEID criteria to be pulled out of "ME/CFS." At least one IOM panel member has indicated that their remit did not include making recommendations on the disposition of the Fukuda or Empirical definitions.[263] There are also still open questions about how SEID is intended to fit with the CCC, which is used in research. At the same time, news reports and some doctors are interpreting the new name as a simple rebranding of CFS and have recommended CBT and GET for its treatment, ironic given that the IOM focused on a systemic intolerance of exertion as the core symptom. As a result, the term "SEID" appears to be at risk of being absorbed into the CFS hodgepodge of disparate names and criteria. This will do nothing to clarify the nature of ME.

The Classification of CFS in Medical Dictionaries

Another issue that has contributed to the confusion on the nature of this disease is the handling of CFS in the medical dictionaries. As noted by Dr. Geza Balint of the National Institute of Rheumatology and Physiotherapy in Hungary, the roots of modern disease classification are found in the work of Thomas Synderham, a 17th century English physician who advocated that diseases be classified with the same care used to classify plants. He made this recommendation in order to

correct the practice in place at the time of grouping diseases together based on "a common phenomenon…whilst they are in their nature as dissimilar as possible."[264]

Today, quite a few classification and terminology systems exist and are used for medical records, insurance billing, and mortality and morbidity tracking. Because of their usage, they broadly influence how medical providers view ME: that is, whether they see ME as a real disease or a non-specific symptom and whether they view the disease as organic or psychiatric.

The first of these medical dictionaries is the *International Classification of Diseases* (*ICD*), published by the World Health Organization (WHO). As noted earlier, the WHO placed ME in the neurological chapter of *ICD* in 1969.[265] In 1992, WHO added the term "CFS" to the neurological chapter in the *ICD-10* and assigned it the same code as ME (G93.3).[266] According to a report given to the CFS Coordinating Committee (CFSCC) in 2001, the United States National Center for Health Statistics (NCHS, part of the CDC and responsible for *ICD* implementation in the U.S.) originally intended to follow the direction set by WHO in the *ICD-10* when it implemented the U.S. version, the *ICD-10-CM*.[267] But by 2003, in parallel with the studies being done with the Empirical Definition, NCHS decided to reclassify CFS from the neurological chapter in the *ICD-10-CM* to the "Symptoms and Signs" chapter. This change positioned CFS as a subtype of "chronic fatigue" under the heading of "Malaise and Fatigue."[268] That made CFS little more than a footnote of the symptom of chronic fatigue.

However, this change does not comply with WHO standards for the *ICD-10*, in which the same disease cannot be placed in multiple chapters.[269] This change is contrary to the classification of CFS by other countries that also have their own clinical modification of ICD-10.[270] Yet, NCHS has refused to comply with the WHO classification standards and the practice in other nations. NCHS has persisted in this position despite proposals and recommendations from CFSAC, a medical professional organization (IACFS/ME), and patient groups, all of which called for CFS to be moved back to the neurological chapter.[271] When *ICD-10-CM* is rolled out in 2015,[272] CFS will be classified in the "Symptom and Signs" chapter as a subcategory of "Malaise and Fatigue." NCHS's decision achieves the goal stated by NIH's Dr. Stephen Straus that "the notion of a discrete form of fatiguing illness will evaporate."[273] But it also provides further justification for separating ME out from CFS. CFS cannot be considered equivalent to ME yet simultaneously be categorized so differently in the ICD-10-CM.

Issues have arisen with the classification of the term "CFS" in the U.K as well. In 2001, the U.K.'s WHO Collaborating Centre (at Kings College in London) categorized CFS as a mental health illness equivalent to neurasthenia in the U.K. specific "WHO Guide to Mental Health in Primary Care."[274] This caused a number of authors and even textbooks to either state that CFS was classified as both a neurological and psychiatric illness, while some stated it is only classified as a psychiatric illness.[275] However, the World Health Organization issued a ruling in 2001 and again in 2004 that these statements were incorrect; the correct classification of CFS in *ICD-10* was as a neurological disease and not as a psychological disease.[276]

WHO's handling of CFS in ICD-10 follows the pattern seen in other diseases, such as Alzheimer, which is classified as a neurological illness, despite the presence of irritability, a psychological symptom. Unfortunately, the classification issue is not settled in the U.K. In 2014, the U.K Department of Works and Pensions published a continuing medical education program for disability analysts, which incorrectly stated that, *ICD-10 classified* "CFS/ME" under both neurological disorders (G93.3) and also as neurasthenia (F48.0, under "neurotic, stress related and somatoform disorders").[277]

Other classification dictionaries and terminology systems also perpetuate this confusion about the nature of ME. The second example is the *Systematized Nomenclature of Medicine--Clinical Terms (SNOMED CT),* produced by the International Health Terminology Standards Development Organization.[278] *SNOMED CT*, which is important to the implementation of electronic health records in the United States and likely elsewhere, lists CFS as a multisystem disorder but also as a mental disorder. Because ME is listed as a synonym of CFS, it is also classified as both a multisystem disorder and a mental disorder in *SNOMED CT*.

A third example is the READ codes, used as standard terminology in clinical practice in England.[279] The READ codes classify CFS as both a neurological disorder and as a form of neurasthenia, under somatoform disorders in the mental health disorders section. As in SNOMED CT, ME is considered a synonym of CFS and carries this same dual classification.

A final example is the controversial *Diagnostic and Statistical Manual of Mental Disorders (DSM-5*), published by the American Psychiatric Association in 2013. While neither ME or CFS are directly coded in the *DSM-5,* the terms "ME" and "CFS" have often been cited in the scientific literature as forms of "somatoform disorder," "somatization disorder," or "functional somatic syndromes", terms that are older variants of terms that are in the DSM-5.[280] For example, at a 2006 conference on "Somatic Presentations of Mental Disorders" held by the American Psychiatric Association in collaboration with WHO and NIH, Professor Wessely described CFS as an example of a functional somatic syndrome while another speaker described CFS as an example of somatoform disorder.[281] Equating CFS and ME to these terms both reflects and reinforces a psychogenic view of this disease.

The *DSM-5* contains a disorder called "somatic symptom disorder" (SSD), an updated term for "somatization disorder" found in the *DSM-IV*. According to *DSM-5*, SSD "is characterized by somatic symptoms that are either very distressing or result in significant disruption of functioning and is also characterized by excessive and disproportionate thoughts, feelings, and behaviors regarding those symptoms."[282] To be given a diagnosis of SSD, the patient only needs to have one symptom that persists for six months, as long as the medical provider has decided, in his or her own judgment, that the patient is "excessively concerned" with his or her health. SSD can be diagnosed in any patient, regardless of whether their symptoms are medically explained or not.[283]

Numerous experts, including particularly Dr. Allen Frances, chair of the *DSM-IV* Task Force, have highlighted the serious risk of over-psychologizing bodily symptoms from the misuse of *DSM-5*'s somatic symptom disorder. According to Frances, somatic symptom disorder is especially concerning since the judgment of when to diagnose somatic symptom disorder is "based on vague wording that can't possibly lead to reliable diagnosis."[284]

This is not just an academic concern. Frances and also Dr. Diane O'Leary of Diagnostic Rights have pointed out that defining somatic symptom disorder too broadly leads to medical conditions being dismissed without proper investigation. In a letter to the *DSM-5* Workgroup responsible for the somatic symptom disorder category, Frances warned of the impact of such a misdiagnosis, stating, "When psychiatric problems are misdiagnosed in the medically ill, the patients are stigmatized as 'crocks' and the possible underlying medical causes of their problems are much more likely to be missed."[285]

Expanding on Frances' point, O'Leary noted that female heart attack patients under the age of 55 are seven times more likely to be sent home from the E.R. than males of the same age because

medical staff assume their problems are not real.[286] She went on to note that, according to a survey of the American Autoimmune Diseases Association, "a staggering forty-five percent of autoimmune disease patients report having been denied medical care because doctors mistakenly diagnosed their symptoms as somatoform." The risk of a misdiagnosis of somatic symptom disorder is further demonstrated in a recent study of 6,233 fibromyalgia, rheumatoid arthritis, and osteoarthritis patients. That study found that almost all of fibromyalgia patients and a substantial portion of the rheumatoid arthritis patients would be diagnosed with a mental health disorder using the somatic symptom disorder criteria.[287]

If the risk of a somatic symptom disorder misdiagnosis is significant for rheumatoid arthritis patients, then the risk is even more serious for patients with misunderstood diseases. One example is Connecticut teenager Justina Pelletier, who was diagnosed with mitochondrial disorder but was then rediagnosed with a somatoform disorder by another doctor and detained for a year in a psychiatric facility against her family's wishes.[288] A similar story has been playing out with Denmark's Karina Hansen, diagnosed with ME, but then forcibly removed from her home in February 2013 and placed into a psychiatric facility where she has been held against her will ever since.[289] Karina has been given a diagnosis of "pervasive arousal withdrawal syndrome"[290] and is being treated for that by staff from the Research Clinic for Functional Disorders and Psychosomatics, which is run by Dr. Per Fink.[291] Fink's theory is that CFS, fibromyalgia, irritable bowel syndrome (IBS) and other "functional" diseases are in reality a single disease called "bodily distress syndrome," which is caused by emotional and bodily stress that is treatable by cognitive behavioral therapy (CBT), graded exercise therapy (GET) and anti-depressants. Fink has pointed to the NICE Guideline for CFS/ME as evidence to support the use of CBT and GET in his treatment regimen.[292]

The problems with *DSM-5* are not limited to somatic symptom disorder or to the criticisms made by Dr. Frances. Dr. Thomas Insel, director of the National Institute of Mental Health (NIMH), has criticized the lack of scientific rigor in the *DSM-5*. This has resulted in diagnoses based on "clusters of clinical symptoms, not any objective laboratory measure."[293] He stated that this would be equivalent to organizing medical diagnoses around the "nature of chest pain or the quality of fever," an approach that was abandoned long ago because "symptoms alone rarely indicate the best choice of treatment." Insel decisively stated, "…we can't succeed if we continue using *DSM* categories as the "gold standard." Instead, Insel said that NIMH would be moving to an objectively based nosology "based on emerging research data, not on the current symptom-based categories." This is a remarkable and forward-thinking position for the director of the National Institute of Mental Health. But it also begs the question of symptom-based categories are still tolerated for ME, particularly when evidence exists to support a more objectively defined nosology.

Efforts are currently underway to establish the new *ICD-11* and to align the mental health chapter of the *ICD-11* with the *DSM-5*.[294] The terms "CFS" and "ME" have both been removed from the beta (draft) version of *ICD-11*, making it unclear how these terms will be classified going forward.[295] How the handling of somatic symptom disorder in *ICD-11* and *DSM-5* will be reconciled is also unclear. At this time, one approach that is apparently being considered is similar to the *DSM-5* somatic symptom disorder approach described above.[296] Another approach appears to include aspects of Dr. Fink's concept of bodily distress syndrome (BDS).

Another potential change in *ICD-11* is that a single disease term may be able to be placed in two separate chapters. Given the history, this could lead to pressure to classify ME in both the mental health chapter and the neurological chapter.[297]

Depending on the decisions made regarding the classification of CFS and ME in *ICD-11*, how *DSM-5* and *ICD-11* reconcile differences in somatic symptom disorder and the potential for dual classification of the terms "CFS" and "ME," ME patients could be at high risk of being diagnosed with a somatic disorder. This would reinforce the disbelief and inappropriate treatments that patients receive today and leave them without adequate care for the actual disease from which they suffer.

The February 2015 Institute of Medicine report called for a new ICD code for SEID, separate from chronic fatigue and neurasthenia.[298] However, the panel did not make a recommendation regarding which chapter the term should be placed and as a result, this is an open issue that needs to be resolved. Doing so requires that the issue of whether the SEID criteria and the CCC criteria are intended to be two different definitions (one clinical and one research) for the same disease also needs to be resolved.

Disease Experts and HHS Face Off

In October 2012, the CFS Advisory Committee (CFSAC) issued the following recommendation:

> CFSAC recommends that you will promptly convene (by 12/31/12 or as soon as possible thereafter) at least one stakeholders' (Myalgic Encephalomyelitis (ME)/Chronic Fatigue Syndrome (CFS) experts, patients, advocates) workshop in consultation with CFSAC members to reach a consensus for a case definition useful for research, diagnosis and treatment of ME/CFS beginning with the 2003 Canadian Consensus Definition for discussion purposes.[299]

CFSAC's intent was clear: fast action involving disease experts and patients, with the CCC as a starting point.

Patient advocates supported that recommendation through petitions and a position paper to Secretary Sebelius, Assistant Secretary of Health Howard Koh, CDC Director Thomas Frieden and NIH Director Francis Collins on May 12, 2013.[300] That position paper called for the adoption of the Canadian Consensus Criteria, the discontinuation of the term CFS because it is not specific, and the open engagement of the ME stakeholders. HHS rejected the advocates' recommendation. In its response, HHS reiterated its broad focus on "CFS and *other similar medically unexplained chronically fatiguing illnesses* such as ME, fibromyalgia syndrome, neurasthenia, multiple chemical sensitivities, and chronic mononucleosis.[301] (Emphasis added)

Then, in August 2013, with no discussion with CFSAC or the community, HHS suddenly and unilaterally announced their intent to contract with the Institute of Medicine (IOM), part of the National Academy of Sciences, for one million dollars to develop new clinical diagnostic criteria.[302]

Patient advocates objected, citing the fact that HHS had acted unilaterally, that the study would involve non-experts to create the new definition, and that the recent IOM study on treatment of Gulf War illness (GWI) had been strongly criticized by Gulf War advocates for using criteria (chronic multi-symptom illness) that were so broad "as to include nearly any human health condition."[303] Finally, ME advocates also objected because the IOM, by its own admission, had had virtually no experience in developing disease criteria. At the time the contract was awarded, the only other definition study conducted by the IOM was the one for "chronic multi-symptom illness" in Gulf War veterans. In the final report for the GWI definition study, the IOM stated that it was ultimately unable to establish a new definition because of the state of the evidence for Gulf War Illness.[304] Given that the evidence base for this disease is likely at least as convoluted as that for

Gulf War Illness, advocates expected that similar challenges would make it difficult to reach an evidence-based recommendation for this disease.

It wasn't just ME advocates who were concerned with the plans to have the IOM develop new criteria. In October 2013, fifty internationally renowned ME experts sent a letter to Secretary Sebelius, calling on HHS to adopt the 2003 Canadian Consensus Criteria for both research and clinical care.[305] These experts also urged HHS to abandon its plans to contract with groups like the Institute of Medicine (IOM) to develop criteria. They stated that such efforts were wasteful, unnecessary, and threatened to move "ME/CFS science backward by engaging non-experts in the development of a case definition for a complex disease about which they are not knowledgeable."

HHS refused to accept the experts' recommendation to adopt the Canadian Consensus Criteria,[306] in part because the Canadian Consensus Criteria does not include evidence from the last ten years.[307] The irony of that statement is that HHS has also rejected the last ten years of replicated evidence for PEM as a hallmark symptom that can be objectively measured and continues to dispute the importance of PEM as a required symptom.[308] One must ask to what extent HHS rejected the Canadian Consensus Criteria simply because it does not fit HHS beliefs about the nature of this disease.

HHS's Current Definition-Related Initiatives

Having rejected the recommendation of the CFSAC regarding the CCC and with little involvement of CFSAC or the community, HHS kicked off three initiatives: the IOM initiative, the NIH Pathways to Prevention (P2P) Initiative and the related Agency for Healthcare Research and Quality (AHRQ) Evidence Review.[309] A fourth initiative, the CDC Multi-Site Clinical Assessment was already underway and was also intended to address the case definition. Collectively, these initiatives will shape how this disease is viewed and how it is defined, researched and treated for years to come.

The first of the HHS initiatives, the IOM initiative, used a mixed panel of ME experts and those unfamiliar with the disease to establish an "evidence-based clinical diagnostic criteria for ME/CFS," intended to be targeted to general practitioners.[310] The IOM held two public meetings, accepted written input from the public and was to incorporate input from the CDC Multi-site Clinical study and the NIH Pathways to Prevention initiative (although the output of the P2P was not ready in time).[311] In addition, the CDC also recommended that IOM use data from the CDC population-based surveillance study. This was concerning because the most recent CDC surveillance study used the Empirical definition, which increased the prevalence and resulted in the misdiagnosis of patients with major depressive illness.

In addition to the concern with the use of non-experts, as noted above, another significant concern was the lack of specificity in how the scope of disease was defined in the contract, with numerous, ill-defined terms included.[312] This was a critical shortcoming, particularly given the controversies with the definitions and names outlined above. This author asked for clarification on this issue when the contract first became available. Remarkably, HHS said that it was leaving it up to the IOM panel to determine what specific disease these new diagnostic criteria will describe.[313] But it is crucial to ask whether it is standard practice to contract a group like IOM to not only develop diagnostic criteria for a disease, but also first decide what scope of disease those criteria will encompass.

The final IOM report, released in February 2015, produced an extensive review of the biomedical literature on the immunological, neurocognitive, neuroendocrine, orthostatic, energy metabolism,

and sleep dysfunctions associated with the key symptoms.[314] It recognized post-exertional malaise as a hallmark symptom, required for a diagnosis, along with unrefreshing sleep and either cognitive dysfunction or orthostatic intolerance. Based on these criteria, it replaced the diagnosis of exclusion with a positive diagnostic approach and recommended a new name: "systemic exertion intolerance disease." The report emphasized that the disease is not a psychological illness, but rather a complex, multi-system disease that causes severe functional impairment. The report highlighted the stigma and neglect that patients had experienced at the hands of the medical community. Finally, it noted the "relative paucity of research" to date and stated that "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."

While the evidence review was generally well received, advocates and experts have expressed legitimate concerns that the recommended criteria fail to adequately convey the neurological symptoms experienced and the severity of the disease as experienced by the most severely ill patients.[315] Concerns have also been raised that the criteria are largely subjective (as no objective tests are required), the Clinical Guide as provided misses critical information that is in the report itself and the criteria and the recommended symptom assessment tools have not been operationalized or tested.[316] (For instance, some of the assessment tools have not been used in this patient population, cutoffs and other instructions for their use have not been provided and/or the report acknowledges that they would be hard to use clinically.)

Also concerning is the current lack of clarity on whether the SEID criteria are intended to describe the same disease as the ME-ICC and the CCC and whether the Fukuda and Empirical criteria will continue to be used for those patients who do not meet the SEID criteria.[317] For instance, as it currently stands, the same disease could be called "SEID" clinically and yet be called "ME/CFS" in a research study that uses the CCC and yet the patient only has one disease. More problematic is that the SEID are often being interpreted as a rebranding of CFS for which the current CFS descriptions and treatments are appropriate. For instance, a Medscape article referred to the work of Professor Wessely and recommended CBT and GET.[318] Medscape has also provided a case study, in which CFS and SEID are treated as synonymous and the Fukuda and SEID criteria are treated as representing the same disease even though the patient in the case study does not have PEM, a requirement for the SEID criteria.[319] This demonstrated tendency to throw SEID into the CFS pot reinforces the concerns that SEID will become a new wastebin diagnosis in the hands of doctors who do not understand the nature of the disease.

To date, HHS has not stated what they intend to do about the SEID criteria or about the existing CFS website, the Fukuda or Empirical CFS definitions or the findings and recommendations based on Empirical or Oxford definition studies. But it is essential that any forward plans clearly separate out the neuroimmune disease from the CFS umbrella.

The second HHS initiative is CDC's Multi-Site Clinical Assessment, which is intended to characterize ME/CFS patients in order to improve the measurement of the "illness domains of CFS"[320] The clinicians involved are all considered experts in the disease. No case definition is being used to guide patient selection; instead, the clinicians have been asked to use their expert judgment. Instead, clinicians from the specialty clinics have been instructed to include patients diagnosed with CFS, ME, and also post-infective fatigue. The terms "CFS" and "post-viral fatigue syndrome" are ill-defined and do not require the hallmark PEM. This raises the question of whether these diagnostic labels represent the same disease and whether all Multi-Site study clinicians apply them in the same way.[321] At the IOM public meeting in January 2014, Dr. Lily Chu, who sat on the IOM panel, asked CDC's Dr. Beth Unger if the diagnoses would be cross-validated

across the clinics involved in the Multi-Site study. Dr. Unger said she would leave it up to the clinics to decide if they wanted to do that.[322] Remarkably, particularly given the historic confusion on these terms and the decision to not use a case definition for patient selection, this was not a planned part of the study.

The first phase of the Multi-Site study focused on patient-reported outcomes, while the second phase has added in some lab tests. Because of the importance of PEM as a hallmark symptom and the extensive evidence on the use of CPET, patient advocates requested that the CDC use the 2-day cardiopulmonary exercise test (CPET) to objectively demonstrate which patients have PEM and its associated energy production impairment.[323] But the CDC declined. Instead, they decided to use one day of exercise followed by cognitive testing. To my knowledge, this approach has never been evaluated, let alone replicated, as a method to objectively demonstrate post-exertional malaise and impairment of energy production. Further, both Dr. Christopher Snell and the report of the NIH 2011 State of Knowledge Workshop[324] have stated that one day of exercise is insufficient to distinguish between ME and deconditioning. In my son's experience, when CPET and cognitive testing were simultaneously given on two consecutive days, the CPET clearly demonstrated energy production impairment, while the findings of the cognitive test were ambiguous with one measure improving on the second day.

CDC said that it decided to not use the 2-day CPET because of the cost of CPET, the potential risk of harm to the patient and the burden to patients who would have to stay an extra night. But the irony in CDC's rationale is that the cost of this test pales in the face of the $19-24 billion annual economic impact and the harm done to patients even today as a result of the treatment recommendations that the CDC provides in its clinical education guidelines.

The third initiative is NIH's Pathways to Prevention (P2P) initiative (previously called the Evidence-based Methodology Workshop for ME/CFS), a process intended for *non-controversial* areas of science[325] and largely driven by those who, by design, are not allowed to have expertise in this disease.[326] NIH's description of the intended goal of this initiative has morphed over time, making it difficult to know what HHS was trying to achieve. In response to the original 2012 CFSAC recommendation, HHS stated that the goal of P2P was to "address the issue of case definitions appropriate for ME/CFS research" and acknowledged that this effort was intended to address the research case definition issue, the highest priority issue identified at the 2011 NIH State of Knowledge meeting.[327]

But in a May 2013 CFSAC discussion, Dr. Susan Maier of the NIH said that it would not result in a new case definition. Instead, she described goals of "identifying scientific and methodological weaknesses," and evaluating the evidence for "case definitions, for outcomes, for interventions, and for treatments."[328] In a January 2014 email, Dr. David Murray, director of the NIH Office of Disease Prevention, told Dr. Francis Collins that the P2P Workshop would review the different definitions used in research in order to "clarify the type of patients that are captured under each definition" and how those patients respond to therapy. The intent was to help researchers decide on the best-case definition.[329]

Finally, the Program Book used in the P2P Workshop stated that the goal was to identify research gaps, identify scientific and methodological weaknesses and suggest research needs.[330] In the end, despite a letter from advocate Jennifer Spotila and this author to Dr. Collins outlining concerns such as the lack of clarity of goals, the conflation of definitions and the use of non-experts,[331] the P2P agenda, and the supporting AHRQ Evidence Review lumped all definitions together, regardless of the differences across case definitions. The P2P Workshop and the AHRQ Evidence Review then

focused on diagnostics and treatments, an inexplicable choice in a disease in which there are no approved diagnostics or treatments.

The Panel's first input, the 2014 draft AHRQ Evidence review,[332] lumped together studies across eight CFS (Oxford, Fukuda, Reeves, Holmes) and ME (Canadian, Revised Canadian, ME-ICC and London) definitions and based on that grouping, made recommendations for all CFS and ME patients, regardless of which definition was used in the underlying studies. The review focused on self-reported symptoms and psychological and exercise treatments, while excluding studies on most biomarkers, on cutting-edge ME research on immunological, neurological, and energy production issues, and on treatments such as Rituxan. The full extent of the problems with the approach used in AHRQ's Evidence Review are remarkable and beyond the scope of this book.[333] For patients, perhaps the most immediate concern is that the final AHRQ Evidence Review did not question the scientific validity and ethicality of basing treatment recommendations for ME patients on studies where patients were selected using the Oxford criteria. This creates a significant risk of harm to ME patients because the Evidence Review states that the final report may be used in medical care guidelines and reimbursement decisions.

Like the AHRQ Evidence Review, the Panel's second input—the Workshop agenda topics and selected speakers—also excluded broad swaths of research, an approach described by advocate Jennifer Spotila as "science-lite."[334] For instance, the workshop sessions included "Social Determinations of Health" and "Self-Management" topics but none of the sessions featured neurological, autonomic, or energy production dysfunction. In addition, the speakers selected for the session on fostering innovative research, arguably the most important session, had a research focus on psychosocial theories, perceptional issues and pain research.[335] These topics are far from the mainstream biomedical focus of research in this disease, as seen in the three different 2014 disease conferences held at Stanford, London (InvestInME) and San Francisco (IACFS/ME).

Also, like the AHRQ Evidence Review, the P2P Workshop agenda was not structured to discuss the originally posed question of whether the ME and CFS definitions represented the same patient population or not, or to consider the implications of that question for forward recommendations. That both the AHRQ Evidence Review and the NIH P2P Workshop failed to ask such a fundamental question, while ignoring the science that would have highlighted the issues, was inexplicable and unacceptable.

The resultant draft P2P recommendations, released in December 2014, acknowledged that the needs of patients had not been met, stated that the disease was not psychological, and made a number of recommendations for research that reflected recommendations already made by CFSAC for many years.[336] But the report failed to address the definitional muddle, beyond calling for the Oxford criteria to be retired. It continued to support CBT and GET as treatments, even though those recommendations were based on studies done with the Oxford criteria. It called for additional studies into biopsychosocial parameters, multimodal treatment (an approach to psychotherapy), homeopathy and self-management. At the same time, the report failed to specifically call for studies on immune modulators, antivirals, and similar disease modifying treatments. Finally, the report failed to call on HHS to provide a fair share of NIH funding, failed to address the NIH institutional issues and stigma that have driven researchers away and failed to fix HHS's broken approach to engaging this community.

The final P2P report was due on April 15, 2015 but was delayed on April 2 when advocate Jennifer Spotila discovered that comments, including extensive comments submitted by CFSAC, were missing from a FOIA request.[337] NIH acknowledged that comments had not been forwarded to the

P2P panel and set a new release date of June 16, 2015 so that the panel could review all of the missing comments. But on April 20, 2015, Spotila noted that her latest FOIA was still missing comments that had been submitted.[338] The mishandling of comments raises concerns with the integrity of the process and the final product since the additional comments are being reviewed after the fact. Spotila has notified both NIH and the Inspector General for HHS and the issue is currently open.

Collectively, these four initiatives underscore the significant problems that continue to hold this disease back—particularly the confusion resulting from the definitional and naming muddle, the impact that years of limited and misdirected research funding have had on the state of the evidence base, the lack of coordination in HHS' efforts toward this disease as seen across these four initiatives and the failure to consider the input of stakeholders in the initiation of these efforts and how they were conducted.

The vast differences in the evidence reviews done by IOM and AHRQ are one good indication of the definitional muddle this disease faces. Each review encompasses different definitions and as a result, different slants on the evidence. But the simplest indication of the confusion is the fact that the IOM report noted neurological, immunological, and energy production dysfunction and centered its definition on a physiologically driven systemic intolerance to exercise while the AHRQ Evidence Review cited the PACE trial and recommended CBT and GET, used in the PACE trial to convince patients that they are not really sick and just need to exercise.

Irreconcilable Differences – One Disease or Many

HHS's View: Many Definitions, The Same Disease

Even before HHS's latest definition initiatives, at least twenty different definitions had been used for CFS and ME.[339] (Appendix 1 lists the most commonly used and/or more commonly referenced in the U.S.) These definitions vary dramatically in terms of what symptoms are required, whether primary psychiatric illness is included or excluded, the choice of approaches and methods used to diagnose patients, and the resultant prevalence rates (Appendix 2). As Dr. Leonard Jason has discussed, the dramatic differences in these factors reflect fundamental differences in how the disease has been conceptualized.[340] This has led to incompatible and ultimately irreconcilable disease theories battling over the soul of this disease.

Dr. Beth Unger of the CDC underscored one of the biggest differences between CFS and ME definitions at a 2013 CFSAC meeting, when she asked, "If a patient doesn't have [post-exertional malaise], would you not manage them as a CFS patient?"[341] That statement reflects CDC's long-standing focus on unexplained fatiguing illnesses, in which PEM is an optional symptom. Such a statement ignores the importance and distinctiveness of PEM and its associated biological dysfunction. The CDC reportedly took a similar position in its 2014 submission to the IOM initiative. In that submission, the CDC said that the requirement for PEM/PENE was a *limitation* of the Canadian Consensus Criteria and the ME International Consensus Criteria because such a requirement would exclude patients who do not have PEM/PENE.[342]

The other major difference is seen in the disease theories, where the psychosocial model of fear-avoidance and deconditioning[343] stands in stark contrast to the biomedical model of neurological, immunological, and energy production dysfunction. Most people would reasonably conclude that the same disease process is unlikely to respond both to a drug like Rituxan that kills part of the

immune system and also to psychotherapy intended to convince you that you are not really sick but rather just have a fear of activity that has caused deconditioning.

What makes this situation even worse—for both progressing research and for the quality of medical care—is that these disparate definitions are explicitly treated as equivalent to each other. Based on this untested assumption, the diagnostic and treatment recommendations resulting from studies in *any* of these definitions are applied to *all* CFS and ME patients, without regard to whether those definitions represent the same conditions or not. One example of this is the CDC CFS website's clinical guidance, which states that all of these disparate definitions describe the same group of patients,[344] for whom the same diagnostic and treatment approaches are appropriate. The CDC CFS website further states that these same diagnostic and treatment guidelines can also be used for "CFS-like" illness.[345] "CFS-like" illness is defined as six months of fatigue but not including the other Fukuda symptom requirements—essentially little more than chronic fatigue.

This one-size-fits-all approach to diagnosis, treatment, and management of all CFS and ME patients is the one used by the vast majority of medical education sites. Cognitive behavioral therapy (CBT) and graded exercise therapy (GET), studied in Oxford or Fukuda populations, are almost always recommended for all CFS and ME patients with no explanation of the difference between the two or the nature of PEM. Yet, for the sickest ME patients, exercise can have grave consequences. Even for those who are less severely ill, exercise has been shown to exacerbate dysfunction in energy metabolism and other systems and is known to cause harm that can result in prolonged and potentially irreversible crashes.[346]

There are substantial medical and ethical concerns about the appropriateness of such one-size-fits-all clinical recommendations. This is especially true when scientific logic and the published evidence of biological pathologies suggest that these definitions do not all represent the same disease.

Such one-size-fits-all approaches are also seen in research and evidence reviews, where CFS and ME definitions are treated as equivalent, and where modified and/or non-standard criteria have been used as acceptable substitutes. For example, the 2011 PACE trial stated that CBT and GET were effective for patients diagnosed by Oxford, and also for patients diagnosed by the CDC criteria and the London criteria. But the criteria used were non-standard criteria which were then further modified by PACE.[347] In both cases, it is impossible to know what types of patients were encompassed by the CDC and London criteria used by PACE.

Another example is the handling of the diverse definitions in evidence reviews, which invariably lump ME and CFS definitions together, ignoring differences between them. The example already given is the 2014 AHRQ Evidence Review, which mixed and matched eight different CFS and ME definitions without regard to differences in inclusion or exclusion criteria or patient selection methods used. Treatment recommendations based on one definition were then applied to patients described by any definition.

Some evidence reviews include not only *any* CFS and ME definition, but also include studies that do not meet a specific definition, as long as the patients have some duration of chronic fatigue. For example, in 2014, Dr. Lillebeth Larun, of the Norwegian Knowledge Centre for the Health Services, published the protocol for a planned Cochrane evidence review of GET in CFS.[348] The protocol acknowledged the existence of multiple definitions and that, therefore, the study would define "CFS" to be six months of medically unexplained, disabling fatigue. Studies of other disorders were

included as long as 90 percent of the patients met these non-specific chronic fatigue criteria. No exclusionary conditions were mentioned, and no other symptoms, such as PEM, were required.

Another example is the 2008 Cochrane Evidence Based Review for CBT in CFS.[349] It included Oxford, Fukuda, and Australian definition studies, but also included studies where the symptom requirements of Fukuda were dropped, or where patients could have just three or four months of fatigue even if no "CFS" definition was met. The 2001 AHRQ evidence review[350] and the 2005 York evidence review, used in the development of the NICE Guidelines,[351] followed a similar approach.

Leaving aside the small and questionable claims of treatment efficacy and the reported methodological issues, these studies and reviews beg the question of whether it is scientifically valid and ethical to base recommendations on comparisons across such diverse definitions. Collectively, these ME and CFS definitions share nothing more than the ubiquitous symptom of chronic fatigue and the lack of a medical explanation. Treating the disparate ME and CFS definitions as equivalent to each other is bad science, particularly given that there is no proof of biological relatedness. Collectively, this kind of definitional gymnastics is unethical and has greatly compounded the confusion surrounding this disease.

The View of ME Experts: Many Definitions, Different Diseases

As demonstrated by the 2013 letter to Secretary Sebelius by fifty international disease experts calling for the adoption of the Canadian Consensus Criteria, ME experts have strongly disagreed with CDC's assertion that these definitions represent the same disease or set of closely related diseases. Their disagreement reflects the fact that there are significant differences in hallmark criteria, levels of functional impairment and disability, the relation to primary psychiatric illness, and the accompanying theories of disease pathology.

The most fundamental difference is the singular focus on the ill-defined symptom of fatigue in the CFS definitions and their failure to require hallmark criteria such as PEM, unrefreshing sleep, and cognitive dysfunction. Instead, as Dr. Leonard Jason of DePaul University discussed in a 2014 study, Fukuda (and Empirical by implication) uses "polythetic criteria," which require only fatigue plus any combination of four of eight other symptoms.[352] The use of such polythetic criteria, combined with the failure to require hallmark criteria, could lead to other conditions being misdiagnosed as CFS. For example, in a 2010 presentation for the CFIDS Association of America (now the Solve ME/CFS Initiative), Jason showed how one particular combination of Fukuda symptoms (fatigue plus the symptoms of unrefreshing sleep, joint pain, muscle pain, and impairment in concentration) could describe patients with depression.[353] At the NIH P2P Workshop, Jason stated that in a review of 53 Fukuda studies, hallmark symptoms occurred at different rates; for example, across studies, PEM was reported in 25-100 percent of patients, while unrefreshing sleep was reported in 16-100 percent, demonstrating substantially different populations.[354]

Dr. Luis Nacul, of the London School of Hygiene and Tropical Medicine, put a sharp edge on this point in his 2014 presentation at the NIH P2P Workshop. He highlighted the non-specificity of Fukuda and pointed out that Fukuda symptoms could be grouped into 163 distinct combinations.[355] Yet, only 35 of these combinations require PEM (PENE). This begs the question of what illnesses are encompassed by the other 128 Fukuda combinations.

Looking at this issue of lack of definitional specificity from another perspective, Jason's 2014 study demonstrated that only sixty percent of the patients that satisfied Fukuda also satisfied the ME-ICC.[356] Similarly, in a large (143,000 person) 2011 British prevalence study, Nacul found that the prevalence of patients who met the Fukuda was 0.19 percent, while that for the Canadian Consensus Criteria was 0.11 percent, about sixty percent of the prevalence for Fukuda.[357] In a 2012 study, Dr. Michael Maes, of Maes Clinics in Thailand, found that only about 50 percent of Fukuda CFS patients had post-exertional malaise.[358] PACE itself stated that of the 640 participants selected by Oxford, only 427 (67 percent) met PACE's modified version of Reeves 2003, while only 329 (51 percent) met PACE's modified version of the London Criteria. Admittedly, it is impossible to know what types of patients are encompassed by these criteria as modified by PACE, but at the very least, this reinforces the point that these definitions are not all selecting the same populations.

The second major difference pointed out by researchers is how the definitions and the selected assessment tools treat psychiatric illness. In a 1997 study, Jason pointed out that key decisions (such as the inclusion or exclusion of psychiatric illness and the choice of psychiatric assessment instruments) were influenced by "a societal and political context in which CFS was assumed to be a psychologically determined problem."[359] One example is the Empirical definition's choice of requiring a low score on only *one* scale of the SF-36 (including just the role emotional scale), which could select patients with mental but not physical illness.[360] In a 2012 review, Yvonne Christley, nurse lecturer at the University of West Scotland highlighted this problem, stating, "The differing approaches to the identification and definition of CFS are potentially compounding and strengthening associations between CFS and psychiatric disorders by taking too broad an approach to case identification."[361]

The third difference between CFS and ME definitions reported by researchers are the differences in the level of patient function, disease severity and disability. In a 2001 report examining the loosening of criteria in Fukuda compared to the earlier Holmes definition, Dr. DeBecker, of Brussels, Belgium, stated that the Holmes definition had had less clinical heterogeneity and more symptom severity than that seen in the Fukuda definition.[362] Similarly, Jason reported "more symptomatology and functional impairment" in patients selected by Holmes than in those selected by Fukuda.[363] In a series of studies over the last ten years, Jason has also shown that patients meeting ME definitions, such as the Canadian Consensus Criteria or the ME International Consensus Criteria, have more severe symptoms and physical impairment than those meeting Fukuda.[364]

Similarly, in his 2011 prevalence study, Dr. Nacul reported that fatigue, pain, "sleep dysfunction and symptoms related to immunological, neurological/cognitive, and psychological functions" were significantly greater in patients who met the Canadian Consensus Criteria than those who met Fukuda. He stated that this suggested a difference between Fukuda patients and Canadian Consensus Criteria patients that reflected the Canadian Consensus Criteria's more restrictive criteria, including its requirement for PEM.[365] In a 2012 study, Maes demonstrated that those Fukuda patients who had post-exertional malaise also had more severe illness, more severe feelings of infection, greater neurocognitive impairment, and significantly higher levels of immune-inflammatory blood markers than those Fukuda patients who did not experience PEM.[366]

The fourth difference between the ME and CFS definitions is the breadth of the neurological, immunological, autonomic, and energy production impairment described in the Canadian Consensus Criteria and ME International Consensus Criteria. None of the Oxford, Fukuda and Empirical definitions describe these dysfunctions. They instead exclude any conditions in which there is a medical explanation for the symptoms. Researchers have demonstrated these biological

pathologies and associated biomarkers, and also demonstrated how these differentiate ME patients from those with deconditioning, depression, non-specific causes of chronic fatigue, and a number of chronic illness.

These studies, particularly those on the distinctive symptom of PEM and its underlying energy production impairment, are a direct counterpoint to those who promote the psychosocial theory of CFS, who believe that as many as 70-75 percent of these patients have psychiatric illness.[367] They are also a direct counterpoint to those who embrace the idea of a spectrum of conditions organized around medically unexplained fatigue.

Such biological differences are seen in the clinical setting as well, not just the research setting. In a 2004 study on Fukuda's lack of specificity, Dr. Gwen Kennedy of Scotland showed that three different groups of patients—those with CFS, Gulf War Illness and Organophosphate exposure—all met the Fukuda CFS definition, and presumably would have been diagnosed as CFS. Yet, each had differences in simple, easily performed clinical outcome measures that would have differentiated the cases, if such testing had been done.[368]

The differences in inclusion and exclusion criteria and in the diagnostic methods lead to a lack of diagnostic reliability due to what Jason has referred to as "criterion variance"[369] and poorly "operationalized" criteria.[370] The obvious examples include differences in the ways that patients' level of functioning is evaluated. Less obvious, as noted by Jason, is that most studies record only the presence or absence of symptoms, and do not consider the frequency and severity of those symptoms.[371]

Such diagnostic unreliability is especially problematic in the Oxford, Fukuda and Empirical definitions. As a result, even when just the Fukuda definition was used across all studies, it is still difficult to be certain of what population was studied. CDC's Dr. William Reeves made exactly this point in a 2005 study, when he noted that because Fukuda studies failed to specify how "disability, fatigue and symptom occurrence were elucidated," it was "difficult to assess the validity of diagnostic criteria," making it "essentially impossible to compare results between [Fukuda] studies critically."[372]

Reeves also demonstrated that, even in CDC's hands, Fukuda was not reliable. In the same 2005 study, he noted that the Fukuda-based methods used in the 2003 surveillance study for diagnosing CFS "showed *scant stability over time*," with "poor correlation between illness classification" when patients were rediagnosed two years later *using the same methods* as in 2003.[373]

Similar concerns were raised with Oxford's lack of specificity by the British Group on Scientific Research into Myalgic Encephalomyelitis (GSRME), a panel chaired by Dr. Ian Gibson, a member of Parliament and previous professor of biology. This group, an outgrowth of the All Party Parliamentary Group on ME, contained members from both Houses of Parliament, and was established to increase public understanding of scientific research, to evaluate progress in the development of a full program of research, and to identify research and funding requirements for ME.[374] The resultant report, the 2006 Gibson Inquiry, stated that the Oxford definition was focused on little more than "long-term tiredness," and included a broad spectrum of patients. As Dr. Gibson stated, "One problem with investigating CFS/ME is that the 'Oxford Criteria', the guideline for selecting patients for research trials, is very vague and focuses on fatigue rather than the numerous other symptoms of CFS/ME. As such, *the knowledge we do have of the illness may have been gleaned from people who did not genuinely have the condition"* (emphasis added).

A claim of disease heterogeneity is often put forward as the explanation for the differences across studies. This viewpoint states that the differences in findings reflect the heterogeneity and complexity of the underlying disease, and that these diverse and broad definitions represent the true continuum of this disease. This is inherent in the psychosocial model, and also in HHS' continued embrace of Fukuda and the Empirical definition, its medical education, and its framing of the 2014 IOM, P2P, and AHRQ initiatives, where differences between the various definitions are treated as equivalent or a continuum of related conditions.

But such claims of the heterogeneity of "CFS" mask the reality.

Yes, ME, with its different onset and triggering events, the influence of genetics, the differences in immunological and neurological markers, the varying levels of severity, the differences in environmental and microbiome factors, and the differences in disease progression over time is undoubtedly heterogeneous. When this disease is finally unraveled, we will likely see patient subgroups stratified based on such factors, which are then used to best target treatments. This kind of stratification has been at the heart of advancing treatments for diseases like breast cancer.

But the "heterogeneity" of CFS is different. CFS "heterogeneity" has been artificially created by lumping unrelated definitions and conditions together based on the singular factor of medically unexplained fatigue, with no proof that they encompass the same or closely related diseases. Imagine attempting to study the nature of bluebirds, by first lumping them together with dragonflies and flying fish because they all "fly" and all lay eggs. You would never be able to learn how bluebirds breed or breathe. And yet, this is what we have done to ME for thirty years, dumped it into a wastebin of unrelated diseases, based on the existence of the ubiquitous, ill-defined symptom of fatigue for which there is not yet a medical explanation.

Putting a sharp edge on this point, in 2011, Dr. Bruce Carruthers, the lead author of the Canadian Consensus Criteria and the ME International Consensus Criteria, stated, "There is a poignant need to untangle the web of confusion caused by mixing diverse and often overly inclusive patient populations in one heterogeneous, multi-rubric pot called 'chronic fatigue syndrome."[375]

HHS's claim that these diverse definitions represent the same group of patients is particularly difficult to comprehend because HHS staff has acknowledged that CFS is not a discrete diagnostic entity,[376] and that these symptom-based definitions do not all represent the same disease. For example, echoing statements made in the 1996 Royal Colleges Joint report,[377] Dr. Stephen Straus of the NIH stated, "Neither the American [Fukuda] nor the Oxford criteria assume the [chronic fatigue] syndrome to be a single nosological entity."[378] Another example is the report of NIH's 2000 "State of Science Consultation," which stated that in the absence of a biological marker, "there is no assurance that any complex of symptoms corresponds to a biological state," an acknowledgement of their diagnostic unreliability.[379] More specifically, a 2010 article co-authored by CDC's Reeves stated, "The 1994 International CFS case definition and the Canadian Consensus Criteria are different and do not necessarily identify similar groups of ill persons.…The physical findings in persons meeting the Canadian definition may signal the presence of a neurologic condition considered exclusionary for CFS."[380] And until it was removed in July 2012, one of the CDC medical education courses distinguished between CFS and ME, stating that ME referred to "well-documented outbreaks of disease," but was "accompanied by neurological and muscular signs and has a case definition distinct from that of CFS."[381] ME obviously didn't change its nature in 2012. What changed was the interpretation of the scope of disease encompassed by the term "CFS."

But Dr. Reeves' earlier assessment was correct. The 2003 Canadian Consensus Criteria and other

ME definitions do not define the same group of patients as those defined by the 1994 Fukuda definition. And that is exactly the point that ME experts have been making. Lumping these definitions together based solely on unexplained chronic fatigue, with no regard for the differences in symptoms and the underlying biological pathologies, is the antithesis of the kind of scientific excellence that has made progress in cancer by carefully delineating the real biological differences between patient groups.

The View of ME Patients

For decades, patients have given a consistent view on the nature of this disease through testimony at government meetings; submissions to various initiatives like the current IOM and P2P initiatives: last year's FDA review of Ampligen; the April 2013 FDA "Voice of the Patient;"[382] and patient testimony in YouTube videos, books, and news stories. This view consistently calls out PEM as a mandatory hallmark feature, an unwanted badge by which patients recognize each other. At the FDA Patient Focused Drug Development Initiative Meeting in April 2013, held to document the patients' perspective on their disease, ME patients universally described the ubiquitous and debilitating symptom of PEM. They described PEM as the symptom that exacerbates "all symptoms to extreme levels that generally lead to complete incapacitation," including "complete exhaustion, inability to get out of bed to eat, intense physical pain (including muscle soreness), incoherency, blacking out and memory loss, and flu- like symptoms."[383] Similarly, a 2013 survey of Norwegian patients reported, "For the whole group and each sub-group the gravest symptom was a significant exercise-induced energy failure, as a result of physical or mental strain."[384]

Patients have also consistently rejected the idea that this disease is driven by psychological or behavioral problems. Yet, frustratingly, that position has been used by some researchers and news articles as proof that patients are deeply prejudiced against mental illness, are anti-psychiatric or are irrationally unwilling to accept psychiatric treatment or research that doesn't fit their theory of the disease. For example, Professor Wessely stated, "For many it is better to have an incurable disease such as CFS than a psychological disorder even if that might be treatable."[385] Dr. Brurberg of the Norwegian Knowledge Centre for the Health Services in Oslo stated that "patient groups and researchers with vested interests in the belief that ME is a distinct somatic disease seem unwilling to leave the position that ME is an organic disease only."[386]

But such statements misrepresent the concerns of patients. ME patients are not objecting to the positive support that psychiatry could provide in dealing with the tremendous physical, emotional, social and financial losses that they face. My son would welcome such therapeutic support. But what he got instead was a psychiatrist who browbeat him with questions on what made him think he was sick and why he wanted to go on disability; his negative reaction to that line of questioning was then used as proof that he had mental illness. What ME patients overwhelming object to is the fact that in both clinical care and in research, too many focus on social, behavioral, and psychiatric factors to explain the patient's condition, while ignoring or trivializing the evidence of biological disease.

Such a singular focus on social, psychological and behavioral factors to the exclusion of biological factors is unscientific and offensive to anyone who has seen an ME patient's vibrant health abruptly blow up. ME is not the first disease to be so trapped by psychological theories. The scientific literature is littered with examples of "medically unexplained" diseases being automatically redefined as psychological illness.[387] But cold mothers did not cause autism, multiple sclerosis was not hysterical paralysis and stress reduction techniques, and talk therapy didn't cure stomach ulcers. Antibiotics did, as Dr. Thomas Borody of Sydney, Australia demonstrated in

1987.[388] Patients who have ME will not get better with talk therapy geared to convincing them that they are not really ill, or with exercise to reverse their presumed deconditioning. ME patients will get better when there are therapies that target the underlying neurological, immunological and energy production pathologies that wrack their bodies.

It's important to make one final note. There have been reports over the years, especially in the British media, that some researchers have been harassed and/or have received death threats.[389] Researchers who have adopted the biopsychosocial approach, including those associated with PACE trial publications, appear to have most often reported these actions. But researchers studying the XMRV retrovirus and some researchers pursuing a biomedical approach have also reported harassment. Because of reports of harassment, the NIH no longer makes the list of CFS grant reviewers public, although the nature of that particular harassment is not clear.

Death threats are a serious charge and even one death threat is unacceptable. And while patients' anger at being dismissed, marginalized and stigmatized for thirty years by the government, the medical community and the media is completely understandable, harassment of researchers can be counterproductive to the goal of advancing an understanding of the disease if biomedical researchers leave the field.

The media, particularly in the U.K., continues to report death threats and harassment today as seen in a 2015 Economist article[390] on the 2015 PACE "mediating effects" study.[391] It is not clear from this article whether those reports are of current or past events. The article also does not specify the nature of the harassment.

But as patient advocates rightly point out, it's important to clarify what actions are being constituted as harassment. Insight into this comes from the Tymes Trust, a U.K. ME charity, which obtained, via FOIA, U.K. Research Council documents concerned with the startup of a newly formed research initiative.[392] According to Tymes Trust, the documents discussed harassment of researchers and specified freedom of information requests and parliamentary questions as examples of harassment. The U.K. Information Commissioner's Office (ICO) took a similar position in the response of another FOIA request. The ICO rejected that FOIA, which sought information about the PACE trial, because it was determined to be "vexatious" and "had the effect of harassing the public authority."[393]

But these actions are legal and have been undertaken because of legitimate concerns with the current situation. In addition to the FOIA examples cited above Lady Margaret Mar has often raised the plight of ME patients in Parliament. Reporting these actions to the media under the blanket label of harassment is deceptive and begs the question of whether this label is intended to marginalize the patient community and dismiss or draw attention away from the legitimate concerns being raised.

The View from the Outside

The choices made in how CFS has been defined affect more than just ME patients. As a diagnostic entity, CFS has become a wastebin diagnosis that can be applied to anyone who goes to the doctor with a complaint of fatigue. For example, one study found that over thirty percent of multiple sclerosis patients had first been misdiagnosed with CFS or "malaise or fatigue" before being correctly diagnosed with multiple sclerosis.[394] In Britain, a seventeen-year old patient, Sophie Coldwell,[395] was diagnosed with "CFS" because she complained of fatigue. Ten days later, she died

of leukemia. Patients with depression, sleep disorder, and an indeterminate number of other fatiguing conditions can be easily misdiagnosed with CFS.

Then there are the patients diagnosed with CFS whose subsequent, serious illnesses are dismissed as not serious, simply because they have a diagnosis of CFS. Author and ME patient Toni Bernhardt described the story of one patient whose potentially fatal case of pneumonia was almost dismissed because he had CFS.[396]

More broadly, there is a lesson to be learned about overly broad criteria in the concerns raised with *DSM-5's* somatic symptom disorder.[397] As Dr. Diane O'Leary pointed out, defining somatic symptom disorder "too narrowly may obstruct access to mental health care, but defining it too broadly will…[obstruct] access to needed medical diagnosis and care."[398] O'Leary added that this is especially problematic when doctors are advised by medical societies (O'Leary's example is the American Association of Family Physicians) or clinical guidelines to make an early diagnosis of somatoform disorders to save time and reduce costs.[399] As Laurie Endicott Thomas, medical writer and author of *Not Trivial,* told Dr. Allen Frances, such advice can be dangerous. "Once doctors have dismissed an illness as psychosomatic, they stop looking for the correct diagnosis and the patient may never get the right treatment."[400]

How did somatic symptom disorder become so poorly defined when, as Dr. Frances says, "anyone with common sense" can immediately see that SSD is "impossibly broad and non-specific."[401] Dr. Frances suggested that at least part of the problem is that "experts always want to focus increased attention on their pet topic, want to expand its boundaries, and worry much more about missed than about mislabeled patients." This is reminiscent of Dr. Peter White's 2009 editorial, published in conjunction with an Empirical study, when he called for widening the net to capture all patients who are "so chronically tired and unwell that they can't live their lives" to their fullest potential.[402]

But Dr. Per Dalen, the Swedish psychiatrist, pointed out there is likely a second factor at work in the case of somatic symptom disorder—a different standard of scientific proof used for psychiatric diagnoses. Dalen stated, "Many doctors would never let themselves be caught with woolly ideas about the possible causes of cancer, multiple sclerosis, or cardiovascular diseases. But just mention the word somatization, and they will feel free to engage in uncritical speculation."[403]

As Dalen pointed out, such somatization theories thrive when medical science has not yet provided an explanation. In a 2010 review, Annemarie Jutel of the Otago Polytechnic in New Zealand examined the handling of medically unexplained symptoms across studies.[404] She found that half of the reviewed literature treated medically unexplained symptoms as psychological disorders, and interchangeably used terms like somatoform illness with medically unexplained symptoms. As she pointed out, assigning psychological causation based on the *lack of evidence*, as opposed to its presence, is problematic in that it relies on a diagnosis by exclusion, and fails to recognize the *"limitations of knowledge."* Just as importantly, she also noted a "pervasive" tendency to treat medically unexplained symptoms as a "unified condition that could be considered under one light, a kind of diagnosis of the undiagnosable."

There is also a lesson to be learned in how fibromyalgia has been defined. In *The Fibromyalgia Story*, Dr. Kristin Barker, a sociologist at Oregon State University, stated that the diagnostic criteria for fibromyalgia "have been tautologically constructed and they remain subjectively determined and inconsistently applied."[405] She went on to state, "No convincing evidence indicates that the symptoms that are gathered under this diagnostic label have any coherence as a discrete and unitary condition." Barker concluded that, fibromyalgia is an "intellectual abstraction created

through social processes." Such a construct may have social utility for doctors faced with hard-to-diagnose patients and insurance requirements for a specific diagnostic code. But such a construct does little to advance research into the underlying biological pathologies.

Similar influences have shaped the clinical entity called "CFS."

The Impact of Poorly Characterized Definitions

Today, CFS is a veritable Rorschach test whose interpretation morphs depending on the person viewing it, the definition they employ, and the disease theory they espouse. In one moment, we hear about studies claiming that "CFS" patients "recover"[406] with a regimen of cognitive behavioral therapy (CBT) and graded exercise therapy (GET) to eradicate their fear of activity, unhelpful illness beliefs, and deconditioning.[407] In the next moment, we hear that ME patients are responding to antivirals,[408] Ampligen, and Rituxan.[409] That the dueling disease theories vary so fundamentally underscores the depth and breath of the problems that have resulted from how CFS has been defined as a clinical entity.

The magnitude of the public health catastrophe that has resulted from this definitional chaos cannot be overstated.

More than any other single factor, this is at the heart of our country's tragic failure to address the ME crisis for the last thirty years. It has wasted precious dollars and time studying mixed patient cohorts that have no biological relationship to each other or to ME. It has polluted research, making it impossible to replicate findings across studies and casting doubt over all results. It has impeded the development of diagnostic biomarkers, leaving the diagnosis of this disease one of subjectivity and exclusion.[410] It has virtually stalled drug development, and made it almost impossible to attract private and commercial investment in the disease.[411] It has resulted in flawed epidemiological studies, and faulty, inflated prevalence numbers.[412] It has generated such disdain and skepticism in the research community that researchers[413] avoid the disease like leprosy out of a fear that it could kill their careers, a point made by Dr. Vincent Racaniello of Columbia.[414]
It has left clinicians confused about the nature of this disease, ultimately viewing it as mental illness or bogus. It has made it extremely difficult to get insurance reimbursement, because most tests and treatments are viewed as experimental. It has stigmatized terribly disabled patients and sentenced them to abysmal clinical care. Worst of all, it has dramatically altered the perception of ME by the public at large, ensuring that neither the disease nor its victims are taken seriously.[415]

Dr. Bruce Carruthers, lead author on the 2011 ME International Consensus Criteria, summed up the situation simply when he said, "Patient sets that include people who do not have the disease [ME] lead to biased research findings, inappropriate treatments and waste scarce research funds."[416] Speaking of the web of confusion created by the diverse CFS definitions, he further stated, "We believe this is the foremost cause of diluted and inconsistent research findings, which hinders progress, fosters skepticism, and wastes limited research monies."[417]

CFS as a Social and Political Creation

It is obvious from the history of "CFS" and the irreconcilable views on the nature of this disease that the global concept of "CFS" is not a reflection of the biology of the disease. Rather, it is a product of social and political forces. Dr. H. James Wedner made exactly that point, at the 1993 annual meeting of the Infectious Disease Society of America,[418] when he stated:

> [CFS] is neither a disease nor a syndrome. It is a case definition based upon a list of definitional criteria developed by a committee… The criteria were constructed to accommodate not only clinical problems but also social and political ones.

When myalgic encephalomyelitis gained widespread national attention following the outbreaks in the 1980s, the disease had the unfortunate coincidence of being a complex, chronic, multi-system illness with a dizzying array of symptoms that primarily affects women. Standard lab tests were all normal, and the abnormalities that were found were inconsistent or considered exotic. Early theories of a potential viral etiology lost what institutional support there might have been when the first anti-viral treatment trial failed to deliver the expected efficacy. Gender and the inability to find a medical explanation triggered dismissal, disbelief, or the knee-jerk reaction by medical providers that the problem must be a psychological one. And ME lacked whatever "protection" it might have if a medical society or scientific discipline "owned" it.

ME was exiled to the medical wasteland that exists outside of the traditional scientific disciplines, research institutes and medical societies that drive the medical research and clinical care of diseases in this country. It became a pariah, discarded by all.

In such a vacuum, the players with the power and vested interest to do so—those within HHS responsible for this disease and a group of British psychiatrists—were the ones left to define the nature of this disease, according to their own cognitive biases and their disregard for both ME patients and the small group of unaffiliated disease experts that studied and treated them. And by at least 1987, these powerful players had decided that the disease seen in Incline Village was not an organic illness, but rather a form of non-specific chronic fatigue that was most likely a psychological problem. As Dr. Richman pointed out, this conceptual shift resulted in and was paralleled by a significant shift in research that increasingly focused on psychiatric and psychosocial issues.[419]

It wasn't just that these groups were able to influence the evolution of disease criteria. They were able to exert influence in four additional ways. First, because of their power and access to resources, a significant portion of the budget spent on CFS globally over the last thirty years employed overly broad definitions and studied psychological and behavioral problems, instead of ME and its associated biological pathologies.[420] Examples include CDC's studies on childhood trauma and personality disorders that used the Empirical definition and the U.K. PACE trial. At £5.0 million, PACE was the largest and most expensive study ever done for this disease anywhere, costing about what NIH spends in one year.

The second factor is the ability of these groups to get papers published in top-tier journals while many of the unaffiliated researchers performing biomedical research were relegated to what specialists in other fields might consider second and third-tier journals. A neurologist that my son saw was skeptical of his doctor's recommendation for Rituxan, in part because of where the study had been published and in his report raised concerns about its usage. It is very difficult to influence the "dominant paradigm" of how a disease is viewed, when the biomedical research is relegated to journals that the mainstream medical and research communities view as less important or relevant scientifically.

The third factor was greater access to the media by these groups: when they published research, that research was more likely to be reported than the research of the unaffiliated researchers conducting biomedical research. For example, in 2009, a number of news sources, including Science Daily, NewScientist and Medscape[421] reported on a CDC Empirical definition study that

found that childhood abuse was associated with a 6-fold increase in risk of CFS. In an article in *Psychology Today*, journalist Pamela Weintraub perceptively asked if the real issue was not child abuse, but rather abuse of research resulting from ill-defined disease definitions.[422] But her question was drowned out by the drumbeat of publicity from other news sources that passed on the reports of child abuse, perverting everyone's perceptions about the nature of ME. Similarly, in 2013, PACE trial claims of recovery reverberated around the world, yet few if any news outlets probed the disputes clouding those claims.[423] It should be no surprise that those recommendations—and the psychological theories behind them—have made their way into some mainstream medical education information, including in the U.S.[424]

It's not just whether research gets covered but how it gets covered. In the U.K, the Science Media Center (which provides information and views of scientists on scientific issues) provided quotes from six scientists regarding the 2011 PACE trial, all overwhelmingly positive, with glowing support for the results of the trial.[425] But when Columbia University, working in conjunction with scientists from Harvard and Stanford, reported that they had found a distinctive immune profile that proved it was a biological illness and showed distinct stages of the disease,[426] the seven quotes provided by the Science Media Center were largely skeptical of the study.[427]

The fourth factor is that when ME patients inevitably objected to having their disease treated as a behavioral or psychological problem to the exclusion of the underlying biological pathologies, these powerful groups were able to leverage their access to media and the scientific literature to further delegitimize patients. They did this by turning valid patient objections into proof that ME patients are irrational, anti-scientific, motivated by financial self-interest (e.g. disability benefits), or are so biased against psychiatry and psychiatric illness that they would rather stay sick than be helped.[428] At the same time, patient attempts to have their disease treated as an organic disease were claimed to be an unscientific attempt to force an unnatural split between the mind and the body. This is a particularly disingenuous concern when voiced by those who have virtually ignored the biology of the disease and have a vested interest in maintaining a psychological view of the disease.

It is possible that other groups, including commercial interests, may have played a role in how the definition of this disease has been shaped over time. The U.K.'s 2006 Gibson Inquiry stated, "There have been numerous cases where advisors to the DWP [the U.K. Department for Work and Pensions, responsible for welfare, pensions and disability programs][429] have also had consultancy roles in medical insurance companies. Particularly the Company UNUM Provident. Given the vested interest private medical insurance companies have in ensuring CFS/ME remain classified as a psychosocial illness, there is blatant conflict of interest here."[430]

A recent example of such financial interests was seen in the PACE trial, in which some of the study authors declared conflicts of interest as a result of their work with the insurance industry.[431] One of those insurance companies is Swiss Re. Based on the PACE trial and a webinar by one of the PACE investigators, Swiss Re recommended CBT and GET to its claims professionals and discouraged pacing.[432] The material encouraged claims professionals to "Check that private practitioners are delivering active rehabilitation therapies, such as those [PACE] described in this article, as opposed to sick role adaptation." The article also stated that ME was considered a neurological disease while CFS could be classified as neurasthenia, a mental illness classification, which might potentially lead to an exclusion.

In its 2007 Chief Medical Officer's Report, entitled *Mind over Matter. Exploring the issues of Mental Ill Health,*[433] Unum included an article by British psychiatrist Dr. Christopher Bass[434] that

positioned CFS as a non-organic disease in which "illness perceptions and beliefs" and "psychosocial factors" play a role "in the maintenance and prognosis of this disease." Bass stated that studies had demonstrated the effectiveness of CBT for the treatment of CFS.[435]

Certainly neither the positions of Unum or Swiss Re nor the statements of conflicts of interest listed in published CFS studies prove collusion or undue influence. And like all businesses, the insurance industry is concerned with managing costs. But the Unum and Swiss Re reports appear to provide a remarkable level of endorsement of a treatment approach that has been based on studies in ill-defined patient populations and is grounded in an unproven disease theory that has ignored conflicting biological evidence.

In the *Handbook of Medical Sociology,* Dr. Kristen Barker of Oregon State University discussed the role that organizations, such as managed care organizations, have played in influencing "the type and amount of conditions discovered."[436] Barker noted that diagnosing a contested illness in patients who have medically unexplained symptoms typically limits costs for tests and referrals because the typical treatment recommended is comparatively cheap—"pain, sleep, and anti-depressant medications, as well as behavioral and exercise therapies." She concluded, "managed care organizations may use contested-illness diagnoses as part of their agenda for cost containment."

Speaking more generally, in *The Social Construction of Illness: Key Insights and Policy Implications,* Dr. Peter Conrad of Brandeis University examined how such social factors shape the understanding of disease and how that understanding then shapes policies and attitudes toward the disease.[437] As Dr. Conrad states, no disease is inherently stigmatizing; rather it is the societal response to that disease that is stigmatizing. The response by doctors to medically unexplained disease is also a social response. As reported by Dr. Allen Frances, Dr. Thomas Szasz, psychiatrist and author of "The Myth of Mental Illness," stated, "In the days of the Malleus, if the physician could find no evidence of natural illness, he was expected to find evidence of witchcraft: today, if he cannot diagnose organic illness, he is expected to diagnose mental illness."[438]

When one steps back and really looks closely at what has happened to ME, there can be no question that the collective concept of CFS, as it has come to be defined today, is a political and social construct that has little to do with the objectively observed biological pathophysiology of ME.

So the real question is not whether CFS is a social and political construction. There can be no doubt that it is. The real question is what social and political factors were at play in the creation of "CFS" in 1988, and in the perpetuation of the concept of "CFS" ever since? What social and political purposes were served that could have justified burying ME in this way? Why was the scientific and medical community so blind to the ample and long-standing evidence of biological pathologies of ME, and the obvious debility of ME patients? Why have so many researchers tolerated such definitional confusion and scientific sloppiness for so long, without questioning the scientific validity of it?

Dr. Straus' 1994 letter to Dr. Fukuda conveys a personal bias about the validity of this disease and a willingness to use one's political power to make the disease "evaporate". But clearly other factors are at play, some in a driving role and others part of the supporting cast. One key factor is undoubtedly the gender-driven interpretation of disease, and the vision of hysterical or overreaching women (as Richman and O'Leary described earlier). Another key factor is the way in which the medical community in general responds to diseases for which they do not yet have a

medical explanation. This includes the cognitive bias and self-interest of psychologists who, in the absence of a medical explanation, have pushed the psychologicalization of this disease. This kind of psychological expansionism has reached new heights in DSM-5.[439]

Just as important are NIH's institute-driven processes for allocating money and resources, which can result in the neglect of those diseases that don't fit in and the potential hesitancy of researchers to criticize the actions of the agency that funds their work. Closely related to this is the nature of medical specialties and societies, typically organized around a given part of the body or a particular practice of medicine, such as pediatrics or general practice. In both cases, such segmented models may work well for those who fit inside their boxes but are primed to run over those who do not.

Other factors include the commercial ties between "ME/CFS" researchers and the insurance industry, the interest of the insurance industry for cost containment, and the business practices of medical offices concerned with saving money and time spent on "difficult" patients. Finally, it is the very human challenge that any of us would face in letting go of a conceptual model that has infused our life's work, even when that model is no longer appropriate, particularly if one's professional status and income stream has been built on that model.

But let's be very clear. The dominant paradigm that has evolved as a result of these social and political forces does not reflect the biological reality of this disease. Further, because of the strength of those social and political forces, that dominant paradigm has been impervious to the biological reality of ME and the physical, emotional, financial, and highly stigmatized reality of ME patients.

What has happened to ME patients is not only morally and ethically wrong, but also scientifically wrong. One million Americans and seventeen million people worldwide have been sentenced to a level of suffering, disability, abysmal medical care, and disbelief that the rest of us can never imagine until ME strikes us, suddenly, arbitrarily and without any prior warning. We all should be incredulous that this situation came about to begin with. We all should be outraged that it has been allowed to thrive, virtually unchallenged, for three decades. We must demand that it stop now.

Summary

The story of CFS is the story of how flawed federal public policy, personal biases, politics, professional agendas, sloppy science, arrogance, lack of caring and neglect has effectively buried a disease—and its victims —for thirty years.

Prior to my son's becoming ill, I naively thought that a disease's definition and the description of its nature was a reflection of the biology of the disease. In spite of working in the pharmaceutical industry for 31 years, I was oblivious to the way that social forces and powerful institutions could construct the very meaning of a disease and hold it hostage. I have been shocked to see how such a devastating organic disease could be buried or "evaporated," as NIH's Dr. Stephen Straus had hoped, and replaced with an ultimately indefinable wastebin of medically unexplained fatigue. I have been shocked to see the continued drive for ever broader, non-specific definitions that has mixed and matched disparate conditions when everything I know about science says that you need to carefully control sources of heterogeneity if you want your science to make sense. Or perhaps that has always been the point—to not have the science make any sense.

The call by the fifty experts to adopt the Canadian Consensus Criteria was a call to implement criteria that reflect the disease that patients actually have, to finally put a stop to the semantic confusion on the nature of the disease and the out-of-control, man-made heterogeneity seen in the various CFS definitions. The fact that HHS has refused to adopt that recommendation while moving forward with its own initiatives that fail to explicitly address this fundamental confusion leaves me speechless.

3. The Standard of Medical Care Today

I've had patients who met post-traumatic stress disorder criteria… where their trauma was their interaction with their physician around this illness. They came to a doctor with Chronic Fatigue Syndrome; they left the doctor with PTSD."

— Dr. Nancy Klimas (ME Expert, 2009)[440]

Of all the problems caused by the definitional confusion outlined above, the one that does the most immediate and severe damage to ME patients (especially the newly sick patient) is the abysmal, too often abusive, medical care that patients receive at the hands of their doctors.

Imagine going to your doctor with cancer or multiple sclerosis and having him roll his eyes and dismiss you outright, or tell you that there is nothing wrong with you and you are just depressed, deconditioned, or as one doctor told my son, suffering a spiritual crisis. Imagine that same doctor recommending talk therapy to change your "perception" of being ill. Imaging a doctor insisting, as my son's did, that you must do aerobic exercise while refusing to discuss the CPET testing that shows why that is a bad idea. Imagine having doctors dismiss your life-threatening heart attack as not real or not serious, simply because you have a CFS diagnosis. And yet, these are the experiences of the majority of the ME patients that I have met. It's disturbing how few patients report anything different.[441]

The best way to understand the situation that ME patients face in seeking medical care is to consider the following:

First, as a result of the definitional issues outlined above, the medical community either doesn't believe that ME exists, believes it's a psychological, deconditioning, or nutritional problem or else believes that patients are just malingering.

Second, because of the lack of progress in research in the last thirty years, there are no approved diagnostic tests or disease modifying treatments for ME. Even disease experts are limited in what they can do to help ME patients.

Third, even sympathetic doctors struggle to effectively care for ME patients because medical schools seldom teach the disease. Further, the current clinical guidelines and medical education information are so minimal that doctors cannot differentiate a true case of ME from any of a number of causes of medically unexplained chronic fatigue. Even if they could differentiate ME patients, they would be misled on how to provide any relief.

Fourth is the inaccessibility of medical providers capable of and willing to treat this disease. Experts are few, primary care physicians disbelieve and/or are overwhelmed by the disease's complexity, and specialists see it as someone else's problem. Complicating these factors, the most severely ill patients may be too ill to go to a doctor's office.

Fifth, there are a number of institutional barriers, particularly insurance reimbursement policies and evolving medical office business practices that have widened the chasms through which these patients plunge.

As a result, the medical care that an ME patient receives is so bad that many patients ultimately give up or actively avoid doctors. This is unacceptable and must change. Even in spite of the lack of

approved diagnostics and treatments, there are available treatment options for ME patients that could relieve some of the misery that shrouds their lives. We can and must do better.

Update:
The IOM report recognized the hallmark nature of a systemic intolerance of activity and incorporated this into the recommended name and made post-exertional malaise a mandatory symptom of the SEID criteria. This definitively distinguishes the IOM criteria from Fukuda CFS. But the IOM recommendation has been largely interpreted in the media as a rebranding of CFS with some articles recommending the use of CFS treatment recommendations like CBT and GET.[442] Some of the medical education providers have already taken this approach in their medical education with one source treating SEID as a synonym of CFS and the SEID criteria an alternative to Fukuda.[443] These responses show a deep misunderstanding of the nature of the exertional intolerance described in the IOM report.

On April 7, 2015, CDC archived the CDC CFS Toolkit on its site, years after CFSAC and patients called for its removal. The CDC CFS Toolkit is still included in the discussion below in part because of timing and in because the Toolkit has been disseminated so broadly, influencing doctors' current perceptions, attitudes and beliefs about the disease.

Medical Disbelief and Abuse

In the United States and presumably in other developed countries, medical care strongly relies on testing as part of the diagnostic process. But as Jason pointed out, while ME patients have a range of symptoms affecting multiple organ systems, there are no accepted biomarkers or other "confirming laboratory abnormalities."[444] Clinical guidance based on Fukuda often recommends a standard set of tests that are typically negative for ME patients. And from the moment the lab tests come back negative, or a patient admits that he has already been given a diagnosis of CFS, patients smash into an impervious wall of medical disbelief and dismissal. Doctors disbelieve patients, dismiss the seriousness of their illness, insist that patients just need to exercise or go to talk therapy, suggest that they are doing too much or doing too little, or tell them that their disease is not real.[445] Doctors humiliate patients for daring to continue to believe what their own bodies are telling them—that there is something drastically wrong. In a 2010 study of doctors' knowledge and attitudes that reflected this disbelief and lack of misunderstanding, Brimmer reported that only 57 percent of doctors agreed that "a diagnosis of CFS can inhibit a patient's motivation to get better,"[446] while another 13 percent did not know if it could impact motivation.

Even "experienced" patients, those who know what their disease is and who may even be under the care of world-renowned experts, are not immune from this medical disbelief when they encounter medical providers outside of the ghettoized field of ME experts.

In an excellent two part series, author and ME patient Toni Bernhard shared her own experiences, and the experiences of her readers, with doctors who changed their whole demeanor at the mere mention of a diagnosis of chronic fatigue syndrome.[447] Ms. Bernhard described watching one doctor disengage when she said she had chronic fatigue syndrome. Bernhard wrote, "He swiveled on his stool, put his note pad down, turned back to me as if we'd just met."[448] Ms. Bernhardt also described the story of one patient who was nearly released from the hospital with a potentially fatal case of pneumonia. The doctor admitted that he almost dismissed the patient as not really sick because he had a CFS diagnosis.[449] Jen Brea, a Harvard PhD candidate when she became ill, was told that she had a conversion disorder and that "there was no organic basis" for her illness.[450] When ME patient Pat Fero's son first became ill with ME, the pediatric specialist told the primary

care doctor that the child was just "mimicking his mother's CFS behaviors."[451] One group of doctors laughed about her 10-year old son's disease—in front of him. When Fero's son died of ME at age 23, the coroner found myocarditis; his heart was full of viral infection, not surprising given that immune dysfunction and cardiac problems have been demonstrated in this disease.[452] The standard care for myocarditis includes rest, not the exercise that ME patients are invariably told to do.

This medical dismissal and haranguing can be so negative and invalidating,[453] that many patients withhold their diagnosis from doctors, or avoid doctors at all costs, gambling their lives that they can afford to ignore severe chest pain or a bad cough. One ME patient died of injuries sustained in a car accident after she chose to avoid the emergency room rather than risk the mistreatment that she had learned to expect from doctors.[454]

Even healthy family members are not immune from this abuse. A doctor once severely berated me for refusing to accept that my son was suffering from a mental illness and declared my son's doctor "a criminal" for prescribing a particular drug regimen for him.

The patients' experience of medical care in other countries is not much better and can be significantly more abusive as a result of governmental endorsement of the psychosocial model of CFS. The British National Health Service uses the NICE Guideline for "CFS/ME",[*455*] which severely limit the amount of testing that is done or drugs used, and instead recommends CBT and GET as defined by psychosocial studies. Given that the majority of British ME patients use the National Health Service, the choice that patients get is graded exercise therapy along with CBT to address their thoughts and feelings about being ill. Try to imagine that you have cancer or multiple sclerosis, and this is the only medical choice that you are given.

The extreme end of such abuse and disbelief is the sectioning of ME patients into psychiatric facilities. British patient Sophia Mirza, the young woman described earlier, had been sectioned into a psychiatric ward against her will, after doctors decided she had "made herself ill." Her condition was made irreversibly worse before they finally released her thirteen days later. According to her mother, Criona WIlson, "Sophia's ordeal in a psychiatric ward devastated her fragile health. She went into a hellhole, devoid of energy. She could never come back from that."[456] Another example is the case of the 25 year old Danish ME patient Karina Hansen,[457] also noted above, who was forcibly removed from her home in February 2013 and held against her will in a psychiatric facility.[458] As of May 2015, Karina has still not been allowed to leave the clinic, her parents have not been allowed to see her, and her family, legal bills mounting, has lost their an appeal to get her released.[459]

This is not just a European problem as evidenced by the story of U.S. ME patient Ryan Baldwin, also noted above.[460] A more recent example is Justina Pelletier, the Connecticut teen with a mitochondrial disease diagnosed by a specialist at Tufts. A separate group of doctors rejected that diagnosis, and instead diagnosed Justina with somatic symptom disorder, the controversial DSM-5 diagnosis. In February 2013, those doctors reported suspicions of medical child abuse, and successfully petitioned the court to have Justina removed from the family and placed in a psychiatric hospital in Boston. In March 2014, the state agreed with the doctors that Justina suffered from somatic symptom disorder, criticized the parents' advocacy for their daughter, and granted permanent custody to the state. That decision was reversed in June of 2014 and Justina was finally released to her parent's custody.[461]

While Justina does not have ME, her case and that of ME patient Ryan Baldwin demonstrates that, even in the U.S., patients with contested diseases like ME and mitochondrial disease can be easily sectioned into a psychiatric facility because doctors dismiss the organic nature of their disease. ME patients are particularly at risk for this kind of medical abuse for the reasons outlined in the chapter "What is CFS?"

This lack of understanding has been and continues to be widespread. In a 1997 paper, J.S. Anderson reported that about three quarters of patients had had negative experiences with medical providers.[462] Jason reported that in a 1999 study, Green found that "95 percent of individuals seeking medical treatment for CFS reported feelings of estrangement and 70 percent believed that others uniformly attributed their CFS symptoms to psychological causes." [463] A 2011 CDC study of CFS knowledge among health care providers revealed that 14 percent believed that CFS is a psychiatric illness, and while 70 percent believed that CFS is partly a psychiatric illness.[464] A 2012 meta-analysis of 34 studies by Anderson reinforced the themes of stigma, challenges with getting a diagnosis, and the skepticism, minimization and misunderstanding on part of the medical provider.[465] In a 2014 study, Bayliss reported that some doctors hold negative attitudes that the patients who get "CFS/ME" (the term used in the paper) include those "who have hypochondriasis, are unmotivated, pessimistic or are difficult to help."[466] In a 2015 podcast on "This Week in Virology," host Vincent Racaniello shared the advice given to him by a physician friend as he was seeking medical answers for his son's chronic illness: "Do not have him diagnosed with CFS because no one will then try and help him. She said, don't. They'll say that's it, we can't do anything."[467] While this is an isolated report, it resonates with the experience of many patients whose disease is treated as a pariah and represents a deeply disturbing and inexcusable attitude on the part of doctors.

The February 2015 Institute of Medicine report acknowledged the degree of stigma and medical disbelief, stating, "Despite Dr. Ramsay's work and a U.K. independent report recognizing that ME is not a psychological entity (CFS/ME Working Group, 2002), the health care community generally still doubts the existence or seriousness of this disease."[468] The initial reactions by the medical community to the IOM report have reinforced the truth of IOM's assertion. In an article on the IOM report on the American Academy of Family Physicians, many of the commenting doctors stated frank disbelief in the disease and in the IOM report itself. Examples of the comments included "Political correctness gone made" and "It's time to call these constellations of symptoms what they are, which is largely psychological."[469] This level of dismissal, particularly in the face of the IOM report, is remarkable.

Such widespread skepticism and dismissal of ME patients creates tremendous stress and risk of mistreatment for ME patients seeking medical care. Ultimately, this is the reason that so many ME patients avoid doctors. For those of us who are healthy or who are sick with an "acceptable" disease like cancer or rheumatoid arthritis, it is easy to sit in judgment that avoiding doctors and withholding information is irrational and risky. Before my son became sick, I would have agreed. But as a mother, I have come to understand in my gut why Criona Wilson, Sophia Mirza's mother, said, "I had to keep her safe from [doctors]. Imagine, keeping her safe from the doctors!"[470] When you have been humiliated, ridiculed and dismissed by doctors for years, when you have been told yet again that it is all in your head, when you have been blamed for not getting better, and when doctors have given you ill-advised treatments that have made you worse, what choice would you make? You would do what you need to do to protect both your body and your psyche, especially if the effort of getting to the doctor led to such a severe PEM-induced physical penalty.

The pervasiveness of the patients' reports of dismissal, mistreatment, and medical abuse should be enough to lead to a cry for change. But it's not just patients; the medical community itself has highlighted the ill treatment that patients experience at the hands of their doctors. Following Hurricane Andrew, Dr. Nancy Klimas, one of the leading ME clinician-researchers and currently at NOVA Southeastern University, examined the prevalence of post-traumatic stress disorder (PTSD) in those with chronic diseases. She confirmed that people with chronic diseases did have a higher prevalence of PTSD. But she also found that patients with this disease had even higher PTSD rates. Upon further investigation, she found that the source of that stress was not the disease itself, but rather the patients' experience with the medical community.[471] She explained further, "A common theme in the trauma was an exposure to a health-care situation that was demoralizing and demeaning."

This problem is so bad that Dr. Jose Montoya of Stanford University has said, "It is my dream that our medical community will produce a formal apology to patients for not having believed them all these years that they were facing a real illness."[472] The Norwegian government already has apologized. In 2011, following the publication of the study that reported that Rituxan helped ME patients, the Norwegian Directorate of Health stated "I think that we have not cared for people with ME to a great enough extent. I think it is correct to say that we have not established proper health care services for these people, and I regret that."[473]

Inadequate and Misinformed Medical Care

Even when the ME patient reaches a sympathetic doctor, that doctor is not likely to understand the nature of ME or how to appropriately assess and treat ME's multi-system dysfunctions.[474]

A 2010 CDC study found that 70 percent of medical providers said that "CFS" was difficult to diagnose, treat and manage.[475] Some doctors will admit that they are ill prepared to deal with ME. For instance, Matina, an ME patient in the United States, made a concerted effort to find a primary care doctor. But when she explained her condition at the first visit, the doctor replied that her condition was much too complex for that doctor to deal with. The doctor agreed to handle any acute issues like bladder infections, but said that any issues related to ME would have to be handled by a specialist. The closest ME specialist is three hours away, a difficult trip for Matina.

Referral to mainstream specialists (outside of ME specialists) does not help as many specialists typically focus in one area of the body or a particular type of disease. This, combined with the erroneous information about the disease, leaves them ill-prepared to grapple with the multi-system dysfunction of ME. Further, because there has been so little research and because the CFS evidence base is so polluted with ill-defined patient cohorts, the specialist has little scientific foundation to understand the disease in the context of his or her own particular specialty. Compounding this problem is the fact that much of the biomedical research on this disease has been published in journals that that specialist might consider second or third tier journals.

In my son's case, one neurologist expressed serious concern with the use of Rituxan, based on his view that the study had been published in a second-tier journal and also on his judgment that CFS wasn't serious enough to warrant such a serious treatment. To his credit, the neurologist at least tried to understand the disease, but ultimately was unable to do anything to help.

The lack of understanding of the nature of ME, and the inability to provide medical relief to ME patients is bad enough. But worse, because of erroneous medical education, too many doctors prescribe talk therapy and exercise, treatments that can hurt or further disable ME patients.[476]

This belief that CBT is an appropriate and effective treatment was even evident at the Ampligen FDA Advisory Committee meeting in December 2012. At that meeting, committee member Dr. Sean Hennessey asked Hemispherix "to summarize the data on cognitive behavioral therapy which I understand to be effective against chronic fatigue [sic]."[477] Did Dr. Hennessey understand that CFS and chronic fatigue are not the same thing, or that CBT was being prescribed to CFS patients to reverse "false illness beliefs" and get them to exercise in spite of their bodily symptoms? Even if he thought that the purpose of CBT was to help a patient cope, would he have felt it appropriate to ask such a question in the review of a cancer drug?

Dr. Hennessey is certainly not alone in thinking that CBT and GET are appropriate treatments. An infectious disease specialist from a top-tier university prescribed aerobic exercise to my son. It caused my son to crash for two days because of post-exertional malaise, a reaction that allowed him to diagnose himself. And yet, when he told the infectious disease specialist about this reaction, her response was to insist that he continue to exercise. The diagnostic and therapeutic implications of this hallmark symptom of exercise-induced exacerbation of symptoms were meaningless to her. Unfortunately, Matthew's experience is not unique. As noted by Jason, in a 1997 study, Tremlow "found that 66 percent of individuals with this disease believed that they were made worse by their doctors' care" as compared to general medical patients.[478]

More recently, two of my son's doctors, one a primary care doctor and the other an opthoneurologist, also insisted that he adopt an aerobic exercise plan. Yet, stunningly, both refused to look at the results of his two-day CPET test that showed the aerobic energy production impairment that would cause a negative reaction to exercise. Even CBT itself can induce harm when its purpose is to convince patients that their perceptions and beliefs are keeping them sick. Aside from the psychological damage done by trying to convince an ME patient that their disease is not organic, encouraging an ME patient to ignore their symptoms, as is done with PACE style CBT, can be physically harmful when it causes ME patients to exceed their bodily limits.

Under-diagnosis and Misdiagnoses

Given the lack of understanding and the widespread dismissal, it is not surprising that there is significant under-diagnosis of ME. Studies by the CDC and by Dr. Leonard Jason of DePaul University indicate that roughly 80-90 percent of patients with this disease are not diagnosed.[479] As a result, patients end up on a medical merry-go-round—going to 5, 10, or more doctors, sometimes over a period of years—just to receive a diagnosis. Even the CDC acknowledges that it can take years to get a diagnosis.

Predictably, other treatable diseases are too often misdiagnosed as CFS and patients are left without appropriate medical care, simply because they went to a doctor with a complaint of fatigue. One example is a study of 260 patients who were referred to a specialist clinic in England. All had a CFS diagnosis and met the Fukuda criteria. But, upon further examination, forty percent were found to not have CFS; of those, 47 percent had fatigue due to another chronic illness, 20 percent had primary sleep disorder, 15 percent had psychiatric illness and four percent had cardiovascular disorder.[480] Similarly, a 2012 study at a different specialist clinic in Britain found that 50 percent of patients had been misdiagnosed with CFS.[481] Finally, a 2014 article stated that some U.K. patients with post-traumatic hypopituitarism (PTHP) had been incorrectly diagnosed with CFS.[482].

As Dr. Diane O'Leary noted, any overly broad definition can result in this kind of misdiagnosis.[483] CFS definitions such as Oxford and Fukuda cannot help but sweep into the CFS diagnosis those who do not have ME because these criteria lack the specificity needed to do anything different.

Medical Care in the Hands of ME Experts

Compared to many other ME patients, my son is very lucky. After only ten months, ten doctors, two plane rides across 2000 miles, and his own persistence in researching his adverse reaction to exercise which resulted in a self-diagnosis, he was not only able to get a confirmation of his diagnosis, but was eventually able to see one of the few ME experts in the country. This expert used objective measures to assess the immunological, neurological, autonomic and gastrointestinal problems that Matthew was experiencing,[484] and then used that information to prescribe treatments to address some of his symptoms. She recommended sleep medication and medication for his orthostatic intolerance, both of which made a notable difference. She assessed the severity of his post-exertional malaise using the 2-day CPET test that Dr. Snell had pioneered and then used that to support a successful application for disability. She recognized and treated the cause of a gastrointestinal problem that his gastrointestinal specialist had dismissed for many, many months. She connected him with a rheumatologist who used his immunological blood markers to recommend off-label treatments more typically used in autoimmune disease and cancer. These treatments have provided some improvement in his energy metabolism when nothing else did.

Matthew is still sick by healthy standards and the standards of other chronically ill patients and even of the elderly. But at least he is no longer pinned flat in a darkened bedroom, doing virtually nothing in a fruitless attempt to minimize his pain and suffering. Our hope is that his doctors find some combination of treatments that will give him enough space to achieve some quality of life. But the future is uncertain because his current treatment regimen, which is not approved for this disease, costs about $40,000 - $60,000 a year out of pocket, an expense that cannot be paid indefinitely. And even if we could, there are no guarantees that he won't relapse and go further down the rabbit hole again.

But even with that uncertainty and limited improvement, patients like Matthew who have been able reach an ME specialist and try drugs such as Ampligen, antivirals and Rituxan, are not the norm. Very few ME patients can access an ME expert or even get useful, inexpensive symptomatic treatments like Fluorinef.[485]

The Underlying Problems

It would be a mistake to attribute the level of misunderstanding, disbelief and mistreatment that ME patients experience to the complexity of ME, or to the failure of research to unravel the etiology or identify treatments. Yes, even when properly defined, ME is a complex disease. But there are other complex diseases that are not nearly as misunderstood. For example, AIDS has cardiac, neurological, dermatological, immunological, and other aspects, often induced by seemingly disparate coinfections. At the same time, there are other diseases whose underlying pathology is unknown and for which there are no treatments, yet those patients are not discarded.

Bad definitions, the lack of ME biomedical research, the confounded state of the CFS evidence base and the propensity of the medical community to recast unknown conditions as psychiatric problems have all contributed to the poor quality of medical care that patients receive.

But more directly, the bad medical care is caused by outdated and erroneous clinical guidelines and medical information, the lack of medical school training, the lack of knowledgeable and willing medical providers, and a number of secondary barriers resulting from medical office business practices and insurance policies.

Outdated and Erroneous Clinical Guidelines

In the U.S., clinical guidelines and medical information for this disease are provided by the CDC and a number of secondary medical information providers (such as Medscape, UpToDate and Mayo Clinic), many of which base their information on CDC's information. In the U.K., Britain's National Health Service provides the *NICE Guideline for CFS/ME*. While the focus of this discussion is on current clinical guidelines and medical information, it's important to note that the lack of ME-appropriate clinical guidelines and medical information is a long-standing problem that was discussed in the 1999 GAO report and in numerous congressional appropriations reports since at least 1995.[486] It has also been the frequent subject of CFSAC discussions and recommendations, most recently in March of 2014, when CFSAC called HHS to conduct educational efforts that would specifically target the disease described by the Canadian Consensus Criteria.[487]

Descriptions of the Disease

Almost without exception, the mainstream clinical guidelines and medical information in the U.S. focus on fatigue, and reference Fukuda as the basis of the disease description. The CDC states that there are multiple definitions that include the Canadian Consensus Criteria and the ME International Consensus Criteria, but treats them as less preferred alternatives to Fukuda.[488] As a result, ME is subsumed into the CFS medical education. Broadening the definition even further, the CDC CFS Toolkit (archived on April 7, 2015) explicitly broadens the scope of disease to include "CFS-like" illness, essentially chronic fatigue, in its diagnostic and treatment recommendations.[489]

The resultant disease descriptions are vague, and convey the idea that the problem is one of a non-specific form of medically unexplained fatigue and tiredness, not something more specific and serious. For instance, many sites use statements that describe CFS as "overwhelming fatigue not relieved by bed rest." Some sites equate the fatigue of CFS to tiredness with one HHS CFS site stating, "A person with CFS feels completely worn-out and overtired."[490] Post-exertional malaise is typically described with phrases like "Extreme tiredness after exercising that lasts more than 24 hours"[491] or as an attribute of fatigue that "may get worse after physical or mental exertion and a full night's sleep provides no relief."[492] The CDC CFS Toolkit (archived on April 7, 2015) stated that PEM is "extreme, prolonged exhaustion and sickness following physical or mental activity." These descriptions fail to begin to describe the nature of PEM, how to identify it, or its implications in terms of diagnosis and treatment.

A few sites, such as Medscape, acknowledge the underlying organic nature of the disease with its infectious triggers, immune dysfunction and cognitive dysfunction.[493] Unlike most sources, Medscape provides some additional information on post-exertional malaise although it does not describe it as a mandatory symptom. But much more often, the medical information sources give either a vague and confusing view of the nature of the disease, or else emphasize psychological aspects. For instance, the Mayo Clinic states that a risk factor for the disease is "difficulty managing stress."[494] Epocrates, a clinical decision support system, states that an "action-proneness" personality trait and a history of both over- and underactivity levels are strong risk factors.[495] The CDC CFS Toolkit (archived on April 7, 2015) stated that people with this disease are more likely to have "obesity, insulin resistance, metabolic syndrome" and "non-melancholic depression."[496]

A number of sites state that the disease is associated with depression, and that many CFS patients have depression. WebMD states that the depression is secondary,[497] but many sites fail to make this distinction. A number of sites convey a confusing view on the connection between this disease and psychiatric illness. For instance, Medscape specifically states that anxiety disorders, somatoform disorders, nonpsychotic or melancholic depression, and neurasthenia are not exclusionary for this disease, potentially strengthening the linkage to mental disorder in a diagnosis that is one of exclusion.[498] Confusingly, one CDC continuing medical education course indicates that major depressive disorder is not exclusionary even though Fukuda states that certain forms of major depressive disorder are exclusionary.[499]

Some medical education sources establish a more direct link to psychological illness. For instance, the Mayo Clinic states that the symptoms of the disease are often "linked to mood."[500] CDC's CFS website highlights child abuse as a risk factor,[501] even though the study that demonstrated this was done with the highly disputed Empirical definition. The American Family Physician echoes this statement that childhood trauma raises the risk of getting the disease.[502] Epocrates states that "psychological disturbance" and "emotional instability" are risk factors.[503] For its part, the Cleveland Clinic Center for Continuing Education, in its CFS course that expired in September 2014, directly referenced PACE and stated that patients who believe that there is a physical cause for their disease have a poorer prognosis than those who do not.[504] The American Family Physician website for CFS provides a link to the 2012 Yancey article that stated the poor prognosis was tied to belief that the disease was organic, "some sort of sickness benefit (i.e. financial incentive)," or membership in a support group.[505] Would such statements be made for diseases like cancer, multiple sclerosis, or AIDS?

Diagnostic Approaches

In the U.S., the recommended diagnostic approach is typically based on the fatigue-focused Fukuda criteria. That approach is a diagnosis of exclusion, in which doctors are advised to eliminate other causes of chronic fatigue, using a minimal set of tests that are typically normal in ME patients. Doctors are advised to check for the simple presence (as opposed to severity and frequency) of any four of eight Fukuda symptoms. But as Jason and Nacul pointed out above, this polythetic symptom requirement is non-specific and thus fails to contribute to diagnostic accuracy. Further, the diagnostic recommendations do not require hallmark criteria such as PEM, and some do not even list PEM as one of the optional symptoms. Finally, the recommendations only exclude some forms of psychiatric illness, but allow other primary psychiatric illness; the specific psychiatric illnesses allowed can vary considerably by source. For its part, NICE requires fatigue and PEM, but does not require other hallmark criteria and allow primary psychiatric illness.[506]

Reflecting this minimalist diagnostic approach, the CDC CFS website states that there are no lab tests for CFS, and only recommends lab tests just to rule out other disorders.[507] UpToDate, a broadly used clinical decision support system endorsed by a number of medical societies,[508] states that the diagnosis is made based on symptoms, medical history, and physical exam but the only symptom actually required is fatigue. It states that *no* urine or blood tests are necessary to diagnose the disease, only to rule out other diseases.[509] The Cleveland Clinic Center for Continuing Education's educational material, available until September 2014, took a similar approach to diagnosis.[510] Even simple and useful tests used by ME disease experts—tilt table tests to assess orthostatic intolerance or serological tests to assess high viral titers—are typically either not mentioned or are explicitly excluded, as NICE does.[511]

Driven by the view that this disease is a psychological and/or somatoform illness, some proponents of the psychosocial model of CFS have put an even stronger emphasis on this

minimalist testing approach, advising doctors to avoid "excessive" testing.[512] The rational is that such testing could cause "iatrogenic harm" (physician-caused harm), if it encourages patients to believe that their illness has an organic cause, or if it delays the start of "appropriate" treatment, which is typically described as CBT and GET. Similarly, as Dr. Diane O'Leary reported, the American Association of Family Physicians urges "doctors to make *early* diagnoses of somatoform disorders in order to save time and to reduce cost." (Emphasis added).[513] Medscape recommends a similar approach for the diagnosis of somatoform disorder in children, emphasizing the importance of avoiding unnecessary tests, and getting the patient and family to "accept the psychological basis rather than the destructive belief that the psychological basis was a result of a lack of medical evidence."[514]

As a result of the recommended diagnostic approaches and the propensity to view this disease as a psychological or somatoform illness, a CFS diagnosis is a diagnosis of fatigued *leftovers*, which is too often assumed to be mental or behavioral problem. In Annemarie Jutel's words, a CFS diagnosis is a "diagnosis of the undiagnosable."[515]

Treatment Approaches

Across the vast majority of medical education sources, the most common treatment recommendations are one-size-fits-all recommendations for cognitive behavioral therapy (CBT) and graded exercise (GET), followed by recommendations for lifestyle changes such as sleep hygiene, stress management, and dietary changes.[516] Pharmacological treatments are largely discouraged, or, when recommended, are recommended primarily for depression, pain, and sleep.[517]

It is important to understand that the terms "CBT" and "GET" are each used ambiguously, referring to different treatment approaches with different therapeutic objectives.[518] For instance, CBT can be used to help patients cope with the limitations imposed by any chronic illness. But in the case of CFS, the therapeutic intent of CBT, as described in studies such as PACE, is to get patients to challenge the thoughts, perceptions, and illness beliefs that are believed to be keeping them ill.[519] Some medical education sources have explicitly adopted this model of CBT. For instance, MedPageToday's KevinMD, produced in collaboration with the American College of Physicians, states that CBT is used to break "the cycle of effort avoidance [and] decline in physical conditioning and increase in fatigue and can work well in combination with graded exercise."[520] Citing PACE, the Cleveland Clinic Center for Continuing Education's educational material, available until it expired in September 2014, recommended CBT to "change the cognitive responses that are thought to perpetuate CFS, such as fears about symptoms or activity."[521] Epocrates recommends CBT to modify thoughts and behaviors thought to be "maintaining or exacerbating symptoms and impairment."[522] UpToDate recommends CBT to address "beliefs and behaviors that can interfere with a patient's recovery."[523] CDC's medical education information discusses the use of CBT to help chronically ill patients cope. However, the references cited by the CDC for the use of CBT in this disease reference the psychosocial studies that use CBT to challenge illness beliefs.[524] Such references could reasonably be expected to lead medical providers to use PACE style CBT.

The second most commonly recommended treatment is GET. In CFS research, GET has been typically studied in conjunction with CBT to reverse the presumed deconditioning believed to result from avoidance of activity.[525] As described in the PACE manual, patients are instructed, "it is their planned physical activity, and not their symptoms, that determine what they are asked to do."[526] Patients are encouraged to see bodily symptoms as normal and not as "signs of progressive pathology." In other words, patients are encouraged to ignore their bodily symptoms and push past them.

GET is recommended by a number of sources, including the NICE guideline for CFS/ME and the CDC's CFS guidelines. The CDC CFS Toolkit (archived on April 7, 2015) recommended that patients decrease activity if they experience symptoms but then references the 2008 GET Guide from St Bartholomew's Hospital, which promotes GET to break the cycle of activity avoidance, deconditioning, and increased fatigue. The Cleveland Clinic Center for Continuing Education's educational material, available until it expired in September 2014, stated that the goal of GET is to help "the patient gradually return to their normal physical activities."[527] The Mayo Clinic states that strength and endurance will improve with graded exercise.[528] (This statement is true for deconditioned patients, but is of questionable relevance for treating the disability seen in ME). As noted above, KevinMD also recommends graded exercise to reverse physical deconditioning. Referencing PACE, UpToDate recommends GET and states that GET and CBT can result in "significantly reduced fatigue."[529] Other sites discuss the need to start slow and build up, with the idea that this will increase patient functioning and quality of life. For instance, the CDC CFS Toolkit (archived on April 7, 2015) stated that the intent is to start "from a very low, basic level of exercise and/or activity and gradually increasing it to a level where people can go about their daily life."[530] The CFS Toolkit did parenthetically note, "the level of activity may not be the same as before the CFS diagnosis." But this only calls into question what level of impact GET is expected to have.

Even when the medical education sites do not explicitly attribute the symptoms of the disease to deconditioning, the failure to clearly describe PEM and its associated energy production impairment has led doctors to make uninformed, inappropriate, and too-often harmful treatment recommendations. This risk of harm from these exercise recommendations is so great that CFSAC has discussed the need for a black box warning against exercise on CDC's CFS website.[531]

In contrast to the mainstream treatment recommendations for CBT and GET, Jason[532] and various ME patient surveys[533] have reported that "pacing" is one of the most effective disease management strategies available. Pacing, a form of energy management used to minimize PEM, involves a close monitoring of one's "energy envelope" and maintaining a fine balance between resting and very carefully planned activity, restricted in both length and timing. For severely ill patients, pacing can mean saving all of their energy to do the most essential activities of daily living. As Dr. Ken Friedman, one of the authors of the IACFS/ME Primer, told Medscape Medical News, "If you're lying in bed and you can't move your head and you have to speak in whispers, GET therapy is not going to help you, and were you to attempt it, it would most likely kill you."[534]

For my son, even at his best, pacing has meant strict rest for a few days to be able to do a few hours of activity. Unfortunately, few medical education sources discuss pacing at all. The CDC CFS (archived on April 7, 2015) did mention pacing but the information given is inadequate to guide a patient in its practice.[535] For its part, the NICE Guideline recommends *against* practices used in pacing; more specifically, it recommends against more than 30 minutes of rest at a time, and against maintaining activity at lower levels in order to allow the body to heal.[536]

Unlike the widespread recommendations for CBT and GET, very few medical information sources recommend pharmacological therapies. When they do, the recommendations are typically for treatment of depression, anxiety, pain, and sleep. For instance, the CDC CFS Toolkit (archived on April 7, 2015) recommended using as few medications as possible, and then focuses its treatment recommendations for coping, CBT, GET, and sleep hygiene.[537] Other CDC CFS educational sources focus medication recommendations on sleep, pain, depression, and orthostatic intolerance. The Mayo Clinic recommends anti-depressants and sleeping pills.[538] While anti-depressants have helped some ME patients improve sleep dysfunction, anti-depressants are not believed to target

the primary biomedical issues in this disease.[539] For its part, UpToDate recommends *against* the use of anti-depressants and also against antibiotics, anti-virals, and immune modulators.[540] Medscape recommends against antivirals, vitamins, and anti-depressants.[541] Family Doctor, provided by the American Academy of Family Physicians, states that medication can treat "some of the symptoms, such as muscle aches, sleep problems, anxiety and depression," and recommends using "lists" to help with cognitive issues.[542] Only rarely do the medical information resources recommend the use of drugs for orthostatic intolerance (a type of dysautonomia), the CDC being one site to do so.[543] The NICE Guideline limits the use of drugs largely to pain and sleep problems.[544] NICE specifically recommends against the use of fludrocortisone and antivirals, drugs that ME experts use to successfully treat autonomic issues or high viral load.

Such diagnostic and treatment recommendations leave even the supportive medical provider ill-prepared to treat ME, while simultaneously reinforcing the idea that this is a psychological condition. In the U.S., both CFSAC and patient groups have made numerous requests for changes to the CDC CFS Website. Additionally, in 2012, both CFSAC and patient groups formally recommended that the CDC CFS Toolkit be taken down out of a concern that the Toolkit was harming patients by miseducating doctors on the nature of ME.[545] In Britain, as reported in the 2006 Gibson Inquiry report press release, Des Turner, chair of the All Party Parliamentary Group on ME, rejected the NICE Guideline for CFS/ME as "not fit for man or beast" while Dr. Ian Gibson, chair of the Group on Scientific Research into Myalgic Encephalomyelitis (ME) called the NICE Guideline "useless."[546]

Alternative, More Appropriate Clinical Guidelines

You may ask why some of our supposedly premier medical information providers are using such inappropriate and even harmful diagnostic and treatment guidelines. Are there no alternatives?

There actually are. By at least 1978, attendees at the Royal Society of Medicine conference described the distinctive muscle fatigability.[547] In a 1986 publication, Dr. Melvin Ramsay stated, "those patients who are given a period of enforced rest from the onset have the best prognosis."[548] More recently, ME experts have developed two ME specific clinical guidelines: the *CFS/ME: A Primer for Clinical Practitioners*,[549] produced by the International Association for CFS/ME and based on the Canadian Consensus Criteria, and the *Myalgic Encephalomyelitis - Adult and Pediatric: International Consensus Primer for Medical Practitioners*,[550] based on the 2011 ME International Consensus Criteria.

Both primers provide a full description of the biological nature of the disease, including a discussion of PEM/PENE. Both describe the diagnostic and treatment approaches used by ME experts, including the use of diagnostic tests and pharmacological treatment. The IACFS/ME Primer also specifically highlights the problems with the use of CBT and GET, rejecting claims of efficacy. The IACFS/ME Primer states, "The premise that cognitive therapy (e.g., changing 'illness beliefs') and graded activity can 'reverse' or cure the illness is not supported by post- intervention outcome data."[551] Instead, the IACFS/ME Primer gives extensive information about the nature of PEM, and warns about the negative impact of exercise.

In 2012, CFSAC has recommended that the IACFS/ME Primer be made widely available. HHS did place a formatted version of the 2012 IACFS/ME primer on the Guidelines.Gov site. But the CDC has refused to update the CDC CFS website to provide a link to the Primer, remove the CDC CFS Toolkit,[552] or make some of the other website changes requested by CFSAC and patients to decrease the risk of harm to patients.[553] Based on a discussion at the May 2013 CFSAC, the CDC

was continuing to develop its own educational material, and resisted requests by CFSAC to provide input to CDC's efforts.[554]

If you compare the disease description and the diagnostic and treatment recommendations in the IACFS/ME primer and the ME-ICC primer against the information provided in any of the sources noted above, the inadequacy of the mainstream medical information sources is inescapable. Using CBT to convince ME patients that their fear of activity is keeping them sick? Prescribing GET to patients whose disease causes an adverse physical reaction to exercise? Explicitly recommending against the basic tests and medications that are routinely used by ME experts to help give desperately ill patients some relief?

The clinical information provided in the mainstream medical education sources are incapable of providing a foundation for an appropriate treatment plan for ME, and only serve to reinforce the idea that ME is a mental disorder or not real at all. That, more than anything, is the source of the medical abuse and mistreatment that patients receive at the hands of doctors.

Medical School Education

A second factor contributing to the bad medical care is the challenge of educating the nation's future doctors on the nature of this disease. This is a crisis because so many of the current ME experts are reaching retirement age.

In a 2008 study on the coverage of CFS in 129 medical textbooks, Dr. Leonard Jason reported that about 40 percent had some mention of CFS, but the coverage was very minimal with only 125 pages in total dedicated to CFS across the 129 textbooks. Additionally, at a CFSAC presentation on this study in October 2008, Jason noted that only thirty percent of the 129 textbooks mentioned treatment, most commonly for "cognitive behavior therapy, anti-depressants, graded exercise or exercise, and supplements."[555] This echoes what is seen in today's medical education sources as described above. At the same CFSAC meeting, Ms. M. Brownell Anderson, Senior Director of Educational Affairs, *American Association of Medical Colleges* stated that of 130 U.S. medical schools and 17 Canadian medical schools, only two had listed CFS in the database of medical school curricula. She described CFS as an "orphan topic." Brownell Anderson's statement that CFS was an orphan topic was not surprising given that all of the medical societies, scientific specialties, and the NIH institutes had orphaned this disease outside of everyone's sphere of interest.

Jason's conclusion was that healthcare professionals needed to be adequately trained on this disease through "up-to-date, non-biased information in their textbooks" and that such information could help raise awareness about this disease.[556]

In a 2013 survey, Dr. Mark Peterson, together with Dr. Leonard Jason's team, surveyed medical schools to determine how many schools included this disease in their curricula, or had a treatment or research program. Only 50 percent of schools responded, and of those, less than 30 percent included CFS in their curricula, less than 30 percent had a treatment program, and only 15 percent had a research program.[557] This reinforces the fact that, even today, doctors come out of medical school with no specific knowledge of ME, leaving them reliant on the medical information sources noted above or on articles published through the medical media, such as the wide coverage of PACE.

This failure of medical schools to provide disease-appropriate curricula is not unique to the United States. The "Taking ME Forward" group has recently released a study of the curricula of medical schools in Scotland.[558] When CFS is mentioned, it is equated to "Medically Unexplained Symptoms"

or "Functional Somatic Syndrome." When ME is mentioned, it is equated to CFS, or described as a "Somatoform Disorder." Reflecting Annemarie Jutel's findings on how medically unexplained symptoms are handled in the literature, these schools have explicitly cast this disease as a psychiatric disease.[559]

CDC has said that it intends to address the medical education gap through standardized patient videos. These videos will be made available for medical school curricula through the MedEd Portal.[560] But to my knowledge, the CFSAC has not been allowed to provide any input into how the disease is being described in these videos. From a personal conversation with Dr. Unger, I understand that the CDC does not intend to describe PEM as mandatory in these videos,[561] a view that is consistent with Dr. Unger's previous statements about the role of PEM as an optional symptom of a broader "CFS" umbrella of fatiguing conditions. From that conversation, I also understand that information about PEM will only be included in supplemental material. The failure to highlight PEM as a mandatory symptom in these videos is a critical problem because it obscures the nature of ME, leaving medical students with a vaguely defined condition of medically unexplained chronic fatigue. Failing to describe PEM as a required symptom is the medical equivalent of failing to highlight the importance of chest pain in an angina diagnosis, an action that would be considered negligent.

Inaccessibility of Knowledgeable and Willing Doctors

A third factor is the inability of patients to access knowledgeable and willing doctors. The stark reality is that many ME patients are not able to access doctors willing and capable of treating them, even with symptomatic relief. Across the U.S. today, there are probably less than 20 ME expert clinicians for an estimated one million ME patients—roughly one for every 50,000 patients. Waiting lists are long. To see one of these doctors, patients often travel great distances, and must pay both medical and travel costs out of pocket. Some patients have been able to receive care from local primary care doctors or specialists who have learned enough to be able to help them. In my son's case, he sees an expert on the other side of the country but lost his primary care doctor when she insisted that he do aerobic exercise. But many patients go without any kind of doctor. The inaccessibility of medical care is exacerbated by the lack of an "owning" medical specialty, and will become much worse over the next 5-10 years as many of the current ME specialists retire.

Notably, some of the existing private ME clinical centers have engaged medical interns in their practice to address the need for physician training. Such efforts will help ensure knowledge transfer from existing practitioners before they retire. But these are small, privately funded efforts that cannot address the magnitude and time-sensitivity of the problem. This situation is a crisis that must be addressed.

Other Contributing Factors

Other issues include doctors' office business practices and the insurance reimbursement policies and practices. In England, NHS guidelines restrict the care that patients receive unless they go to private doctors. In the U.S., insurance policies and practices limit coverage for diagnostics and treatment, dramatically impacting the quality of medical care that is available. First, these practices emphasize shorter appointments that are inappropriate for patients with such a complex illness. Reimbursement for longer visits is generally limited, meaning that either the doctors charge less or else patients pay out of pocket. This is not just a U. S. issue. Recently, Dr. Alison Bested resigned from the Complex Chronic Disease Program in British Columbia (an ME treatment center) in part because of "administrative directives to reduce the time doctors spent with patients,"[562] which she felt compromised care for this patient group.

Insurance policies and practices also affect coverage of the needed tests and treatments, either because the typical medical guidelines state that these tests and treatments are unnecessary or because they are considered experimental as a result of the lack of research funding. One example of this is an Aetna policy, which does not cover immune testing, tilt table testing, or many other forms of testing used by ME experts because Aetna considers these experimental.[563] Another example is a Tricare policy, which states that coverage is limited to individual symptoms, and does not cover diagnostic tests for CFS.[564]

Complicating the situation further, insurance policies and coverage can be state specific, a particular problem known to those with Lyme disease, where some states severely restrict the duration of antibiotic treatment. Additionally, other cross-state issues arise because some insurance reimbursement policies regarding in-network and out-of-network providers can lead to required tests and/or treatments to not be covered when the ordering physician is in a different state than where the treatment or test is performed. For patients who travel across state lines because they cannot find a local doctor to treat them, this creates additional barriers.[565]

A final example of a barrier is the emergence of new business models for medical care, at least in the United States. Some offices are now establishing concierge models in which the patient pays an annual fee to be a patient of the practice. Some patients may not be able to afford that fee. But a more subtle problem is that complex ME patients may not be "invited" to continue with the practice. This was the case for two brothers with ME, both seen at the same medical practice. But when that practice adopted a concierge model, only one of the brothers, the less ill of the two, was "invited" to join; the other was not. Finding a doctor willing to treat an ME patient is made significantly more difficult by such business practices.

As a result of such policies, reimbursement for medical care is either non-existent or very poor, effectively limiting the testing and treatments that patients are able to access, even when their doctor has the knowledge to order them.

Summary

Given these issues, it would be remarkable if ME patients were able to access reasonable medical care. Even with the uncertainty of my son's future situation, I cannot emphasize strongly enough that the improvement he has seen has only been possible because he had the financial resources to access a knowledgeable expert and tests and treatments that insurance would not reimburse. But what about all those patients whose only medical choice is a doctor who doesn't understand, doesn't believe, or thinks that PACE-style CBT and GET are appropriate treatments?

All ME patients, but especially new ME patients who are still trying to understand what has happened to their bodies, are being hurt today: by stigma, by disbelief, and by inappropriate or harmful treatment recommendations pulled directly from the PACE trial, the CDC CFS website and the websites of secondary medical education providers.

I'll never know if my son might have been able to escape the worst horrors of this disease if doctors had simply followed Dr. Ramsay's guidance that the best prognosis resulted from enforced rest.[566] Instead, my son's doctors not only failed to warn him not to do vigorous exercise, but also dismissed his reports that exercise had caused him to crash. It's not just the physical damage. The medical abuse and dismissal that he has experienced has resulted in a level of psychic damage from which he may never recover. Immediately changing these medical practices will not undo the

physical and emotional damage done to my son. But it could help to protect another patient from suffering that same deep damage at the hands of their doctors.

This is not an academic problem that can wait for more years of study. This is an urgent crisis that can and must be addressed immediately to protect the health of those patients who are not yet sick. The medical and research community must reject the application of the psychosocial model to ME and recognize hallmark criteria like PEM. The medical establishment and the insurance industry must adopt clinical diagnostic and treatment guidelines like IACFS/ME's *CFS/ME: A Primer for Clinical Practitioners* [567] and the *Myalgic Encephalomyelitis - Adult and Pediatric: International Consensus Primer for Medical Practitioners*.[568] And the medical community must acknowledge ME as a real and devastating multi-system illness, separate and distinct from the collection of disparate conditions encompassed by the "CFS" label.

As noted in the introduction, HHS has not endorsed the IOM recommendations yet. In addition to ensuring that doctors unfamiliar with the disease can reliably use the criteria, it will be important to provide adequate information on the nature of the disease and on appropriate treatment recommendations. Otherwise, as has already been seen, doctors will continue to be confused on the nature of the disease and will recommend existing CFS treatments, particularly CBT and GET. Driving the needed change in medical care will be difficult to achieve if the CDC doesn't stop using the term "CFS" and doesn't modify its website to remove findings based on Oxford and Empirical definition studies.

4. "Fatally Flawed" Epidemiological Strategy

> *CDC has spent years looking in the wrong places… The agency has downplayed or dismissed abundant evidence that CFS is an organic disease, or cluster of diseases, characterized by severe immune-system and neurological dysfunctions as well as the frequent presence of multiple viral infections.*
>
> — David Tuller, journalist, describing critics' view of CDC's strategy. 2011[569]

Epidemiology, a cornerstone of public health policy and planning, studies the cause of a disease, who it affects, how it is transmitted, what risk factors are associated with its development, how it progresses over time, how it can be treated, and how it can be prevented.[570]

Dr. Andrew Moss, an emeritus professor of epidemiology at the University of California, San Francisco, and an early AIDS investigator, told journalist David Tuller that there is no tool more essential to the study of epidemiology than the case definition.[571] Moss explained, "If you recognize something is happening, you need a case definition so you can count it. You need to know whether the numbers are going up or down, or whether treatment and prevention work. And if you have a bad case definition, then it's very difficult to figure out what's going on."

Given the similarities between the disease seen in Incline Village and the earlier outbreaks, it's fair to say that HHS's epidemiological efforts on this disease go back to 1934, when Dr. Alexander Gilliam, Assistant Surgeon in the United States Public Health Service, investigated an outbreak in Los Angeles. CDC's Dr. Donald Henderson was involved in some of the subsequent outbreaks and, together with Dr. Alexis Shelokov of NIAID at the NIH, published a 1959 review that summarized 34 separate outbreaks.[572]

But following the outbreaks in Incline Village and Lyndonville, CDC's epidemiological approach inexplicably abandoned the legacy of researchers like Shelokov, Henderson, and Gilliam, and instead adopted a fatigue-focused case definition that bore little resemblance to the disease seen in Incline Village and the earlier outbreaks.

In a 2012 article comparing progress in AIDS and CFS since the 1980s, Dr. Vincent Racaniello of Columbia University[573] pointed out that CDC's use of a strict case definition and a strong epidemiological approach led to rapid progress in researching, diagnosing and treating AIDS in the 1980s. In sharp contrast, for this disease, the CDC adopted a series of non-specific, fatigue-focused, and increasingly broad case definitions that failed to accurately describe ME, while throwing it into a wastebin of medically unexplained fatigue, confounding it with psychiatric illness. As Racaniello noted, the CDC further compounded these definitional issues when it "dismissed evidence that CFS is an organic disease," focused its efforts on "psychiatric and trauma-related causes" and redirected funds intended for the study of this disease to other diseases.[574]

As reported by Tuller, ME experts described CDC's CFS epidemiological strategy as "fatally flawed."[575] As a result, in spite of an active CDC epidemiological program spanning thirty years and costing an estimated $120-125 million,[576] we still know very little about the etiology, the biomedical risk factors, the progression and prognosis, the diagnosis and treatment, or the prevention of ME.

On its own, CDC's failure to make progress is bad enough. But what is even more damning is that CDC's epidemiological strategy has made the situation worse by creating what Dr. Bruce

Carruthers (lead author on the 2011 ME International Consensus Criteria) referred to as a "web of confusion" over the nature of this disease. This web of confusion is so deep and so twisted that even the most determined efforts have been unable to untangle it, especially when the CDC was the organization enabling and/or promoting it.

Note on usage of terminology
Historically, all agencies have used the term "CFS." Today, the CDC still primarily uses the term "CFS" while the NIH typically uses the term "ME/CFS" and FDA refers to it as "CFS", "ME/CFS" or "ME and CFS." Regardless of the term used, all HHS programs lump all of the disparate CFS and ME definitions together. As above, the term "ME" or "this disease" will be used in this chapter when referring to the disease described in Chapter 1. The term "CFS" or "ME/CFS" will be used to refer to the programs at the CDC, the NIH and the FDA.

Case Definition and Methodological Issues

Dr. Andrew Moss stated that if you have a "bad case definition, then it's very difficult to figure out what's going on." At its core, CDC's CFS epidemiological efforts have been shackled by the bad case definitions and patient selection approaches that have been discussed throughout this paper.

Compounding these definitional and case ascertainment issues are methodological issues in how the epidemiological studies were conducted.[577] In a 2009 review of CDC epidemiological studies, Dr. Leonard Jason pointed out that the use of physician referral in CDC's early prevalence studies could have easily underestimated the prevalence of the disease by not accounting for patients with limited access to health care.[578] On the other hand, CDC's more recent epidemiological studies used an "unwellness" screen that looked not just for patients with fatigue, but also for patients with problems in memory or concentration, unrefreshing sleep or pain. As discussed earlier, this "Empirical approach" to identifying cases of CFS resulted ,in a 10-fold increase in prevalence and a significant percentage of patients with major depressive disorder being misdiagnosed with CFS.[579]

It's instructive to examine how these definitional and methodological issues affected the selectivity and reliability of a CFS diagnosis in CDC's studies. For instance, between 1997 and 2000, the CDC conducted a surveillance study in Wichita,[580] which included patient follow-up at 12, 24 and 36 months. Diagnosis was based on the Fukuda definition and the standard set of instruments in place at the time. It's notable that of the 60 CFS patients in the study, more than 60 percent were currently employed with a median workweek of 40 hours; only 17 percent were unemployed due to the "fatiguing illness."[581] This stands in sharp contrast to the significantly high levels of unemployment (35 to 69 percent and as high as 87 percent) typically reported in studies and surveys of patients.[582]

What is even more remarkable is that only 21 percent of the patients were still classified as having CFS at the two- and three-year follow-ups, and only 7.5 percent of the patients maintained a CFS classification two years in a row. Recovery for ME patients is typically estimated at only five to ten percent,[583] and from what I have seen in patients, the level of improvement seen within a year or two is small and often temporary; certainly not enough to no longer be considered to have ME. Even after 25 years, Molly Brown of DePaul University demonstrated in a 2012 paper that a group of 25 adolescents from the Lyndonville outbreak still had significant impairment compared to controls, even though 80 percent of them self-reported that they no longer had a CFS diagnosis.[584]

From December 2002 to July 2003, the CDC then reevaluated these Wichita patients, as part of its study to assess the Empirical definition and approach to diagnosing CFS.[585] This study, published in 2005, rediagnosed 190 subjects from the original study, first using the same Fukuda-based criteria used in the Wichita study (Reeves 2005: Table 2) and then using the newly defined Empirical definition and approach (Reeves 2005: Table 5). When the subjects were rediagnosed using *the same criteria* used in the original Wichita study, twenty-one percent (12 of the original 58 CFS patients) were now excluded because of exclusionary conditions. Only 10 percent (6 of the original 58) were still classified as having CFS while 69 percent (40 out of the original 58) were now classified as being in remission or having "insufficient fatigue" (fatigue without the required CFS criteria). At the same time, four subjects not originally classified as CFS were now classified as CFS and six additional subjects with major depressive disorder (MDD) were now listed as also having a CFS diagnosis.

Reeves 2005: Table 2 (from the 2005 study report):
Recruitment and Current Classifications of 190 Subjects; 37 participants with medical or psychiatric exclusions other than melancholic depression excluded

	Current Classification by Surveillance Criteria					
Classification During Surveillance *	CFS	ISF	Remission	Control	Exclusion	Total
CFS	6	27	5	0	8	46
ISF	4	31	9	0	4	48
Remission	0	0	0	48	2	50
CFS but has MDD **	5	9	2	0	5	21
ISF but has MDD **	1	9	8	0	7	25
Total	16	76	24	48	26	190

NOTE: Diagnosis at both time points used the Wichita study surveillance criteria.
* Indicates diagnosis of CFS *at least once* during surveillance study.
** According to Fukuda, major depressive disorder (MDD) is exclusionary..

The 2005 study concluded that the Fukuda-based criteria and patient selection methods used in the Wichita surveillance study "showed *scant stability over time*" (emphasis added), which it stated "could reflect the cyclic nature of CFS and changes over time"[586] but also acknowledged that it could be due to problems with the instruments used to select patients in the surveillance study. Again, this level of diagnostic instability and the extremely low percentage of patients who maintained a CFS diagnosis from one year to the next are inconsistent with what I have seen in my son or other patients. Even when they experience improvement, they still experience the hallmark symptoms of the disease.

As a second step in the 2005 study, the CDC then reassessed 164 of these same patients using the Empirical definition approach to identifying cases of CFS, and found that only ten of the sixteen patients who had been rediagnosed as CFS using the original surveillance criteria also met the Empirical criteria for CFS *when both criteria were applied at the same time*. The study does not clearly state whether all six of the patients originally diagnosed with CFS in the surveillance study were in that group of ten. At the same time, the Empirical definition and approach diagnosed 33 additional CFS patients, patients who had not been diagnosed with CFS using the surveillance criteria. Significantly, the 2005 study reported that *only 25 percent* of the patients diagnosed as CFS by the surveillance criteria were also diagnosed as CFS according to the Empirical definition.

Reeves 2005: Table 5 (from the 2005 study report):
Illness classification at the time of the clinical study by surveillance criteria and by standardized clinically empirical criteria of 164 study participants with no medical or

psychiatric exclusions.				
Current Classification using Surveillance Criteria	Current Classification using the Empirical approach			
	CFS	ISF	Not ill	Total
CFS	10	6	0	16
ISF	32	38	6	76
Remission	1	13	10	24
Control	0	4	44	48
Total	43	61	60	164

This is a remarkably low level of concordance, which the 2005 study acknowledged, stating "there was minimal association between the empirical classification and classification by the [Wichita] surveillance criteria." The CDC said this might be due to disease fluctuation, but primarily attributed the difference to the unreliability of the diagnostic approaches used in the Wichita study. Remarkably, in the 2005 study, Reeves concluded that the Empirical definition had addressed the problems with the earlier approach to diagnosing CFS, stating that the new approach "may be less affected by the day-to-day fluctuation of the illness and rather reflect the underlying chronic illness process." The 2005 paper stated that it wasn't possible to assess the diagnostic validity of most Fukuda CFS studies and called for all future research to use the Empirical approach.

By at least 2008, researchers outside of the CDC had rejected the Empirical definition because of its lack of specificity as demonstrated in the overly inflated prevalence numbers and the fact that 38 percent of patients with major depressive disorder would be misdiagnosed with CFS.[587] The Empirical approach has never been used outside of CDC.

Yet, the CDC continues to publish Empirical studies, as recently as 2015. In 2011, Dr. Leonard Jason questioned Dr. Beth Unger on this and she stated that the CDC had compared the Wichita method of patient selection to the Empirical approach and found that "the populations are quite comparable."[588] Given the differences in prevalence and the misdiagnosis of major depressive disorder, this is a surprising statement. Unfortunately, CDC's analysis demonstrating this has never been published. But even if true, its relevance to ME patients is not clear since neither Fukuda as used in Wichita or the Empirical method published in 2005 requires hallmark criteria of the disease.

Perhaps even more remarkably, ten years after the 2005 Reeves Empirical study was published, the CDC still uses Fukuda as the basis of its clinical guidelines and Fukuda is still the most widely used definition in research, even though CDC's own studies demonstrated how unreliable it is. The bottom line is that CDC's epidemiological strategy for this disease has been built on case definitions and methods that are both unreliable in use and non-specific in their failure to require hallmark criteria.

Studies into Prevalence, Risk Factor and Prognosis

Prevalence

To Dr. Moss' point, such non-specific and unreliable definitions have made it extremely difficult to even count how many people have ME.

Prevalence estimates for the Fukuda, Oxford and Empirical definitions range from 0.07 percent to 6.42 percent (Appendix 2 and Brurberg 2014[589]). This variance reflects differences in how the

prevalence study was conducted (e.g. population based or clinic, self-report or investigator diagnosed). But just as importantly if not more so, it represents the significant differences in the definitions and methods used to identify patients.

For instance, the most broadly accepted prevalence estimate for this disease is Jason's 1999 prevalence estimate of 0.42 percent, which translates to about 1.3 million U.S. patients in 2013.[590] In a 2011 U.K. study, Dr. Luis Nacul estimated the prevalence of Fukuda at 0.19 percent and that of the Canadian Consensus Criteria at 0.11 percent, less than 60 percent of the Fukuda estimate.[591] Both the Jason and Nacul prevalence estimates are substantially below the Empirical estimate of 2.54 percent,[592] the upper limit of four million often used by HHS, or Wessely's Fukuda-based estimate of 2.6 percent.[593] Jason has pointed out that the Empirical definition prevalence estimate is substantially closer to the rates of several mood disorders,[594] suggesting that the selected population may encompass a significant percent of patients with such disorders. Jason's point is reinforced by the fact that when Wessely excluded psychiatric illness in his Fukuda-based CFS prevalence estimates, the prevalence rate dropped to 0.5 percent.

Estimates of incidence also show considerable variance. Nacul estimated incidence at 15 per 100,000, while in a large 2014 study of 5809 people, Dr. Inger Bakken at the Norwegian Institute of Public Health estimated incidence at 25.8 per 100,000 people.[595] Both of these incidence estimates are substantially below the estimated incidence of 180 per 100,000 reported in the 2003 CDC study by Reyes.[596]

Risk Factors

The same definitional and methodological problems that have resulted in such varied prevalence estimates have also thwarted attempts to identify what factors, including risk factors, are associated with the onset of the disease. For instance, a number of studies published by the CDC between 2006 and 2012 reported that patients had maladaptive coping,[597] personality disorders,[598] and a history of childhood adversity and trauma.[599] A 2006 CDC study determined that the single factor of depression was capable of distinguishing patients from controls.[600] These studies used the empirical case definition and approach to identifying CFS cases. Given the diagnostic problems noted with the Empirical definition, it's critical to question what kinds of patients were actually studied.

And yet, even today, the Empirical findings continue to be applied to this disease, particularly in medical education. For instance, as discussed in the chapter on medical care, the CDC CFS website and other medical education sources state that a history of childhood adversity is a risk factor for this disease.[601] In the case of the CDC website, the supporting references include the study on childhood trauma noted above; another study that used a non-standard definition for CFS; studies on the relation between depression on the one hand and post-traumatic stress disorder or childhood trauma/abuse on the other; and a study that investigated childhood abuse in functional somatic syndrome, defined to include self-reported CFS, fibromyalgia, irritable bowel syndrome or multiple chemical sensitivity.[602] But studies on child abuse in depression, post-traumatic stress disorder and functional somatic syndrome have little relevance to child abuse as a risk factor for ME.

In contrast, Dr. Jason's 2001 study reported that a history of abuse *was not* a significant predictor of CFS when stricter case selection criteria were used.[603] Notably, in a 2002 study, Jason reported that a history of child abuse *was* associated with *other* conditions that can be associated with long term fatigue, such as PTSD and anxiety disorders.[604] One simple explanation for CDC's finding of

child abuse in "CFS" is that CDC's "CFS" cohort included patients with various psychiatric disorders and was not representative of patients with ME. At a CFSAC discussion in 2012, Dr. Peter Rowe, an expert clinician who specializes in pediatric patients, iterated this view, questioning the CDC's study and stating that he doesn't see high levels of physical or sexual abuse.[605]

CDC is not the only group to report risk factors associated with personality, lifestyle, and trauma. For instance, in a 2006 review, Dr. Judith Prins reported that studies had shown that neuroticism, introversion, and inactivity in childhood were found to increase the likelihood of CFS.[606] And the 2011 PACE trial stated that a perfectionist personality is a precipitating factor for CFS.[607] But in a 2009 study, Dr. Jason explored coping styles, optimism, and perceived social support and found more optimism and less venting and focusing on symptoms in patients with this disease than those with either medically explained chronic fatigue and/or unexplained fatigue.[608] In a review of the literature in that 2009 study, Dr. Jason concluded that the risk factors for this disease included factors such as the greater prevalence in women, an increased debility with age, higher prevalence in minorities, lower socioeconomic status, and stressful life events preceding the illness, but not psychological factors.

A second class of risk factor relates to familial or genetic factors, an area of interest given the results of twin studies and the occasional co-occurrence of CFS among family members. In April 2006, the CDC published 14 articles in Pharmacogenomics that reported the results of a large study examining the genetics of CFS.[609] At a press conference widely covered by the mainstream press, the CDC reported that the study had demonstrated the "underlying biological basis" for CFS in a group of "genes that are related to those parts of brain activity that mediate the stress response." The CDC went on to explain that the study had targeted "50 genes and 500 polymorphisms in genes that are active in the HPA axis pathways." (The HPA or hypothalamic-pituitary-adrenal axis, three organs in the neuroendocrine system that controls the reaction to stress and is involved in the regulation of other body systems.) The CDC also noted that there were diagnostic and treatment implications of the study, stating, "We use this information in our physician education program, to teach them about the illness" so they can diagnose it.[610] The New York Times headlined the link between CFS and genetics and stress, and quoted Dr. Reeves as stating that the study "demonstrated that people with chronic fatigue syndrome were unable to deal with everyday challenges and adversity, including injuries, illnesses, divorce and stressful jobs."[611] In other words, CDC's conclusion was that the disease was a result of the inability to manage life's stresses.

But others quickly disagreed with CDC's interpretation. In a May 2006 article in Science Magazine, Jocelyn Kaiser, quoting the concerns of other researchers, questioned the findings of this study because of the small sample size, and because of the "unusual" phone-survey approach used to identify cases of CFS. She especially questioned the study's focus on a narrow set of genes all related to stress, and CDC's resultant finding that CFS was due to three specific genes within that narrow set of genes.[612] As reported by Kaiser, Dr. Nancy Cox of the University of Chicago pointed out that other sets of genes might have had similar correlation *if the CDC had studied them*. Kaiser also reported the concerns of researchers with a lack of robustness in the study. For instance, Kaiser reported that Dr. Jonathan Kerr (at the time at the Imperial College in London) stated that the technology used in the study was not adequate to definitively state that a specific set of genes were involved.

Craig Maupin, of CFIDS Report, further highlighted the above concerns, particularly with respect to the problems with how these patients were diagnosed; these CFS patients originated in the Wichita study, and then were further characterized by the Empirical approach. As noted above,

significant concerns had been raised with the reliability of the diagnosis of CFS in this cohort of patients. Maupin also highlighted concerns with how the study was being used, stating, "Critics have charged that it was irresponsible of the CDC to announce changes to the way CFS is handled clinically after limiting their study to just those genes involved in the way the brain handles stress response."[613]

Prognosis

Beyond prevalence and risk factors, the CDC has also assessed the long-term risks associated with having the disease along with the disease prognosis and the factors that contribute to poor prognosis. One example is a 2010 CDC study that concluded that CFS patients had a higher prevalence of maladaptive personality disorders (paranoid, schizoid, avoidant, obsessive-compulsive and depressive personality disorders) and these could contribute to poorer response to treatment if not adequately addressed.[614] In 2015, the CDC reported an increased risk of gynecological problems including "menstrual abnormalities, endometriosis, pelvic pain, hysterectomy, and early menopause."[615] Both of these studies used the Empirical approach, calling into question what kinds of patients were studied and how these findings apply to patients with ME.

CDC is not alone in linking prognosis to such factors. For instance, a number of researchers, particularly in the U.K., have associated poor prognosis with factors like a patient's belief that the disease has an organic cause. One such study is a 1999 review by Professor Wessely.[616] However, that conclusion appears to have been based on a study in a mixed cohort of patients that included both CFS and chronic fatigue patients, making it problematic to even make conclusions about CFS, let alone ME. Such statements about the linkage between prognosis and factors like illness beliefs are still prevalent in research, medical education, and the public perception today, as evidenced by the PACE trial and the Yancey article, noted above, which attributed poorer prognosis to a belief that the illness is organic and to the patient having a financial benefit in the form of sickness benefits.

The study of prognosis is complicated not only by patient selection problems, but also by lack of agreement on how outcomes should be measured. One important outcome is "recovery" which is typically defined subjectively, not objectively, and is defined differently across different studies.[617] For instance, based on its four-city surveillance study, the CDC stated that 50 percent of patients "recovered" and most recovered in the first five years.[618] But in that study, recovery was defined by the patient. Further, the study acknowledged that "recovery" didn't necessarily reflect "complete symptom-free recovery." Inappropriate measures of recovery only add to the muddle created by patient selection issues.

For its part, the PACE trial originally defined one of its primary outcomes as a score of 85 or more on the physical subscale of the SF-36 (used to assess functional health and well being) but changed that to a score or 60 after the study started.[619] This score is below the entry criteria of 65 used in the PACE study, meaning that patients *could have degraded since the start of the trial and still be classified as recovered*. In a separate paper on the PACE trial, published in 2014, Dr. Trudie Chalder, of Kings College, London, and one of the PACE investigators, defined recovery as no longer meeting the Oxford criteria *or* the Fukuda criteria.[620] The paper defined total recovery as feeling much better *and* scoring below 18 on the Chalder Fatigue Questionnaire *and* scoring 65 or higher on the SF-36. But it's important to note that whether the SF-36 score used is 60 or 65, both are significantly below the response of healthy people of the same age range as the study participants.[621] Complicating the assessment of recovery further, using a criterion of whether a

patient still meets either the Oxford or the Fukuda criteria is questionable, given the demonstrated instability over time of a diagnosis by Fukuda that was reported by Reeves.[622] While this author is unaware of studies that demonstrate that Oxford has the same issue, it would seem reasonable to suggest that Oxford may suffer from the same diagnostic unreliability, given that it is even less specific.

Some researchers have examined biomedical factors associated with prognosis. For instance, one study conducted by staff at the National Cancer Institute (NCI) that examined 1.2 million cases of cancer and 100,000 controls reported an increased prevalence of B cell lymphoma.[623] The Chronic Fatigue Initiative, a $10 million initiative funded by the Hutchins family to study potential causes of the disease,[624] reported that of 59 deaths in a small survey of 960 people, 38 percent died of cancer, 19 percent of cardiovascular disease and 19 percent were due to suicide.[625] Jason did a retrospective analysis of a patients' memorial list and found that patients are more likely to die from cancer, cardiac disease, and suicide,[626] Jason's study also found that patients were likely to die 10-25 years earlier than those with the same condition in the general population. Admittedly, the study has methodological limitations but its findings are difficult to ignore especially when considered in the context of the findings seen in the NCI and the Chronic Fatigue Initiative studies. There is also additional evidence from patient autopsies, such as Sophia Mirza's autopsy finding of dorsal root ganglionitis (inflammation of dorsal root ganglion at the entry point to the spinal column)[627] and Casey Fero's finding of viral myocarditis (virally caused inflammation of the heart).[628] It is stunning that the disease could continue to be attributed to a fear-based avoidance of activity in the face of such findings.

In a presentation on "Social Determinants of Health" at the 2015 NIH Pathways to Prevention Workshop on ME/CFS, Abigail Brown reviewed the studies that had been done to determine the personal, social, economic, health and environmental factors that affect the health status of patients with ME and CFS and pointed out the lack of consistency of the findings. She attributed this inconsistency to such factors as reliance on self-reported diagnosis, inconsistently applied case definitions, lack of replication of studies, and a psychogenic bias.[629] These are not newly discovered issues. These issues have been understood for many years but have just been ignored.

The bottom line, as widely demonstrated by the 2015 Institute of Medicine report,[630] the 2014 NIH Pathways to Prevention Workshop draft report,[631] and the 2014 AHRQ Evidence Review[632] is that we know virtually nothing about the prevalence, risk factors, and prognosis of this disease and what little we think we know is sparse, conflicted, and of questionable relevance to ME patients. The failure to produce any meaningful knowledge about such simple facets of a disease is perhaps the most damning condemnation of CDC's epidemiological strategy and the epidemiological studies that have been done to date.

Missed Opportunities

It's not just an issue of what epidemiological studies the CDC has done, but also what studies the CDC has chosen not to do. The biggest missed opportunity has been the failure to conduct longitudinal studies to understand the natural history of this disease. Little is known about what happens to ME patients over their lifetime; how the disease progresses; what complications patients suffer; what their true risk of cancer; heart disease or other diseases is; what they can do to mitigate against those risks; and what patients' expected lifespan is. When premature death strikes the community unexpectedly, as it too often does, it hits patients hard because they know they all live with this dark cloud of uncertainty hanging over their heads.

One mechanism that could be used to better understand the disease's natural history would be to follow-up on the previous cluster outbreaks such as those in Incline Village and Lyndonville. Incline Village is especially ideal since Dr. Daniel Peterson, one of the clinicians who first reported the outbreak, is still in active practice there, although approaching retirement. Knowing the value of such an investigation, CFSAC made a formal recommendation to HHS in 2012 to "allocate specific funds to study patients with ME/CFS from past cluster outbreaks." [633] HHS's response was that the *CDC had not been able to confirm any outbreaks*, stating:

> Studying CFS clusters or outbreaks, if they are detected, is a worthwhile project. To date, CDC has not been able to confirm the occurrence of outbreaks of CFS. Studies of potential outbreaks or clusters would greatly benefit from better understanding the different spectrums of CFS and clearly defining what constitutes an outbreak or a cluster. Clinicians caring for CFS patients are in the best position to detect potential clusters.[634]

This response is as befuddling as it is infuriating. Dr. Peterson and Dr. Paul Cheney, clinicians in Incline Village, contacted the CDC thirty years ago about outbreaks of this disease, as did Dr. David Bell. Dr. William Reeves denied that Incline Village was a cluster, as noted in PrimeTime Live's 1996 investigation, but Assistant Secretary of Health Dr. Phillip Lee disagreed with that statement.[635] In an October 1999 meeting between CDC Director Dr. Jeffrey Koplan and patients, the CDC again acknowledged that there had been "clusters of CFS cases" and said that the CDC had investigated some of them, although apparently had not published reports on them.[636]

And yet in 2012, the CDC said that it could not confirm clusters or outbreaks.

Was the CDC now saying that Incline Village was not a cluster? Was Dr. Elaine DeFrietas, of Wistar Institute, who investigated a potential retroviral cause, correct when she suggested that the CDC didn't want to admit to a cluster because that would imply an infectious factor?[637] But even ignoring the implication of an infectious component, was the CDC saying that nothing could be learned from the Incline Village patients, and that it would not be worth following up on those patients before Dr. Peterson retires from medical practice, or the Incline Village outbreak patients all die? CDC's response is scientifically nonsensical and irresponsible.

The Funding Drain

Using such poorly defined definitions and methods wastes money because the results of such studies are meaningless. But waste from misguided CFS research is not the only source of the funding concerns with the CDC. Over the years, the CDC has spent an extremely small portion of its total budget on this disease. Between 2010 and 2014, that averaged about $4.7M/year out of a total budget of $5.4 to $6.4 Billion annually.[638] Compounding that problem is the misuse and the redirection to other diseases of the scarce funds that were allocated. As a result of patient advocacy efforts, including those by the CFIDS Association of America and a "whistleblower" report by CDC's Dr. William Reeves,[639] the Department of Health and Human Services Office of Inspector General released a report in May 1999 that stated that the CDC had misdirected, or was unable to account for, about $12.9 million of the funds intended for the CFS program over a four-year period (1995-1998). Compounding that problem, it then lied to Congress about the misuse.[640]

A subsequent 2000 report by the U.S. General Accounting Office (now called the Government Accountability Office) noted this misuse and redirection of funds, and further noted that CDC's processes and funding issues had impeded research into this disease.[641] In his 2011 article, David Tuller highlighted the GAO report's statements that the CDC had "shortchanged the CFS program" and had ignored "congressional requests to support important research initiatives."[642]

In his October 1999 meeting with community representatives, CDC Director Dr. Jeffrey Koplan acknowledged CDC's serious mistakes in how the CFS program had been managed.[643] He stated that the CDC would restore $12.9 million over four years, monitor spending of CFS funds, submit an operating plan and budget to Congress, require mandatory training in budgeting, and conduct an internal review of CDC fiscal policies. He also committed to "reinvigorating CDC's efforts to understand CFS and to prevent it."

Even if the problems with CDC's epidemiological work were just ones of financial mismanagement, the impact of the budget training efforts on CDC's financial management practices is questionable. At the October 28, 2008 CFSAC meeting, Kim McCleary, CEO of CFIDS Association of America, again raised issues of financial mismanagement of the CFS program. But her concerns were much broader than simple financial management. McCleary described CDC research as a "bust of shameful scientific leadership, zero accountability, invisible outcomes, and millions and millions of dollars stuck in suspended animation, if not wasted… only government contractors seem to be benefiting from millions spent for which there are no worthwhile outcomes for American taxpayers or CFS patients."[644]

Failed Strategic Planning and CDC's Insularity

According to CDC's CFS website, CDC's epidemiological approach for CFS from 2001 to 2005 focused on the assessment of etiological factors and diagnostic markers, the determination of whether CFS was a single disease or not, and the assessment of prevalence and risk factors.[645] In support of these efforts, the CDC instituted a peer review of its CFS program.[646] Then, in 2009, the CDC published a formal strategic plan, intended to increase awareness of etiology, improve diagnostics and treatment, improve clinical management of patients through medical education, and move CFS into the mainstream of public health concerns.[647]

It is to CDC's credit that it published specific objectives, held program reviews, and published a formal strategic plan. The NIH does not appear to have ever published a strategy and the internal plan that they have discussed does not appear to be a proper strategy. But the 2009 CDC strategy was received negatively both by CFSAC and the patient community, with the CFIDS Association of America submitting a formal response to CDC.[648] The concerns raised by the CFIDS Association of America included the CFS strategy's reliance on studies done with the flawed Empirical definition, a lack of innovation, a lack of precision and clarity in terminology, a lack of clarity on timelines, and a lack of clarity on which objectives could be met with the available budget. The CFIDS Association of America also raised concerns with the insularity of CDC's program and the potential that CDC's emphasis on stress and the use of CBT could threaten progress being made by researchers in the field. The wrong definition, the wrong disease model, the failure to engage researchers, poor financial planning—factors that had plagued CDC's CFS program for years. The CFIDS Association of America concluded "we cannot more strongly state our view that implementation of the proposed plan is highly unlikely to yield meaningful advances in reducing the burden of illness posed by CFS."

The CFIDS Association of America's point about CDC's failure to engage researchers was a long-standing issue that had been brought up in the GAO report[649] and in the peer reviews of CDC's program going back to at least 1999. At that time, the CDC program peer reviewers noted a lack of collaboration with researchers both within and outside of CDC.[650] A similar concern was raised in the 2008 peer review of the CDC CFS program.[651] CFSAC members again raised this issue at the May 2009 review of the strategic plan.[652] For instance, Dr. Klimas called on Dr. Reeves of the CDC

to examine how the CDC was going to work with disease experts as partners. At the same meeting, Dr. James Oleske, CFSAC chair, told Dr. Reeves that the CDC CFS program treated investigators paternalistically. In the CFIDS Association of America response to the strategic plan, Kim McCleary added that the "while its language emphasizes collaboration and partnership, its design reinforces the isolated conduct of one small group of investigators, working at the direction of the branch chief without connection to colleagues inside the agency and at other institutions."[653]

Dr. Reeves, who had headed the CDC CFS program since 1992, was reassigned in 2010, following community-wide protest to his failed leadership. Adding to the issues described above, the community expressed concerns with the focus on psychological issues, the nature and quality of the science being conducted, the failure to follow-up on the suggestions of the CDC CFS program peer reviewers, the lack of engagement with other public health agencies and the overall failure to achieve any outcomes in twenty-five years. In his October 2009 testimony, Dr. Fred Friedberg, current president of IACFS/ME, summarized the failure best when he stated "After 25 years (and over $100 million) of CDC research, chronic fatigue syndrome remains a stigmatized illness without substantive progress on public health policy or objective diagnosis and treatment. And their new five-year $25 million plan fails to inspire any confidence that change will occur."[654]

Today, CDC's controversial 2009 strategic plan has been marked as "archived" and has not been replaced with an updated plan.

Dr. Elizabeth Unger was named head of the CDC CFS program in 2010. To her credit, she has since established closer ties to expert clinicians through the multi-site clinical study to assess patients diagnosed with "CFS, post-infective fatigue (PIF) or myalgic encephalomyelitis (ME)."[655] However, as discussed previously, she has also declined CFSAC and patient input on CDC's CFS clinical guidelines, has continued to question the importance of PEM as a hallmark symptom, has failed to address the significant risk of exercise recommendations, and has not acted urgently to achieve any substantial outcomes for patients over the last five years. Even changes as simple as specifying PEM as a hallmark criteria and highlighting its diagnostic and therapeutic significance could have provided greater protection in the last five years to newly diagnosed patients against long-term damage than my son was given.

Summary

Given these kinds of problems over three decades, it is not surprising that experts and researchers in this disease told journalist David Tuller that CDC's CFS epidemiological strategy was fatally flawed. Tuller summarized the critics' view of the reasons for that failure as follows:

> CDC has spent years looking in the wrong places… The agency has downplayed or dismissed abundant evidence that CFS is an organic disease, or cluster of diseases, characterized by severe immune-system and neurological dysfunctions as well as the frequent presence of multiple viral infections. Instead, say the critics, the agency has focused major resources on investigating proposed psychiatric and trauma-related factors and associations.[656]

These failures have not only directly impacted clinical care but also hobbled CDC's ability to achieve its own goals of elucidating disease pathophysiology, prevalence, diagnostic markers, etiological agents, risk factors, and the natural history of this disease. As a result, as Tuller stated, "the CDC's research program has yielded little or no actionable information about causes, biomarkers, diagnostic tests, or pharmaceutical treatments. Nor has the agency done much to

track long-term outcomes—such as cancer rates, heart attacks and suicides—among people with the illness."

Thirty years have passed since Incline Village and five years have passed since my son became ill. Yet, despite having an active research and medical education program for all those years and spending an estimated $120-125 million, the CDC has not produced a single measurable outcome that has produced a meaningful difference in patients' lives.[657] For all the money and time that has been put into this program since 1984, virtually no tangible outcomes have been produced even today, thirty years later, that help us understand CFS and how to diagnose, treat, and prevent it. ME patients remain sentenced to lives of terrible debility, suffering, and stigma, often for decades.

If that were all, it would be damnable enough. But what makes CDC's misguided, too often unilateral efforts in epidemiology and medical education so inexcusable is that they have produced an incomprehensible level of bedlam, which has held this disease and its victims in an invisible trap, unable to escape.

5. Research and Drug Development

"Research on other fatiguing illnesses, such as cancer and multiple sclerosis, is done on patients who have those diseases. There is a current, urgent need for ME research using patients who actually have ME."

—Dr. Bruce Carruthers, Lead author, ME International Consensus Criteria[658]

Overview

As a mother of an ME patient and a professional who spent 31 years in the pharmaceutical industry, it has been both agonizing and infuriating to come to understand what was known about ME before my son was even born, and to see how little progress has been made in ME research and drug development in all these years.

Researchers in the 1970s, 1980s and early 1990s were reporting objective evidence of neurological dysfunction, immune abnormalities, and autonomic and energy production issues. They also noted findings indicative of an underlying pathogen.[659] Studies have long demonstrated potentially useful biomarkers that are being used in the clinical practice of ME experts today. One small pharmaceutical company began performing drug clinical trials in the late 1980s. Today, a very small group of disease experts use a range of treatments off-label to help ME patients.

The obvious question is why this knowledge and experience never translated into validated diagnostics, FDA-approved treatments, appropriate clinical care, and a better understanding of the underlying biological dysfunction seen in ME.

According to the 2014 *Biopharmaceutical Research Industry Profile*, produced by the Pharmaceutical Research and Manufacturers of America (PhRMA), the industry spent $48.5 billion on research and development in 2012. Much of this money was spent in the later part of the research and drug development pipeline where clinical trials are being conducted.[660] In the same year, the NIH spent an additional $30.9 billion in research, with much of that money spent in the early part of the research and drug development pipeline, particularly in basic and translational research.

Much of this basic research is done in NIH-funded academic settings and produces the novel biological technologies (e.g. biomarkers) and the deep knowledge of the disease pathologies and potential avenues of drug intervention that are an essential prerequisite for the subsequent development of effective drug therapies. Over about the last 15 years, the pharmaceutical industry has established broad-ranging collaborations with academia to leverage this knowledge in order to expedite the development of safe and effective drugs. While such collaborations have become the backbone of the industry across diseases, they are a particularly important strategy for complex and challenging diseases. Citing a collaboration focused on Alzheimer and Parkinson's Disease, a Tufts study on academic-industry partnerships stated, "extensive collaboration between public and private sectors [is] necessary to facilitate the development of effective treatments" for complex diseases.[661]

But what happens when the NIH fails to provide even marginally adequate funding for basic research, and that research funding is difficult to access? What happens when the academic institutes are hostile to the idea of their researchers spending time on a disease? In the case of ME, a very small group of researchers has lived on shoestring, unpredictable budgets, and/or have run studies without *any* funding. But the vast majority of researchers have ignored the disease and

simply gone elsewhere. The resultant lack of vested researchers and the lack of the basic disease knowledge required to develop effective treatments makes investment in ME a bad business decision for pharmaceutical companies.

Obviously, the definitional issues have thwarted progress in research, as a result of conflicted research findings and irreconcilable theories about the nature of the disease. And even when properly defined, ME is a complex disease that would be challenging to unravel under any circumstances. But the combination of paltry NIH research funding and the institutional barriers and biases have only further compounded these problems, ensuring that ME would remain medically unexplained.

Today, there are signs of hope in ME research and development. Research findings from long ago are being dusted off and reinvestigated. Old and new technologies are being applied for the first time to better understand the disease pathologies. New avenues of scientific investigation are being pursued and new researchers from other fields are beginning to take an interest. A few small clinical trials of repurposed drugs, such as Rituxan, are in the planning stages. And a recently announced study by the End ME/CFS Project will examine the most severely affected ME patients in order to understand the core of the disease at a molecular level.[662]

But the NIH is not funding the vast majority of this exciting work, and NIH scientists are not involved. As journalist David Tuller said in 2011, the bulk of the most exciting research being done today is being funded privately, often by families of patients, grants from private foundations, and even through patient-driven crowd sourcing.[663] The public component, the NIH research funding that has been the lynchpin of research and drug development efforts in other diseases, is almost non-existent. NIH spending has averaged just $5 million a year for a total of $139.5 million spent in 28 years,[664] an amount that pales in comparison to the amount spent on similarly disabling diseases.

NIH's official position, seen in its recent rejection of the 2014 CFSAC recommendation for an RFA, is that such a commitment is not warranted because "there remains a lack of definitive evidence regarding the etiology, diagnosis, and treatment for ME/CFS."[665] And yet, these privately funded researchers have found plenty to research as evidenced by recent publications from Stanford[666] and Columbia,[667] the Rituximab clinical trials being conducted in Norway, and the research recommendations in the 2015 Institute of Medicine report.[668]

Given the complexity of ME and the debility of these patients and the reality of research and development in this country, it is not clear how far this private model can go toward unraveling the etiology. But what is clear is that, when the promise of these initiatives produces outcomes that make a real difference in patients' lives, it will be in spite of what HHS and the NIH have done for the last thirty years, not because of it.

NIH Research: Underfunded, Misdirected, Uncoordinated and Orphaned

Like all issues with this disease, the reasons for the lack of progress in research are not always straightforward. From one perspective, we have failed to make progress with basic and translational research for the same reasons that CDC's epidemiological research has failed—non-specific, unreliable definitions and approaches for selecting patients for research studies.[669] The impact of that on research was discussed in the chapter "What is CFS?"

But there are also a number of other critical issues, primarily related to the NIH but reflected in academia and the medical societies that have negatively impacted research into this disease.

First and foremost, NIH funding for basic research of ME/CFS is almost nonexistent. At $5 million a year out of a $30 billion annual NIH budget, the amount is absurd by any standards. But it is especially preposterous for such a complex disease with this level of prevalence, disease burden, and economic impact. The February 2015 IOM report pulled no punches on this issue, stating, "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."[670]

A second issue is the historical bias that this disease is psychogenic, which has led to an excessive focus on behavioral and psychological issues and/or the poor reception at the NIH of grant requests for biomedical research. This has made it difficult for researchers to get the support of their institutions to pursue biomedical research and difficult for them to access what little NIH funding is available.

A third issue exacerbates this bias—the Special Emphasis Panel (SEP) process used by the NIH to review grant requests for this disease. Collectively, these issues have driven potential and existing researchers from the field, while simultaneously siphoning research funds to other diseases.

A fourth and very significant issue is the positioning of this disease in NIH's Office of Research on Women's Health (ORWH) over the last 15 years, effectively exiling the disease outside of NIH's institute-driven structure. This has created a huge barrier because the institutes, not ORWH, are the ones with the money to spend and they have largely failed to make a serious commitment to this disease. The institutes appear to be largely interested in only the narrow aspects of the disease that overlap with their own goals. This makes it nearly impossible for researchers to get funding for the kinds of studies that are needed to advance the field but also difficult to establish the kind of research strategy that is needed to make progress. To this point, the NIH has never developed a research strategy, at least not one developed with the open collaboration of the community and shared publicly.

To make progress, the NIH must address the miserly funding and also the bias, the institutional barriers, and the lack of a strategic commitment and engagement that has stalled research progress for so many years. Doing so will require a level of leadership and political will from the NIH that has not been demonstrated in thirty years.

NIH Research Funding is Paltry and Inaccessible

NIH Funding for Research Not Commensurate with Disease Burden or Economic Impact

NIH funding for ME/CFS is almost non-existent. In 2014, NIH's funding for ME/CFS was estimated at $5 million out of a total NIH budget of $30.1 billion.[671] This places ME/CFS at #226 out of 234 diseases funded by the NIH. The amount spent is about one half of that spent on hay fever,[672] four percent of that spent on multiple sclerosis and six percent of that spent on lupus, even though ME has a similar burden of disease and greater prevalence than multiple sclerosis or lupus. More dramatic is the 600-fold disparity with HIV/AIDS funding, even though, according to Dr. Nancy Klimas, her HIV patients are doing well thanks to "three decades of research and billions of dollars invested" while her CFS patients remained very ill and unable to work.[673]

NIH awarded a total of $134.5 million for CFS and ME research between 1991 and 2014. According to the Solve ME/CFS Initiative (formerly the CFIDS Association of America), during the same time frame, about $400 million was spent on each of fibromyalgia and irritable bowel syndrome (IBS), while about $4 billion was spent on multiple sclerosis.[674] This disparity in funding translates directly into the limited size of the evidence base with about 5500 articles for this disease and roughly ten times as many for multiple sclerosis.

The underfunding is even starker when the prevalence is considered. According to an analysis done by Dr. Andreas Kogelnik, ME clinician and founder of the Open Medicine Institute, the per-patient funding level for this disease is less than any other disease and far below that of other diseases of similar prevalence and/or morbidity.[675] For instance, annual funding for this disease is about five dollars per patient, while that for multiple sclerosis is about $255 per patient and HIV/AIDS is about $2,482 per patient. To be equitable based on disease burden and prevalence, ME funding would have to be roughly $250 million a year.

2014 NIH funding and prevalence for selected diseases[676]

Disease area	Funding *(millions)*	Prevalence	$ Spent per patient
HIV/AIDS	$2,978	1,200,000[677]	$2,482
Lupus	$99	350,000 [678]	$283
Multiple sclerosis	$102	400,000[679]	$255
Autism	$188	3,500,000 [680]	$54
ME/CFS	$5	1,000,000	$5

This low level of research funding is not an historical anomaly. Since the inception of NIH's ME/CFS program in about 1987, NIH funding for this disease has never been higher than $7.2 million (in 2002) and averaged about $5.0 million since 1987.[681] The change in the NIH budget for CFS from 1995 to 2014 represents a decrease of about 27 percent at a time when total NIH funding increased about 166 percent.

To make matters worse, even the small amount of money spent by the NIH on ME/CFS research has been raided to support research in other disease areas. For instance, according to advocate Jennifer Spotila, the NIH reported that they spent $4.5 million on ME/CFS in 2012, but roughly $800,000 (18 percent) was spent on other diseases.[682] At the September 2004 CFSAC, the CFIDS Association of America reported that between 1999 and 2003, $5.8 million of the total NIH funding of $31.6 million was redirected to studies on other diseases, including twelve studies on such topics as the "psychobiology of ethnicity, stress and disease, studies on vascular disease or chronic muscle diseases and studies on muscle disorders and Lyme disease."[683] As Kim McCleary, CEO of CFIDS Association of America pointed out, this redirection of roughly 20 percent of the already low NIH research funding for this disease occurred at a time when NIH funding increased 76 percent. For the year 2003, this redirection left less than $4 million dedicated to ME/CFS out of a reported ME/CFS budget of $6.3 million. The 2004 CFIDS Association of America report called on the NIH to reverse the "shocking decline in CFS research and to build a robust program commensurate with the magnitude of the illness." The report included recommendations to stimulate extramural research through activities such as the issuance of an RFA and the establishment of research and clinical "Centers for Excellence."

A similar redirection of research funds was identified for the years 2000 to 2009 through a FOIA-driven analysis done by patient advocates Charlotte von Salis and Pat Fero. At the 2011 NIH State

of Knowledge Workshop, Fero reported that between the years of 2000 and 2009, $18 million of the ten-year $54.3 million research budget designated for this disease was actually spent on other diseases.[684] Ms. Fero examined the funding for the years 2006-2008 more closely and found that of 161 grant requests that were reviewed, 28 were approved with 36 percent of those (10) going to ME/CFS for a total of $3.2 million while 64 percent (18) went to other diseases. Fero stated that it appeared that pain, sleep and especially fatigue in *any* disease could be approved by the CFS Special Emphasis Panel (SEP), the panel responsible for the first level of grant review of CFS applications at NIH.[685]

While the actual dollar amounts involved are small, this represents a significant percentage of the total research funds available for the study of this disease but siphoned off to other diseases—roughly 20 percent for much of 1999 to 2012 and likely higher between 2004 and 2009.

The inadequacy of NIH's funding is even starker when you compare the level of funding to the burden that this disease imposes on patients. One measure of the impact of this disease is the estimated annual economic impact of $19-24 billion in lost productivity and direct medical costs. As big as this number is, it is likely an underestimate because it does not include factors such as the lost wages of caregivers, or the full cost of medical care if knowledgeable doctors and treatments were available. But even at $19-24 billion, this annual economic impact is roughly 4,200 times the amount of money that the NIH spends annually on this disease, demonstrating a remarkable short-sightedness by the NIH in its failure to address this health crisis for so many years.

Economic impact is only one measure of the burden of disease. A more patient-centered measure is the World Health Organization's (WHO) Disability Adjusted Life Year (DALY), a measure that considers mortality, the incidence and duration of disease, the level of disability due to morbidity, and the age of disease onset.[686] The World Health Organization has calculated DALY for a number of diseases, including HIV, congestive heart failure, chronic obstructive pulmonary disease (COPD), and multiple sclerosis. WHO did not calculate the DALY for this disease, but the Australian government did in 2003, estimating the DALY for this disease to be higher than AIDS and multiple sclerosis in the Australian population.[687] This gives an objective measure of the level of morbidity that further calls into question the lack of funding for this disease compared to other diseases.

While not quantitative, the 2015 Institute of Medicine Report on this disease also noted the magnitude of the burden of this disease, pointing out that patients are "more functionally impaired than those with other disabling illnesses, including type 2 diabetes mellitus, congestive heart failure, hypertension, depression, multiple sclerosis, and end-stage renal disease."[688] While the level of funding provided by the NIH is dependent on a number of factors, not just disease burden, it's critical for funders and congressional leaders to ask why the funding at the NIH has been so far out of alignment with disease burden for this disease, particularly given the lack of any effective treatment.[689]

Over the years, CFSAC, patient advocates, and Congress have made repeated requests for increased funding, targeted to specific research needs. CFSAC made repeated funding recommendations in 2004, 2005, 2006, 2011, 2012, and again in June of 2014.[690] Also in 2014, both IACFS/ME and a group of congressional leaders, spearheaded by Representatives Lofgren and Eshoo of California, submitted separate requests for funding directly to Dr. Francis Collins, director of NIH.[691] Finally, while not specifying a specific amount, congressional appropriations reports going back to at least 1995 have included recommendations for funding and targeted research, most recently in 2012-2013.[692]

Yet in spite of these targeted requests and the fact that the funding provided so clearly falls far short of an equitable share, NIH's financial commitment to this disease has remained flat, and virtually non-existent for thirty years. As noted in a Stanford article on this disease by Kris Newby, the harsh reality is that at $5 million, this level of NIH funding is not sufficient to support a university research lab.[693] Without adequate support from the NIH, it is virtually impossible to attract researchers to advance the basic and translational research needed to move the field forward.

Reasons for Low Funding

NIH has provided a number of reasons why funding has remained so low for so many years. Budgets are shrinking. Researchers are not interested in this disease. Researchers are not submitting high quality applications or asking the right questions. The science isn't ready; there is too little known about the disease to warrant targeted investment at this time.

But these reasons do not stand up to scrutiny.

First, there is the contention that the problem is shrinking budgets. Yes, NIH budgets (excluding the supplemental appropriations in 2009 and 2010 from the American Recovery and Reinvestment Act) have been relatively flat in actual dollars over the last five years or so.[694] But that does not explain NIH's failure to provide a fair share of total NIH funding that is commensurate with the significant burden of this disease and its huge economic impact on our families and our country. Shrinking budgets also do not explain why funds allocated to ME/CFS were then redirected to other diseases. Nor do shrinking budgets explain the refusal to issue targeted funding through an RFA, or why ME/CFS funding fell in absolute dollars at a time when the overall NIH budget rose so significantly. And even as NIH's overall budget flattened, some areas have still seen significant increases. As advocate Jennifer Spotila reported, the NIH spent $386 million in pain research in 2011, and reportedly spent almost $100 million more in 2012.[695] As Spotila said, the issue is not shrinking budgets, but NIH's priorities and the priorities of its institutes.

Second is the claim of a lack of interest on the part of researchers. This claim is hard to reconcile with the fact that at least six privately funded ME research foundations and centers have been created in the last few years to meet the interest in the disease and the critical need for research funds.[696] Through private funding, Stanford has been conducting a major, multidisciplinary, multi-year initiative to investigate this disease[697] and held its first conference in 2014.[698] The End ME/CFS Project is a newly formed collaboration of world-renowned leaders in such fields as immunology, genetics, neurobiology and sports fatigue;[699] they are aggressively raising private funds to reach a $5 million annual goal. A group of researchers, the OMI-Merit group, met to jointly develop a prioritized list of critical projects awaiting research funding,[700] and patients have undertaken their own fundraising efforts here and internationally to address the demand for research funding. For its part, CFSAC has repeatedly told the NIH that the problem is not a lack of interest on the part of research but the chilling effects of low research budgets and institutional barriers and bias.

Third is the NIH claim that researchers are not submitting high quality applications or asking the right questions. But the NIH has not said what it thinks the "right questions" are; it has not released its own plan nor has it collaborated with the research community to create a strategic plan that would shed light on that. Based on comments from researchers who have had grants

rejected and the choice of agenda topics in NIH's 2014 Pathways to Prevention Workshop the NIH does not appear to have the same perspective as researchers on the important research questions. For instance, Dr. Ian Lipkin, a world-renowned researcher, referred to as the "world's most celebrated virus hunter,"[701] told the audience at the Sept 2013 patient teleconference (PCOCA) held by the CDC, that he was unable to get the funds needed from the NIH to pursue needed studies into the microbiome.[702] In an interview with Mindy Kitei, Dr. Lipkin also said that he was told by one person that this is a "psychosomatic illness" and by another that "this is a herpes virus infection," so "there's no reason to look at the gut."[703] His grant submission received a poor score and was not funded. As a result, Lipkin resorted to the unusual approach of "crowdsourcing" to secure funding for his study.[704] Other seasoned researchers have reported similar challenges with getting funding for this disease that they do not experience for other diseases.

Fourth, the NIH has claimed that the science isn't ready, that the field needs to wait for a scientific breakthrough, or that there is a lack of evidence, as the NIH told CFSAC in its response to the 2014 RFA request noted above. NIH's Dr. Terrel Hoffeld, administrator for the CFS SEP, told advocate Craig Maupin the same thing in 2005; that the problems with this disease were the result of a scarcity of breakthroughs.[705] Dr. Dennis Mangan, retired chair of the NIH Trans-ME/CFS Working Group echoed this theme in a 2012 article published on CFIDS Association of America, in which he stated that a breakthrough would be required to get an increase in NIH funding and attract new researchers.[706] But at the same time, as Dr. Fletcher reported at the May 2013 CFSAC, she and Dr. Nancy Klimas, both currently at Nova Southeastern University, were told that the field is not ready for their research idea.[707]

Like the rest of the small group of ME researchers, Dr. Klimas and Dr. Fletcher are world-renowned experts and leaders in this field. Between them, they have extensively studied biomarkers and various treatment approaches, making it difficult to imagine that the field is not ready for their ideas. Klimas, Fletcher, and other experts studying this disease have demonstrated widespread dysfunctions in immunological, neurological, endocrine and energy production systems. They have demonstrated and are using biomarkers to help them diagnose ME, to recommend and monitor treatments, and to secure disability for their ME patients. They have formulated plans for clinical trials on promising, already approved drugs. The scientific opportunities litter the floor, waiting to be funded.

In its 2015 report recommending new diagnostic criteria, the Institute of Medicine provided an extensive literature review of the range of biomedical findings. But the report went on to highlight the dearth of research funding,[708] stating

> …the [IOM] committee was struck by the relative paucity of research on ME/CFS conducted to date. 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…More research is essential.

"Remarkably little research funding has been made available." It's clearly not lack of interest or the science not being ready. So why is the NIH funding so low and why have researchers had such a difficult time accessing that funding?

Continued Bias and Misunderstanding of the Nature of the Disease

One issue that has impeded the flow of funding is the misperceptions and bias against the disease, seen in both the research community at large and in the views of the NIH, as demonstrated by the

statements of key leaders over the years and through past NIH workshops.[709] There were the early statements from Dr. Straus that cast this disease as psychological, and endorsed the psychosocial model in which patients' illness beliefs and inactivity perpetuated the debility. NIH workshops, such as the previously discussed NIH workshops held in 1991 and 2000, fostered similar views.[710] Even the 2003 NIH conference on "Neuroimmune Mechanisms and Chronic Fatigue Syndrome," which discussed biomedical issues also called for a continued focus on *issues of psychological distress and altered perception*.[711] Advocate Craig Maupin noted that Dr. Debra Buchwald, the chair of the conference, supported a "perception-based model for CFS by emphasizing brain, central nervous system, neuroendocrine, and HPA axis findings common to a wide variety of psychiatric disorders that cause fatigue."[712]

Following the 2003 Neuroimmune conference, the NIH issued an RFA in 2006 for "CFS and spectrum disorders," defined by the RFA to include post-traumatic stress disorder, fibromyalgia, irritable bowel syndrome, temporomandibular disorder and chemical sensitivities among other diseases.[713] It is unclear what scientific rationale was used by the NIH to justify lumping together CFS, temporomandibular disorder and especially post-traumatic stress disorder as part of the same spectrum. When grants were awarded, five of the seven grants focused on biomedical research in CFS, while one was for pain in fibromyalgia and one was for cognitive behavioral stress management.[714]

This apparent disconnect between NIH's view of the disease and how experts view the disease is still evident today in NIH's 2014 Pathways to Prevention (P2P) Workshop and the AHRQ Evidence Review that supported it. Both the P2P Workshop agenda topics and the AHRQ Evidence Review effectively ignored broad swaths of key biomedical research. For instance, the P2P Workshop, whose goal included the identification of key gaps in research, did not include a session on post-exertional malaise, energy metabolism dysfunction, or neurological dysfunction, notable exclusions given the demonstrated importance of these impairments. At the same time, speakers chosen for a key session on fostering innovative research to advance treatments were closer to the psychosocial approach to this disease than to the kinds of innovative biomedical research being pursued by disease experts and noted in the 2015 Institute of Medicine report on this disease.

It is clear from NIH leaders like Dennis Mangan (now retired) and Dr. Harvey Alter[715] that at least some NIH leaders do not have the biases of Dr. Straus and the idea that this disease is part of a spectrum that includes post-traumatic stress disorder. Yet it is also clear that significant bias and misunderstanding still persist. For instance, as mentioned, Dr. Ian Lipkin's comment in 2014 that his recent NIH request for funding had received very poor scores, with one reviewer commenting that this disease was psychogenic.[716] Other researchers have reported similar attitudes, including Dr. Montoya who stated that some reviewers might be unwilling to approve funding because they believe it's "all in the head."[717] There can be little doubt that such bias and preconceived notions on the nature of this disease are still having a negative impact on the approval of grant requests that do not fit in with NIH's and/or the reviewer's conceptualization of the disease.

New Researchers Not Entering the Field

The second factor that has impeded the flow of research funds is that current researchers are often not submitting requests for additional NIH funding, and new researchers are not entering the field. This is a critical issue, because the NIH has made it clear that the total budget for this disease will only be increased when there are more grant applications.[718]

As recently as November 2011, NIH staff told CFSAC that no new researchers had entered the field in the previous two years. Just as importantly, once approved the first time, investigators were tending not to come back a second time.[719] Further, as reported by advocate Jennifer Spotila, Dr. Susan Maier, chair of the NIH ME/CFS Working Group, told CFSAC in October 2012 that 18 percent of funding requests were funded in 2012.[720] Spotila pointed out, an 18 percent approval rate would have translated to only about 20 to 22 applications being submitted, a very small number of applications for such a complex disease, and far too few to make forward progress.

Why would new and existing researchers not submit grant requests? At the 2007 CFSAC meeting, Dr. Ronald Glaser stated that the "word was out" that it was hard to get funding for this disease, a fact that could discourage researchers from even entering the field.[721] Other researchers have said that their colleagues warned them not to enter the field because it would kill their careers. When Dr. Jose Montoya, ME clinician and researcher at Stanford University, told his mentor in 2005 that he wanted to research this disease, his mentor predicted that doing so would leave him homeless.[722] Presenters at the 2011 NIH State of Knowledge Workshop reported on "the stigma of ME/CFS research on faculty at academic institutions."[723] The combination of stigma and a lack of funding have forced some researchers to leave the field, while others never joined to begin with.

This dearth of researchers obviously has a direct effect on the breadth of research being conducted into this disease. The ability to retain existing researchers and attract new researchers is critical for any complex, multi-system disease, where a broad range of investigative expertise and approaches is required to understand the disease pathology. It's especially critical when the NIH uses the number of grants to throttle the level of funding. But in the case of ME, the inability to attract new researchers to the field will soon become a crisis because so many of the current ME researchers and researcher-clinicians are approaching retirement age, at which point their hard-won knowledge and expertise will be irretrievably lost.

To be fair, the NIH appears to be equally frustrated by the situation. At the May 2013 CFSAC meeting, Dr. Maier begged CFSAC members to go out and find people who would submit grants to the NIH and personally promised to help them.[724] But CFSAC members are not in a position to achieve this kind of systemic change without committed institutional support from the NIH in the form of the issuance of RFAs, a fair and adequate level of funding, and the removal of the institutional barriers and bias. And researchers and their academic institutions are unlikely to pursue the study of a disease that has been so stigmatized and neglected by HHS and the medical community at large.

Scientific Review Process for Grants and the Special Emphasis Panel (SEP)

The third factor affecting the ability of researchers to access research funds is the nature of the scientific review process used to review and approve grants. According to the NIH website, the first level of review is conducted by a scientific review group of non-governmental scientists with expertise in the given research area. The second level of review is conducted by the Advisory Councils or Boards of the Institutes and Centers that might fund a given initiative. These groups also include non-governmental representatives chosen for their expertise. To receive a grant, applications need to be recommended for funding by both the first level and the second level review groups, but the directors of the Institutes and Centers make the final funding decisions.[725]

If the disease has a significant number of researchers and grant applications, a permanent or standing study section performs the first level of application review. However, for this disease, the first level of review is handled primarily by an ad hoc (temporary) group called a Special Emphasis

Panel (SEP). The CFS SEP is established anew for each review cycle, based on the expertise needed for the types of applications that have been submitted.[726] The NIH has said that it is not possible to have a standing committee specifically for this disease because only 6-18 applications are submitted per study section, not enough to warrant a standing committee.[727] While the CFS SEP handles most ME/CFS grant requests, grant requests can occasionally be reviewed by one of the standing review committees.

Organizationally, each SEP resides in an Integrated Review Group (IRG), which consists of a cluster of study sections and SEPs that are organized around a general science area. The CFS SEP had been located in the Musculoskeletal, Oral, and Skin Sciences (MOSS) IRG but was then moved to the Integrative, Functional, and Cognitive Neuroscience (IFCN) IRG in about 2010. This author is unaware of the reason for this change or its impact on SEP composition and receptiveness to grants.

In addition to the CFS SEP being an ad hoc committee, the CFS SEP has historically covered not only CFS but also fibromyalgia and what the NIH had labeled "other chronic polysystemic morbidity syndromes,"[728] which also included at least temporomandibular disorder. As advocate Craig Maupin noted in a 2005 article on the NIH and the CFS SEP, the term "chronic polysystemic morbidity syndromes" has had little usage outside of NIH's CFS SEP.[729] NIH's Dr. Terrel Hoffeld (the administrator for the CFS SEP at the time) told Maupin that these different entities had been integrated together into one SEP because there were similarities across them, and each was a syndrome, not a disease. According to Maupin, "For Hoffeld and NIH officials, viewing CFS as one of many related conditions is a key to scientific success." But what kinds of similarities were they focused on? Maupin's concern was that NIH's decision to integrate "controversial and emerging women's illnesses" into one SEP would result in "reviewers who espouse[d] the same 'perception-based' psychiatric theories across these syndromes."

It's important to note that while the NIH was focused on "CFS and spectrum disorders" in the 2006 RFA and "chronic polysystemic morbidity syndromes" in the CFS SEP, the CDC was focusing on chronic unwellness and establishing the broadened Empirical definition during this same time period. This level of misalignment on the conceptualization of the disease between the CDC and the NIH is striking and calls into question not only the scientific rational that each agency used to justify these groupings, but also how the CDC and the NIH intended to integrate research across such fundamentally different ways of characterizing the scope and nature of the disease.

Aside from the bias that such a "chronic polysystemic morbidity syndromes" approach would engender, the combination of the SEP being ad hoc and the SEP's encompassing disparate diseases meant that some grants approved under the CFS budget had nothing to do with this disease, a point demonstrated by both Pat Fero and Kim McCleary. But it also meant that those reviewing grant requests for this disease were more likely to not have expertise in this disease.

Both advocates and CFSAC have raised this issue of inadequate SEP member expertise. In a review of the 2004 SEP members, Craig Maupin found that of 30-40 different reviewers, only six demonstrated some interest in CFS and only three were predominantly focused on CFS. Further, of those 6, three were focused on behavioral issues.[730] Dr. Ronald Glaser raised similar issues at a CFSAC in November 2007, when he reported that over the previous three years, only 15 percent of the members of the Special Emphasis Panel had ever worked on anything related to this disease. He emphasized that the field wasn't moving forward "because of the nature of the study sections."[731] Similarly, in 2008, CFSAC member Dr. Hartz raised a concern with the apparently large number of dentists reviewing CFS grants. Dr. Hanna, of NIH's Office of Research on Women's

Health, responded that some dentists were experts in pain.[732] ME patients may experience significant pain. But pain is not the core of this disease and a focus on pain is unlikely to lead to disease modifying treatments.

Researchers have run into other challenges in getting a grant request approved by the SEP. At the November 2011 CFSAC, Dr. Jason described the issue that researchers face in responding to reviewer requests to revise a grant request. Because of the ad hoc nature of the SEP, the panel members that request a change to a grant application are not the same as the panel members that review those changes once made.[733] The new panel member likely lacks context for the original concerns, and may have different issues that they want to see addressed instead. This issue is not unique to this disease. Dr. Cheryl Kitt of NIH's Center for Scientific Review, told CFSAC members at this meeting that there were about one thousand SEPs. However, such a change in panel membership could be particularly challenging for this disease because of the widespread bias and misperceptions around the nature of this disease.

One way of judging whether there is an issue with NIH's overall review process is the rate of approval of submitted grant requests. It is difficult to get definitive estimates on this because of the confidentiality of the process. At the May 2013 CFSAC, Dr. Fletcher stated that she had been told that the overall level of approval of grants for this disease was around six percent,[734] a rate similar to the seven percent that advocate Pat Fero found in her FOIA-driven analysis of NIH spend between 2000 and 2009.[735] But Dr. Susan Maier told the October 2012 CFS Advisory Committee meeting that 18 percent of funding requests were funded in 2012.[736] But what is more important is the number of grant applications because the NIH has stated that the research budget allocated by the NIH will not increase until more researchers apply.

Since 2011, the CFS SEP was changed to focus on ME/CFS instead of the "chronic polysystemic morbidity syndromes" focus seen in earlier CFS SEPs. Likely as a result, it appears that the practice of approving grants for other diseases under the CFS budget has decreased significantly, although in 2013, the practice still existed to some extent with two grants totaling $161K.[737] There are also indications that the SEPs contain more disease experts than they have in the past, although it is difficult to verify that because the NIH no longer publishes the SEP roster for this disease (it does for other diseases).[738]

But given the issues reported above by Dr. Lipkin and Dr. Fletcher, the SEP grant review process still appears to suffer from a level of bias and misunderstanding that is significant enough to impede access to research funds. And more importantly, regardless of what the SEP decides, the final funding decisions are made by the institutes.

Funding Challenges and NIH's Institute Structure

The fourth factor that affects the ability of researchers to access NIH research funds is the challenge of getting the attention and priority of the NIH institutes and centers that fund all research. This is particularly challenging when the disease is not "owned" by one of the institutes.

Kris Newby, communications manager for the Stanford Center for Clinical and Translational Research and Education, spoke to this point in a 2014 article on the work of Dr. Montoya at Stanford, in which she stated, "The NIH funding process favors well-defined diseases that fit neatly into medical specialties." She went on to note that these medical societies often have lobbying efforts to advance their needs.[739]

As it stands today, this disease does not have a home within one of the medical specialties, or within NIH's research institutes and centers, which are typically organized around a medical specialty like neurology, or around a special focus area like environmental health science or minority health. CFS was originally located in the National Institute of Allergy and Infectious Diseases (NIAID), but then was moved to NIH's Office of the Director in 1999, and then to the Office of Research on Women's Health (ORWH) in 2001. The stated reason for these moves was to help foster collaboration across institutes and also across agencies.[740] To achieve that collaboration, the NIH established the Trans-NIH CFS (ME/CFS) Working Group, lead by the Office of Research on Women's Health.[741] The Trans-NIH ME/CFS Working Group is responsible for "convening meetings of the working group, coordinating communications about ME/CFS, and sharing information about NIH ME/CFS research and activities within the NIH, among other HHS agencies, and to the broader extramural research and advocate communities."[742] In a 2005 discussion with Craig Maupin, NIH's Dr. Hanna stated that the "Trans-NIH Workgroup members act as liaisons for CFS within their individual institutes, petitioning their institutes for funds for requests for [RFAs], centers, or other collaborative projects."[743]

But the ability of the Trans-NIH ME/CFS Working Group to progress the needs of this disease is limited. Neither the Trans-NIH ME/CFS Working Group nor ORWH have budget for research in this disease. Ultimately, the authority for final funding decisions rests with the NIH institutes and Centers and the decisions to fund grant requests are made in the context of the needs and goals of the individual institute or center. The 2000 GAO report emphasized this point, stating that the purpose of the second level of the scientific review process for grant approval is to "evaluate applications in relation to the needs of the institute or center and the priorities of its director." As a result, the council may vote to change the first level review recommendations made by the SEP.[744] But the obvious problem is that ME has not been a priority for any institute. At best, with the possible exception of the National Institute of Neurological Disorders and Stroke, the institutes and centers appear to be interested in only a narrow aspect of ME as it relates to the goals of that particular institute or center.

It is helpful to look at a specific funding announcement to see how this might impact researchers submitting a grant request for this disease. One of the current funding announcements listed on the Trans-NIH ME/CFS website is to explore the etiology, diagnosis, pathophysiology, and treatment of ME/CFS.[745] The funding announcement lists the particular priority or interest of each of the institutes, offices, and centers that are participating in the funding opportunity. In this case, the Institute of Nursing Research (NINR) is specifically interested in research to define the relationship between behavioral interventions and biological outcomes. Between 2010 and 2013, about 40 percent of the NIH grants funded by NINR were focused directly on behavioral interventions. The National Institute of Diabetes and Digestive and Kidney Diseases stated an interest in investigating potential relationships between ME/CFS and urologic chronic pelvic pain syndromes, including Interstitial Cystitis/Painful Bladder Syndrome (IC/PBS) and Chronic Prostatitis/Chronic Pelvic Pain Syndrome (CP/CPPS). Of the $486K funded between 2010 and 2013, 68 percent was spent on a study examining "Pain and Sensory Processing in IC/PBS and Fibromyalgia" The remainder was spent on "Neural mechanism of glucagon-like-peptide-1 receptor-mediated nausea /malaise."[746] Neither of these grants studied CFS, let alone ME.

The National Institute of Allergy and Infectious Diseases (NIAID) did not indicate a specific area of interest, but stated that requests for funding for clinical trials had to be submitted to what appears to be an institute specific process. Of all the institutes, the listing of priorities provided by the National Institute of Neurological Disorders and Stroke (NINDS) is centered the most directly on this disease in its call for research "directed at the pathogenesis of ME/CFS affecting the brain,

autonomic, and the peripheral nervous system." Yet, ME/CFS is not listed in an A-Z listing of diseases on the NINDS website, calling into question where this disease falls in the priorities of that institute.

Why are these descriptions of interest by the NIH institutes in the funding announcements important? They demonstrate the gulf that exists between ME as a disease on the one hand and the core priorities of the NIH institutes that fund all research on the other. This gulf could readily account for a considerable portion of the challenges that have impeded access to research funds, and limited the ability to progress research. It also demonstrates the fractured interface with the NIH that researchers have to navigate to progress research, particularly clinical trials for treatments for this disease. It's hard to imagine how an effective, coordinated, fully-funded, cross-institute strategy could ever be cobbled together from such narrow slices of interest and such a fractured interface. The result is that of the $5.3 million spent in 2014, the National Institute of Allergy and Infectious Diseases granted a total of $2.1 million, the National Institute of Neurological Disorders and Stroke granted $1.9 million, and three other institutes spent much less.

Getting the attention of the institutes is not unique to this disease. As reported by advocate Craig Maupin in 2005, Kim McCleary has stated that advocacy leaders across various multi-system diseases have long recognized "the challenges of funding multi-systemic illnesses within the NIH's segmented structure."[747] Notably, many of these other leaders have reported hearing the same things that the ME community has heard: "We don't believe in this condition," "This is simply not a priority for our institute," and "We don't get enough good fundable applications."

A more recent and much more visible example of the challenges with navigating across NIH's institute structure is the Human Microbiome Project, a $173 million, five-year long study conducted under the auspices of the National Human Genome Research Institute (NHGRI). In a July 2013 Nature article, journalist Beth Mole reported that with the first phase completed, the "home" for the Microbiome Project was changing and future funding would be "scattered" across 16 of the 27 NIH institutes. But microbiome researchers raised concerns that progress will falter unless there is a base that continues to provide basic resources (including money and technical expertise), promulgates standards, and further nurtures the basic science. In spite of the likely widespread, cross-institute interest in microbiome research, this concern is well-founded, given the experience of ME and CFS in cobbling together a cross-institute strategy and funding plan.

As with ME/CFS, the NIH often uses such trans-NIH workgroups, committees, and other similar groups to foster collaboration across institutes and centers. Of the 181 such groups that existed as of October 2014,[748] three-quarters were focused on crosscutting issues like common disease processes, broadly applicable scientific technology, information management needs or common practices and processes. Only about 40 of the 181 were focused on disease-specific issues and some of these were focused on just a narrow aspect of the specific disease. But what is particularly notable is that of all the disease-specific trans-NIH workgroups and committees, it appears that the only one not headed by one or more institutes or centers is the Trans-NIH ME/CFS Working Group, headed by NIH's Office of Research on Women's Health, leaving this disease poorly positioned to compete in NIH's Institute- and Center- driven structure.

Given the lack of progress since the Trans-NIH ME/CFS Working Group was instituted, it's critical to ask whether this approach is working. The answer is clear. For myalgic encephalomyelitis, positioning this disease in the NIH's Office of Research on Women's Health and attempting to use the Trans-NIH ME/CFS Working Group to coordinate across the NIH has failed to achieve the needed outcomes for patients. In November of 2011, Dr. Klimas highlighted this issue in a CFSAC

discussion with NIH's Dr. Cheryl Kitt, Deputy Director of the Center for Scientific Review, stating, "Using an interagency coordinating committee to try to patch together the funding has dramatically limited access to program projects and center grants. That must be tackled head on. It has been a recurrent theme. We have mentioned it many, many, many times."[749]

And yet, four years after that discussion, the problem remains.

Groundhog Day

In the movie, *Groundhog Day*, an arrogant, self-centered weatherman, played by Bill Murray, is doomed to repeat the same day over and over again, until he finally learns that his actions and behaviors are keeping him stuck in a time loop. Watching exchanges between CFSAC and the NIH and reading CFSAC minutes is like watching a time loop, helpless to make it stop.

In the case of NIH funding, the time loop looks like this. As noted above, the NIH has said that funding will not increase, unless there are more funding requests submitted.[750] That would require that new researchers enter the field. But as often pointed out at a CFSAC meeting in 2008, researchers are discouraged from entering the field because of the difficulty of getting funding approved, and the potentially negative impact on their careers due to institutional bias. According to CFSAC member Dr. Ronald Glaser, the review process, the SEP, and the hurdles in the review process are "just out of line with a fair review process."[751]

At that 2008 CFSAC meeting, Dr. Jason also recommended that the NIH issue an RFA (Request for Application) as a mechanism to attract researchers. Dr. Jason's rationale[752] was that an RFA would be a more effective mechanism to attract new researchers because it would have set-aside funding. NIH's more usual R01 funding grants[753] did not have set aside funding and had failed to expand the pool of researchers. As evidence of the RFA's ability to incentivize researchers, Jason pointed out that 29 grant applications had been submitted following the 2006 RFA. Dr. Hanna of the NIH responded to Jason's recommendation that the NIH would be holding a meeting in two years that could lead to an RFA. But she went on to state that it was up to the "organizations" (which she left unspecified) to encourage their members to go after the available funding opportunities. But as Dr. Glaser had just noted, researchers were not applying because of the barriers to getting funding. As further evidence of this problem, Dr. Klimas pointed out a 2011 CFSAC meeting that the CFIDS Association of America had received 24 applications for a small $648K 2008 grant opportunity[754] and urged the NIH to examine what is wrong when a small foundation such as the CFIDS Association of America can get a bigger response than the NIH.[755]

CFSAC has made repeated requests to increase funding and has specifically recommended an RFA, most recently in 2012 and in 2014.[756] Further, in 2014, both IACFS/ME[757] and a group of congressional leaders, spearheaded by Representatives Lofgren and Eshoo,[758] sent letters directly to Dr. Francis Collins, director of the NIH, each requesting an RFA in the amount of $7-10 million. The IACFS/ME letter called for that amount annually for five years.

HHS's response has been non-germane to the recommendation and has resorted to the claim that not enough is known yet. In HHS's response to the 2012 CFSAC recommendation, it never specifically mentioned the RFA recommendation.[759] Instead, HHS provided an explanation of its grant process and a list of existing R01 funding announcements. Similarly, Dr. Collins did not address Lofgren's and Eshoo's specific request for an RFA when he responded to them but instead

just referenced the more general funding opportunities that had already failed to result in increased funding.[760]

When HHS rejected the 2014 CFSAC recommendation for an RFA, they did so more directly, stating that "there remains a lack of definitive evidence regarding the etiology, diagnosis, and treatment" of this disease.[761] HHS went on to state that an RFA would not be an effective strategy and that "RFAs are designed to build upon recommendations that have been identified through cutting-edge research findings in the extant literature, that address unmet NIH Institute mission-specific objectives, or that incorporate findings from workshops and conferences on specific topics." As with the 2012 rejection and the rejection of Lofgren's request, the NIH pointed CFSAC to the existing R01s, the same funding mechanisms that had failed to overcome the bias, misperception, and institute-driven organizational issues that have held this disease hostage for years. Finally, the NIH acknowledged the lack of researchers and proposed to address that through training and career development awards to "demonstrate commitment to *training the future generation* of ME/CFS researchers." But meanwhile, the *current* generation of ME researchers—and more tragically, the current generation of ME patients—is left blowing in the wind.

This is a stunning rejection of repeated CFSAC requests for research funding, given the congressional support and the caliber of science being published and the research needs identified at both the NIH State of Knowledge Workshop in 2011 and the three separate ME conferences held in 2014, the Stanford ME/CFS conference, the IACFS/ME conference and the Invest in ME conference.[762] These research needs have since been extensively documented by the 2015 Institute of Medicine Report, which blunt in its findings that there was a "paucity of research" and "remarkably little research funding," particularly given the number of people affected.[763] It remains to be seen how the NIH will respond to the Institute of Medicine report's findings.

And what happened to that meeting that NIH's Dr. Hanna had told the 2008 CFSAC meeting that the NIH was going to hold in two years? [764] The one that she suggested could lead to an RFA? The NIH did hold a meeting three years later: the 2011 State of Knowledge Workshop.[765] But the NIH never issued an RFA after that meeting and has not done so since, seven years after Dr. Hanna's suggestion.

Similar years-long "groundhog day" discussions between CFSAC and the NIH have occurred on a number of topics, but these never seem to get resolved. For instance, in an extensive 2011 CFSAC discussion with NIH leaders, Klimas highlighted the specific problems associated with getting funding for clinical trials, a critical issue for this field because of the state of research. She asked for NIH help to resolve that issue. Yet, this problem does not appear to have been addressed. In a 2015 webinar, Dr. Klimas said that she had presented a proposal for a phase 1 trial that had been rejected six times over five years. The rationale for the study was based on a solid system biology analysis that showed the importance of a specific inflammatory cytokine. An FDA-approved drug already exists for this particular cytokine and is being used in rheumatoid arthritis patients. Yet it was rejected. She has been unable to get this proposal approved because the reviewers do not believe "that the illness is serious enough to use drugs that you would use in rheumatoid arthritis."[766]

At the November 2011 CFSAC meeting, Dr. Klimas also suggested that the NIH consider the approaches it has used elsewhere to jump-start a field. One example she gave was in the field of geriatrics, in which NIH's "Center on Aging went from a 'sketch' area of doing science to one of the most predominant and well-respected areas of doing science."[767] According to Dr. Klimas, this transformation was achieved "mainly because the NIH made a full-court press effort to draw in

people from other fields." Dr. Janine Clayton of the Office of Research on Women's Health (ORWH) at the NIH acknowledged the concerns that Dr. Klimas had raised, including those with getting funding for clinical trials, and committed to take these issues back to the NIH.

Four years later, nothing has changed.

Groundhog Day. Stuck in a time loop that is a product of institutional bureaucracy, arrogance, isolation, cognitive biases, and the utter refusal to listen to what disease experts and patients have been saying for decades. As Dr. Jason asked the NIH at the 2008 CFSAC, "Given the enormity of the issues that we're faced with, how do we get more grants submitted and funded? If this were another field such as HIV/AIDS, this would not be acceptable."[768]

In the case of Groundhog Day, it's Bill Murray who suffered the consequences that resulted from his arrogance and egocentrism. Tragically, in the case of ME, it is the patients that have paid the ultimate price for NIH's refusal to act.

The Impact of Patient Selection and Study Design on Research

Lack of funding and institutional barriers are not the only issues impeding research. NIH's own 2011 State of Knowledge Workshop pointedly noted, "If the rules for identifying who is a patient and who is not differ, then problems will occur, not only for a patient seeking an accurate diagnosis, but for the entire scientific enterprise."[769] The February 2015 Institute of Medicine reinforced this point, stating, "The operational ambiguity has important consequences for research in ME/CFS, as different studies operationalize the criteria in different ways, limiting comparisons across studies.

Having different case definitions also has resulted in diagnostic unreliability and confusion for clinicians, patients, and their families."[770] As discussed throughout this paper, the impact of the case definition and patient selection issues on the research "scientific enterprise" has been devastating.

Yet, as of January 2015, the NIH has rejected the experts' recommendation to adopt the Canadian Consensus Criteria as the single case definition for research and has not announced plans to establish an alternative. HHS has said that the P2P effort could form the basis of an initiative at some unspecified future date to establish a research case definition.[771] But as drafted, the P2P report and the supporting AHRQ Evidence Review contribute little to this fundamental issue because they continue to confound all the CFS and ME definitions and ignore much of the biomedical research. The NIH could recommend that the IOM clinical definition be used in research but it's unknown how that compares to the CCC. Further, the IOM criteria, as currently defined, are subjective and not sufficiently operationalized to ensure diagnostic reliability.[772]

In addition to research case definition, the other key issue is that of study design, a topic which Dr. Peter Rowe, a clinician at John Hopkins who specializes in pediatric ME, discussed at FDA's April 2013 Scientific Drug Development Workshop.[773] Of all the ME study design issues, Rowe pointed out that the most fundamental issue is the choice of which patients to include in the study, based on factors such as type of onset, genetics, blood levels of various markers, severity, duration of illness, types of comorbidities, concomitant medications, and even a patient's history of unsuccessful treatments.[774] The study design must also account for day-to-day fluctuations of the disease and the post-exertional exacerbation of symptoms, both of which complicate the assessment of efficacy and safety. If not managed carefully, such factors can result in uninterpretable results and/or swamp the efficacy signal in any study. These problems are

inherent in the study of ME because of its complexity, but are especially problematic in the small studies that ME researchers have been able to afford to date.

Further, at the same meeting, Dr. Chris Snell pointed out that researching a complex, multi-system disease like ME requires the combined expertise of varied specialties, a fact that creates a major economic and coordination challenge.[775] Such challenges with study design and cross-specialty coordination are not going to be achieved with the current annual NIH budget of $5 million or by using the Trans-NIH ME/CFS Working Group to coordinate across disinterested NIH institutes. Making progress on this disease is going to require a dramatic increase in funding and a new model of coordination and collaboration, the kind of serious private-public partnership that the Tufts report on *Academic-Industry Partnerships for Biopharmaceutical Research & Development* described.[776] To date, the NIH has failed to provide both the public funding and the leadership required to spur such partnerships.

NIH's Strategic Intent for This Disease

Lack of a Strategic Plan for This Disease

Given the magnitude of disease burden and the complexity of ME, with its multi-system, cross-institute reach, you would expect that the NIH would have a well-articulated strategic plan for research. Such a plan would have been developed collaboratively with stakeholders and would be organized around the key research questions that need to be addressed. It would have clearly defined, time-bound objectives to ensure focus, alignment, and coordination of scarce resources to make forward progress. It would provide the benchmarks to monitor progress. And it would be broadly communicated and readily accessible by all stakeholders.

Such plans do exist for other diseases. For instance, there is a national plan for Alzheimer's disease that includes defined goals and research milestones.[777] In 2014, legislation was passed in the U.S. House of Representatives to establish a research plan and scientific framework for vector-borne diseases, including Lyme disease.[778] A cross-NIH Action Plan for Muscular Dystrophies, approved in December 2005, outlines specific research objectives, thus providing a focus for coordination of research.[779] And there are national plans for other diseases, such as Autism. But to my knowledge, the NIH has never developed a strategy for this disease, at least not one developed collaboratively with key stakeholders and shared publicly.

The NIH has held a number of workshops[780] between 1985 and the 2014 Pathways to Prevention Workshop. According to Dr. Charles Wells of NIH's Office of Research on Women's Health, the 2011 State of Knowledge Workshop had identified a number of research gaps, including "weak study designs, unknown etiology, lack of validated biomarkers, lack of case definition and diagnosis, more genetic studies needed, more experts needed in the new discipline of synthetic biology, more of a system biology approach needed, symptomatic treatment, and paucity of investigators."[781] The 2011 NIH State of Knowledge Workshop report even highlighted specific biomarkers that needed to be validated, including natural killer cell function and specific cytokines.[782] Many of these same needs had been repeatedly highlighted by CFSAC, in other scientific conferences and in the literature.

At the October 2012 CFSAC, Dr. Susan Maier, chair of NIH's Trans-NIH ME/CFS Working Group, told CFSAC that, as a result of the 2011 State of Knowledge Workshop, the NIH had developed a "prioritized plan for implementing ME/CFS research" and that plan was being implemented.[783]

Based on the information provided to CFSAC, the plan appeared to be tactical, process-oriented, and/or focused on initiatives organized around a common symptom like pain. For instance, the list of accomplishments provided for the Trans-NIH ME/CFS Working Group included NIH-wide initiatives such as the 2012 Chronic Overlapping Pain Conditions Workshop, the creation of the MAPP initiative for the study of chronic pelvic pain, and a "research training course on fatigue and sleep." But as NIH's Dr. Eleanor Hanna had cautioned CFSAC in October 2010, in an initiative like MAPP, "the diseases get 'lumped in together' with pain as the only organizing factor."[784] Such initiatives do not target the core neurological, immunological, or energy production dysfunction in this disease and are unlikely to unravel the core disease or produce disease-modifying treatments. Like the parochial interests expressed by the NIH institutes in the ME/CFS funding announcements, such a narrow lens is not a substitute for a disease-specific, cross-institute strategy.

In reality, though, it is not possible to know exactly what is included in NIH's plan, because the NIH has not publicly shared their plan. In a personal email exchange in December 2012, NIH's Dr. Maier said that one of the plan's first priorities was to conduct an evidence review of "definitions and outcomes" (the 2014 AHRQ Evidence Review and the 2014 P2P Workshop).[785] But beyond that, Maier said that the prioritized plan could not be shared "because it is an internal, dynamic working document open to changes in light of new discovery." Of course the plan will change. All plans change. But how are key stakeholders—patients and disease experts—to assess the plan, to provide input, or to monitor the progress being made if the plan is secret? Just as importantly, patients and researchers alike are left to guess what the NIH thinks is important. This is particularly frustrating because the NIH has said that researchers are not asking "the right question" and/or proposing research for which the field is not ready.

Failure to Follow-up on Key Research Questions

The impact of the lack of a publicly shared research strategy can be seen in the decades-long failure to make progress on the most fundamental research questions and needs.

There is probably no more fundamental research need than that for a validated biomarker. One potential biomarker is the finding of natural killer cell (NK) function. This finding has been reported a number of times over the years, including in a 1987 paper by Dr. M. Caligiuri,[786] a 1990 paper by Dr. Nancy Klimas,[787] and a 2013 paper by Dr. Ekua Brenu of Griffith University in Australia.[788] It was reported at the 2011 State of Knowledge Workshop and also in the mainstream press. CFSAC has discussed the use of natural killer cell activity as a diagnostic marker that could be used, if not alone at least in conjunction with other signs and symptoms, to help diagnose this disease. Both the IACFS/ME Primer and the *Myalgic Encephalomyelitis - Adult and Pediatric: International Consensus Primer for Medical Practitioners* discuss decreased natural killer cell activity as a marker for this disease. Experts use it in their practice. Yet, natural killer cell function is still not validated or officially endorsed as a diagnostic tool for this disease, although the 2015 Institute of Medicine report has acknowledged its value in supporting a diagnosis.[789]

A second biomarker example is the use of cardiopulmonary exercise testing (CPET). A number of medical societies consider CPET to be the gold standard for testing functional capacity, including the American College of Cardiology, the American Heart Association, and the American Medical Association. CPET is used in a number of disease areas to assess functional capacity.[790] According to Dr. Chris Snell, a search of Clinicaltrials.gov (a repository of clinical trials being conducted) shows CPET referenced in over 400 clinical trials, across a range of diseases.[791] In some of those trials, measures from CPET are used as a primary outcome measure. Snell's use of CPET to assess

ME's energy metabolism dysfunction has been replicated by a number of other researchers,[792] and a number of ME clinicians use CPET in disability evaluations, which the Social Security Administration accepts as proof of functional impairment. In my son's case, the judge who finally approved his application for disability called out CPET as a deciding factor. In addition to its use in disability evaluation, researchers have shown that CPET can distinguish ME patients from those with depression, deconditioning, and a number of chronic illnesses[793] As with some diagnostic tools used in other diseases, CPET would need to be used with caution and would not be appropriate for severely ill ME patients. But it has significant potential that, like natural killer cell function, has not been translated into an accepted diagnostic tool. Like natural killer cell, the IOM report acknowledged both the utility of this tool and the caution for its use in severely ill patients.

Given the strategic importance of establishing a biomarker, the obvious question is why the NIH has not more aggressively used its funding mechanisms and influence to collaborate with researchers to resolve this issue.

NIH has squandered other opportunities to advance the field. For instance, as a product of his XMRV study, Dr. Ian Lipkin, of Columbia University, established a biobank of 147 well-characterized patients and 146 matched controls. Patients had to meet *both* the Fukuda and Canadian definitions, had to meet well-defined exclusion criteria, and had to have a viral-like onset consistent with an infectious disease.[794] Because of the rigor of characterization, these samples have strategic value for their potential to advance key research questions like biomarkers. As discussed in an interview with Dr. Vincent Racaniello in 2012, Lipkin stated that funds would be set aside to study these samples. Further, in the 2014 U.S. Senate appropriations report, congressional leaders stated that these samples could "help speed diagnostics and a better understanding of the pathophysiology of this severely disabling condition" and specifically requested "a special funding opportunity to spur research into ME/CFS."[795] But the NIH did not set aside funds for these samples. Further, in a personal email, NIH staff stated that the samples would be distributed on a first-come, first-served basis.[796] How much opportunity has been wasted by not issuing an RFA for these samples and by not using a more strategic approach in deciding how these samples were consumed?

The point here is not the disposition of one particular set of samples or the failure to push for the validation of one particular biomarker. Rather, these examples demonstrate a pattern of behavior that appears to be unfocused, uncommitted, and ultimately misguided. Meandering at best.

Closing of Cooperative Research Centers

Another lost opportunity was in the decision to close the cross-disciplinary ME/CFS Cooperative Research centers.

As reported in the 2000 GAO report, the National Institute of Allergy and Infectious Diseases (NIAID) had sponsored Cooperative Research Centers, beginning in 1991, to "augment the existing grant program and to provide a sustained multidisciplinary approach" to research.[797] The intent of these centers was to "advance the field by bridging the basic science and clinical research arenas." The research centers pursued "coordinated projects in the fields of immunology, virology, medicine, and clinical epidemiology." According to a 1999 NIAID press release, the first-year cost for three centers at that time was $1.9 million,[798] not a large amount of money by NIH standards. But by at least 2003, NIAID decided to withdraw funding for these centers, according to comments made by NIH's Dr. Eleanor Hanna at the September 2003 CFSAC.[799] According to advocate Craig Maupin of CFIDS Report, Hanna stated that the research centers were expensive and there was "not enough commitment from individual institutes to fund new centers."[800]

As Dr. Snell highlighted at the 2013 FDA Scientific Drug Development Meeting, cross-disciplinary research, of the kind that the collaborative research centers could have provided, is essential to unraveling this disease. In a 2014 article by Kris Newby of Stanford University, Dr. Jose Montoya emphasized this point as well in a discussion of a privately funded study whereby "experts in immunology, rheumatology, genetics, bioengineering, anesthesiology, neuroradiology, cardiology, psychiatry, infectious diseases and bioinformatics [worked] together," using a variety of tools and technologies to look for underlying abnormalities across systems.[801] The strength and success of this approach was apparent at the 2014 Stanford conference[802] and in Stanford's recent publication of a study showing brain abnormalities.[803]

But as Newby pointed out, NIH funding is not traditionally awarded in this way. The article noted, "NIH funding is awarded through medical specialty groups that tend to favor research that tests one narrow hypothesis about a disease," an approach that is slow and can take years to "build on discoveries." This is an obvious problem for any complex, multi-system disease where such integration is essential. But it's particularly challenging when that multi-system disease exists in the shadowy world outside of the circle of interest of medical specialties and NIH institutes.

Recognizing the importance of a cross-discipline approach, CFSAC has recommended the reestablishment of centers of excellence on eight occasions since 2004 and is currently developing another recommendation to establish such centers.[804] NIH's Pathways to Prevention draft report has also recommended the establishment of "a network of collaborative centers working across institutions and disciplines."[805] But to date, the NIH has not reinstituted the collaborative research centers, leaving it up to private funders, such as those behind the Stanford initiative, to progress this critical need.

Summary

The most obvious and frequently noted problems with how the NIH has tackled this disease is its failure to provide a fair share of funding and address the case definition issues. Both of these must be addressed immediately as they are impeding the entire scientific enterprise.

But these are just the most visible manifestations of two bigger problems: how complex, multi-system diseases are researched and what happens to contested diseases, particularly when that disease is orphaned outside of the medical societies, the NIH institutes, and the academic centers that drive biomedical research and delivery of medical care in this country.

Private funders and disabled, stigmatized patients can not solve these problem and the Trans-NIH ME/CFS Working Group is not capable of making up for the lack of commitment on the part of the institutes. Kick-starting the ME research pipeline is going to require that the NIH exercise significant political will to address the scientific, institutional, and bureaucratic issues and biases that have imprisoned ME since 1985. The NIH must provide a share of funding that is commensurate with the burden of disease. The NIH must make a significant, strategic, fully funded, cross-institute commitment, done in true collaboration with the ME community, to finally address this complex, chronic disease.

Until that happens, the rest of the scientific enterprise, particularly the development of disease-modifying drugs and the provisioning of appropriate medical care, is not going to stay stalled, leaving patients to suffer for decades more.

Drug Development

Under the best of circumstances, drug development is expensive and risky. According to the 2014 Biopharmaceutical Research Industry Profile, one approved drug may require the screening of tens of thousands of compounds and take ten to fifteen years. Even once a compound reaches clinical trials, only 16 percent will be approved.[806] Further, as of 2007, the cost of one approved drug was estimated to be $1.2 billion, counting the cost of failures, a cost that is undoubtedly higher today. Adding to that cost and to the overall risk are more recent factors that include a longer, more demanding regulatory environment and the uncertainty of whether the payers (e.g. insurance companies) will pay for the drug once it is approved.

Given the range of issues that have plagued this disease, particularly the definitional problems and the lack of basic research, validated diagnostics, and clinical outcome measures, it is not surprising that virtually no pharmaceutical company has chosen to invest in this disease. Only one company, a small biotech called Hemispherx, has had a sustained focus in drug development. It's drug, Ampligen, is the only investigational drug to have been reviewed for drug approval by FDA. Ultimately, in spite of an outpouring of patient support, the committee and FDA rejected the drug out of a concern that efficacy had not been adequately demonstrated. This decision left an estimated one million patients without any approved treatment.

But what the Ampligen history and experience did was lay bare the insurmountable challenges faced in trying to progress the development of any drug for this disease, particularly because of issues regarding definition, outcome measures, funding, and stigma discussed throughout this paper.

History of ME and CFS at the FDA

Prior to 2011, applications for product development for this disease had been assigned to at least six different review divisions within the Office of New Drugs (OND), reportedly on the basis of the proposed mechanism of action of the drug.[807] Across these divisions, various endpoints had been used to assess the efficacy (effectiveness) of treatment. As seen with the medical societies and the NIH institutes, this was a disease with no home at FDA, complicating the development of new drugs.

In 2011, FDA consolidated all reviews for this disease to the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) to "allow for a coordinated and consistent process for review of products being developed." This change was also intended to allow the "development of expertise within this area, and provide a single point of contact" for those outside of FDA.

According to Dr. Kweder of FDA, as of Nov 2012, there had been only nine Investigational New Drug Applications (IND, an application required to investigate a drug) ever filed with the FDA for this disease. Only four of those nine INDs had had active research in the four years prior to 2012; one commercial IND for Ampligen, filed by Hemispherx, and three other much smaller research (non-commercial) INDs. According to Kweder, the INDs from commercial companies are usually the only ones that lead to a marketed drug. As of 2012, Hemispherx was the only commercial company to file a New Drug Application (NDA, the submission to apply for drug approval) for its drug Ampligen.[808]

Because of industry intellectual property restrictions, the FDA cannot publish what INDs have been filed, making it difficult to know if other INDs have been filed since 2012. An alternative indication of early industry interest is Clinicaltrials.gov. As of September 2014, there were only 17

clinical trials for drug therapy that were not terminated and that showed activity in the last three years.[809] These included two trials for Ampligen, three for Rituxan (all in Norway), and two for sodium oxybate (used in narcolepsy). Aside from these, there were ten trials for ten different drugs, three by U.S.-based organizations and only one being conducted by a commercial company (Ritalin, also called Methylphenidate, used for ADHD and narcolepsy).

This is a remarkable level of pharmaceutical industry disinterest, given the size of the potential market, the level of patient debility, and the lack of any other approved treatments. That level of disinterest in the face of a potentially substantial market is a good gauge of the magnitude of the problems associated with this disease.

The Ampligen Experience

Hemispherx's drug, Ampligen, has been in clinical trials since 1988,[810] during which time the FDA has assigned it to five different review divisions at the FDA. During that time, the drug has had such a significant impact on quality of life for some patients that they have been willing to move away from their families, and pay $20,000 a year out of pocket for twice-a-week infusions that keep them tethered to one of the few treatment centers in the country authorized to provide Ampligen.

The most recent review of Ampligen, which was based on two studies, was with the Arthritis Advisory Committee in December 2012. Most advisory committee members acknowledged that Ampligen had had an obvious positive impact on some patients' quality of life. But approval was denied primarily on the grounds that the company failed to meet the standard required to demonstrate efficacy.[811] That denial came in spite of the FDA receiving over 700 public comments on the application, along with the impassioned pleas of patients who spoke directly to the impact of Ampligen on their quality of life. One of those patients was Mary Schweitzer, a former professor of history. Schweitzer has described the dramatic *Awakenings* type change that occurred when she went onto Ampligen, and also the devastating and total relapses that have occurred when she has had to go off of it.[812] Her most recent withdrawal from the drug happened when the head of the medical practice providing Ampligen died, and the FDA would not let the medical practice continue administering the drug.

Ampligen doesn't help all ME patients, and some patients have reported doing worse on Ampligen. But Schweitzer is certainly not alone in the degree of improvement that she experienced on Ampligen. Nor is she alone in the magnitude of relapse experienced when Ampligen was withdrawn.

There is little question that in the case of ME, the bad definitions, the lack of progress in research, the complexity of the disease, and the lack of agreed-upon clinical outcome measures would make it extremely difficult for any drug company to demonstrate the efficacy required for drug approval. The definitional morass would make it difficult to clearly define the drug indication (the specific condition and population of patients for which the drug is intended), which is required for the drug label. And from a review perspective, these issues could cause the reviewers to misunderstand the nature of the disease, as committee member Dr. Sean Hennessey appeared to during the 2012 Ampligen review, when he asked about cognitive behavioral therapy, which he understood to be effective for the treatment of "chronic fatigue [sic]."[813].Such misunderstanding would make it difficult to accurately assess the risk-benefit of any treatment from the perspective of patients whose lives can be completely swallowed up by this disease.

In the case of Ampligen, approval was further complicated by the submission itself, with the FDA and some members of the advisory committee raising questions regarding Hemispherx' reporting of adverse events and the nature of analyses done. For his part, the industry representative on the Ampligen Advisory Committee, Dr. Brian Kotzin, stated that Hemispherix' submission had "inadequacies and irregularities that make me feel that it doesn't rise to the industry standard in terms of demonstrating either efficacy or safety."[814] As reported by Solve ME/CFS Initiative, the final advisory committee vote was split; those voting against approval were concerned with the weakness of the efficacy signal and deficiencies in the submission, while those voting for approval felt that post-marketing studies could address the concerns.[815] Patients have rightly questioned FDA's refusal to consider "conditional approval" for Ampligen, an FDA approval option that would allow these concerns to be addressed through post-approval studies while allowing patients to access the drug. From the patients' perspective, the rejection of conditional approval was unacceptable, given the profound impact of the disease and the lack of any approved drugs.

Statistics and submission quality aside, it is clear that patients like Mary Schweitzer showed a significant positive response while on Ampligen and a devastating relapse upon stopping Ampligen. Schweitzer and the others on Ampligen live in dread of the possibility of losing access to the drug and receding back into the tortured hole of this disease. But the vast majority of patients have not had the opportunity to see if Ampligen could help them. The need to relocate to one of the few treatment centers, the significant out of pocket costs, and even regulatory limits that restrict the number of patients simultaneously on Ampligen to just 100 make it an unreachable dream.

Insurmountable Barriers to Pharmaceutical Investment in Drug Development

To its credit and in sharp contrast to the other HHS agencies, the FDA has recently begun to directly engage patients[816] through open teleconferences and a two-day workshop, held in April of 2013. The first day of the workshop was the Patient Focused Drug Development Initiative Workshop, which was intended to help the FDA and drug sponsors better understand the severity of this disease, the impact of the disease on quality of life, and the risk-benefit choice from the perspective of the patient.[817] The second day was a Scientific Drug Development Workshop, which targeted the pharmaceutical industry and interested clinician-researchers and was intended to identify ways to expedite development of treatments and encourage pharmaceutical investment.

Unfortunately, in spite of FDA sponsorship, very few pharmaceutical companies attended. Given the challenges of this disease and the resultant drug development risks for pharmaceutical companies, this was not surprising. Like the Ampligen review, these FDA meetings put a sharp edge on the insurmountable challenges that have prevented the kind of serious pharmaceutical investment required to bring effective treatments to market.

In a Sept 2012 call with patients,[818] Dr. Sandra Kweder of the FDA highlighted this issue, stating that the failure to "define the condition well and the failure to define outcome measures" discourages drug development investment by pharmaceutical companies.[819] At the April 2013 Scientific Drug Development Meeting, Dr. Woodcock, Director of the FDA, said that the lack of clarity on endpoints and patient selection creates challenges in drug development.[820] At the same meeting, Ms. Roth, Director of Regulatory Affairs at Lily, called for clarity on what criteria are used for this disease as a drug indication (the specific disease condition for which a drug is approved), what endpoints are to be used for registration, and what threshold is needed to demonstrate the "substantial evidence" of drug effectiveness required for drug approval.[821] She also noted the disease heterogeneity and questioned whether would be an "academic research organization" in place to help get the right patients into the trials. It's important to note that the collaborative

research centers that could have helped with this issue were closed in the early 2000s and have not been reopened or since, despite repeated CFSAC recommendations to do so.

Adding to these concerns, Dr. Theresa Michele of FDA acknowledged, in a 2013 call with patients, the need to clarify the disease definition and stated that she had heard from pharmaceutical companies that they were concerned that they would "have difficulty getting reimbursement for approved products because the definitions are so wishy-washy that insurers may not be willing to pay for a product."[822] And yet, at the same meeting, in response to whether ME and CFS were being lumped together, Dr. Janet Maynard stated, "We're sort of leaving it up to pharmaceutical companies to define which patient population they would like to study and establish that [sic]."[823] This does little to address the problem of wishy-washy definitions.

As an output of the Patient Focused Drug Development Initiative meeting, FDA produced the Voice of the Patient Report, in which patients conveyed a consistent picture of ME and its hallmark symptoms of PEM and cognitive dysfunction,[824] a description that reflected the Canadian Consensus Criteria and the ME International Consensus Criteria. Patients also gave an in-depth view of the level of debility experienced by patients and how that influenced the risk that patients would take for even small increases in quality of life. My son has accepted the risks of taking Rituxan because the alternative of being bedbound in a darkened room was so terrible. The idea that ME is not a serious enough disease to warrant such a serious drug, as one neurologist told my son, is ridiculous and reflects a profound misunderstanding of the disease that must be corrected in both those reviewing new drugs and those considering what drugs to prescribe.

And yet in its subsequent draft industry guidance,[825] FDA missed the opportunity to leverage the patient voice as it was intended—to inform drug development. Instead, the FDA guidance failed to recognize the hallmark criteria that patients described as mandatory and instead accepted any definition for trials and treated CFS and ME as equivalent. As Maynard had indicated FDA would, the draft guidance *left it up to the sponsor* to decide what criteria they would use. Finally, adding to the expense of pharmaceutical investment, the FDA's guidance also incorporated an upper prevalence limit of four million, an estimate that can only be justified by an Empirical definition study. This inflated prevalence would then dictate the need for larger studies for an ME drug, which would then increase the cost of drug development and add to the factors that discourage pharmaceutical investment.

As much as the FDA has done to open lines of communication with the ME community, it squandered the opportunity to chart a new course for drug development. Further, given the combination of the ill-defined disease definition, the lack of basic research, and the uncertainty around the expected standard of efficacy assessment, it is difficult to imagine that this draft industry guidance can do much to mitigate against the high level of drug development and regulatory risk that pharmaceutical companies face with this disease.

6. Failure in Other Support Systems

The disbelief and confusion surrounding this disease has not only impeded research and degraded medical care. It has also eroded other mechanisms of support as well—support from the patient's family, discussed earlier, but also accommodations at school and work, and the ability to obtain coverage through disability and health insurance plans. These support mechanisms are fundamental to patient's daily lives. A full analysis of these issues is outside of the scope of this book but will be briefly discussed for context.

The ME Patient and Schools

The disbelief and misunderstanding that has taken over our medical providers has also affected school administrators, nurses, and teachers, making it very difficult for ME student to obtain the kinds of accommodations necessary to deal with their limited energy and significant cognitive issues. Too often, school administrations have interpreted the ME child as school-phobic,[826] malingering or lying. One parent told this author that she was berated for not forcing her son to go to school and was required by the nurse to bring a doctor's note to school every week until she finally refused to do so. Parents are told that they are contributing to their children's condition, and in both Europe and the U.S., there are reports of parents having formal complaints lodged against them, including Munchausen by proxy, child abuse, and/or neglect.[827]

In 2014, Jane Colby, Director of Britain's Tymes Trust, reported on 121 cases over 25 years, in which the Trust had advised families who were being investigated by Child Protection over their handling of their child's ME.[828] Typically, these investigations were attempting to force school attendance or the acceptance of potentially harmful treatments, such as CBT and GET, even though the NICE Guideline said that patients had the right to refuse treatment. In some of these cases, the parents found themselves charged with child abuse or neglect and the threat that the child could be placed in a psychiatric facility. Such investigations place a tremendous emotional strain on the patient and the family and inevitably create a significant financial burden on the entire family because of the cost of legal services to defend their loved one.

In the U.S., the threat of children being removed from the home is less frequent than in England but it has occurred, as in the case of Ryan Baldwin discussed earlier.[829] More frequently, the conflict plays out over the child's attendance and the eligibility of the child for an Individualized Educational Plan (IEP), required for students with disabilities to establish the accommodations needed for success in education.[830] But disbelief in the disease combined with a lack of understanding of the disease and knowledge on the best way to accommodate ME continue to create challenges for both parents and educators.

The ME Patient and Work

Many if not most of ME patients are too ill to work. But for the ME patient who is only mildly ill and able to work, significant accommodation in the workplace is likely still required. The U.S. Department of Labor requires employers to make "reasonable" accommodations which can include changes such as shifting to a later schedule, changing to part time work, moving to a quieter environment, or changing to a less demanding job.[831] My son's employer did all of these things, and also allowed him to take an extended leave of absence prior to his resignation. But even with accommodations, the patient may not be able to work at the level required by the job.

Disability

Obtaining public or private disability for ME in the U.S. is significantly challenging, in part because the state of medical care for ME patients is so inadequate that patients can have difficulty in obtaining the required medical documentation. If an ME patient cannot get adequate medical documentation, including proof of functional impairment, the disability reviewers will have no basis to approve the application. But even when there is substantial documentation from a disease expert, the reviewers and adjudicators may dismiss the evidence because of their own misunderstandings and misperceptions about the nature of the disease. A U.S. Social Security Administration (SSA) judge reportedly told one patient that CFS is not real. In my son's case, the SSA reviewer decided that my son's avoidance of noisy places was due to depressive withdrawal associated with major depressive disorder. This reviewer ignored the fact that ME is known to cause noise sensitivity and that SSA's own mental health examiner had found no evidence of mental illness. ME patients with private disability plans face an added challenge of proving that they are not suffering from a mental disorder, which would frequently result in limitations on disability benefits.

Information from the Social Security Administration appears to support patients' reports of the difficulty getting disability for this disease. At the October 4, 2012 CFSAC meeting, Arthur R. Spencer, Associate Commissioner of the Office of Disability Programs of the Social Security Administration, stated that between 2001 and 2011, the disability allowance rate for CFS (as a primary diagnosis) at the initial level was about 21 percent.[832] This was substantially below the national average of 34-35 percent that he reported across all diseases. Spencer also stated that at the reconsideration level, it was very small, only about 14 percent, whereas at the administrative law judge level, the approval rate for this disease was 70-80 percent.

What was more remarkable was that Social Security Administration listed so few patients as receiving SSA disability benefits for CFS. At a November 2011 presentation, Michele Schaefer, acting Deputy Director of the Office of Medical Listings Improvement of the Social Security Administration, told CFSAC that as of June 2009, only about 14,000 people were receiving disability from SSA for a primary or secondary impairment of CFS. Of the 14,000 patients on disability for CFS, 11,848 of these were receiving SSDI (Title II – disability based on work benefits) benefits and 2033 were receiving SSI benefits (Title XVI – disability for those that fall below income limits).[833]

TITLE II AND TITLE XVI DISABLED BENEFICARIES IN CURRENT PAY FOR IMPAIRMENT 9330 - CHRONIC FATIGUE SYNDROME AS OF MAY 2009

	TITLE II				TITLE XVI		
IMPAIRMENT IS	WORKER	WIDOW	DISABLED ADULT CHILD	TOTAL	TITLE XVI ADULT	TITLE XVI CHILDREN	TOTAL RECIPIENTS
PRIMARY	5,993	134	72	6,199	1,014	20	1,034
SECONDARY	5,505	112	32	5,649	979	20	999
TOTAL	11,498	246	104	11,848	1,993	40	2,033

DATE PREPARED: JUNE 23, 2009
PREPARED BY: ORDP/ODP/ODPMI

Admittedly, patients with this disease may be receiving disability benefits for a different diagnosis. But even so, this is a remarkably low number given that there may be up to an estimated one million Americans with this disease, of whom an estimated 35 to 69 percent (with one study reporting 87 percent) are unable to work and only an estimated five to ten percent recover.[834] If 80

percent of patients are not diagnosed and 50 percent are disabled, that would translate into an estimated 100,000 patients eligible for disability. At the very least, such low numbers from the Social Security Administration for disability due to CFS further indicate how difficult it is to get disability for this disease. While the reason for this discrepancy is not clear, something is clearly amiss that deserves an explanation.

In April 2014, the Social Security Administration issued ruling SSR 14-1p, which provides updated guidance for assessing disability cases that incorporates information from the Canadian Consensus Criteria and the ME International Consensus Criteria.[835] According to Steve Krafchick, a disability attorney and previous CFSAC member, and Dr. Suzanne Vernon, Scientific Director of Solve ME/CFS Initiative, "It is apparent from this revised ruling that the important clinical observations included in the [Canadian Consensus Criteria] and the [ME International Consensus Criteria] are helping to clarify these core signs and symptoms."[836] The 2015 Institute of Medicine Report includes information on SSR 14-1p and provides additional information on assessing disability in ME patients.[837]

However, changes in SSA's disability guidelines are not automatically reflected in the private disability practices or the guidance given to doctors. The 2011 edition of the *American Medical Association's Guides to the Evaluation of Work Ability and Return to Work* states that there are no objective measures, that symptoms are subjective, and that the increase in these symptoms upon activity does not indicate that harm is being done if there are no objective measures that demonstrate harm.[838] The guide goes on to state that the issue is the patient's ability to tolerate the symptoms that arise and concludes that there is no basis for the physician to certify disability and that "the decision of whether or not the rewards of work outweigh the symptoms experienced is the patients choice." Clearly, this trivializes the physical disability that is caused by ME, and does not reflect the Social Security ruling.

Practices can also be substantially different in other countries. In Britain, the recently released training manual used by the Department of Work and Pensions to train disability analysts for "CFS/ME" equates the disease to both neurasthenia and somatic symptom disorder.[839]

Health Insurance

As noted in the section on medical care, health insurance policies often limit what diagnostics and treatments are covered. Some policies state that all diagnostics and treatments are considered experimental for CFS,[840] while other policies deny particular diagnostics and treatments. Insurance policies can limit coverage for the extended medical visits required to effectively diagnose and treat this disease. Insurance may not pay for some of the tests required to make a successful disability claim. For instance, heavily referencing CDC's CFS website and UpToDate, the *Aetna Clinical Policy Bulletin for CFS*, last updated in June of 2014, states that only a minimal set of tests are to be used for diagnosis and considers even a tilt table test as experimental.[841] Since no drugs are approved for this disease, drugs are prescribed off-label and may not be covered. Then, there are geographic issues that arise with some insurers in which coverage across state lines is restricted.

With the exception of those few patients that can pay out of pocket, such health insurance policies make it difficult or impossible for the patient to not only get the medical care that they need but also to get the tests that are required for a successful disability application.

Across the board, the failures in these support mechanisms represent a substantial failure of the safety net that should be in place to support all patients. For ME patients and the caregivers of ME patients, the additional burden of trying to secure school accommodations, disability, and/or medical insurance is overwhelming. Some patients give up without ever accessing the needed support.

7. HHS's Commitment and Engagement

The history of ME leaves little doubt that HHS's public policy toward this disease since the outbreaks in the 1980s—disease definition, epidemiological research, allocation of resources (people and money), the choice of research done and not done, and the nature of medical education provided—has been woefully misguided and is ultimately why HHS has failed to achieve a single tangible outcome for patients.

What makes HHS' failure all the more damning is that patients, disease experts, the IACFS/ME (the international disease organization), HHS's own CFS Advisory Committee, and even congressional leaders have made repeated calls for a redirection in HHS's handling of this disease. But ultimately, those efforts have not made a difference. HHS has continued on its own path, rejecting the input of these key stakeholders, refusing to openly and transparently engage this community, acting unilaterally, failing to be accountable for the lack of progress, and ultimately refusing to treat this disease with the seriousness that was required.

The war on this disease will not be won—it won't even be honestly fought—until HHS changes the model by which it engages this community. Given HHS' track record, achieving that is likely going to require significant, continued congressional oversight.

Dismissal of Stakeholders and Lack of Transparency.

In 2009, President Obama initiated the Open Government Initiative, intended to establish an unprecedented level of openness, transparency, public participation, and collaboration, with the goal of increasing public trust and governmental accountability.[842] The Open Government Initiative is also intended to improve the government's bottom-line effectiveness and efficiency by enabling the U.S. government to leverage the full breadth and depth of expertise found in those who work outside of the government. Such external expertise is essential.

Each government agency has defined its own set of initiatives to advance the President's goals. For its part, HHS's Open Government program appears to be focused on providing more open access to data, and encouraging the development of technology to leverage that data.[843] Those are laudable goals. But, remarkably, what seems to be missing from HHS's Open Government plan is a goal to openly, transparently, and collaboratively engage the *key* stakeholders of its work—the patients, clinicians, and researchers who are both the most knowledgeable and the most impacted by HHS's public health policies and actions. In the age of personalized medicine and patient-powered research and medicine, this is a critical gap that underscores the problems that ME patients, advocates, clinicians, and researchers have faced in trying to redirect HHS's public policy for ME.

The bald reality is that for the last thirty years, HHS, particularly the CDC and the NIH, have not only failed to openly engage this community, but have arrogantly dismissed the input of CFSAC,

patients and disease experts. HHS has refused to share information about its plans, while unilaterally pursuing its own misguided agenda. Predictably, HHS's actions have eroded the trust of the ME community and the community's ability to hold HHS accountable for making progress on this disease. Just as importantly, HHS's actions have isolated HHS from the very stakeholder expertise needed to unravel the mess that has evolved as a result of thirty years of bad public policy.

Background: Mechanisms for Community Engagement and Cross-Agency Coordination

HHS has had very limited and too often one-directional forms of community engagement and communication mechanisms in place going back at least 20 years. According to the 2000 GAO report,[844] HHS first assembled an interagency CFS committee composed of just federal researchers sometime before 1994 in order to ensure coordination of federal research efforts for this disease. Non-federal scientists and patient advocates were added to that group as consultants in 1994-1995. Then, in 1996, the Secretary of Health chartered the CFS Coordinating Committee (CFSCC), in part "to *ensure interagency coordination and communication* regarding CFS," to facilitate awareness of research and educational needs, and to identify collaborative opportunities.[845]

But, by 2000, the GAO report found that the CFSCC had made "only limited progress in meeting its goals to improve agencies' coordination of CFS research activities, programs, and education efforts."[846] Further, as reported by GAO, HHS agency officials themselves acknowledged that the meetings had had "*no effect on the direction of research at either CDC or NIH*" (emphasis added). HHS' justification for this was that "a change in the direction of research generally occurs as a result of relevant scientific or technical breakthroughs,"[847] presumably reflecting HHS' belief that the state of science did not justify a change in direction. As discussed above, this same catch-22 still exists today, as seen in NIH's rejection of CFSAC's 2014 recommendation for targeted research funding because the NIH felt that there is a "lack of definitive evidence" on the disease.[848] It is unclear what breakthrough the NIH has been waiting for, especially when one considers that the 2015 IOM report noted the paucity of research and numerous places where research was needed.[849]

The last meeting of the CFSCC was held in January 2001, after which HHS disbanded CFSCC, apparently with no discussion with either CFSCC members or the patient community[850] and its replacement, the CFS Advisory Committee (CFSAC), was not established until September 2003, thirty two months later. During this period of time [2001-2003], the GAO report had just been issued, the decision was made to stop funding the collaborative research centers,[851] and a decision was made to move this disease to the NIH Office of Research on Women's Health, after having moved it out of NIAID in 1999. This was a critical period in the history of this disease with some important policy changes being made, yet the only mechanism for engagement with the community had been disbanded.

When the new CFS Advisory Committee (CFSAC) was established in September 2003, it was reportedly structured to bring it "in line with other HHS committees, where federal members would be ex officio non-voting members."[852] Few of the original CFSCC members were appointed to it.[853] Reasons for the thirty-two month gap since the disbanding of the CFSCC and for the failure to provide continuity by appointing at least some of the CFSCC members to the CFSAC are unclear. HHS suggested that the lag was due to HHS' reorganization of its advisory committees,[854] while Dr. Jason, CFSCC member, stated that some of those involved with CFSCC's name change effort believed that the CFSCC "might have been disbanded because it was getting too political (e.g.

making progress on changing the name) and that might have threatened some" at HHS.[855]

CFSAC's charter states that CFSAC's role is to *provide advice and recommendations* to HHS on issues related to this disease.[856] It's notable that this charter role no longer includes the CFSCC's original role to enable interagency coordination and communication. This is a critical need, but at the current time it is unclear how and to what extent HHS achieves cross-agency coordination, a topic discussed further below.

In addition to its charter-defined role to provide advice and recommendations, Dr. Howard Koh, previous Assistant Secretary of Health, told patient advocates in 2012 that CFSAC is the mechanism by which stakeholders are intended to engage HHS and provide input on HHS activities.[857] At the current time, CFSAC meetings are held either in person or by webinar, and according to previous CFSAC members, HHS typically defines the agenda. The public is allowed to provide on-the-record comments, but only rarely are they given the opportunity to ask questions. For CFSAC to effectively play both the advisory role and the community liaison role that Dr. Koh had ascribed to it, it is essential that HHS communicate openly and transparently with CFSAC and the community at large. It is also essential that HHS appoint CFSAC members who have the highest level of expertise in this field. But most importantly, HHS needs to take CFSAC's recommendations seriously, and follow through on them, something that has not happened, as discussed below.

For its part, the CDC has established a separate mechanism, the biannual Patient-Centered Outreach and Communication Activity (PCOCA) Conference Call to which the CDC has directed advocates to submit any questions of CDC officials. The PCOCA call includes a presentation on a topic of interest (decided by the CDC with little or no apparent input from the community) and time to ask questions of the speaker, which must be submitted ahead of time. The call also is intended to provide time to ask general questions of the CDC not related to the presentation, again submitted ahead of time. But typically, there is only time for one or two general questions. This leaves the vast majority of important community questions (and many have been submitted) unanswered from one call to the next.[858]

FDA's model of engaging the community has been far more productive than CDC's. Over the last two years, FDA has conducted a number of notably interactive meetings as discussed above. While useful and greatly appreciated, the FDA process and drug development in general is largely downstream from the most fundamental bottlenecks, arising out of policies and actions at CDC and NIG, that have impeded progress in this disease.

For the most part, the NIH has not engaged the community outside of highly structured meetings such as the 2011 State of Knowledge Workshop and the 2014 Pathways to Prevention Workshop and the comparatively one-way discussion at CFSAC. NIH staff has responded to emails

Deaf Ears for ME

The point of President Obama's Open Government Initiative is to increase openness, transparency, collaboration, and public participation in order to increase trust and government accountability. But in the case of this disease, HHS has done the exact opposite, destroying trust in the process.

There is no better example of HHS's failure to openly and collaboratively work with CFSAC, ME experts, and patients than HHS's recent actions regarding establishment of a case definition. As discussed previously, in October 2012, CFSAC recommended that HHS hold a conference of experts, patients, and advocates to reach consensus on a definition for research and clinical use, starting with the Canadian Consensus Criteria.[859] In May 2013, CFSAC members asked about the

status of this recommendation. Dr. Nancy Lee, the designated federal official (DFO) for CFSAC, reminded CFSAC that CFSAC's role was only to give advice to HHS and refused to discuss HHS's plans for further action, stating that this issue had caused great controversy in a CFSAC subcommittee.[860] This led to a heated discussion in which two CFSAC members alleged that they had been intimidated and/or threatened with eviction for speaking their minds on this issue. The CFSAC chair moved on to the next agenda topic and made no commitment to follow up on these allegations.[861]

In June 2012, patient organizations and advocates asked William Schulz, HHS General Counsel, to investigate the alleged intimidation. Schulz turned the investigation over to Dr. Koh, who responded in October 31 2012 that the designated federal official (DFO) for CFSAC "has authority to engage in private conversations with individual members of CFSAC."[862] But the community had never questioned the authority of the DFO to have private conversations. The community's concern was with the allegations of intimidation of CFSAC members, a concern that Dr. Koh's response simply ignored. HHS did not follow up any further.

This dismissal of the allegations of intimidation would be remarkable enough on their own. But then, in the fall of 2013, with no further discussion at CFSAC (although it appears that the CFSAC chair was aware of it), HHS unilaterally entered into the contract with IOM to develop new diagnostic criteria. This disregarded not only CFSAC's recommendation, but also community petitions and letters voicing concerns.[863] The IOM initiative also proceeded forward in the face of an unprecedented letter from fifty disease experts to Secretary Sebelius calling for the adoption of the Canadian Consensus Criteria for both research and clinical use and recommending that HHS not pursue separate efforts (e.g. IOM] to define its own criteria.[864]

But even ignoring the controversy over the IOM and its eventual product, the IOM initiative was never intended to address the research case definition, as called for in both the CFSAC recommendation and in the letter from the fifty experts. Two years after the original CFSAC recommendation and 3.5 years after the 2011 NIH State of Knowledge Workshop report acknowledged the case definition as the most important issue, there has been no progress in implementing a research case definition and no publicly shared plans to do so.

This is just one CFSAC recommendation. Since its inception in 2003, CFSAC has made numerous other recommendations to move research and clinical care forward.[865] In addition to the case definition issue, the CFSAC recommendations, which have been further supported by patients and experts,[866] have called for action in areas such as:

- Regional centers of excellence (Dates requested: 9/04, 8/05, 5/07, 5/09, 10/09, 10/10, 5/11)
- Increased research funding, including explicit recommendations for an RFA (Dates requested: 11/06, 5/11, 11/11, 10/12, 5/13, 3/14, 6/14)
- Research specifically directed to biomedical research into etiology, diagnostics, identification and validation of biomarkers and treatment (Dates requested: 9/04, 8/05, 5/11, 5/13)
- Medical education and medical care; changes to the CDC CFS website to address outdated and erroneous information (Dates requested: (9/04, 8/05, 10/09, 5/10, 6/12, 3/14 plus additional recommendations to CDC directly from a CFSAC subcommittee)
- Evaluation of historical clusters and the study of severe ME patients (Dates requested: (10/12)

In a summary of the 2004-2013 CFSAC recommendations, HHS had incorrectly indicated that a number of these recommendations had been completed, even though the intent of the recommendation was not achieved (e.g. HHS marked a recommendation for an RFA as completed, even though only an R01 was available).[867] However, in May 2013, CFSAC reviewed and reaffirmed that most of the previously made recommendations had not been satisfied.[868]

In March 2014, Dr. Susan Levine, current chair of the CFSAC, spoke explicitly to HHS's long-standing failure to progress CFSAC recommendations, questioned why their recommendations had languished at HHS and whether there were legal options to address the issue.[869]

Why indeed. CFSAC can give advice in the form of recommendations, but as HHS staff has pointed out, HHS—and its individual agencies—do not have to follow it. Demonstrating how little regard the agencies had for CFSAC recommendations, Dr. Reeves told CFSAC members in May 2008 that CFSAC "exists to make recommendations to the Secretary of Health and Human Services, not to the Deputy Director of Science for CDC."[870] Given that attitude, it is not surprising that CFSAC recommendations on virtually every issue have been largely ignored.

As far back as 1995, ME advocates have gone to congressional leaders and held briefings for them. In a May 1995 briefing sponsored by John Porter (R-IL) and Senator Harry Reid (D-NV), Dr. Mark Loveless, an infectious disease specialist, stated, "I have treated more than 2,000 AIDS and CFS patients in my career. And the CFS patients are more sick and more disabled every single day than my AIDS patients are, except for the last two months of life."[871]

Congressional leaders and other government offices have also highlighted many of these issues, and sought a redirection in HHS's approach. For example, the 2000 GAO report noted that the agencies had failed to seek out the input of external researchers and the patient advocate community, when there had been opportunities to do so. Further, congressional leaders have included language in appropriations reports requesting specific actions on this disease dating back to at least 1995 and likely earlier.[872] Examples of the appropriations report language directed at NIH include:

- **1995** – Additional funding focused on promising areas of biomedical research. Consideration given to establishing a coordinator with Institute-wide authority to provide leadership on CFIDS [paraphrased]
- **1998** – "The Committee urges the Institute to examine this illness, addressing a comprehensive variety of care needs which include educating providers in assessment, diagnosis and treatment, case management, rehabilitative efforts and the establishment of chronic fatigue assessment and treatment centers."
- **2000** – "Despite the Committee's supportive report language encouraging NIH to provide additional resources for CFS research, funding has not increased. This is especially disturbing in light of past budget increases given to NIH overall"
- **2003** – "The Committee is disappointed that since NIH released its long awaited CFS program announcement in December 2001, it has yet to reverse 8 years of declining CFS research funding. The Committee urges the NIH to issue an RFA that would emphasize multi-disciplinary studies to understand the cause and progression of CFS in adults and children as well as identify diagnostic markers and effective treatments."
- **2006** – "The Committee supports the CFS Advisory Committee's recommendation to establish five Centers of Excellence within the United States that would effectively utilize state of the art knowledge concerning the diagnosis, clinical management, treatment and clinical research of persons with CFS."

- **2011** – "Within 1 year following that [SOK] workshop, the Committee urges NIH to develop a CFS research plan outlining a coordinated strategy for intramural and extramural research on CFS and related funding opportunity announcements."

Appropriations report language has also been made of CDC and to a lesser extent of other agencies. Yet, even with such congressional support over many years, no meaningful outcomes have been achieved for patients and nothing has changed for patients.

There have been some successes. For instance, the concerns raised by the advocate community led to the 1999 Inspector General Report and the 2000 GAO report. In 2009, a patient organization, Mothers Against ME (MAME), successfully petitioned for live-streaming of CFSAC meetings as an accommodation for patients too sick to attend.[873] As a result of community protests against his failed leadership, Dr. Reeves was removed as the leader of the CDC CFS program in 2010. Patients, with the support of their congressional leaders, successfully petitioned the FDA to hold the FDA Workshop for Drug Development in ME/CFS and the Patient Focused Drug Development Initiative Workshop. In 2013, advocate, lawyer, and patient Jennifer Spotila worked with Public Citizen (a group whose purpose is to serve as the people's voice in Washington) to successfully force CFSAC to address a Federal Advisory Committee Act (FACA) violation in the process used to formulate its consolidated, prioritized recommendations.[874]

But these are small successes that have done little to change HHS' public policy or achieve meaningful outcomes that would have made a difference in patient lives. The inescapable reality is that regardless of what input HHS receives from CFSAC, experts, patients, and other branches of government, HHS and its agencies have not significantly changed their direction or their public policy toward this disease.

Lack of Transparency

Compounding the impact of HHS's disregard of community input is HHS's refusal to act openly and transparently. HHS's decision to unilaterally engage the IOM and pursue the P2P initiative without discussion at CFSAC has already been discussed, as has NIH's unwillingness to share the prioritized plan developed as a result of the 2011 State of Knowledge Workshop.

Another example is the conflicting statements on whether there is a cross-agency strategy for this disease. In mid-2012, Dr. Francis Collins told President Obama that HHS had launched an HHS internal Ad Hoc Workgroup, led by Dr. Koh, which was "working to develop a Department-wide strategy to address this disease."[875] In an October 2012 response to a joint advocacy request for a coordinated, strategic, fully funded response, Dr. Koh stated that the Ad Hoc Workgroup had been assembled to "increase and better coordinate" HHS efforts, develop "a strategic, coordinated response," and "provide evidence of a greater sense of focus and urgency,"[876] a statement that appears to focus on optics over substance. But then in October 2012, in sharp contrast to what Dr. Collins told President Obama, HHS staff in the Office of Women's Health told patient advocates that HHS was not developing a strategy for this disease because it "already has too many strategies."[877] This statement was made within three months of Dr. Collins telling President Obama that the Ad Hoc Workgroup was developing a cross-HHS strategy.

In a recent email, HHS staff told this author that the Ad Hoc Workgroup produced one report and then was disbanded two years ago.[878] That report, which was publicly released, was nothing more than a retrospective compilation of the tactical activities that each agency had already performed or were currently performing—organized by agency. This report was not a department-wide

strategy. This begs the question of why the Ad Hoc Workgroup was created, and why Dr. Collins told President Obama that a department-wide strategy was being developed when it was not.

This incident further demonstrates HHS' pattern of acting unilaterally and in isolation from stakeholder input. If the Ad Hoc Workgroup had been intended to create a strategy, it was doing so with little direct input from stakeholders, because, according to Dr. Koh, the Ad Hoc Workgroup and its charge were "inherently internal to HHS."[879] Koh explained that the lack of direct input from stakeholders would be addressed because "some of the members are also ex officio members of the CFS Advisory Committee (CFSAC) where they hear the stakeholder perspective." But such limited engagement of the stakeholders—via the restricted, largely one-way discussions at CFSAC over a total of no more than four days a year—is incapable of providing the breadth of stakeholder perspective necessary to craft an appropriate response to this disease. HHS has virtually isolated itself from the input and expertise of those who live with, study, and research this disease. Such isolation is guaranteed to result in a misguided public health response.

As with many of the challenges facing this disease, the lack of transparency of HHS staff and agencies is a long-standing problem, one faced both by CFSAC and its predecessor, CFSCC. The GAO report specifically noted that patient advocates serving on CFSCC "have been unable to obtain timely information from the CDC and the NIH necessary to carry out their advisory function and to be responsive to constituents."[880]

To address the dearth of information from HHS, patients have often resorted to FOIA. But those responses can be delayed, non-responsive, incomplete, or heavily redacted, requiring the filing of repeated requests. Patient and lawyer Jennifer Spotila has filed a number of FOIAs; in March 2014, she wrote that some of her requests had been pending for years and others were virtually useless because of unwarranted redaction.[881] Spotila has also pointed out that in the case of her request for names of the members of NIH's Special Emphasis Panel for CFS, she has had to use a FOIA to gain access to information that is publicly available for other diseases. Patient and lawyer Jeannette Burmeister successfully sued HHS to obtain thousands of records of information about the IOM contract after HHS failed to meet the response deadline for the FIOA that she had filed.[882] According to Spotila, such challenges in accessing information at HHS are not unique to this disease. As she noted, the Center for Effective Government, a nonprofit organization focused on protecting "core governing processes from undue influence," evaluated FOIA responses across agencies and found that HHS performed very poorly across the board, receiving a score of "D-" in its handling of FOIA requests.[883]

It's notable that U.K advocates have also had to resort to FOIA to access information about the governmental policies and actions toward this disease. U.K. advocate, patient, and lawyer Valerie Elliott Smith filed a FOIA to gain access to the U.K. "Secret Files on ME/CFS."[884] These files included documents from the U.K. Medical Research Council (MRC, the group that coordinates and funds medical research in the U.K.) and the U.K. Department of Work and Pensions (DWP). Smith observed that the files demonstrated an "abject dismissal of patient input by government agencies." The files from DWP included correspondence with Dr. Peter White and Professor Wessely actively advocating against the listing of CFS/ME as a neurological disease and dismissing the viewpoints of those advocating a biomedical view as "partisan views put forward by pressure groups."

Even when HHS does provide information, the information can be confusing and/or in direct conflict with other, publicly available information, as with the statement made to President Obama regarding the creation of the department-wide strategy. In another example, outlined by advocate

Jennifer Spotila, the NIH has issued multiple, conflicting statements about the purpose of the Pathways to Prevention (P2P) Initiative, fluctuating between statements that its purpose was to address the research case definition and statements that it would identify research gaps.[885] According to Burmeister's FOIA requests, Dr. David Murray, Director of the Office of Disease Prevention at the NIH, told Dr. Collins that the workshop would review the various case definitions to clarify the types of patients captured under each.[886] But as noted above, the P2P agenda and the supporting AHRQ Evidence Review lumped all the definitions together and, as a result, failed to consider the differences in the types of patients captured under each case definition. (The one exception was the rejection of the Oxford definition by P2P although the draft report did not reject the findings of Oxford studies). The P2P Workshop was not designed to do what Murray told Collins that it would do.

The IOM report also noted that the Pathways to Prevention Workshop goal changed, stating that P2P was "originally intended to complement the present study by developing a research case definition for ME/CFS" but that NIH staff later stated that the goal was to suggest a research agenda for ME/CFS based on an unbiased review of the evidence."[887]

The lack of transparency and clarity isn't just a problem experienced by members of the public. Even some within HHS have highlighted this as an issue. In March of 2014, Dr. David Wright resigned his position as director of Office of Research Integrity (ORI), which is in the Office of the Assistant Secretary of Health (OASH). In a scathing resignation letter to then Assistant Secretary of Health Dr. Howard Koh that was published on Science Insider,[888] Dr. Wright stated that he resigned because the organizational culture of OASH was "seriously flawed"—"secretive, autocratic and unaccountable." He added that the environment is "intensely political" and "decisions are often made on the basis of political expediency and to obtain favorable 'optics'."

The Office of Women's Health (OWH), which coordinates HHS's response to this disease, is also within the Office of Assistant Secretary of Health and was under Dr. Koh until his resignation in 2014. When I read Dr. Wright's letter, I could not help but think of HHS' unilateral action on CFSAC's case definition recommendation that led to the IOM and P2P or NIH's failure to make its research plan public. With the notable exception of some of the efforts made by FDA in the last few years, Dr. Wright's experience with OASH reflects this community's experience with HHS—secretive, autocratic and unaccountable.

Lack of Expertise on CFSAC

Given HHS's intent, as stated by Dr. Koh, that CFSAC is the mechanism for stakeholder engagement, it is essential that HHS appoint experts in this field. HHS has appointed members that are international leaders in this field—Dr. Jose Montoya, Dr. Nancy Klimas, Dr. Leonard Jason, and Dr. Mary Ann Fletcher, to name a few. And yet, on too many occasions, CFSAC members have either lacked the experience with this disease and/or misunderstood the nature of the disease. For instance, one CFSAC member asked a CFSAC presenter whether there was "any evidence of childhood depression as a marker, as a precursor, as part of the natural history of this disease that would help identify different categories at a potentially early stage."[889] (The presenter rejected the idea that depression or childhood abuse was a marker of the disease.) Other CFSAC members have embraced CFS as an umbrella of fatiguing illnesses where hallmark criteria like PEM are considered optional or called for an umbrella that includes psychological issues.

There is no question that members with strong research and clinical expertise from areas like neurology and immunology would be invaluable to the CFSAC, given the multi-system

dysfunctions of this disease. But when CFSAC members misunderstand the nature of the disease or are focused on chronic fatigue or the linkage between this disease and depression, they are likely too grounded in the misperceptions of this disease or too unaware of the political challenges that this field faces to chart a path out of the morass that such misperceptions and political forces have created. This lack of expertise and disease knowledge has become especially problematic as only four of the eleven current members have a substantial focus on this disease in their professional careers and one is a patient.[890]

Compounding the lack of expertise, there appears to be little orientation of new CFSAC members to help them understand the range of issues that need to be addressed, making lack of experience in the field an even bigger liability.

Violations of the Federal Advisory Committee Act (FACA)

By law, CFSAC is required to abide by the Federal Advisory Committee Act (FACA), which emphasizes "open meetings, chartering, public involvement and reporting."[891] For instance, FACA requires that all recommendations be discussed and voted on in public. But that hasn't always happened. One example of a FACA violation was noted above, in the process used to compile and prioritize its previously recommended but still open recommendations.[892] More recently, Spotila investigated a FACA violation in which HHS staff changed six medical education recommendations approved at the March 2014 CFSAC meeting by eliminating the requirement for compliance with the Canadian Consensus Criteria.[893] A seventh recommendation for funding commensurate with disease prevalence and economic burden was eliminated completely. Such changes are clear violations of the federal rules established to govern advisory committees.

HHS' original response, which was to these modified recommendations, was that it was already working on them. But that was only true when the requirement for the Canadian Consensus Criteria was eliminated.[894] Individually, any of these actions might be the result of oversight or a careless mistake. But this is part of a broad and long-standing pattern of ignoring the input of this community, of failing to be open and transparent, and of acting arrogantly and unilaterally. In the words of Dr. David Wright, "secretive, autocratic and unaccountable."

It's worth noting that in its response to the updated medical education recommendations that included the recommendation to provide funding commensurate with the disease burden, HHS stated, "Agencies have the responsibility for determining funding for all diseases and conditions, *unless directed by Congress."* Taking all of these problems together, this community has no choice but to pursue a legislative solution to the decades-long failure of HHS policy toward this disease, including the lack of funding. And yet, the likelihood of successfully petitioning Congress is small because of the debility of the patient community and the unwillingness of many members of Congress to address disease-specific issues. The lives of patients lie crushed by the unwillingness of both HHS and Congress to act.

Lack of Coordination across Agencies

Compounding the problems outlined above is the failure of the agencies to even coordinate with each other. This was highlighted in the 2000 GAO report, which found little evidence of coordination on research conducted by the CDC and the NIH in spite of HHS's claims that "interagency coordination occurs through frequent and regular communication about CFS across the two agencies [the CDC and the NIH]."[895] The report went on to say that while CFSCC (precursor of CFSAC) had helped keep federal agencies and the public informed of current activities, it "had not been successful in meeting its goal: [sic] to ensure interagency coordination."[896] The GAO

report also stated the CFSCC "had not provided an effective forum for developing coordinated research programs,"[897] pointing out that while each agency reported on its activities, few questions were asked of the presenters, issues raised in public testimony were not addressed, and there was little discussion on how to coordinate those activities.[898] Fifteen years later, little has changed.

At the time of the GAO, it was hoped that changes such as the movement of the committee from NIAID to NIH's Office of the Director would have a positive impact on the coordination problems. But CFSAC, now in the Office of Women's Health, does not have the remit to ensure cross-agency collaboration and coordination that CFSCC did. The Office of Women's Health is also not positioned to ensure coordination across agencies. The Trans-NIH ME/CFS committee could at least enable coordination across NIH institutes but, as noted above, has been largely ineffectual in doing so. In the fifteen years since the GAO report, interagency coordination does not appear to have improved substantially.

For instance, at the time that the CDC presented its strategic plan in 2009, one of the primary areas of concern raised by CFSAC members and the patient community was the lack of clarity on where the missions of the CDC and the NIH overlapped, as stated by Kim McCleary of CFIDS Association in her testimony.[899] She also went on to express frustration with the lack of consistency in how the case definition and measurements were defined across agencies and the impact that that would have on comparing results across studies. At that time, the CDC was broadening the definition of CFS to encompass chronic unwellness, as seen in the Empirical definition.

During this same timeframe, NIH's SEP was lumping CFS into a spectrum of "chronic polysystemic morbidity syndromes" that included fibromyalgia and at least temporomandibular disorder, and in its 2005 RFA, the NIH had described CFS as "one of a family of disorders that includes fibromyalgia, irritable bowel syndrome, posttraumatic stress disorder, temporomandibular disorder, chemical sensitivities and others."[900] The inability of the CDC and the NIH to even agree on the scope and nature of the disease, let alone the case definition, is a striking display of their lack of coordination.

Another example of a lack of coordination is the failure to deliver the cross-agency strategy promised to President Obama by Dr. Collins, as noted above.[901] Not only was there no cross-agency strategy, but there was little evidence of cross-agency coordination or commitment to address this disease.

A more recent example can be seen in the definition, planning, and execution of the four HHS initiatives, executed simultaneously but without coordination, to address the definition of the disease, the diagnostics and treatment, and the gaps in research.[902] These initiatives defined the scope of disease in different ways and had timelines that made it difficult to synergize on the activities. For instance, the CDC Multi-site Clinical Study did not use any definition, but instead used the patient populations of specialized clinics (known to have a limited demographic) to define the disease. For its part, the AHRQ Evidence Review lumped together eight definitions including Oxford (essentially chronic fatigue), excluded much of the biomedical research, and recommended CBT and GET as treatments based largely on Oxford studies that used the psychosocial fear avoidance/deconditioning theory. The Pathways to Prevention Workshop used the AHRQ Evidence Review and input from workshop speakers, but the sessions did not cover key topics like neurological dysfunction or post-exertional malaise and impairment in energy production. The P2P draft report recommended retirement of Oxford but continued to include findings from Oxford studies. For its part, the IOM initiative did not consider Oxford studies and performed an extensive review of the literature that focused on the biomedical literature that the AHRQ Evidence Review and P2P had ignored.

The consequence of this lack of coordination is that the IOM concluded that the hallmark of the disease was an intolerance to exertion cause systemic impairment while the AHRQ Evidence Review recommended GET, a treatment that would likely cause a relapse due to intolerance to exertion.

This lack of coordination is not only wasteful of both money and time but only adds to the considerable confusion around this disease. Given the history and complexity of this disease, we must have better coordination across agencies.

Lack of Accountability

The most extensively documented and public example of the lack of accountability of HHS toward this disease is the misuse and redirection of the pitifully small funds that have been allocated for this disease at both the CDC and the NIH, as discussed previously. But compounding the siphoning of funding to other diseases noted over the years is the failure to achieve any meaningful outcomes or make measurable progress with the funding that was spent. No diagnostics, no treatments, bad disease definition, and erroneous and harmful clinical guidelines from the CDC. HHS has also failed to take responsibility to reduce the barriers that have resulted from disease stigma and from its own institutional barriers, due in large part to its having exiled ME outside of all of the NIH institutes. In point of fact, far from making measurable progress, HHS actions have significantly moved the disease backwards.

Kim McCleary, previous head of the CFIDS Association (now the Solve ME/CFS Initiative) spoke to both of these issues at the October 28-29, 2008 CFSAC when she stated:

> I am outraged that again we are forced to confront serious funding issues at CDC just as we were 10 years ago in April 1998.
>
> The "boom" of CDC research that occurred during the post "payback" years from 1999-2005 has eroded into what I believe is a "bust" of shameful scientific leadership, zero accountability, invisible outcomes, and millions and millions of dollars stuck in suspended animation, if not wasted.
>
> At least in 1998 science was being conducted that would aid discoveries in other diseases. This time, only government contractors seem to be benefiting from millions spent for which there are no worthwhile outcomes for American taxpayers or CFS patients.
>
> I hope… that you send another vote of strong no-confidence in leadership of this program based on these spending irregularities, the waste of the funds that have been allocated to these projects that have not been spent, and the lack of productivity of the dollars that have been spent.[903]

We are not better off than we were in 2008. Budgets remain appallingly low and the NIH has failed to address the funding or institutional issues that have driven researchers away, despite the fact that these issues have been raised many times by CFSAC. But for me, one of the most personal and jolting demonstrations of HHS's lack of accountability occurred when I told a CDC staff person that a doctor had insisted that my son keep exercising, even when he told her it had caused a severe crash. When I asked if the CDC website could provide a warning about the risk of exercise, the staffer told me that the doctor had misunderstood CDC's CFS exercise recommendations and

dismissed the need to provide a warning on the CFS website. For this staffer, the CDC CFS website content was not the problem. I was shocked to see such isolation from the deleterious impact that HHS's actions had on patients' lives.

Failure to Take ME and ME Patients Seriously

I spent thirty-one years at one of the largest international pharmaceutical companies in the world and have seen how large institutions behave when they consider a problem to be serious and how they behave when an issue is considered unimportant. Ultimately, HHS' actions boil down to the utter failure on the part of HHS to take this disease seriously and respond with the vigor and urgency warranted by this disease.

The ME outbreaks of the 1980s happened at the same time as the AIDS crisis began. And yet AIDS can now be effectively managed, allowing patients to live their lives, as the result of the substantial, sustained commitment by the U.S. government. In "A Tale of Two Viruses: Why AIDS Was Pinned to HIV, but Chronic Fatigue Remains a Mystery," Dr. Vincent Racaniello of Columbia University stated that part of the difference between AIDS and this disease was that AIDS was pinned to a single virus while this disease is "extraordinarily complex."[904] That may be true. But it's insufficient to explain the lack of progress, as there are other equally complex diseases where significant progress has been made.

For instance, cancer, even just breast cancer, is a complex disease. And yet, as a result of the nation's war on cancer, which started in the 1970s,[905] tremendous progress has been made in understanding the complexity and variants of the disease, in implementing early detection, and in developing targeted, personalized treatment regimens that have made a profound impact on patient survival and quality of life. This is in no small part to the almost $5 billion that the National Cancer Institute spends each year on cancer research, an amount that does not include the substantial funding provided by private foundations or spent by the pharmaceutical industry. This progress is also due to the commitment, focus, and quality of the scientific leadership that has been brought to bear from both the federal government and non-governmental groups, including academic centers, the drug industry, and private foundations.

A second example is multiple sclerosis, another complex disease. Between the decade of 1994 and 2006, six treatments were developed for multiple sclerosis, an achievement that the National MS Society notes came about as a direct result of research into the actual disease, not just into the symptoms of the disease.[906] The National Institute for Neurological Diseases and Stroke (NINDS) spent $112 million on multiple sclerosis in 2013 alone, an amount that is roughly equal to what the NIH has spent on ME since its first studies in 1987.[907] The progress made in multiple sclerosis is the result of the commitment, focus, resources, funding, and excellence in scientific leadership that has attacked the problem.

Finally, consider the multi-billion dollar annual commitment by the NIH to AIDS, currently at about $3 billion annually, that has allowed AIDS patients to live full, productive lives. Two of the studies funded in 2015 are clinical trials to assess the use of a long-acting retroviral injectable to prevent HIV infection.[908] The current treatment is an oral medication taken daily. The hope is that the new treatment will decrease the risk of transmission to the uninfected partner due to his/her failure to take the daily, oral medication on a regular basis. Considered on its own, this is certainly an understandable goal.

But what is the political calculation that decided that the goal of decreasing the risk of transfer of disease to the uninfected partner due to non-compliance with an already existing daily medication

regimen is more important than the goal of understanding anything about the core pathology of ME and delivering the very first drug treatment to ME patients?

As ME expert Dr. Klimas observed 6 years ago, her HIV patients are "hale and hearty" due to decades of research while her ME patients remain "terribly ill and unable to work or participate in the care of their families."[909] A 2013 paper in the Journal of the American Medical Society objectively confirmed a change in disease burden, noting that between 1990 and 2010, the DALY (WHO's measure of overall disease burden) for HIV/AIDS had decreased 61%.[910] What has been the political calculation, the political agenda, that has fostered this continued multi-billion dollar level of funding for AIDS when a few million dollars for Collaborative Research Centers for ME patients were withdrawn as too expensive and when ME patients still struggle thirty years later with terrible debility and disbelief? Whatever the calculation has been, it has certainly not been based on the burden of disease or a sense of justice, fairness or compassion.

Such targeted and sustained commitment to AIDS, cancer, and multiple sclerosis stands in stark contrast to the virtually non-existent, uncoordinated, scientifically sloppy response to ME for the last thirty years. Echoing the focused effort to quickly develop the atomic bomb during World War II, Dr. Baraniuk told the NIH at the 2011 State of Knowledge Workshop that we need a "Manhattan Project" for this disease. Four years later, nothing has changed. We have not made progress on ME because HHS has failed to take this disease seriously or respond with even a fraction of the urgency, commitment, and resources that is commensurate with the personal devastation and the national economic impact caused by myalgic encephalomyelitis.

For thirty years, experts, patients, and patient advocates have tried to engage HHS to change federal public health policy toward myalgic encephalomyelitis. But nothing has made a difference. HHS has not only failed to engage this community but has too often outright dismissed it. When patients are so disabled that they have to choose between getting dressed or taking a shower, they are unlikely to be able to exert the power needed to change HHS' policies. Congressional oversight is needed to ensure that HHS fundamentally redirects its public health policy toward this disease and begins to make measurable and meaningful change for patients.

8. Resurrecting ME

Why did this happen to ME and to ME patients? As the 2015 IOM report acknowledged, when you really look at this situation, there is no question that ME is a devastating disease that causes widespread dysfunction. And yet, this disease has been dismissed, marginalized, and stigmatized for decades, not only by the medical establishment and the public but also by the government agency charged with addressing such public health crises.

There is no single answer to why this happened, only a range of players and factors that each contributed in their own way to this situation. These include:

- The personal and political agendas, the cognitive biases, and the arrogance of some individuals, both inside and outside of HHS and also internationally
- A culture at HHS that has been too often secretive and failed to listen to the community
- The willingness of the research and medical community to allow sloppy science and fuzzy, unproven theories about the nature of this disease to flourish unchallenged, for decades.
- The widespread practice of doctors to diagnose what they cannot explain medically as a psychological problem.
- The lack of medical and scientific understanding of complex, chronic disease where dysfunction in multiple, interacting body systems and factors such as genetics, undetected pathogens, environmental toxins, and/or changes to the microbiome may all play a role.
- The institutional challenges of effectively researching multi-system diseases in a world that is organized by NIH research institutes and medical societies.
- The political challenges of gaining attention for diseases that fall outside of the institutional structures of NIH research institutes, academic centers, and medical societies.
- The well-known disparities in how women are treated in clinical practice and how "women's diseases" are researched, still an issue today, twenty years after the enactment of a federal law requiring women to be represented in federally-funded research.[911]
- The interests of governmental and commercial entities, including managed care, in minimizing the cost of insurance and disability claims.

These factors have not just impeded progress in this disease, as the experience of Gulf War Illness, Lyme Disease, and other contested diseases demonstrates. In *Contested Illnesses: Citizens, Science and Health Social Movements,* Dr. Phil Brown, of Brown University, acknowledged that scientific progress can be slow because of the nature and limits of science to understand difficult problems. But progress can also be slow simply because the dominant paradigm that has been adopted toward a disease does not enable forward progress on the science. In that case, as Brown noted, the time that it takes to make progress can be more dependent on "who the stakeholders are in the formation of the [dominant paradigm] and what sorts of institutional, political, social and other barriers impede challenges to it."[912] In the case of Gulf War Illness, Brown explained that the "prevailing systems of scientific, government and military power" have made it difficult for veterans to challenge how their disease is being studied and treated.

These factors play an outsized role in the case of contested diseases like ME, Lyme disease, and Gulf War illness and are likely to have an impact on our ability to tackle the societal cost of chronic

diseases in general, capitalize on the promise of personalized medicine and patient-powered medicine, and equitably allocate scarce resources for medical research and medical care. But what is likely unique about ME is the degree to which all of these factors have been in play at once—and particularly the degree to which these factors have been at play in a patient population that has been too disabled, isolated, and powerless to force change.

Myalgic encephalomyelitis is not an intractable scientific problem. It is a societal and political problem whose solution is fairly basic and solvable if there were the commitment and political will to address it. As the IOM report itself suggests, fundamental change is needed in every facet of HHS's policies and actions toward this disease. The following are suggestions of the kinds of elements that would need to be included in a reinvigorated response by the U.S. government. The specifics need to be defined by a collaboration of key stakeholders.

1. **Engagement:** Establish a new stakeholder engagement model that is fully open, collaborative, and transparent to ensure that disease experts, patients, and patient advocates have input into HHS policies and actions.
2. **Strategy and Oversight:** Establish a comprehensive, coordinated, cross-agency strategy, developed with full, open, and ongoing community participation, infused with a sense of urgency, and grounded in well-defined objectives and measurable benchmarks. This strategy must include specific research and epidemiological sub-strategies and provide for ongoing congressional oversight to ensure forward progress.
3. **Definition:** Resolve the widespread confusion on the nature of this disease that has resulted from conflating ME with a disparate collection of medically unexplained fatiguing conditions that are encompassed by the "CFS" definitions. This will require an appropriate universal case definition, authored by disease experts, that accurately reflects the severity and nature of ME, is diagnostically reliable, and is aligned across research and clinical use. Discontinue the use of the term "CFS" and the use of overly broad CFS definitions such as Fukuda, Empirical, and Oxford. Discontinue the practice of applying findings and recommendations based on the Empirical and Oxford definition studies to ME patients.
    - Note: Concerns with the IOM criteria, particularly as expressed in the accompanying Clinical Guide,[913] still need to be addressed. Examples of these concerns include the criteria's subjectivity; gaps in information, particularly around the recently ill and the severely ill; the lack of criteria operationalization and validation; and the medical community's conflating SEID with CFS.
4. **Funding:** Provide funding for biomedical research and epidemiological studies commensurate with the disease burden and use it to aggressively advance understanding of disease etiology, pathology, diagnostics, treatment, and natural history in patients across the spectrum of disease severity and patient age, race, and socioeconomic status. Based on disease prevalence, economic impact, and qualitative statements of disease burden, NIH funding should be an estimated $250 million annually to be comparable to the per patient funding of diseases of similar burden. CDC funding should be similarly expanded to support the needed epidemiological studies and distribution of medical education.
5. **Regional Treatment Centers:** Establish and fully fund regional treatment centers that integrate clinical care and research, thereby addressing the severe crisis in clinical care for ME patients, the need for multi-disciplinary integrated research and the need to connect patients with clinical trials. Implement an outreach strategy to reach the severely ill, homebound patients.

6. **Disease Experts:** Aggressively recruit new researchers and clinicians to expand the base of experts in order to adequately support the research and clinical needs. This is an especially critical issue because many of the current researchers and clinicians are reaching retirement age.
7. **Medical Education and Medical Care:** In true partnership with disease experts, establish medical education on the nature of ME and appropriate guidance on the best practices to diagnose, manage, and treat the disease, modeled after existing medical education like the IACFS/ME Primer. Proactively reeducate the medical community about the nature of ME and work with medical schools to incorporate ME into medical school curricula.
8. **Insurance, Disability, and School Accommodations:** Work with the Department of Education to establish appropriate accommodations for school-age ME patients. Ensure that Medicare covers tests and treatments as they become available. Continue to improve the Social Security guidance for this disease and ensure that all reviewers and adjudicators are fully trained.
9. **Leadership:** Resolve the organizational and institutional barriers and the lack of committed leadership within both the NIH and the CDC that are impeding progress. This includes moving this disease into an appropriate NIH institute and actively reducing the barriers that are impeding engagement by researchers. Aggressively partner with academic centers to inspire their interest in the disease and with mainstream medical societies to identify a medical specialty willing to take responsibility for this disease.

9. Summary

In the last thirty years, AIDS has become a livable, treatable illness and great strides have been made in the war on cancer. But in the same thirty years, since the outbreaks in the 1980s, time has stood still for patients with ME. HHS has made so little progress that a 1990 Newsweek article and a 1996 PrimeTime investigative report still sound like current events.

But worse than standing still, time has gone backwards from the science that was beginning to blossom in the 1970s and 1980s, recasting ME as a psychological problem and imprisoning ME patients in an unscientific collection of medically unexplained fatiguing illnesses. HHS's public health policies and actions have turned ME and ME patients into pariahs, untouchable by the very people who should have been helping them. This was not a public health response but an exercise in obfuscation.

Today, ME remains an untreatable illness that crushes patients bodies with debility and their souls with disbelief. Comparing the progress on cancer or AIDS to the lack of progress on ME, the difference is stunning.

The story of what has happened to ME and ME patients is a story about the ugly side of medical care and public health policy in this country—the personal and institutional agendas and politics, the sloppy science, the lack of caring, the neglect and arrogance, and the outright refusal to listen to patients or to the researchers and clinicians trying to help them. It is the story of what happens to a disease exiled outside of the research institutes, academic centers, and medical specialties that drive biomedical innovation and delivery of health care. It is the story of a federal response that failed to achieve a single meaningful outcome in thirty years, sentencing my son and all ME patients to lives of terrible debility and stigma while saddling our country with a huge economic burden.

As the IOM report has shown, this is not an intractable scientific problem. This is a political and social problem that has turned ME and its victims into pariahs, untouchable by the very people who should be helping them. This is scientifically, medically, and ethically unacceptable and must stop.

What ME patients need now is HHS leaders and congressional leaders to exert political will, driven by a deep-seated sense of moral responsibility and justice. To correct the decades-long injustice, HHS must act with the vigor that characterized the fight against HIV/AIDS and implement sweeping changes in its policies, actions, leadership, and commitment to this disease. The medical community must learn about this disease and provide the kind of medical care that ME patients need. Our congressional leaders must implement the oversight needed to ensure that HHS makes forward progress. And all of us—HHS, families, the medical and research communities, the media, and the public at large—must start anew and rebuild this story so that ME patients can regain their rightful place among us.

9. Appendices and References

Appendix 1: Summary of the Primary CFS, ME/CFS and ME Definitions

The CDC CME "Diagnosis and Management of CFS" lists five definitions - Oxford, Fukuda, Canadian Consensus Criteria, ME-ICC and Pediatric. The Nice guidelines are used in Britain. Holmes is seldom if ever used today.

Definition Name	Label Used (1)	Key Symptoms in the definition	Psychiatric Illness allowed?	PEM Re-quired	Comment
Holmes criteria (1988)[914]	CFS	6 months chronic fatigue eight symptoms out of eleven		No	Replaced by Fukuda. Patients show more signs of infectious process than Fukuda[915]
1991 Oxford [916]	CFS	6 months severe fatigue that affects mental or physical function.	Schizophrenia, manic-depressive illness excluded. Anxiety, depression allowed	No	PEM not recognized. Myalgia, sleep, mood disturbance may be present – it &other symptoms not required
1994 CDC Fukuda[917]	CFS	6 months fatigue plus any 4 of memory impairment, sore throat, tender lymph nodes, muscle pain, joint pain, headaches of new type, unrefreshing sleep, PEM	Major depressive & bipolar disorder, schizophrenia excluded. Anxiety somatoform & other types of psych disorder allowed	No	PEM one of optional symptoms but not required. Fukuda Includes more depressed and less symptomatic patients than CCC [918]
2003 Canadian Consensus Criteria (CCC)[919]	ME/CFS	PEM plus two neurological/cognitive plus 1 of autonomic, immunological & neuroendocrine symptoms	Primary psychiatric illness excluded	Yes	Requires PEM plus combination of these symptoms. 6 month wait
2005 CDC Empirical (Reeves) Criteria [920]	CFS	Operationalization of Fukuda	Depression, anxiety, somatoform disorders not exclusionary	No	Led to ten-fold prevalence increase. Jason has shown 38 percent of patients with depression fit criteria.[921]
Pediatric Case Definition for ME & CFS (2006) Jason et al [922]	ME/CFS	3 months of fatigue plus PEM, unrefreshing sleep, neurocognitive, pain plus one of autonomic, neuroendocrine, immune	Schizophrenia, Bipolar, depressive disorders exclusionary. May have concomitant anxiety, depression, somatoform	Yes	3 month waiting period.
NICE Clinical Guideline (2007)[923]	CFS	4 months chronic fatigue, PEM plus any one of 10 symptoms	Appears to allow primary psychiatric illness	Consid er CFS if PEM	Pain, cognitive and sleep difficulties considered key. 3 months in child
2011 ME Internationa l Consensus Criteria (ME-ICC)[924]	ME	PENE plus neurological, immunological, energy metabolism /ion transport, infections	Primary psychiatric illness excluded	Yes	Requires PENE plus combination of these symptoms. No waiting period

1. Other less commonly used definitions can be found here: Brurberg, K., et al. Case definitions for chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME): a systematic review. BMJ Open 2014;4:e003973 doi:10.1136/bmjopen-2013-003973 http://bmjopen.bmj.com/content/4/2/e003973.long#T1

Appendix 2: Estimated Prevalence Rates across Key Definitions

Prevalence estimates are suspect because of the varied "CFS" definitions, but the best estimates are that ME affects less than one million Americans of all ages, races, and socioeconomic groups and 17 million people worldwide. Prevalence estimates vary widely depending on the definition and methodology used. The following are the most of the major prevalence studies. The 2012 estimate is based on a U.S. census population of 314M total population, 240M adults and 179M adults between the ages of 18 and 59.[925]

Author	***Rate***	***2012 estim.***	***Reference***
Gunn 1993 Modified Holmes 1989-91	0.000073 2.0 to 7.3 per 100,000	6280 to 22,922	Gunn WJ, Connell DB, Randall B. "Epidemiology of chronic fatigue syndrome: The Centers-for-Disease-Control study." In *Chronic Fatigue Syndrome.* Ciba Found. Symp. B.R. Bock & J. Whelan (Eds.), New York: John Wiley & Sons. 1993. 173:83-101). http://www.ncbi.nlm.nih.gov/pubmed/8387910
Price 1992	0.0074% (1 of 13,538)	23,236	Price RK, North CS, Wessely S, Fraser VJ (1992). Estimating the prevalence of chronic fatigue syndrome and associated symptoms in the community. *Public Health Rep.* Sept-Oct, 1992; 107:514–522. http://www.ncbi.nlm.nih.gov/pubmed/1329134
Wessely 1997 Oxford/ Fukuda	2.2 /2.6% 0.7 /0.5% when no psych	6.91M – Oxford/ 8.16M - Fukuda	Wessely S, Chalder T, Hirsch S, Wallace P, Wright D. "The prevalence and morbidity of chronic fatigue and chronic fatigue syndrome: a prospective primary care study." *Am J Public Health.* September 1997; 87(9):1449–1455. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1380968/ Multiple criteria were used. Oxford prevalence reported as 2.2%
Reyes 1997 Holmes For period 1989-1993	0.00004 to 0.000087	12,560 to 27,318	Reyes M, Gary H, Dobbins J, Randall B, Steele L, Fukuda K, Holmes G, Connell D, Mawle A, Schmid S, Stewart J, Schonberger L, Gunn W, & Reeves W. Surveillance for chronic fatigue syndrome--four U.S. cities, September 1989 through August 1993. *MMWR CDC Surveill Summ.* Feb 21, 1997; 46(SS-2):1-13. http://www.ncbi.nlm.nih.gov/pubmed/12412768, http://www.cdc.gov/mmwr/preview/mmwrhtml/00046433.htm
Jason – 1999. Fukuda	0.0042 (422 per 100000)	1,318,800	Jason LA, Richman JA, Rademaker AW, Jordan KM, Plioplys AV, Taylor R, McCready W, Huang, CF, Piloplys, S. "A community-based study of chronic fatigue syndrome." *Archives of Internal Medicine* October 1999; 159(18): 2129-2137. PMID: 10527290. http://dx.doi.org/10.1001/archinte.159.18.2129 Survey of 28673 people in 1993
Reyes 2003	0.0024 (235 per 100000)	753,600	Reyes M, Nisenbaum R, Hoaglin D, Unger E, Emmons C, Randall B, Stewart J, Abbey S, Jones J, Gantz N, Minden S, Reeves W. "Prevalence and incidence of chronic fatigue syndrome in Wichita, Kansas." *Arch Intern Med.* July 14, 2003;163(13):1530-6. http://archinte.jamanetwork.com/article.aspx?articleid=215827
Reeves 2007 Empirical	0.0254	7,957,600 (6.1M in adults)	Reeves WC, Jones JJ, Maloney E, Heim C, Hoaglin DC, Boneva R, Morrissey M, Devlin R. "Prevalence of CFS in metropolitan, urban and rural Georgia populations." *Population Health Metrics,* 2007; 5(5). PMID: 17559660 http://dx.doi.org/10.1186/1478-7954-5-5
Nacul 2011 Canadian Fukuda	0.0011 0.0019	345,400 596,600	Nacul L., Lacerda E, Pheby D, Campion P, Molokhia M, Fayyaz S, Leite J, Poland F, Howe A, Drachler M. "Prevalence of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) in three regions of England: a repeated cross-sectional study in primary care." *BMC Medicine* July 2011, 9:91 http://dx.doi.org/10.1186/1741-7015-9-91
Vincent 2012 Fukuda Fukuda w PEM	0.00071 0.00026 (36% of Fukuda)	222,940 81,640	Vincent A, Brimmer D, Whipple M, Jones J, Boneva R, Lahr B, Maloney E, St. Sauver J, Reeves W. "Prevalence, Incidence, and Classification of Chronic Fatigue Syndrome in Olmsted County, Minnesota, as Estimated Using the Rochester Epidemiology Project." *Mayo Clinic Proceedings* December 2012; 87(12): 1145-1152. http://www.mayoclinicproceedings.org/article/S0025-6196(12)00923-8/references Fukuda with PEM called out because this an approximation for CCC.

For more information, also see Brurberg K, Fønhus A, Larun L, Flottorp S, Malterud K. "Case definitions for chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME): a systematic review." *BMJ Open* February 7, 2014; 4(2): e003973. PMID: 24508851. http://dx.doi.org/10.1136/bmjopen-2013-003973

Appendix 3: Key Resources

Videos

1. *Forgotten Plague Trailer.* Forgotten Plague. M.E. and the Future of Medicine. Directed by Ryan Prior and Nicole Castillo. Expected release 2015. Last accessed March 3, 2015. http://mecfsdocumentary.com/video/
2. *Canary in a Coal Mine Trailer.* Directed by Jen Brea. Expected release 2016-2017. Last accessed March 3, 2015. http://www.canaryinacoalminefilm.com/#!video/cp63http://mecfsdocumentary.com/video/
3. News story about two sisters with ME. *Menschen - das Magazin*. April 2014. (subtitled in English). https://www.youtube.com/watch?v=XgZ1ayI7J6w and https://www.youtube.com/watch?v=fws-oAExvAs
4. *Voices from the Shadows*. Produced by Natalie Boulton and Josh Natalie. 2011
   Trailer http://www.youtube.com/watch?feature=player_embedded&v=fxZG4QVkO2k
   Web site - http://voicesfromtheshadowsfilm.co.uk/
5. Ginny Ryan. "Battle with Chronic Fatigue Syndrome." *ABC Channel 13 Wham*. Rochester, New York. Uploaded May 2011. http://www.youtube.com/watch?feature=player_embedded&v=oeLal4nfrck. Story about Ben Di Pasquale.
6. ME patient Laurel, testimony to U.S. Health and Human Services CFS Advisory Committee. October 2009. http://www.youtube.com/watch?v=LvweCk44WHs
7. Dr. David Bell, physician who treated patients at the Lyndonville outbreak, discusses ME/CFS and a very severe 19-year-old patient. About 2010 http://vimeo.com/34099309
8. CFIDS Association of America. Briefing to members of United States Congress. May 8, 2008. https://www.youtube.com/playlist?list=PLD6A85AB3B63B31FB
9. *I Remember ME*. Directed by Kim Snyder. 2000. https://www.youtube.com/watch?v=401--WCB5dc and http://en.wikipedia.org/wiki/I_Remember_Me
10. *PrimeTime Live.* Hosts Sam Donaldson and Nancy Snyderman. ABC News. Broadcast in 1996. http://www.youtube.com/watch?v=AW0x9_Q8qbo and http://vimeo.com/13048135
11. "*Living Hell: The Real World of Chronic Fatigue Syndrome."* Produced by Authentic Pictures in association with the CFIDS Foundation, San Francisco. Video undated but reported as 1993. The lack of change in 20 years is disturbing
    - Part 1 - http://www.youtube.com/watch?v=KGFVXacPuho
    - Part 2 - http://www.youtube.com/watch?v=Q0EjR2yepHg
    - Part 3 - http://www.youtube.com/watch?v=1stOT72UCQw
    - Part 4 - http://www.youtube.com/watch?v=bGphVlRKovY
    - Part 5 - http://www.youtube.com/watch?v=wD363vqG38U
    - Part 6 - http://www.youtube.com/watch?v=ISteyLtnxOo
12. Larry King. "Living Hell." *McNeil Lehrer.* 1992. King interviews patient and advocate Tom Hennessy. https://www.youtube.com/watch?v=SyB49g_l9Sg&list=UUaCAv_xLayn32wR9cXjHSTQ

Books and Articles on ME and on the History

1. Leonard Jason. *Principles of Social Change.* Oxford University Press, January 2013. Jason uses ME in some of its cases, providing additional history.
2. Hilary Johnson. "Chasing the Shadow Virus: Chronic Fatigue Syndrome and XMRV." *Discover Magazine*. March 2013. http://discovermagazine.com/2013/march/17-shadow-virus#.Uc9q1utQ3es
3. Vincent Racaniello. "A Tale of Two Viruses: Why AIDS Was Pinned to HIV, but Chronic Fatigue Remains a Mystery." *The Crux. Discover Blogs.* January 12, 2012. http://blogs.discovermagazine.com/crux/2012/01/12/hiv-in-xmrv-out-how-scientists-deduce-what-does-and-doesnt-cause-a-disease/
4. David Tuller. "Chronic Fatigue Syndrome and the CDC: A Long, Tangled Tale." *Virology Blog About Viruses and Viral Disease,* November 23, 2011. http://www.virology.ws/2011/11/23/chronic-fatigue-syndrome-and-the-cdc-a-long-tangled-tale/
5. Tara Parker-Pope. "An Author Escapes from Chronic Fatigue Syndrome." *New York Times.* February 4, 2011. Interview of Laura Hillenbrand, Author and ME patient. http://well.blogs.nytimes.com/2011/02/04/an-author-escapes-from-chronic-fatigue-syndrome/

6. Scott Jordan Harris review of *Voices from the Shadows.* Published by Roger Ebert.com. February 10, 2012. http://www.rogerebert.com/far-flung-correspondents/a-howl-of-desperation-for-those-who-cannot-howl
7. Laura Hillenbrand. "A Sudden Illness." *New Yorker Magazine.* July 7, 2003. http://www.newyorker.com/magazine/2003/07/07/a-sudden-illness
8. Hilary Johnson. *Osler's Web: Inside the Labyrinth of the Chronic Fatigue Syndrome Epidemic*. Crown Publishing Group, New York. 1996. Available on Amazon. Extensive research into the handling of this disease from the start of the Incline Village outbreaks in 1984 until 1996. Later release includes a brief 2006 update.
9. Sarah Sholnik. "Chronic Fatigue Victims Finally Get Some Respect—and Clues to the Cause of Their Misery." *People Magazine.* April 15, 1991. http://www.people.com/people/article/0,,20114907,00.html
10. Lawrence Altman. "Chronic Fatigue Syndrome Finally Gets Some Respect." *New York Times.* December 4, 1990. Last accessed March 5, 2015. http://www.nytimes.com/1990/12/04/science/chronic-fatigue-syndrome-finally-gets-some-respect.html
11. Newsweek staff. "Chronic Fatigue Syndrome." *Newsweek*. November 11, 1990. http://www.thedailybeast.com/newsweek/1990/11/11/chronic-fatigue-syndrome.html and http://www.newsweek.com/chronic-fatigue-syndrome-205712
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Summary of pre-1980 ME epidemics and review articles.

1. Dr. J. Gordon Parish. "Reference index of papers published on epidemics of ME 1934-80." http://www.meresearch.org.uk/wp-content/uploads/2012/11/ResearchPublications1934-1980.pdf

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Compilation and Summaries of Published Scientific Literature

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2. ME Research UK. "Research Database." Research literature from 1956-2013. Last accessed December 31, 2014. http://www.meresearch.org.uk/information/research-database/
3. Margaret Williams. Grey information about ME/CFS
   - Williams, Margaret. "'Grey' Information about ME/CFS." Part 1 covers 1956-1990. Compiled April 2011. http://www.investinme.org/Article422%20Grey%20Information%20About%20ME-CFS.htm
   - Williams, Margaret. "'Grey Information about ME/CFS. Part 2 - 1991 – 1993." Compiled May 2011. http://www.investinme.org/Article422-2%20Grey%20Information%20about%20ME%20CFS%20Part%20II.htm
   - Williams, Margaret. "'Grey Information about ME/CFS. Part 3 -1994." Compiled November 2011. http://www.investinme.org/Article422-3%20Grey%20Information%20about%20ME%20CFS%20Part%20III.htm
4. Lisa Petrison. "ME and ME Medical Abnormalities." *Paradigm Change.* Last updated December 4, 2014. http://paradigmchange.me/me-medical-abnormalities/

U.K. Reports on CFS and ME

This document focuses primarily on events within the U.S. and only selectively discusses parallel events in the U.K. ME charities in the U.K. have many useful articles on events there, particularly the InvestInME site. (http://www.investinme.org/InfoCentre%20Background.htm). Selected U.K. documents, some of which discussed in this document, are listed below

1. Margaret Mar, Countess of Mar. Presentation to the Royal Society of Medicine. "The Politics of ME/CFS" March 18, 2015. Posted by ME advocate Tom Kindlon on March 18, 2015. Last accessed on April 2, 2015. http://www.twitlonger.com/show/n_1sl9f51
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3. U.K. Group on Scientific Research into Myalgic Encephalomyelitis (M.E.). "Inquiry into the status of CFS / M.E. and research into causes and treatment." (The Gibson Inquiry). U.K. Group on Scientific Research into Myalgic Encephalomyelitis (M.E.). Chaired by Dr. Ian Gibson. November, 2006. www.erythos.com/gibsonenquiry/Docs/ME_Inquiry_Report.pdf
4. CFS/ME Working Group. "A Report of the CFS/ME Working Group. Report to the Chief Medical Officer of an Independent Working Group. CFS/ME Working, Allen Hutchinson, chairman. January 2002. http://webarchive.nationalarchives.gov.uk/20130107105354/http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_4064945.pdf.
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5. NHS Services for people with Chronic Fatigue Syndrome/Myalgic Encephalitis. The National Task Force on CFS/ME 1998 (link unavailable)
6. Alex Sleator. "Chronic Fatigue Syndrome/ME". House of Commons Library. December 1, 1998. http://www.parliament.uk/briefing-papers/RP98-107.pdf.
   Discusses the controversies surrounding the disease and the creation of a working group to "promote a better understanding," to produce advice and provide evidence that supports that advice. (page 41)
7. Royal Colleges of Physicians, Psychiatrists, and General Practitioners. "Chronic Fatigue Syndrome. Report of a joint working group of the Royal Colleges of Physicians, Psychiatrists, and General Practitioners." October 1996. http://books.google.com/books/about/Chronic_Fatigue_Syndrome.html?id=RRId4npKxDsC
8. "Report from the National Task Force on Chronic Fatigue Syndrome (CFS), Post Viral Fatigue Syndrome (PVFS), Myalgic Encephalomyelitis." Dr. David Tyrrell, Task Force Chairman. An initiative of the registered charity Westcare, supported by the Department of Health. September 26, 1994. Last accessed March 3, 2015. http://www.actionforme.org.uk/Resources/Action%20for%20ME/Documents/get-informed/national%20task%20force.pdf

Appendix 4: Timeline of ME and CFS Key Events

1934	Los Angeles Outbreak – first recorded outbreak of disease
1948-49	Akureyri, Iceland Outbreak
1955	Royal Free Hospital, London, England. Outbreak among hospital staff
1956	Term benign myalgic encephalomyelitis introduced in Lancet editorial for disease seen at Royal Free hospital
1959	Dr. E.D. Acheson of State University of New York, college of Medicine of New York, summarizes outbreaks in "Clinical Syndrome Variously Called Benign Myalgic Encephalomyelitis, Iceland Disease and Epidemic Neuromyasthenia"[926]
1959	Dr. Donald Henderson, epidemiologist at CDC and Dr. Alexis Shelokov of the National Institute of Allergy and Infectious Diseases (NIAID) published summary of 23 worldwide outbreaks of the disease.
1969	Benign myalgic encephalomyelitis (ME) added to WHO *ICD-8*. (added to *ICD-9* n 1975)
1970	McEvedy and Beard publish 2 articles which question the organic basis of the Royal Free outbreak and the other epidemics and reinterpret them as mass hysteria
1978	Royal Society of Medicine conference to plan future research directions
1984-85	Outbreaks in Incline Village, Nevada and Lyndonville, New York
1986, 1988	Ramsay publishes the first ME specific case definition. Requires hallmark post-exertional fatigability
1986	CDC publishes first Morbidity and Mortality Weekly Report describing disease seen in Incline Village. The term "Syndrome of Chronic Fatigue" used to refer to the disease
1987	First CDC definition meeting.
1987	Nightline Report in which Straus described the disease as "so subjective that patients will commonly feel better no matter what you give them."
1988	HHS publishes the Holmes CFS Definition – first of a series of fatigue-focused definitions that do not require hallmark criteria like post-exertional fatigability
1988	Steven Straus publishes article that states "The demography of this syndrome reflects an excessive risk for educated adult white women….A less casual appraisal, however, often uncovers histories of unachievable ambition, poor coping skills, and somatic complaints…"http://www.ncbi.nlm.nih.gov/pubmed/2836490
1989	Golden Girls has an episode "Sick and Tired" that covers chronic fatigue syndrome.
1990	Newsweek cover story on Chronic Fatigue Syndrome describes early outbreaks
1991	U.K. publishes Oxford definition. Requires only medically unexplained chronic fatigue and includes primary psychiatric illness
1991	First Cooperative Research Center funded by NIH
1992	WHO adds the term "CFS" to *ICD-10* as synonym of ME
1994	HHS publishes Fukuda definition. Doesn't require hallmark criteria like PEM and allows inclusion of psychiatric illness
1995	First congressional briefing about CFS
1999	Inspector General releases report stating that CDC misused $12.9M in funds
2000	GAO releases report on HHS mishandling of CFS. CDC holds workshop to look at case definition. Name change committee formed
1999-2001	NIH moved disease to Office of the Director and then to Office of Research in Women's Health.
2001	CFS Coordinating Committee (CFSCC) disbanded by HHS. CFSAC not created until 2003.
By 2003	Collaborative research centers closed because institutes wouldn't provide funding, according to 2003 CFSAC discussion
2003	Disease experts publish Canadian Consensus Criteria, the first criteria since Ramsay to require hallmark criteria. Excludes primary psychiatric illness
2005	HHS publishes Empirical (Reeves) Criteria. Doesn't require hallmark criteria. Expanded prevalence 10-fold and resulted in 38 percent of major depressive disorder patients being diagnosed with CFS
2010	Reeves replaced as head of CDC CFS program after community outcry over failed leadership, financial mismanagement
2011	26 disease experts publish ME International Consensus Criteria. Builds on Canadian Consensus Criteria. Requires hallmark criteria and excludes primary psychiatric illness
2011-13	CDC rejects recommendations and proposals by CFSAC, patient orgs to move CFS back to neurological chapter in *ICD-10-CM*. (was put in Signs and Symptoms in violation of WHO standards)
2013	Fifty international disease experts call for adoption of the Canadian Consensus Criteria. HHS rejects their recommendation.
2014	HHS conducts the OPM and P2P initiatives and the AHRQ Evidence Review

Additional info: https://web.archive.org/web/20131413120200/http://www.cfids.org/about/timeline.asp

Bibliography

All online references were accessed for the first time between January 2012 and the date of release of this document. All online references were re-accessed in December 2014 to confirm the source and the link. Unless specifically noted otherwise, the date of last access for all sources is December 2014.

Where required, translations were done with Google Translate.

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[1] Maupin, Craig. "CDC AND NIH Officials Discussed 'Desirable Outcome' of Seeing A Distinct Illness 'Evaporate'." *The CFS Report*., March 2014. http://www.cfidsreport.com/News/14_Chronic_Fatigue_Syndrome_Definition_IOM_Straus.html

Discussion of the letter from Dr. Stephen Straus at NIH to Dr. Keiji Fukuda at CDC. The letter, which is undated, was written about the time of the publication of Fukuda in 1994. The letter was obtained by Craig Maupin of CFIDSReport.com by FIOA and released in March of 2014. FOIA Number No.38767. The letter itself can be accessed directly at https://dl.dropboxusercontent.com/u/89158245/Straus%20to%20Fukuda%20letter%201994.docx

[2] Institute of Medicine of the National Academies. "Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness." Institute of Medicine of the National Academies. Prepublication copy. February 10, 2015. Last accessed February 16, 2015. https://www.iom.edu/Reports/2015/ME-CFS.aspx

[3] The following articles speak to patient difficulties with getting treatment and are discussed more fully in the chapter on medical care.

- Bernhard, Toni. "The Stigma of Chronic Fatigue Syndrome." *Turning Straw into Gold, Psychology Today,* April 10, 2011. http://www.psychologytoday.com/blog/turning-straw-gold/201104/the-stigma-chronic-fatigue-syndrome
- Bernhard, Toni. "The Stigma of Chronic Fatigue Syndrome II: Readers Respond." *Turning Straw into Gold, Psychology Today,* May 6, 2011 http://www.psychologytoday.com/blog/turning-straw-gold/201105/the-stigma-chronic-fatigue-syndrome-ii-readers-respond

[4] Fluge O, Mella O. "Can ME/CFS Respond to Immunomodulatory Treatment?" *Dagens Medicin.* March 20, 2015. Last accessed on March 29, 2015. Translated by Google Translate. http://www.dagensmedisin.no/debatt/-kan-mecfse-respondere-pa-immunmodulerende-behandling/

The authors stated, "For us working in the field of oncology, the contrasts attitudes, investments, research and understanding of disease mechanisms in ME / CFS striking, and we have concluded that it is appropriate to conduct clinical trials, based on our clinical observations and subsequent hypotheses."

Note that this is a comment on an article published by Dr. Mats Reimer in *Dagens Medicin.* March 11, 2015. Last accessed on March 29, 2015. Translated by Google Translate. http://www.dagensmedisin.no/debatt/eksperimentelle-tester-og-behandlinger-for-cfsme/

[5] Selected cardiac and cancer risk studies

- Chang CM, Warren JL, Engels EA. "Chronic fatigue syndrome and subsequent risk of cancer among elderly US adults." *Cancer* December 2012; 118(23): 5929-36. PMID: 22648858. http://dx.doi.org/10.1002/cncr.27612
  Discusses increased risk of non-Hodgkin's lymphoma.
- Frith J, Zalewski P, Klawe JJ, Pairman J, Bitner A, Tafil-Klawe M, Newton JL. "Impaired blood pressure variability in chronic fatigue syndrome--a potential biomarker." *QJM* June 2012; 105(9): 831-8. PMID: 22670061. http://dx.doi.org/10.1093/qjmed/hcs085
- Miwa K, Fujita M. "Small Heart With Low Cardiac Output for Orthostatic Intolerance in Patients With Chronic Fatigue Syndrome." *Clin Cardiol* December 2011; 34(12): 782-786. PMID: 22120591. http://dx.doi.org/10.1002/clc.20962
- Hollingsworth KG, Hodgson T, Macgowan GA, Blamire AM, Newton JL. "Impaired cardiac function in chronic fatigue syndrome measured using magnetic resonance cardiac tagging." *J Intern Med* March 2012; 271(3): 264-270. PMID: 21793948. http://dx.doi.org/10.1111/j.1365-2796.2011.02429.x
- Peckerman A, LaManca JJ, Dahl KA, Chemitiganti R, Qureishi B, Natelson BH. "Abnormal impedance cardiography predicts symptom severity in chronic fatigue syndrome." *Am J Med Sci* August 2003; 326(2): 55-60. PMID: 12920435. http://www.ncbi.nlm.nih.gov/pubmed/12920435

[6] Moore, Billie. Statement to Health and Human Services CFS Advisory Committee. October 2012. *CFS Advisory Committee Website.* www.hhs.gov/advcomcfs/meetings/presentations/moore_billie_100412.pdf

[7] Loveless, Mark. Statement to Congress on CFS Awareness Day, May 12, 1995.

Loveless was an infectious disease specialist and head of the CFS and AIDS Clinic at Oregon Health Sciences University who has been frequently quoted as saying, "I have treated more than 2,000 AIDS and CFS patients in my career. And the CFS patients are MORE sick and MORE disabled every single day than my AIDS patients are, except for the last two months of life!" This statement is often quoted. This is one source from that time.

- Listening to CFIDS. "Yuppie Flu is Dead." *Listening to CFID.* Editor Sue Boetcher. Page undated, copyrighted 1996-1999. Page last accessed April 25, 2015. http://wwcoco.com/cfids/yuppieflu.html

Also see:

- *I Remember ME*. Directed by Kim Snyder. 2000. https://www.youtube.com/watch?v=401--WCB5dc
  In this movie, Dr. Dan Peterson, clinician treating patients at Incline Village said that the disease can render the severely affected as sick as AIDS patients in the last two months of their lives.
- The CDC has also said that the disease can be as debilitating as multiple sclerosis and congestive heart failure.

[8] The best descriptions of ME can be found in two case definitions and the associated clinical guidelines.

Definitions

- Carruthers BM, van de Sande MI, De Meirleir KL, Klimas NG, Broderick G, Mitchell T, Staines D, Powles ACP, Speight N, Vallings R, Bateman L, Baumgarten-Austrheim B, Bell DS, Carlo-Stella N, Chia J, Darragh A, Jo D, Lewis D, Light AR, Marshall-Gradisbik S, Mena I, Mikovits JA, Miwa K, Murovska M, Pall ML, Stevens S. "Myalgic Encephalomyelitis: International Consensus Criteria." *Journal of Internal Medicine* October 2011; 270(4): 327–338. PMID: 21777306. http://dx.doi.org/10.1111/j.1365-2796.2011.02428.x and http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2796.2011.02428.x/full
  This is the most recently developed ME criteria and gives extensive information with references regarding the nature of the abnormalities.
- Carruthers BM, Jain AK, De Meirleir KL, Peterson DL, Klimas NG, Lerner 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." *Journal of Chronic Fatigue Syndrome* 2003; 11(1): 7-117. http://mefmaction.com/images/stories/Medical/ME-CFS-Consensus-Document.pdf

Primers

- International Association for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis. "Chronic Fatigue Syndrome Myalgic Encephalomyelitis: A Primer for Clinical Practitioners 2014 Edition." International Association for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis. 2012, revised 2014. http://www.iacfsme.org/LinkClick.aspx?fileticket=iD3JkZAZhts%3d&tabid=509
  This primer is based on the Canadian Consensus Criteria. The IACFS/ME is an international organization of clinicians and researchers involved in the study of ME/CFS and the clinical care of patients with ME/CFS. The 2012 version was abstracted and placed onto Guidelines.gov - http://www.guideline.gov/content.aspx?id=38316
- Carruthers BM, van de Sande MI, De Meirleir KL, Klimas NG, Broderick G, Mitchell T, Staines D, Powles ACP, Speight N, Vallings R, Bateman L, Bell DS, Carlo-Stella N, Chia J, Darragh A, Gerken A, Jo D, Lewis D, Light AR, Light K, Marshall-Gradisnik S, McLaren-Howard J, Mena I, Miwa K, Murovska M, Steven S. "Myalgic Encephalomyelitis – Adult and Paediatric: International Consensus Primer for Medical Practitioners." Co-editors B.M. Carruthers and M.I. van de Sande. Published by Carruthers and van de Sande, 2012. http://www.hetalternatief.org/ICC primer 2012.pdf
  This primer is based on the ME International Consensus Criteria.
- The following document is a guideline specific to psychiatrists produced by a psychiatrist who is also a patient.
  - Stein, Eleanor. "Assessment and Treatment of Patients with ME/CFS: Clinical Guidelines for Psychiatrists." 2005. Last accessed May 13, 2015. http://sacfs.asn.au/download/guidelines_psychiatrists.pdf

Videos

- Komaroff, A. "The Biology of Chronic Fatigue Syndrome." Video of presentation at Internal Medicine Ground Rounds at Stanford University Stanford Medical School. March 26, 2014. Published online on March 28, 2014. https://www.youtube.com/watch?v=VCowKm4N2Ow
  Discussion starts at minute 6:38, during which Dr. Komaroff summarized key biological findings across systems
- Komaroff, A. "One Person's Highlights of the Biological Research Presentations". Video of summary presentation at the 11th International IACFS/ME Conference: Translating Science Into Clinical Practice, March 20-23, 2014. Published online on April 12, 2014. http://www.prohealth.com/library/showarticle.cfm?libid=18864
  This presentation was given on the last day of the conference and summarized the highlights seen in the presentations given at the conference.

Peer-Reviewed Literature

Although the etiology of ME is not yet known, much is known about the range of multi-system dysfunction underlying these symptoms as seen in the following selected peer-reviewed articles. Given that ME, because of its association with "CFS", has been conflated with depression, it is important to note that abnormalities like post-exertional malaise, brain hypoperfusion and hypometabolism, joint and muscle pain, and headaches distinguish ME from depression. It is also worth considering the implications of the Norwegian study of Rituximab in ME patients, which suggest autoimmune disease, given the effectiveness of B-cell depleting drug in 67% of patients, for which all patients but two in the placebo group met the Canadian Consensus Criteria as well as the Fukuda criteria.

- VanNess JM, Stevens SR, Bateman L, Stiles TL, Snell CR. "Post-exertional malaise in women with chronic fatigue syndrome." *J Womens Health (Larchmt)*. February 2010, 19(2): 239-244. PMID: 20095909. http://dx.doi.org/10.1089/jwh.2009.1507
  One of a series of papers from the Pacific Fatigue Clinic, now the Workwell Foundation that has used cardiopulmonary exercise testing to demonstrate the associated changes in energy utilization and anaerobic threshold that occur as a result of post-exertional malaise.
- Light AR, White AT, Hughen RW, Light KC. "Moderate exercise increases expression for sensory, adrenergic, and immune genes in chronic fatigue syndrome patients but not in normal subjects." *J Pain* October 2009; 10(10): 1099-112. PMID: 19647494. http://dx.doi.org/10.1016/j.jpain.2009.06.003
  Landmark paper showing abnormal gene expression of sensory, adrenergic and immune genes following exercise. One of the papers that demonstrated the underlying pathophysiology associated with PEM.
- Freeman, R. Komaroff, A. "Does the chronic fatigue syndrome involve the autonomic nervous system?" The American Journal of Medicine April 1997; 102(4):357-364. PMID: 9217617. http://dx.doi.org/10.1016/S0002-9343(97)00087-9
  Beth Israel Deaconess Medical Center researcher Roy Freeman described the changes in sympathetic and parasympathetic functioning that underlie the orthostatic intolerance noted in ME patients.
- Komaroff AL, Cho TA. "Role of infection and neurologic dysfunction in chronic fatigue syndrome." *Semin Neurol* July 2011 31(3): 325-337. PMID: 21964849. http://dx.doi.org/10.1055/s-0031-1287654
  Komaroff reviewed the neurological abnormalities of the disease, including neurocognitive, sleep, autonomic, and sensory disturbances, cognitive impairments and pain along with changes in the brain that include hypoperfusion, reduced brain matter, and protein changes in the cerebral spinal fluid.
- Klimas NG, Koneru AO. "Chronic fatigue syndrome: inflammation, immune function, and neuroendocrine interactions." *Curr Rheumatol Rep* December 2007; 9(6): 482-7. PMID: 21756995 http://dx.doi.org/10.1007/s11926-007-0078-y and http://web.archive.org/web/20101120223121/http://cfids-cab.org/cfs-inform/Reviewcfs/klimas.koneru07.pdf
  Klimas described immunological abnormalities and chronic immune activation seen by elevated inflammatory cytokines; immune function defects seen in decreased natural killer (NK) cell function and viral reactivation.
- Lange G, Streffner J, Cook D, Bly B, Christodoulou C, Liu W, Deluca J, Natelson BH. "Objective evidence of cognitive complaints in chronic fatigue syndrome: A BOLD fMRI study of verbal working memory." *NeuroImage* June 2005; 26(2): 513-524. PMID: 15907308. http://dx.doi.org/10.1016/j.neuroimage.2005.02.011
- Myhill, S. Booth,N., McLaren-Howard, J. "Chronic fatigue syndrome and mitochondrial dysfunction." *Int J Clin Exp Med* January 2009; 2(1): 1–16. www.ijcem.com/files/IJCEM812001.pdf
  Myhill described mitochondrial dysfunction as did Carruthers who also described oxidative stress, as well as cardiovascular impairment and abnormal thermoregulatory responses.
- Papanicolaou DA, Amsterdam JD, Levine S, McCann SM, Moore RC, Newbrand CH, Allen G, Nisenbaum R, Pfaff DW, Tsokos GC, Vgontzas AN, Kales A. "Neuroendocrine aspects of chronic fatigue syndrome." *Neuroimmunomodulation* February 2004; 11(2):65-74. PMID: 14758052. http://dx.doi.org/10.1159/000075315
- Fluge O, Bruland O, Risa K, Storstein A, Kristoffersen EK, Sapkota D, Næss H, Dahl O, Nyland H, Mella O. "Benefit from B-Lymphocyte Depletion Using the Anti-CD20 Antibody Rituximab in Chronic Fatigue Syndrome. A Double-Blind and Placebo-Controlled Study." *Plos One* Oct 2011; 6(10): e26358. http://dx.doi.org/10.1371/journal.pone.0026358
  Fluge demonstrated a response for about 2/3 of patients treated with Rituximab. This seminal study has caused researchers to consider the possibility that the disease is an autoimmune disease.
- Brenu EW, Staines DR, Baskurt OK, Ashton KJ, Ramos SB, Christy RM, Marshall-Gradisnik SM. "Immune and hemorheological changes in chronic fatigue syndrome." *J Transl Med* January 2010; 8: 1. http://dx.doi.org/10.1186/1479-5876-8-1
- Rowe, P. *General Information Brochure On Orthostatic Intolerance And Its Treatment.* Chronic Fatigue Clinic. John Hopkins Children's Center. March 2014. http://www.dysautonomiainternational.org/pdf/RoweOIsummary.pdf

[9] Carruthers BM, van de Sande MI, De Meirleir KL, Klimas NG, Broderick G, Mitchell T, Staines D, Powles ACP, Speight N, Vallings R, Bateman L, Bell DS, Carlo-Stella N, Chia J, Darragh A, Gerken A, Jo D, Lewis D, Light AR, Light K, Marshall-Gradisnik S, McLaren-Howard J, Mena I, Miwa K, Murovska M, Steven S. "Myalgic Encephalomyelitis – Adult and Paediatric: International Consensus Primer for Medical Practitioners." Co-editors B.M. Carruthers and M.I. van de Sande. Published by Carruthers and van de Sande, 2012. http://www.hetalternatief.org/ICC primer 2012.pdf
Post-exertional malaise (PEM), called post-exertional neuroimmune exhaustion (PENE) in this paper or post-exertional fatigability is described as a pathological low threshold of fatigability that causes an intense exacerbation of symptoms for hours, days, or weeks following even minimal physical or mental activity.

[10] The symptom of PEM is widely recognized by patients and experts as a hallmark, required symptom and has been described as such since at least 1977 as discussed later on. However, there are disputes over how to measure PEM objectively. This lack of agreement on how to measure PEM objectively leads some to state that PEM cannot be a required symptom. However, this results in overly broad definitions such as FUkuda that encompass patients who do not have ME

[11] Sleffel, L. Summary of a presentation by Dr. Paul Cheney. "New insights into the pathophysiology and treatment of CFS." Presentation sponsored by the CFIDS and FMS Support Group of Dallas-Fort Worth. Videotaped in Dallas, Texas, October 2001. http://web.archive.org/web/20101213145758/http://cfids-cab.org/cfs-inform/Optimists/cheney.presentation.html

Sleffel's summary of Cheney's comments included the following quote: "When you ask 'What is it that most affects you?' the answer, reflected back at you almost like one big drum roll, is almost always the same thing. 'I have an energy problem that affects my life; my brain doesn't work very well, and I hurt.' Although five percent don't hurt. So this is an energy-brain-pain illness, and that's what disables these people."

[12] Bailey R, B Laurel, Buchanan R, Crowhurst L, Munson P, Peacey R. "Severe ME Patients' Letter to the IOM." Sent to the Institute of Medicine's Committee on Diagnostic Criteria for ME/CFS. December 16, 2014. Last accessed February 28, 2015. https://www.dropbox.com/s/qqdmemsa5e3bu75/Severe%20Patients'%20Letter%20to%20IOM.pdf?dl=0

[13] Institute of Medicine of the National Academies. "Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness." Institute of Medicine of the National Academies. Prepublication copy. February 10, 2015. Last accessed February 16, 2015. https://www.iom.edu/Reports/2015/ME-CFS.aspx

The IOM report noted:

- "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."
- "Despite Dr. Ramsay's work and a U.K. independent report recognizing that ME is not a psychological entity (CFS/ME Working Group, 2002), the health care community generally still doubts the existence or seriousness of this disease. This perception may partly explain the relatively limited research efforts to study ME in fields other than psychiatry and psychology."

[14] Komaroff AL, Cho TA. "Role of infection and neurologic dysfunction in chronic fatigue syndrome." *Semin Neurol* July 2011; 31(3): 325-337. PMID: 21964849. http://dx.doi.org/10.1055/s-0031-1287654

Reviews neurological changes along with the role of infection as a triggering event.

[15] Lange G, Streffner J, Cook D, Bly B, Christodoulou C, Liu W, Deluca J, Natelson BH. "Objective evidence of cognitive complaints in chronic fatigue syndrome: A BOLD fMRI study of verbal working memory." *NeuroImage* June 2005; 26(2): 513-524. PMID: 15907308. http://dx.doi.org/10.1016/j.neuroimage.2005.02.011

Also see: Lange, G. "Neurocognitive Manifestations in ME/CFS." Presentation, IOM Public Meeting on Diagnostic Criteria for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome, April 2014. www.iom.edu/~/media/Files/Activity Files/Disease/MECFS/Lange.ppt

[16] Nakatomi Y, Mizuno K, Ishii A, Wada Y, Tanaka M, Tazawa S, Onoe K, Fukuda S, Kawabe J, Takahashi K, Kataoka Y, Shiomi S, Yamaguti K, Inaba M, Kuratsune H, Watanabe Y. "Neuroinflammation in Patients with Chronic Fatigue Syndrome/Myalgic Encephalomyelitis: An 11C-(R)-PK11195 PET Study." *J Nucl Med* June 1, 2014; 55(6): 945-950. PMID: 24665088. http://dx.doi.org/10.2967/jnumed.113.131045

PET is positron emission tomography, which uses imaging techniques to show functional processes.

[17] Goldman, Bruce. "Study finds brain abnormalities in chronic fatigue patients." Stanford Medicine News Center. October 28, 2014 http://med.stanford.edu/news/all-news/2014/10/study-finds-brain-abnormalities-in-chronic-fatigue-patients.html

This study was picked up by the Science Daily and mainstream media. Two examples include:

- Science Daily. "Brain abnormalities found in chronic fatigue patients." Science Daily. Source Stanford University Medical Center. October 29, 2014. http://www.sciencedaily.com/releases/2014/10/141029084118.htm
  Wilson, Jacque. "Chronic Fatigue Syndrome is Real, Researchers Say." CNN. October 30, 2014. http://www.cnn.com/2014/10/30/health/chronic-fatigue-syndrome/

[18] Zinn M, Zinn M, Maldonado J, Norris J, Valencia I, Montoya J. "EEG peak alpha frequency is associated with chronic fatigue syndrome: a case-control observational study." Abstract of presentation given at the IACFE/ME conference, March 2014. http://www.iacfsme.org/DesktopModules/DigitalDownload/2014Syllabus25.pdf

Zinn et al reported "decreased Peak Alpha Frequency (PAF) across 58% of the entire cortex compared to controls" and stated "these findings are consistent with reduced efficiency of thalamo-cortical connections in CFS participants."

Also see

- Zinn M, Zinn M, Maldonado J, Norris J, Valencia I, Montoya J. " Cortical hypoactivation during resting state EEG suggests central nervous system pathology in patients with Chronic Fatigue Syndrome: A source analysis pilot study. Abstract of presentation given at the IACFE/ME conference, March 2014. Last accessed March 31, 2015.http://www.iacfsme.org/DesktopModules/DigitalDownload/2014Syllabus25.pdf

Zinn et al also reported "evidence of widespread cortical hypoactivation in CFS patients as demonstrated by increased delta and decreased beta2 sources" and stated that the findings "provide objective quantification of central

nervous system dysregulation in CFS sufferers." The authors showed how the symptoms of ME/CFS are seen in executive function disorders that include diseases like Alzheimer and Parkinson.

[19] Komaroff, A. "One Person's Highlights of the Biological Research Presentations". Video of summary presentation at the 11th International IACFS/ME Conference: Translating Science Into Clinical Practice, March 20-23, 2014. Published online on April 12, 2014. http://www.prohealth.com/library/showarticle.cfm?libid=18864

[20] Freeman, R. Komaroff, A. "Does the chronic fatigue syndrome involve the autonomic nervous system?" The American Journal of Medicine April 1997; 102(4):357-364. PMID: 9217617. http://dx.doi.org/10.1016/S0002-9343(97)00087-9

[21] Rowe PC, Bou-Holaigah I, Kan JS, Calkins H. "Is neurally mediated hypotension an unrecognised cause of chronic fatigue?" *Lancet* March 11, 1995; 345(8950): 623-4. PMID: 7898182. http://dx.doi.org/10.1016/S0140-6736(95)90525-1

[22] Komaroff, A. "The Biology of Chronic Fatigue Syndrome." Video of presentation at Internal Medicine Ground Rounds at Stanford University Stanford Medical School. March 26, 2014. Start time 6:38. Published online on March 28, 2014. https://www.youtube.com/watch?v=VCowKm4N2Ow Minute 22:20
Summarizes key biological findings across systems

[23] EvengaÊrd B, Briese T, Lindh G, Lee S, Lipkin WI. "Absence of evidence of Borna disease virus infection in Swedish patients with Chronic Fatigue Syndrome." *Journal of NeuroVirology* October 1999; 5(5): 495-499. PMID: 10568886. http://dx.doi.org/10.3109/13550289909045378

[24] Lipkin, I. Presentation at U.S. Centers for Disease Control and Prevention Patient-Centered Outreach and Communication Activity (PCOCA) teleconference, September 2013. Transcript available at http://phoenixrising.me/archives/19083 and https://docs.google.com/file/d/0B-NT-7M70igudmZVSVJUTnZVclU/edit Page 10
Dr. Lipkin discussed the 1999 study referenced in the last footnote and its relevance.

[25] Hornig M, Montoya J, Klimas N, Levine S, Felsenstein D, Bateman L, Peterson D, Gottschalk CG, Schultz A, Meredith X, Eddy L, Komaroff A, Lipkin I. "Distinct plasma immune signatures in ME/CFS are present early in the course of illness." *Science Advances* Feb 27, 2015; 1(1):e1400121 Last accessed March 29, 2015. DOI: 10.1126/sciadv.1400121 http://advances.sciencemag.org/content/1/1/e1400121

[26] Komaroff AL. "Is human herpesvirus-6 a trigger for chronic fatigue syndrome?" *J Clin Virol* December 2006; 37 Suppl 1:S39-46. PMID: 17276367. http://dx.doi.org/10.1016/S1386-6532(06)70010-5
Ablashi DV, Eastman HB, Owen CB, Roman MM, Friedman J, Zabriskie JB, Peterson DL, Pearson GR, Whitman JE. "Frequent HHV-6 reactivation in multiple sclerosis (MS) and chronic fatigue syndrome (CFS) patients." *J Clin Virol* May, 2000; 16(3): 179-91. PMID: 10738137. http://dx.doi.org/10.1016/S1386-6532(99)00079-7
Also see

- Lerner AM, Beqaj SH, Fitzgerald JT, Gill K, Gill C, Edington J. "Subset-directed antiviral treatment of 142 herpesvirus patients with chronic fatigue syndrome." *Virus Adaptation and Treatment* May 2010; 2 47-57. http://dx.doi.org/10.2147/VAAT.S10695

[27] Lerner AM, Dworkin HJ, Sayyed T, Chang CH, Fitzgerald JT, Beqaj S, Deeter RG, Goldstein J, Gottipolu P, O'Neill W. "Prevalence of abnormal cardiac wall motion in the cardiomyopathy associated with incomplete multiplication of Epstein-barr Virus and/or cytomegalovirus in patients with chronic fatigue syndrome." *In Vivo* July-August, 2004; 18(4): 417-24. PMID: 15369178. https://sciencescape.org/paper/15369178

[28] Lipkin, Ian presenting on "The Dr. Oz Show: Chronic fatigue syndrome. ME/CFS SEID" Published to YouTube on March 6, 2015. Last accessed March 29, 2015. https://www.youtube.com/watch?v=YqcU1htErRA. Minute 5:44

[29] Komaroff AL, Cho TA. "Role of infection and neurologic dysfunction in chronic fatigue syndrome." *Semin Neurol* July 2011 31(3): 325-337. PMID: 21964849. http://dx.doi.org/10.1055/s-0031-1287654

[30] Hickie I, Davenport T, Wakefield D, Vollmer-Conna U, Cameron B, Vernon SD, Reeves WC, Lloyd A; Dubbo Infection Outcomes Study Group. "Post-infective and chronic fatigue syndromes precipitated by viral and non-viral pathogens: prospective cohort study." *BMJ* September 16, 2006; 333(7568): 575. PMID: 16950834 http://dx.doi.org/10.1136/bmj.38933.585764.AE

[31] Komaroff, A. "The Biology of Chronic Fatigue Syndrome." Video of presentation at Internal Medicine Ground Rounds at Stanford University Stanford Medical School. March 26, 2014. Start time 6:38. Published online on March 28, 2014. https://www.youtube.com/watch?v=VCowKm4N2Ow Minute 22:20
Summarizes key biological findings across systems

[32] For decades, researchers suspected that ME was caused by a virus. Although many researchers still suspect viral or infectious agent causation (and there is evidence to support this belief), theories about the pathology of the disease has become dramatically broader since 2011, when two Norwegian oncologists published a groundbreaking study involving the B-cell depleting drug Rituxan. The origin of their study dates back to 2003, when their treatment of an ME patient for non-Hodgkin's lymphoma serendipitously resulted in a major reduction of her ME symptoms. The patient was so struck by the magnitude of the change that she begged her oncologist to follow up on the discovery. He did and, in 2006, he and a partner published a three-person study reporting similar results. They followed this up with the 2011 study, a double-blind, placebo-controlled study of 30 patients. In that study, they found that 67% of patients in the active group experienced a moderate reduction in symptoms, while only 15% of patients in the control group

experienced the same. One patient improved significantly and went from being bed bound to being able to ski. For a disease with no approved treatments and no reliably effective off-label treatments, the finding that depleting patients' immune systems resulted in significant reduction of symptoms was a revelation.

Study references include:

- Fluge, O. Mella, O. "Clinical impact of B-cell depletion with the anti-CD20 antibody rituximab in chronic fatigue syndrome: a preliminary case series." *BMC Neurology* July 2009, 9:28. http://dx.doi.org/10.1186/1471-2377-9-28
- Fluge O, Bruland O, Risa K, Storstein A, Kristoffersen EK, Sapkota D, Næss H, Dahl O, Nyland H, Mella O. "Benefit from B-Lymphocyte Depletion Using the Anti-CD20 Antibody Rituximab in Chronic Fatigue Syndrome. A Double-Blind and Placebo-Controlled Study." *Plos One* Oct 2011; 6(10): e26358. http://dx.doi.org/10.1371/journal.pone.0026358
- Further information on the first patient can be found in this blog
  Jelstad, Jorgen. "The Drug." *De Bortgjemte.* June 7, 2012. Last accessed March 31, 2015. http://debortgjemte.com/2012/06/07/the-drug/Fds

[33] A useful source for toxic mold is the following site, which includes links to researchers studying this issue.

- ParadigmChange. "Toxic Mold Illness Diagnosis." *ParadigmChange.* Undated. http://paradigmchange.me/diagnosis/

[34] Ramsay AM, Dowsett EG, Dadswell JV, Lyle WH, Parish JG. "Icelandic disease (benign myalgic encephalomyelitis or Royal Free disease)." *Br Med J* May 21, 1977; 1(6072): 1350. PMCID: PMC1607215 http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1607215/

[35] Arnold DL, Bore PJ, Radda GK, Styles P, Taylor DJ. "Excessive intracellular acidosis of skeletal muscle on exercise in a patient with a post-viral exhaustion/fatigue syndrome. A 31P nuclear magnetic resonance study." *Lancet* June 23, 1984; 323(8391):1367-9. PMID: 6145831. http://dx.doi.org/10.1016/S0140-6736(84)91871-3

- The authors stated, "A patient with prolonged post-viral exhaustion and excessive fatigue was examined by 31P nuclear magnetic resonance. During exercise, muscles of the forearm demonstrated abnormally early intracellular acidosis for the exercise performed. This was out of proportion to the associated changes in high-energy phosphates. This may represent excessive lactic acid formation resulting from a disorder of metabolic regulation."
- For a summary with references on mitochondrial dysfunction and PEM in ME, see Dechene, L. "Mitochondrial Dysfunction, Post-Exertional Malaise and CFS/ME." MassCFIDS. Source undated. https://www.masscfids.org/resource-library/13-basic-information/302-mitochondrial-dysfunction-post-exertional-malaise-and-cfsme

[36] Wong R, Lopaschuk G, Zhu G, Walker D, Catellier D, Burton D, Teo K, Collins-Nakai R, Montague T. "Skeletal muscle metabolism in the chronic fatigue syndrome. In vivo assessment by 31P nuclear magnetic resonance spectroscopy." *Chest.* December, 1992: 102(6): 1716-22. PMID: 1446478. http://dx.doi.org/10.1378/chest.102.6.1716

The authors stated, "CFS patients reach exhaustion much more rapidly than normal subjects, at which point they also have relatively reduced intracellular concentrations of ATP. These data suggest a defect of oxidative metabolism with a resultant acceleration of glycolysis in the working skeletal muscles of CFS patients. This metabolic defect may contribute to the reduced physical endurance of CFS patients. Its etiology is unknown. Whether CFS patients' overwhelming tiredness at rest has a similar metabolic pathophysiology or etiology also remains unknown."

[37] References on CPET

A. Studies using CPET to demonstrate post-exertional malaise in ME/CFS patients.

- Davenport TE, Stevens SR, Baroni K, Van Ness M, Snell CR. "Diagnostic accuracy of symptoms characterizing chronic fatigue syndrome." *Disabil Rehabil* 2011; 33(19-20): 1768-75. PMID: 21208154 http://dx.doi.org/10.3109/09638288.2010.546936
- Snell C, Stevens S, Davenport T, Van Ness M. "Discriminative Validity of Metabolic and Workload Measurements for Identifying People With Chronic Fatigue Syndrome." *Physical Therapy* November 2013; 93(11): 1484-1492. PMID: 23813081. http://dx.doi.org/10.2522/ptj.20110368
- VanNess JM, Stevens SR, Bateman L, Stiles TL, Snell CR. "Post-exertional malaise in women with chronic fatigue syndrome." *J Womens Health (Larchmt)* February 2010; 19(2): 239-44. PMID: 20095909. http://dx.doi.org/10.1089/jwh.2009.1507

B. Replication studies by Keller and Vermeulen.

- Keller, B., Pryor, J., Giloteaux, L. Inability of myalgic encephalomyelitis/chronic fatigue syndrome patients to reproduce VO2peak indicates functional impairment. Journal of Translational Medicine April 2014, 12:104. PMID: 24755065. http://dx.doi.org/10.1186/1479-5876-12-104
- Keller B, Micale F. "Exercise Testing to Quantify Effects of Fatigue on Functional Capacity in Patients With CFS." Abstract of presentation given at IACFS/ME Biennial Conference; Translating Evidence Into Practice. 2011. Ottawa, Ontario, Canada. http://iacfsme.org/LinkClick.aspx?fileticket=%2BG6GTkbP33I%3D&tabid=499 Page 12

- Vermeulen RC, Kurk RM, Visser FC, Sluiter W, Scholte HR. "Patients with chronic fatigue syndrome performed worse than controls in a controlled repeated exercise study despite a normal oxidative phosphorylation capacity." *J Transl Med,* 2010. 8: p. 93. http://dx.doi.org/10.1186/1479-5876-8-93

C. Presentations

- Snell, C. "Repeated CPET Results as Clinical Endpoints for ME/CFS Research." Presentation to U.S. Food and Drug Administration, Center for Drug Evaluation and Research (CDER). "Drug Development For Chronic Fatigue Syndrome And Myalgic Encephalomyelitis: Public Workshop. Day Two. Scientific Drug Development Meeting." April 26, 2013. http://www.fda.gov/downloads/Drugs/NewsEvents/UCM355406.pdf (Page 201)
  - Video http://www.tvworldwide.com/events/fda/130425/globe_show/default_go_archive.cfm?gsid=2251 Snell discussion starts at minute 48.30. Discussed how CPET can distinguish between deconditioning and ME at minutes 75-84. Discussed CPET as a biomarker at minute 53.

  Additional information on the parameters measured with CPET and used to assess magnitude of reduced functional capacity:
  - VO2Max – Maximal Oxygen Consumption – Snell stated that it is "strongly correlated with endurance performance capability" and "dependent on cardiovascular limitations"
  - Anaerobic Threshhold – Heart rate at which body starts producing energy anaerobically.
  - Level of effort – demonstrates that the patient is giving good effort.
  - Workload – Snell stated that there is a "big drop off on workload on second day workload" - this means that at a lower level of work, the patient is starting to produce energy anaerobically which is less efficient

  Its worth noting that according to Dr. Snell, production of energy anaerobically is associated with a buildup of lactic acid which is "associated with pain, reduced muscle function, altered enzyme activity and cessation of activity." (page 208 of transcript). (Snell notes that the exception are highly trained athletes who can reuse lactic acid.
- Snell C, Stevens S. "Cardiopulmonary Exercise Testing (CPET) & Evaluating Functional Capacity." Presentation to U.S. Department of Health and Human Services CFS Advisory Committee. October 12, 2010. *CFS Advisory Committee Website.*
  - Slides - http://www.hhs.gov/advcomcfs/meetings/presentations/presentation_10132010_snell-stevens.pdf
  - Video – starting at 4:38 - http://hhs.granicus.com/MediaPlayer.php?view_id=5&clip_id=99; http://media-02.granicus.com:443/ondemand/hhs/hhs_b947e197-a39c-4c51-8b89-077723983c8c.mp3
  - Presentation includes references to statements by various medical societies about the use of CPET
- Snell, C. "Clinical exercise testing in CFS/ME research and treatment " Presentation at a meeting sponsored by RME, the Swedish Patient organization in Stockholm, Sweden on Sept 11, 2012 as part of the research conference. http://www.youtube.com/watch?feature=player_embedded&v=nL49DwGRs30
- Snell, C. "Cardiopulmonary Exercise Testing for the Clinical Assessment of Fatigue." Presentation at an event cosponsored by the Orange County Integrative Medical Center and the Workwell Foundation. Source undated. Posted online July 9, 2013. http://ocimc.wordpress.com/2013/07/09/cpet-presentation-with-dr-snell-of-the-workwell-foundation/

General references on the use of CPET and on findings from other diseases.

- American Thoracic Society (ATS) and the American College of Chest Physicians (ACCP). *ATS/ACCP Statement: Cardiopulmonary Exercise Testing.* Adopted by the ATS Board of Directors, March 1, 2002 and by the ACCP Health Science Policy Committee, November 1, 2001. http://www.thoracic.org/statements/resources/pfet/cardioexercise.pdf
- Balady G, Arena R, Sietsema K, Myers J, Coke L, Fletcher G, Forman D, Franklin B, Guazzi M, Gulati M, Keteyian S, Lavie C, Macko R, Mancini D, Milani R. "Clinician's Guide to Cardiopulmonary Exercise Testing in Adults. A Scientific Statement From the American Heart Association." *Circulation* 2010;122;191-225; http://dx.doi.org/10.1161/CIR.0b013e3181e52e69

  Developed on behalf of the American Heart Association Exercise, Cardiac Rehabilitation, and Prevention Committee of the Council on Clinical Cardiology; Council on Epidemiology and Prevention; Council on Peripheral Vascular Disease; and Interdisciplinary Council on Quality of Care and Outcomes Research.
- Braam AW, de Haan SN, Vorselaars AD, Rijkers GT, Grutters JC, van den Elshout FJ, Korenromp IH. "Influence of repeated maximal exercise testing on biomarkers and fatigue in sarcoidosis." *Brain, Behavior, and Immunity* October 2013; 33:57-64. PMID: 23727274. http://dx.doi.org/10.1016/j.bbi.2013.05.006
  According to the paper, impairment was found on both days of a 2 day test protocol but no additional impairment was demonstrated during the second day. This is different than in ME.
- Hansen, J. Sun, X., Yasunobu, Y., Garafano, R. Gates, G. Barst, R. Wasserman, K. "Reproducibility of Cardiopulmonary Exercise Measurements in Patients With Pulmonary Arterial Hypertension" *Chest* September 2004; 126;816-824. PMID: http://dx.doi.org/10.1378/chest.126.3.816. http://chestjournal.chestpubs.org/content/126/3/816.full.html
  Discussed reproducibility of the test on repeat measurements in this disease

[38] Snell, C. "Repeated CPET Results as Clinical Endpoints for ME/CFS Research." Presentation to U.S. Food and Drug Administration, Center for Drug Evaluation and Research (CDER). "Drug Development For Chronic Fatigue Syndrome And Myalgic Encephalomyelitis: Public Workshop. Day Two. Scientific Drug Development Meeting." April 26, 2013. http://www.fda.gov/downloads/Drugs/NewsEvents/UCM355406.pdf (Page 201)
Video http://www.tvworldwide.com/events/fda/130425/globe_show/default_go_archive.cfm?gsid=2251
Starting at minute 48.30. Snell discussed how CPET can distinguish between deconditioning and ME at minutes 75-84. Snell discussed CPET as a biomarker at minute 53. Snell also discussed that patients with deconditioning are typically the same or better on the second day while patients with ME are worse. In other presentations, Dr. Snell has also said that patients with a number of other chronic diseases and depression do not exhibit this pattern
Also see

- Keller, B., Pryor, J., Giloteaux, L. Inability of myalgic encephalomyelitis/chronic fatigue syndrome patients to reproduce VO2peak indicates functional impairment. Journal of Translational Medicine April 2014, 12:104. PMID: 24755065. http://dx.doi.org/10.1186/1479-5876-12-104
  The paper stated, "ME/CFS patients currently represent a unique class of ill patients who do not reproduce maximal CPET measures, unlike individuals with cardiovascular disease, lung disease, end-stage renal disease, pulmonary arterial hypertension and cystic fibrosis."

[39] Sleffel, L. Summary of a presentation by Dr. Paul Cheney titled "New insights into the pathophysiology and treatment of CFS." Presentation sponsored by the CFIDS and FMS Support Group of Dallas-Fort Worth. Videotaped in Dallas, Texas, October 2001. http://web.archive.org/web/20101213145758/http://cfids-cab.org/cfs-inform/Optimists/cheney.presentation.html
Sieffel reported that Cheney spoke to the creation of reactive oxygen species, including super oxide dismutase, by the mitochondria and that these reactive oxygen species have to be further metabolized in order to keep them from having a toxic effect on the body. According to Sieffel, Cheney said that if that breakdown doesn't happen and too many of these toxic reactive oxygen species build up, then the body shuts down the process and you have to produce energy by anaerobic glycolysis.

[40] Myhill, S. Booth,N., McLaren-Howard, J. "Chronic fatigue syndrome and mitochondrial dysfunction." *Int J Clin Exp Med* January 2009; 2(1): 1–16. www.ijcem.com/files/IJCEM812001.pdf
Speaking to an ATP test, the paper stated that "Only 1 of the 71 patients overlaps the normal region. The 'ATP profile' test is a powerful diagnostic tool and can differentiate patients who have fatigue and other symptoms as a result of energy wastage by stress and psychological factors from those who have insufficient energy due to cellular respiration dysfunction."

[41] He J, Hollingsworth K, Newton J, Blamirea A. "Cerebral vascular control is associated with skeletal muscle pH in chronic fatigue syndrome patients both at rest and during dynamic stimulation." *Neuroimage Clin* 2013; 2: 168–173. PMID: 24179772. http://dx.doi.org/10.1016/j.nicl.2012.12.006
Also see

- Hollingsworth KG, Jones DE, Taylor R, Blamire AM, Newton JL. "Impaired cardiovascular response to standing in chronic fatigue syndrome." *Eur J Clin Invest* July 2010; 40(7): 608-15. PMID: 20497461. http://dx.doi.org/10.1111/j.1365-2362.2010.02310.x
- Newton J. "Understanding Muscle Dysfunction in M.E./CFS." Video of presentation given at the annual meeting of Action on ME in London. November 8, 2013. http://www.prohealth.com/library/showarticle.cfm?libid=18528
  Newton reported a number of findings including a large increase in acid in skeletal muscle with exercise along with a reduction in anaerobic exercise.

[42] Brown AE, Jones DE, Walker M, Newton JL. "Abnormalities of AMPK Activation and Glucose Uptake in Cultured Skeletal Muscle Cells from Individuals with Chronic Fatigue Syndrome." *PLoS ONE.* April 2, 2015. 10(4): e0122982. Last accessed April 4, 2015. http://dx.doi.org/10.1371/journal.pone.0122982
The paper found differences in "increased myogenin expression in the basal state, impaired activation of AMPK, impaired stimulation of glucose uptake and diminished release of IL6" and suggested that the differences were due to genetic or epigenetic mechanism that might provide a novel treatment target.

[43] Kennedy G, Spence VA, McLaren M, Hill A, Underwood C, Belch JJ. "Oxidative stress levels are raised in chronic fatigue syndrome and are associated with clinical symptoms." *Free Radic Biol Med* September 1, 2005; 39(5): 584-9. PMID: 16085177. http://dx.doi.org/10.1016/j.freeradbiomed.2005.04.020

[44] Examples of researchers investigating the relationship between inflammation, oxidative and nitrosative stress, and mitochondrial dysfunction are

- Pall ML. "Elevated, sustained peroxynitrite as the cause of chronic fatigue syndrome." *Med Hypotheses* 2000; 54:115–125. PMID: 10790736. http://dx.doi.org/10.1054/mehy.1998.0825
- Pall ML. "Elevated peroxynitrite as the cause of chronic fatigue syndrome: Other inducers and mechanisms of symptom generation." *J Chronic Fatigue Syndr* 2000; 7(4): 45–58. http://informahealthcare.com/doi/abs/10.1300/J092v07n04_05?journalCode=wcfs

- Maes M, Twisk F. "Chronic fatigue syndrome: Harvey and Wessely's (bio)psychosocial model versus a bio(psychosocial) model based on inflammatory and oxidative and nitrosative stress pathways." *BMC Med* June 15, 2010;8:35. PMID: 20550693. http://dx.doi.org/10.1186/1741-7015-8-35

[45] Komaroff, A. "The Biology of Chronic Fatigue Syndrome." Video of presentation at Internal Medicine Ground Rounds at Stanford University Stanford Medical School. March 26, 2014. Start time 6:38. Published online on March 28, 2014. https://www.youtube.com/watch?v=VCowKm4N2Ow
Summarizes key biological findings across systems Minute 22:20

[46] Light AR, White AT, Hughen RW, Light KC. "Moderate exercise increases expression for sensory, adrenergic, and immune genes in chronic fatigue syndrome patients but not in normal subjects." *J Pain* October 2009; 10(10): 1099-112. PMID: 19647494. http://dx.doi.org/10.1016/j.jpain.2009.06.003

[47] Carnethon, M, Craft L. Autonomic Regulation of the Association Between Exercise and Diabetes *Exerc Sport Sci Rev* 2008; 36(1): 12-18. http://www.medscape.com/viewarticle/568392_3

The paper stated, "The autonomic nervous system is a division of the peripheral nervous system that controls automated body functions including heart rate, blood pressure, digestion, and metabolism. The autonomic nervous system is subdivided into the parasympathetic and sympathetic components that work antagonistically to provide a very fine degree of control over their target organs. In general, the parasympathetic nervous system predominates during rest by slowing heart rate, lowering blood pressure, and promoting digestion. The sympathetic nervous system is responsible for mounting responses to physical and psychological stimuli. In response to a challenge, the sympathetic nervous system boosts heart rate and blood pressure and directs blood flow away from digestion to maintain glucose in the blood stream so that it can be used for immediate energy for the well-known 'fight or flight' response."

[48] Cockshell SJ, Mathias JL. "Cognitive Functioning in People With Chronic Fatigue Syndrome: A Comparison Between Subjective and Objective Measures." *Neuropsychology* May 2014; 28(3): 394-405. PMID: 24364389 http://dx.doi.org/10.1037/neu0000025
Additional information on this study is available on Phoenix Rising at this link: http://phoenixrising.me/archives/24259?preview_id=24259

[49] Carruthers BM, Jain AK, De Meirleir KL, Peterson DL, Klimas NG, Lerner 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." *Journal of Chronic Fatigue Syndrome* 2003; 11(1): 7-117. http://mefmaction.com/images/stories/Medical/ME-CFS-Consensus-Document.pdf

The 2003 Canadian Consensus Criteria for ME/CFS was developed by an expert consensus panel at the request of Health Canada and with the intent of developing a clinical definition that addressed the pathogenesis of the disease and provided diagnostic and treatment protocols.

In marked contrast to the definitions discussed above, the CCC was the first definition since Ramsay's 1988 definition to put the focus on post-exertional fatigability and the other characteristic immune, neurological, and endocrine abnormalities by which ME experts identify patients. In recognition of the fact that U.S. patients frequently refer to ME as "CFS," while patients abroad largely refer to the disease as ME, the CCC used the label "ME/CFS." While a logical decision, the use of "ME/CFS," "CFS/ME," "CFS," and even chronic fatigue "CF" as alternative names for ME has ultimately compounded confusion about the nature of the disease produced by the use of overbroad and overlapping case definitions. People are using the same terms and meaning very different things.
Also see the following overview of the CCC, produced in 2005.

- Carruthers B, van de Sande M. "Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: A Clinical Case Definition and Guidelines for Medical Practitioners. An Overview of the Canadian Consensus Document" Published by Carruthers B, can de Sande M. 2005. http://www.name-us.org/DefintionsPages/DefinitionsArticles/ConsensusDocument%20Overview.pdf

[50] Carruthers BM, van de Sande MI, De Meirleir KL, Klimas NG, Broderick G, Mitchell T, Staines D, Powles ACP, Speight N, Vallings R, Bateman L, Baumgarten-Austrheim B, Bell DS, Carlo-Stella N, Chia J, Darragh A, Jo D, Lewis D, Light AR, Marshall-Gradisbik S, Mena I, Mikovits JA, Miwa K, Murovska M, Pall ML, Stevens S. "Myalgic Encephalomyelitis: International Consensus Criteria." *Journal of Internal Medicine* October 2011; 270(4): 327–338. PMID: 21777306. http://dx.doi.org/10.1111/j.1365-2796.2011.02428.x and http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2796.2011.02428.x/full

To address what the authors described as a "web of confusion" created by the overly broad CFS definitions and the mixing and matching of names, twenty-six researchers and clinicians from thirteen countries published the Myalgic Encephalomyelitis International Consensus Criteria (ME-ICC) in 2011. Although it used the CCC as a starting point, requiring what it called post-exertional neuroimmune exhaustion and symptoms reflecting neurological, immunological/gastrointestinal/genitourinary, and energy production/transportation impairments, the ME-ICC did not include the CCC definition's requirement that doctors wait six months before diagnosing the disease. Significantly, the ME-ICC called for patients meeting the ME-ICC criteria to be removed from the NICE criteria and the Reeves Empirical criteria. Further, the companion ME International Consensus Primer for Medical Practitioners, published in 2012, called for patients meeting the ME-ICC criteria to be removed from the broader CFS or CFS/ME criteria, including the Oxford, Reeves (Empirical), Fukuda, and CCC case definitions.

[51] Spotila, Jennifer. "Post-Exertional Malaise in Chronic Fatigue Syndrome." CFIDS Association. 2010. http://solvecfs.org/wp-content/uploads/2013/10/pem-series.pdf. Four part series developed for the CFIDS Association.
Examines PEM, how patients experience it, the objective evidence for it and what patients can do to cope with it.

[52] Bernhard, Toni. "The Stigma of Chronic Fatigue Syndrome." *Turning Straw into Gold, Psychology Today,* April 10, 2011. http://www.psychologytoday.com/blog/turning-straw-gold/201104/the-stigma-chronic-fatigue-syndrome

[53] Table 2 in the Appendix contains a summary of the major prevalence studies. Prevalence estimates vary widely, depending on the definition used, the method used to ascertain cases, whether it's based on a community sample or not and other similar factors. Further discussion of the issues that affect prevalence is in the chapter on epidemiology.

[54] Komaroff, A. "The Biology of Chronic Fatigue Syndrome." Video of presentation at Internal Medicine Ground Rounds at Stanford University Stanford Medical School. March 26, 2014. Published online on March 28, 2014. https://www.youtube.com/watch?v=VCowKm4N2Ow Discussion starts at minute 6:38, Minute 11:20 for reference for CFS occurring as early as age 5.

[55] Jason, L., Richman, J. "How Science Can Stigmatize: The Case of Chronic Fatigue Syndrome." *Journal of Chronic Fatigue Syndrome* 2007; 14(4): 85-103. http://informahealthcare.com/doi/abs/10.3109/10573320802092146 and http://web.archive.org/web/20120228222416/http://www.cfids-cab.org/cfs-inform/CFS.case.def/jason.richman.07.txt

[56] Snell, C. "Repeated CPET Results as Clinical Endpoints for ME/CFS Research." Presentation to U.S. Food and Drug Administration, Center for Drug Evaluation and Research (CDER). "Drug Development For Chronic Fatigue Syndrome And Myalgic Encephalomyelitis: Public Workshop. Day Two. Scientific Drug Development Meeting." April 26, 2013. http://www.fda.gov/downloads/Drugs/NewsEvents/UCM355406.pdf (page 201)
Video http://www.tvworldwide.com/events/fda/130425/globe_show/default_go_archive.cfm?gsid=2251 Snell starts at minute 48.30.
Dr. Snell discussed this in the FDA meeting where he made the comment in the context of the PACE trial. He showed how the 6 minute walk test results (1.9mph – 2.3mph) equated to a work capacity of 2 METS which equates to 7ml.min/kg O2) defined by Weber/NYHA. Dr. Snell said that this is the level that is seen in ME patients. This level is considered severely disabled and a patient at this level is "unlikely to be eligible for heart transplant because they would not survive it" *(*Minute 72 – 76)

[57] The estimate for unemployment can be seen in

- Taylor R, Kielhofner G. "Work-related impairment and employment-focused rehabilitation options for individuals with chronic fatigue syndrome: A review." *Journal of Mental Health*. 2005, 14(3): 253-267 http://dx.doi.org/10.1080/09638230500136571
  The paper stated, "Few studies of work-related impairment and work-focused rehabilitation in CFS exist. Rates of unemployment ranged from 35–69% and rates of job loss ranged from 26–89%."
- Collin S, Crawley E, May M, Sterne J, Hollingworth W, UK CFS/ME National Outcomes Database. "The impact of CFS/ME on employment and productivity in the UK: a cross-sectional study based on the CFS/ME national outcomes database." *BMC Health Services Research* 2011, **11**:217. Last accessed February 14, 2015. http://dx.doi.org/10.1186/1472-6963-11-217
  The paper stated that 50.1% "had discontinued their employment 'because of fatigue-related symptoms'."
- Reynolds, K., Vernon, S., Bouchery, E. and Reeves, W. "The economic impact of chronic fatigue syndrome." Cost Effectiveness and Resource Allocation 2004, 2:4. PMID: 15210053. http://dx.doi.org/10.1186/1478-7547-2-4
  The paper stated:
  - "For women and men, we estimated about a 27% reduction in employment attributable to CFS."
  - "We estimated a 37% decline in household productivity and a 54% reduction in labor force productivity among people with CFS.

[58] Chu L. "US ME/CFS Patient Survey – April to May 2013". Survey performed in preparation for the FDA Stakeholder Workshop April 25,26, 2013. Preliminary results submitted to FDA: http://iacfsme.org/LinkClick.aspx?fileticket=pMB2%2bjKy7EQ%3d&tabid=36 and http://iacfsme.org/LinkClick.aspx?fileticket=YkMRCzqkxnQ%3d&tabid=36.
Final results submitted to IOM: http://www.iacfsme.org/LinkClick.aspx?fileticket=PuRykxCauTk%3D&tabid=36
The paper stated that of 623 respondents, "Only 13% were employed, with almost all citing ME or CFS as the reason why they could not work. For even basic personal care, 89% had to change their pre-illness routine; at least a quarter needed assistance from another person or special equipment (e.g. shower chairs, wheelchair, etc.). On their worse days, 61% were bedridden. On their best days, 75% were primarily homebound and could only do some light housework or less."

[59] Ibid.
Also see:

- International Association for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis. "Chronic Fatigue Syndrome Myalgic Encephalomyelitis: A Primer for Clinical Practitioners 2014 Edition." International Association for

Chronic Fatigue Syndrome/Myalgic Encephalomyelitis. 2012, revised 2014. http://www.iacfsme.org/LinkClick.aspx?fileticket=iD3JkZAZhts%3d&tabid=509

[60] Severe patients are discussed further in the section on medical care. Examples include

- Harding, L. "She went into a hellhole': A mother's candid account of her daughter's battle with ME." *Daily Mail: Mail Online*. Published by Associated Newspapers LTD. May 15, 2010. http://www.dailymail.co.uk/home/you/article-1277519/Criona-Wilson-recalls-daughters-losing-battle-ME-She-went-hellhole.html

Also see

- Meridian Tonight TV News. Accessed through the InvestInME site. http://www.investinme.org/Mediatelevision2.htm
  This includes two reports – the first covers Sophia's condition, her sectioning and her death as reported by her mother while the second also covers the coroner's report, which had just been released.
- Gammel, Carol. "Lynn Gilderdale: how a 14-year-old was condemned to a life lived from a bed." *The Telegraph* Jan 26, 2010. http://www.telegraph.co.uk/news/uknews/law-and-order/7074234/Lynn-Gilderdale-how-a-14-year-old-was-condemned-to-a-life-lived-from-a-bed.html
- Swain, Gill. "Trapped in bed for 14 years with chronic fatigue." *Daily Mail: Mail Online.* Published by Associated Newspapers LTD. July 5, 2006. http://www.dailymail.co.uk/health/article-393915/Trapped-bed-14-years-chronic-fatigue.html

[61] Few longitudinal studies have been done and to this author's knowledge, none have been done on patients characterized by the Canadian Consensus Criteria. The following sources provide information on prognosis. The 5-10% is for full recovery, not just improvement in some symptoms.

- International Association for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis. "Chronic Fatigue Syndrome Myalgic Encephalomyelitis: A Primer for Clinical Practitioners 2014 Edition." International Association for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis. 2012, revised 2014. http://www.iacfsme.org/LinkClick.aspx?fileticket=iD3JkZAZhts%3d&tabid=509
- Cairns R, Hotopf M. "A systematic review describing the prognosis of chronic fatigue syndrome." *Occup Med (Lond)*. January 2005; 55(1): 20-31. PMID: 15699087. http://dx.doi.org/10.1093/occmed/kqi013

[62] Jason LA, Corrdai K, Gress S, Williams S, Torres-Harding S. "Causes of Death Among Patients With Chronic Fatigue Syndrome." *Health Care for Women International* 2006; 27(7): 615–626. http://dx.doi.org/10.1080/07399330600803766

Jason analyzed 166 patients from a US memorial register who had died with ME/CFS. He stated, "The three most prevalent causes of death were heart failure, suicide, and cancer, which accounted for 59.6% of all deaths. The mean age of those who died from cancer and suicide was 47.8 and 39.3 years" compared to 72 and 48 years respectively in the general US population."

Also see:

- Chang CM, Warren JL, Engels EA. "Chronic fatigue syndrome and subsequent risk of cancer among elderly US adults." *Cancer* December 2012, 118(23): 5929-36. PMID: 22648858. http://dx.doi.org/10.1002/cncr.27612

[63] Marcus, A. "Applying Venture Philanthropy to Chronic Fatigue Syndrome." *Wall Street Journal Health Blog*. Sept 15, 2011. http://blogs.wsj.com/health/2011/09/15/applying-venture-philanthropy-to-chronic-fatigue-syndrome/

[64] Carlson S, Hornig M, Klimas K, Ironson G, March D, Komaroff A. "The Chronic Fatigue Initiative (CFI)- Findings from the CFI Cohort Study and Pathogen Discovery & Pathogenesis Project." Presentation at International Association for CFS/ME. *Translating Science into Clinical Care.* International Association for CFS/ME Conference in San Francisco, California. March 20-23, 2014. Conference Report by Dr. Rosamund Vallings - http://www.masscfids.org/resource-library/15-conference-reports/514-iacfsme-conference-2014-summary-rosamund-vallings-

[65] In 2004, Reynolds reported a 54% reduction in labor force productivity and $20,000 in lost income per patient for a total of $9.1 billion across the U.S, which translates to a total population of 455,000 patients. In 2008, using prevalence estimates of 836,000 (rate of 422 per 100,000) from the 1999 Jason prevalence study and the $20,000 per person estimate from Reynolds, Jason reported estimated lost productivity at $17B. Jason also estimated direct medical costs at $2,342 per patient in a community based sample and $8,675 per patient for patients in a tertiary setting. Using the prevalence of 836,000 patients, he estimated direct medical costs ranging from $2B to $7B and an estimated total economic impact of $18B to $24B for lost productivity and direct medical costs.

These estimates of economic burden are dependent on studies of disease burden and prevalence, which are biased by the definition used, the patient selection methods used and also by estimates of unemployment and average wage. Today's estimates of unemployment range from 35% to as high as 87 %. The 2012 national average wage, as reported by the Social Security Administration was $44,321.67 and the 2012 U.S. population estimate of 314M. The prevalence rate of 422 per 100,000 reported by Jason was based on Fukuda while Nacul showed that the Canadian Consensus Criteria had 58% of the prevalence seen for Fukuda.

- Reynolds, K., Vernon, S., Bouchery, E. and Reeves, W. "The economic impact of chronic fatigue syndrome." *Cost Effectiveness and Resource Allocation* 2004, 2:4. PMID: 15210053. http://dx.doi.org/10.1186/1478-7547-2-4

- Jason LA, Richman JA, Rademaker AW, Jordan KM, Plioplys AV, Taylor R, McCready W, Huang, CF, Piloplys, S. "A community-based study of chronic fatigue syndrome." *Archives of Internal Medicine* October 1999; 159(18): 2129-2137. PMID: 10527290. http://dx.doi.org/10.1001/archinte.159.18.2129
- Jason L, Benton M, Valentine L, Johnson A, Torres-Harding S. "The Economic impact of ME/CFS: Individual and societal costs." *Dynamic Medicine* April 2008, 7:6. PMID: 18397528. http://dx.doi.org/10.1186/1476-5918-7-6

Data on population estimates..

a. United States Census Bureau, *Intercensal Estimates of the United States Population by Age and Sex, 1990-2000: All Months.* http://www.census.gov/popest/data/intercensal/national/index.html
b. United States Census Bureau, *National Intercensal Estimates (2000-2010)* http://www.census.gov/popest/data/intercensal/national/nat2010.html
c. United States Census Bureau, *National Totals: Vintage 2010-2013.* http://www.census.gov/popest/data/national/totals/2013/index.html and http://factfinder2.census.gov/bkmk/table/1.0/en/PEP/2013/PEPAGESEX

		Intercensal data - resident			
Year	Total	ME patients total (1)	Adults	ME Adults(1)	Children < 18
1999 January 1	277,789,896	1,172,273	206,170,711	870,040	71,619,185
2000 April 1	281,424,600	1,187,612	209,129,570	882,527	72,295,030
2008 April	304,093,966	1,283,277	229,989,364	970,555	74,104,602 -
2012 Jul 1	313,873,685	1,324,547	240,165,506	1,013,498	73,728,088
2013	316,128,839	1,334,064	242,542,967	1,023,531	73,585,872

T 1) based on 0.422% prevalence rate. (Total population * 0.422%)

[66] Petersen, D. Seminar On ME/CFS in the Swedish Parliament. October 29, 2013. http://rme.nu/seminarium-om-mecfs-i-sveriges-riksdag-16-oktober-2013 and http://www.youtube.com/watch?feature=player_embedded&v=AAnR2nIrkF4 Minute 3:40

Petersen stated, "Most of the patients are disabled in contrast to other diseases, HIV, diabetes, etc, which are devastating disease but people continue to work."

[67] Massey University, University of New Zealand. "Stigma of chronic fatigue illness adds to suffering" May 13, 2014. http://www.voxy.co.nz/health/stigma-chronic-fatigue-illness-adds-suffering-survey/5/189853 and http://www.massey.ac.nz/massey/about-massey/news/article.cfm?mnarticle_uuid=8689D1E6-DD19-C2AD-390E-FC170EEF020C

The article stated, "Survey respondents reported a very low quality of life, he [Baken] says. 'The average respondent was in the bottom 10 per cent of the population for measures such as the NIH PROMIS physical health scale [a measure of physical quality of life developed by the National Institute of Health in the US].' The survey author, Dr. Don Baken was quoted as saying, 'What's particularly interesting about all these findings is that this group reported worse scores than those with other neurological conditions such as Parkinson's and Multiple Sclerosis.'"

[68] Bateman, Lucinda. "Diagnostic Criteria for Systemic Exertion Intolerance Disease. Discussion of a new clinical criteria for ME/CFS." Published March 8, 2015.Last accessed March 10, 2015. https://www.youtube.com/watch?v=X4Tnt2d-5S8 Minute 23

Bateman discusses the differences fatigue in this disease from other diseases. She lists the following SF-36 vitality scores for different conditions: She stated the SF-36 Vitality subsection has three questions that have "different ways of asking about fatigue" which are added up to make the vitality score. The scores that she reported were

a) healthy people = 60
b) hemodialysis = 49
c) major depression = 40
d) rheumatoid arthritis = 52
e) CFS = 15-25
f) CFS and multiple chemical sensitivity = 15
stage 3 congestive heart failure = 29
Chronic Hepatitis C without cirrhosis = 48
systemic sclerosis, scleroderma = 45
FM = 38-39
CFS + FM = 20
CFS, FM and MCS=11

Bateman concluded, "This is stunning. That is an impressive impact, that is not just fatigue."

[69] "The Story of Sophia and M.E." InvestInME. Published shortly after her death. Last accessed March 29, 2015. http://www.investinme.org/Article-050%20Sophia%20Wilson%2001.htm

[70] Harding, L. "She went into a hellhole': A mother's candid account of her daughter's battle with ME." *Daily Mail: Mail Online.* Published by Associated Newspapers LTD. May 15, 2010. http://www.dailymail.co.uk/home/you/article-1277519/Criona-Wilson-recalls-daughters-losing-battle-ME-She-went-hellhole.html

Regarding Sophia Mirza's cause of death, Harding stated, "The coroner ruled that the 32-year-old had died of complications due to myalgic encephalomyelitis, a landmark verdict in the UK. A neuropathologist told the court that Sophia's spinal cord was inflamed, with three quarters of her sensory cells displaying significant abnormalities."

Regarding Sophia's sectioning into a psychiatric facility, Harding stated, – "In July 2003, the bell of the flat rang, hands hammered on the door. 'Sophia had told me she wasn't going to a mental hospital willingly and they would have to break in. I was scared beyond belief. The door smashed down, two policemen came in, the psychiatrist, the doctor, the social worker. They went to Sophia's room and put on the light. She hadn't had the light on in years.' Within 13 days, the Mental Health Review Tribunal discharged her but, according to Criona, Sophia's ordeal in a psychiatric ward devastated her fragile health. 'She went into a hellhole, devoid of energy. She could never come back from that."
See also:

- Wilson, Criona. "Sophia's Story." Sophie and M.E. May 2006. http://www.sophiaandme.org.uk/sophia%20&%20m.e.%20her%20story.html
  Criona Wilson is Sophia's mother. A video of Sophia's mom talking about her daughter's condition is located at https://www.youtube.com/watch?v=7mZMpvtD3rg
- Meridian Tonight TV News. Undated but broadcast after Sophia's death. Provided by InvestInME website. http://www.investinme.org/Mediatelevision2.htm
  This includes two reports – the first covers Sophia's condition, her sectioning and her death as reported by her mother while the second also covers the coroner's report, which had just been released.
- "Fatigue Syndrome Ruling Welcomed." BBC June 23, 2006. http://news.bbc.co.uk/2/hi/uk_news/5112050.stm
  Covers coroner's report.
- Barking, Havering and Redbridge Hospitals. Neuropathology Report. February 23, 2006. Last accessed April 25, 2015. http://www.sophiaandme.org.uk/neuropathologicalreport.html
- Additional information on the inquest and coroner's report can be found on the sites listed above. http://www.investinme.org/Article-050%20Sophia%20Wilson%2001-RIP.htm

[71] Gammel, Carol. "Lynn Gilderdale: how a 14-year-old was condemned to a life lived from a bed." *The Telegraph* Jan 26, 2010. http://www.telegraph.co.uk/news/uknews/law-and-order/7074234/Lynn-Gilderdale-how-a-14-year-old-was-condemned-to-a-life-lived-from-a-bed.html
Also

- Swain, Gill. "Trapped in bed for 14 years with chronic fatigue." *Daily Mail Mail Online* July 5, 2006. Published by Associated Newspapers LTD. http://www.dailymail.co.uk/health/article-393915/Trapped-bed-14-years-chronic-fatigue.html
  Includes the quote about only getting "accusations that she was pretending."
- Fernandez, Colin. "Why was this loving mother ever put on trial? Judge's anger as woman is cleared of attempted murder for helping her daughter die after 17 years of suffering" *Daily Mail Mail Online*. Published by Associated Newspapers LTD. January 26, 2010. http://www.dailymail.co.uk/news/article-1245930/Kay-Gilderdale-cleared-attempted-murder-daughter-Lynn.html

[72] Greg and Linda Crowhurst, "The Pain Consumes You." *Stonebird.* February 2015. Last accessed February 27, 2015. http://carersfight.blogspot.com/2015/02/the-pain-consumes-you.html

[73] Greg and Linda Crowhurst, "Understanding Paralysis : a repeated torture." *Stonebird.* February 2015. Last accessed February 27, 2015. http://carersfight.blogspot.com/2015/02/understanding-paralysis-repeated-torture.html
Greg and Linda have surveyed other patients with paralysis and documented the experience of paralysis in the following paper

- Greg and Linda Crowhurst. "Paralysis, a qualitative study of people with Severe Myalgic Encephalomyelitis." August 8, 2013. Last accessed February 25, 2015. http://forums.phoenixrising.me/index.php?attachments/paralysis-study-crowhurst-08-08-13-pdf.5499/

[74] Bailey, E. *The Sound of A Wild Snail Eating.* Algonquin Books. August 2010

[75] Anderson JS, Ferrans CE. "The quality of life of persons with chronic fatigue syndrome." *J Nerv Ment Dis* June 1997; 185(6): 359-67. PMID: 9205421. http://www.ncbi.nlm.nih.gov/pubmed/9205421

[76] Maupin, C. "The Unseen Price of CFS." *The CFS Report* May 5, 2008. http://www.cfidsreport.com/Articles/CFS/Societal_Costs-CFS.htm

[77] Schweitzer, Mary, Moderator. "Obama-Biden Transition Project, Health Care Community Discussion Report." December 30, 2008. http://www.cfids-me.org/dhhs/longreport.pdf Page 6

[78] Studies of of stigma, delayed diagnosis, financial, occupational and personal consequences of this disease

- Asbring P, Narvanen AL. "Women's experiences of stigma in relation to chronic fatigue syndrome and fibromyalgia." *Qual Health Res* 2002; 12(2): 148-60. PMID: 11837367. http://dx.doi.org/10.1177/104973230201200202
- Assefi NP, Coy TV, Uslan D, Smith, WR, Buchwald, D. "Financial, occupational, and personal consequences of disability in patients with chronic fatigue syndrome and fibromyalgia compared to other fatiguing conditions." *J Rheumatol.* April 2003; 30(4): 804-8. PMID: 12672203. http://www.jrheum.org/content/30/4/804.abstract
- Dickson A, Knussen C, Flowers P. "Stigma and the delegitimation experience: An interpretative phenomenological analysis of people living with chronic fatigue syndrome." *Psychol Health* October 2007; 22(7): 851-67. http://dx.doi.org/10.1080/14768320600976224
- Green J, Romei J, Natelson BH. "Stigma and chronic fatigue syndrome." *J Chronic Fatigue Syndr* 1999; 5(2): 63-75.

http://informahealthcare.com/doi/abs/10.1300/J092v05n02_04?src=recsys

- Guise J, McVittie C, McKinlay A. "A discourse analytic study of ME/CFS (Chronic Fatigue Syndrome) sufferers' experiences of interactions with doctors." *J Health Psychol.* April 2010; 15(3): 426-35. PMID: 20348363. http://dx.doi.org/10.1177/1359105309350515
- Jason LA, Taylor RR. "Measuring attributions about chronic fatigue syndrome." *J Chronic Fatigue Syndr* 2001; 8(3-4): 31- 40. http://informahealthcare.com/doi/abs/10.1300/J092v08n03_04
- Jason LA, Taylor RR, Stepanek Z, Piloplys, S. "Attitudes regarding chronic fatigue syndrome: The importance of a name." *J Health Psychol* Jan 2001; 6(1): 61-71. PMID: 22049238. http://hpq.sagepub.com/content/6/1/61.abstract

[79] Anderson JS, Ferrans CE. "The quality of life of persons with chronic fatigue syndrome." *J Nerv Ment Dis* June 1997; 185(6): 359-67. PMID: 9205421. http://www.ncbi.nlm.nih.gov/pubmed/9205421

[80] Massey University, University of New Zealand. "Stigma of chronic fatigue illness adds to suffering" May 13, 2014. http://www.voxy.co.nz/health/stigma-chronic-fatigue-illness-adds-suffering-survey/5/189853 and http://www.massey.ac.nz/massey/about-massey/news/article.cfm?mnarticle_uuid=8689D1E6-DD19-C2AD-390E-FC170EEF020C

The article quoted Dr. Don Baken as saying, "Many respondents felt stigmatised by the condition. Half indicated that they often felt embarrassed by their physical limitations and about a third felt embarrassed about the disease itself. Only about 15 per cent said that they never felt blamed for their condition by others." Dr. Baken also stated, "Because of the nature of the condition and the stigma that many feel because of it, it's difficult for this group to advocate for themselves." Dr. Baken went on to state, "More needs to be done to understand the impact of this condition and how society can support the people who suffer from it."

[81] Asbring P, Närvänen AL. "Ideal versus reality: physicians perspectives on patients with chronic fatigue syndrome (CFS) and fibromyalgia." *Soc Sci Med* August 2003; 57(4): 711-20. PMID: 12821018. http://dx.doi.org/10.1016/S0277-9536(02)00420-3

The paper stated, "The results also illuminate the physician's interpretations of patients in moralising terms. Conditions given the status of illness were regarded, for example, as less serious by the physicians than those with disease status. Scepticism was expressed regarding especially CFS, but also fibromyalgia. Moreover, it is shown how the patients are characterised by the physicians as ambitious, active, illness focused, demanding and medicalising. The patient groups in question do not always gain full access to the sick-role, in part as a consequence of the conditions not being defined as diseases"

[82] Jason, L. "Ending the stigma of ME/CFS." Presentation for the Dutch support group, ME/CVS Vereniging. 10 September 2014. *http://www.meassociation.org.uk/2014/09/ending-the-stigma-of-mecfs-new-professor-leonard-jason-video-18-september-2014/*

Jason stated, "Everyone feels fatigue at some point…Ordinary fatigue that most people experience is something that probably goes away when they go on vacation or are not stressed out for some many responsibilities. So most people think of fatigue in completely different ways than patients who have ME. So when a patient with ME says they don't have energy or don't have endurance or don't the stamina, individuals say I have all this stuff I have to do and I keep doing it so why cant you. And worst than that all, you don't look you're sick. The combination of those different characterizations leads to incredible societal attributions toward patients that probably is almost like the 21st century of lepers, what it might have been like 200 years for people with that other disease."

Other information on stigma:

- *Medical stigma – see the Medical Care chapter*
- *Family stigma* – Schweitzer, Mary, Moderator. "Obama-Biden Transition Project, Health Care Community Discussion Report." December 30, 2008. http://www.cfids-me.org/dhhs/longreport.pdf Page 6. The paper stated, that patients are "cast out by spouses or parents, scolded and disdained by siblings, and even abandoned by their churches "
- Stigma from the public. Examples include:
  - Simmons, Matt. CFS/ME: The Tortuous Disease." Uploaded August 2009. https://www.youtube.com/watch?v=IOflARSgNnE&feature=player_embedded#at=34 first 23 seconds Composite YouTube featuring Ricky Gervais, talking about ME in a comedy skit – "ME? Not MS - not the crippling wasting disease. No, the thing that makes you say 'I dont wanna go to work today.'"
  - Beiber, J. "Obama Chronic Fatigue Syndrome." The Mercury Columns. September 13, 2013. http://www.pottsmerc.com/opinion/20130915/john-c-beiber-obama-chronic-fatigue-syndrome

    The column stated, "If President 0bama really wants 0bamacare to be fully implemented, he should push for full medical benefits for "Obama Chronic Fatigue Syndrome." OCFS is a complicated disorder with symptoms of depression, headache, nausea, aversion to TV and radio news, fear of the IRS, NSA and extreme pain in the ears upon hearing words and phrases such as Benghazi, Egypt, Syria, Fast & Furious, Solyndra, Immigration Amnesty and Joe Biden."

[83] Jason L, Richman J, Friedberg F, Wagner L, Taylor R, Jordan K. "Politics, science, and the emergence of a new disease." *American Psychologist* September 1997; 52(9): 973-983. PMID: 9301342. http://dx.doi.org/10.1037/0003-066X.52.9.973

Jason makes the point that "depression that accompanies a prolonged illness may be better conceptualized as demoralization rather than a discrete psychiatric illness, particularly in ambiguous illnesses in which patients have difficulty gaining recognition that they have a legitimate nonpsychiatric illness."

[84] Moore, Billie. Statement to Health and Human Services CFS Advisory Committee. October 2012. *CFS Advisory Committee Website.* www.hhs.gov/advcomcfs/meetings/presentations/moore_billie_100412.pdf Matthew spoke anonymously in this testimony.

[85] Comeford, Barbara. "Presentation to the Chronic Fatigue Syndrome Advisory Committee." Presented at CFSAC on behalf of the New Jersey Chronic Fatigue Syndrome Association. October 2008. www.njcfsa.org/wp-content/uploads/2010/08/5-2-Presentation-to-the-Chronic-Fatigue-Syndrome-Advisory-Committee1.pdf Comeford is a disability attorney specializing in ME/CFS.

[86] Jackson, S. "Example School Accommodations for Kids with CFS." *Learning to Live With CFS*. March 23, 2012. http://livewithcfs.blogspot.com/2012/03/example-school-accommodations-for-kids.html

[87] Van Hoof E, De Becker P, De Meirleir K. "Pediatric Chronic Fatigue Syndrome and Munchausen-By-Proxy: A Case Study." *Journal of Chronic Fatigue Syndrome* 2006; 13(2-3): 45-53. http://informahealthcare.com/doi/abs/10.1300/J092v13n02_02
Blakemore Brown, L. "Autism and ME/CFS. A Modern Day Scandal." *Medical Misdiagnosis Research.* December 6, 2010. http://medicalmisdiagnosisresearch.wordpress.com/2010/12/06/autism-and-mecfs/

[88] Holder, Nelda. "Home for the holidays". *Mountain Xpress* (Asheville, North Carolina). Jan 6, 2010. http://www.mountainx.com/article/26040/Home-for-the-holidays and http://www.bringingryanhome.com/

[89] Straus S, Komaroff S, Wedner HJ. "Chronic Fatigue Syndrome: Point and Counterpoint." *The Journal of Infectious Diseases* July 1994; 170(1): 1-6. PMID: 8014482. http://dx.doi.org/10.1093/infdis/170.1.1

In 1993, Dr. Stephen Straus mediated a discussion at the annual meeting of the Infectious Disease Society of America. One of the speakers, Dr. H. James Wedner, Professor of Immunology and Allergy at Washington University and a clinician who had treated CFS patients, made the following statements:

- CFS "is neither a disease nor a syndrome. It is a case definition based upon a list of definitional criteria developed by a committee… The criteria were constructed to accommodate not only clinical problems but also social and political ones."
- "…There has been a creeping movement to include other types of medical conditions under the rubric of CFS. For example, various forms of post-infectious fatigue, fibromyalgia, and non-psychiatric and depressive disorders were permitted by consensus of a National Institutes of Health (NIH) workshop. Somatoform disorders and panic disorder became part of what could be encompassed within the CFS case definition. This serves to broaden the scope of the clinical entity to the point at which it is no longer definable."

The reference to the NIH Workshop is to the 1991 NIH Workshop that recommended relaxing the Holmes criteria.

[90] Sharpe M, Archard L, Banatvala J, Borysiewicz L, Clare A, David A, Edwards R, Hawton K, Lambert H, Lane R, McDonald E, Mowbray J, Pearson D, Peto T, Preedy V, Smith A, Smith D, Taylor D, Tyrrell D, Wessely S, White P. "A report—chronic fatigue syndrome." *J Roy Soc Med* February 1991; 84(2): 118-121. PMID: 1999813. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1293107/

As listed in the Oxford CFS definition, the criteria are:

a) "A syndrome characterized by fatigue as the principal symptom"
b) "A syndrome of definite onset that is not life long."
c) "The fatigue is severe, disabling and affects physical and mental functioning."
d) "The symptom of fatigue should have been present for a minimum of 6 months during which it was present for more than 50% of the time."
e) "Other symptoms *may* be present, particularly myalgia, mood and sleep disturbance."

The criteria then list exclusions of medical conditions known to cause fatigue and certain psychiatric illness – "schizophrenia, manic depressive illness, substance abuse, eating disorder or proven organic brain disease".

The Oxford definition describes fatigue as follows:

- "When used to describe a symptom this is a subjective sensation and has a number of synonyms including, tiredness and weariness. A clear description of the relationship of fatigue to activity is preferred to the term fatiguability…The symptom of fatigue should not be confused with impairment of performance as measured by physiological or psychological testing. The physiological definition of fatigue is of a failure to sustain muscle force or power output."

[91] Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A and the International Chronic Fatigue Syndrome Study Group. "The chronic fatigue syndrome: a comprehensive approach to its definition and study." *Ann Intern Med* 1994; 121(12): 953-9. PMID: 7978722. http://www.ncf-net.org/patents/pdf/Fukuda_Definition.pdf and http://dx.doi.org/10.7326/0003-4819-121-12-199412150-00009

[92] Reeves W, Wagner D, Nisenbaum R, Jones J, Gurbaxani B, Solomon L, Papanicolaou D, Unger E, Vernon S, Heim C. "Chronic Fatigue Syndrome – A clinically empirical approach to its definition and study." *BMC Medicine* December 2005; 3:19. PMID: 16356178. http://dx.doi.org/10.1186/1741-7015-3-19

The Empirical definition is referred to by a variety of names as covered in the section on the Empirical definition. This paper uses the term Empirical definition when referring to the approach to defining cases outlined in the 2003 and 2005 papers from Dr. Reeves and CDC

[93] Straus S, Komaroff S, Wedner HJ. "Chronic Fatigue Syndrome: Point and Counterpoint." *The Journal of Infectious Diseases* July 1994; 170(1): 1-6. PMID: 8014482. http://dx.doi.org/10.1093/infdis/170.1.1

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[94] Outbreaks occurred in a number of countries, including the United States, United Kingdom, Iceland, and Australia, and were referred to by a number of different disease names, including Benign Myalgic Encephalomyelitis (ME), Iceland Disease, and Akureyri Disease. In the U.S., there was an outbreak in Los Angeles in 1934. In 1986, British physician Melvin Ramsay established a definition that described the essential features of the disease that he had observed at London's Royal Free Hospital in the 1950s and used the term ME. One of the most complete compilations of outbreaks is the following compilation by Dr. J. Gordon Parish of the U.K.

- Gordon, J. "Reference index of papers published on epidemics of ME 1934-80 (collected by Dr J. Gordon Parish)". Undated but includes a review article from 1980. http://www.meresearch.org.uk/wp-content/uploads/2012/11/ResearchPublications1934-1980.pdf

[95] Royal Free Hospital Sources

- Acheson,E.D. "The clinical syndrome variously called benign myalgic encephalomyelitis, Iceland disease and epidemic neurasthaenia." *JAMA* April 1959; 26(4): 569- 595. PMID: 13637100. http://dx.doi.org/10.1016/0002-9343(59)90280-3 and *www.name-us.org/DefintionsPages/DefinitionsArticles/Acheson1959.pdf*
- Compston, N. "An outbreak of encephalomyelitis in the Royal Free Hospital Group, London in 1955." *Postgraduate Medical Journal* November 1987; 54(637): 722–724. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2425309/

  This paper stated "Those of the Medical Staff of the Royal Free Hospital who witnessed the epidemic in 1955 were firmly of the conclusion that they were dealing with an organic disease complicated by encephalomyelitis in which myalgia was a dominant feature. Objective evidence of brain stem and spinal cord involvement was observed."
- "Royal Free Hospital." Wikipedia. http://en.wikipedia.org/wiki/Royal_Free_Hospital

[96] Newsweek. "Chronic Fatigue Syndrome." *Newsweek Magazine,* November 11, 1990. http://www.thedailybeast.com/newsweek/1990/11/11/chronic-fatigue-syndrome.html
The article pointed out that the disease was not transmitted by the same routes as AIDS as it was as likely to be seen in siblings as in spouses.

[97] Anonymous. "A New Clinical Entity?" *Lancet.* May 26, 1956. 267(6926): 789-790. http://dx.doi.org/10.1016/S0140-6736(56)91252-1

The editorial, published anonymously stated, "For this reason, the term " benign myalgic encephalomyelitis "' may be acceptable. It in no way prejudices the arguments for or against a single or a related group of causal agents : and it does describe some of the striking features of a syndrome characterized by (1)symptoms and signs of damage to the brain and spinal cord, in a greater or lesser degree ; (2) protracted muscle pain with paresis and cramp : (3) emotional disturbances in convalescence ; (4) normal c.s.F. ; (5) involvement, in some variants, of the reticuloendothelial system; (6) 6) a protracted course with relapses in severe cases; and (7) a relatively benign outcome. [Author's note – meaning that death did not occur immediately after onset.] It remains to identify this syndrome more precisely; but we believe its characteristics are now sufficiently clear to differentiate it from poliomyelitis, epidemic myalgia, glandular fever, the forms of epidemic encephalitis already described, and, need it be said, hysteria."

[98] Review papers

- Acheson,E.D. "The clinical syndrome variously called benign myalgic encephalomyelitis, Iceland disease and epidemic neurasthaenia." *JAMA* April 1959; 26(4): 569- 595. PMID: 13637100. http://dx.doi.org/10.1016/0002-9343(59)90280-3 and *www.name-us.org/DefintionsPages/DefinitionsArticles/Acheson1959.pdf*
- Parish, JG. "A Review of 'The Clinical Syndrome Variously Called Benign Myalgic Encephalomyelitis, Iceland Disease and Epidemic Neuromyasthenia.'" Source undated.

http://www.meresearch.org.uk/information/publications/acheson-review/
This was a review of Acheson's 1959 paper cited in the last reference. Dr. Gordon Parish was a patron of ME Research UK.

- Henderson D, Shelokov A. "Epidemic Neuromyasthenia—Clinical Syndrome?" *N Engl J Med* April 9, 1959; 260(15): 757-764. PMID: 13644582. http://dx.doi.org/10.1056/NEJM195904092601506
  The authors stated "Careful appraisal reveals differences among the epidemics but most of these concern minor details."
- Gordon, J. "Reference index of papers published on epidemics of ME 1934-80 (collected by Dr J. Gordon Parish)". Undated but includes a review article from 1980. http://www.meresearch.org.uk/wp-content/uploads/2012/11/ResearchPublications1934-1980.pdf
- Ramsay AM, Rundle A. "Clinical and biochemical findings in ten patients with benign myalgic encephalomyelitis." *Postgraduate Medical Journal* December 1979; 55(654):856-7.
  http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2425703/

[99] Henderson D, Shelokov A. "Epidemic Neuromyasthenia—Clinical Syndrome?" *N Engl J Med* April 9, 1959; 260(15): 757-764. PMID: 13644582. http://dx.doi.org/10.1056/NEJM195904092601506
The authors stated "Careful appraisal reveals differences among the epidemics but most of these concern minor details."

[100] "History of Chronic Fatigue Syndrome." Wikipedia.
http://en.wikipedia.org/wiki/History_of_chronic_fatigue_syndrome

[101] "Epidemic myalgic encephalomyelitis." *British Medical Journal* 3 June 1978; 1(6125): 1436–1437.
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1604957/

This article was the lead article resulting from a symposium held in 1978 with the permission of the Council of the Royal Society of Medicine. As noted on page 1437 of the article "Epidemic myalgic encephalomyelitis", the attendees at the symposium agreed that:

- "the cardinal clinical features show that the disorder is an encephalomyelitis; "Iceland disease" is not specific enough; and "neuromyasthenia" suggests a relation to myasthenia gravis whereas the muscle fatigability is different, as are the electrophysiological findings. Indeed, the exhaustion and tiredness are similar to that described by patients with multiple sclerosis. From the patient's point of view the designation benign is also misleading, since the illness may be devastating. Originally the term was used because no deaths had been recorded from myalgic encephalomyelitis.
- "Some authors have attempted to dismiss this disease as hysterical, but the evidence now makes such a tenet unacceptable."
- "The organic basis is clear – from the finding that the putative agent can be transferred to monkeys, the detection of an increased urinary output of creatine, the persistent finding of abnormal lymphocytes in the peripheral blood of some patients, the presence of lymphocytes and an increased protein concentration in the cerebrospinal fluid of occasional patients and the neurological findings."

The editorial concluded "We still know nothing about the nature and cause of epidemic myalgic encephalomyelitis, but outbreaks are still occurring. Future epidemics should be studied by a collaborative team of neurologists, epidemiologists, virologists, and immunologists. Its findings would be important not only for the study of epidemic myalgic encephalomyelitis but also for other neurological disorders, including multiple sclerosis."
The full proceedings from the symposium were published later in the year in the Postgraduate Medical Journal

- Postgraduate Medical Journal November 1978: 54(637): 709-774.
  http://pmj.bmj.com/content/54/637.toc#Articles
  The Forward to the full proceedings: http://pmj.bmj.com/content/54/637/709.full.pdf+html
  This entire issue was devoted to the proceedings of this symposium. According to the Forward of this issue, the goal was to "bring the condition to the attention of the profession." Speakers included those from the U.S., Ireland and the U.K. from a range of disciplines. The symposium discussed the "outbreaks, possible etiology and the clinical findings" and management of future outbreaks. The Forward stated that the symposium asked the following 5 questions:
  1. "Is there a definite nosological entity?"
  2. "Is it organic, psychogenic or hysterical in origin?"
  3. "Does 'epidemic neuromyasthenia' describe the condition correctly?"
  4. "What are the main criteria for the diagnosis of the syndrome?"
  5. "How should it be studied?"

[102] Ramsay issued two articles on the definition, one in 1986 and one in 1988. Some sources indicate that Ramsay published the definition in 1981 but this author's research was unable to confirm that.

- Ramsay, M. "Myalgic Encephalomyelitis: A Baffling Syndrome With a Tragic Aftermath." Published 1986. http://www.meactionuk.org.uk/ramsey.html and http://www.name-us.org/DefintionsPages/DefRamsay.htm#MYALGIC_ENCEPHALOMYELITIS_:_A_Baffling_Syndrome_With_a_Tragic_Aftermath

- Ramsay, M. *Myalgic Encephalomyelitis and Postviral Fatigue States: The Saga of Royal Free Disease,* Gower Medical Publishing Corporation, London, 2nd ed. 1988.
  Extract provided by Connie Nelson to Mary Schweitzer who provided it on http://www.cfids-me.org/ramsay86.html
- Ramsay AM, Rundle A. "Clinical and biochemical findings in ten patients with benign myalgic encephalomyelitis." *Postgraduate Medical Journal* December 1979; 55(654):856-7. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2425703/
  The article states that one of the dominant clinical features of the disease is "Abnormal muscular fatigability and weakness. Muscular power was restored by a period of rest but recurred following further activity." The study findings are discussed with "particular reference to recent suggestions that the permeability of cell membranes may be impaired by changes in intracellular energy mechanisms."

[103] Ramsay, AM. "The clinical identity of the myalgic encephalomyelitis syndrome." Published in an article by ME Association in late 1980s or early 1990s. http://web.onetel.com/~kickback/THE%20CLINICAL%20IDENTITY%20OF%20ME.html
Dr. Ramsay notes the confusion that arose because of the use of the term post-viral fatigue states in the 1988 publication above and reinforced the hallmark symptoms of ME, which included "A unique form of muscle fatiguability whereby, even after a minor degree of physical effort, 3,4,5 days or longer elapse before full muscle power is restored." The article also stated "The unique form of muscle fatiguability described above is virtually a sheet-anchor in the diagnosis of Myalgic Encephalomyelitis and without it a diagnosis should not be made."

[104] Arnold DL, Bore PJ, Radda GK, Styles P, Taylor DJ. "Excessive intracellular acidosis of skeletal muscle on exercise in a patient with a post-viral exhaustion/fatigue syndrome. A 31P nuclear magnetic resonance study." *Lancet* June 23, 1984; 323(8391):1367-9. PMID: 6145831. http://dx.doi.org/10.1016/S0140-6736(84)91871-3

[105] Newton J. "Understanding Muscle Dysfunction in M.E./CFS." Video of presentation given at the annual meeting of Action on ME in London. November 8, 2013. http://www.prohealth.com/library/showarticle.cfm?libid=18528
Newton discussed a number of findings including a large increase in acid in skeletal muscle with exercise along with a reduction in anaerobic exercise.
Also see
- Brown AE, Jones DE, Walker M, Newton JL. "Abnormalities of AMPK Activation and Glucose Uptake in Cultured Skeletal Muscle Cells from Individuals with Chronic Fatigue Syndrome." *PLoS ONE.* April 2, 2015. 10(4): e0122982. Last accessed April 4, 2015. http://dx.doi.org/10.1371/journal.pone.0122982
- Jones DE, Hollingsworth KG, Jakovljevic DG, Fattakhova G, Pairman J, Blamire AM, Trenell MI, Newton JL. "Loss of capacity to recover from acidosis on repeat exercise in chronic fatigue syndrome: a case-control study." *Eur J Clin Invest.* Feb 2012; 42(2): 186-94. Last accessed April 4, 2015. http://dx.doi.org/10.1111/j.1365-2362.2011.02567.x
- Newcastle University Press Office. "You and ME: working together to discover causes of CFS/ME." Newcastle University. April 23, 2013. http://www.ncl.ac.uk/press.office/press.release/item/you-and-me-working-together-to-discover-biological-causes-of-cfs-me#.UXa0goI89q5
- He J, Hollingsworth K, Newton J, Blamirea A. "Cerebral vascular control is associated with skeletal muscle pH in chronic fatigue syndrome patients both at rest and during dynamic stimulation." *Neuroimage Clin* 2013; 2: 168–173. PMID: 24179772. http://dx.doi.org/10.1016/j.nicl.2012.12.006
- Devlin, Hannah. "Biological breakthroughs offer fresh hope for ME sufferers." *The Times.* April 23, 2013. http://www.meassociation.org.uk/2013/04/biological-breakthrough-offers-fresh-hope-for-me-sufferers-the-times-23-april-2013/

[106] In addition to the specific sources cited here, other sources on the Incline Village and Lyndonvville outbreaks are listed in the "Key Resources" appendix, especially the early articles and videos.

[107] Johnson, Timothy. Nightline. ABC News. Video is undated reported as circa 1987
- Part 1 - http://www.youtube.com/watch?v=CqpvRC_YurY&feature=player_embedded
- Part 2 - http://www.youtube.com/watch?v=ta39YmPCUQ0&feature=player_embedded Part 2

[108] Newsweek. "Chronic Fatigue Syndrome." *Newsweek Magazine,* November 11, 1990. http://www.thedailybeast.com/newsweek/1990/11/11/chronic-fatigue-syndrome.html

[109] "Living Hell: The Real World of Chronic Fatigue Syndrome." Produced by Authentic Pictures in association with the CFIDS Foundation, San Francisco. Video undated but reported as 1993.
- Part 1 - http://www.youtube.com/watch?v=KGFVXacPuho
- Part 2 - http://www.youtube.com/watch?v=Q0EjR2yepHg
- Part 3 - http://www.youtube.com/watch?v=1stOT72UCQw
- Part 4 - http://www.youtube.com/watch?v=bGphVlRKovY
- Part 5 - http://www.youtube.com/watch?v=wD363vqG38U
- Part 6 - http://www.youtube.com/watch?v=ISteyLtnxOo

[110] *PrimeTime Live.* Hosts Sam Donaldson and Nancy Snyderman. ABC News. Broadcast in 1996. http://www.youtube.com/watch?v=AW0x9_Q8qbo.

Investigation of handling of the Incline Village and Lyndonville outbreaks.

[111] Johnson, Hilary. *Osler's Web: Inside the Labyrinth of the Chronic Fatigue Syndrome Epidemic*. Crown Publishing Group, New York. 1996. Available on Amazon.

[112] *PrimeTime Live.* Hosts Sam Donaldson and Nancy Snyderman. ABC News. Broadcast in 1996. http://www.youtube.com/watch?v=AW0x9_Q8qbo. Minute: 2:28

[113] Ibid. Minute 3:43

[114] Ibid. Minute 4:48

Hilary Johnson said "The tone behind the scenes at the CDC was one of complete and utter ridicule. Employees at the CDC would make jokes about this disease. If anyone eve said I'm tired, they would be teased about having this fake, bogus disease."

[115] Ibid. Minute 6:23

[116] Ibid. Minute 6:10

[117] Ibid. Minute 3:50

[118] United States Centers for Disease Control. *Mortality and Morbidity Weekly Report*, May 30 1986. 35(21);350-2. http://www.cdc.gov/mmwr/preview/mmwrhtml/00000740.htm

CDC also published a paper in the Journal of the American Medical Association in May of 1987, which was dismissive of the Incline Village patients.

- Holmes GP, Kaplan JE, Stewart JA, Hunt B, Pinsky PF, Schonberger LB. "A Cluster of Patients with a Chronic Mononucleosis-like Syndrome: Is Epstein-Barr Virus the Cause?" *JAMA* May 1, 1987; 257(17): 2297-302. PMID: 3033337. http://dx.doi.org/10.1001/jama.1987.03390170053027

[119] *PrimeTime Live.* Hosts Sam Donaldson and Nancy Snyderman. ABC News. Broadcast in 1996. http://www.youtube.com/watch?v=AW0x9_Q8qbo. Minute: 5:05

Regarding the 1986 report, Dr. Cheney said "the overall message, the tone of the paper was that this did not appear to be anything - at all"

[120] Straus S, Dale J, Tobi M, Lawley T, Preble O, Blaese M,, Hallahan C, Henle W. "Acyclovir Treatment of the Chronic Fatigue Syndrome." *N Engl J Med* December 29, 1988; 319(26): 1692-1698. PMID: 2849717. http://dx.doi.org/10.1056/NEJM198812293192602

[121] Richman J, Jason L, Taylor R, Jahn S. "Feminist Perspectives On The Social Construction Of Chronic Fatigue Syndrome." *Health Care for Women International* October 2000. 21(3): 173-185. PMID: 11111464. http://dx.doi.org/10.1080/073993300245249

Richman quotes Ware and Kleinman to say "'Liberated' by feminism to enter previously all-male occupations, women in the 1970's found themselves exhorted to 'have it all' by combining a demanding career with a rich and fulfilling family life. This meant juggling a number of incompatible identities." (Ware and Kleinman, 1992, p. 554). (Page 176).

[122] Johnson, Timothy. Part 1. Nightline. ABC News. Video is undated reported as circa 1987. http://www.youtube.com/watch?v=CqpvRC_YurY&feature=player_embedded. Minute 7:20.

[123] Ibid. Minute 7:40.

[124] Brody, Jane. "Health, Personal Health." *New York Times*. New York, New York. Archives. July 28, 1988. http://www.nytimes.com/1988/07/28/us/health-personal-health.html?src=pm&pagewanted=1

Dr. Straus was interviewed for this report, in which he emphasized psychological issues at the root of the disease. According to Brody, Dr Straus said that "many patients were psychologically 'different' long before they developed the syndrome. He described some patients as having been anxious and depressed with various neurotic symptoms for years before becoming ill. In other cases, patients were motivated, dynamic, driven individuals who were functioning at peak levels when stricken. Some may be under an undue amount of stress trying to maintain busy lives."

[125] Straus SE, Dale JK, Wright R, Metcalfe DD. "Allergy and the Chronic Fatigue Syndrome." *Journal of Allergy and Clinical Immunology* May 1988; 81(5)" 791-795. PMID: 2836490. http://dx.doi.org/10.1016/0091-6749(88)90933-5

Straus stated "The demography of this syndrome reflects an excessive risk for educated adult white women. This may reflect either a bias toward the cohort of sufferers who can best afford a sophisticated medical evaluation or some unique constitutional frailty of such individuals. Most patients with this syndrome report excellent prior health. Some had engaged in competitive sports or at least aggressively maintained physical conditioning. A less casual appraisal, however, often uncovers histories of unachievable ambition, poor coping skills, and somatic complaints…It is difficult and at times unpleasant to address the demands of such patients or to test hypotheses as to the etiology of their woes."

[126] Holmes GP, Kaplan JE, Stewart JA, Hunt B, Pinsky PF, Schonberger LB. "A Cluster of Patients with a Chronic Mononucleosis-like Syndrome: Is Epstein-Barr Virus the Cause?" *JAMA* May 1, 1987; 257(17): 2297-302. PMID: 3033337. http://dx.doi.org/10.1001/jama.1987.03390170053027

The paper states: "Since the 1930s, several reports have described syndromes of chronic debilitating fatigue associated with low-grade fever, myalgias, arthralgias, sore throat, headaches, neurological complaints, and a variety of other symptoms. Although these syndromes are remarkably similar, they have been described by several names,

including Akureyri disease, Iceland disease, atypical poliomyelitis," benign myalgic encephalomyelitis, epidemic neuromy- asthenia, encephalomyelitis, and postviral syndrome."

[127] Holmes G, Kaplan J, Gantz N, Komaroff A, Schonberger L, Straus S, Jones J, Dubois R, Cunningham-Rundles C, Pahwa S, Tosato G, Zegans L, Purtilo D, Brown N, Schooley R, Brus I. "Chronic Fatigue Syndrome: A Working Case Definition." *Annals of Internal Medicine.* March 1, 1988; 108(3): 387-389. PMID: 2829679. http://dx.doi.org/10.7326/0003-4819-108-3-387 *and* http://www.ncf-net.org/patents/pdf/Holmes_Definition.pdf

The introduction spoke about chronic Epstein-Barr virus syndrome and said that despite its name, "both the diagnostic value of Epstein-Barr virus serologic tests and the proposed causal relationship between Epstein-Barr virus infection and patients who have been diagnosed with the chronic Epstein-Barr virus syndrome remain doubtful. We propose a new name for the chronic Epstein-Barr virus syndrome—the chronic fatigue syndrome—that more accurately describes this symptom complex as a syndrome of unknown cause characterized primarily by chronic fatigue."

[128] Tuller, David. "Chronic Fatigue Syndrome and the CDC: A Long, Tangled Tale." *Virology Blog About Viruses and Viral Disease,* November 23, 2011. http://www.virology.ws/2011/11/23/chronic-fatigue-syndrome-and-the-cdc-a-long-tangled-tale/

Dr. Racaniello states: "In its 1988 paper on the illness, a CDC-led team of researchers cast doubt on the Epstein-Barr hypothesis and rechristened the phenomenon "chronic fatigue syndrome" to discourage unproven assumptions about viral origins."

[129] Jason, L., Richman, J. "How Science Can Stigmatize: The Case of Chronic Fatigue Syndrome." *Journal of Chronic Fatigue Syndrome* 2007; 14(4): 85-103. http://informahealthcare.com/doi/abs/10.3109/10573320802092146 and http://web.archive.org/web/20120228222416/http://www.cfids-cab.org/cfs-inform/CFS.case.def/jason.richman.07.txt

[130] The Holmes definition was discussed at a roundtable discussion at the end of the First International Symposium on the Immunobiology and Pathogenesis of Persistent Virus Infections held by CDC in April 1987. This conference and the position taken by Drs. Parish and Shelokov were discussed in:

- Hyde, B. "A Brief History of Myalgic Encephalomyelitis and an Irreverent History of Chronic Fatigue Syndrome." presented at the London Conference, May 12, 2006. http://www.imet.ie/imet_documents/BYRON_HYDE_little_red_book.pdf
- Dr. Hyde states that he also attended the meeting but left when Drs. Parish and Shelokov did. (Page 19, 23). This article also gives an extensive review of the problems with the Holmes definition
- Marshall E, Williams M, Hooper M. "What is ME? What is CFS? Information for Clinicians and Lawyers." December 2001. http://www.investinme.org/Article-020 What is ME What is CFS.htm and http://www.meactionuk.org.uk/What_Is_ME_What_Is_CFS.htm

[131] Ibid.

[132] Schwartz RB, Komaroff AL, Garada BM, Gleit M, Doolittle TH, Bates DW, Vasile RG, Holman BL. "SPECT imaging of the brain: comparison of findings in patients with chronic fatigue syndrome, AIDS dementia complex, and major unipolar depression." *AJR Am J Roentgenol* April 1994; 162(4): 943–951. PMID: 8141022. http://www.ajronline.org/doi/abs/10.2214/ajr.162.4.8141022

The article stated:

- "The midcerebral uptake index was found to be significantly lower ($p < .002$) in the patients with chronic fatigue syndrome and patients with AIDS dementia complex (.650) than in patients with major depression or healthy control subjects."
- "The pathophysiologic process in the CNS of patients with CFS would seem more similar to that in patients with ADC [AIDS Dementia Complex] than that in patients with unipolar depression."
- "Although neuropathologic data in patients with CFS are unavailable, the findings in CFS are consistent with hypothesis that CFS also results from viral infection of neurons, glia, on vasculature."

[133] Jason, L, Torres-Harding, S, Jurgens, A, Helgerson, J. "Comparing the Fukuda et al. Criteria and the Canadian Case Definition for Chronic Fatigue Syndrome, Journal of Chronic Fatigue Syndrome 2004; 12(1): 37-52. http://informahealthcare.com/doi/abs/10.1300/J092v12n01_03?src=recsys and http://web.archive.org/web/20120216181206/http://www.cfids-cab.org/cfs-inform/CFS.case.def/jason.etal04.pdf

Jason states, "However, problems emerged in doing research with this case definition, Katon et al. found that patients with CFS were indistinguishable from those with chronic fatigue who did not meet the 1988 Holmes et al. criteria (4). Another concern with the original CFS criteria was that the requirement of eight or more minor symptoms could inadvertently select for individuals with psychiatric problems."

The referenced Katon paper is:

- Katon WJ, Buchwald DS, Simon GE, Russo JE, Mease PJ. "Psychiatric illness in patients with chronic fatigue and those with rheumatoid arthritis." *J Gen Intern Med* July-August 1991; 6(4): 277-85. PMID: 1890495. http://www.ncbi.nlm.nih.gov/pubmed/1890495 and http://link.springer.com/article/10.1007%2FBF02597420#page-1

[134] In the early 1990s, researchers and clinicians were reporting a variety of immune abnormalities, neurological issues and evidence of viral infection. There were even reports of B- cell abnormalities at that time. Margaret Williams from the U.K. has compiled documentation about the early research studies.

- Part 1 – 1956-1990. Compiled April 2011. http://www.investinme.org/Article422%20Grey%20Information%20About%20ME-CFS.htm
- Part 2 - 1991 – 1993. Compiled May 2011. http://www.investinme.org/Article422-2%20Grey%20Information%20about%20ME%20CFS%20Part%20II.htm
- Part 3 -1994. Compiled November 2011. http://www.investinme.org/Article422-3%20Grey%20Information%20about%20ME%20CFS%20Part%20III.htm
- Tuller, David. "Chronic Fatigue Syndrome and the CDC: A Long, Tangled Tale." *Virology Blog About Viruses and Viral Disease,* November 23, 2011. http://www.virology.ws/2011/11/23/chronic-fatigue-syndrome-and-the-cdc-a-long-tangled-tale/
- Klimas NG, Salvato FR, Morgan R, Fletcher MA. "Immunologic abnormalities in chronic fatigue syndrome." *J Clin Microbiol* June 1990; 28(6): 1403-10. PMID: 2166084. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC267940/

[135] Tuller, David. "Chronic Fatigue Syndrome and the CDC: A Long, Tangled Tale." *Virology Blog About Viruses and Viral Disease,* November 23, 2011. http://www.virology.ws/2011/11/23/chronic-fatigue-syndrome-and-the-cdc-a-long-tangled-tale/.

The quotes are from the Tuller article, which references the following study:

- Buchwald D, Cheney PR, Peterson DL, Henry B, Wormsley SB, Geiger A, Ablashi DV, Salahuddin SZ, Saxinger C, Biddle R, Kikinis R, Jolesz FA, Folks T, Balachandran N, Peter JB, Gallo R, Komaroff AL."A chronic illness characterized by fatigue, neurologic and immunologic disorders, and active human herpesvirus type 6 infection." *Ann Intern Med.* January 15, 1992; 116(2): 103-13. PMID: 1309285. http://dx.doi.org/10.7326/0003-4819-116-2-103

  The authors of this study also stated, "The active replication of HHV-6 most likely represents reactivation of latent infection, perhaps due to immunologic dysfunction."

[136] Lusso P, Ensoli B, Markham P, Ablashi D, Salahuddin SZ, Tschachler E, Wong-Staal F, Gallo R. "Productive dual infection of human CD4+ T lymphocytes by HIV-1 and HHV-6." Letters to Nature. Nature January 26, 1989; 337(6205), 370-373. PMID: 2463490. http://dx.doi.org/10.1038/337370a0

The letter stated, "Although infection by HIV-1 has been implicated as the primary cause of AIDS and related disorders[3,4], cofactorial mechanisms may be involved in the pathogenesis of the disease." The paper discussed several viruses like herpesviruses, papovaviruses, and adenoviruses as potential cofactors which could contribute to the disease.

[137] Tuller, David. "Chronic Fatigue Syndrome and the CDC: A Long, Tangled Tale." *Virology Blog About Viruses and Viral Disease,* November 23, 2011. http://www.virology.ws/2011/11/23/chronic-fatigue-syndrome-and-the-cdc-a-long-tangled-tale/

Tuller stated, "In a letter to the journal listing more than a dozen purported methodological flaws, the CDC—with Dr. Reeves as the lead author—dismissed the Harvard study and its findings in unusually blunt terms. 'We conclude that the disease…described is not the chronic fatigue syndrome or any other clinical entity and that they showed no association with active HHV-6 replication,' wrote Dr. Reeves and his colleagues."

The letter sent in response to the Buchwald paper is:

- Reeves W, Pellett P, Gary H. "The Chronic Fatigue Syndrome Controversy." *Ann Intern Med.* August 15, 1992; 117(4): 343-344. PMID: 1322077. http://dx.doi.org/10.7326/0003-4819-117-4-343

ME/CFS Forum, a patient advocacy forum also has a reference to this letter.
http://www.mecfsforums.com/wiki/ME/CFS_Timeline

- MECFS Forum quotes the letter as saying "To the Editors: Buchwald and colleagues conclude that the chronic fatigue observed in their patients may reflect an immunologically mediated inflammatory process of the central nervous system and may be associated with human herpesvirus 6 (HHV-6). The authors, however, failed to consider organic causes of chronic fatigue for analysis as a separate category and referred to neurologic symptoms without specifying diagnostic criteria. The study also lacked appropriate controls; this was not a cohort study with matched controls, as stated in the abstract, but a case series with variously selected nonmatched controls..."

  MECFS Forum goes on to quote the letter as saying "We conclude that the disease Buchwald and co-workers described is not chronic fatigue syndrome or any other clinical entity, and that they showed no association with active HHV-6 replication."

[138] *PrimeTime Live.* Hosts Sam Donaldson and Nancy Snyderman. ABC News. Broadcast in 1996. http://www.youtube.com/watch?v=AW0x9_Q8qbo. Minute 10:15

It's worth noting that the same report interviews Dr. Phillip Lee, Assistant Secretary of Health who states that he does believe that Lake Tahoe represented a cluster of the disease and that not everyone agreed with CDC's conclusions. Unfortunately, that did not change what CDC did.

[139] Department of Health and Human Services. Recommendations of the Chronic Fatigue Syndrome Advisory Committee to the Secretary of Health. October 3-4, 2012. *CFS Advisory Committee Website.*
Department of Health and Human Services. "Responses to Recommendations from the Chronic Fatigue Syndrome Advisory Committee. Ref: October 3-4, 2012 CFSAC Meeting." Undated. Last accessed April 1, 2015. http://www.hhs.gov/advcomcfs/recommendations/response-from-ash-10-2012.pdf

- The CFSAC Recommendation stated, "Allocating specific funds to study patients with ME/CFS from past cluster outbreaks" http://www.hhs.gov/advcomcfs/recommendations/10032012.html
- The HHS response to this recommendation stated, "Studying CFS clusters or outbreaks, if they are detected, is a worthwhile project. To date, CDC has not been able to confirm the occurrence of outbreaks of CFS. Studies of potential outbreaks or clusters would greatly benefit from better understanding the different spectrums of CFS and clearly defining what constitutes an outbreak or a cluster."

[140] Hyde, B. "A Brief History of Myalgic Encephalomyelitis and an Irreverent History of Chronic Fatigue Syndrome." presented at the London Conference, May 12, 2006.
http://www.imet.ie/imet_documents/BYRON_HYDE_little_red_book.pdf

[141] McEvedy C, Beard A. "Royal Free Epidemic of 1955: A Reconsideration." *Br Med J* January 3, 1970; 1(5687): 7–11. PMID: 5411611. http://dx.doi.org/10.1136/bmj.1.5687.7

The authors state: "From a re-analysis of the case notes of patients with Royal Free disease it is concluded that there is little evidence of an organic disease affecting the central nervous system and that epidemic hysteria is a much more likely explanation. The data which support this hypothesis are the high attack rate in females compared with males; the intensity of the malaise compared with the slight pyrexia; the presence of subjective features similar to those seen in a previous epidemic of hysterical overbreathing [sic]; the glove-and-stocking distribution of the anaesthesia [sic]; and the normal findings in special investigations."
McEvedy C, Beard A. "Concept of Benign Myalgic Encephalomyelitis." *Br Med J.* January 3, 1970; 1(5687): 11–15. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1700895/

The authors state "We believe that a lot of these epidemics were psychosocial phenomena caused by one of two mechanisms, either mass hysteria on the part of the patients or altered medical perception of the community."

[142] Selected correspondence in response to McEvedy and Beard

- Scott BD. "Epidemic malaise." *Br Med J* January 17, 1970. 1 (5689): http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1699088/?page=1
- Compston N, Dimsdale H, Ramsay A, Richardson A.."Epidemic malaise." *Br Med J* February 7, 1970;
- 1(5692): 362–363. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1699022/?page=1
- Acheson ED. "Epidemic malaise." *Br Med J* February 7, 1970; 1(5692): 363. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1698971/?page=1
- Galpine JF. "Epidemic malaise." Br Med J February 21, 1970; 1(5694): 501. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1699416/?tool=pmcentrez&forumid=331851
- Poskanzer DC. "Epidemic malaise." *Br Med J* May 16, 1970; 2 (5706): 420–1. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1700311/?page=1
- Parish JG. "Epidemic malaise.". *Br Med J* July 4, 1970; 3 (5713): 47–8. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1700986/?page=2

[143] McEvedy C, Beard A. "Concept of Benign Myalgic Encephalomyelitis." *Br Med J* January 3, 1970; 1(5687): 11-15. Last accessed February 9, 2015. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1700895/

Of one of the outbreaks, the paper stated on page 13, "In our view, the "epidemic" was an artifact due to an altered medical perception of the community. The corollary to this view is that the syndrome which characterized the patients after admission was due to (1) a rising anxiety level on the part of patients who were under threat of paralysis and (2) a concentration of medical examination on the central nervous system." The paper went on to state that the symptoms experienced by the patients were because of "a preoccupation with poliomyelitis on the part of both doctors and patients."

[144] Abbey SE, Garfinkel PE. "Neurasthenia and chronic fatigue syndrome: the role of culture in the making of a diagnosis." *Am J Psychiatry* December 1991;148(12):1638-46. PMID: 1957925. http://www.ncbi.nlm.nih.gov/pubmed/1957925

The authors stated "Chronic fatigue syndrome is an increasingly popular diagnosis consisting of multiple psychiatric and somatic symptoms. It bears a striking resemblance to the nineteenth-century diagnosis of neurasthenia. Both disorders arose during periods characterized by a preoccupation with commerce and material success and major changes in the role of women. They illustrate the role of culture in the development of a new diagnosis that emphasizes a "medical" rather than "psychiatric" etiology. The authors argue that chronic fatigue syndrome will meet the same fate as neurasthenia--a decline in social value as it is demonstrated that the majority of its sufferers are experiencing primary psychiatric disorders or psychophysiological reactions and that the disorder is often a culturally sanctioned form of illness behavior."

Letters in response to this article are here: http://ajp.psychiatryonline.org/article.aspx?articleID=169098 and http://www.docstoc.com/docs/69274336/I-Am-Psychiatry-December-Dr-Abbey-and-Dr--neurasthenia

[145] Richman J, Jason L, Taylor R, Jahn S. "Feminist Perspectives On The Social Construction Of Chronic Fatigue Syndrome." *Health Care for Women International* October 2000. 21(3): 173-185. PMID: 11111464. http://dx.doi.org/10.1080/073993300245249

[146] Richman J, Jason L. "Gender Biases Underlying the Social Construction of Illness States: The Case of Chronic Fatigue Syndrome." *Current Sociology* May 2001; 49(3): 15-29. PMID: http://dx.doi.org/10.1177/0011392101049003003

[147] While the quotes listed here are from the 1980s, this view can not be dismissed as an antiquated view, no longer held. Here is an example of a more recent paper presenting the same approach.

- Harvey S, Wessely S. "Chronic fatigue syndrome: identifying zebras amongst the horses." *BMC Me*d October 2009; 7: 58. PMID: 19818158. http://dx.doi.org/10.1186/1741-7015-7-58

The following paper was written in response to this paper.

- Maes M, Twisk F. "Chronic fatigue syndrome: Harvey and Wessely's (bio)psychosocial model versus a bio(psychosocial) model based on inflammatory and oxidative and nitrosative stress pathways." *BMC Med* June 15, 2010;8:35. PMID: 20550693. http://dx.doi.org/10.1186/1741-7015-8-35

[148] Wessely S, David A, Butler S, Chalder T. "Management of chronic (post-viral) fatigue syndrome." *J R Coll Gen Pract* January 1989; 39(318): 26–29. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1711569/ and http://www.simonwessely.com/Downloads/Publications/CFS/4.pdf

The authors stated "A model is outlined of an acute illness giving way to a chronic fatigue state in which symptoms are perpetuated by a cycle of inactivity, deterioration in exercise tolerance and further symptoms. This is compounded by the depressive illness that is often part of the syndrome. The result is a self-perpetuating cycle of exercise avoidance….Cognitive behavioural therapy… helps the patient understand how genuine symptoms arise from the frequent combination of physical inactivity and depression, rather than continuing infection, while a behavioural approach enables the treatment of avoidance behaviour and a gradual return to normal physical activity."

[149] Wessely, S., Powell, R. "Fatigue syndromes: A comparison of chronic "postviral" fatigue with neuromuscular and affective disorders." *Journal of Neurology, Neurosurgery, and Psychiatry* 1989; 52:940-948 http://jnnp.bmj.com/content/52/8/940.

This study compared three different groups. The first was patients with unexplained fatigue, which they labeled "CFS." The second group had "peripheral fatigue", namely neuromuscular disorders. The third group had what the authors called "central fatigue;" the patients were diagnosed with major depression. The neuromuscular disease included myasthenia gravis, myopathies, Guillan-Barre syndrome and "a variety of rare genetic or metabolic muscle disorders" but excluded "Neurological disorders with central involvement" like MS. The study stated that the "CFS" patients "more closely resembled patients with psychiatric disorders than patients with neuromuscular disorders associated with peripheral fatigue."

[150] Wessely, S. "Old wine in new bottles: Neurasthenia and 'me'." *Psychological Medicine* February 1990; 20(1): 35-53. PMID: 2181519. http://dx.doi.org/10.1017/S0033291700013210

Richman J, Jason L. "Gender Biases Underlying the Social Construction of Illness States: The Case of Chronic Fatigue Syndrome." *Current Sociology* May 2001; 49(3): 15-29. PMID: http://dx.doi.org/10.1177/0011392101049003003

[151] Wessely S, David A, Butler S, Chalder T. "Management of chronic (post-viral) fatigue syndrome." *J R Coll Gen Pract* January 1989; 39(318): 26–29. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1711569/ and http://www.simonwessely.com/Downloads/Publications/CFS/4.pdf

The authors state "The development and persistence of chronic fatigue syndrome can be understood using a cognitive-behavioral model. This is used to explain the observed progression from the avoidance of most forms of activity during the initial acute illness which is both necessary and adaptive to chronic avoidance behaviors which are maladaptive."

Also see

- Hooper M. and members of the ME Community, Department of Life Sciences, University of Sunderland. "The Mental Health Movement: Persecution of Patients? Background Briefing for the House of Commons [UK] Select Health Committee." December 2003. http://www.meactionuk.org.uk/SELECT_CTTEE_FINAL_VERSION.htm
  Hooper et al summarized sources that demonstrated a psychological view of this disease. Another source, included in Hooper's list is
  - Wessely S. "Chronic fatigue and myalgia syndromes." In *Psychological Disorders in General Medical Settings*. Edited by N Sartorius et al. Published by Huber 1990.

    Wessely et al stated "Most CFS patients fulfil diagnostic criteria for psychiatric disorder. Symptoms include muscle pain and many somatic symptoms, especially cardiac, gastrointestinal and neurological. Do any of these symptoms possess diagnostic significance? The answer is basically negative. It is of interest that the 'germ theory' is gaining popularity at the expense of a decline in the acceptance of personal responsibility for illness. Such attribution conveys certain benefits, in other words, there is avoidance of guilt and blame. It is this author's belief that the interactions of the attributional, behavioural and affective factors is responsible for both the initial presentation to a physician and for the poor prognosis."

[152] Borrell-Carrió F, Suchman A, Epstein R. "The Biopsychosocial Model 25 Years Later: Principles, Practice, and Scientific Inquiry." *Ann Fam Med* November-December 2004; 2(6): 576-582. PMID: 15576544 http://dx.doi.org/10.1370/afm.245

[153] Jason, L. Letter to the Editor, Psychology Today, May 12, 2005 in response to "Chronic Fatigue: How Your Mind makes You Sick" published in May-June 2005 issue. http://www.theoneclickgroup.co.uk/news.php?id=785#newspost
The first paragraph of the original article that Jason is responding to can be found here:

- Schorr, Melissa. "Is It All In My Head?" Psychology Today. May-June 2005. https://web.archive.org/web/20050506170832/http://cms.psychologytoday.com/articles/pto-20050503-000002.html

[154] There is a group of doctors in England and another group in Netherlands that promote what they refer to a "biopsychosocial" or "psychosocial" model of CFS. The following two articles discuss this theory. The work of Wessely is referred to as the "biopsychosocial" approach where the work of Vercoulen was described by Maes as a psychosocial approach. Both models emphasize psychological and social factors as far more important than biological factors, which are typically relegated to triggering the illness and possibly to deconditioning caused by inactivity

- Harvey S, Wessely S. "Chronic fatigue syndrome: identifying zebras amongst the horses." *BMC Me*d October 2009; 7: 58. PMID: 19818158. http://dx.doi.org/10.1186/1741-7015-7-58
- Vercoulen JH, Swanink CM, Galama JM, Fennis JF, Jongen PJ, Hommes OR, van der Meer JW, Bleijenberg G. "The persistence of fatigue in chronic fatigue syndrome and multiple sclerosis: development of a model." *J Psychosom Res.* December 1998; 45(6):507–517. PMID: 9859853. http://dx.doi.org/10.1016/S0022-3999(98)00023-3

[155] This proposed protocol for a review of exercise in CFS, issued in 2014, contains the following description of the "Biopsychosocial" model for CFS.

- Larun L, Odgaard-Jensen J, Brurberg KG, Chalder T, Dybwad M, Moss-Morris RE, Sharpe M, Wallman K, Wearden A, White PD, Glasziou PP. "Exercise therapy for chronic fatigue syndrome (individual patient data)." *Cochrane Database of Systematic Reviews* April 2014, Issue 4. http://dx.doi.org/10.1002/14651858.CD011040

  The authors state that the biopsychosocial model for CFS "distinguishes between precipitating and maintaining factors. Precipitating factors may include acute infective illness and/or excessive stress, while the illness is maintained by the interaction of behavior, thoughts, emotions and physiology."

  According to the authors, in this model, patients experienced "exacerbations of symptoms" when they tried to get back to normal following an acute illness. This convinced patients that they had an ongoing illness and led to patients becoming inactive and concerned about their health.

  This inactivity is postulated to lead to "physiological changes such as cardiovascular and muscular deconditioning, dysregulation of the hypothalamic-pituitary-adrenal axis and disrupted circadian rhythms. In this deconditioned state, any activity is liable to produce symptoms, the experience of which reinforces the fearful beliefs and hence reinforces the avoidance of activity (fear avoidance)."

  Note that this article states that the Editorial Group for this review is the Cochrane Depression, Anxiety and Neurosis Group. The Cochrane Collaboration Depression, Anxiety and Neurosis Review Group (CCDAN) is responsible for preparing Cochrane reviews that cover a broad range of mental health issues including mood disorders, anxiety disorders, somatoform disorders and eating disorders. (http://ccdan.cochrane.org/editorial-team)

[156] Regarding the "biopsychosocial" approach, Dr. Michael Maes pointed out that both the "biopsychosocial" approach as described by Professor Wessely and the similar psychosocial approach described by Dr. J. Vercoulen focused either entirely or almost entirely on psychosocial factors and ignored the existing biological evidence, particularly that for immune activation, inflammation, oxidative stress and persistent or reactivating infections and the fact that exercise intensifies the biology pathophysiology

- Maes M, Twisk F. "Chronic fatigue syndrome: Harvey and Wessely's (bio)psychosocial model versus a bio(psychosocial) model based on inflammatory and oxidative and nitrosative stress pathways." *BMC Med* June 15, 2010; 8:35. PMID: 20550693. http://dx.doi.org/10.1186/1741-7015-8-35

Dr. Maes was responding in part to these two articles, especially the first one:

- Harvey S, Wessely S. "Chronic fatigue syndrome: identifying zebras amongst the horses." *BMC Me*d October 2009; 7: 58. PMID: 19818158. http://dx.doi.org/10.1186/1741-7015-7-58
- Vercoulen JH, Swanink CM, Galama JM, Fennis JF, Jongen PJ, Hommes OR, van der Meer JW, Bleijenberg G. "The persistence of fatigue in chronic fatigue syndrome and multiple sclerosis: development of a model." *J Psychosom Res.* December 1998; 45(6):507–517. PMID: 9859853. http://dx.doi.org/10.1016/S0022-3999(98)00023-3

[157] Dr. Wessely's theory of activity avoidance is behind the large PACE trial.
White PD, Goldsmith KA, Johnson AL, Potts L, Walwyn R, DeCesare JC, Baber HL, Burgess M, Clark LV, Cox DL, Bavinton J, Angus BJ, Murphy G, Murphy M, O'Dowd H, Wilks D, McCrone P, Chalder T, Sharpe M. "Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): a randomised trial." *The Lancet* March 5, 2011; 377(9768): 823-836. PMID: 21334061. http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(11)60096-2/fulltext

The PACE trial, done in patients that met the Oxford definition, tested cognitive behavioral therapy (CBT) and graded exercise therapy (GET) which were used, according to the Trial publication, "on the basis of the fear avoidance theory of chronic fatigue syndrome" that "assume that the syndrome is perpetuated by reversible physiological changes of deconditioning and avoidance of activity." The theory underlying CBT is often described as "false illness beliefs".

[158] Examples of CFS being referred to as Somatorm illness.

- Fink, Per. "Somatoform disorders – functional somatic syndromes – Bodily distress syndrome. Need for care and organisation of care in an international perspective - EACLPP Lecture." Presentation to European Association for Consultation-Liaison Psychiatry and Psychosomatics. Undated. http://www.eaclpp.org/tl_files/content/Presentations/EACLPP_Per Fink_Somatoform Disorders.pdf
  Also see information on somatoform disorders on the website for Per Fink's Clinic, The Research Clinic for Functional Disorders and Psychosomatics at Aarhus University Hospital www.functionaldisorders.dk
- First, Michael. "Somatic Presentations of Mental Disorders." Summary of presentations given at the conference cosponsored by the APA in collaboration with WHO and NIH. Sept 6-8, 2006 in Beijing, China. http://www.dsm5.org/research/pages/somaticpresentationsofmentaldisorders(september6-8,2006).aspx
  The conference was the eighth in a series of 12 NIH-funded conferences on "The Future of Psychiatric Diagnosis: Refining the Research Agenda." Dr. First included the following summaries on talks given at the conference:
  - First described Wessely's presentation on the functional somatic syndromes which included irritable bowel syndrome, CFS, fibromyalgia and others, which he stated occurred regularly in common practice.
  - "Laurence Kirmayer MD (Montreal, Canada) presented on the role of cultural models in the phenomenology of somatoform disorders in which "cognitive processes and social responses can lead to more symptoms….Similarly,in chronic fatigue syndrome, symptoms lead to activity restriction which in turn leads to more symptoms."

[159] This article by Dr. Maes includes additional explanation of the "biopsychosocial model" as does the PACE trial itself

- Maes M, Twisk F. "Chronic fatigue syndrome: Harvey and Wessely's (bio)psychosocial model versus a bio(psychosocial) model based on inflammatory and oxidative and nitrosative stress pathways." *BMC Med* June 15, 2010; 8:35. PMID: 20550693. http://dx.doi.org/10.1186/1741-7015-8-35
- White PD, Goldsmith KA, Johnson AL, Potts L, Walwyn R, DeCesare JC, Baber HL, Burgess M, Clark LV, Cox DL, Bavinton J, Angus BJ, Murphy G, Murphy M, O'Dowd H, Wilks D, McCrone P, Chalder T, Sharpe M. "Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): a randomised trial." *The Lancet* March 5, 2011; 377(9768): 823-836. PMID: 21334061. http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(11)60096-2/fulltext
  - The study report states that PACE subscribes to the "fear avoidance theory of chronic fatigue syndrome" that "assume that the syndrome is perpetuated by reversible physiological changes of deconditioning and avoidance of activity." Page 825
  - Additional information is provided in the PACE trial manuals, available through the PACE Trial information website http://www trial.org/trialinfo/
    - PACE trial CBT Manual
      Burgess M, Chalder T. "PACE Manual for Therapists. Cognitive Behavioral Therapy for CFS/ME." MREC Version 2. November 2004. http://www.pacetrial.org/docs/cbt-therapist-manual.pdf
      The manual states "It is important to include the precipitating factors, e.g., illness, life-events, working excessively hard, perfectionist personality etc. It is also important to discuss the maintaining factors, e.g., erratic or reduced activities, disturbed sleep patterns, unhelpful illness beliefs and any other unhelpful cognitions etc." (Page 81)
    - PACE trial GET Manual
      PACE Trial Management Group. "PACE Manual for Therapists. Graded Exercise Therapy for CFS/ME.".Version 2. http://www.pacetrial.org/docs/get-therapist-manual.pdf .
      The manual states "GET assumes that CFS/ME is perpetuated by deconditioning (lack of fitness), reduced physical strength and altered perception of effort consequent upon reduced physical activity." (Page 20). The manual also states "Planned physical activity and not symptoms are used to determine what the participant does." (Page 21)

[160] White PD, Goldsmith KA, Johnson AL, Potts L, Walwyn R, DeCesare JC, Baber HL, Burgess M, Clark LV, Cox DL, Bavinton J, Angus BJ, Murphy G, Murphy M, O'Dowd H, Wilks D, McCrone P, Chalder T, Sharpe M. "Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): a randomised trial." *The Lancet* March 5, 2011; 377(9768): 823-836. PMID: 21334061. http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(11)60096-2/fulltext

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Subsequent publications on the PACE trial included one publication claiming patients recovered and another that claimed that the effect of CBT and GET was mediated by changes in 'fear avoidance beliefs."

- White PD, Goldsmith K, Johnson AL, Chalder T, Sharpe M, PACE Trial Management Group. "Recovery from chronic fatigue syndrome after treatments given in the PACE trial." Psychol Med. October 2013' 43(10): 2226-2235. PMID: 23363640. http://dx.doi.org/10.1017/S0033291713000020
- Prof Trudie Chalder T, Goldsmith K, White P, Sharpe M, Pickles A. "Rehabilitative therapies for chronic fatigue syndrome: a secondary mediation analysis of the PACE trial." The Lancet Psychiatry. February 2015; 2(2); p141–152. Last accessed on January 27, 2015. http://dx.doi.org/10.1016/S2215-0366(14)00069-8
  This paper stated that it investigated "putative treatment mechanisms" and concluded, "Our main finding was that fear avoidance beliefs were the strongest mediator for both CBT and GET. Changes in both beliefs and behaviour mediated the effects of both CBT and GET, but more so for GET. The results support a treatment model in which both beliefs and behaviour play a part in perpetuating fatigue and disability in chronic fatigue syndrome."

[161] Comments on issues with the conduct of the PACE trial can be found in published comments on the above trials and also in the following sources

- Comments submitted on PACE Trial protocol. *BMC Neurology*. 2010. http://www.biomedcentral.com/1471-2377/7/6/comments#310638
- Rapid Responses to the Chalder 2015 mediation paper. *BMJ* January 2015; 350: h227. Last accessed February 1, 2015. http://www.bmj.com/content/350/bmj.h227/rapid-responses
- Hooper, Malcolm. "MAGICAL MEDICINE: HOW TO MAKE A DISEASE DISAPPEAR." InvestInME. February 2010. http://www.investinme.org/Documents/Library/magical-medicine.pdf
  Provides an extensive review of PACE and related issues. The document states that is provides "Background to, consideration of, and quotations from the Manuals for the Medical Research Council's PACE Trial of behavioural interventions for Chronic Fatigue Syndrome / Myalgic Encephalomyelitis, together with evidence that such interventions are unlikely to be effective and may even be contra-indicated."
- ME Association. "ME Association response to PACE trial recovery paper." Submitted to *Psychological Medicine.* February 16, 2013. http://www.meassociation.org.uk/2013/02/me-association-response-to-pace-trial-recovery-paper-15-february-2013/ Sent to in response to the following paper:
  White PD, Goldsmith K, Johnson AL, Chalder T, Sharpe M, PACE Trial Management Group. "Recovery from chronic fatigue syndrome after treatments given in the PACE trial." Psychol Med. October 2013' 43(10): 2226-2235. PMID: 23363640. http://dx.doi.org/10.1017/S0033291713000020
- ME Association (UK). "Pace Trial" Letters and reply. Journal of Psychological Medicine. August 2013." From the Journal of Psychological Medicine. *http://www.meassociation.org.uk/2013/07/pace-trial-letters-and-reply-journal-of-psychological-medicine-august-2013/*
- Petrison, Lisa. "Problems with the PACE Study." *ParadigmChange*. http://paradigmchange.me/pace/
  Selected issues highlighted by Petrison include:
  - Patient selection based on Oxford criteria
  - Patients are designated to be recovered at an SF-36 score of 60 while they need a score of 65 to get into the trial (higher score is less sick)
  - The effect sizes were small, a point made by Snell below
  - Focus was on fatigue and ignored symptoms like cognitive issues
  - Inflated claims of recovery and improvement
- Snell, C. "Repeated CPET Results as Clinical Endpoints for ME/CFS Research." Presentation to U.S. Food and Drug Administration, Center for Drug Evaluation and Research (CDER). "Drug Development For Chronic Fatigue Syndrome And Myalgic Encephalomyelitis: Public Workshop. Day Two. Scientific Drug Development Meeting." April 26, 2013. http://www.fda.gov/downloads/Drugs/NewsEvents/UCM355406.pdf
  Video http://www.tvworldwide.com/events/fda/130425/globe_show/default_go_archive.cfm?gsid=2251
  Minute 72 – 76 Snell converted the PACE trial 6 minute walk test results (1.9mph – 2.3mph) to a work capacity of 2 METS which equates to 7ml.min/kg O2) defined by Weber/NYHA. Dr. Snell said that this is level that is seen in ME patients. This level is considered severely disabled and according to Snell would "unlikely to be eligible for heart transplant because they would not survive it"

[162] Kindlon, T. "Objective measures found a lack of improvement for CBT & GET in the PACE Trial: subjective improvements may simply represent response biases or placebo effects in this non-blinded trial." BMJ January 18, 2015; 350 http://www.bmj.com/content/350/bmj.h227/rr-10
This is a rapid response to the February 2015 Chalder paper on "Rehabilitative therapies for chronic fatigue syndrome: a secondary mediation analysis of the PACE trial."

[163] Kindlon T. "Reporting of Harms Associated with Graded Exercise Therapy and Cognitive Behavioural Therapy in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome." *Bulletin of the IACFS/ME* Fall 2011; 19(2):59-111. http://www.iacfsme.org/BULLETINFALL2011/Fall2011KindlonHarmsPaperABSTRACT/tabid/501/Default.aspx

Kindlon reports, "However, exercise-related physiological abnormalities have been documented in recent studies and high rates of adverse reactions to exercise have been recorded in a number of patient surveys. "Fifty-one percent of survey respondents (range 28-82%, n=4338, 8 surveys) reported that GET worsened their health while 20% of respondents (range 7-38%, n=1808, 5 surveys) reported similar results for CBT.

[164] Dalen, Per. "Somatic medicine abuses psychiatry — and neglects causal research" Copyright 2003. Available on http://www.art-bin.com/art/dalen_en.html
Dalen's article was also quoted in the following:

- Williams, Margaret. "Some concerns about the National Institute for Health and Clinical Excellence (NICE) Guideline issued on 29th September 2006 on Diagnosis and Management of Chronic Fatigue Syndrome/Myalgic Encephalomyelitis in Adults and Children." October 19, 2006. http://www.meactionuk.org.uk/Concerns_re_NICE_Draft.pdf
- Margaret Williams, U.K. advocate, made selected quotes of this article available at http://www.meactionuk.org.uk/Quote_by_M_Williams_from_Per_Dalen_Jan_2003.htm

[165] Yancey J, Thomas S. "Chronic Fatigue Syndrome: Diagnosis and Treatment." *American Family Physician* October 15, 2012; 86(8):741-746. PMID: 23062157 http://www.aafp.org/afp/2012/1015/p741.html
For patient reaction to this article see:
Bernhard, Toni. "Another Blow to Chronic Fatigue Syndrome Sufferers." *Turning Straw into Gold, Psychology Today,* November 2, 2012. http://www.psychologytoday.com/blog/turning-straw-gold/201211/another-blow-chronic-fatigue-syndrome-sufferers.

[166] National Alliance on Mental Illness (NAMI). "Treatment and Services. Cognitive Behavioral Therapy." Last Reviewed July 2012.
http://www.nami.org/Content/NavigationMenu/Inform_Yourself/About_Mental_Illness/About_Treatments_and_Supports/Cognitive_Behavioral_Therapy1.htm

[167] Schluederberg A, Straus S, Peterson P, Blumenthal S, Komaroff A, Spring S, Landay A, Buchwald D. "NIH Conference. Chronic Fatigue Syndrome Research Definition and Medical Outcome Assessment." *Annals of Internal Medicine* August 1992; 117(4): 325-31. PMID: 1322076. http://annals.org/article.aspx?articleid=705740 (abstract) and http://annals.org/data/Journals/AIM/19757/AIME199208150-00010.pdf (full text)

This paper recommended that the new definition be made less restrictive to include patients with certain psychiatric disorders - major depressive episodes (not including those with psychotic features), panic disorder (with or without ag- oraphobia), generalized anxiety disorder, and somatoform disorder. The paper stated that to ensure replicability, it would be necessary to note features like time of onset, whether recurrent or not, whether active at time of onset of CFS, response to therapy, etc. The paper also stated that these patients had to be handled separately in analysis. The rationale as stated in the paper for grouping in psychiatric illness this was that it would "foster an integrative approach that gives consideration to issues relating to comorbidity and possible common pathogenic pathways in patients with CFS and psychic stress. Such an approach should lead to a better understanding of factors underlying CFS."
Authors Note: This paper makes the case that these psychiatric cases are included in the definition but separated for analysis. But in practice, most of the scientific papers I have seen treat them as a single group and do not stratify patients.
Other key points

- The report noted considerable discussion on how to best include psychiatric patients and on "techniques for quantifying and qualifying the degree of psychiatric suffering."
- The participants agreed that there were no laboratory tests for diagnosis and that tests should be done just to exclude other diseases using "an economical but comprehensive battery of laboratory tests."
- Acknowledged contributors included Susan E. Abbey, MD; Michael A. Caligiuri, MD; Chun C. Chao, PhD; Paul R. Cheney, PhD, MD; Patricia K. Coyle, MD; Mark A. Demitrack, MD; Robert Fekety, MD; Don L. Goldenberg, MD; Walter Gunn, PhD; Wayne J. Katon, MD; Andrew R. Lloyd, MB BS; Nicole Lurie, PhD; Peter Manu, MD; Anita Stewart, PhD; Warren Strober, Robert J. Suhadolnik, PhD; and Simon Wessely, MRC Psych. According to the text, the participants were involved in the creation of Holmes, Oxford or the Australian definition.

[168] Straus, Stephen. "Defining the Chronic Fatigue Syndrome." Editorial. *Arch Intern Med* August 1992; 152(8): 1569-1570. http://archinte.jamanetwork.com/article.aspx?articleid=616488

Straus discussed the NIH 1991 Workshop and stated, "A workshop convened jointly last year in Bethesda, Md [sic], by the National Institute of Allergy and Infectious Diseases and the National Institute of Mental Health and organized to review the status of the CDC case definition in research, ascertained that most investigators, including those conducting the ongoing CDC prevalence study of chronic fatigue syndrome in four US cities, accept a concurrent diagnosis of depression or anxiety disorder. Still others accept such problems when they predate chronic fatigue but were not active when the fatigue itself began. Until prospectively acquired data reveal whether either of these is a reasonable strategy, the suggestion made was that investigators document psychiatric problems and stratify for them in data analysis."

[169] Jacobson D. "Chronic Fatigue Debate Still Going Strong." *Hartford Courant*. December 25, 1989. Accessed through *Los Angeles Times*. http://articles.latimes.com/1989-12-25/local/me-751_1_chronic-fatigue-syndrome

The article headline states "Thousands who suffer from the syndrome, and their doctors, claim it's caused by a virus. But researchers say the syndrome is rare, if it exists at all, and psychological." The article body states"…the University of Connecticut researchers [which included Dr. Manu], say people with CFS symptoms start with a history of recurrent mental illness, including depression, panic attacks and other disorders. Their physical symptoms then emerge from patients' unspoken "psycho-emotional conflicts."

[170] Dalen, Per. "Somatic medicine abuses psychiatry — and neglects causal research" Copyright 2003. Available on http://www.art-bin.com/art/dalen_en.html

[171] Hyde BM, Goldstein J, Levine P. "The clinical and scientific basis of myalgic encephalomyelitis/chronic fatigue syndrome." Publisher Nightingale Research Foundation, Ottawa. 1992.

The dedication states "This book and the Cambridge Symposium were to be the joint work of an informal association of British physicians who meet under the title of the EME or the Epidemic Myallgic Encephalomyelitis Study Group."

[172] Centers for Disease Control and Prevention, National Center for Health Statistics, Office of the Center Director, Data Policy and Standards. "A Summary of Chronic Fatigue Syndrome and Its Classification in the International Classification of Diseases." March 2001 http://web.archive.org/web/20140611042505/http://www.co-cure.org/ICD_code.pdf

[173] Ibid.

This summary from NCHS states, "WHO published ICD-10 in 1992 and included many modifications, among them relocation of some diagnoses to different chapters within the classification. WHO created a new category G93, Other disorders of brain, in Chapter VI, Diseases of the Nervous System, and created a new code G93.3, Postviral fatigue syndrome, a condition which was previously in the symptom chapter of ICD-9. WHO also moved benign myalgic encephalomyelitis to the new code G93.3. The alphabetic index contains other terms, such as chronic fatigue syndrome, that WHO considers synonymous or clinically similar."

Note that the ICD-10 has a tabular listing that lays out the primary categories and terms of ICD. It also has an alphabetical index which indexes additional terms back to the terms of the tabular index. ME is in the tabular listing at G93.3 and CFS is in the alphabetical index at G93.3

[174] Straus S, Komaroff S, Wedner HJ. "Chronic Fatigue Syndrome: Point and Counterpoint." *The Journal of Infectious Diseases* July 1994; 170(1): 1-6. PMID: 8014482. http://dx.doi.org/10.1093/infdis/170.1.1

[175] Lloyd A, Hickie I, Boughton R, Spencer,O. Wakefield D. "Prevalence of chronic fatigue syndrome in an Australian population." *Med JAust* 1990;153:522-528. PMID: 2233474. http://www.ncbi.nlm.nih.gov/pubmed/2233474

[176] Sharpe M, Archard L, Banatvala J, Borysiewicz L, Clare A, David A, Edwards R, Hawton K, Lambert H, Lane R, McDonald E, Mowbray J, Pearson D, Peto T, Preedy V, Smith A, Smith D, Taylor D, Tyrrell D, Wessely S, White P. "A report—chronic fatigue syndrome." *J Roy Soc Med* February 1991; 84(2): 118-121. PMID: 1999813. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1293107/

The criteria for Oxford CFS are:

a) "A syndrome characterized by fatigue as the principal symptom"
b) "A syndrome of definite onset that is not life long"
c) "The fatigue is severe, disabling and affects physical and mental functioning"
d) "The symptom of fatigue should have been present for a minimum of 6 months during which it was present for more than 50% of the time"
e) "Other symptoms *may* be present, particularly myalgia, mood and sleep disturbance"

Fatigue is described as follows:

"When used to describe a symptom this is a subjective sensation and has a number of synonyms including, tiredness and weariness. A clear description of the relationship of fatigue to activity is preferred to the term fatiguability…The symptom of fatigue should not be confused with impairment of performance as measured by physiological or psychological testing. The physiological definition of fatigue is of a failure to sustain muscle force or power output."

[177] Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A and the International Chronic Fatigue Syndrome Study Group. "The chronic fatigue syndrome: a comprehensive approach to its definition and study." *Ann Intern Med* 1994; 121(12): 953-9. PMID: 7978722. http://www.ncf-net.org/patents/pdf/Fukuda_Definition.pdf and http://dx.doi.org/10.7326/0003-4819-121-12-199412150-00009

[178] Jason L, Richman J, Friedberg F, Wagner L, Taylor R, Jordan K. "Politics, science and the emergence of a new disease." *American Psychologist* September 1997; 52(9): 973-983. PMID: 9301342 http://www.ncbi.nlm.nih.gov/pubmed/9301342

Jason discusses the impact of how a disease is conceptualized on the definition and treatment of CFS. He states, "If inappropriate use of the case definition leads to the inclusion of individuals who only have a psychiatric condition, this heterogeneity of psychiatric and CFS patients will present difficulties in interpreting the results of epidemiologic and treatment studies."

[179] M. Sharpe was listed as one of Fukuda's authors and S. Wessely was on the International Chronic Fatigue Study Group which was also listed as an author and included authors of the Oxford, Holmes and apparently the Australian definition.

[180] Jason L, Richman J, Friedberg F, Wagner L, Taylor R, Jordan K. "Politics, science and the emergence of a new disease." *American Psychologist* September 1997; 52(9): 973-983. PMID: 9301342 http://www.ncbi.nlm.nih.gov/pubmed/9301342

[181] On page 955, the Fukuda definition states the following psychiatric exclusions: "Any past or current diagnosis of a major depressive disorder with psychotic or melancholic features; bipolar affective disorders; schizophrenia of any subtype; delusional disorders of any subtype; dementias of any subtype; anorexia nervosa; or bulimia nervosa." No other psychiatric disorders are listed as being exclusionary.

[182] Jason, L. "Defining CFS: Diagnostic Criteria and Case Definition". Presented at CFIDS Association webinar, April 14, 2010..http://web.archive.org/web/20120425130843/http://www.cfids.org/webinar/jason-slides041410.pdf On slides 10 and 12, Jason's presentation discusses the fact that Fukuda does not require core symptoms and that depressed patients can have fatigue plus 4 of the Fukuda symptoms - unrefreshing sleep, joint pain, muscle pain and impairment in concentration. Oxford is even broader than Fukuda and specifically allows the inclusion of psychiatric patients.

[183] Komaroff AL, Cho TA. "Role of infection and neurologic dysfunction in chronic fatigue syndrome." *Semin Neurol* July 2011 31(3): 325-337. PMID: 21964849. http://dx.doi.org/10.1055/s-0031-1287654
This paper reviews neurological changes along with the role of infection as a triggering event. Two examples stated in the paper are:

- "multiple studies have demonstrated hypofunction of corticotropin-releasing (CRH) neurons in the hypothalamus, and hypocortisolism (distinct from Addison disease). This downregulation of the hypothalamic–pituitary–adrenal (HPA) axis in CFS stands in contrast to the upregulation seen in major depression."
- "Neuropsychological testing of cognition has revealed abnormalities in patients with CFS, abnormalities not explained by a coexisting depression."

[184] Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A and the International Chronic Fatigue Syndrome Study Group. "The chronic fatigue syndrome: a comprehensive approach to its definition and study." *Ann Intern Med* 1994; 121(12): 953-9. PMID: 7978722. http://www.ncf-net.org/patents/pdf/Fukuda_Definition.pdf and http://dx.doi.org/10.7326/0003-4819-121-12-199412150-00009
The Fukuda definition states:

"The complexities of the chronic fatigue syndrome and the methodologic problems associated with its study 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. We propose a conceptual framework and a set of guidelines that provide such an approach. Our guidelines include recommendations for the clinical evaluation of fatigued persons, a revised case definition of the chronic fatigue syndrome, and a strategy for subgrouping fatigued persons in formal investigations."

"We propose a conceptual framework (Figure 1) to guide the development of studies relevant to the chronic fatigue syndrome. In this framework, in which the chronic fatigue syndrome is considered a subset of prolonged fatigue (>1 month), epidemiologic studies of populations defined by prolonged or chronic fatigue can be used to search for illness patterns consistent with the chronic fatigue syndrome. Such studies, which differ from case- control and cohort studies based on predetermined criteria for the chronic fatigue syndrome, will also produce much-needed clinical and laboratory background information."

[185] Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A and the International Chronic Fatigue Syndrome Study Group. "The chronic fatigue syndrome: a comprehensive approach to its definition and study." *Ann Intern Med* 1994; 121(12): 953-9. PMID: 7978722. http://www.ncf-net.org/patents/pdf/Fukuda_Definition.pdf and http://dx.doi.org/10.7326/0003-4819-121-12-199412150-00009

The Fukuda definition stated, "In formal studies, cases of the chronic fatigue syndrome and idiopathic chronic fatigue should be subgrouped before analysis or stratified during analysis by the presence or absence of essential variables, which should be routinely established in all studies."

[186] Harvey S, Wessely S. "Chronic fatigue syndrome: identifying zebras amongst the horses." *BMC Me*d October 2009; 7: 58. PMID: 19818158. http://dx.doi.org/10.1186/1741-7015-7-58

The authors stated, "Currently, most diagnostic criteria suggest CFS should not be diagnosed when an active medical or psychiatric condition is identified which may explain the fatigue. This implies that the aetiology of 'unexplained' CFS is different to that of the 'explained' fatigue seen in those with a diagnosed medical condition."

[187] Wessely S, Chalder T, Hirsch S, Wallace P, Wright D. "The prevalence and morbidity of chronic fatigue and chronic fatigue syndrome: a prospective primary care study." *Am J Public Health* September 1997; 87(9): 1449–1455. PMID. 9314795. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1380968/

[188] Jason, L., Richman, J. "How Science Can Stigmatize: The Case of Chronic Fatigue Syndrome." *Journal of Chronic Fatigue Syndrome* 2007; 14(4): 85-103. http://informahealthcare.com/doi/abs/10.3109/10573320802092146 and

http://web.archive.org/web/20120228222416/http://www.cfids-cab.org/cfs-inform/CFS.case.def/jason.richman.07.txt

[189] Harvey S, Wessely S. "Chronic fatigue syndrome: identifying zebras amongst the horses." *BMC Me*d October 2009; 7: 58. PMID: 19818158. http://dx.doi.org/10.1186/1741-7015-7-58

The authors stated "Thus, current recommendations advising a range of simple investigations (Appendix) for those with persistent fatigue seem well placed. Jones et al. did find some 'zebras' but, as expected, these were relatively rare. A simple mental state examination appears to remain the most productive single investigation in any new person presenting with unexplained fatigue."

[190] Examples of Oxford studies include

- White PD, Goldsmith KA, Johnson AL, Potts L, Walwyn R, DeCesare JC, Baber HL, Burgess M, Clark LV, Cox DL, Bavinton J, Angus BJ, Murphy G, Murphy M, O'Dowd H, Wilks D, McCrone P, Chalder T, Sharpe M. "Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): a randomised trial." *The Lancet* March 5, 2011; 377(9768): 823-836. PMID: 21334061. http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(11)60096-2/fulltext
- Sharpe M, Hawton K, Simkin S, et al. "Cognitive behaviour therapy for the chronic fatigue syndrome: a randomized controlled trial." *BMJ* 1996; 312(7022): 22-6. PMID: 8555852. http://dx.doi.org/10.1136/bmj.312.7022.22

Articles discussing the biopsychosocial approach

- Nijs J, Roussel N, Van Oosterwijck J, De Kooning M, Ickmans K, Struyf F, Meeus M, Lundberg M. "Fear of movement and avoidance behaviour toward physical activity in chronic-fatigue syndrome and fibromyalgia: state of the art and implications for clinical practice." *Clin Rheumatol* May 3, 2013; 32(8):1121-9. PMID: 23639990. http://dx.doi.org/10.1007/s10067-013-2277-4
- Prins J, van der Meer J, Bleijenberg G. "Chronic fatigue Syndrome." *The Lancet* January 28, 2006; 367(9507): 346-355. PMID: 16443043. http://dx.doi.org/10.1016/S0140-6736(06)68073-2

[191] Jason L, Najar N, Porter N, Reh C. "Evaluating the Centers for Disease Control's Empirical Chronic Fatigue Syndrome Case Definition." *Journal of Disability Policy Studies* Published online October 2008, in print September 2009; 20(2): 93-100. http://dx.doi.org/10.1177/1044207308325995 and http://web.archive.org/web/20090816013354/http://www.co-cure.org/Jason-7.pdf

The comments here were made relative to the Empirical definition but are general to the comments that Dr. Jason has made about how the approaches used to assess cases of "CFS" could increase the percentage of "CFS" patients that had psychiatric illness or other conditions while failing to require that patients had the hallmark criteria of ME such as PEM. He also raised the concern that these assessment approaches and criteria might lead to the conclusion that only "distress and unwellness characterize CFS, thus inappropriately supporting a unitary hypothetical construct called 'functional somatic syndrome'." Collectively, these factors would result in more patients, including more patients with primary psychiatric illness, being diagnosed as having "CFS" and also result in CFS itself being equated to psychiatric illness.

[192] Maupin, Craig. "CDC AND NIH Officials Discussed 'Desirable Outcome' of Seeing A Distinct Illness 'Evaporate'." *The CFS Report*, March 2014. http://www.cfidsreport.com/News/14_Chronic_Fatigue_Syndrome_Definition_IOM_Straus.html

Discussion of the letter from Dr. Stephen Straus at NIH to Dr. Keiji Fukuda at CDC. The letter, which is undated, was written about the time of the publication of Fukuda in 1994. The letter was obtained by Craig Maupin of CFIDSReport.com by FIOA and released in March of 2014. FOIA Number No.38767.. The letter itself can be accessed directly at https://dl.dropboxusercontent.com/u/89158245/Straus%20to%20Fukuda%20letter%201994.docx

[193] Royal Colleges of Physicians, Psychiatrists, and General Practitioners. "Chronic Fatigue Syndrome. Report of a joint working group of the Royal Colleges of Physicians, Psychiatrists, and General Practitioners." October 1996. www.theoneclickgroup.co.uk/documents/ME-CFS_docs/Royal Colleges Report-CFS.doc, http://books.google.com/books/about/Chronic_Fatigue_Syndrome.html?id=RRId4npKxDsC

Requested by the Chief Medical Officer of the Department of Health in the United Kingdom of the Academy of Medical Royal Colleges. Jointly produced by the Royal College of Physicians of London, Royal College of Psychiatrists, Royal College of General Practitioners. According to the report, the Chief Medical Officer requested for the report to "advise on matters such as diagnosis, clinical practice, aetiology and service provision" of chronic fatigue syndrome.

[194] Editors of the Lancet. "Frustrating Survey of Chronic Fatigue." October 12, 1996; 348(9033): 971. http://dx.doi.org/10.1016/S0140-6736(05)64917-3 and http://www.thelancet.com/journals/lancet/article/PIIS0140-6736%2805%2964917-3/fulltext

The editorial stated "Psychiatry has won the day for now. A decade hence, when an organic cause for at least some cases of CFS may have emerged, it would be tempting to ask the committee to reconvene. We believe that the report was haphazardly set-up, biased, and inconclusive, and is of little help to patients or their physicians. Or as the Department of Health weakly put it, the report will "provide a further contribution to the ongoing debate".

[195] Straus, Stephen. "Chronic fatigue syndrome. "Biopsychosocial approach" may be difficult in practice." *BMJ* October 5, 1996. 313:831. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2359057/pdf/bmj00562-0007.pdf

[196] The American Association for Chronic Fatigue Syndrome is now called the International Association for CFS/ME. According to the IACFS/ME website, "The late Governor Rudy Perpich, who was a Board Member, worked hard to influence his fellow politicians in other states and in Washington, DC to recognize CFS. In recognition of Gov. Perpich's distinguished service to the IACFS/ME, the Board of Directors established a Senior Lectureship Award in his memory. This award is presented to a distinguished CFS/FM scientist, physician or healthcare worker every two years at the IACFS/ME conferences." http://www.iacfsme.org/formeriacfsawardees/tabid/209/default.aspx

[197] Dr. Phillip Lee, Assistant Secretary of Health. Acceptance Speech, Rudy Perpich Award. Bi-Annual Research Conference of the American Association for Chronic Fatigue Syndrome. October 10-11, 1998. http://www.cfids-me.org/mpwc/lee.html

Dr. Lee made the following comments during his acceptance speech"

- "Chronic Fatigue Syndrome, Wedner tells us, is neither a disease nor a syndrome. It is a committee definition."
- "The approach to CFS is now dominated by the "biopsychosocial" approach that gives excessive emphasis to the social, behavioral, and emotional factors in the presentation and perpetuation of symptoms. The "bio" seems to be missing. While I believe in the psychosocial determinants of health paradigm, this approach to CFS has gone too far. "
- "The problem is evidence in the proposed ICD-9 codes for CFS, and the 1996 report of the Joint Working Group of the Royal Colleges of Physicians, Psychiatrists and General Practitioners on Chronic Fatigue Syndrome in the United Kingdom. The Royal Colleges convened a working group after a request from the UK's Chief Medical Officer. The group recommended that the term encephalomyelitis be dropped in the UK and that it be replaced by CFS."
- "Third, the current approaches to CFS, except in a few hands, do not take sufficient cognizance of the research on brain positron emission tomography, cognitive function, possible biomarkers, electron microscopy, the evidence from past outbreaks, or a number of the studies presented here."
- "Finally, the overlap of symptoms with Gulf War Syndrome, fibromyalgia, and multiple chemical sensitivities merit a thorough re-examination and the development of a comprehensive strategic plan for research."
- "Dr. Stephen Straus of the NIH had a very different view and one that I strongly disagree with. He wrote in the *British Medical Journal*: 'The report constitutes, arguably, the finest contemporary position statement in the field, and physicians and patients are well advised to read it, but it is sure to engender disagreement on both sides of the Atlantic.'' Indeed, it has engendered disagreement."

[198] Centers for Disease Control and Prevention, National Center for Health Statistics, Office of the Center Director, Data Policy and Standards. "A Summary of Chronic Fatigue Syndrome and Its Classification in the International Classification of Diseases." March 2001 http://web.archive.org/web/20140611042505/http://www.co-cure.org/ICD_code.pdf

As discussed in the section on the medical dictionaries, ME was in the neurological chapter of WHO's ICD-9 (at code 323.9 Encephalitis of unspecified cause). CFS was never added to ICD-9 but instead added to ICD-10 in 1992 at the same code as ME (G93.3).

The U.S. added the term "CFS" to the ICD-9-CM in 1991, pointing to "Malaise and Fatigue", code 780.7. This is the same code where post-viral fatigue syndrome had been located in WHO's ICD-9 and also in the ICD-9-CM.

[199] National Institute of Health. "Chronic Fatigue Syndrome. State-of-the-Science Consultation." Report of the NIH State of Science CFS Consultation. February 6-7, 2000.
http://webharvest.gov/peth04/20041027092632/www.niaid.nih.gov/dmid/meetings/cfsreport.htm

Note that this conference commissioned the 2001 Evidence Review:

U.S. Department Health and Human Services. Agency for Healthcare Research and Quality. "Defining and Managing Chronic Fatigue Syndrome." By Mulrow, CD, Ramirez, G, Cornell, JE, Allsup K. September 2001. Evidence Reports/Technology Assessments Number 42.

- AHRQ Publication No: 02-E001 – Details http://www.ncbi.nlm.nih.gov/books/NBK33797/
- AHRQ Publication No: 01-E061 – Summary - http://www.ncbi.nlm.nih.gov/books/NBK11946/

This report found that it was difficult to find treatments to recommend for CFS other than behavioral therapy or exercise treatments.

[200] CFIDS Association of America. "CAA Response to the NIH "State of the Science" Meeting." January 24, 2000.
https://web.archive.org/web/20000302182302/http://www.co-cure.org/infoact2.htm

Summary of events as reported by CFIDS Association- After two months of requests by Kim Kenney (McCleary) of the CFIDS Association, Dr. David Morens, the CFS Program Officer at NIH finally stated "the purpose of this conference was to help guide NIH's CFS research priorities" and there were four attendees - Professor Simon Wessely, Professor Michael Sharpe, Dr. Mark Demitrack and Dr. Stephen Straus. Dr. Morens further said that CFSCC had not been involved in planning the conference even though CFSCC had recommended the meeting. Seven others also attended but the others were reported to not be expert in this disease.

[201] Hanna, Eleanor Presentation at U.S. Department of Health and Human Services CFS Advisory Committee. September 29, 2003. *CFS Advisory Committee Website.* https://wayback.archive-

it.org/3919/20140324192720/http:/www.hhs.gov/advcomcfs/meetings/minutes/csfac_mins_2003.09.29r_pdf.pdf discussion of history of advisory committee and the sponsorship of the February 2000 NIH conference are on page 10 Also see

- U.S. Government Accountability Office. *CHRONIC FATIGUE SYNDROME: CDC and NIH Research Activities Are Diverse, but Agency Coordination Is Limited. (GAO Report* HEHS-00-98). U.S. Government Accountability Office, Washington, D.C. June 2, 2000. http://www.gao.gov/assets/240/230415.pdf and http://www.gao.gov/products/HEHS-00-98 Page 73, Discusses the communication and planning around this committee.

[202] The following sources from that time provide additional background on the controversy generated by this meeting.

- CFIDS Association of America. "CAA Response to the NIH "State of the Science" Meeting." January 24, 2000. https://web.archive.org/web/20000302182302/http://www.co-cure.org/infoact2.htm Summary of events as reported by CFIDS Association. Dr. Morens further said that CFSCC had not been involved in planning the conference even though CFSCC had recommended the meeting.
- Walker, V. "A monumentous week for CFIDS Pressure mounts for CDC, NIH." CFIDS Association of America. Winter 2000. http://web.archive.org/web/20130424133259/http://www.cfids.org/archives/2000/2000-1-article02.asp Report post meeting.
- Schweitzer, Mary. Problems with U.S. Government Agencies." 2000. http://www.cfids-me.org/marys/nihprobs.html

[203] National Institute of Health. "Chronic Fatigue Syndrome. State-of-the-Science Consultation." Report of the National Institutes of Health State of Science CFS Consultation. February 6-7, 2000. http://webharvest.gov/peth04/20041027092632/www.niaid.nih.gov/dmid/meetings/cfsreport.htm and http://webharvest.gov/peth04/20041031153356/http://www.niaid.nih.gov/dmid/meetings/cfspart.htm

NIH modified the meeting from the original 4 participants to include 11 people, none of whom had expertise in this disease. Nancy Klimas and Patient Kathy Rabin were added later and are not listed as participants. It is unclear whether Klimas and Rabin were given the opportunity to speak.

Listed meeting participants included: Gail H. Cassell, (Chair, Infectious Disease Research, Eli Lilly), Mark A. Demitrack, (Eli Lilly), Charles C. Engel, (Deployment Health Clinical Center), Helen Mayberg (Psychiatry and Medicine(Neurology), University of Toronto), Kevin McCully (Department of Exercise Science, University of Georgia), William C. Reeves (Centers for Disease Control and Prevention), Michael Sharpe (Departments of Psychiatry and Clinical Neurosciences, University of Edinburgh), Joan Shaver (Professor and Dean, College of Nursing, University of Illinois at Chicago), Simon Wessely (Academic Department of Psychological Medicine, Guy's, King's and St. Thomas's School of Medicine and Institute of Psychiatry), Lon R. White,(Senior Neuroepidemiologist, Hawaii Center for Health Research), Barry Wilson (Department of Environmental Toxicology, University of California)

[204] Ibid. The NIH conference report language echoed the later focus on chronic unwellness and a broader case definition based on empirical analysis of populations. This was played out in the Empirical definition (see below). The report made the following statements:

- "It is important to distinguish between the research case definition that is intended to help design research studies and the identification of individual patients at the community and clinical level. The case definition was developed by physicians who see patients and by the characteristics of those patients who are seen by physicians. They are therefore likely to be highly selected and unrepresentative of the true spectrum of illness."
- "Empirical case definitions using information from people in population surveys may be derived from factor analysis, e.g., data from persons studied in population surveys. Factor analysis may be a useful exploratory tool for further refining the case definition."
- "In persons with chronic unwellness, there seem to be two categories of predominant symptom patterns that can be broadly classified as cognitive and inflammatory (although there is no definitive evidence of inflammation)."

The report also states that requiring fatigue first may be approaching the issue backwards but then goes on to compare CFS to PTSD and burnout. The report also calls out the importance of subgrouping, something that doesn't appear to have been done. The report goes on to state:

- "Fatigue and sleep disorders may be the result of the two predominant symptom patterns, cognitive and inflammatory. Thus, requiring fatigue first could be approaching the issue backwards."
- "Stress reactions and immune regulation are more sensitive in women than in men. Women's physiology is more cyclical in nature. These factors need to be taken into account in study design."
- "The idea of a chronic stress activation pattern may be worthy of pursuit. There is much evidence for a stress component to CFS. Additionally, a range of conditions associated with stress or trauma has been related to hypocortisol. Thus, there is considerable symptom overlap in PTSD, nurses and "burnout," teachers who report living under chronic stress, CFS, FMS, and idiopathic chronic pain."
- "Predisposing factors, precipitating factors, and perpetuating factors need to be distinguished and studied. Understanding perpetuating factors and factors predicting recovery are important issues. Iatrogenic factors, such as medical treatment, involved in perpetuation or recovery need also to be considered."

- "Research and clinical experience suggests a higher prevalence in CFS of depression, generalized anxiety disorder, and panic disorders than in other ill groups."

[205] Department of Health and Human Services Chronic Fatigue Syndrome Coordinating Committee. "Chronic Fatigue Syndrome. State of the Science Conference" Report of the HHS Chronic Fatigue Syndrome Coordinating Committee (CFSCC) State of Science Conference October 22-23, 2000. http://web.archive.org/web/20111121094434/http://www.co-cure.org/SOS.pdf

The conference report stated, "The goals of the meeting were to focus on CFS research areas in which information is both mature and exciting; summarize current knowledge and identify important gaps in knowledge; garner the perspective of expert investigators not currently working on the problem of CFS; and identify expert investigators who might be attracted to study CFS as a clinical problem."

The report also stated, "Seven topic areas of medical research were identified: neuroendocrinology; cognition; chronic pain; sleep; immunology; orthostatic intolerance/neurally mediated hypotension; and fatigue, functional status, and disability. For each topic, a clinical scientist studying CFS (CFS expert) was asked to present the most provocative aspects of current knowledge; then scientists working in that same research area, but not studying CFS (subject experts), were asked to provide additional information and insights from that discipline that could enhance understanding of CFS."

Author's note: Its worth noting that psychiatric issues were not discussed except to discount their importance as an explanation for cognitive issues. Rather than psychiatric issues and dysregulation of thought and belief, the October 2000 report found that a majority had viral-like illnesses preceding the onset of CFS and discussed dysregulation of biological control systems. Rather than looking for clues in mood disorders, this report discussed the potential relevance of multiple sclerosis research

[206] U.S. Government Accountability Office. *CHRONIC FATIGUE SYNDROME: CDC and NIH Research Activities Are Diverse, but Agency Coordination Is Limited. (GAO Report* HEHS-00-98). U.S. Government Accountability Office, Washington, D.C. June 2, 2000. http://www.gao.gov/assets/240/230415.pdf and http://www.gao.gov/products/HEHS-00-98
Key findings included lack of coordination, inadequate communication, CDC misuse of funds
Also see

- "GAO Criticizes CDC, NIH Handling of Chronic Fatigue Research." Reuters. 2000. Reuters report accessed on the The National CFIDS Foundation website. http://www.ncf-net.org/library/GAOCriticizesCDC.htm
- CFIDS Association of America. "Agency Activities: CDC Scandal." Undated http://web.archive.org/web/20080829025914/http://cfids.org/advocacy/cdc-scandal.asp

[207] "The Trans-NIH Working Group on Chronic Fatigue Syndrome." Trans-NIH CFS WorkGroup, National Institutes of Health. Website as of November 2005. https://web.archive.org/web/20051110230137/http://orwh.od.nih.gov/cfs/cfsWG.html

[208] Maupin, Craig. "The NIH and CFS." *The CFS Report,* September 2005. http://www.cfidsreport.com/Articles/NIH/NIH_CFS_1.htm and http://www.cfidsreport.com/Articles/NIH/NIH_CFS_2.htm

Excellent series that covers many facets of NIH approach to NIH including the rational for moving to the Office of Research on Women's Health According to Maupin, Dr. Donna Dean stated that the intent in moving CFS was to make it easier to reach across institutes. She also said that she had been given the responsibility "of trying to straighten out, as much as I could, the mess that the NIH had gotten into with CFS (and the mess that DHHS had gotten into)." She further added "It was important to get the NIH CFS program leadership somewhere where people were focusing on scientific kinds of issues, on a scientific approach to medical conditions, without the encumbrances and biases of the past."

Also see

- Hanna, E. Presentation to and discussion with U.S. Department of Health and Human Services CFS Advisory Committee. CFSAC Meeting. July 17,2006. *CFS Advisory Committee Website.* http://www.hhs.gov/advcomcfs/meetings/minutes/cfsac060717_min.html (page 18)
  Dr. Hanna's presentation -. https://wayback.archive-it.org/3919/20140324192720/http:/www.hhs.gov/advcomcfs/meetings/presentations/presentation060717_ppt.ppt
- Hanna, Eleanor Presentation at U.S. Department of Health and Human Services CFS Advisory Committee. CFSAC Meeting. September 29, 2003. *CFS Advisory Committee Website.* https://wayback.archive-it.org/3919/20140324192720/http:/www.hhs.gov/advcomcfs/meetings/minutes/csfac_mins_2003.09.29r_pdf.pdf Page 10

[209] As reported in other parts of this paper, Dr. Straus has made numerous statements that conveyed his psychogenic views of this disease. The following statement is one that he made in 2001, about the same time that CFS was moved into ORWH.

- Dreifus, C. "A CONVERSATION WITH: STEPHEN STRAUS; Separating Remedies From Snake Oil." *The New York Times.* New York, New York. April 3, 2001 http://www.nytimes.com/2001/04/03/health/a-conversation-with-stephen-straus-separating-remedies-from-snake-oil.html?pagewanted=all&src=pm

Dr. Straus stated that individuals who have had CFS for years lose hope and "They then take on a series of maladaptive behaviors which sustain their illness because they become so focused and so phobic: they avoid exercise, disrupt their sleep patterns. It gets harder and harder for them to regain normalcy."

[210] Insight into another potential driver behind this change comes from an interview between patient advocate Craig Maupin and HHS's Donna Dean. Dr. Donna Dean reportedly stated that the responsibility she had been given was "the function of trying to straighten out, as much as I could, the mess that the NIH had gotten into with CFS (and the mess that DHHS had gotten into)." She further added "It was important to get the NIH CFS program leadership somewhere where people were focusing on scientific kinds of issues, on a scientific approach to medical conditions, without the encumbrances and biases of the past."
Source: Maupin, Craig. "The CFS program at the NIH – Past, present, and future" *The CFS Report,* September 2005. http://www.cfidsreport.com/Articles/NIH/NIH_CFS_2.htm
Author's note: Another source for this information has not been identified.

[211] CDC held three closed meetings/working groups between 2000 and 2002 to discuss the issues with Fukuda and its usage. These included

- Centers for Disease Control and Prevention. "Case Definition Workshop.May 1-3, 2000." *CDC CFS Website*. Last updated, July 21, 2010. http://www.cdc.gov/cfs/meetings/case_def_05_2000.html
  The website states "Participants at the first workshop (May 2000) agreed that the 1994 International CFS Research Case Definition was not optimal, that it should be revised, and that future revisions should be based on empirically derived data (if possible from defined populations). Three groups were formed to discuss the following issues: how a case definition should be used for research; how population groups should be identified for studies and how classification instruments should be standardized."
- Centers for Disease Control and Prevention. "Case Definition Workshop. May 20-23, 2001" *CDC CFS Website*. Last updated July 21, 2010. http://www.cdc.gov/cfs/meetings/case_def_05_2001.html
  The website states, "The second meeting (June 2001) focused on ambiguities of the 1994 case definition and on what instruments would provide the best objective measures of the major dimensions of CFS. We agreed to prepare a review article critiquing the 1994 case definition. We also agreed that CDC would take the lead in facilitating communication about the CFS case definition and in forming an International Collaborative Group to test standard instruments and collect data that could be used to propose an empiric data-based revision to the case definition."
- Centers for Disease Control and Prevention. "Case Definition Workshop. May 21-22, 2002. *CDC CFS Website*. Last updated July 21, 2010. http://www.cdc.gov/cfs/meetings/case_def_05_2002.html
  The website states, "The overall objective of the third meeting was to maintain the momentum of the International Collaborative Group and continue the work to more precisely define CFS. The specific aim was to discuss how standard instruments measuring the major symptom domains of CFS could be used internationally in clinical research settings. During the meeting, three working groups sought to develop strategies" to a) uniformly apply standardized instruments, b) optimally measure fatigue and other symptoms and psychiatric comorbidity and c) identify procedures to identify "symptom dimensions among persons with CFS and other unexplained chronically fatiguing illnesses."
  Author's note: CDC's conclusions on the May 2002 meeting link conveyed their overwhelming focus on chronic fatigue – they planned a study to "identify symptom dimensions among persons with unexplained chronic fatigue; determine the variability of symptom dimensions across the sites; measure the associations between symptom dimensions and other health constructs; and determine the feasibility of conducting an international multicenter study of unexplained chronic fatigue."

[212] Reeves W, Lloyd A, Vernon S, Klimas N, Jason L, Bleijenberg G, Evengard B, White P, Nisenbaum R, Unger E. and the International Chronic Fatigue Syndrome Study Group. "Identification of ambiguities in the 1994 chronic fatigue syndrome research case definition and recommendations for resolution." *BMC Health Services Research* December 31, 2003, 3(1):25. PMID: 14702202. http://dx.doi.org/10.1186/1472-6963-3-25
The report states "The International Chronic Fatigue Research Group members included: Susan Abbey (University of Toronto, Toronto, Canada), Catherine Campbell (Centers for Disease Control and Prevention, Atlanta, GA), Dedra Buchwald (University of Washington, Seattle, WA), Anthony Cleare (Institute of Psychiatry, Guy's, King's, and St. Thomas School of Medicine, London, UK), Nelson Gantz (Pinnacle Health System, Harrisburg, PA), Ron Glaser (Ohio State University, Columbus, OH), Christine Heim (Emory University, Atlanta, GA), Ian Hickie (University of New South Wales, Sydney, Australia), Gail Ironson University of Miami, Miami, FL), Ann-Britt Jones (Centers for Disease Control and Prevention, Atlanta, GA), James Jones (National Jewish Medical Center, Denver, CO), Kevin Karem (Centers for Disease Control and Prevention, Atlanta, GA), K. Kimberly Kenney (CFIDS Association of America, Charlotte, NC), Hirohiko Kuratsune (Osaka University, Osaka, Japan), Gudrun Lange (New Jersey Medical School, Newark, NJ), Kathleen McCormick (SRA, Rockville, MD), Andrew Miller (Emory University, Atlanta, GA), Harvey Moldofsky (Centre for Sleep and Chronobiology, Toronto, Canada), Benjamin Natelson (New Jersey Medical School, East Orange, NJ), Thomas J. O'Laughlin (Physical Medicine, Rehabilitation & Electromyography, Fresno, CA), Dimitris A. Papanicolaou (Emory University, Atlanta, GA), Mangalathu Rajeevan (Centers for Disease Control and Prevention, Atlanta, GA), John

Stewart (Centers for Disease Control and Prevention, Atlanta, GA), Eng Tan (Scripps Institute), Vicki Walker (CFIDS Association of America, Charlotte, NC)."

The instruments recommended by this paper included in part (1) the Medical Outcomes Survey Short Form-36 (SF-36), to measure functional impairment; (2) a comprehensive instrument, such as the Checklist Individual Strength (CIS) or the Multidimensional Fatigue Inventory (MFI), to obtain reproducible quantifiable measures of fatigue,; and (3) the CDC Symptom Inventory to document the occurrence, duration and severity of the symptom complex

Author's Note: The recommendations for instruments included the use of the Composite International Diagnostic Instrument to assess psychiatric illness. The Structured Clinical Interview for DSM-IV Axis 1 was suggested as an alternative but the report states that this requires trained individuals to administer the test. The report acknowledges that these two tools produce different results but states that the differences should be handled by stating clearly which instrument was used and discussing the resultant issues.

[213] U.S. Department of Health and Human Services CFS Advisory Committee. CFSAC Meeting May 2009. *CFS Advisory Committee Website.* https://wayback.archive-it.org/3919/20140324192720/http:/www.hhs.gov/advcomcfs/meetings/minutes/cfsac052709min.pdf. Page 65. Discussion on the Empirical definition including an exchange between Dr. Reeves and Dr Jason.

Regarding exclusion of major depressive disorder, Dr. Reeves stated, "When we diagnose the 20 percent of patients who have major depressive disorders, we say, "You have CFS and you have a major depressive disorder…. Major depressive disorder should not be considered exclusionary. For the purpose of research studies, melancholic depression is exclusionary as are bipolar disorders. It was decided that if you have major depressive disorder, it must be identified, and then it's a stratification variable."

Dr. Jason asked "Under SF-36, one subscale of the four has to meet criterion, one of which is "role emotional." Every person who has a major depressive disorder would hit the disability criteria based on role emotional. Does that pose any problem with the empiric case definition?"

Dr. Reeves replied "The 2003 work group did not recommend scales, so we selected the scales that we selected because we felt that they best represented the type of disability or the type of fatigue. Major depressive disorder on the role emotional is an important one, but that's also an important source of disability in people who don't have major depressive disorders, so those without CFS and without a major depressive disorder may be low in that as well." Also see

- Jason, L., Richman, J. "How Science Can Stigmatize: The Case of Chronic Fatigue Syndrome." *Journal of Chronic Fatigue Syndrome* 2007; 14(4): 85-103. http://informahealthcare.com/doi/abs/10.3109/10573320802092146 and http://web.archive.org/web/20120228222416/http://www.cfids-cab.org/cfs-inform/CFS.case.def/jason.richman.07.txt

  Jason stated that Reeves 2005 was different than what had been agreed to in the 2003 paper. Reeves 2005 only excluded patients with a current condition of major depressive disorder. Reeves 2005 included patients who were below the 25th percentile on any one of the SF-36, including just the role emotional scale. Jason's point is the empirical case definition would inadvertently bring in those with MDD and those who had "problems with work or other daily activities as a result of emotional problems" without any impairment in physical functioning.

[214] Reeves W, Wagner D, Nisenbaum R, Jones J, Gurbaxani B, Solomon L, Papanicolaou D, Unger E, Vernon S, Heim C. "Chronic Fatigue Syndrome – A clinically empirical approach to its definition and study." *BMC Medicine* December 2005; 3:19. PMID: 16356178. http://dx.doi.org/10.1186/1741-7015-3-19

- The Empirical definition was based on the feedback the above series of CDC workshops between 2000 to 2002 to identify issues with the Fukuda definition and then on a December 2002 to July 2003 study conducted by the CDC to empirically establish the definition. The 2002 study included patients that had been previously identified in the CDC's Witchita CFS Surveillance study
- The 2005 report states that when the case definition used in the Witchita surveillance study to "classify subjects when they entered this clinical study only 16 had a current classification of CFS, 76 of ISF, 48 were not fatigued controls, and remission was identified in 24 recruited as CFS/ISF who no longer reported fatigue. Most (87%) of the 46 subjects enrolled because they were considered CFS during surveillance did not meet the same case definition criteria at the time of the clinical study: most (58.7%) were classified as ISF and 10.9% were in remission."

[215] Publications for the Wichita Surveillance study include

- Reyes M, Nisenbaum R, Hoaglin DC, Unger ER, Emmons C, Randall B, Stewart JA, Abbey S, Jones JF, Gantz N, Minden S, Reeves WC. "Prevalence and incidence of chronic fatigue syndrome in Wichita, Kansas." *Arch Intern Med* Juy 14, 2003; 163(13): 1530-6. PMID: 12860574. http://dx.doi.org/10.1001/archinte.163.13.1530
- Solomon L, Nisenbaum R, Reyes M, Papanicolaou DA, Reeves WC. "Functional status of persons with chronic fatigue syndrome in the Wichita population." *BMC Hlth Quality Life Outcomes* October 31, 2003, 1:48. PMID: 14577835. http://dx.doi.org/10.1186/1477-7525-1-48
- Nisenbaum R, Jones JF, Unger ER, Reyes M, Reeves WC. "Clinical course of chronic fatigue syndrome in Wichita, Kansas." *BMC Hlth Quality Life Outcomes* October 3, 2003, 1:49. http://dx.doi.org/10.1186/1477-7525-1-49

This report stated, "About one-third of CFS subjects retained the classification after 1 year of follow-up (Table (Table 6). At 2 and 3 years follow-up, only 21% of the subjects were classified as having CFS. Most transitioned into a non-CFS state because of insufficient symptoms or fatigue severity, absence of fatigue, or identification of an exclusionary condition. Overall, 23.1% (15 of 65) were eventually diagnosed with permanent exclusions."

[216] Reeves W, Wagner D, Nisenbaum R, Jones J, Gurbaxani B, Solomon L, Papanicolaou D, Unger E, Vernon S, Heim C. "Chronic Fatigue Syndrome – A clinically empirical approach to its definition and study." *BMC Medicine* December 2005; 3:19. PMID: 16356178. http://dx.doi.org/10.1186/1741-7015-3-19

The report states: "This study showed scant stability of CFS over time, when diagnosed by the usual algorithm (based on patients' subjective responses to direct questions as to whether they feel fatigued, if they perceive their fatigue causes substantial reduction in daily activities, and whether at least 4 case defining symptoms are present). There was poor correlation between illness classification during surveillance (recruitment classification) and classification by the same criteria during the clinical study. While this might reflect fluctuation in illness over time, illness categories (CFS, ISF, Remission, non-fatigued) defined by this surveillance classification scheme were not consistent with respect to overall illness severity."

[217] Jason, L., Richman, J. "How Science Can Stigmatize: The Case of Chronic Fatigue Syndrome." *Journal of Chronic Fatigue Syndrome* 2007; 14(4): 85-103. http://informahealthcare.com/doi/abs/10.3109/10573320802092146 and http://web.archive.org/web/20120228222416/http://www.cfids-cab.org/cfs-inform/CFS.case.def/jason.richman.07.txt

References the following study

- Cairns R, Hotopf M. "A systematic review describing the prognosis of chronic fatigue syndrome." *Occup Med (Lond)*. January 2005; 55(1): 20-31. PMID: 15699087. http://dx.doi.org/10.1093/occmed/kqi013

[218] Ibid. Jason stated, "There was little agreement between the Empirical method of classifying individuals and the more traditional method of comparing whether an individual met the case definition on their critical symptoms."

[219] Reeves WC, Jones JJ, Maloney E, Heim C, Hoaglin DC, Boneva R, Morrissey, M., Devlin, R. "Prevalence of chronic fatigue syndrome in metropolitan, urban and rural Georgia." *Population Health Metrics,* 2007; 5:5. PMID: 17559660. http://dx.doi.org/10.1186/1478-7954-5-5

This paper reports a prevalence rate of 0.0254 versus 0.0024 found in the 2003 Reyes study ("Prevalence and incidence of chronic fatigue syndrome in Wichita, Kansas"). See Table 2 in the Appendices

[220] White PD. "How common is chronic fatigue syndrome; how long is a piece of string?" *Population Health Metrics* 2007; 5:6. http://dx.doi.org/10.1186/1478-7954-5-6

[221] Jones J, Lin J, Maloney E, Boneva R, Nater U, Unger E, Reeves W. "An evaluation of exclusionary medical/psychiatric conditions in the definition of chronic fatigue syndrome." *BMC Med* October 12, 2009; 7: 57. PMID: 19818157http://dx.doi.org/10.1186/1741-7015-7-57.

This article looks at the health status of patients that meet Empirical criteria and those who would meet it except for exclusionary diagnoses. The conclusion is that those who fail to meet CFS criteria because of exclusionary conditions also need care. The paper stated, "As those with CFS suffer from personal, social, workplace and observed financial losses, should not all individuals fulfilling CFS inclusion criteria, with or without exclusionary diagnoses, be considered in future public health planning? For instance, would both groups benefit from prevention and intervention efforts such as cognitive behavioral therapy and graded exercise therapy? A similar question could be asked of those who are unwell but who do not reach the diagnostic threshold."

Also see:

Aslakson E, Vollmer-Conna U, Reeves WC, White PD. "Replication of an Empirical Approach to Delineate the Heterogeneity of Chronic Unexplained Fatigue" *Population Health Metrics*. October 5, 2009, **7**:17. http://dx.doi.org/10.1186/1478-7954-7-17

This paper made the following statements:

- "The broadening of the concept of CFS to include patients with fewer symptoms but similar disability is supported by this replication."
- "Conclusion: These data support the hypothesis that chronic medically unexplained fatigue is heterogeneous and can be delineated into discrete endophenotypes that can be replicated. The data do not support the current perception that CFS represents a unique homogeneous disease and suggests broader criteria may be more explanatory."
- "What are the clinical implications of this work? Future research studies should now examine for moderators of outcome that include obesity, metabolic syndrome, sleep problems, depression, and having multiple symptoms."

Author's Note: Note that the study reported that these were the factors associated with CFS.

[222] Jason, L., Richman, J. "How Science Can Stigmatize: The Case of Chronic Fatigue Syndrome." *Journal of Chronic Fatigue Syndrome* 2007; 14(4): 85-103. http://informahealthcare.com/doi/abs/10.3109/10573320802092146 and http://web.archive.org/web/20120228222416/http://www.cfids-cab.org/cfs-inform/CFS.case.def/jason.richman.07.txt for comments on a number of these studies.

[223] Ibid.

[224] Ibid. Jason stated:

Jason noted that a CDC study claimed that it was able to effectively distinguish CFS patients on the basis of a depression score. However the biological factors were ineffective as they achieved little more than would be seen by chance. The study that he is referring to is:

- Gurbaxani BM, Jones JF, Goertzel B, Maloney EM. "Linear data mining the Wichita clinical matrix suggests sleep and allostatic load involvement in chronic fatigue syndrome." *Pharmacogenomics* April 7, 2006; 7(3): 455-465. PMID: 16610955. http://dx.doi.org/10.2217/14622416.7.3.455

[225] Woodruff Health Sciences Center News. "Childhood Trauma and Chronic Fatigue Syndrome Risk Linked." Woodruff Health Sciences Center News, Emory University, Atlanta, Georgia. January 7, 2009. http://shared.web.emory.edu/emory/news/releases/2009/01/childhood-trauma-chronic-fatigue-syndrome-risk-linked.html#.UscXy_aE4YQ

Press release "Results of the study confirm that childhood trauma, particularly emotional maltreatment and sexual abuse, is associated with a six-fold increased risk for CFS."

Study being reported:

- Heim C, Nater UM, Maloney E, Boneva R, Jones JF, Reeves WC. "Childhood Trauma and Risk for Chronic Fatigue Syndrome." *Archives of General Psychiatry* January 2009; 66(1): 72-80.. PMID: 19124690. http://dx.doi.org/10.1001/archgenpsychiatry.2008.508

[226] Nater UM, Jones JF, Lina JS, Maloneya E, Reeves WC, Heim C. "Personality Features and Personality Disorders in Chronic Fatigue Syndrome: A Population-Based Study" in *Psychotherapy and Psychosomatics.* August 2010; 79(5): 312–318. PMID: 20664306. http://dx.doi.org/10.1159/000319312

This study states, "Our results suggest that CFS is associated with an increased prevalence of maladaptive personality features and personality disorders. This might be associated with being noncompliant with treatment suggestions, displaying unhealthy behavioral strategies and lacking a stable social environment. Since maladaptive personality is not specific to CFS, it might be associated with illness per se rather than with a specific condition."

[227] CDC authors published the following study on maladaptive coping styles in CFS in 2012 that was used the empirical definition.

- Nater U , Maloneya E, Lin J, Heim C, Reeves WC. "Coping Styles in Chronic Fatigue Syndrome: Findings from a Population-Based Study" Psychother Psychosom February 2012; 81(2): 127–129. http://dx.doi.org/10.1159/000329996

See also

- Alpha Galileo News Service. "Do patients with chronic fatigue syndrome have impairments in coping?" News release. Alpha Galileo News Service. http://www.alphagalileo.org/ViewItem.aspx?ItemId=121978&CultureCode=en
  The article states "Relative to the well group, those with CFS had statistically significantly higher mean scores in the escape-avoidance, confrontive, distancing, self-controlling, and accepting responsibility coping styles."
  Requires login to get contact details but it appears to be the Journal of Psychotherapy and Psychosomatics

[228] Hooper, Malcolm. "MAGICAL MEDICINE: HOW TO MAKE A DISEASE DISAPPEAR." InvestInME. February 2010. http://www.investinme.org/Documents/Library/magical-medicine.pdf

Hooper makes this point on Page 43, where he states, "In summary, the evidence for the beneficial effect of GET in ME/CFS is not persuasive: if a sample of ME/CFS patients contains a large number of patients with purely psychiatric reasons for their fatigue, then it is hardly surprising to find that psychosocial factors are important – this is tautology and reveals little about ME/CFS (with grateful acknowledgement to David Sampson for his analysis)."

[229] Jason L, Najar N, Porter N, Reh C. "Evaluating the Centers for Disease Control's Empirical Chronic Fatigue Syndrome Case Definition." *Journal of Disability Policy Studies* Published online October 2008, in print September 2009; 20(2): 93-100. http://dx.doi.org/10.1177/1044207308325995 and http://web.archive.org/web/20090816013354/http://www.co-cure.org/Jason-7.pdf

Jason stated, "In conclusion, this study suggests that the Reeves et al. (2005) empirical case definition has broadened the criteria such that some individuals with a purely psychiatric ill- ness will be inappropriately diagnosed as having CFS. The Reeves et al. empirical case definition used specific instruments (such as the Medical Outcomes Survey Short- Form-36) to make diagnostic decisions but included dimensions within them such as role emotional functioning that were not specific for this illness…assessment and criteria that fail to capture the unique characteristics of these illnesses might inaccurately conclude that only distress and unwellness characterize CFS, thus inappropriately supporting a unitary hypothetical construct called "functional somatic syndrome."

Additional useful information can be found at:

- Jason, L., Richman, J. "How Science Can Stigmatize: The Case of Chronic Fatigue Syndrome." *Journal of Chronic Fatigue Syndrome* 2007; 14(4): 85-103. http://informahealthcare.com/doi/abs/10.3109/10573320802092146 and http://web.archive.org/web/20120228222416/http://www.cfids-cab.org/cfs-inform/CFS.case.def/jason.richman.07.txt

  The issues that Jason called out were a) how patients were screened (not just fatigue but also pain,

concentration, unrefreshing sleep) which accounted for a 13% increase b) the use of the standardized criteria of the Empirical definition – this resulted in 3 times as many cases c) a symptom severity and frequency scoring mechanism that led to a diagnosis even if just 2 symptoms, one moderate and one severe at the same time d) symptoms only had to be experienced for the last month, not the past 6 as specified in Fukuda e) patients diagnosed as CFS even if they only had role emotional score on SF-36 at a level that almost all clinically depressed patients would meet. If patients were not diagnosed based on the role emotional factor alone, many of the depressed patients would not be diagnosed as having CFS. The Medical Outcomes SF-36 is an instrument that assesses functional health and well being

- Jason, L. "Problems with the New CDC CFS Prevalence Estimates." *International Association fo CFS/ME.* Undated. http://www.iacfsme.org/IssueswithCDCEmpiricalCaseDefinitionandPrev/tabid/105/Default.aspx

[230] Jason, L., Richman, J. "How Science Can Stigmatize: The Case of Chronic Fatigue Syndrome." *Journal of Chronic Fatigue Syndrome* 2007; 14(4): 85-103. http://informahealthcare.com/doi/abs/10.3109/10573320802092146 and http://web.archive.org/web/20120228222416/http://www.cfids-cab.org/cfs-inform/CFS.case.def/jason.richman.07.txt

[231] Taylor RR, Jason LA. "Sexual abuse, physical abuse, chronic fatigue, and chronic fatigue syndrome: a community-based study." *J Nerv Ment Dis* October 2001; 189(10): 709-15. PMID: 11708672. http://www.ncbi.nlm.nih.gov/pubmed/11708672

[232] Taylor RR, Jason LA. "Chronic fatigue, abuse-related traumatization, and psychiatric disorders in a community-based sample." *Soc Sci Med* July 2002; 55(2): 247-56. PMID: 12144139. http://www.ncbi.nlm.nih.gov/pubmed/12144139

This study stated, "These findings suggest that a history of abuse, particularly during childhood, may play a role in the development and perpetuation of a wide range of disorders involving *chronic fatigue* (emphasis added). Among individuals with chronic fatigue, PTSD and other anxiety disorders appear to demonstrate the strongest association with abuse history."

[233] In a personal discussion with Dr. Unger, she said that the Empirical definition was not an empirical definition but just an operationalization of Fukuda. Another example

- U.S. Centers for Disease Control and Prevention. "Diagnosis and Management of Chronic Fatigue Syndrome" *CDC Chronic Fatigue Syndrome.* CME created: June 27, 2012. Page last updated: May 16, 2014. http://www.cdc.gov/cfs/education/diagnosis/index.html (Chapter 1, Page 5)

  Note that the description of Fukuda definition includes reference to the recommendations to add standardized measures to the case definition in 2003. These recommendations were used for the 2005 Empirical definition. The 2005 Empirical definition is not listed separately.

[234] Brurberg K, Fønhus A, Larun L, Flottorp S, Malterud K. "Case definitions for chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME): a systematic review." *BMJ Open* February 7, 2014; 4(2): e003973. PMID: 24508851. http://dx.doi.org/10.1136/bmjopen-2013-003973

[235] The higher prevalence estimate of 4 million resulted from an Empirical definition study. This estimate is listed on various HHS websites and is often quoted in medical education material from a variety of secondary sources. This estimate continues to be used in HHS documentation. Examples include was used in the FDA Ampligen hearing and in the Voice of the Patient report from the FDA.

- U.S. Food and Drug Administration (FDA), Center for Drug Evaluation and Research (CDER). *The Voice of the Patient. Chronic Fatigue Syndrome and Myalgic Encephalomyelitis.* Report Date: September 2013. Report based on public testimony submitted at the Patient-Focused Drug Development Initiative Meeting for Chronic Fatigue Syndrome and Myalgic Encephalomyelitis held on April 25, 2013. http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM368806.pdf
  Meeting agenda, transcript and video can be found at:
  - U.S. Food and Drug Administration, Center for Drug Evaluation and Research (CDER). "FDA Workshop on Drug Development for Chronic Fatigue Syndrome (CFS) and Myalgic Encephalomyelitis (ME)" U.S. Food and Drug Administration, Center for Drug Evaluation and Research (CDER). Meeting April 25-26, 2013. Page last updated December 11, 2014. http://www.fda.gov/Drugs/NewsEvents/ucm369563.htm
- U.S. Department of Health and Human Services. Center for Drug Evaluation and Research (CDER). U.S. Food and Drug Administration. *ARTHRITIS ADVISORY COMMITTEE MEETING FDA Briefing Package.* Prepared for Ampligen Advisory Committee Meeting on December 20, 2012. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/UCM332514.pdf
  In the briefing materials, the upper limit of 4 million was used. (Page 3).

The upper prevalence was also discussed at the meeting in the context of determining what size safety studies were needed. Larger and thus more expensive studies resulting from a 4 M prevalence would create a disincentive to pharmaceutical investment

- Department of Health and Human Services. Center for Drug Evaluation and Research (CDER). U.S. Food and Drug Administration. *ARTHRITIS ADVISORY COMMITTEE MEETING FDA Briefing Package.* Prepared for Ampligen Advisory Committee Meeting on December 20, 2012.

www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/UCM345463.pdf (page 394)

[236] U.S. Department of Health and Human Services CFS Advisory Committee. CFSAC Meeting. November 9, 2011. *CFS Advisory Committee Website.* http://www.hhs.gov/advcomcfs/meetings/minutes/cfsac_min-11092011.pdf (page 24)

Dr. Jason asked Dr. Unger about the continued publication of Empirical study results (the 2005 Empirical definition has been discredited) and how the CDC intended to evolve the criteria? Dr. Unger's response was that they had done a study comparing "the standardized approach to applying the Fukuda definition [Empirical definition] and the approach that we had used in the past in the Wichita studies. Everyone will find it very reassuring that the patient populations are quite comparable." According to Dr. Unger, a study was to have been published in early 2012 but so far, that study does not appear to have been published.

[237] Boneva RS, Lin JS, Unger ER. "Early menopause and other gynecologic risk indicators for chronic fatigue syndrome in women." *Menopause: The Journal of The North American Menopause Society.* February 2015; 22(8). Last accessed February 5, 2015. http://dx.doi.org/10.1097/gme.0000000000000411

[238] U.K National Institute for Health and Care Excellence (NICE). *Chronic fatigue syndrome/myalgic encephalomyelitis (or encephalopathy). Diagnosis and management of CFS/ME in adults and children.* (NICE clinical guideline 53). August 2007. http://guidance.nice.org.uk/CG53 and http://www.nice.org.uk/guidance/cg53/evidence

Examples of concerns raised by patient organizations with the NICE Guidelines for CFS/ME:

- Invest In ME. "Nice Guidelines for Clinical Practice." Invest In ME. Last updated April 3, 2011. http://www.investinme.org/iime%20campaigning-nice-guidelines%20iime%20response.htm
- Gibson, Ian. "NICE WITNESS STATEMENT from Dr Ian Gibson MP." Invest In ME. Last updated March 19, 2009. http://www.investinme.org/Article-301%20Ian%20Gibson%20NICE%20Guideline%20Witness%20Statement.htm

  Dr. Gibson stated "NICE claims that both CBT and graded exercise therapy are supported by an adequate evidence base, however, the GDG relied on a very small number of controversial randomised control trials (RCTs). The patient selection criteria for participating in the trials were too wide and therefore allowed non-ME/CFS suffers to participate. It is also misleading to refer to CBT & GET as `treatments' of `choice'. They cannot properly be described as treatments, since, as NICE admits, they do not address the core pathology of ME."
  Gibson also stated "That NICE did not adequately take into account the general international biomedical evidence base was highlighted by the GSRME committee of senior parliamentarians I chaired in 2005-6 who were concerned with both the psychiatric dominance in the current UK ME research programmes and patient selection criteria they use. I am therefore disappointed that the NICE GDG did not adopt or endorse high quality internationally recognised patient selection and diagnostic criteria such as the Canadian Criteria even though the latter were mentioned in the Guideline."
  Gibson went on to state, "The NICE GDG also failed to endorse the World Health Organisation definition of ME/CFS as a neurological disorder despite the fact the Department of Health and Government Ministers have repeatedly confirmed that they do agree with this classification. I do not believe that the NICE CFS/ME Guidelines are fit for purpose."

[239] Bagnall A, Hempel S, Chambers D, Orton V, Forbes C. "The diagnosis, treatment and management of chronic fatigue syndrome (CFS) / myalgic encephalomyelitis (ME) in adults and children." Centre for Reviews and Dissemination University of York. October 2005. http://www.nice.org.uk/guidance/cg53/evidence/chronic-fatigue-syndrome-myalgic-encephalomyelitis-full-guideline-appendix-12

Definitions examined included the 1988 Holmes, 1991 Oxford, 1994 Fukuda, 1990 Australian, 1990 Dowsett, 1994 London and 2003 Canadian definitions. The report states "Systematic Evidence Review to support the development of the NICE clinical guideline for CFS/ME in adults and children"

[240] U.K. National Institute for Health and Clinical Excellence. Centre for Clinical Practice. "Static list - candidate guidelines post consultation." December 2013. http://www.nice.org.uk/media/default/About/what-we-do/NICE-guidance/NICE-guidelines/Clinical-guidelines/Clinical-guidelines-static-list.pdf

Includes extensive comments from stakeholders raising concerns with the decision to place a disease on the static list.

[241] Dowsett EG, Ramsay AM, McCartney RA, Bell EJ. "Myalgic encephalomyelitis--a persistent enteroviral infection?" *Postgrad Med J*. 1990; 66: 526-30. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2429637/

[242] There is some dispute on what the official version of the London criteria are. The most common reference appears to be the one below. But other authors have said that the National Task Force does not list authors, were not published or submitted for peer review and were only one of a set of possible criteria. There are also some disputes over whether London criteria were ever used in any study. Most recently, the PACE trial said they assessed ME patients using the London criteria. For the purposes of this paper, the research done did not show that the London criteria had had a significant impact on the evolution of the case definition. If additional information surfaces, this will need to be investigated further. One source of the London Criteria is:

- Dowsett EG, Goudsmit E, Macintyre A, Shepherd CB. "London Criteria For M.E. Report from The National Task Force on Chronic Fatigue Syndrome (CFS), Post Viral Fatigue Syndrome (PVFS), Myalgic Encephalomyelitis (ME)." Westcare, 1994. pp. 96-98. http://www.meassociation.org.uk/2011/02/london-criteria-for-m-e/

- The London Criteria was published in 1994 in the Task Force Report and was subsequently made use of in a small number of research studies, including the research carried out by Costa et al which demonstrated brain stem hypoperfusion. (ref: Costa D et al. "Brainstem perfusion is impaired in patients with myalgic encephalomyelitis/chronic fatigue syndrome." *Quarterly Journal of Medicine,* 1995, 88, 767 – 773.)

[243] Carruthers BM, Jain AK, De Meirleir KL, Peterson DL, Klimas NG, Lerner 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." *Journal of Chronic Fatigue Syndrome* 2003; 11(1): 7-117. http://mefmaction.com/images/stories/Medical/ME-CFS-Consensus-Document.pdf

The 2003 Canadian Consensus Criteria for ME/CFS was developed by an expert consensus panel at the request of Health Canada and with the intent of developing a clinical definition that addressed the pathogenesis of the disease and provided diagnostic and treatment protocols.

In marked contrast to the definitions discussed above, the CCC was the first definition since Ramsay's 1988 definition to put the focus on post-exertional fatigability and the other characteristic immune, neurological, and endocrine abnormalities by which ME experts identify patients. In recognition of the fact that U.S. patients frequently refer to ME as "CFS," while patients abroad largely refer to the disease as ME, the CCC used the label "ME/CFS." While a logical decision, the use of "ME/CFS," "CFS/ME," "CFS," and even chronic fatigue "CF" as alternative names for ME has ultimately compounded confusion about the nature of the disease produced by the use of overbroad and overlapping case definitions, because people are using the same terms and meaning very different things.

Also see the following overview of the CCC, produced in 2005.

- Carruthers B, van de Sande M. "Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: A Clinical Case Definition and Guidelines for Medical Practitioners. An Overview of the Canadian Consensus Document" Published by Carruthers B, can de Sande M. 2005. http://www.name-us.org/DefintionsPages/DefinitionsArticles/ConsensusDocument%20Overview.pdf

[244] Harvey S, Wessely S. "Chronic fatigue syndrome: identifying zebras amongst the horses." *BMC Me*d October 2009; 7: 58. PMID: 19818158. http://dx.doi.org/10.1186/1741-7015-7-58

The authors stated "Depression is very common amongst those with fatigue, with recent studies using the British birth cohorts showing over 70% of adults reporting CFS have evidence of psychiatric disorder prior to their fatigue symptoms beginning."

[245] Nacul L., Lacerda E, Pheby D, Campion P, Molokhia M, Fayyaz S, Leite J, Poland F, Howe A, Drachler M. "Prevalence of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) in three regions of England: a repeated cross-sectional study in primary care." *BMC Medicine* July 2011, 9:91 http://dx.doi.org/10.1186/1741-7015-9-91

[246] International Association for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis. "Chronic Fatigue Syndrome Myalgic Encephalomyelitis: A Primer for Clinical Practitioners 2014 Edition." International Association for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis. 2012, revised 2014. http://www.iacfsme.org/LinkClick.aspx?fileticket=iD3JkZAZhts%3d&tabid=509

[247] Hyde, Byron. "The Nightingale Definition of Myalgic Encephalomyelitis (M.E.)". Hyde, Byron. 2006. Updated 2007. Page last accessed February 19, 2015. http://www.hfme.org/whydepapers.htm#390403648

[248] Jason L, Jordan K, Miike T, Bell DS, Lapp C, Torres-Harding S, Rowe K, Gurwitt A, DeMeirleir K, Van Hoof EA. "A Pediatric Case Definition for Myalgic Encephalomyelitis and Chronic Fatigue Syndrome." *J Chronic Fatigue Syndr*. 2006; 13(2-3): 1-44. http://informahealthcare.com/doi/abs/10.1300/J092v13n02_01 and http://solvecfs.org/wp-content/uploads/2013/06/pediatriccasedefinitionshort.pdf

[249] Carruthers BM, van de Sande MI, De Meirleir KL, Klimas NG, Broderick G, Mitchell T, Staines D, Powles ACP, Speight N, Vallings R, Bateman L, Baumgarten-Austrheim B, Bell DS, Carlo-Stella N, Chia J, Darragh A, Jo D, Lewis D, Light AR, Marshall-Gradisbik S, Mena I, Mikovits JA, Miwa K, Murovska M, Pall ML, Stevens S. "Myalgic Encephalomyelitis: International Consensus Criteria." *Journal of Internal Medicine* October 2011; 270(4): 327–338. PMID: 21777306. http://dx.doi.org/10.1111/j.1365-2796.2011.02428.x and http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2796.2011.02428.x/full

To address what they described as a "web of confusion" created by the overly broad CFS definitions and the mixing and matching of names, twenty-six researchers and clinicians from thirteen countries published the Myalgic Encephalomyelitis International Consensus Criteria (ME-ICC) in 2011. Although it used the CCC as a starting point, requiring post-exertional neuroimmune exhaustion and symptoms reflecting neurological, immunological/gastrointestinal/genitourinary, and energy production/transportation impairments, the ME-ICC did not include the CCC definition's requirement that doctors wait six months before diagnosing the disease. Significantly, the ME-ICC called for patients meeting the ME-ICC criteria to be removed from the NICE criteria and the Reeves Empirical criteria. Further, the companion ME International Consensus Primer for Medical Practitioners, published in 2012, called for patients meeting the ME-ICC criteria to be removed from the broader CFS or CFS/ME criteria, including the Oxford, Reeves (Empirical), Fukuda, and CCC case definitions.

The requirement for 6 months prior to diagnosis is not required in other diseases and was dropped in this definition.

[250] Ibid. The ME-ICC describes the difference between fatigue and fatigability as follows:

"Fatigue in other conditions is usually proportional to effort or duration with a quick recovery and will recur to the same extent with the same effort or duration that same or next day. The pathological low threshold of fatigability of ME described in the following criteria often occurs with minimal physical or mental exertion and with reduced ability to undertake the same activity within the same or several days."

[251] Carruthers BM, van de Sande MI, De Meirleir KL, Klimas NG, Broderick G, Mitchell T, Staines D, Powles ACP, Speight N, Vallings R, Bateman L, Bell DS, Carlo-Stella N, Chia J, Darragh A, Gerken A, Jo D, Lewis D, Light AR, Light K, Marshall-Gradisnik S, McLaren-Howard J, Mena I, Miwa K, Murovska M, Steven S. "Myalgic Encephalomyelitis – Adult and Paediatric: International Consensus Primer for Medical Practitioners." Co-editors B.M. Carruthers and M.I. van de Sande. Published by Carruthers and van de Sande, 2012. http://www.hetalternatief.org/ICC primer 2012.pdf

[252] Scottish Public Health Network (ScotPHN). Health Care Needs Assessment of Services for people living with ME/CFS. by Mackie P, Dougall R, Conacher A. Version 29.11.10. September 24, 2010, Revised November 30, 2010. http://www.scotphn.net/pdf/Final_report_web_version_271110.pdf and http://www.scotphn.net/projects/previous_projects/care_needs_for_those_experiencing_me_cfs
Page 36 states that CCC is recommended for ME and NICE is recommended for CFS.
Also see

- NHS Scotland. *Scottish Good Practice Statement on ME-CFS.* The Scottish Government, Edinburgh, 2010. www.show.scot.nhs.uk/App_Shared/docs/MainDoc.pdf
  This document also states that CCC is used for ME. "The Scottish Parliament Cross Party Group on M.E. is also strongly supportive of the Canadian Consensus Document definition. It has been adopted for general use in Australia and New Zealand. The Gibson Inquiry (2006) recently reviewed diagnostic criteria and concluded that the Canadian Consensus Document definition was a useful contribution to defining the clinical condition of ME-CFS. Reflecting the lack of accord, the Scottish Public Health Care Network's Health Care Needs Assessment of Services for people living with ME-CFS, has recommended the 'pragmatic use' of the Canadian Consensus Document for the clinical, symptomatic definition of ME."

[253] Smith C, Wessely, S. "Unity of Opposites? Chronic fatigue syndrome and the challenge of divergent perspectives in guideline development" *J Neurol Neurosurg Psychiatry February 2014; 85(2): 214-219. PMID: 23160704. http://dx.doi.org/doi:10.1136/jnnp-2012-303208 and* http://jnnp.bmj.com/content/85/2/214.full

[254] Public Health Agency of Canada. "A-Z Chronic Diseases." Public Health Agency of Canada. Last updated on February 4, 2013. http://www.phac-aspc.gc.ca/cd-mc/az-index-eng.php

[255] Norway Health Directorate. "National guidelines - Patients with CFS / ME - Study diagnosis, treatment and care." Published February 2014.. Translations done with Google translate. http://www.helsedirektoratet.no/helse-og-omsorgstjenester/cfs-me/Sider/default.aspx.

The guidelines recommend CBT and GET and state, "The ruling largely agreed that the causes, the development and maintenance of CFS / ME should be understood as multifactorial, and that the disease is caused by a interact between biological and psychosocial factors." The guidelines list Fukuda, Canadian and the Jason 2006 Pediatric Case definition

Background on the consultation draft that proposed ME-ICC and the response of Norwegian GPs.

- Norway Directorate of Health. "Consultation Draft. Patients with CFS / ME: Investigation, diagnosis, treatment, rehabilitation, nursing and care. For GPs, health and care in the municipalities and specialist health." Published by Norway Directorate of Health. Translated with Google Translate. May 5, 2012. http://www.helsedirektoratet.no/Om/hoyringar/Documents/cfs-me/horingsutkast.pdf
- Norway College of General Practice. "Consultation - draft circular on CFS / ME." Norwegian College of General Practice. November 15, 2012. http://translate.googleusercontent.com/translate_c?depth=1&hl=en&rurl=translate.google.com&sl=no&tl=en&twu=1&u=http://legeforeningen.no/Fagmed/Norsk-forening-for-allmennmedisin/Horingsuttalelser/Horing--utkast-til-rundskriv-om-CFSME-/&usg=ALkJrhhCx_dx7bilY_tG5JDBputAC0F5Zg
  Document in response to the Consultation draft by the Norwegian College of General Practice (NFA). The NFA stated that they could not endorse the ME-ICC and instead recommended Fukuda. They also stated that the document had exceeded the knowledge supported by the evidence in some areas. They also stated that the document minimized the importance of cognitive therapy. The current guidelines reflect this change.
- Norwegian ME Association. "Norwegian College of General Practice (NFA) would not recommend GPs to use the international consensus criteria." Norwegian ME Association. Nov 17, 2012 http://translate.google.com/translate?hl=en&sl=no&tl=en&u=http%3A%2F%2Fme-foreningen.com%2Fmeforeningen%2F%3Fp%3D4450
  Response of the Norwegian ME Association to the NFA statement

[256] The following reference is no longer online in December 2014 and the links to Euromut are redirected to http://www.partenamut.be. It appears that Euromut was merged with Partena in 2014. Euromut was a Belgian Health Insurance company that recommended the use of the CCC for diagnosis of patients as seen in the following notes. Pages last accessed January 2013. All translations by Google Translate.

http://www.euromut.be/cs/ContentServer?packedargs=typeSubAsset2%3DM509_Article&c=M509_Dossier&childpagename=Mut509%2FLayout&p=1239006699187&pagename=Mut509_Wrapper&cid=1255618087871

The Euromut pages at the time stated, "CFS is a complex disease in which the immune system is disturbed and that above all characterized by a disproportionate increase in complaints by a small effort. This occurs in 100% of the patients, and is the hallmark of CFS."
http://www.euromut.be/ContentServer/particulier/Dossiers/dossier.syndrome-de-fatigue-chronique-SFC-fr/article.sfc-les-causes

The page at the time described the biopsychosocial model's focus on personality and factors like stress and stated that the view was being challenged because it fails to account for the physical pain. It went on to say that "Unlike the biopsychosocial model, the discussion within the biomedical model shows visible irregularities and anomalies. More than 400 scientific studies provide evidence of biomedical nature of the disease . CFS usually occurs after a viral infection or a severe weakening of the immune system as a result of physical or emotional overload . CFS is often related to different viruses and different bacterial infections. This results in a chain reaction of physical abnormalities , which explain the typical symptoms of CFS."
http://www.euromut.be/ContentServer/particulier/Dossiers/dossier.syndrome-de-fatigue-chronique-SFC-fr/article.sfc-le-diagnostic

The page at the time also stated "A correct diagnosis of CFS is benefited by the handling of the Canadian criteria , with post-exertional malaise is a mandatory criterion." It went on to state "Tests as diagnostic aids: For a correct diagnosis, a blood test is an asset. Regular blood tests generally do not reveal much, unlike specialized targeted tests. Respiratory and blood tests are tracking intolerances to foods. A stress test or a bike , preferably a double test test clearly demonstrates the unique feature of exercise intolerance . Most CFS patients get abnormal neurological examination . A SPECT scan shows reduced irrigation in the brain , the tilt test shows orthostatic intolerance. Neuropsychological tests are an overview of problems with memory and concentration."

[257] Maupin, C. "The NIH and CFS: The CFS Community's Concerns'" *The CFS Report* September 2005. http://www.cfidsreport.com/Articles/NIH/NIH_CFS_4.htm

[258] Jason, L., Richman, J. "How Science Can Stigmatize: The Case of Chronic Fatigue Syndrome." *Journal of Chronic Fatigue Syndrome* 2007; 14(4): 85-103. http://informahealthcare.com/doi/abs/10.3109/10573320802092146 and http://web.archive.org/web/20120228222416/http://www.cfids-cab.org/cfs-inform/CFS.case.def/jason.richman.07.txt Jason performed two studies, one in medical trainees and the other in college undergraduates to assess perception based on the name.

[259] U.S. Department of Health and Human Services CFS Advisory Committee. "Position Statement Concerning the Name Change Proposal." CFS Advisory Committee. December 8, 2003. Available on the CFIDS Association of America website. http://web.archive.org/web/20131721202500/http://www.cfids.org/advocacy/cfsac-statement.asp
Also see minutes of following meeting for discussion on name change:

- U.S. Department of Health and Human Services CFS Advisory Committee. CFSAC Meeting. September 29, 2003. *CFS Advisory Committee Website.* http://www.hhs.gov/advcomcfs/meetings/minutes/csfac_mins_2003.09.29r_pdf.pdf

[260]. Hanna, Eleanor Presentation at U.S. Department of Health and Human Services CFS Advisory Committee. CFSAC Meeting. September 29, 2003. https://wayback.archive-it.org/3919/20140324192720/http:/www.hhs.gov/advcomcfs/meetings/minutes/csfac_mins_2003.09.29r_pdf.pdf
Includes discussion on CFS's placement in NIH and how the CFSCC and CFSAC were organized and placed (Page 10)

[261] Centers of Disease Control and Prevention. National Center for Health Statistics. "ICD-9-CM Coordination and Maintenance Committee Meeting. Summary of Volumes 1 and 2, Diagnosis Presentations." September 14, 2011 (Minutes). http://www.cdc.gov/nchs/data/icd/2011SeptemberSummary.pdf and *http://www.cdc.gov/nchs/icd/icd9cm_maintenance.htm*

The NCHS minutes on this meeting state, "There was general agreement, by those in the audience, that the term "myalgic encephalomyelitis" is not seen in medical records."

[262] Institute of Medicine of the National Academies. "Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness." Institute of Medicine of the National Academies. Prepublication copy. February 10, 2015. Last accessed February 16, 2015. https://www.iom.edu/Reports/2015/ME-CFS.aspx

[263] Bateman, L. "Dr. Bateman answers IOM questions from the community: Part 1." Phoenix Rising. March 31, 2015. Last accessed April 3, 2015. http://forums.phoenixrising.me/index.php?threads/dr-bateman-answers-iom-questions-from-the-community-part-1.36628/#post-580904

Dr. Bateman was an IOM panel member

[264] Balint G, Buchanan W, Dequeker J. "A brief history of medical taxonomy and diagnosis." *Clin Rheumatol* March 2006; 25(2): 132-135. PMID: 16453080. http://dx.doi.org/10.1007/s10067-004-1051-z

The authors stated, "We all know that the term thistle is applied to a variety of plants, nevertheless, he would be a careless botanist, indeed who contented himself with the general description of a thistle; who only exhibited the marks by which the class was identified; who neglected the proper and peculiar signs of the species, and who overlooked the characters by which they were distinguished from each other. On the same principle, it is not enough

for a writer to merely note down the common phenomena of some multiform disease; for, although it may be true that all complaints are not liable to the same amount of variety, there are still many which authors treat alike, under the same heads, and without the shadows of a distinction, whilst they are in their nature as dissimilar as possible".

[265]Centers for Disease Control and Prevention, National Center for Health Statistics, Office of the Center Director, Data Policy and Standards. "A Summary of Chronic Fatigue Syndrome and Its Classification in the International Classification of Diseases." March 2001 http://web.archive.org/web/20140611042505/http://www.co-cure.org/ICD_code.pdf

As discussed in the section on the medical dictionaries, ME was in the neurological chapter of WHO's ICD-9 (at code 323.9 Encephalitis of unspecified cause). CFS was never added to ICD-9 but instead added to ICD-10 in 1992 at the same code as ME (G93.3).

The U.S. added the term "CFS" to the ICD-9-CM in 1991, pointing to "Malaise and Fatigue", code 780.7. This is the same code where post-viral fatigue syndrome had been located in WHO's ICD-9 and also in the ICD-9-CM.

[266] The ICD-10 has a tabular listing that lays out the primary categories and terms of ICD. It also has an alphabetical index, which indexes additional terms back to the terms of the tabular index. ME is in the tabular index at G93.3 and CFS is in the alphabetical index at G93.3.

[267] Background sources for the original decision to follow WHO's placement as a neurological disease.

- Walker, Vicky. "A monumentous week for CFIDS." CFIDS Association of America. Winter 2000. http://web.archive.org/web/20131418034400/http://www.cfids.org/archives/2000/2000-1-article02.asp This CFIDS report on the 2000 CFS Coordinating Committee states "The Centers for Disease Control and Prevention (CDC) announced that in 2002 the U.S. diagnostic code for CFS will be moved from "General symptoms-Malaise and fatigue" (780.71) [the code in ICD-9-CM] to "Other disorders of the brain" (G93.], which is the code the World Health Organization (WHO) established in ICD-10 in 1992 for CFS, post-viral fatigue syndrome and benign myalgic encephalomyelitis. In 1998 the U.S. created a separate code (distinct from the WHO code) for CFS. Dr. Klimas, Kim [McCleary] and I [Vicky Walker] worked closely with the National Center for Health Statistics over the past 18 months to provide scientific evidence supporting our position that the U.S. should adopt the WHO designation, providing worldwide consistency in CFS classification and a more scientifically appropriate code for CFS. Hopefully this coding change will have a positive impact on insurance reimbursement and validation of CFS."
- Centers for Disease Control and Prevention, National Center for Health Statistics, Office of the Center Director, Data Policy and Standards. "A Summary of Chronic Fatigue Syndrome and Its Classification in the International Classification of Diseases." March 2001 http://web.archive.org/web/20140611042505/http://www.co-cure.org/ICD_code.pdf This summary states "In keeping with the placement in the ICD-10, chronic fatigue syndrome (and its synonymous terms) ***will remain at G93.3*** in ICD-10-CM."

[268] Background on the transfer of CFS from the neurological chapter to the Symptoms chapter in ICD-10-CM:

- In 2003, CFS was split into a CFS Postviral, left in the neurological chapter and a "CFS, not Postviral," moved into the Symptoms chapter. This was apparently done after the public comment period on the original draft but before the process was put in place for the public to make changes.
  National Center for Health Statistics (NCHS). *Pre-release Draft, June 2003. International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM)*.
  https://web.archive.org/web/20050311110546/http://www.cdc.gov/NCHS/about/otheract/icd9/icd10cm.htm
- In the 2007 release, CFS was removed from the neurological chapter and the "not Postviral" restriction was removed from CFS in the Symptoms chapter It appears that during this time, NCHS had incorporated feedback from earlier public comment periods. It does not appear that there was a formal request for this change from the public. At least, I was unable to find a formal proposal submitted through normal changes for this change Centers for Disease Control and Prevention, National Center for Health Statistics. FTP Page for downloads of the ICD-10-CM.
  https://web.archive.org/web/20101023063503/http://ftp.cdc.gov/pub/Health_Statistics/NCHS/Publications/ICD10CM/2007/
- From 2004 to 2012, CFSAC recommended that CFS be placed in the neurological chapter on a number of occasions as documented in CFSAC minutes and recommendations lists. Two formal proposals were submitted by patient advocate groups to the NCHS to reclassify CFS back to the neurological chapter
  - Centers for Disease Control, National Center for Health Statistics. "ICD-9-CM Coordination and Maintenance Committee Meeting September 14, 2011 Diagnosis Agenda" http://www.cdc.gov/nchs/data/icd/TopicpacketforSept2011a.pdf
  - Centers for Disease Control, National Center for Health Statistics. "ICD-9-CM Coordination and Maintenance Committee Meeting September 19, 2012 Diagnosis Agenda" http://www.cdc.gov/nchs/data/icd/Topic_packet_for_September_19_2012.pdf
- The current version of the ICD-10-CM, which is intended to be rolled out in October, 2015

Centers for Disease Control and Prevention, National Center for Health Statistics (NCHS). *International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM)*. Last updated September 26, 2014.. http://www.cdc.gov/nchs/icd/icd10cm.htm

[269] Placing CFS in the Symptoms chapter does not align with WHO's ICD-10 standards.

As noted more fully in references on the next page, "Andre L'Hours, the Technical Officer at the WHO headquarters in Geneva who is responsible for the ICD, confirmed that it was "unacceptable" if the same disorder had been included in two places in the ICD-10 and that the same disorder could not be differently categorized under the one WHO banner."

[270] Countries either use the ICD-10 directly or create a clinical modification of the ICD-10. The U.S. clinical modification is called ICD-10-CM while Canada's is called ICD-10-CA and Germany's is called ICD-10-GM. In the German and the Canadian version, CFS is classified at G93.3, not in the Symptom chapter as done in the U.S.

- German Institute of Medical Documentation and Information. "ICD-10-GM Version 2015. Chapter 6. Diseases of the Nervous System. (G00-G99)," Page Status listed as September 19, 2014.. http://www.dimdi.de/static/de/klassi/icd-10-gm/kodesuche/onlinefassungen/htmlgm2015/block-g90-g99.htm
  Note that Chronic fatigue syndrome is "Chronisches Müdigkeitssyndrom" in German.
- Canadian Institute for Health Information. International Statistical Classification of Diseases and Related Health. Tenth Revision. Volume One. Tabular List." 2009. http://www.cihi.ca/cihi-ext-portal/pdf/internet/icd_10_ca_vol1_2009_en. Note that a new version of the ICD-10-CA was issued in 2012 but it is not accessible without a license.

[271] The National Center for Health Statistics (NCHS) actions goes against recommendations by CFSAC, a recommendation by the International Association of CFS/ME and two formal requests by patient advocates to have CFS put back into the neurological chapter. The U.S. will categorize "CFS" as a subcategory of chronic fatigue when it rolls out the ICD-10-CM in October 2015.

- U.S. Department of Health and Human Services CFS Advisory Committee. "Recommendations Chart since 2004." CFS Advisory Committee. *CFS Advisory Committee Website.* Last updated February 4, 2013. https://wayback.archive-it.org/3919/20140324192829/http://www.hhs.gov/advcomcfs/recommendations/cfsac_recommendationschart.pdf
- Formal proposals by patient advocates to National Center for Health Statistics
  - Centers for Disease Control and Prevention, National Center for Health Statistics, Office of the Center Director, Data Policy and Standards. "A Summary of Chronic Fatigue Syndrome and Its Classification in the International Classification of Diseases." March 2001 http://web.archive.org/web/20140611042505/http://www.co-cure.org/ICD_code.pdf
  - From 2004 to 2012, CFSAC recommended that CFS be placed in the neurological chapter on a number of occasions as documented in CFSAC minutes and recommendations lists. Two formal proposals were submitted by patient advocate groups to the NCHS to reclassify CFS back to the neurological chapter
    - Centers for Disease Control, National Center for Health Statistics. "ICD-9-CM Coordination and Maintenance Committee Meeting September 14, 2011 Diagnosis Agenda" http://www.cdc.gov/nchs/data/icd/TopicpacketforSept2011a.pdf
    - Centers for Disease Control, National Center for Health Statistics. "ICD-9-CM Coordination and Maintenance Committee Meeting September 19, 2012 Diagnosis Agenda" http://www.cdc.gov/nchs/data/icd/Topic_packet_for_September_19_2012.pdf
- IACFS/ME. IACFS/ME Newsletter, Attachment 1. December 2012 https://www.google.com/url?q=http://www.iacfsme.org/LinkClick.aspx%3Ffileticket%3D6hIveKzhBQo%253D%26tabid%3D516&sa=U&ei=oayRVODCIvP9sATr-YCACw&ved=0CBgQFjAB&sig2=TE3jR6ca_tZcTNV40GVLXQ&usg=AFQjCNHf_RYvgNfka0Tp2tWdmEFYuITPQw
  Comments submitted to NCHS during open comment period following the September 2012 proposal.
- Dimmock M. Chapo-Kroger L, Munoz M. Email exchange with Dr. Daulaire, U.S. member of the Executive Board of the World Health Organization at that time. Request to intervene and abide by WHO standards was unsuccessful in getting CFS reclassified to the neurological chapter. https://dl.dropboxusercontent.com/u/89158245/ICD-10-CM%20letter%20to%20Daulaire%20May%202013.docx
  - In his June 28, 2013 response, Dr. Daulaire stated, "I welcome your continued input to the Coordination and Maintenance Committee during future meetings as reaching consensus in this process will be critical moving forward. The issue of determining the appropriate classification of CFS is important and I agree that we must strive to achieve a placement of the disease that is understood within the medical community and can advance our knowledge of this serious and complex syndrome."

[272] Centers for Medicare and Medicaid Services. "Press release: Deadline for ICD-10 allows health care industry ample time to prepare for change." July 31, 2014. http://www.cms.gov/Newsroom/MediaReleaseDatabase/Press-releases/2014-Press-releases-items/2014-07-31.html.

New deadline set for October 1, 2015

[273] Maupin, Craig. "CDC AND NIH Officials Discussed 'Desirable Outcome' of Seeing A Distinct Illness 'Evaporate'." *The CFS Report,* March 2014. http://www.cfidsreport.com/News/14_Chronic_Fatigue_Syndrome_Definition_IOM_Straus.html

Discussion of the letter from Dr. Stephen Straus at NIH to Dr. Keiji Fukuda at CDC. The letter, which is undated, was written about the time of the publication of Fukuda in 1994. The letter was obtained by Craig Maupin of CFIDSReport.com by FIOA and released in March of 2014. FOIA Number No.38767. The letter itself can be accessed directly at https://dl.dropboxusercontent.com/u/89158245/Straus%20to%20Fukuda%20letter%201994.docx

[274] U.K. WHO Collaborating Center at Kings College. "*WHO Guide to Mental Health In Primary Care*. Chronic Fatigue and Chronic Fatigue Syndrome - F48.0." U.K. WHO Collaborating Center at Kings College. May 9, 2001. http://web.archive.org/web/20010509001333/http://cebmh.warne.ox.ac.uk/cebmh/whoguidemhpcuk/disorders/f48-0.html

It is not clear exactly when this was first published but it was on the May 9, 2001 version of this page.

[275] Prins J, van der Meer J, Bleijenberg G. "Chronic fatigue Syndrome." *The Lancet* January 28, 2006; 367(9507): 346-355. PMID: 16443043. http://dx.doi.org/10.1016/S0140-6736(06)68073-2

This article by Prins had even stated that "During the past few years, the UK collaborating centre of the WHO Guide to Mental Health in Primary Care unified CFS and ME in a single psychiatric code." While the UK Collaborating Center did attempt to classify CFS as a psychiatric code, it was against WHO guidelines.

[276] Correspondence from Andre L'Hours, Technical Officer at the WHO. A similar situation arose in England in 2001 when CFS was listed under both Mental and Behavioral Disorders/Neurasthenia and Nervous System Disorders. In a June 2001 press release reported by numerous patient organizations at the time, "Andre L'Hours, the Technical Officer at the WHO headquarters in Geneva who is responsible for the ICD, confirmed that it was "unacceptable" if the same disorder had been included in two places in the ICD-10 and that the same disorder could not be differently categorized under the one WHO banner."

Multiple organizations reported L'Hours statement at the time.

- U.K. Group on Scientific Research into Myalgic Encephalomyelitis (M.E.). "Inquiry into the status of CFS / M.E. and research into causes and treatment." (The Gibson Inquiry). U.K. Group on Scientific Research into Myalgic Encephalomyelitis (M.E.). Chaired by Dr. Ian Gibson. November, 2006.
  - Report - www.erythos.com/gibsonenquiry/Docs/ME_Inquiry_Report.pdf and
  - Press release - http://www.erythos.com/gibsonenquiry/Docs/Press_Release_26Nov06.rtf
- Colby, Jane and Williams, Margaret. "Classification Principles provided by the World Health Organisation re ME/CFS." January 26, 2004. https://web.archive.org/web/20101120230720/http://cfids-cab.org/cfs-inform/CFS.case.def/who.classification.me.cfs04.txt
- Hooper, Malcolm. "MAGICAL MEDICINE: HOW TO MAKE A DISEASE DISAPPEAR." InvestInME. February 2010. http://www.investinme.org/Documents/Library/magical-medicine.pdf

  Hooper states, that the WHO response on January 23, 2004 was, "According to the taxonomic principles governing ICD-10, it is not permitted for the same condition to be classified to more than one rubric". (Page 8)

[277] U.K. Department for Work and Pensions. *Continuing Medical Education Programme. Chronic Fatigue Syndrome / Myalgic Encephalomyelitis (CFS/ME) - Guidelines for the Disability Analyst.* Version 7, Module 6, Published May 28, 2014. http://www.actionforme.org.uk/Resources/Action%20for%20ME/dwp-training-doc-for-assessors-on-me.pdf
Note that according to this description, G93.3 only gets used when there is a viral trigger or where the symptoms do not meet Neurasthenia to begin with. The Neurasthenia criteria are very broad and would capture any ME patient. Specifically, the document states, "There are two classifications in use in the ICD 10. CFS/ME can be classified under neurological disorders as G93.3 (Benign myalgic encephalomyelitis), or under neurotic, stress-related and somatoform disorders as F48.0 (neurasthenia). "

- "From the ICD 10: G93.3 Benign myalgic encephalomyelitis – to be used where specific trigger such as a viral disease and/or where the symptoms do not fulfill the criteria for F48.0 (World Health Organization - UK Collaborating Centre, 2004)."
- "F48.0 Neurasthenia – which has the following diagnostic features: a. Either persistent and distressing complaints of increased fatigue after mental effort, or persistent and distressing complaints of bodily weakness and exhaustion after minimal effort; b. At least two of the following: (feelings of muscular aches and pains, dizziness, tension headaches, sleep disturbance, inability to relax, irritability, dyspepsia"

The document goes on to state that neither are acceptable, that the Association of British Neurologists rejects CFS as a neurological condition and that the problem is because this disease "straddles both physical and mental health spectrums."

Author's note: There are many organic diseases that cause psychiatric issues but they are not similarly treated.

[278] International Health Terminology Standards Development Organisation. *Systematized Nomenclature of Medicine--Clinical Terms (SNOMED CT).* http://www.ihtsdo.org/snomed-ct//

According to the site, SNOMED CT is owned, maintained and distributed by the International Health Terminology Standards Development Organisation (IHTSDO). The IHTSDO is a not-for-profit association which is owned and governed by its national Members."

Other sources include:

- U.S. National Library of Medicine. "SNOMED Clinical Terms® (SNOMED CT®)." Page last updated July 18, 2014. http://www.nlm.nih.gov/research/umls/Snomed/snomed_main.html
- Multiple browsers are available, including,
  The National Center for Biomedical Ontology. "Systematized Nomenclature of Medicine--Clinical Terms (SNOMED CT." *BioPortal*
  http://bioportal.bioontology.org/ontologies/SNOMEDCT?p=classes&conceptid=http%3A%2F%2Fpurl.bioontology.org%2Fontology%2FSNOMEDCT%2F52702003
  IHTSDO SNOMED CT Browser. International Health Terminology Standards Development Organisation. Release: United States Edition 20150301. Last accessed April 20, 2015
  http://browser.ihtsdotools.org/

[279] U.K. Health and Social Care Information Center. *Read Codes.*Last accessed April 2, 2015.
http://systems.hscic.gov.uk/data/uktc/readcodes

This site states "Read Codes are a coded thesaurus of clinical terms and have been used in the NHS since 1985. There are two versions: version 2 (v2) and version 3 (CTV3 or v3), they provide the standard vocabulary by which clinicians can record patient findings and procedures in health and social care IT systems across primary and secondary care (e.g. General Practice surgeries and pathology reporting of results)."
The Read Codes, Clinical Terms Version 3 (CTV3) can be viewed at:

- The National Center for Biomedical Ontology. "READ Codes." *BioPortal*
- http://bioportal.bioontology.org/ontologies/RCD?p=classes&conceptid=http%3A%2F%2Fpurl.bioontology.org%2Fontology%2FRCD%2FXa01F
  - CFS is listed as a Mental Health Disorder under Neurotic Disorder/Somatoform Disorder/Neurasthenia/CFS.
  - CFS is also listed under Neurological Disorder/CFS (no subcategories)
  - ME is listed as a synonym of CFS

Author's note: Health and Social Care Information Center is an executive non-departmental public body, sponsored by the U.K. Department of Health.

[280] Examples of CFS being referred to as Somatorm illness.

- Fink, Per. "Somatoform disorders – functional somatic syndromes - Bodily distress syndrome. Need for care and organisation of care in an international perspective." Lecture to the EACLLP. Undated.
  http://web.archive.org/web/20130525203725/http://www.eaclpp.org/tl_files/content/Presentations/EACLPP_Per%20Fink_Somatoform%20Disorders.pdf
  Author's note: Per Fink runs The Research Clinic for Functional Disorders at Aarhus University Hospital in Denmark. The website for that clinic is at www.functionaldisorders.dk
- First, Michael. "Somatic Presentations of Mental Disorders." Summary of presentations given at the conference cosponsored by the APA in collaboration with WHO and NIH. Sept 6-8, 2006 in Beijing, China.
  http://www.dsm5.org/research/pages/somaticpresentationsofmentaldisorders(september6-8,2006).aspx
- "Gulf War and Health Volume 9: Treatment for Chronic Multisymptom Illness." Institute of Medicine. Jan 23, 2013. http://www.iom.edu/Reports/2013/Gulf-War-and-HealthTreatment-for-Chronic-Multisymptom-Illness.aspx. This report states that it calls medically unexplained symptoms chronic multi-symptom illness. It also states that terms such as "medically unexplained symptoms, medically unexplained physical symptoms, somatoform disorders (for example, somatization disorder, undiffer- entiated somatoform disorder, and pain disorder), and functional somatic syndromes" are often used for patients with unexplained symptoms and includes CFS in that group. (Page 22, 140).

[281] First, Michael. "Somatic Presentations of Mental Disorders." Summary of presentations given at the conference cosponsored by the APA in collaboration with WHO and NIH. Sept 6-8, 2006 in Beijing, China.
http://www.dsm5.org/research/pages/somaticpresentationsofmentaldisorders(september6-8,2006).aspx
The conference was the eighth in a series of 12 NIH-funded conferences on "The Future of Psychiatric Diagnosis: Refining the Research Agenda." Dr. First included the following summaries of two presentations given at that meeting:

- First described Wessely's presentation on the functional somatic syndromes which included irritable bowel syndrome, CFS, fibromyalgia and others, which he stated occurred regularly in common practice. First stated that Wessely said that "A latent class analysis of functional somatic symptoms in the community suggests the presence of five classes: a chronic fatigue-like entity, a pan/myalgia-like entity, an irritable bowel syndrome-like entity, a depression entity, and an anxiety entity. Dr Wessely concluded that we should accept the existence of a concept of functional somatic symptoms/syndromes that differ from anxiety and depression, and that within this broad category we still need to respect the integrity of fibromyalgia, irritable bowel syndrome, chronic fatigue syndrome, and their cultural variants."
- "Laurence Kirmayer MD (Montreal, Canada) presented on the role of cultural models in the phenomenology of somatoform disorders in which "cognitive processes and social responses can lead to more

symptoms….Similarly,in chronic fatigue syndrome, symptoms lead to activity restriction which in turn leads to more symptoms."

[282] American Psychiatric Association. "Somatic Symptom Disorder." American Psychiatric Association. 2013. www.dsm5.org/Documents/Somatic Symptom Disorder Fact Sheet.pdf
Fact sheet on SSD that includes the following information:

- "Somatic symptom disorder (SSD) is characterized by somatic symptoms that are either very distressing or result in significant disruption of functioning, as well as excessive and disproportionate thoughts, feelings and behaviors regarding those symptoms."
- "To be diagnosed with SSD, the individual must be persistently symptomatic (typically at least for 6 months)"
- "The DSM-IV diagnosis of somatization disorder required a specific number of complaints from among four symptom groups. The SSD criteria no longer have such a requirement; however, somatic symptoms must be significantly distressing or disruptive to daily life and must be accompanied by excessive thoughts, feelings, or behaviors."
- "Another key change in the DSM-5 criteria is that while medically unexplained symptoms were a key feature for many of the disorders in DSM-IV, an SSD diagnosis does not require that the somatic symptoms are medically unexplained"

The article goes on to state that unlike DSM-IV, in DSM-5, a diagnosis can be given even when the symptoms have a medical explanation. The rationale is that this removes "the mind-body separation implied in DSM-IV" that leads clinicians to miss an SSD diagnosis, thereby preventing patients from getting the help that they need.

[283] All patients, even those with well-known physical diseases like cancer, can be given a bolt-on mental illness diagnosis if their medical provider decides that the patient is too concerned with his illness or health. But ME patients are at particular risk of having this be the sole diagnosis that they receive. And in fact, in spite of being classified as a neurological disease in the ICD-10, in the U.K. today, CBT and GET are the only treatments offered to many patients in the UK, via NHS clinics and according to NICE G53 Guideline for CFS/ME.

[284] The inclusion of SSD in the DSM-5 has created significant concern for patients with ME because of this association of CFS with somatic disorder. Dr. Allen Frances has discussed this issue and the impact on patients whose diseases have been labeled as a somatic disorder.

- Frances, A. "Mislabeling Medical Illness As Mental Disorder." *DSM5 In Distress. Psychology Today.* December 8, 2012. http://www.psychologytoday.com/blog/dsm5-in-distress/201212/mislabeling-medical-illness-mental-disorder

See also

- Frances, A. "Diagnostic Ethics: Harms vs Benefits of Somatic Symptom Disorder." *The Blog*. Huffington Post, December 16, 2013. Updated February 15, 2014. http://www.huffingtonpost.com/allen-frances/diagnostic-ethics-harms-v_b_4450653.html
  This article discusses the guidelines by the American Association of Family Physicians which urges doctors to make early diagnoses of somatoform disorders in order to save time and to reduce costs. Dr. Frances quotes Dr. Diane O'Leary who heads the Coalition for Diagnostic Rights. The website for the Coalition for Diagnostic Rights is: http://www.diagnosticrights.org/the-coalition/

O'Leary also submitted the following letter to BMJ on SSD

- O'Leary, D. "The new somatic symptom disorder in DSM-5 risks mislabeling many people as mentally ill." March 2013; 346. http://dx.doi.org/10.1136/bmj.f1580

[285] Frances, A. "Bad News: DSM 5 Refuses to Correct Somatic Symptom Disorder." *DSM5 In Distress. Psychology Today.* January 16, 2013. http://www.psychologytoday.com/blog/dsm5-in-distress/201301/bad-news-dsm-5-refuses-correct-somatic-symptom-disorder

[286] Frances, A. "Diagnostic Ethics: Harms vs Benefits of Somatic Symptom Disorder." *The Blog*. Huffington Post, December 16, 2013. Updated February 15, 2014. http://www.huffingtonpost.com/allen-frances/diagnostic-ethics-harms-v_b_4450653.html

[287] Wolfe F, Walitt BT, Katz RS, Häuser W "Symptoms, the Nature of Fibromyalgia, and Diagnostic and Statistical Manual 5 (DSM-5) Defined Mental Illness in Patients with Rheumatoid Arthritis and Fibromyalgia." *PLoS ONE,* February 2014; 9(2): e88740. http://dx.doi.org/10.1371/journal.pone.0088740
Also see:
Wilcken, Hugo, "DSM Criteria useless in Fibromyalgia: experts." Rheumatology Update. February 21, 2014. http://www.rheumatologyupdate.com.au/latest-news/dsm-5-criteria-useless-in-fibromyalgia-experts.
The author stated "We are dubious that the DSM-5 approach can distinguish validly and reliably which fibromyalgia patients are and which are not mentally ill, particularly in clinical care settings where diagnosis will come most often from generalists," they concluded."

[288] Swidey N, Wen P. "No release for Conn. teen caught in hospital dispute", *Boston Globe (Boston, Mass.)* Dec 21, 2013 http://www.bostonglobe.com/lifestyle/health-wellness/2013/12/21/state-retains-custody-teen-limbo-children-hospital-for-months/5TGcy5X8IxQusdtXgRmXdK/story.html

[289] Sources include:

- ME Association, Denmark. "Karina Hansen is a severely ill Danish patient who was forcibly taken from her home on Feb 12th." May 9, 2013. Reposted on *Voices from the Shadows*. http://voicesfromtheshadowsfilm.co.uk/2013/karina-hansen-is-a-severely-ill-danish-patient-who-was-forcibly-taken-from-her-home-update-may-2013-9th/
- Letter by Karina's parents submitted to Stig Gerdes for Parliament hearing on March 19, 2014. http://www.ft.dk/samling/20131/almdel/suu/bilag/311/1347104/index.htm Translated with Google
- O'Leary, Diane. "The Coalition's Letter to the Danish Minister of Health on Karina Hansen's Behalf." May 19, 2014. http://www.diagnosticrights.org/the-coalitions-letter-to-the-danish-minister-of-health-on-karina-hansens-behalf/
- Swift P. "British Doctor Wants to Rescue ME Patient Held at Danish Hospital." Liberty Voice. February 10, 2014 http://guardianlv.com/2014/02/british-doctor-wants-to-rescue-me-patient-held-at-danish-hospital-video/ Note that Karina was at one point reportedly also given a diagnosis of "Pervasive arousal withdrawal syndrome," which is characterized by social withdrawal and a refusal to walk, eat, talk or perform self-care. The conceptualization of this disorder appears to vary as noted below but includes the idea of autonomic system hyper-arousal that appears to be at the heart of Per Fink's Bodily distress syndrome modelFor more information on this condition, see
- Nunn K, Lask B, Owen I. "Pervasive refusal syndrome (PRS) 21 years on: a re-conceptualisation and a renaming." European Child & Adolescent Psychiatry March 2014; 23(3): 163-172. PMID: 23793559. http://dx.doi.org/10.1007/s00787-013-0433-7

[290] Letter by Karina's parents submitted to Stig Gerdes for Parliament hearing on March 19, 2014. http://www.ft.dk/samling/20131/almdel/suu/bilag/311/1347104/index.htm. In Danish. Use Google translate

[291] Fox, Richard. "New Disease Discovery Could Be the Answer to 'Mystery Illness'" Doctor's Health Press. January 9, 2013. http://www.doctorshealthpress.com/pain-articles/new-disease-discovery-could-be-the-answer-to-mystery-illness - This article is based on work of Dr. Per Fink referenced above

- Fink, Per. "Somatoform disorders – functional somatic syndromes - Bodily distress syndrome. Need for care and organisation of care in an international perspective." Lecture to the *EACLLP*. Undated. http://web.archive.org/web/20130525203725/http://www.eaclpp.org/tl_files/content/Presentations/EACLPP_Per%20Fink_Somatoform%20Disorders.pdf
- The Research Clinic for Functional Disorders at Aarhus University Hospital in Denmark. The website for that clinic is at www.functionaldisorders.dk

[292] Fink, Per. "Stig Gerdes helps to intensify conflicts "Dagens Medicin June 6, 2014. http://translate.google.com/translate?hl=en&sl=da&u=http://www.dagensmedicin.dk/opinion/debat/stig-gerdes-er-med-til-at-optrappe-konflikter

As evidence of the efficacy of the treatment approaches, Dr. Fink stated, "In addition to textbooks, we published in the American Journal of Physicians in 2010, a status article in Danish, where SG can find the documentation. Since 2010, there have been several new review articles published in high-ranking journals such as JAMA and Lancet."

He also stated "Danish College of General Practitioners has issued a clinical guideline for functional disorders, which also evidence levels are listed, and there are also foreign clinical guidelines, for example. National Institute of Health in England for CFS/ME. Around treatment concludes these clearly show that there is good scientific evidence that cognitive therapy, graded rehabilitation and sometimes antidepressants can help patients with functional disorders, regardless of what name they are dealt with, for example. fibromyalgia, irritable bowel syndrome, chronic fatigue syndrome/ME and bodily distress syndrome."

[293] Statement by National Institute of Mental Health Director Thomas Insel. "Transforming Diagnosis. National Institute of Mental Health." U.S. National Institute of Mental Health. April 29, 2013. http://www.nimh.nih.gov/about/director/2013/transforming-diagnosis.shtml

[294] It is difficult to state definitely what is being considered for ICD-11 at this time. It appears that there are two different types of options being considered, Bodily Stress Syndrome and Bodily Distress Disorder:

- Bodily stress syndrome – Based on a 2012 article, the approach being considered by the Primary Care Consultation Group (PCCG) at that time. The concept drew heavily on Per Fink's model (discussed above), but also has some psychobehavioral criteria that are more reflective of DSM-5's concept of SSD. Reference is: Lam TP, Goldberg DP, Dowell AC, Fortes S, Mbatia JK, Minhas FA, Klinkman MS. "Proposed new diagnoses of anxious depression and bodily stress syndrome in ICD-11-PHC: an international focus group study." Family Practice 2012. 30(1): 76-87. http://dx.doi.org/10.1093/fampra/cms037
- Bodily distress disorder (BDD) appears to be the concept being advanced by the Expert Working Group on Somatic Distress and Dissociative Disorders and the term entered into the Beta draft. The current Beta draft definition for BDD is based on wording from the work group's 2012 emerging proposals paper [ref] which had described a disorder that appeared to be a bolt-on diagnosis for any disease, with a disorder model close to DSM-5's Somatic symptom disorder. One reference for the approach is:

Creed F, Gureje O. "Emerging themes in the revision of the classification of somatoform disorders." Int Rev Psychiatry; December 2012; 24(6): 556-67. PMID: 23244611. http://dx.doi.org/10.3109/09540261.2012.741063

Additional references:

- Chapman, Suzy. "DX Revision Watch. Monitoring the development of DSM-5 and ICD-11." http://dxrevisionwatch.com/ Chapman is an advocate who has closely tracked the current status of DSM and ICD implementation. DX Revision Watch is her blog.
- This article suggests a model like Per Fink's and states that FM, CFS and other somatic disorders will be classified together as bodily stress syndrome.
  Luciano JV, Barrada JR, Aguado J, Osma J, García-Campayo J. "Bifactor Analysis and Construct Validity of the HADS: A Cross-Sectional and Longitudinal Study in Fibromyalgia Patients." Psychol Assess. December 2, 2013 http://www.uam.es/becarios/jbarrada/papers/hads.pdf
  The paper stated, "…In the upcoming primary healthcare version of the ICD-11 (ICD-11-PHC), FM will be classified as part of bodily stress syndrome (BSS; Lam et al., 2013). This new diagnosis will group patients who might have previously been considered different (e.g., those with FM, chronic fatigue syndrome, irritable bowel syndrome, and so on)" (Page 18)

[295] World Health Organization (WHO). "ICD-11 Beta Draft (Joint Linearization for Mortality and Morbidity Statistics)." http://apps.who.int/classifications/icd11/browse/l-m/en

[296] World Health Organization (WHO). "ICD-11 Beta Draft (Joint Linearization for Mortality and Morbidity Statistics).”." http://apps.who.int/classifications/icd11/browse/l-m/en#/http%3a%2f%2fid.who.int%2ficd%2fentity%2f767044268

Using the search term "bodily distress", the following definition was returned: "Bodily distress disorder is characterized by high levels of preoccupation regarding bodily symptoms, unusually frequent or persistent medical help-seeking, and avoidance of normal activities for fear of damaging the body. These features are sufficiently persistent and distressing to lead to impairment in personal, family, social, educational, occupational or other important areas of functioning. The most common symptoms include pain (including musculoskeletal and chest pains, backache, headaches), fatigue, gastrointestinal symptoms, and respiratory symptoms, although patients may be preoccupied with any bodily symptoms. Bodily distress disorder most commonly involves multiple bodily symptoms, though some cases involve a single very bothersome symptom (usually pain or fatigue)."

[297] Per a personal discussion with Suzy Chapman of DX Revision Watch. In ICD-10, any given disease could only be in one chapter. However, in ICD-11, terms can be dual listed. For instance, In ICD-11, the Dementias and Alzheimer are primarily coded for in the Neurological chapter but they are secondary listed under Mental and behavioural disorders, under Neurocognitive disorders. This potential for dual listing could have important implications for this disease.

[298] Institute of Medicine of the National Academies. "Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness." Institute of Medicine of the National Academies. Prepublication copy. February 10, 2015. Last accessed February 16, 2015. https://www.iom.edu/Reports/2015/ME-CFS.aspx

[299] U.S. Department of Health and Human Services CFS Advisory Committee. CFSAC Meeting Recommendations. October 3-4, 2012 http://www.hhs.gov/advcomcfs/recommendations/10032012.html

[300] Letter from ME patient advocacy community to Secretary of Health Sebelius, Assistant Secretary of Health Dr. Howard Koh, CDC Director Dr. Thomas Frieden and NIH Director Dr. Francis Collins. "Need for Focused Attention on Myalgic Encephalomyelitis (ME)." May 12, 2013. https://dl.dropboxusercontent.com/u/89158245/DHHS%20Definition%20Initiatives%20May%2012%202013.pdf

[301] Email from Dr. Beth Unger of CDC to Mary Dimmock in response to May 12, 2013 letter. "Response to signatories of May 12 letter c/o Marry Dimmock." Received by email on June 5, 2013. Copied to word document for sharing with advocates who signed the letter. https://dl.dropboxusercontent.com/u/89158245/Dr%20Unger%20response%20to%20definition%20letter%20June%205%202013.pdf

[302] Institute of Medicine. "Diagnostic Criteria for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome." (Activity Description). Undated. Project started in 2013 and continues until early 2015. http://www.iom.edu/Activities/Disease/DiagnosisMyalgicEncephalomyelitisChronicFatigueSyndrome.aspx
Additional information including the cost is available at
Health and Human Services. "FAQs on an HHS contract with the IOM to recommend clinical diagnostic criteria for ME/CFS." *CFSAC Advisory Committee Website*. Undated. Last accessed May 5, 2015. http://www.hhs.gov/advcomcfs/notices/faqs-iom.html

[303] "Background on the letter from ME/CFS experts stating consensus on the Canadian Consensus Criteria and on the HHS announcement on the IOM contract." Sept 25, 2013. Updated on Oct 10, 2013. https://dl.dropboxusercontent.com/u/89158245/MECFS%20Action%20Alert%20Background%20Sept%2025%202013.pdf
Includes summary of patient advocates concerns with the IOM and the handling of the GWI.

[304] Institute of Medicine. "Chronic Multisymptom Illness in Gulf War Veterans: Case Definitions Reexamined." (Report) March 12, 2014 http://www.iom.edu/Reports/2014/Chronic-Multisymptom-Illness-in-Gulf-War-Veterans-Case-Definitions-Reexamined.aspx
Also see media article describing report

- Ruiz, Rebecca "Experts Can't Decide On Definition For Mysterious Gulf War Illness." *Forbes* March 12, 2014 http://www.forbes.com/sites/rebeccaruiz/2014/03/12/experts-cant-decide-on-definition-for-gulf-war-illness/

[305] Letter from Dr. Christopher Snell on behalf of fifty ME/CFS experts to Secretary Sebelius, Department of Health and Human Services. Originally sent on September 23, 2014. Resent on October 25, 2014 with additional signatures. https://dl.dropboxusercontent.com/u/89158245/Case%20Definition%20Letter%20Sept%2023%202013.pdf

The letter states "We strongly urge the U.S. 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. In addition, we strongly urge you to abandon efforts to reach out to groups such as the Institute of Medicine (IOM) that lack the needed expertise to develop "clinical diagnostic criteria" for ME/CFS. Since the expert ME/CFS scientific and medical community has developed and adopted a case definition for research and clinical purposes, this effort is unnecessary and would waste scarce taxpayer funds that would be much better directed toward funding research on this disease. Worse, this effort threatens to move ME/CFS science backward by engaging non-experts in the development of a case definition for a complex disease about which they are not knowledgeable."

[306] Letter from Secretary Kathleen Sebelius, U.S. Department of Health and Human Services to Dr. Christopher Snell in response to the October 25, 2014 letter from fifty experts. November 12, 2013. https://dl.dropboxusercontent.com/u/89158245/Nov%2012%202013%20Secretary%27s%20Response%20to%20MECFS%20experts.pdf

[307] U.S. Department of Health and Human Services. "FAQs on an HHS contract with the IOM to recommend clinical diagnostic criteria for ME/CFS." CFS Advisory Committee Website. Undated. http://www.hhs.gov/advcomcfs/notices/faqs-iom.html

[308] U.S. Department of Health and Human Services CFS Advisory Committee. CFSAC May 22-23, 2013 meeting. https://www.youtube.com/watch?v=VJ7VqYJTsWI&list=PLrl7E8KABz1FGfzllYcomOoI9agz8-6QL&index=12

Exchange between Dr. Unger and CFSAC members on PEM in which CDC's Dr. Unger questioned the importance of PEM as a symptom rhetorically asked the question "If a patient doesn't have [post-exertional malaise], would you not manage them as a CFS patient?" (Minutes 25-45)

[309]U.S. Department of Health and Human Services CFS Advisory Committee. CFSAC Meeting. May 23, 2013. http://www.hhs.gov/advcomcfs/meetings/minutes/cfsacmay23_final_508.pdf

Dr. Lee stated, "Let me also say that the department took the recommendation which asked for research and clinical definitions and let that be advice from the committee. The original recommendation said something about working on both clinical and research definitions. What we decided to do with that amidst a good bit of controversy among the [CFSAC] subcommittee calls—which I don't think we have the time to revisit—we discussed that NIH had the wonderful and already funded process to think about the research case definition. It may not be the goal of the workshop to come out with a research case definition, but there will be so much good evidence that that can be the next step. We are now actively pursuing methods to address the clinical research definition part."
Also see

- U.S. Department of Health and Human Services CFS Advisory Committee. CFSAC Meeting. December 11, 2013. http://www.hhs.gov/advcomcfs/meetings/minutes/cfsac-minutes-dec-11.pdf
  Dr. Lee stated, "This was advice from an advisory committee. We took that advice. We applied our own judgment as to how we know to disseminate widely in the medical community. We believe that the IOM was the best way to go. We are hoping that we will come up with the outcome that you all are envisioning, which is that clinical care providers know a whole lot more about CFS and can make better diagnoses."

[310] Institute of Medicine. "Diagnostic Criteria for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome." (Activity Description). Undated. Project started in 2013 and continues until early 2015. http://www.iom.edu/Activities/Disease/DiagnosisMyalgicEncephalomyelitisChronicFatigueSyndrome.aspx
The activity description states:

- "An Institute of Medicine (IOM) committee will comprehensively evaluate the current criteria for the diagnosis of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS). The committee will consider the various existing definitions and recommend clinical diagnostic criteria for the disorder to address the needs of health providers, patients, and their caregivers."
- "The committee will also distinguish between disease subgroups, develop a plan for updating the new criteria, and make recommendations for its implementation. Any recommendations made by the committee will consider unique diagnostic issues facing people with ME/CFS, specifically related to: gender, across the lifespan, and specific subgroups with substantial disability."
- "Specifically the IOM will:

- Conduct a study to identify the evidence for various diagnostic clinical criteria of ME/CFS using a process with stakeholder input, including practicing clinicians and patients;
- Develop evidence-based clinical diagnostic criteria for ME/CFS for use by clinicians, using a consensus-building methodology;
- Recommend whether new terminology for ME/CFS should be adopted;
- Develop an outreach strategy to disseminate the definition nationwide to health professionals."

HHS has previously stated that new definitions should be data driven so it's unclear why they have chosen a consensus approach for this. Dr. Belay of CDC stated, "My second point is that I think the definitions should be data-driven. We should not be creating a case definition in a vacuum. It has to be supported by data."

- Reference:
  U.S. Department of Health and Human Services. CFS Advisory Committee. June 14, 2012. *CFS Advisory Committee Website.* www.hhs.gov/advcomcfs/meetings/minutes/cfsac20120514.pdf. Page 41.

311 U.S. Department of Health and Human Services. "National Academies Umbrella Contract. Statement of Work/Request for Proposal. Project Title: Diagnostic Criteria for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome." Undated https://dl.dropboxusercontent.com/u/57025850/MECFS%20IOM%20SOW.pdf

312 Ibid.

Both the Statement of Task (SOT) on the IOM website and the Statement of Work (SOW) provided by HHS are vague on this issue. The SOT uses the term "ME/CFS" without defining what is meant by it. The SOW does define the term "ME/CFS", stating that: "ME/CFS shall be used to refer to Myalgic Encephalomyelitis (ME), Chronic Fatigue Syndrome (CFS), Chronic Fatigue and Immune Dysfunction Syndrome (CFIDS), Neuroendocrine Immune Disorder, and *other terminologies in use for this illness*." (emphasis added)

It is important to ask what these terms really mean. Is the term "ME" referring to the disease described by the Canadian Consensus Criteria? Does CFS include Oxford, Fukuda without PEM?

313 Prior to the IOM meeting, both Kate Meck of IOM and Dr. Nancy Lee of HHS stated in personal emails to this author that the scope had not been decided yet. But when asked more specifically how ME would be handled, Dr. Lee referenced the SOT statement about the creation of subgroups and indicated that ME would become a subgroup or part of a spectrum of the broader "CFS" illnesses. She also stated that for the sake of the target audience - primary care physicians - it was better to start broader and then define subgroups. Dr. Lee's charge to the IOM panel did not provide any further direction on this issue.

314 Institute of Medicine of the National Academies. "Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness." Institute of Medicine of the National Academies. Prepublication copy. February 10, 2015. Last accessed February 16, 2015. https://www.iom.edu/Reports/2015/ME-CFS.aspx

315 Ellis, Clark. "Dr. Bateman answers IOM questions from the community: Part 1." *Phoenix Rising.* March 31, 2015. Last accessed April 22, 2015. http://phoenixrising.me/archives/26563.

316 Multiple sources list concerns; a few examples include

- InvestInME. "Invest In ME Response To Institute Of Medicine Document "Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining An Illness." InvestInME. March 21, 2015. Last accessed April 22, 2015. http://www.investinme.org/Documents/IOM%20Contract/Invest%20in%20ME%20Response%20to%20INSTITUTE%20of%20MEDICINE%20Beyond%20ME-CFS%20Redefining%20an%20Illness.pdf
- Jason, L. "The IOM's effort to dislodge chronic fatigue syndrome." *OUPBlog*. March 4, 2015. Last accessed April 22, 2015 http://blog.oup.com/2015/03/iom-chronic-fatigue-syndrome-systemic-exertion-intolerance-disease/#sthash.8KURl5Yv.dpuf
- Friedberg, F. "Institute of medicine report on chronic fatigue syndrome: case definition issues and future directions." *Fatigue: Biomedicine, Health & Behavior.* Published online April 14, 2015. Last accessed April 19, 2015. http://dx.doi.org/10.1080/21641846.2015.1024003

317 Ellis, Clark. "Dr. Bateman answers IOM questions from the community: Part 1." *Phoenix Rising.* March 31, 2015. Last accessed April 22, 2015. http://phoenixrising.me/archives/26563.

318 Auwaerter, Paul. "Managing Systemic Exertion Intolerance Disease (SEID)." *Medscape Multispecialty*. March 3, 2015. Last accessed March 30, 2015. http://www.medscape.com/viewarticle/840635

Auwaerter stated, "What do I do in my office? Simon Wessely and colleagues,[5] who did a fair amount of work on chronic fatigue syndrome and Gulf War syndrome, and others have suggested that graded exercises, conditioning to build up tolerance, and cognitive-behavioral therapy are some of the best strategies to help people feel better."

319 Asad, Z. "A 35-Year-Old Woman With Fatigue and Joint Pain." *Medscape.* April 14, 2015. Last accessed April 20, 2015. http://reference.medscape.com/viewarticle/842828

- The case study describes a patient with fatigue, "muscle stiffness, joint pain, recurrent headaches, and an inability to concentrate" but the patient does not have PEM. The case study adds on that the patient is "an obese woman with poor hygiene," is "stressed by her symptoms," has had "multiple unprotected sexual encounters,", and "has visited multiple physicians in the last few months with the same symptoms and is not

satisfied with the work-up." Physical exam and labs are normal with the exception of a slight elevation of ANA and hyperlipidemia.

- The article lists Fukuda criteria, states that the IOM renamed this to SEID and then lists the SEID criteria as an alternative to the Fukuda criteria. Upper prevalence rate is 2.5%, a rate seen in Empirical studies.
- The article recommends CBT and GET and says that prolonged rest "showed no benefit and indirect evidence of harm."

[320] U.S. Centers for Disease Control and Prevention. "Multi-site Clinical Assessment of CFS.: *Chronic Fatigue Syndrome*. Last updated April 8, 2013. http://www.cdc.gov/cfs/programs/clinical-assessment/

Author's note: CDC has decided against using the replicated CPET to objectively measure the hallmark post-exertional malaise and instead is using a mechanism to detect the presence of this most critical symptom that to my knowledge has not been replicated or validated. Finally, because of issues with study design, the participants are largely white, female, with insurance, highly educated and not the most severe. This does not represent demographic of ME.

Regarding inclusion and exclusion, the description states, "The study started in 2012 and aims to enroll 450 patients. Any patient (aged 18 – 70 years) that is managed or diagnosed with CFS, post-infective fatigue (PIF) or myalgic encephalomyelitis (ME) at any of seven participating clinical sites is eligible for participating in this study. Study exclusions include illness onset at age older than 62 years, HIV infection, current pregnancy, or dementia."

[321] Post-infective fatigue is an ill-defined term. The closest case definition found during research for this review is post-infectious fatigue syndrome as defined in the Oxford definition, where it is described as "a subtype of CFS which either follows an infection or is associated with a current infection". This would be a very broad category of illness given that the only other criteria of Oxford is 6 months of chronic fatigue that affects mental and physical function and is medically unexplained.

[322] Unger, B. Presentation "Methodology for the CDC Multi-site Clinical Study." at Institute of Medicine Diagnostic Criteria for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Public Meeting. January 27, 2014. Presentation: http://www.youtube.com/watch?v=Ulkc_GKtxhI#t=810 Q&A: http://www.youtube.com/watch?v=U9D59TU-JUY During Q&A at the IOM public hearing in January 2014, these issues were raised:

- Dr. Chu asked "I can understand why you are asking clinicians to come up with their own idea of who fits the CFS diagnosis. And I wondered if there was any thought given to see if there were any patients where three or two different physicians, they might not examine them but looking at the data we think this patient have CFS."
- Dr. Unger replied: "The clinicians involved in the study have not exchanged data so to speak in terms of that. We would have to let them decide if they wanted to undergo that exercise but I think they are confident in their diagnostic skills."
- At the same meeting, Dr. Klimas also asked Dr. Unger whether there would be any effort to compare the diagnosis to the various definitions. Dr. Jason has developed a tool that allows this comparison to be made by using the questions from the DePaul inventory. It was not clear if this would be done.

[323] Exchange between patient community and CDC on performing CPET testing during the CDC Multi-site study.

- Letter from patient advocates to Dr. Beth Unger of CDC requesting the incorporation of 2 day CPET into the CDC CFS Multi-site study. July 22, 2013. https://dl.dropboxusercontent.com/u/89158245/Advocates%20letter%20to%20CDC%20on%20CEPT%20July%202013.doc
- Response from Dr. Unger to Donna Pearson regarding the patient advocate request to use CPET in the CDC Multi-site study. August 30, 2013. https://dl.dropboxusercontent.com/u/89158245/Dr.%20Unger%20Response%20to%20CPET%20letter%20July%202013.pdf

[324] National Institute of Health. "State of the Knowledge Workshop. Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) Research Workshop Report." April 7-8, 2011. http://orwh.od.nih.gov/research/me-cfs/pdfs/ORWH_SKW_Report.pdf *Page 14*

[325] National Institute of Health. Office of Disease Prevention. *Pathways to Prevention Program*. Process Description. https://prevention.nih.gov/programs-events/pathways-to-prevention Last updated December 11, 2014. The P2P process involved a day-and-a-half Workshop, conducted in December 2014 by a panel of "non-experts" (scientists who were not allowed to have ever studied, treated or published on this disease.) Based on two inputs—the Workshop's topics and speakers and the 2014 draft AHRQ Evidence Review—the Panel developed go-forward recommendations. Input from experts was primarily limited to those who were selected to speak and what appears to have been limited input by experts in the planning for the workshop and evidence review. The P2P site states "P2P workshops are designed for topics that have incomplete or underdeveloped research, difficulty producing a report synthesizing published literature, and are generally not controversial."
Additional information on the process available at:

- Spotila, J. "Behind Closed Doors." *OccupyCFS*. January 6, 2014. http://www.occupycfs.com/2014/01/06/behind-closed-doors/

[326] The P2P process calls for disease experts to have input on the questions used in the Evidence Review, the Workshop agenda topics, and the choice of Workshop speakers. But that input appears to have been limited, based on feedback from those involved,[326] and given the absence of key topics from the agenda, the selection of certain speakers, and the failure to ask critical questions. The rest of the P2P process—the AHRQ Evidence Review, the P2P Workshop and the final P2P recommendations—was driven by non-experts.
See
Spotila, J. "Will the Real P2P Please Stand Up." *OccupyCFS* May 19, 2014.
http://www.occupycfs.com/2014/05/19/will-the-real-p2p-please-stand-up/
Spotila stated "Multiple sources who are in a position to know what happened at the January 2014 Working Group meeting told me that the questions in the study protocol were not the questions defined at the meeting."

[327] National Institute of Health. Office of Disease Prevention. *Pathways to Prevention Program*. Page last updated December 11, 2014. http://prevention.nih.gov/p2p/default.aspx
The NIH Pathways to Prevention Initiative was originally called the Evidence based Methodology Workshop.
The original purpose of the P2P workshop was described in HHS' response to the October 2012 CFSAC recommendation to convene a meeting to reach consensus on the case definition.

- Department of Health and Human Services. "Response to Recommendations from the Chronic Fatigue Syndrome Advisory Committee. Ref October 3-4, 2012, CFSAC Meeting." Department of Health and Human Services. Undated. hhs.gov/advcomcfs/recommendations/response-from-ash-10-2012.pdf

  The response to the CFSAC recommendation stated "The National Institutes o f Health (NIH) is convening an Evidence-based Methodology Workshop process (outlined in recommendation 3b) to address the issue of case definitions appropriate for ME/CFS research. However, it will not cover in detail a clinical case definition. The Office of the Assistant Secretary for Health, Department of Health and Human Services, is actively pursuing options for a separate effort that would work in coordination with the NIH process, but result in a case definition useful for clinicians who see patients with symptoms that may be ME/CFS."

  The response also stated, "As part of a broader approach to support ME/CFS research, the Trans-NIH ME/CFS Research Working Group recently completed a planning exercise to prioritize approaches to enhance ME/CFS research excellence identified by attendees of the 2011 State of the Knowledge Workshop, which included input from researchers, clinicians, patients and patient advocate groups. To address the highest priority identified, which was "case definition issues," the Working Group submitted a competitive application for an Evidence-based Methodology Workshop (EbMW) on ME/CFS coordinated by the NIH Office of Disease Prevention."

The original recommendation was "CFSAC recommends that you will promptly convene (by 12/31/12 or as soon as possible thereafter) at least one stakeholders' (Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) experts, patients, advocates) workshop in consultation with CFSAC members to reach a consensus for a case definition useful for research, diagnosis and treatment o fME/CFS beginning with the 2003 Canadian Consensus Definition for discussion purposes."
Also see the IOM report, which noted the change in the goal of the P2P workshop.

- Institute of Medicine of the National Academies. "Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness." Institute of Medicine of the National Academies. Prepublication copy. February 10, 2015. Last accessed February 16, 2015. https://www.iom.edu/Reports/2015/ME-CFS.aspx
  The IOM report stated, "The NIH P2P workshop was originally intended to complement the present study by developing a re- search case definition for ME/CFS (CFSAC, 2012). However, in remarks on behalf of the P2P workshop process at the committee's first public session, Susan Maier, Deputy Director for NIH's Office of Research on Women's Health, stated that the goal of the P2P workshop was not to develop a re- search case definition but to suggest a research agenda for ME/CFS based on an unbiased review of the evidence. She also expressed a desire to work with this committee throughout the P2P process. However, the planning group for the P2P workshop declined to share any data with the committee."

[328] U.S. Department of Health and Human Services. CFS Advisory Committee. CFSAC Meeting May 23, 2013. *CFS Advisory Committee Website.* http://www.hhs.gov/advcomcfs/meetings/minutes/cfsacmay23_final_508.pdf
Dr. Maier described the P2P as follows:

- Page 6 - Dr. Maier stated that the purpose of this workshop is to "identify methodological and scientific weaknesses in a scientific area and move the field forward through the unbiased and evidence-based assessment of a very complex clinical issue."
- Page 9 – Dr. Maier stated, "The purpose of the workshop is to evaluate the research evidence surrounding the multiple case definitions and to address the validity, reliability, and ability of the current case definitions to identify individuals with the illness, identify individuals within the subgroups with the illness who can be differentiated by a case definition, and/or to identify responders or non-responders based on some element of the case definition as informed by the evidence. This is all used to advance the research. It's really an analysis of the science that supports the case definitions in the sense that the outcomes are telling us something or the

outcomes are not telling us something. Where are the gaps? Where does the evidence show up? Where does it not?"

- Page 11 – Dr. Maier stated, "The goal of the evidence-based methodology workshop is to understand and identify how the evidence shows up for case definitions, for outcomes, for interventions, and for treatments. If it turns out that some interventions have more impact or a more positive outcome for post-exertional malaise, then we're going to know that post- exertional malaise in a case definition is probably going to be a good thing to do. The workshop is not advocating any specific case definition. It is simply a method to review it, to understand where the evidence shows up, where the gaps are, and where we need to move forward."

[329] Burmeister, Jeannette. "P2P FOIA Documents, Part 7—Collins, Murray and Maier: Trouble in NIH Paradise." *Thoughts about ME*. November 23, 2014. http://thoughtsaboutme.com/2014/11/23/p2p-foia-documents-part-7-collins-murray-and-maier-trouble-in-nih-paradise/
FOIA documents https://www.dropbox.com/s/ak305vlb9367kq8/FOIA_P2P_Batch%237.pdf?dl=0 (Page 18)
The email from Murray to Collins stated, "Our P2P workshop will review the various definitions for ME/CFS that have been used in research studied to clarify the type of patients that are captured under each definition and how those patients respond to the various therapeutic options. This will inform future research by providing a better understanding of the implications of choosing one definition over another as studies are being designed.

[330] National Institute of Health. Office of Disease Prevention. "NIH Pathways to Prevention Workshop: Advancing the Research on Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. Program Book. December 9-10, 2014" National Institute of Health. Office of Disease Prevention. https://prevention.nih.gov/docs/programs/mecfs/ODP-MECFS_ProgramBook.pdf

[331] Spotila J, Dimmock M. "Collins: Please Stop P2P." *OccupyCFS.* June 2, 2014. Last accessed February 20, 2015. http://www.occupycfs.com/2014/06/02/collins-please-cancel-p2p/

[332] The AHRQ Evidence Review was conducted by an "Evidence Practice Center" contracted by HHS that has expertise in performing evidence reviews but is not familiar with ME or the politics and issues surrounding "CFS".
Protocol.

- U.S. Agency for Healthcare Research and Quality. "Evidence-based Practice Center Systematic Review Protocol. Project Title: Diagnosis and Treatment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)." May 1, 2014. http://www.effectivehealthcare.ahrq.gov/ehc/products/586/1906/chronic-fatigue-protocol-140501.pdf

The protocol stated, "An examination of the comparative effectiveness and harms of treatments for ME/CFS is important to guide clinical practice, which underscores the need for a systematic review on this topic. This report focuses on the clinical outcomes surrounding the attributes of fatigue, especially post-exertional malaise and persistent fatigue, and its impact on overall function and quality of life because these are unifying features of ME/CFS that impact patients."

Key Questions listed in the protocol include: "1) What methods are available to clinicians to diagnose ME/CFS and how do the use of these methods vary by patient subgroups? 2) What are the (a) benefits and (b) harms of therapeutic interventions for patients with ME/CFS and how do they vary by patient subgroups?"

Inclusion criteria for Question 1 are: "Symptomatic adults (aged 18 years or older) with fatigue"
Inclusion criteria for Question 2 are: "Adults aged 18 years or older, with ME/CFS, without other underlying diagnosis"

Final Evidence Review

- U.S. Agency for Healthcare Quality and Research. "Executive Summary. Diagnosis and Treatment of Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome. Evidence Report/Technology Assessment Number 219." U.S. Agency for Healthcare Quality and Research. December 11, 2014. AHRQ Pub. No. 15-E001-1-EF http://effectivehealthcare.ahrq.gov/ehc/products/586/2005/chronic-fatigue-executive-141211.pdf
- U.S. Agency for Healthcare Quality and Research. "Research Review. Diagnosis and Treatment of Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome. Evidence Report/Technology Assessment Number 219." U.S. Agency for Healthcare Quality and Research. December 9, 2014. AHRQ Pub. No. 15-E001-EF http://effectivehealthcare.ahrq.gov/ehc/products/586/2004/chronic-fatigue-report-141209.pdf

Draft Evidence Review - is no longer posted on the AHRQ site but copies are available here:

- U.S. Agency for Healthcare Quality and Research. "Diagnosis and Treatment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome." September 2014. https://dl.dropboxusercontent.com/u/89158245/AHRQ%202014%20Evidence%20Review%20-%20chronic-fatigue-draft-140922.pdf
- U.S. Agency for Healthcare Quality and Research. "Diagnosis and Treatment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. Appendixes." September 2014. https://dl.dropboxusercontent.com/u/89158245/AHRQ%202014%20Evidence%20Review%20-%20chronic-fatigue-draft-appendixes-140922.pdf

[333] Spotila, J. "Comments on the P2P Systematic Evidence Review." *OccupyCFS. October 18, 2014.* http://www.occupycfs.com/2014/10/18/comments-on-p2p-systematic-evidence-review/

Spotila has covered the P2P Workshop extensively over the last year. Other comments on OccupyCFS include

- http://www.occupycfs.com/2014/01/06/behind-closed-doors/
- http://www.occupycfs.com/2014/01/13/more-on-p2p/
- http://www.occupycfs.com/2014/05/02/protocol-for-disaster/
- http://www.occupycfs.com/2014/05/19/will-the-real-p2p-please-stand-up/#comments
- http://www.occupycfs.com/2014/05/22/p2p-agenda-fatigue/
- http://www.occupycfs.com/2014/03/06/systematic-overreaching/.

This post discusses a systemic review of the 20 ME/CFS definitions and the conclusions that were drawn. Regarding the focus on diagnostics and treatment, the IOM contract states that P2P will provide input but the timelines of IOM and P2P were not aligned in a way that allowed that to happen.

[334] National Institute of Health. Office of Disease Prevention. P2P Workshop Agenda. Last updated on 12/9/2014. . https://prevention.nih.gov/programs-events/pathways-to-prevention/upcoming-workshops/me-cfs/agenda
For a review of this agenda, see

- Spotila, J. "P2P: Not This Science." *OccupyCFS.* November 17, 2014. http://www.occupycfs.com/2014/10/31/p2p-agenda-what-the-huh/

[335] Spotila, J. "P2P Agenda: What the huh?" *OccupyCFS.* October 31, 2014. http://www.occupycfs.com/2014/10/31/p2p-agenda-what-the-huh/
One of these speakers was Debra Buchwald. Based on the following research, it appears that Buchwald adheres strongly to the PACE style recommendations for CBT and GET to address illness perceptions and deconditioning. Buchwald, together with N. Afari, another speaker for the session on fostering innovative research, also authored a CFS review, which adopted a psychosocial model and recommended CBT and GET to address the "perceptions, attributions and coping skills" that "may help perpetuate the illness"

- Sawchuk C. Buchwald D. "Chronic Fatigue Syndrome." Epocrates (An AthenaHealth Company.) Last updated May 2014. Last accessed February 3, 2015. https://online.epocrates.com/noFrame/showPage?method=diseases&MonographId=277&ActiveSectionId=41 and https://online.epocrates.com/u/2911277/chronic+fatigue+%20syndrome
- Afari N, Buchwald D. "Chronic fatigue syndrome: a review." *Am J Psychiatry*. February 2003; 160(2):221-36. Last accessed February 3, 2015. http://www.ncbi.nlm.nih.gov/pubmed/12562565

[336] National Institute of Health. Office of Disease Prevention. "Pathways to Prevention Workshop: Advancing the Research on Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. Deccember 9-10, 2014. Draft Executive Summary." National Institute of Health. Office of Disease Prevention. Published on or about December 18, 2014. https://prevention.nih.gov/docs/programs/mecfs/ODP-MECFS-DraftReport.pdf

[337] Spotila, J. "P2P Mistrial." OccupyCFS. April 3, 2015. Last accessed April 20, 2015. http://www.occupycfs.com/2015/04/03/p2p-mistrial/
and Spotila, J. "Did P2P Receive Your Comments." OccupyCFS. March 17, 2015. Last accessed April 20, 2015. http://www.occupycfs.com/2015/03/17/did-p2p-receive-your-comments/

[338] Spotila, J. "P2P Missteps Continue." OccupyCFS. April 20, 2015. Last accessed April 20, 2015. http://www.occupycfs.com/2015/04/20/p2p-missteps-continue/

[339] Brurberg K, Fønhus A, Larun L, Flottorp S, Malterud K. "Case definitions for chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME): a systematic review." *BMJ Open* February 7, 2014; 4(2): e003973. PMID: 24508851. http://dx.doi.org/10.1136/bmjopen-2013-003973

[340] Jason L, Richman J, Friedberg F, Wagner L, Taylor R, Jordan K. "Politics, science and the emergence of a new disease." *American Psychologist* September 1997; 52(9): 973-983. PMID: 9301342 http://www.ncbi.nlm.nih.gov/pubmed/9301342
Also see:

- Jason, L.A., & Richman, J.A. (2007). How science can stigmatize: The case of chronic fatigue syndrome. *Journal of Chronic Fatigue Syndrome. 2007; 14(4)*, 85-103. http://informahealthcare.com/doi/abs/10.3109/10573320802092146

[341] U.S. Department of Health and Human Services CFS Advisory Committee. CFSAC May 22-23, 2013 meeting. https://www.youtube.com/watch?v=VJ7VqYJTsWI&list=PLrl7E8KABz1FGfzllYcomOoI9agz8-6QL&index=12 (minutes 25-45)

Exchange between Dr. Unger and CFSAC members on PEM in which CDC's Dr. Unger questioned the importance of PEM as a symptom rhetorically asked the question "If a patient doesn't have [post-exertional malaise], would you not manage them as a CFS patient?"

Adding to this is the response to the patient advocacy joint letter calling for the adoption of the Canadian Consensus Criteria in which Dr. Unger stated that CDC is committed to studying "CFS and other similar medically unexplained chronically fatiguing illnesses such as ME, fibromyalgia syndrome, neurasthenia…"

- Letter from ME patient advocacy community to Secretary of Health Sebelius, Assistant Secretary of Health Dr. Howard Koh, CDC Director Dr. Thomas Frieden and NIH Director Dr. Francis Collins. "Need for Focused Attention on Myalgic Encephalomyelitis (ME)." May 12, 2013.

https://dl.dropboxusercontent.com/u/89158245/DHHS%20Definition%20Initiatives%20May%2012%202013.pdf

- Email from Dr. Beth Unger of CDC to Mary Dimmock in response to May 12, 2013 letter. "Response to signatories of May 12 letter c/o Marry Dimmock." Received by email on June 5, 2013. Copied to word document for sharing with advocates who signed the letter. https://dl.dropboxusercontent.com/u/89158245/Dr%20Unger%20response%20to%20definition%20letter%20June%205%202013.pdf

The ambiguity around the importance of PEM, the apparent continued focus on "CFS" regardless of the symptom of PEM and the focus on medically unexplained chronically fatiguing illnesses that include neurasthenia, a mental illness, amplifies the concerns that HHS's definitional efforts are not focused on a definition for ME.

[342] Institute of Medicine. "Diagnostic Criteria for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome." (Activity Description) Public File requested by advocate Jennifer Spotila.
The IOM public file for the initiative to develop new clinical diagnostic criteria contains the following document, which was reportedly submitted to IOM by CDC.
https://dl.dropboxusercontent.com/u/89158245/IOM%20submission%20from%20CDC%20CFS%20Case%20Definition%20Issues%20with%20Appendices%201_28_14-under%20NCEZID%20review.docx

[343] Articles discussing the biopsychosocial approach

- Nijs J, Roussel N, Van Oosterwijck J, De Kooning M, Ickmans K, Struyf F, Meeus M, Lundberg M. "Fear of movement and avoidance behaviour toward physical activity in chronic-fatigue syndrome and fibromyalgia: state of the art and implications for clinical practice." *Clin Rheumatol* May 3, 2013; 32(8):1121-9. PMID: 23639990. http://dx.doi.org/10.1007/s10067-013-2277-4
- Prins J, van der Meer J, Bleijenberg G. "Chronic fatigue Syndrome." *The Lancet* January 28, 2006; 367(9507): 346-355. PMID: 16443043. http://dx.doi.org/10.1016/S0140-6736(06)68073-2

[344] U.S. Centers for Disease Control and Prevention. "Diagnosis and Management of Chronic Fatigue Syndrome" *CDC Chronic Fatigue Syndrome.* CME created: June 27, 2012. Page last updated: May 16, 2014.
http://www.cdc.gov/cfs/education/diagnosis/index.html
This CME describes multiple case definitions as representing the same group of patients for which the same diagnosis and treatment is appropriate. (Page 1-9) In the past, CDC stated Fukuda and CCC were different and CFS and ME were different

- In October 2009, the *CDC CFS website* described ME as a separate illness.
  U.S. Centers for Disease Control and Prevention. "Basic Facts." *CDC Chronic Fatigue Syndrome*. Archived page last updated in May 2006. http://web.archive.org/web/20091026164234/http://cdc.gov/cfs/cfsbasicfacts.htm
  The site states. "Similar Medical Conditions: A number of illnesses have been described that have a similar spectrum of symptoms to CFS. These include fibromyalgia syndrome, myalgic encephalomyelitis, neurasthenia, multiple chemical sensitivities, and chronic mononucleosis. Although these illnesses may present with a primary symptom other than fatigue, chronic fatigue is commonly associated with all of them."
- Switzer WM, Jia H, Hohn O, Zheng HQ, Tang S, Shankar A, Bannert N, Simmons G, Hendry RM, Falkenberg VR, Reeves WC, Heneine W. "Absence of Evidence of Xenotropic Murine Leukemia Virus-related Virus Infection in Persons with Chronic Fatigue Syndrome and Healthy Controls in the United States." *Retrovirology*. July 1, 2010, 7: 57. http://dx.doi.org/10.1186/1742-4690-7-57
  The document states "The 1994 International CFS case definition and the Canadian Consensus Criteria are different and do not necessarily identify similar groups of ill persons... The physical findings in persons meeting the Canadian definition may signal the presence of a neurologic condition considered exclusionary for CFS.

[345] U.S. Centers for Disease Control and Prevention. "CDC CFS Toolkit." *CDC Chronic Fatigue Syndrome*. Last updated September 6, 2011. Last accessed April 8, 2015. http://www.cdc.gov/cfs/toolkit/index.html and http://www.cdc.gov/cfs/pdf/cfs-toolkit.pdf
The CDC CFS Toolkit states that one set of clinical guidelines is suitable for CFS patients and even for "CFS-like" illness (6 months of fatigue but fails to meet the other symptom requirements for CFS). Other documents, like the 2012 CDC "Diagnosis and Management CFS" CME referenced above also give a single set of guidelines for all 5 definitions.

[346] See discussions on PEM, energy metabolism dysfunction and CPET, the Lights Gene expression studies and the work of Cockshell on cognitive impairment following activity .
Also see Kindlon T. "Reporting of Harms Associated with Graded Exercise Therapy and Cognitive Behavioural Therapy in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome." *Bulletin of the IACFS/ME* Fall 2011; 19(2):59-111.
http://www.iacfsme.org/BULLETINFALL2011/Fall2011KindlonHarmsPaperABSTRACT/tabid/501/Default.aspx

[347] White PD, Goldsmith K, Johnson AL, Chalder T, Sharpe M, PACE Trial Management Group. "Recovery from chronic fatigue syndrome after treatments given in the PACE trial." Psychol Med. October 2013' 43(10): 2226-2235. PMID: 23363640. http://dx.doi.org/10.1017/S0033291713000020

- This publication stated that they analyzed the data using ME criteria and the International (CDC) criteria.
- Regarding assessment for the CDC criteria , the publication stated

- "The research assessor used participant ratings to judge whether participants met the International (CDC) criteria for CFS at 52 weeks (Reeves et al. 2003)…"
- "For the purposes of this study, the four or more symptoms needed to be present within the previous week of the assessment date, rather than the previous 6 months (Reeves et al. 2003)."
- "The prevalence of the case-level International (CDC) definition of CFS may have been inaccurate because we only examined for accompanying symptoms in the previous week, not the previous 6 month."

Note that Reeves 2003 was the approach developed through CDC workshops and published in 2003. The Empirical definition is Reeves 2005. The 2003 definition was seldom used. The change from six months to one week of symptoms was also a substantial change.

- Regarding the ME criteria, this paper gives the reference for the London criteria as "Report on chronic fatigue syndrome (CFS), post viral fatigue syndrome (PVFS) and myalgic encephalomyelitis (ME). Westcare, Bristol: The National Task Force, 1994.".However, while using the same reference, on page 824, the 2011 PACE trial publication states that it used version 2 of the London Criteria. It is unclear what this refers to, or why they did not use the Canadian Consensus Criteria or the newer ME International Consensus Criteria.
  For further information on this, see:
  - ME Association. "London Criteria for M.E. – for website discussion." ME Association. February 21, 2011. http://www.meassociation.org.uk/2011/02/london-criteria-for-m-e/
    Lists the original London criteria along with their understanding of version 2 of that criteria as it was modified for use in the PACE trial

[348] Larun L, Odgaard-Jensen J, Brurberg KG, Chalder T, Dybwad M, Moss-Morris RE, Sharpe M, Wallman K, Wearden A, White PD, Glasziou PP. "Exercise therapy for chronic fatigue syndrome (individual patient data)." *Cochrane Database of Systematic Reviews* April 2014, Issue 4. http://dx.doi.org/10.1002/14651858.CD011040

The protocol specifies that patients over 17 will be included and that it will include any trials that meet the following criteria for CFS:

- "Fatigue or a synonym is a prominent symptom;"
- "Fatigue is medically unexplained (i.e. other diagnosis known to cause fatigue such as psychiatric disorders and cancer should be excluded);"
- "Fatigue is sufficiently severe to significantly disable or distress the patient; and"
- "Fatigue has persisted for at least six months."

The paper also states that it will include studies for disorders other than CFS as long as 90% of the patients meet the above criteria.

[349] Price JR, Mitchell E, Tidy E, Hunot V. Cognitive behaviour therapy for chronic fatigue syndrome in adults. *Cochrane Database of Systematic Reviews* July 16, 2008, (3): CD001027. PMID: 18646067. http://dx.doi.org/10.1002/14651858.CD001027.pub2
The paper stated "All studies specified inclusion criteria requiring that participants had fatigue as their main or major complaint, the minimum duration of fatigue being six months in 12 studies, at least four months in one study, and at least three months in the two remaining studies. There was heterogeneity of other recruitment criteria between studies. Seven studies used the 'CDC' ('Fukuda') criteria for inclusion. One of these studies waived the requirement of four of eight additional symptoms included in the CDC criteria to be present. Three studies used the 'Oxford' criteria for participant inclusion. The sample in Deale fulfilled CDC as well as Oxford criteria. Two studies used the 'Australian' criteria. Three studies did not use standard CFS criteria. Two of these studies used a score of at least 4 on the Chalder fatigue scale as the basis for inclusion."

[350] U.S. Department Health and Human Services. Agency for Healthcare Research and Quality. "Defining and Managing Chronic Fatigue Syndrome." By Mulrow, CD, Ramirez, G, Cornell, JE, Allsup K. September 2001. Evidence Reports/Technology Assessments Number 42.

- AHRQ Publication No: 02-E001 – Details http://www.ncbi.nlm.nih.gov/books/NBK33797/
- AHRQ Publication No: 01-E061 – Summary - http://www.ncbi.nlm.nih.gov/books/NBK11946/

[351] Bagnall A, Hempel S, Chambers D, Orton V, Forbes C. "The diagnosis, treatment and management of chronic fatigue syndrome (CFS) / myalgic encephalomyelitis (ME) in adults and children." Centre for Reviews and Dissemination University of York. October 2005. http://www.nice.org.uk/guidance/cg53/evidence/chronic-fatigue-syndrome-myalgic-encephalomyelitis-full-guideline-appendix-12

The report stated "Systematic Evidence Review to support the development of the NICE clinical guideline for CFS/ME in adults and children"

[352] Jason L, Brown A, Evans M, Sunnquist M, Newton J. "Contrasting chronic fatigue syndrome versus myalgic encephalomyelitis/chronic fatigue syndrome." *Fatigue, Biomedicine, Health & Behavior* March 20, 2013; 1(3): 168-183/ PMID: 23914329. http://dx.doi.org/10.1080/21641846.2013.774556
Also see

- 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." *Eval Health Prof* December 7, 2011; 35(3): 280-304 http://dx.doi.org/10.1177/0163278711424281

- Brown A, Jason L, Evans M, Flores S. "Contrasting Case Definitions: The ME International Consensus Criteria vs. the Fukuda et Al. CFS Criteria." *North American Journal of Psychology* March 2013; 15(1); http://www.questia.com/library/1G1-322563471/contrasting-case-definitions-the-me-international. Brown et al examined the ME-ICC and the Fukuda and found that the ME-ICC identified a much tighter group of patients (39 compared to 113 for Fukuda) with more functional impairments and physical, mental and cognitive problems than in those patients meeting the Fukuda criteria. The paper also raised a concern that ME-ICC included more psychiatric co-morbidities than Fukuda because of the number of symptoms required and concluded that a focus on a smaller number of hallmark symptoms like post-exertional malaise would be critical. Finally, the paper acknowledged the need for more study because this study used a questionnaire designed for Fukuda CFS, that they were unable to assess one of the key ME-ICC criteria because of the available data and the study did not look at homebound or bedbound patients.
- Jason L, Sunnquist M, Brown A, Evans M, Newton J. "Are Myalgic Encephalomyelitis and chronic fatigue syndrome different illnesses? A preliminary analysis." *Journal of Health Psychology* First published online February 2014; 1–13. http://dx.doi.org/10.1177/1359105313520335

353 Jason, L. "Defining CFS: Diagnostic Criteria and Case Definition". Presented at CFIDS Association webinar, April 14, 2010..http://web.archive.org/web/20120425130843/http://www.cfids.org/webinar/jason-slides041410.pdf Slide 10, 12. Jason's presentation discussed the fact that Fukuda does not require core symptoms and that depressed patients have the same symptoms as one combination of Fukuda symptoms. Oxford is even broader than Fukuda and specifically allows the inclusion of psychiatric patients.

354 Jason, L. Presentation at "NIH Pathways to Prevention: Advancing the Research on Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (Day 1)." National Institutes of Health. December 9, 2014. http://videocast.nih.gov/summary.asp?Live=14723&bhcp=1. Time 1:06

355 Nacul, L. Presentation at "NIH Pathways to Prevention: Advancing the Research on Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (Day 1)." National Institutes of Health. December 9, 2014. http://videocast.nih.gov/summary.asp?Live=14723&bhcp=1. Time 2:28.
Nacul made the following statements at P2P

- "The first question we need to answer is "What." What are we interested in studying? What is ME/CFS? And I am sure that each and every one of you in this audience will have a concept in your own minds of what ME or CFS means. But I doubt many of you will agree with each other about what this concept is. So basically, we are not sure what we are studying. And this is the main limitation to describe the epidemiology of any condition."
- "Let me illustrate what I mean. If we use the Fukuda criteria, CDC 1994, which is probably the most widely used criteria, its quite non-specific. It's a negative criteria." It mentions in this criteria not explained by disease, not relieved by rest, not due to exertion and so on."
- "[Unclear]… asks for the need for 4 out of 8 symptoms to be present so that definition is met. And this means 163 combinations of symptoms or possible combinations of symptoms that patients may have to be classified as having CFS. If for example we added post-exertional malaise as one of the criteria, a compulsory criteria, then the number of combinations of symptoms that make a diagnosis would drop to about 35. So it seems that there may be an advantage of having more restrictive criteria.

356 Jason L, Brown A, Evans M, Sunnquist M, Newton J. "Contrasting chronic fatigue syndrome versus myalgic encephalomyelitis/chronic fatigue syndrome." *Fatigue, Biomedicine, Health & Behavior* March 20, 2013; 1(3): 168-183/ PMID: 23914329. http://dx.doi.org/10.1080/21641846.2013.774556
Also see

- 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." *Eval Health Prof* December 7, 2011; 35(3): 280-304 http://dx.doi.org/10.1177/0163278711424281
- Brown A, Jason L, Evans M, Flores S. "Contrasting Case Definitions: The ME International Consensus Criteria vs. the Fukuda et Al. CFS Criteria." *North American Journal of Psychology* March 2013; 15(1); http://www.questia.com/library/1G1-322563471/contrasting-case-definitions-the-me-international. Brown et al examined the ME-ICC and the Fukuda and found that the ME-ICC identified a much tighter group of patients (39 compared to 113 for Fukuda) with more functional impairments and physical, mental and cognitive problems than in those patients meeting the Fukuda criteria. The paper also raised a concern that ME-ICC included more psychiatric co-morbidities than Fukuda because of the number of symptoms required and concluded that a focus on a smaller number of hallmark symptoms like post-exertional malaise would be critical. Finally, the paper acknowledged the need for more study because this study used a questionnaire designed for Fukuda CFS, that they were unable to assess one of the key ME-ICC criteria because of the available data and the study did not look at homebound or bedbound patients.
- Jason L, Sunnquist M, Brown A, Evans M, Newton J. "Are Myalgic Encephalomyelitis and chronic fatigue syndrome different illnesses? A preliminary analysis." *Journal of Health Psychology* First published online February 2014; 1–13. http://dx.doi.org/10.1177/1359105313520335

[357] Nacul L., Lacerda E, Pheby D, Campion P, Molokhia M, Fayyaz S, Leite J, Poland F, Howe A, Drachler M. "Prevalence of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) in three regions of England: a repeated cross-sectional study in primary care." *BMC Medicine* July 2011, 9:91 http://dx.doi.org/10.1186/1741-7015-9-91

[358] Maes M, Twisk F., Johnson C. "Myalgic Encephalomyelitis (ME), Chronic Fatigue Syndrome (CFS), and Chronic Fatigue (CF) are distinguished accurately: Results of supervised learning techniques applied on clinical and inflammatory data." December 30, 2012; 200(2-3): 754-760. PMID: 22521895. http://dx.doi.org/10.1016/j.psychres.2012.03.031

[359] Jason L, Richman J, Friedberg F, Wagner L, Taylor R, Jordan K. "Politics, science and the emergence of a new disease." *American Psychologist* September 1997; 52(9): 973-983. PMID: 9301342 http://www.ncbi.nlm.nih.gov/pubmed/9301342

Jason stated, "Over the past ten years, a series of key decisions were made concerning the criteria for CFS diagnosis and the selection of psychiatric instruments, which scored CFS symptoms as medical or psychiatric problems. At least some of these decisions may have been formulated within a societal and political context in which CFS was assumed to be a psychologically determined problem."

[360] Jason, L., Richman, J. "How Science Can Stigmatize: The Case of Chronic Fatigue Syndrome." *Journal of Chronic Fatigue Syndrome* 2007; 14(4): 85-103. http://informahealthcare.com/doi/abs/10.3109/10573320802092146 and http://web.archive.org/web/20120228222416/http://www.cfids-cab.org/cfs-inform/CFS.case.def/jason.richman.07.txt

[361] Christley Y, Duffy T, Martin CR. "A review of the definitional criteria for chronic fatigue syndrome." *J Eval Clin Pract* February 2012;18(1):25-31. PMID: 21029269. http://dx.doi.org/10.1111/j.1365-2753.2010.01512.x

[362] De Becker P, McGregor N, De Meirleir K. "A definition-based analysis of symptoms in a large cohort of patients with chronic fatigue syndrome." *J Intern Med.* September 2001; 250(3): 234-40. PMID: 11555128. http://dx.doi.org/10.1046/j.1365-2796.2001.00890.x

This paper, which compares Holmes and Fukuda, stated, "The CFS patients fulfilling the Holmes criteria have an increased symptom prevalence and severity of many symptoms. Patients fulfilling the Fukuda criteria were less severely affected patients which leads to an increase in clinical heterogeneity. Addition of certain symptoms and removal of others would strengthen the ability to select CFS patients."

[363] Jason LA, Torres-Harding SR, Taylor RR, Carrico AW. "A comparison of the 1988 and 1994 diagnostic criteria for chronic fatigue syndrome." *J Clin Psychol Med Settings.* December 2001; 8(4):337–343. http://dx.doi.org/10.1023/A:1011981132735

[364] Jason L, Brown A, Evans M, Sunnquist M, Newton J. "Contrasting chronic fatigue syndrome versus myalgic encephalomyelitis/chronic fatigue syndrome." *Fatigue, Biomedicine, Health & Behavior* March 20, 2013; 1(3): 168-183/ PMID: 23914329. http://dx.doi.org/10.1080/21641846.2013.774556

Also see

- Jason, L, Torres-Harding, S, Jurgens, A, Helgerson, J. "Comparing the Fukuda et al. Criteria and the Canadian Case Definition for Chronic Fatigue Syndrome, Journal of Chronic Fatigue Syndrome 2004; 12(1): 37-52.
- http://informahealthcare.com/doi/abs/10.1300/J092v12n01_03?src=recsys and http://web.archive.org/web/20120216181206/http://www.cfids-cab.org/cfs-inform/CFS.case.def/jason.etal04.pdf
- 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." *Eval Health Prof* December 7, 2011; 35(3): 280-304 http://dx.doi.org/10.1177/0163278711424281
- Brown A, Jason L, Evans M, Flores S. "Contrasting Case Definitions: The ME International Consensus Criteria vs. the Fukuda et Al. CFS Criteria." *North American Journal of Psychology* March 2013; 15(1); http://www.questia.com/library/1G1-322563471/contrasting-case-definitions-the-me-international. Brown et al examined the ME-ICC and the Fukuda and found that the ME-ICC identified a much tighter group of patients (39 compared to 113 for Fukuda) with more functional impairments and physical, mental and cognitive problems than in those patients meeting the Fukuda criteria. The paper also raised a concern that ME-ICC included more psychiatric co-morbidities than Fukuda because of the number of symptoms required and concluded that a focus on a smaller number of hallmark symptoms like post-exertional malaise would be critical. Finally, the paper acknowledged the need for more study because this study used a questionnaire designed for Fukuda CFS, that they were unable to assess one of the key ME-ICC criteria because of the available data and the study did not look at homebound or bedbound patients.
- Jason L, Sunnquist M, Brown A, Evans M, Newton J. "Are Myalgic Encephalomyelitis and chronic fatigue syndrome different illnesses? A preliminary analysis." *Journal of Health Psychology* First published online February 2014; 1–13. http://dx.doi.org/10.1177/1359105313520335

[365] Nacul L., Lacerda E, Pheby D, Campion P, Molokhia M, Fayyaz S, Leite J, Poland F, Howe A, Drachler M. "Prevalence of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) in three regions of England: a repeated cross-sectional study in primary care." *BMC Medicine* July 2011, 9:91 http://dx.doi.org/10.1186/1741-7015-9-91

[366] Maes M, Twisk F., Johnson C. "Myalgic Encephalomyelitis (ME), Chronic Fatigue Syndrome (CFS), and Chronic Fatigue (CF) are distinguished accurately: Results of supervised learning techniques applied on clinical and inflammatory data." December 30, 2012; 200(2-3): 754-760. PMID: 22521895. http://dx.doi.org/10.1016/j.psychres.2012.03.031

[367] Harvey S, Wessely S. "Chronic fatigue syndrome: identifying zebras amongst the horses." *BMC Me*d October 2009; 7: 58. PMID: 19818158. http://dx.doi.org/10.1186/1741-7015-7-58
The authors also stated, "Depression is very common amongst those with fatigue with recent studies using the British birth cohorts showing over 70% of adults reporting CFS have evidence of psychiatric disorder prior to their fatigue symptoms beginning."

[368] Kennedy G, Abbot N, Spence V, Underwood C, Belch J. "The Specificity of the CDC-1994 Criteria for Chronic Fatigue Syndrome: Comparison Of Health Status in Three Groups of Patients Who Fulfill the Criteria." *Ann Epidemiol* February 2004; 14(2): 95–100. PMID: 15018881. http://dx.doi.org/10.1016/j.annepidem.2003.10.004

[369] Jason L, Sunnquist M, Brown A, Evans M, Newton J. "Are Myalgic Encephalomyelitis and chronic fatigue syndrome different illnesses? A preliminary analysis." *Journal of Health Psychology* First published online February 2014; 1–13. http://dx.doi.org/10.1177/1359105313520335
Also see the following for an earlier reference

- Jason, L, Torres-Harding, S, Jurgens, A, Helgerson, J. "Comparing the Fukuda et al. Criteria and the Canadian Case Definition for Chronic Fatigue Syndrome, Journal of Chronic Fatigue Syndrome 2004; 12(1): 37-52. http://informahealthcare.com/doi/abs/10.1300/J092v12n01_03?src=recsys and http://web.archive.org/web/20120216181206/http://www.cfids-cab.org/cfs-inform/CFS.case.def/jason.etal04.pdf

[370] Poorly operationalized means that the criteria lack an explicit protocol on how the criteria are to be applied (e.g. what instruments, what thresholds, etc)Jason has discussed this issue in many papers. One of the most recent is:
Brown A. Jason L. "Validating a measure of myalgic encephalomyelitis/chronic fatigue syndrome symptomatology." *Fatigue: Biomedicine, Health & Behavior* July 23, 2014. 2(3): 132-152. http://dx.doi.org/10.1080/21641846.2014.928014

[371] Jason L, Sunnquist M, Brown A, Evans M, Vernon S, Furst J, Simonis V. "Examining case definition criteria for chronic fatigue syndrome and myalgic encephalomyelitis." *Fatigue: Biomedicine, Health & Behavior* 2014 2(1): 40–56. PMID: 24511456. http://www.ncbi.nlm.nih.gov/pubmed/24511456

[372] Reeves W, Wagner D, Nisenbaum R, Jones J, Gurbaxani B, Solomon L, Papanicolaou D, Unger E, Vernon S, Heim C. "Chronic Fatigue Syndrome – A clinically empirical approach to its definition and study." *BMC Medicine* December 2005; 3:19. PMID: 16356178. http://dx.doi.org/10.1186/1741-7015-3-19
This paper stated, "most studies of CFS merely note that they used the 1994 case definition and they do not generally specify how disability, fatigue and symptom occurrence were elucidated. Thus, it is difficult to assess the validity of their diagnostic criteria and essentially impossible to compare results between studies critically."

[373] Ibid.
The report stated, "This study showed scant stability of CFS over time, when diagnosed by the usual algorithm (based on patients' subjective responses to direct questions as to whether they feel fatigued, if they perceive their fatigue causes substantial reduction in daily activities, and whether at least 4 case defining symptoms are present). There was poor correlation between illness classification during surveillance (recruitment classification) and classification by the same criteria during the clinical study. While this might reflect fluctuation in illness over time, illness categories (CFS, ISF, Remission, non-fatigued) defined by this surveillance classification scheme were not consistent with respect to overall illness severity."

[374] U.K. Group on Scientific Research into Myalgic Encephalomyelitis (M.E.). "Inquiry into the status of CFS / M.E. and research into causes and treatment." (The Gibson Inquiry). U.K. Group on Scientific Research into Myalgic Encephalomyelitis (M.E.). Chaired by Dr. Ian Gibson. November, 2006.

- Report - www.erythos.com/gibsonenquiry/Docs/ME_Inquiry_Report.pdf and
- Press release - http://www.erythos.com/gibsonenquiry/Docs/Press_Release_26Nov06.rtf
- Publication: Gibson I. "A New Look at Chronic Fatigue Syndrome/Myalgic Encephalomyelitis." *J Clin Pathol.* February 2007; 60(2): 120–121. http://dx.doi.org/10.1136/jcp.2006.042432 and http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1860614 (full text)

In 2005, Dr. Gibson chaired a cross-party ME/CFS science inquiry with members from both Houses of Parliament, The Group on the Scientific Research into ME (GSRME). The report was issued in November 2006. The report stated that the inquiry was necessary because the Chief Medical Officers Working Group Report on CFS/ME (CMO Report), published in 2002, had not led to the change that was desired and because some of the CMO recommendations for further research had been ignored. This report specifically noted this with regards to the NICE guidelines, stating,

"This is most apparent from the recent NICE draft guideline, which makes recommendations for research into the existing treatments, but does not mention the possibility of organic causes." The Group on Scientific Research into Myalgic Encephalomyelitis was a NICE Stakeholder.
Author's note: Many of the issues raised in this report are the same issues raised in this paper – overly broad definitions, lack of funding for biomedical research.

Also see Dr. Gibson's comments to NICE on the NICE guidelines for CFS/ME.

- Gibson, Ian. "NICE Witness Statement from Dr Ian Gibson MP." *InvestInME*. Page last updated March 19, 2009. http://www.investinme.org/Article-301%20Ian%20Gibson%20NICE%20Guideline%20Witness%20Statement.htm
  Dr Ian Gibson's witness statement in support of the Judicial Review case of the NICE "CFS/ME" Guideline (CG53) online brought by ME patients. Dr. Gibson stated "NICE claims that both CBT and graded exercise therapy are supported by an adequate evidence base, however, the GDG relied on a very small number of controversial randomised control trials (RCTs). The patient selection criteria for participating in the trials were too wide and therefore allowed non-ME/CFS suffers to participate. It is also misleading to refer to CBT & GET as `treatments' of `choice'. They cannot properly be described as treatments, since, as NICE admits, they do not address the core pathology of ME."

[375] Carruthers BM, van de Sande MI, De Meirleir KL, Klimas NG, Broderick G, Mitchell T, Staines D, Powles ACP, Speight N, Vallings R, Bateman L, Baumgarten-Austrheim B, Bell DS, Carlo-Stella N, Chia J, Darragh A, Jo D, Lewis D, Light AR, Marshall-Gradisbik S, Mena I, Mikovits JA, Miwa K, Murovska M, Pall ML, Stevens S. "Myalgic Encephalomyelitis: International Consensus Criteria." *Journal of Internal Medicine* October 2011; 270(4): 327–338. PMID: 21777306. http://dx.doi.org/10.1111/j.1365-2796.2011.02428.x and http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2796.2011.02428.x/full

[376] Prins J, van der Meer J, Bleijenberg G. "Chronic fatigue Syndrome." *The Lancet* January 28, 2006; 367(9507): 346-355. PMID: 16443043. http://dx.doi.org/10.1016/S0140-6736(06)68073-2
Prins also stated "Although they differ, all case definitions select severely fatigued groups of patients."

[377] Royal Colleges of Physicians, Psychiatrists, and General Practitioners. "Chronic Fatigue Syndrome. Report of a joint working group of the Royal Colleges of Physicians, Psychiatrists, and General Practitioners." October 1996. www.theoneclickgroup.co.uk/documents/ME-CFS_docs/Royal Colleges Report-CFS.doc, http://books.google.com/books/about/Chronic_Fatigue_Syndrome.html?id=RRId4npKxDsC
The report stated, "CFS can be operationally defined. However, there is still no evidence that it is an independent diagnostic entity. In the current state of knowledge it remains possible, and perhaps probable, that CFS represents the arbitrarily defined end of a spectrum of symptomatic and functional impairments, which may have a number of causes."

[378] Straus, Stephen. "Chronic fatigue syndrome. "Biopsychosocial approach" may be difficult in practice." *BMJ* October 5, 1996. 313:831. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2359057/pdf/bmj00562-0007.pdf
Straus states, "In essence, it [Fukuda] classifies a constellation of prolonged and debilitating symptoms as worthy of medical attention and study…. Related case criteria were developed by consensus at Oxford in 1991. Neither the American (Fukuda] nor the Oxford criteria assume the syndrome to be a single nosological entity."

[379] National Institute of Health. "Chronic Fatigue Syndrome. State-of-the-Science Consultation." Report of the National Institutes of Health State of Science CFS Consultation. February 6-7, 2000. http://webharvest.gov/peth04/20041027092632/www.niaid.nih.gov/dmid/meetings/cfsreport.htm

[380] Switzer WM, Jia H, Hohn O, Zheng HQ, Tang S, Shankar A, Bannert N, Simmons G, Hendry RM, Falkenberg VR, Reeves WC, Heneine W. "Absence of Evidence of Xenotropic Murine Leukemia Virus-related Virus Infection in Persons with Chronic Fatigue Syndrome and Healthy Controls in the United States." *Retrovirology*. July 1, 2010, 7: 57. http://dx.doi.org/10.1186/1742-4690-7-57

[381] Centers of Disease Control and Prevention. "Diagnosis and Management, Course WB1032." Origin August 2006. Expiration August 8, 2012. Page last updated July 2010. https://web.archive.org/web/20111025081743/http://www.cdc.gov/cfs/education/wb1032/chapter1-1.html
The "Overview of CFS" in this CME states "Various terms are incorrectly used interchangeably with CFS. CFS has an internationally accepted case definition that is used in research and clinical settings. The name chronic fatigue and immune dysfunction syndrome (CFIDS) was introduced soon after CFS was defined; there is no case definition for CFIDS, and the name implies an understanding about the pathophysiology of CFS that is not fully supported in the medical literature. The name myalgic encephalomyelitis (ME) was coined in the 1950s to clarify well-documented outbreaks of disease; however, ME is accompanied by neurologic and muscular signs and has a case definition distinct from that of CFS."
The CDC CFS CME Diagnosis and Management Course WB1032 appears to have been replaced by the Diagnosis and Management of CFS Course WB1888, which treats the Canadian, ME-ICC, Fukuda and Oxford as equivalent.

[382] U.S. Food and Drug Administration (FDA), Center for Drug Evaluation and Research (CDER). *The Voice of the Patient. Chronic Fatigue Syndrome and Myalgic Encephalomyelitis.* Report Date: September 2013. Report based on public testimony submitted at the Patient-Focused Drug Development Initiative Meeting for Chronic Fatigue Syndrome and Myalgic Encephalomyelitis held on April 25, 2013. http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM368806.pdf
Meeting agenda, transcript and video can be found at:

- U.S. Food and Drug Administration, Center for Drug Evaluation and Research (CDER). "FDA Workshop on Drug Development for Chronic Fatigue Syndrome (CFS) and Myalgic Encephalomyelitis (ME)" U.S. Food and Drug

Administration, Center for Drug Evaluation and Research (CDER). Meeting April 25-26, 2013. Page last updated December 11, 2014. http://www.fda.gov/Drugs/NewsEvents/ucm369563.htm

[383] Ibid. The Voice of the Patient Report in part noted the following about Post-exertional malaise:

"Post-exertional malaise or *crashes:* The cognitive and physical symptoms of CFS and ME summarized above were described by participants as being daily realities of their disease, varying in degrees from person to person and from day to day. However, it was their collective experience with acute, debilitating PEM, which participants called a "crash" or "collapse," that received the most attention at the meeting. As one participant said, "The term, 'malaise' to the lay-person is a misnomer, it is much more like a collapse." Participants described a crash as an exacerbation of all symptoms to extreme levels that generally lead to complete incapacitation. Participants described their complete exhaustion, inability to get out of bed to eat, intense physical pain (including muscle soreness), incoherency, blacking out and memory loss, and flu- like symptoms (i.e., sore throat, congestive cough, and others). For example, two participants described their crashes in this way:

- "When people talk about being bedbound, I mean, we're like bricks, we can't be moved. My wife would come in and check on me to see if I was breathing because I would sleep for days at a time. I didn't get up to eat, I didn't get up to go to the rest room."
- "[A crash is] not just the physical pain or it's not just the head pain, it's also more cognitive impairment, more orthostatic intolerance, more neurological issues...they're very interrelated." Participants described how the sudden onset of crashes has put them in dangerous situations, including falling, driving in the wrong direction, unknowingly wandering across a busy street, other instances of extreme confusion in public places, and blacking out."

[384] Norwegian ME Association. "The Norwegian ME Association National Survey. Abridged English Version. May 12, 2014. http://me-foreningen.com/meforeningen/innhold/div/2014/05/ME-Nat-Norwegian-Survey-Abr-Eng-Ver.pdf
Full version in Norwegian- http://me-foreningen.com/meforeningen/innhold/div/2013/05/ME-foreningens Brukerunders%C3%B8kelse-ME-syke-i-Norge-Fortsatt-bortgjemt-12-mai-2013.pdf
Survey conducted in spring, 2012.

[385] Wessely S. "Neurasthenia and chronic fatigue syndrome: Theory and Practice in Britain and America." *Transcultural Psychiatric Review* June 1994;31(2): 173-209. http://dx.doi.org/10.1177/136346159403100206 and http://www.simonwessely.com/Downloads/Publications/CFS/43.pdf

[386] Brurberg K, Fønhus A, Larun L, Flottorp S, Malterud K. "Case definitions for chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME): a systematic review." *BMJ Open* February 7, 2014; 4(2): e003973. PMID: 24508851. http://dx.doi.org/10.1136/bmjopen-2013-003973

[387] Jutel A. "Medically unexplained symptoms and the disease label." *Social Theory & Health* Vol. 8, 3, 229–245 http://dx.doi.org/10.1057/sth.2009.21

[388] Borody TJ, Cole P, Noonan S et al. "Recurrence of duodenal ulcer and *Campylobacter pylori* infection after eradication". *Med. J. Aust.* October 1989; 151(8): 431–5. PMID 2687668. http://www.ncbi.nlm.nih.gov/pubmed/2687668

[389] McKie, Robin. "Chronic Fatigue Syndrome researchers face death threats from militants." *The Guardian.* August 20, 2011 http://www.theguardian.com/society/2011/aug/21/chronic-fatigue-syndrome-myalgic-encephalomyelitis
This article presents the perspective of Professor Wessely but does not include the patient perspective or discussion of the justified concerns that patients have that only psychological research is being funded in Britain.
For another article that includes the patient perspective see:

- "ME Researchers receive death threats from sufferers", *The Telegraph*, July 29, 2011. http://www.telegraph.co.uk/health/healthnews/8669893/ME-researchers-receive-death-threats-from-sufferers.html

[390] The Economist. "Fear to Tread." *The Economist.* January 17, 2015. Last accessed January 27, 2015. http://www.economist.com/news/science-and-technology/21639438-controversial-trial-mysterious-disease-continues-yield-insights-fear

[391] Chalder T, Goldsmith K, White P, Sharpe M, Pickles A. "Rehabilitative therapies for chronic fatigue syndrome: a secondary mediation analysis of the PACE trial." The Lancet Psychiatry. February 2015; 2(2); p141–152. Last accessed on January 27, 2015. http://dx.doi.org/10.1016/S2215-0366(14)00069-8

This paper stated that it investigated "putative treatment mechanisms" and concluded, "Our main finding was that fear avoidance beliefs were the strongest mediator for both CBT and GET. Changes in both beliefs and behaviour mediated the effects of both CBT and GET, but more so for GET. The results support a treatment model in which both beliefs and behaviour play a part in perpetuating fatigue and disability in chronic fatigue syndrome."

[392] Tymes Trust. "Behind the scenes: Setting up the UK CFS/ME Research Collaborative (UK CMRC)." *Tymes Trust.* August 31, 2014. https://www.dropbox.com/s/92m09l9tq55pihh/Behind%20the%20Scenes%20-%20Research%20Collaborative.pdf?dl=0 and http://www.tymestrust.org/txt/alert201407behindthescenes.txt

[393] U.K. Information Commissioner's Office. "Freedom of Information Act 2000 (FOIA). Decision notice." U.K. Information Commissioner's Office.18 March 2015. Last accessed April 10, 2015. https://ico.org.uk/media/action-weve-taken/decision-notices/2015/1043579/fs_50558352.pdf

This response to the FOIA request, submitted by Mr. Matthees, stated "In considering the case in a broad and

holistic way, the Commissioner accepts that the request has, for the reasons set out by QMUL [Queen Mary University of London], had the effect of harassing the public authority. Viewed in the context of the other requests received, online posts and complaints to the Lancet and BMJ, the Commissioner accepts that QMUL is correct to view the request as part of a campaign – despite the complainant's assertion to the contrary."
Also see

- Mr. Matthees, "Timing of changes to PACE Trial recovery criteria." *What Do They Know*. Initial post: April 26, 2014. Last accessed April 15, 2015. https://www.whatdotheyknow.com/request/timing_of_changes_to_pace_trial#comment-59096

394 Berger JR, Pocoski J, Preblick R, Boklage S. "Fatigue heralding multiple sclerosis." *Mult Scler J..* October 2013; 19(11): 1526-32. PMID: 23439577. http://dx.doi.org/10.1177/1352458513477924.

395 "Girl, 17, died of leukaemia 10 days after NHS doctors dismissed illness as TIREDNESS." *SWNS NewsWire UK*. April 11, 2013. http://swns.com/news/girl-17-died-leukaemia-10-days-nhs-doctors-dismissed-illness-tiredness-33956/
Also see

- Lillington, Catherine. "Your life was only just beginning; there is so much you're going to miss out on, but I know you will be watching over me." *Birmingham Mail,* April 11, 2013. http://www.birminghammail.co.uk/lifestyle/health/tragic-solihull-teenager-died-rare-2583629

396 Bernhard, Toni. "The Stigma of Chronic Fatigue Syndrome II: Readers Respond." *Turning Straw into Gold, Psychology Today,* May 6, 2011 http://www.psychologytoday.com/blog/turning-straw-gold/201105/the-stigma-chronic-fatigue-syndrome-ii-readers-respond.

Ms. Tony Bernhardt described a patient who went to the hospital because severe breathing problems. When the doctor saw the diagnosis of CFS, he rolled his eyes, ran a few tests and told him he could go home and sleep it off. When the man's wife strenuously objected, the doctor finally agreed to do an xray, although he seemed most concerned with the expense of it. The xray showed that his lungs were full of pneuomina and he would have died if he had gone home. The doctor apologized and admitted that he had seen the "CFS" diagnosis and assumed that the patient wasn't sick.

397 Frances, A. "Bad News: DSM 5 Refuses to Correct Somatic Symptom Disorder." *DSM5 In Distress. Psychology Today.* January 16, 2013. http://www.psychologytoday.com/blog/dsm5-in-distress/201301/bad-news-dsm-5-refuses-correct-somatic-symptom-disorder

398 Frances, A. "Diagnostic Ethics: Harms vs Benefits of Somatic Symptom Disorder." *The Blog*. Huffington Post, December 16, 2013. Updated February 15, 2014. http://www.huffingtonpost.com/allen-frances/diagnostic-ethics-harms-v_b_4450653.html

Dr. Frances quotes Dr. Diane O'Leary who heads the Coalition for Diagnostic Rights. The website for the Coalition for Diagnostic Rights is: http://www.diagnosticrights.org/the-coalition/

399 Ibid.
Dr. O'Leary points out that advice from the American Association of Family Physicians "urges doctors to make early diagnoses of somatoform disorders in order to save time and to reduce costs" based on the assumption that most complaints are somatoform in nature.

400 Frances, A. "The Only Certainty Is Uncertainty." *The Blog.* Huff Post Science. April 21, 2013. http://www.huffingtonpost.com/allen-frances/uncertainty-science_b_3122447.html

401 Frances, A. "Bad News: DSM 5 Refuses to Correct Somatic Symptom Disorder." *DSM5 In Distress. Psychology Today.* January 16, 2013. http://www.psychologytoday.com/blog/dsm5-in-distress/201301/bad-news-dsm-5-refuses-correct-somatic-symptom-disorder

Frances stated, "The question naturally arises- How could DSM 5 get SSD so wrong and why is ICD 11 so likely to fall into the very same trap? It gains poignancy from the fact that the experts working on DSM 5 and ICD 11 are all very smart, highly experienced, and well meaning. The road to hell is paved with good intentions and bad unintended consequences…. "Experts always want to focus increased attention on their pet topic, want to expand its boundaries, and worry much more about missed than about mislabelled patients…. "Anyone with common sense immediately recognises that the DSM 5 and the likely ICD 11 definitions of SSD are impossibly broad and nonspecific. Such excess could be offered only by otherwise sensible experts who have lost their common sense when it comes to their own field."

402 White PD. "How common is chronic fatigue syndrome; how long is a piece of string?" *Population Health Metrics* 2007; 5:6. http://dx.doi.org/10.1186/1478-7954-5-6

The paper stated: "Our current criteria for diagnosing CFS are *arbitrary*, and we need to widen the net to capture all those people who become so chronically tired and unwell that they can't live their lives to their full potential."[402]

403 Dalen, Per. "Somatic medicine abuses psychiatry — and neglects causal research" Copyright 2003. Available on http://www.art-bin.com/art/dalen_en.html

404 Jutel A. "Medically unexplained symptoms and the disease label." *Social Theory & Health* Vol. 8, 3, 229–245 http://dx.doi.org/10.1057/sth.2009.21

405 Barker, Kristen. *The Fibromyalgia Story*. Temple University Press. June 30, 2005

[406] Comments on the PACE trial outcome measures and how recovery was defined are found in a number of places including the following which lists letters to the journal on the paper

- Hooper, Malcolm. "MAGICAL MEDICINE: HOW TO MAKE A DISEASE DISAPPEAR." InvestInME. February 2010. http://www.investinme.org/Documents/Library/magical-medicine.pdf
- ME Association (UK). "Pace Trial" Letters and reply. Journal of Psychologial Medicine. August 2013." From the Journal of Psychological Medicine. *http://www.meassociation.org.uk/2013/07/pace-trial-letters-and-reply-journal-of-psychological-medicine-august-2013/*
- ME Association (UK). "ME Association response to PACE trial recovery paper." February 16, 2013" *http://www.meassociation.org.uk/2013/02/me-association-response-to-pace-trial-recovery-paper-15-february-2013/*
- *ME Analysis. "Video 7. CBT and Recovery???" ME Analysis YouTube channel. Published April 27, 2014. http://www.youtube.com/watch?v=d_7J5ELjArU&feature=youtu.be*
  The simplest explanation of the recovery controversy is found in this video, which reports for instance, that one of the entry criteria was 65 on the SF-36 health survey scale, a scale that goes from 0 to 100 where 100 is full health. The entry criteria for the PACE trial was reported as 65, a level that is defined as abnormal. Recovery was originally slated at 85 on the SF-36 scale. But the definition of recovery was changed during the trial to be 60, a level that was below the entry criteria for the trial.

[407] White PD, Goldsmith KA, Johnson AL, Potts L, Walwyn R, DeCesare JC, Baber HL, Burgess M, Clark LV, Cox DL, Bavinton J, Angus BJ, Murphy G, Murphy M, O'Dowd H, Wilks D, McCrone P, Chalder T, Sharpe M. "Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): a randomised trial." *The Lancet* March 5, 2011; 377(9768): 823-836. PMID: 21334061. http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(11)60096-2/fulltext

- The study report stated that PACE subscribes to the "fear avoidance theory of chronic fatigue syndrome" that "assume that the syndrome is perpetuated by reversible physiological changes of deconditioning and avoidance of activity." Page 825
- Additional information is provided in the PACE trial manuals, available through the PACE Trial information website http://www trial.org/trialinfo/
  - CBT Manual
    Burgess M, Chalder T. "PACE Manual for Therapists. Cognitive Behavioral Therapy for CFS/ME." MREC Version 2. November 2004. http://www.pacetrial.org/docs/cbt-therapist-manual.pdf
    The manual states "It is important to include the precipitating factors, e.g., illness, life-events, working excessively hard, perfectionist personality etc. It is also important to discuss the maintaining factors, e.g., erratic or reduced activities, disturbed sleep patterns, unhelpful illness beliefs and any other unhelpful cognitions etc." (Page 81)
  - GET Manual
    PACE Trial Management Group. "PACE Manual for Therapists. Graded Exercise Therapy for CFS/ME.".Version 2. http://www.pacetrial.org/docs/get-therapist-manual.pdf .
    The manual states "GET assumes that CFS/ME is perpetuated by deconditioning (lack of fitness), reduced physical strength and altered perception of effort consequent upon reduced physical activity." (Page 20)
    The manual also states "Planned physical activity and not symptoms are used to determine what the participant does." (Page 21)

[408] Petersen D. "Report from Paris: Peterson Reports Antiviral (Vistide) Effective in Treating Herpesvirus Infected Chronic Fatigue Syndrome (ME/CFS) Patients." Simmaron Research. April 9, 2013. http://simmaronresearch.com/2013/04/peterson-conference-presentation-reports-vistide-cidofovir-effective-in-treating-chronic-fatigue-syndrome-mecfs-patients-with-hhv6-and-hcmv-infections/

[409] Fluge and Mella have done two studies on Rituxin in CFS

- Fluge O, Mella O. "Clinical impact of B-cell depletion with the anti-CD20 antibody rituximab in chronic fatigue syndrome: a preliminary case series." *BMC Neurology* July 1, 2009, 9:28. PMID:19566965. http://dx.doi.org/10.1186/1471-2377-9-28
- Fluge O, Bruland O, Risa K, Storstein A, Kristoffersen EK, Sapkota D, Næss H, Dahl O, Nyland H, Mella O. "Benefit from B-Lymphocyte Depletion Using the Anti-CD20 Antibody Rituximab in Chronic Fatigue Syndrome. A Double-Blind and Placebo-Controlled Study." *Plos One* Oct 2011; 6(10): e26358. http://dx.doi.org/10.1371/journal.pone.0026358

[410] Jason L, Najar N, Porter N, Reh C. "Evaluating the Centers for Disease Control's Empirical Chronic Fatigue Syndrome Case Definition." *Journal of Disability Policy Studies* Published online October 2008, in print September 2009; 20(2): 93-100. http://dx.doi.org/10.1177/1044207308325995 and http://web.archive.org/web/20090816013354/http://www.co-cure.org/Jason-7.pdf
Jason noted that this "blurring of diagnostic categories" makes it harder to identify biological markers.

[411] The primary clinical trials for disease modifying treatments for this disease have been on Ampligen in the U.S.. and Rituxan in Norway. Most of the other trials have been for behavioral treatments or for supplements.

[412] Jason, L., Richman, J. "How Science Can Stigmatize: The Case of Chronic Fatigue Syndrome." *Journal of Chronic Fatigue Syndrome* 2007; 14(4): 85-103. http://informahealthcare.com/doi/abs/10.3109/10573320802092146 and http://web.archive.org/web/20120228222416/http://www.cfids-cab.org/cfs-inform/CFS.case.def/jason.richman.07.txt

[413] Tuller, David. "Chronic Fatigue Syndrome and the CDC: A Long, Tangled Tale." *Virology Blog. About Viruses and Viral Disease,* November 23, 2011. http://www.virology.ws/2011/11/23/chronic-fatigue-syndrome-and-the-cdc-a-long-tangled-tale/

Tuller stated that Dr. Racaniello, Higgins Professor of Microbiology & Immunology, Mt. Sinai School of Medicine of CUNY said that "when he used to question colleagues about chronic fatigue syndrome, they would argue that it was an imaginary illness. 'Every time I asked someone about it, they would say it doesn't exist, it isn't a real disease, even as recently as the past year,' he said. 'But once you start paying attention and reading papers, this looks like a chronic or hyper-immune activation. These patients have a lot of signs that their immune systems are firing almost constantly.'" Also see second Tuller article addressing the case definition.

- Tuller, David. "Defining an Illness Is Fodder for Debate." *The New York Times*. New York, New York. March 4, 2011. www.nytimes.com/2011/03/08/health/research/08fatigue.html

[414] One example is Stanford's Montoya, whose mentor "scoffed at the idea" and suggested he could end up homeless if he pursued research into this disease.

- Newby, Kris. "Immune System Disruption. The Search for Answers." *Stanford Medicine. Balancing Act.* Fall 2014. http://stanmed.stanford.edu/2014fall/immune-system-disruption.html

[415] Jason, L, Torres-Harding, S, Jurgens, A, Helgerson, J. "Comparing the Fukuda et al. Criteria and the Canadian Case Definition for Chronic Fatigue Syndrome, Journal of Chronic Fatigue Syndrome 2004; 12(1): 37-52. http://informahealthcare.com/doi/abs/10.1300/J092v12n01_03?src=recsys and http://web.archive.org/web/20120216181206/http://www.cfids-cab.org/cfs-inform/CFS.case.def/jason.etal04.pdf

Jason noted that the "selection of diagnostic signs and symptoms has major implications for which individuals are diagnosed with CFS and how seriously the illness is viewed."

[416] Carruthers BM, van de Sande MI, De Meirleir KL, Klimas NG, Broderick G, Mitchell T, Staines D, Powles ACP, Speight N, Vallings R, Bateman L, Baumgarten-Austrheim B, Bell DS, Carlo-Stella N, Chia J, Darragh A, Jo D, Lewis D, Light AR, Marshall-Gradisbik S, Mena I, Mikovits JA, Miwa K, Murovska M, Pall ML, Stevens S. "Myalgic Encephalomyelitis: International Consensus Criteria." *Journal of Internal Medicine* October 2011; 270(4): 327–338. PMID: 21777306. http://dx.doi.org/10.1111/j.1365-2796.2011.02428.x and http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2796.2011.02428.x/full

[417] Carruthers BM, van de Sande MI, De Meirleir KL, Klimas NG, Broderick G, Mitchell T, Staines D, Powles ACP, Speight N, Vallings R, Bateman L, Bell DS, Carlo-Stella N, Chia J, Darragh A, Gerken A, Jo D, Lewis D, Light AR, Light K, Marshall-Gradisnik S, McLaren-Howard J, Mena I, Miwa K, Murovska M, Steven S. "Myalgic Encephalomyelitis – Adult and Paediatric: International Consensus Primer for Medical Practitioners." Co-editors B.M. Carruthers and M.I. van de Sande. Published by Carruthers and van de Sande, 2012. http://www.hetalternatief.org/ICC primer 2012.pdf

The ME-ICC Primer stated, "There is a poignant need to untangle the web of confusion caused by mixing diverse and often overly inclusive patient populations in one heterogeneous, multi-rubric pot called 'chronic fatigue syndrome'. We believe this is the foremost cause of diluted and inconsistent research findings, which hinders progress, fosters skepticism, and wastes limited research monies."

[418] Straus S, Komaroff S, Wedner HJ. "Chronic Fatigue Syndrome: Point and Counterpoint." *The Journal of Infectious Diseases* July 1994; 170(1): 1-6. PMID: 8014482. http://dx.doi.org/10.1093/infdis/170.1.1
In 1993, Dr. Stephen Straus mediated a discussion at the annual meeting of the Infectious Disease Society of America, at which time Dr. H. James Wedner, Professor of Immunology and Allergy at Washington University and a clinician who had treated CFS patients, made this statement.

[419] Richman J, Jason L, Taylor R, Jahn S. "Feminist Perspectives On The Social Construction Of Chronic Fatigue Syndrome." *Health Care for Women International* October 2000. 21(3): 173-185. PMID: 11111464. http://dx.doi.org/10.1080/073993300245249

[420] U.K. Group on Scientific Research into Myalgic Encephalomyelitis (M.E.). "Inquiry into the status of CFS / M.E. and research into causes and treatment." (The Gibson Inquiry). U.K. Group on Scientific Research into Myalgic Encephalomyelitis (M.E.). Chaired by Dr. Ian Gibson. November, 2006.

- Report - www.erythos.com/gibsonenquiry/Docs/ME_Inquiry_Report.pdf and
- Press release - http://www.erythos.com/gibsonenquiry/Docs/Press_Release_26Nov06.rtf
- Publication: Gibson I. "A New Look at Chronic Fatigue Syndrome/Myalgic Encephalomyelitis." *J Clin Pathol.* February 2007; 60(2): 120–121. http://dx.doi.org/10.1136/jcp.2006.042432 and http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1860614/ (full text)

Regarding spending on this disease in the U.K, the report stated that as of 2006, "The Medical Research Council (MRC) has invested over £11 million in research into ME/CFS but these have focused on the psychosocial aspects of the disease and in particular on controlled trials of treatments of this aspect of the illness." (Page 6)

[421] Science Daily. "Stress, Childhood Trauma Linked To Chronic Fatigue Syndrome In Adults." *Science Daily*. Nov 7, 2006. http://www.sciencedaily.com/releases/2006/11/061107082833.htm
Khamsi, R. "Chronic fatigue syndrome linked to stressful childhood." *NewScientist.* Nov 6, 2006 www.newscientist.com/article/dn10454-chronic-fatigue-syndrome-linked-to-stressful-childhood.html#.
Barclay Laurie. "Childhood Trauma, Stress Linked to Adult Chronic Fatigue Syndrome." *Medscape Multispecialty*, Nov 10, 2006. http://www.medscape.org/viewarticle/547583

[422] Weintraub, P. "Chronic fatigue syndrome & child abuse: Disordered patients or disordered research? Are chronic fatigue patients victims of child abuse or research abuse?" *Emerging Diseases.* Psychology Today, January 13, 2009 http://www.psychologytoday.com/blog/emerging-diseases/200901/chronic-fatigue-syndrome-child-abuse-disordered-patients-or-disordered

[423] Example includes

- Swan, Norman interview of Professor Michael Sharpe and Lancet Editor in Chief, Richard Horton. "Comparison of treatments for chronic fatigue syndrome - the PACE trial." *RN. Australian Broadcasting Network.* April 18, 2011. http://www.abc.net.au/radionational/programs/healthreport/comparison-of-treatments-for-chronic-fatigue/2993296
- Breus, M. "Exercise and CBT Can Help Chronic Fatigue." *Sleep NewZZZ, Psychology Today.* March 7, 2013. http://www.psychologytoday.com/blog/sleep-newzzz/201303/exercise-and-cbt-can-help-chronic-fatigue/comments

[424] See discussion in the Medical Care Chapter for medical education sites that have incorporated psychosocial approaches and theories. Also note article on HealthFinder.Gov, a website of the U.S. Office of Disease Prevention and Health Promotion, which republished a HealthDay article on the 2014 Chalder study that the effect of CBT and GET seen in PACE was primarily due to decreasing patient fear of activity.
HealthDay News. "Therapists Must Ease Patients' Fear When Treating Chronic Fatigue Syndrome: Study" HealthFinder.gov. January 14, 2015. Last accessed February 4, 2015. http://healthfinder.gov/News/Article.aspx?id=695460&source=govdelivery&utm_medium=email&utm_source=govdelivery#.VMB2tKJUJY4.twitter. Note that this site is provided by HHS' Office of Disease Prevention and Health Promotion.

[425] Science Media Center. "expert reaction to Lancet study looking at treatments for Chronic Fatigue Syndrome/ME." Science Media Center. February 17, 2011. Last accessed February 28, 2015. http://www.sciencemediacentre.org/expert-reaction-to-lancet-study-looking-at-treatments-for-chronic-fatigue-syndromeme-2-2/
Further information on the U.K. Science Media Center, including pros and cons, can be found in the following articles:

- Callaway, E. "Science media: Centre of attention." Nature. July 10, 2013. Last accessed February 28, 2015. http://www.nature.com/news/science-media-centre-of-attention-1.13362
- Fiona Fox and Connie St. Louis. "Science media centers & the press, part 1." *The Observatory.* Columbia Journalism Review. June 17, 2013. Last accessed February 28, 2015. http://www.cjr.org/the_observatory/science_media_centers_the_pres.php?page=all

[426] Columbia University Mailman School of Public Health. "Scientists Discover Robust Evidence That Chronic Fatigue Syndrome Is a Biological Illness." Columbia University Mailman School of Public Health. February 27, 2015. Last accessed February 28, 2015. http://www.mailman.columbia.edu/news/scientists-discover-robust-evidence-chronic-fatigue-syndrome-biological-illness

[427] Science Media Center. "expert reaction to biomarkers for CFS/ME." Science Media Center. February 27, 2015. Last accessed February 28, 2015. http://www.sciencemediacentre.org/expert-reaction-to-biomarkers-for-cfsme/

[428] One example of claims that patients are biased against psychiatry or are motivated to continue to be sick, including for financial reasons, can be seen in the following article

- Smith C, Wessely, S. "Unity of Opposites? Chronic fatigue syndrome and the challenge of divergent perspectives in guideline development" *J Neurol Neurosurg Psychiatry February 2014; 85(2): 214-219. PMID: 23160704. http://dx.doi.org/doi:10.1136/jnnp-2012-303208 and* http://jnnp.bmj.com/content/85/2/214.full

  Professor Wessely is responding to the recommendation of the Scottish Health Network to adopt the Canadian Consensus Criteria for ME patients and NICE guidelines for CFS and their questioning the effectiveness of CBT and GET. He described this situation in terms of irreconcilable differences between objectiveness and evidence-based medicine (supporting CBT and GET) versus what he saw as subjectiveness and individual accounts of patients. He stated that the Canadian Criteria had been developed in response to "patient pressure" and said: "Attempting to synthesize patient views into the discourse regarding which criteria should be used to identify patients clinically has led to dangerous criteria being adopted."

  Regarding the fact that Scotland had not endorsed CBT for ME patients, Professor Wessely stated "Again the discussion appears to refer extensively to the survey of patient groups, which are inevitably biased against those who have improved, contain heterogeneous groups of people probably with a wide variety of diagnoses, and a bias as in all self-help groups towards those with poor prognosis."

Professor Wessely asks what lies behind the failure to adopt CBT and GET and states "It strikes us, however, that internet searches of patient group websites and forums reveal a stream of antipsychiatry views, not only rejecting psychiatry in relation to ME/CFS, but also conducting personal attacks on those professionals who are involved in scientific research and review that come to opposing conclusions that are not aligned with these antipsychiatry views."

Finally he states "In conclusion, these are examples of a less than helpful interaction between politics and science, and one in which the former has outweighed the latter."

Other examples have been provided by Dr. Malcolm Hooper in

- Hooper M. and members of the ME Community, Department of Life Sciences, University of Sunderland. "The Mental Health Movement: Persecution of Patients? Background Briefing for the House of Commons [UK] Select Health Committee." December 2003. http://www.meactionuk.org.uk/SELECT_CTTEE_FINAL_VERSION.htm
  - Sharpe M, Chalder T, Palmer I, Wessely S.. "Chronic fatigue syndrome: a practical guide to assessment and management. " *General Hospital Psychiatry* 1997:19:3:185-199. PMID: 9218987. http://dx.doi.org/10.1016/S0163-8343(97)80315-5 and http://www.simonwessely.com/Downloads/Publications/CFS/85.pdf (full text)
    The authors stated, "Many patients receive financial benefits and payment which may be contingent upon their remaining unwell. Gradual recovery may therefore pose a threat of financial loss."
  - Wessely S. "Chronic fatigue syndrome: Symptom and Syndrome." *Annals of Internal Medicine* 2001; 134: 9S: 838-843 http://dx.doi.org/10.7326/0003-4819-134-9_Part_2-200105011-00007 and http://www.researchgate.net/publication/11991809_Chronic_fatigue_symptom_and_syndrome (full text)
    Wessley stated, "Some of the modern impetus to 'allow' a specific chronic fatigue syndrome arises from the various compensation and social insurance schemes operating in developed countries."
  - Sharpe M. "Doctors' Diagnoses and Patients' Perceptions: Lessons from Chronic Fatigue Syndrome" Editorial to *Gen Hosp Psychiat* November 1998; 20(6): 335-338 http://dx.doi.org/10.1016/S0163-8343(98)00055-3 The authors stated, "The application of (a psychiatric diagnosis) may give the physician the satisfaction of having applied a label of which most of his peers would approve. The problem is that many patients not only fail to accept this diagnosis but respond to it with frank hostility."

Additional quotes are available in:

- Hooper M. and members of the ME Community, Department of Life Sciences, University of Sunderland. "The Mental Health Movement: Persecution of Patients? Background Briefing for the House of Commons [UK] Select Health Committee." December 2003. http://www.meactionuk.org.uk/SELECT_CTTEE_FINAL_VERSION.htm

[429] U.K. Department for Work and Pensions. "About us." Undated https://www.gov.uk/government/organisations/department-for-work-pensions/about

According to the DWP website, "The Department for Work and Pensions (DWP) is responsible for welfare, pensions and child maintenance policy. As the UK's biggest public service department it administers the State Pension and a range of working age, disability and ill health benefits to over 22 million claimants and customers."

[430] U.K. Group on Scientific Research into Myalgic Encephalomyelitis (M.E.). "Inquiry into the status of CFS / M.E. and research into causes and treatment." (The Gibson Inquiry). U.K. Group on Scientific Research into Myalgic Encephalomyelitis (M.E.). Chaired by Dr. Ian Gibson. November, 2006.

- Report - www.erythos.com/gibsonenquiry/Docs/ME_Inquiry_Report.pdf and
- Press release - http://www.erythos.com/gibsonenquiry/Docs/Press_Release_26Nov06.rtf
- Publication: Gibson I. "A New Look at Chronic Fatigue Syndrome/Myalgic Encephalomyelitis." *J Clin Pathol.* February 2007; 60(2): 120–121. http://dx.doi.org/10.1136/jcp.2006.042432 and http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1860614/ (full text)

The Gibson Inquiry Report stated, "There have been numerous cases where advisors to the DWP have also had consultancy roles in medical insurance companies. Particularly the Company UNUMProvident. Given the vested interest private medical insurance companies have in ensuring CFS/ME remain classified as a psychosocial illness there is blatant conflict of interest here. The Group find this to be an area for serious concern and recommends a full investigation of this possibility by the appropriate standards body." (Page 30)

Author's note: It is not currently clear if that investigation was done or what the results were. This is an area that needs additional investigation, given the evidence seen in some scientific papers listing competing interests.

[431] White PD, Goldsmith KA, Johnson AL, Potts L, Walwyn R, DeCesare JC, Baber HL, Burgess M, Clark LV, Cox DL, Bavinton J, Angus BJ, Murphy G, Murphy M, O'Dowd H, Wilks D, McCrone P, Chalder T, Sharpe M. "Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): a randomised trial." *The Lancet* March 5, 2011; 377(9768): 823-836. PMID: 21334061. http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(11)60096-2/fulltext

- The report stated, "PDW has done voluntary and paid consultancy work for the UK Departments of Health and Work and Pensions and Swiss Re (a reinsurance company). DLC has received royalties from Wiley. JB was on the guideline development group of the National Institute for Health and Clinical Excellence guidelines for chronic fatigue syndrome and myalgic encephalomyelitis and has undertaken paid work for the insurance industry. GM

has received royalties from Karnac. TC has done consultancy work for insurance companies and has received royalties from Sheldon Press and Constable and Robinson. MB has received royalties from Constable and Robinson. MS has done voluntary and paid consultancy work for government and for legal and insurance companies, and has received royalties from Oxford University Press."

[432] Swiss Re. "Managing claims for chronic fatigue the active way." Swiss Re. September 11, 2012 (date listed in index of searched items). Last accessed March 11, 2015. http://www.swissre.com/clients/newsletters/Managing_claims_for_chronic_fatigue_the_active_way.html

[433] Professor Michael O'Donnell, Chief Medical Officer Unum. *Mind over Matter. Exploring the issues of Mental Ill Health.* Unum Chief Medical Officer's Annual 2007 Report. Unum. 2007. https://meagenda.files.wordpress.com/2008/12/cmoreport2007_up1431.pdf and https://dl.dropbox.com/u/32109159/UnumCMOAnnual Report2007.Wessely.pdf

[434] Bass C, Peveler R, House A. "Somatoform disorders: severe psychiatric illnesses neglected by psychiatrists." *The British Journal of Psychiatry* 2001; *179: 11-14* http://dx.doi.org/10.1192/bjp.179.1.11 and http://bjp.rcpsych.org/content/179/1/11.full
Dr. Chris Bass's research includes the study of somatoform illness and at least in this paper includes CFS as an example of somatoform disease.

[435] Bass, C. "The Interface Between Psychiatric and Physical Disorders." In *Mind over Matter. Exploring the issues of Mental Ill Health.* Unum Chief Medical Officer's 2007 Annual Report. Unum. 2007. https://meagenda.files.wordpress.com/2008/12/cmoreport2007_up1431.pdf and https://dl.dropbox.com/u/32109159/UnumCMOAnnual Report2007.Wessely.pdf

[436] Barker, K. "The Social Construction of Illness. Medicalization and Contested Illness." In Handbook of Medical Sociology. Edited by Bird C, Conrad P. Page 157. Nashville : Vanderbilt University Press, 2010.

[437] Conrad P, Barker K. "The Social Construction of Illness: Key Insights and Policy Implications" *Journal of Health and Social Behavior* 2010 51(1): S67 http://dx.doi.org/10.1177/0022146510383495

[438] Frances, A. "Bad News: DSM 5 Refuses to Correct Somatic Symptom Disorder." *DSM5 In Distress. Psychology Today.* January 16, 2013. http://www.psychologytoday.com/blog/dsm5-in-distress/201301/bad-news-dsm-5-refuses-correct-somatic-symptom-disorder

[439] Numerous articles have criticized the DSM-5 for turning everyday experience, like bereavement into a mental health issue. One of the most vocal has been Dr. Allen Frances, chair of DSM-IV who was quoted in the following article:

- Associated Press. "New psychiatric manual, DSM-5, faces criticism for turning 'normal' human problems into mental illness." *New York Daily News.* May 15, 2013. http://www.nydailynews.com/life-style/health/shrinks-critics-face-new-psychiatric-manual-article-1.1344935#ixzz2uYpU2ath
  The article stated, "Way too much treatment is given to the normal 'worried well' who are harmed by it; far too little help is available for those who are really ill and desperately need it," Dr. Allen Frances writes in "Saving Normal." He is a retired Duke University professor who headed the psychiatry group's task force that worked on the previous handbook. He says the new version adds new diagnoses "that would turn everyday anxiety, eccentricity, forgetting and bad eating habits into mental disorders."

[440] Lehman, Gigi. Interview of Dr. Nancy Klimas. Miami Herald, March 24, 2009. Original source http://www.miamiherald.com/living/story/963475.html no longer available directly. Accessed on http://www.cfsfacts.org/2009/03/nancy-klimas-interview.html
Dr. Klimas' comments were based on the following study

- Lutgendorf SK, Antoni MH, Ironson G, Fletcher MA, Penedo F, Baum A, Schneiderman N, Klimas N. "Physical symptoms of chronic fatigue syndrome are exacerbated by the stress of Hurricane Andrew." Psychosom Med. July – August 1995; 57(4): 310-23. PMID: 7480560. http://www.ncbi.nlm.nih.gov/pubmed/7480560

This article further discussed the issue of physician induced PTSD

- Weir, Kirsten. "Beyond Tired. Chronic fatigue syndrome remains misunderstood and understudied. Psychologists are among those trying to change that." *Monitor on Psychology* (A publication of the American Psychological Association). October 2014. 45(9): 67-70. http://www.apamonitor-digital.org/apamonitor/201410/?lm=1411877831000&articleId=497242&pg=70#pg72

[441] Anderson V, Jason L, Hlavaty L, Porter N, Cudia J. "A Review and Meta-Synthesis of Qualitative Studies on Myalgic Encephalomyelitis/Chronic Fatigue Syndrome."*Patient Educ Couns*. February 2012; 86(2): 147–155. http://dx.doi.org/10.1016/j.pec.2011.04.016

[442] Representative media articles include the following. The comments on the Tucker article give useful insight into the perspective of the medical community on the change . The Auwaerter article recommends exercise

- Tucker, M. "IOM Gives Chronic Fatigue Syndrome a New Name and Definition" *Medscape Multispecialty*. February 10, 2015. Last accessed March 30, 2015. http://www.medscape.com/viewarticle/839532
- Auwaerter, Paul. "Managing Systemic Exertion Intolerance Disease (SEID)." *Medscape Multispecialty*. March 3, 2015. Last accessed March 30, 2015. http://www.medscape.com/viewarticle/840635
  Auwaerter stated, "What do I do in my office? Simon Wessely and colleagues,[5] who did a fair amount of work on chronic fatigue syndrome and Gulf War syndrome, and others have suggested that graded exercises,

conditioning to build up tolerance, and cognitive-behavioral therapy are some of the best strategies to help people feel better."

[443] Gluckman, Stephen. "Patient information: Chronic fatigue syndrome (Beyond the Basics)." Edited by Weller, P. *UpToDate.* Last updated March 19, 2015. Last accessed March 30, 2015. http://www.uptodate.com/contents/treatment-of-chronic-fatigue-syndrome?source=see_link (requires login) and http://www.uptodate.com/contents/treatment-of-chronic-fatigue-syndrome-systemic-exertion-intolerance-disease

The site states, "Many therapies have been tried in chronic fatigue syndrome (CFS), also called systemic exertion intolerance disease (SEID), but only cognitive behavioral therapy (CBT) and graded exercise therapy appear to produce meaningful benefit."

Also see

Asad, Z. "A 35-Year-Old Woman With Fatigue and Joint Pain." *Medscape.* April 14, 2015. Last accessed April 20, 2015. http://reference.medscape.com/viewarticle/842828

- The case study describes a patient with fatigue, "muscle stiffness, joint pain, recurrent headaches, and an inability to concentrate" but the patient does not have PEM. The case study adds on that the patient is "an obese woman with poor hygiene," is "stressed by her symptoms," has had "multiple unprotected sexual encounters,", and "has visited multiple physicians in the last few months with the same symptoms and is not satisfied with the work-up." Physical exam and labs are normal with the exception of a slight elevation of ANA and hyperlipidemia.
- The article lists Fukuda criteria, states that the IOM renamed this to SEID and then lists the SEID criteria as an alternative to the Fukuda criteria. Upper prevalence rate is 2.5%, a rate seen in Empirical studies.
- The article recommends CBT and GET and says that prolonged rest "showed no benefit and indirect evidence of harm."

[444] Jason LA, Fennell P, Taylor RR. *Handbook of chronic fatigue syndrome & fatiguing illness*. New York, NY: John Wiley & Sons, Inc., 2003.

[445] Jason, L., Richman, J. "How Science Can Stigmatize: The Case of Chronic Fatigue Syndrome." *Journal of Chronic Fatigue Syndrome* 2007; 14(4): 85-103. http://informahealthcare.com/doi/abs/10.3109/10573320802092146 and http://web.archive.org/web/20120228222416/http://www.cfids-cab.org/cfs-inform/CFS.case.def/jason.richman.07.txt

The article stated, "If medical personnel believe that CFS is a relatively rare disorder and it is primarily caused by psychiatric explanations, then physicians might minimize or misinterpret the physical complaints of CFS patients, and this could lead to the mistrust and lack of communication that has been reported between patients and medical personnel."

[446] Brimmer DJ, Fredinger F, Lin JS, Reeves W. "U.S. healthcare providers' knowledge, attitudes, beliefs, and perceptions concerning Chronic Fatigue Syndrome (CDC-sponsored survey)." *BMC Family Practice.* 2010; 11: 28. http://www.biomedcentral.com/1471-2296/11/28

[447] Every patient tells stories of doctors who told them they were depressed, dismissed their illness as made up, refused to treat them or recommended treatments that were inappropriate or harmful for ME/CFS patients. The sheer prevalence of these stories provides substantial evidence that there is a serious issue. The series by Toni Bernhard highlighted these issues but these themes are universal across every discussion with patients.

- Bernhard, Toni. "The Stigma of Chronic Fatigue Syndrome." *Turning Straw into Gold, Psychology Today,* April 10, 2011. https://www.psychologytoday.com/blog/turning-straw-gold/201104/the-stigma-chronic-fatigue-syndrome
- Bernhard, Toni. "The Stigma of Chronic Fatigue Syndrome II: Readers Respond." *Turning Straw into Gold, Psychology Today,* May 6, 2011 http://www.psychologytoday.com/blog/turning-straw-gold/201105/the-stigma-chronic-fatigue-syndrome-ii-readers-respond

[448] Ibid.

Ms. Bernhardt described it this way "He listened and then said: "What's the diagnosis?" I was cornered. "Chronic Fatigue Syndrome," I said. I watched him disengage from me. He swiveled on his stool, put his note pad down, turned back to me as if we'd just met and said: "What have you come to see me about today?"

[449] Ibid.

Ms. Tony Bernhardt described a patient who went to the hospital because severe breathing problems. When the doctor saw the diagnosis of CFS, he rolled his eyes, ran a few tests and told him he could go home and sleep it off. When the man's wife strenuously objected, the doctor finally agreed to do an xray, although he seemed most concerned with the expense of it. The xray showed that his lungs were full of pneuomina and he would have died if he had gone home. The doctor apologized and admitted that he had seen the "CFS" diagnosis and assumed that the patient wasn't sick.

[450] Karen Eng. "Illuminating an illness without end: Fellows Friday with Jennifer Brea" *TED Fellows. TED Blog*. October 25, 2013. http://blog.ted.com/2013/10/25/illuminating-an-illness-without-end-fellows-friday-with-jennifer-brea/.

[451] Personal communication with Pat Fero

[452] Schweitzer, Mary. "Casey Fero." Invest in ME. Undated. http://www.investinme.org/Article%20011-Casey%20Fero.htm

[453] Jason, L., Richman, J. "How Science Can Stigmatize: The Case of Chronic Fatigue Syndrome." *Journal of Chronic Fatigue Syndrome* 2007; 14(4): 85-103. http://informahealthcare.com/doi/abs/10.3109/10573320802092146 and http://web.archive.org/web/20120228222416/http://www.cfids-cab.org/cfs-inform/CFS.case.def/jason.richman.07.txt

Jason stated, "If medical personnel believe that CFS is a relatively rare disorder and it is primarily caused by psychiatric explanations, then physicians might minimize or misinterpret the physical complaints of CFS patients, and this could lead to the mistrust and lack of communication that has been reported between patients and medical personnel."

Regarding the disrespectful treatment of patients by providers, Jason stated that 77% of patients reported negative reactions from doctors, 95% said they had "feelings of estrangement" from doctors, 70% felt others believed they had a mental issue, and 66% felt "they were made worse by their doctors care."

[454] Personal communication (name withheld)

[455] U.K National Institute for Health and Care Excellence (NICE). *Chronic fatigue syndrome/myalgic encephalomyelitis (or encephalopathy). Diagnosis and management of CFS/ME in adults and children.* (NICE clinical guideline 53). August 2007. http://guidance.nice.org.uk/CG53 and http://www.nice.org.uk/guidance/cg53/evidence

[456] Harding, L. "She went into a hellhole': A mother's candid account of her daughter's battle with ME." Daily Mail: Mail Online. Published by Associated Newspapers LTD. May 15, 2010. http://www.dailymail.co.uk/home/you/article-1277519/Criona-Wilson-recalls-daughters-losing-battle-ME-She-went-hellhole.html

Also see

- "Fatigue Syndrome Ruling Welcomed." *BBC* June 23, 2006. http://news.bbc.co.uk/2/hi/uk_news/5112050.stm Covers coroner's report
- Additional information on the inquest and coroner's report can be found on *InvestInME.* http://www.investinme.org/Article-050%20Sophia%20Wilson%2001-RIP.htm

[457] ME Association, Denmark. "Karina Hansen is a severely ill Danish patient who was forcibly taken from her home on Feb 12th." May 9, 2013. Reposted on *Voices from the Shadows*. http://voicesfromtheshadowsfilm.co.uk/2013/karina-hansen-is-a-severely-ill-danish-patient-who-was-forcibly-taken-from-her-home-update-may-2013-9th/

Also see

- Letter by Karina's parents submitted to Stig Gerdes for Parliament hearing on March 19, 2014.. http://www.ft.dk/samling/20131/almdel/suu/bilag/311/1347104/index.htm. In Danish. Use Google translate
- Swift, P. "British Doctor Wants to Rescue ME Patient Held at Danish Hospital." *Liberty Voice.* February 10, 2014. http://guardianlv.com/2014/02/british-doctor-wants-to-rescue-me-patient-held-at-danish-hospital-video/

[458] Hansen was placed in the Hammel Neurocenter under the care of a psychiatrist who works at the Research Clinic for Functional Disorders at University Hospital. Aarhus, Denmark that is run by Per FInk. www.functionaldisorders.dk

Also see

- Fink, Per. "Somatoform disorders – functional somatic syndromes - Bodily distress syndrome. Need for care and organisation of care in an international perspective." Lecture to the EACLLP. Undated. http://web.archive.org/web/20130525203725/http://www.eaclpp.org/tl_files/content/Presentations/EACLPP_Per%20Fink_Somatoform%20Disorders.pdf
- Rehfeld E, Schroder A., Fink P. "Specialised Treatment for Severe Bodily Distress Syndromes (STreSS)." *The Research Clinic for Functional Disorders and Psychosomatics, Aarhus University Hospital,* Denmark October, 2009 http://funktionellelidelser.dk/fileadmin/www.funktionellelidelser.au.dk/Publikationer/Treatment_manual__additional_material_.pdf

[459] Jakob Skjoldan. "Skjoldans letter to §71-comitee (sic)." *Justice for ME.* http://justiceforkarina.webs.com/apps/blog/ Letter written to the "§71" committee who oversees forceful hospitalizations in Denmark, and the Parliamentary Health Board.

[460] Holder, Nelda. "Home for the holidays". *Mountain Xpress* (Asheville, North Carolina). Jan 6, 2010. http://www.mountainx.com/article/26040/Home-for-the-holidays and http://www.bringingryanhome.com/

[461] Swidey N, Wen P. "A Medical Collision with a Child in the Middle". Boston Globe, Boston, Massachusetts. Dec 15, 2013. http://www.bostonglobe.com/metro/2013/12/15/justina/vnwzbbNdiodSD7WDTh6xZI/story.html

Swidey N. Wen P. "No release for Conn. teen caught in hospital dispute", Boston Globe, Boston Massachusetts. Dec 21, 2013. http://www.bostonglobe.com/lifestyle/health-wellness/2013/12/21/state-retains-custody-teen-limbo-children-hospital-for-months/5TGcy5X8IxQusdtXgRmXdK/story.html

Other stories that cover the March 2014 decision to grant permanent custody to the state

- Wen, P. "Mass. granted permanent custody of Justina Pelletier." Boston Globe, Boston Massachusetts. March 25, 2014. http://www.bostonglobe.com/lifestyle/health-wellness/2014/03/25/permanent-custody-justina-pelletier-awarded-state-massachusetts/puyPhesGkKE6rGLid2VM2L/story.html

- Larimore, Rachael "The Sad, Scary Story of Sage of Justina Pelletier." *XXFactor.* March 27, 2014. http://www.slate.com/blogs/xx_factor/2014/03/27/justina_pelletier_ruling_boston_children_s_hospital_and_judge_perform_parent.html Covers the court's decision to permanently award custody to the state

Decision to release Justina in June 2014.

- Swidey N, Wen P. "Justina Pelletier heads home after judge ends state custody." June 17, 2014. Boston Globe, Boston Massachusetts. http://www.bostonglobe.com/metro/2014/06/17/judge-orders-custody-justina-pelletier-returned-parents/mDWtuGURNawSuObO0pDX4J/story.html

462 Anderson JS, Ferrans CE. "The quality of life of persons with chronic fatigue syndrome." *J Nerv Ment Dis* June 1997; 185(6): 359-67. PMID: 9205421. http://www.ncbi.nlm.nih.gov/pubmed/9205421

463 Jason, L., Richman, J. "How Science Can Stigmatize: The Case of Chronic Fatigue Syndrome." *Journal of Chronic Fatigue Syndrome* 2007; 14(4): 85-103. http://informahealthcare.com/doi/abs/10.3109/10573320802092146 and http://web.archive.org/web/20120228222416/http://www.cfids-cab.org/cfs-inform/CFS.case.def/jason.richman.07.txt

464 Unger E, Brimmer D, Boneva R, Jones J. "CFS Knowledge And Illness Management Behavior Among U.S. Healthcare Providers and the Public." Abstracts from General Sessions. IACFS/ME Biennial International Conference, Ottawa, Ontario, Canada, September 23, 2011.
http://www.iacfsme.org/LinkClick.aspx?fileticket=%2bG6GTkbP33I%3d&tabid=499 page 130-131.

The paper stated, "When asked if CFS were both medical and psychiatric, 71% of HCP [healthcare providers] agreed as compared to 30% of the public. Two percent of the public considered CFS a psychiatric condition vs 14% of HCP."

465 Anderson V, Jason L, Hlavaty L, Porter N, Cudia J. "A Review and Meta-Synthesis of Qualitative Studies on Myalgic Encephalomyelitis/Chronic Fatigue Syndrome."*Patient Educ Couns*. February 2012; 86(2): 147–155. http://dx.doi.org/10.1016/j.pec.2011.04.016

466 Bayliss K, Goodall M, Chisholm A, Fordham B, Chew-Graham C, Riste L, Fisher L, Lovell K, Peters S, Wearden A. "Overcoming the barriers to the diagnosis and management of chronic fatigue syndrome/ME in primary care: a meta synthesis of qualitative studies." *BMC Family Practice* March 7, 2014, 15:44 http://dx.doi.org/10.1186/1471-2296-15-44

467 Racaniello, Vincent, "TWiV 330: A Swinging Gate." This Week in Virology. March 29, 2015. Last accessed March 30, 2015. http://www.twiv.tv/2015/03/29/twiv-330/ Minute 25:50.

468 Institute of Medicine of the National Academies. "Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness." Institute of Medicine of the National Academies. Prepublication copy. February 10, 2015. Last accessed February 16, 2015. https://www.iom.edu/Reports/2015/ME-CFS.aspx

469 American Academy of Family Physicians. "Chronic Fatigue Syndrome: Renamed and Redefined." American Academy of Family Physicians. March 2, 2015. Last accessed April 8, 2015. http://www.aafp.org/news/health-of-the-public/20150302newchronicfatigue.html
Comments include

- "All of them seem to want disability, disabled parking stickers, amphetamines, narcotics or Xanax...I fear we contribute to this in a big way by legitimizing their complaint."
- "It is time to call these constellations of symptoms what they are, which is largely psychological."
- "I share your frustration of trying to discern the malingerers, depressed, and neurasthenias not otherwise described from fibromyalgia and the newly termed SEID."
- "I'm still counseling them that most of our interventions - narcotics, anxiolytics, stimulants, disability determination, handicapped parking stickers, home rest - only worsen the condition. So I am still left with the advice: "For now, get on with your life as much as you can and avoid medicating your symptoms."
- "Political correctness gone mad."

470 Harding, L. "She went into a hellhole': A mother's candid account of her daughter's battle with ME." Daily Mail: Mail Online. Published by Associated Newspapers LTD. May 15, 2010. http://www.dailymail.co.uk/home/you/article-1277519/Criona-Wilson-recalls-daughters-losing-battle-ME-She-went-hellhole.html

471 Weir, Kirsten. "Beyond Tired. Chronic fatigue syndrome remains misunderstood and understudied. Psychologists are among those trying to change that." *Monitor on Psychology* (A publication of the American Psychological Association). October 2014. 45(9): 67-70.
http://www.apamonitor-digital.org/apamonitor/201410/?lm=1411877831000&articleId=497242&pg=70#pg72

472 Montoya J. "Chronic Fatigue Syndrome." Stanford Hospital Health Library. Undated. Uploaded on March 11, 2011. http://www.youtube.com/watch?v=Riybtt6SChU Minute 6.50 – 7:30

473 The Rituxin story and the Norwegian apology:

- Jørgen Jelstad. "The Drug and the Possibility of Changing Everything." Journal of IiME. June 2012l 6(1): 13-17. http://www.investinme.org/Documents/Journals/Journal%20of%20IiME%20Vol%206%20Issue%201%20Screen.pdf
- European ME Alliance. "Norway's Directorate of Health Apologises for Treatment of ME Patients." European ME Alliance. October 2011. http://www.euro-me.org/news-Q42011-003.htm (Apology in Norwegian:

http://www.tv2.no/nyheter/innenriks/helsedirektoratet-vi-har-ikke-gode-nok-helsetjenester-for-mesyke-3618296.html)

[474] Anderson V, Jason L, Hlavaty L, Porter N, Cudia J. "A Review and Meta-Synthesis of Qualitative Studies on Myalgic Encephalomyelitis/Chronic Fatigue Syndrome."*Patient Educ Couns*. February 2012; 86(2): 147–155. http://dx.doi.org/10.1016/j.pec.2011.04.016 and http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3229648/

[475] Brimmer DJ, Fredinger F, Lin JS, Reeves W. "U.S. healthcare providers' knowledge, attitudes, beliefs, and perceptions concerning Chronic Fatigue Syndrome (CDC-sponsored survey)." *BMC Family Practice.* 2010; 11: 28. http://www.biomedcentral.com/1471-2296/11/28

The paper stated "Healthcare providers agreed with statements that compared to other illnesses CFS is more difficult to diagnose (70%) and more difficult to treat and manage (72%)."

[476] Kindlon T. "Reporting of Harms Associated with Graded Exercise Therapy and Cognitive Behavioural Therapy in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome." *Bulletin of the IACFS/ME* Fall 2011; 19(2):59-111. http://www.iacfsme.org/BULLETINFALL2011/Fall2011KindlonHarmsPaperABSTRACT/tabid/501/Default.aspx
Examples of harms reported by Kindlon in ME/CFS patients include the following:

- "I participated in Graded Exercise therapy via the <name of a ME/CFS specialist unit>. This lead [sic] to a relapse, at home, and made me unable to sit upright for 1 year due to pressure in my head, and chest pain. I then relapsed and ended up in my local NHS Hospital in a cardiac care unit."
- "Graded Exercise Therapy worsened me dramatically and I have no doubt had been a large factor in my being severely affected after 20 years."

[477] U.S. Department of Health and Human Services. Center for Drug Evaluation and Research (CDER). U.S. Food and Drug Administration. *ARTHRITIS ADVISORY COMMITTEE MEETING FDA Briefing Package.* Prepared for Ampligen Advisory Committee Meeting on December 20, 2012. http://www.fdatracker.com/2012/12/20/20121220-fda-arthritis-advisory-committee-meeting-webcast-audio-recording-heb-ampligen/ (2 hours 19 minutes) and www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/UCM345463.pdf (Page 122.)

Dr. Hennessey stated that Hemispherix had stated there were no approved therapies for CFS and then asked for someone "to summarize the data on cognitive behavioral therapy which I understand to be effective against chronic fatigue."

[478] Jason, L., Richman, J. "How Science Can Stigmatize: The Case of Chronic Fatigue Syndrome." *Journal of Chronic Fatigue Syndrome* 2007; 14(4): 85-103. http://informahealthcare.com/doi/abs/10.3109/10573320802092146 and http://web.archive.org/web/20120228222416/http://www.cfids-cab.org/cfs-inform/CFS.case.def/jason.richman.07.txt

[479] Jason, L. "Defining CFS: Diagnostic Criteria and Case Definition". Presented at CFIDS Association webinar, April 14, 2010..http://web.archive.org/web/20120425130843/http://www.cfids.org/webinar/jason-slides041410.pdf
The CDC stated that 80% of patients are not diagnosed. Jason has stated that over 90% of patients are not diagnosed. slide 19 which reported on findings of the 1997-1999 community based survey

[480] Newton J, Mallibard H, Hoad A, Spickett G." The Newcastle NHS Chronic Fatigue Syndrome Service: not all fatigue is the same." *J R Coll Physicians Edinb* 2010; 40(4): 304–7. PMID:21132135. http://dx.doi.org/10.4997/JRCPE.2010.404

This study was of 260 patients in the November 2008 to December 2009 timeframe. The paper stated, "This service evaluation examined the proportion of those referred to a specialist CFS service fulfilling the Fukuda diagnostic criteria for CFS and the alternative fatigue-associated diagnoses…. Of the 40% of patients subsequently found not to have CFS the most common diagnosis was fatigue associated with a chronic disease (47% of all alternative diagnoses); 20% had primary sleep disorders, 15% psychological/psychiatric illnesses and 4% a cardiovascular disorder. Thirteen per cent remained unexplained (5.2% of the total referrals)."

[481] Devasahayam A, Lawn T, Murphy M., White P. "Alternative diagnoses to chronic fatigue syndrome in referrals to a specialist service: service evaluation survey." *JRSM Short Rep* January 2012; 3(1): 4. http://dx.doi.org/10.1258/shorts.2011.011127

The paper stated, "The commonest alternative medical diagnoses of those assessed were sleep disorders and the commonest alternative psychiatric diagnosis was depressive illness. Altogether 184 of 377 (49%) patients had alternative diagnoses to CFS. (21%) of patients received an alternative medical diagnosis, the commonest of which were primary sleep disorders, endocrine disorders, nutritional disorders, and pain disorders (Table 1).. Fifty-four (22%) patients received an alternative psychiatric diagnosis; most commonly a depressive illness, then an anxiety disorder."

[482] Lane J. "How doctors are failing to spot the brain injury that could be behind 30,000 cases of 'chronic fatigue'." *Daily Mail,* Published by Associated Newspapers LTD. May 17, 2014. http://www.dailymail.co.uk/health/article-2631263/How-doctors-failing-spot-brain-injury-30-000-cases-chronic-fatigue.html

[483] Frances, A. "Diagnostic Ethics: Harms vs Benefits of Somatic Symptom Disorder." *The Blog*. Huffington Post, December 16, 2013. Updated February 15, 2014. http://www.huffingtonpost.com/allen-frances/diagnostic-ethics-harms-v_b_4450653.html

Dr. Frances quotes Dr. Diane O'Leary who heads the Coalition for Diagnostic Rights. The website for the Coalition for Diagnostic Rights is: http://www.diagnosticrights.org/the-coalition/

[484] In addition to standard diagnostic procedures and procedures to rule out other illnesses, experts use a number of procedures to diagnose the disease accurately by assessing the multi-system abnormalities outlined above using associated symptoms and biological markers, and ruling out other diseases that might explain the patient's condition. This includes the identification of core symptoms like PENE using the 2-day exercise tests, autonomic dysfunction using tilt table test; immunological dysfunction seen in flu-like symptoms and susceptibility to repeated infections and measured via elevated cytokines, high viral titers, and low natural killer cell function; and neurocognitive dysfunction seen in memory impairment, pain, sleep disturbance, and neurosensory or perceptual disturbances and measured with cognitive tests and imaging. In doing so, ME specialists also run tests to exclude other conditions that present similar symptoms, exclude major psychiatric disorders, and identify co-morbid diseases, such as fibromyalgia.

[485] Corbin L, Natelson B, Rowe P, Komaroff A (moderator). "A Case-based Approach to Chronic Fatigue Syndrome." Medscape Education Family Medicine. April 19, 2013.Last accessed March 2, 2015. Slides 7,9,20,21

[486] U.S. Government Accountability Office. *CHRONIC FATIGUE SYNDROME: CDC and NIH Research Activities Are Diverse, but Agency Coordination Is Limited. (GAO Report* HEHS-00-98). U.S. Government Accountability Office, Washington, D.C. June 2, 2000. http://www.gao.gov/assets/240/230415.pdf and http://www.gao.gov/products/HEHS-00-98

Key findings included lack of coordination, inadequate communication, CDC misuse of funds

Dimmock, M. "Appropriations Request History 1995 – 2013 and 2000 GAO report." January 2014. https://dl.dropboxusercontent.com/u/89158245/Appropriations%20report%20language%20for%20MECFS.pdf

[487] The CDC conducted a $4 million education awareness campaign in 2006-2007. Patients felt that the campaign did more harm than good by branding an erroneous picture of the disease. Background, awareness campaign materials and media communications used include:

- Centers for Disease Control and Prevention. "Home." *Chronic Fatigue Syndrome.* https://web.archive.org/web/20071005224825/http://www.cdc.gov/cfs/ Page undated. Page available in 2007.
- Centers for Disease Control and Prevention. "Brochures." *Chronic Fatigue Syndrome.* Page undated. Page available in 2007. https://web.archive.org/web/20071026155544/http://www.cdc.gov/cfs/brochures.htm
- Centers for Disease Control and Prevention CDC Newsroom. "Press Briefings Transcripts." *CDC Newsroom.* November 3, 2006. http://www.cdc.gov/media/transcripts/t061103.htm
  Transcript of Press Club Event to launch campaign
- Centers for Disease Control and Prevention CDC Newsroom. "Press Release." *CDC Newsroom.* November 3, 2006.. http://www.cdc.gov/media/pressrel/r061103.htm Press Release for the Public Awareness Campaign
- Centers for Disease Control and Prevention. "CDC News. Launches First-Ever Chronic Fatigue Syndrome Awareness Campaign." *CDC in the News.* November 22, 2006. Page last modified November 22, 2006. http://www.cdc.gov/news/2006_11/cfs.htm
- Bazell, Robert. "Chronic fatigue is a real illness, gov't says." NBC Nightly News with Brian Williams. *NBCNews.* November 2, 2006. http://www.nbcnews.com/id/15535705/#.UsSjK_aE4YQ
- CFIDS Association of America."Chronic Fatigue Syndrome. Press Conference." CFIDS Association of America. 2006. https://web.archive.org/web/20070108012320/http://www.cfids.org/sparkcfs/press-conference.asp

Also see

- Reuters. "Criticizes CDC, NIH Handling of Chronic Fatigue Research." Reuters. 2000. Reuters report accessed on the The National CFIDS Foundation website. http://www.ncf-net.org/library/CriticizesCDC.htm
- CFIDS Association of America. "Agency Activities: CDC Scandal." CFIDS Association of America. Undated. Page archived in 2008. http://web.archive.org/web/20080829025914/http://cfids.org/advocacy/cdc-scandal.asp

[488] U.S. Centers for Disease Control and Prevention. "Diagnosis and Management of Chronic Fatigue Syndrome" *CDC Chronic Fatigue Syndrome.* CME created: June 27, 2012. Page last updated: May 16, 2014. http://www.cdc.gov/cfs/education/diagnosis/index.html
Page 3-9. The CME states that Oxford, Fukuda, ME-ICC, CCC and 2006 Pediatric Case Definition describe similar sets of patients and provides a single set of diagnostic and treatment recommendations.

[489] The following are examples of clinical one size fits all guidelines that are based on Fukuda and fail to require patients to have the hallmark symptoms of the disease.

- U.S. Centers for Disease Control and Prevention. "CDC CFS Toolkit." *CDC Chronic Fatigue Syndrome*. Last updated September 6, 2011. Last accessed April 8, 2015. http://www.cdc.gov/cfs/toolkit/index.html and http://www.cdc.gov/cfs/pdf/cfs-toolkit.pdf and http://www.cdc.gov/cfs/pdf/cfs-toolkit.pdf
- U.S. Centers for Disease Control and Prevention. "Diagnosis and Management of Chronic Fatigue Syndrome" *CDC Chronic Fatigue Syndrome.* CME created: June 27, 2012. Page last updated: May 16, 2014. http://www.cdc.gov/cfs/education/diagnosis/index.html

[490] U.S. Department of Health and Human Services. Office of Women's Health. "Chronic Fatigue Syndrome." Office of Women's Health. Last updated September 2014. http://www.womenshealth.gov/publications/our-publications/fact-sheet/chronic-fatigue-syndrome.html

[491] Family Doctor.org. "Chronic Fatigue Syndrome." Family Doctor.org, operated by American Academy of Family Physicians (AAFP). Last updated February 2014. http://familydoctor.org/familydoctor/en/diseases-conditions/chronic-fatigue-syndrome/symptoms.html

[492]WebMD. "Slideshow: A Visual Guide to Chronic Fatigue Syndrome." Last reviewed by WebMD on April 15, 2014. Last accessed February 1, 2015 http://www.webmd.com/chronic-fatigue-syndrome/ss/slideshow-cfs-overview. Also see http://www.webmd.com/chronic-fatigue-syndrome/chronic-fatigue-syndrome-topic-overview

[493] Cunha, Burke. "Chronic Fatigue Syndrome." Chief editor Bronze, M. *Medscape*. Updated August 29, 2014. . http://emedicine.medscape.com/article/235980-overview
The article states "The cause of CFS is unknown, but the disorder is probably an infectious disease with immunologic manifestations."

[494] Mayo Clinic staff. "Chronic Fatigue Syndrome." Mayo Clinic. July 1, 2014. http://www.mayoclinic.org/diseases-conditions/chronic-fatigue-syndrome/basics/risk-factors/con-20022009

[495] Sawchuk C. Buchwald D. "Chronic Fatigue Syndrome." Epocrates (An AthenaHealth Company.) Last updated May 2014. Last accessed February 3, 2015. https://online.epocrates.com/noFrame/showPage?method=diseases&MonographId=277&ActiveSectionId=32 and https://online.epocrates.com/u/2911277/chronic+fatigue+%20syndrome

[496] U.S. Centers for Disease Control and Prevention. "CDC CFS Toolkit." *CDC Chronic Fatigue Syndrome*. Last updated September 6, 2011. Last accessed April 8, 2015. http://www.cdc.gov/cfs/toolkit/index.html and http://www.cdc.gov/cfs/pdf/cfs-toolkit.pdf

[497] WebMD. "Slideshow: A Visual Guide to Chronic Fatigue Syndrome." Last reviewed by WebMD on April 15, 2014. Last accessed February 1, 2015 http://www.webmd.com/chronic-fatigue-syndrome/ss/slideshow-cfs-overview. Also see http://www.webmd.com/chronic-fatigue-syndrome/chronic-fatigue-syndrome-topic-overview

[498] Cunha, Burke. "Chronic Fatigue Syndrome." Chief editor Bronze, M. *Medscape*. Updated August 29, 2014. . http://emedicine.medscape.com/article/235980-overview
This site states that the following are not exclusionary: "Any condition defined primarily by symptoms that cannot be confirmed by diagnostic laboratory tests, including fibromyalgia, anxiety disorders, somatoform disorders, nonpsychotic or melancholic depression, neurasthenia, and multiple chemical sensitivity disorder "
This means that patients with somatoform illness, neurasthenia and some other forms of mental illness can be included in the CFS label.

[499] U.S. Centers for Disease Control and Prevention. "Diagnosis and Management of Chronic Fatigue Syndrome" *CDC Chronic Fatigue Syndrome.* CME created: June 27, 2012. Page last updated: May 16, 2014. http://www.cdc.gov/cfs/education/diagnosis/index.html
Chapter 2 Page 6 asks a question "The following illnesses exclude consideration of CFS" According to the CME, the correct answer is Schizophrenia. The other choices include "a) satisfactorily treated hypothyroidism, b)major depressive disorder, c) irritable bowel syndrome or d) All of the above." But according to Fukuda, certain forms of major depression are exclusionary.

[500] Mayo Clinic staff. "Chronic Fatigue Syndrome." Mayo Clinic. July 1, 2014. Last accessed February 1, 2015. http://www.mayoclinic.org/diseases-conditions/chronic-fatigue-syndrome/basics/alternative-medicine/con-20022009
The site states, "It's difficult to determine whether these therapies actually work, partly because the symptoms of chronic fatigue syndrome often are linked to mood and can vary from day to day."

[501] U.S. Centers for Disease Control and Prevention. "Early Life Stress and Adult CFS." *CDC Chronic Fatigue Syndrome Website*. Page last updated: October 31, 2011. Page last reviewed: November 5, 2014. Last accessed February 1, 2015. Also see
Jones, James. "Emergency Preparedness: Considerations in Chronic Fatigue Syndrome." U.S. Centers for Disease Control and Prevention. August 18, 2011. https://web.archive.org/web/20131110131825/http://www.bt.cdc.gov/coca/calls/2011/callinfo_081811.asp and https://web.archive.org/web/20130331070124/http://www.bt.cdc.gov/coca/summaries/pdf/08_18_11_ChronicFatigue_Transcript_FIN.pdf (Transcript)
This CME, produced by the Centers for Disease Control and Prevention, was intended to educate emergency preparedness staff on the needs of patients with Chronic Fatigue Syndrome. But on page 8, they suddenly start to discuss the problem of early abuse and stresses. While clearly stress has a negative impact on a variety of chronic conditions, I'd question whether this text would ever be seen in an article on cancer.
The specific comments made are:

- "There is a wrinkle, it's a sad wrinkle but it's a powerful wrinkle in the story which makes things even worse. So we now know, and many studies attest to the fact, that individuals who are subjected to various types of adversity early in life, neglect, abuse, it could be the death of a parent, are at greatly increased risk for having stress related disorders later in life and moreover, unfortunately they will often replicate the conflictual and abusive situations in which they grew up. It causes them to lead adult lives characterized either by isolation or conflict. (00:38:25)"

- "When these people have children, the pattern can often be replicated and this is how it passes through the generations. The point for today however is that when something like a natural disaster strikes, it put tremendous stress on this already very stressful, vulnerable system and it makes all the stressors that have been going on chronically much, much worse. (00:38:50)"

[502] American Family Physician. Information from your Family Doctor. Chronic fatigue syndrome." American Family Physician. October 15, 2012; 86(6). http://www.aafp.org/afp/2012/1015/p741-s1.html
This article states *"Childhood trauma (for example, physical or sexual abuse) may raise the risk of getting it."*

[503] Sawchuk C. Buchwald D. "Chronic Fatigue Syndrome." Epocrates (An AthenaHealth Company.) Last updated May 2014. Last accessed February 3, 2015. https://online.epocrates.com/noFrame/showPage?method=diseases&MonographId=277&ActiveSectionId=32 and https://online.epocrates.com/u/2911277/chronic+fatigue+%20syndrome

[504] Cleveland Clinic Center for Continuing Education. CME Issued September 19, 2011. Expired Sept. 19, 2014. http://web.archive.org/web/20140713032224/http://www.clevelandclinicmeded.com/online/casebased/decisionmaking/chronic-fatigue/ . Full course no longer accessible.

This CME stated, "Studies have shown that all of the following are associated with a good outcome: low fatigue severity at baseline, a sense of control over symptoms, and no physical attribution for the syndrome. On the other hand, the following are associated with a poorer prognosis: longer duration of illness, depression and anxiety, higher level of fatigue, and attributing the syndrome to a physical cause."

[505] Yancey J, Thomas S. "Chronic Fatigue Syndrome: Diagnosis and Treatment." *American Family Physician* October 15, 2012; 86(8):741-746. PMID: 23062157 http://www.aafp.org/afp/2012/1015/p741.html

The article stated, "Despite the positive results with CBT and graded exercise therapy, the effects are usually moderate and rarely lead to resolution of CFS. Patients with poor social adjustment, a strong belief in an organic cause for fatigue, or some sort of sickness benefit (i.e., financial incentive) tend to have worse responses to therapy. Unlike with many other illnesses, membership in a CFS support group was associated with worse outcomes."

[506] U.K National Institute for Health and Care Excellence (NICE). Chronic fatigue syndrome/myalgic encephalomyelitis (or encephalopathy). Diagnosis and management of CFS/ME in adults and children. (NICE clinical guideline 53). August 2007. http://guidance.nice.org.uk/CG53

[507] Multiple locations on the CDC CFS website provide information on diagnosis but generally say the same thing. The CDC sites include

- U.S. Centers for Disease Control and Prevention. "Diagnosis and Management of Chronic Fatigue Syndrome" *CDC Chronic Fatigue Syndrome.* CME created: June 27, 2012. Page last updated: May 16, 2014. http://www.cdc.gov/cfs/education/diagnosis/index.html
- U.S. Centers for Disease Control and Prevention. "CDC Toolkit – Making a Diagnosis" *Chronic Fatigue Syndrome.* October 15, 2010. http://www.cdc.gov/cfs/toolkit/diagnosis.html

[508] UpToDate. "About Us." UpToDate by Wolters Kluwer Health. 2014. http://www.uptodate.com/home/about-us
According to it's website, UpToDate is a "physician-authored clinical decision support resource which clinicians trust to make the right point-of-care decisions" and is provided in cooperation with a number of medical associations including American Academy of Allergy, Asthma and Immunology, American College of Rheumatology, American Congress of Obstetricians and Gynecologists, American Gastroenterological Association, The Endocrine Society and its Hormone Health Network and Society of General Internal Medicine. UpToDate is also recommended by the American Academy of Family Physicians.

[509] Gluckman, Stephen. "Patient information: Chronic fatigue syndrome (Beyond the Basics)." Edited by Weller, P. *UpToDate.*

- Last updated February 24, 2015. Last accessed March 31, 2015. http://www.uptodate.com/contents/clinical-features-and-diagnosis-of-chronic-fatigue-syndrome-systemic-exertion-intolerance-disease
- Last updated March 19, 2014 Lsat accessed March 31, 2015 http://www.uptodate.com/contents/treatment-of-chronic-fatigue-syndrome-systemic-exertion-intolerance-disease
- Last updated February 24, 201. Last accessed March 31, 2015. http://www.uptodate.com/contents/chronic-fatigue-syndrome-systemic-exertion-intolerance-disease-beyond-the-basics

This site stated "Chronic fatigue syndrome is usually diagnosed based upon a medical history and physical examination. Blood or urine testing may be done to rule out other conditions, but are not needed to diagnose CFS. In order to be diagnosed with CFS, you must have unexplained, persistent, or relapsing fatigue, plus a number of the additional problems listed above"

[510] Cleveland Clinic Center for Continuing Education. CME Issued September 19, 2011. Expired Sept. 19, 2014. http://web.archive.org/web/20140713032224/http://www.clevelandclinicmeded.com/online/casebased/decisionmaking/chronic-fatigue/ . This course is no longer accessible.

The document stated "Not only are there no characteristic physical signs to help diagnose CFS, but there are no typical abnormalities seen on lab studies. The diagnosis relies solely on the patient history and exclusion of other etiologies for the patient's symptoms. There are no specific lab tests or clinical measurements required to meet the

CDC case definition for CFS, though a number of tests are recommended for their negative predictive value for ruling out other disorders. The case definition is widely used to aide diagnosis in the clinic as well as for research."

511 Examples of diagnostic recommendations in various information sources

- U.S. Centers for Disease Control and Prevention. "Diagnosis and Management of Chronic Fatigue Syndrome" *CDC Chronic Fatigue Syndrome.* CME created: June 27, 2012. Page last updated: May 16, 2014. http://www.cdc.gov/cfs/education/diagnosis/index.html and http://www.cdc.gov/cfs/education/diagnosis/course.html (direct link to course)

  Chapter 2 (page 1) states, "A provisional diagnosis of CFS is the beginning of an attempt to identify a plethora of possible underlying diseases. Currently, a CFS diagnosis can be made only after a thorough physical and mental status exam and appropriate laboratory testing to rule out diseases that may be responsible for the patient's symptoms and for which specific treatments exist."

  Chapter 2 (page 6) includes a question on what diseases are exclusionary. major depressive disorder is a choice but is not the correct one. This is surprising since Fukuda says it is exclusionary.
- American Family Physician. Information from your Family Doctor. Chronic fatigue syndrome." American Family Physician. October 15, 2012; 86(6). http://www.aafp.org/afp/2012/1015/p741-s1.html
  This article stated
  - *"Chronic fatigue syndrome (CFS) is a disorder that causes you to be very tired. It does not go away with rest."*
  - *"You can be diagnosed with CFS only if other diseases have been ruled out. Your doctor may want to do blood or urine tests, or tests for other diseases based on your symptoms."*
- Family Doctor.org. "Chronic Fatigue Syndrome." Family Doctor.org, operated by American Academy of Family Physicians (AAFP). Last updated February 2014. http://familydoctor.org/familydoctor/en/diseases-conditions/chronic-fatigue-syndrome/diagnosis-tests.html

  The site states "CFS is complicated and difficult to diagnose. Some people have a hard time accepting CFS as a disease. It's important to remember that your fatigue is real and that you can work with your doctor to improve your symptoms. The first step is to see if there is any other explainable cause for your fatigue. Your doctor will probably want to review your symptoms and medical history, and give you a physical exam. Your doctor may also want to do some blood tests, but lab testing is not often helpful in the diagnosis of CFS."
- Cunha, Burke. "Chronic Fatigue Syndrome." Chief editor Bronze, M. *Medscape*. Updated August 29, 2014. . http://emedicine.medscape.com/article/235980-overview

  This site states, "According to the Centers for Disease Control and Prevention (CDC), in order to receive a diagnosis of CFS, a patient must (1) have severe chronic fatigue of at least 6 months' duration, with other known medical conditions excluded by clinical diagnosis, and (2) concurrently have 4 or more of the following symptoms. The CDC case definition also states that any unexplained abnormality detected on examination or other testing that strongly suggests an exclusionary condition must be resolved before further classification is attempted."
- U.K National Institute for Health and Care Excellence (NICE). *Chronic fatigue syndrome/myalgic encephalomyelitis (or encephalopathy). Diagnosis and management of CFS/ME in adults and children.* (NICE clinical guideline 53). August 2007. http://guidance.nice.org.uk/CG53 Page 16.

512 U.K. National Health Service "Improving Access to Psychological Therapies(IAPT): Medically Unexplained Symptoms/ Functional Symptoms." U.K. National Health Service. July 2014. http://www.iapt.nhs.uk/silo/files/medically-unexplained-symptoms-postive-practice-guide-2014.pdf

This guide includes CFS as one type of medically unexplained symptom which it also refers to as functional syndromes. Regarding testing, the document states: "Ongoing referral and testing serves to increase patients' anxiety and can be iatrogenic in that it prevents patients from moving forward into appropriate treatment." The guidelines goes on to state that CBT and GET are the appropriate treatments.

The members of the IAPT Medically Unexplained Symptoms Evaluation Task and Finish Group include Professor Mona Moss-Morris and Professor Trudie Chalder, two authors who have authored papers on CFS. Professor Peter White provided additional feedback and comments

Other articles that advocate for this approach include:

- Harvey S, Wessely S. "Chronic fatigue syndrome: identifying zebras amongst the horses." *BMC Me*d October 2009; 7: 58. PMID: 19818158. http://dx.doi.org/10.1186/1741-7015-7-58

  The authors stated, "Yet if the search for unlikely 'zebra' causes of fatigue goes on too long, the risk of iatrogenic harm increases and the opportunity for early focused treatment of CFS may be lost." Note – The most commonly noted example of iatrogenic harm is the harm that results when additional testing encourages patients to think they might have an organic illness.

  The authors also stated, "Depression is very common amongst those with fatigue with recent studies using the British birth cohorts showing over 70% of adults reporting CFS have evidence of psychiatric disorder prior to their fatigue symptoms beginning."

  The authors go on to state that a "simple mental state examination appears to remain the most productive single investigation in any new person presenting with unexplained fatigue."

- Harvey S, Wessely S. 'Tired All the Time? Can new research on fatigue help clinicians?" *British Journal of General Practice.* April 2009; 59(561): 237-239. http://dx.doi.org/10.3399/bjgp09X420284
  Gives advise to clinicians that reinforces this same recommendation and also proposes risk factors that include psychologically or behaviorally factors like previous psychiatric disorder, emotional instability, being overactive as a child, a hyperactive or action-prone personality
- Page L, Wessely S. "Medically unexplained symptoms: exacerbating factors in the doctor–patient encounter." *J R Soc Med* May 2003; 96(5): 223-227. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC539474/
  CFS is included as an example of MUS. Includes discussion of issues with diagnostic practices

[513] Frances, A. "Diagnostic Ethics: Harms vs Benefits of Somatic Symptom Disorder." *The Blog*. Huffington Post, December 16, 2013. Updated February 15, 2014. http://www.huffingtonpost.com/allen-frances/diagnostic-ethics-harms-v_b_4450653.html Dr. Frances discusses the guidelines by the American Association of Family Physicians(AAFP), which urges doctors to make early diagnoses of somatoform disorders in order to save time and to reduce costs. The American Association of Family Physicians Clinical Guidelines Website (http://www.aafp.org/medical-school-residency/program-directors/curriculum.html) provides a list of Curriculum Guidelines, including one for for "Human Behavior and Mental Health." That guideline includes the following paper for Somatoform Disorders

- Oyama O, Paltoo C, Greengold J, "Somatoform Disorders." *Am Fam Physician.* (a journal of the American Academy of Family Physicians) November 1, 2007; Nov 1; 76(9): 1333-1338. http://www.aafp.org/afp/2007/1101/p1333.html
  The Oyama paper states "These disorders should be considered early in the evaluation of patients with unexplained symptoms to prevent unnecessary interventions and testing. Treatment success can be enhanced by discussing the possibility of a somatoform disorder with the patient early in the evaluation process, limiting unnecessary diagnostic and medical treatments, focusing on the management of the disorder rather than its cure, using appropriate medications and psychotherapy for comorbidities, maintaining a psychoeducational and collaborative relationship with patients, and referring patients to mental health professionals when appropriate."

[514] Spratt E. "Somatoform Disorder." Edited by Pataki, C. Medscape. Last updated Mar 4, 2014. http://emedicine.medscape.com/article/918628-overview#a1
Background information and management guidelines for somatoform illness

[515] Jutel A. "Medically unexplained symptoms and the disease label." *Social Theory & Health* Vol. 8, 3, 229–245 http://dx.doi.org/10.1057/sth.2009.21

[516] Examples of generalized treatment recommendations

- U.S. Centers for Disease Control and Prevention. "CDC CFS Toolkit." *CDC Chronic Fatigue Syndrome*. Last updated September 6, 2011. Last accessed April 8, 2015. http://www.cdc.gov/cfs/toolkit/index.html and http://www.cdc.gov/cfs/pdf/cfs-toolkit.pdf
  CDC CFS Toolkit recommends against drugs and for therapies like massage, acupuncture, deep breathing and the use of organizers and word games to help with cognitive issues.
- U.S. Centers for Disease Control and Prevention. "Diagnosis and Management of Chronic Fatigue Syndrome" *CDC Chronic Fatigue Syndrome.* CME created: June 27, 2012. Page last updated: May 16, 2014. http://www.cdc.gov/cfs/education/diagnosis/index.html Includes a discussion of dietary sensitivities
- Mayo Clinic staff. "Chronic Fatigue Syndrome." Mayo Clinic. July 1, 2014. http://www.mayoclinic.org/diseases-conditions/chronic-fatigue-syndrome/basics/lifestyle-home-remedies/con-20022009 and http://www.mayoclinic.org/diseases-conditions/chronic-fatigue-syndrome/basics/treatment/con-20022009
  Site recommends anti-depressants for depression and sleep, sleeping pills, graded exercise and counseling to improve outlook by feeling more in control. Also recommends that patients reduce stress, improve sleep habits and potentially acupuncture and massage for pain.

[517] Ibid. Mayo Clinic recommendation for anti-depressants and sleeping pills.
Other examples

- U.S. Centers for Disease Control and Prevention. "A Case Based Approach to Chronic Fatigue Syndrome." (CME). Centers for Disease Control and Prevention. Released April 19, 2013. http://www.cdc.gov/cfs/news/features/medscape-case-based.html and http://www.medscape.org/viewarticle/782106 and http://www.medscape.org/viewarticle/782106_slide (slides)
  Focuses on sleep hygiene, pain management, exercise, stress management, and CBT but does also include a discussion on the treatment of orthostatic intolerance
- Family Doctor.org. "Chronic Fatigue Syndrome." Family Doctor.org, operated by American Academy of Family Physicians (AAFP). Last updated February 2014. http://familydoctor.org/familydoctor/en/diseases-conditions/chronic-fatigue-syndrome/diagnosis-tests.html
  The site states "Medicine can treat some of the symptoms, such as muscle aches, sleep problems, anxiety and depression."

[518] For further information on the forms of CBT and GET used in PACE, see PACE trial manuals, available through the PACE Trial information website http://www trial.org/trialinfo/

- CBT Manual
  Burgess M, Chalder T. "PACE Manual for Therapists. Cognitive Behavioral Therapy for CFS/ME." MREC Version 2. November 2004. http://www.pacetrial.org/docs/cbt-therapist-manual.pdf
  The manual (P81) states, "It is important to include the precipitating factors, e.g., illness, life-events, working excessively hard, perfectionist personality etc. It is also important to discuss the maintaining factors, e.g., erratic or reduced activities, disturbed sleep patterns, unhelpful illness beliefs and any other unhelpful cognitions etc."
- GET Manual
  PACE Trial Management Group. "PACE Manual for Therapists. Graded Exercise Therapy for CFS/ME.".Version 2. http://www.pacetrial.org/docs/get-therapist-manual.pdf .
  The manual states "GET assumes that CFS/ME is perpetuated by deconditioning (lack of fitness), reduced physical strength and altered perception of effort consequent upon reduced physical activity" (Page 20) and also states "Planned physical activity and not symptoms are used to determine what the participant does." (Page 21)

Also see:

- St Bartholomew's Hospital. "Graded Exercise Therapy. A self-help guide for those with chronic fatigue syndrome/myalgic encephalomyelitis." Produced by Medical Illustration, St Bartholomew's Hospital. Copyrighted by Barts and the London NHS Trust. August 2009. http://www.drleigh.org/wp-content/uploads/2008/12/chronic-fatigue-exercise-program-specifics.pdf
  Note that this Toolkit is referenced by the CDC Toolkit.
  - Centers for Disease Control. "Chronic Fatigue Syndrome. A Toolkit for Medical Providers." No date listed. Website last updated on September 6, 2011. http://www.cdc.gov/cfs/pdf/cfs-toolkit.pdf. Page 12.

[519] White PD, Goldsmith KA, Johnson AL, Potts L, Walwyn R, DeCesare JC, Baber HL, Burgess M, Clark LV, Cox DL, Bavinton J, Angus BJ, Murphy G, Murphy M, O'Dowd H, Wilks D, McCrone P, Chalder T, Sharpe M. "Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): a randomised trial." *The Lancet* March 5, 2011; 377(9768): 823-836. PMID: 21334061. http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(11)60096-2/fulltext

- The PACE trial, done in patients that met the Oxford definition, tested cognitive behavioral therapy (CBT) and graded exercise therapy (GET) which were used "on the basis of the fear avoidance theory of chronic fatigue syndrome" that "assume that the syndrome is perpetuated by reversible physiological changes of deconditioning and avoidance of activity." (Page 825)
- Author's note: This theory regards chronic fatigue syndrome as being reversible and that cognitive responses (fear of engaging in activity) and behavioural responses (avoidance of activity) are linked and interact with physiological processes to perpetuate fatigue."

[520] MedPageToday'sKevinMD. "MKSAP: 32-year-old woman with chronic fatigue syndrome." February 22, 2014. http://www.kevinmd.com/blog/2014/02/mksap-32yearold-woman-chronic-fatigue-syndrome.html
This site is extracted from the American College of Physicians' Medical Knowledge Self Assessment (MKSAP16) https://mksap16.acponline.org/
The section on general issues stated, "CBT in this setting is targeted in part at breaking the cycle of effort avoidance, decline in physical conditioning, and increase in fatigue and can work well in combination with graded exercise in this regard. CBT reduces fatigue and improves functional status."

[521] Cleveland Clinic Center for Continuing Education. CME Issued September 19, 2011. Expired Sept. 19, 2014. http://web.archive.org/web/20140713032224/http://www.clevelandclinicmeded.com/online/casebased/decisionmaking/chronic-fatigue/
The course no longer accessible. The following text is from the version that expired in 2014.

- Question 3 stated "Another diagnostic term, myalgic encephalomyelitis (ME) is frequently used for CFS outside the US and also implies a known pathophysiology, but ME has its own case definition, separate from CFS.(4) " The reference given is Prins J, van der Meer J, Bleijenberg G. "Chronic fatigue Syndrome." *The Lancet* January 28, 2006; 367(9507): 346-355. PMID: 16443043. http://dx.doi.org/10.1016/S0140-6736(06)68073-2 but the Prins article does not seem to suggest that ME has a different case definition and its statements about a different classification in WHO reflect the issues in the UK described in the dictionary section
- Question 8 on graded exercise stated that "[CBT's] goal is to help the patient gradually return to their normal physical activities. Other interventions such as antidepressants may help with associated mood disorders but have not been demonstrated to be beneficial in treating the core symptoms of CFS in those without depression."
- Question 9 on CBT stated "Cognitive behavioral therapy (CBT) aims to change the cognitive responses that are thought to perpetuate CFS, such as fears about symptoms or activity, and social and emotional obstacles."
- Question 10 on Outcomes stated "Studies have shown that all of the following are associated with a good outcome: low fatigue severity at baseline, a sense of control over symptoms, and no physical attribution for the syndrome. On the other hand, the following are associated with a poorer prognosis: longer duration of illness, depression and anxiety, higher level of fatigue, and attributing the syndrome to a physical cause."

[522] Sawchuk C. Buchwald D. "Chronic Fatigue Syndrome." Epocrates (An AthenaHealth Company.) Last updated May 2014. Last accessed February 3, 2015. https://online.epocrates.com/noFrame/showPage?method=diseases&MonographId=277&ActiveSectionId=41 and https://online.epocrates.com/u/2911277/chronic+fatigue+%20syndrome

[523] Gluckman, Stephen. "Patient information: Chronic fatigue syndrome (Beyond the Basics)." Edited by Weller, P. *UpToDate.*

- Last updated February 24, 2015. Last accessed March 31, 2015. http://www.uptodate.com/contents/clinical-features-and-diagnosis-of-chronic-fatigue-syndrome-systemic-exertion-intolerance-disease
- Last updated March 19, 2014 Last accessed March 31, 2015 http://www.uptodate.com/contents/treatment-of-chronic-fatigue-syndrome-systemic-exertion-intolerance-disease
- Last updated February 24, 201. Last accessed March 31, 2015. http://www.uptodate.com/contents/chronic-fatigue-syndrome-systemic-exertion-intolerance-disease-beyond-the-basics

The site states, "The sessions focus on discussing beliefs and behaviors that can interfere with your recovery. CBT will not cure CFS, but it can help you to cope better with your fatigue."

[524] U.S. Centers for Disease Control and Prevention. "Diagnosis and Management of Chronic Fatigue Syndrome" *CDC Chronic Fatigue Syndrome.* CME created: June 27, 2012. Page last updated: May 16, 2014. http://www.cdc.gov/cfs/education/diagnosis/index.html and http://www.cdc.gov/cfs/education/diagnosis/course.html (Chapter 4, page 5 and reference #27 and #28. Note that the course lists reference 27 but reference #28 includes CBT references.)

Page 5 of the CME states, "Cognitive behavioral therapy (CBT) as a symptom management tool is beneficial in many chronic illnesses and diseases, including CFS. Examples of specific cognitive strategies include education on coping and behavioral modification to improve physical and psychological well-being. The goal of CBT is to help the patient understand their illness and to change perceptions, beliefs and behaviors that can contribute to the impact of symptoms. CBT is an important adjunctive therapy in cardiovascular disease, diabetes and cancer, and is central to therapy for many mental health conditions, such as depression and anxiety."

Page 5 of the CME also states "Optimally, CBT results in better adaptation to illness and improved quality of life. Controlled clinical trials in CFS have shown that CBT can improve fatigue and activity levels, but has less impact on other symptoms. People with CFS may try to do more than they can manage which could exacerbate symptoms. Specifically, they engage in a "push-crash" cycle in which they do too much, crash, rest, start to feel a little better, do too much once again, and so on."

Note that the references used to support the CBT recommendation on this CME are for studies that predominantly took a "biopsychosocial" approach to CFS where CBT is used to reverse false illness beliefs. The citations listed in references 27 and 28 include:

- Deale A, Husain K, Chalder T, Wessely S. "Long-term outcome of cognitive behavior therapy versus relaxation therapy for chronic fatigue syndrome: a 5-year follow-up study." *Am J Psychiatry* December 2001; 158(12): 2038-42. PMID: 11729022. http://www.ncbi.nlm.nih.gov/pubmed/11729022 and http://www.simonwessely.com/Downloads/Publications/CFS/139.pdf
- Brooks SK, Rimes KA, Chalder T. "The role of acceptance in chronic fatigue syndrome." *J Psychosom Res*. December 2011;71(6): 411-5. PMID: 22118384 http://dx.doi.org/10.1016/j.jpsychores.2011.08.001

  This paper stated "At baseline, lack of acceptance was the key factor associated with impaired physical functioning and work and social adjustment. Lack of acceptance and doubts about actions were associated with fatigue in a multiple regression analysis. At discharge and follow-up patients showed significantly increased acceptance, as well as reduced Concern over Mistakes, less fatigue and impairment of physical functioning, and improved work and social adjustment."
- Prins JB, Bleijenberg G, Bazelmans E, Elving LD, de Boo TM, Severens JL. "Cognitive behaviour therapy for chronic fatigue syndrome: a multicentre randomised controlled trial." *Lancet.* March 17, 2001; 357(9259): 841-7. PMID: 11265953 http://dx.doi.org/10.1016/S0140-6736(00)04198-2
- Vercoulen JH, Swanink CM, Fennis JF, Galama JM, van der Meer JW, Bleijenberg G. "Prognosis in chronic fatigue syndrome: a prospective study on the natural course." *J Neurol Neurosurg Psychiatry.* 1996;60:489-94. PMID: 8778251. http://jnnp.bmj.com/content/60/5/489.long

  The paper stated, "Sociodemographic variables or treatment by specialists and alternative practitioners did not predict improvement. Predictors of improvement were: subjective sense of control over symptoms, less fatigue, shorter duration of complaints, and a relative absence of physical attributions."
- Wallman KE, Morton AR, Goodman C, Grove R, Guilfoyle AM. "Randomised controlled trial of graded exercise in chronic fatigue syndrome." *Med J Aust.* May 3, 2004;180(9): 444-8. PMID: 15115421. https://www.mja.com.au/journal/2004/180/9/randomised-controlled-trial-graded-exercise-chronic-fatigue-syndrome
- Knoop H, Bleijenberg G, Gielissen MF, van der Meer JW, White PD. "Is a full recovery possible after cognitive behavioural therapy for chronic fatigue syndrome?" *Psychother Psychosom.* 2007;76(3): 171-6. PMID: 17426416. http://dx.doi.org/10.1159/000099844

[525] White PD, Goldsmith KA, Johnson AL, Potts L, Walwyn R, DeCesare JC, Baber HL, Burgess M, Clark LV, Cox DL, Bavinton J, Angus BJ, Murphy G, Murphy M, O'Dowd H, Wilks D, McCrone P, Chalder T, Sharpe M. "Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): a randomised trial." *The Lancet* March 5, 2011; 377(9768): 823-836. PMID: 21334061. http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(11)60096-2/fulltext

[526] PACE Trial Management Group. "PACE Manual for Therapists. Graded Exercise Therapy for CFS/ME.".Version 2. http://www.pacetrial.org/docs/get-therapist-manual.pdf .

The PACE manual for GET states, "The essence of GET is to help the participant to gradually engage and participate in physical activity and aerobic exercise… It is their planned physical activity, and not their symptoms, that determine what they are asked to do, although activity is mutually reviewed on a regular basis and plans may be adjusted depending on general health and symptoms." (Page 18)

The manual also states, "Participants are encouraged to see symptoms as temporary and reversible, as a result of their current physical weakness, and not as signs of progressive pathology. A mild and transient increase in symptoms is explained as a normal response to an increase in physical activity." (Page 18)

[527] Cleveland Clinic Center for Continuing Education. CME Issued September 19, 2011. Expired Sept. 19, 2014. http://web.archive.org/web/20140713032224/http://www.clevelandclinicmeded.com/online/casebased/decisionmaking/chronic-fatigue/

Full course no longer accessible. Question 8 of the expired course was on graded exercise and it stated, "The goal of therapy in CFS is to improve fatigue and increase activity level. A systematic review of 15 randomized control trials found evidence that graded exercise therapy (GET) is efficacious in improving fatigue and physical activity in patients with CFS.(9) The Comparison of Adaptive Pacing Therapy, Cognitive Behavior Therapy, and Specialist Medical Care for Chronic Fatigue Syndrome (PACE) trial was a randomized trial that demonstrated the efficacy of GET, when added to specialist medical care, in improving outcomes in CFS.(10) Graded exercise therapy is a multi-dimensional treatment method that combines patient education with exercise. Its goal is to help the patient gradually return to their normal physical activities."

[528] Mayo Clinic staff. "Chronic Fatigue Syndrome." Mayo Clinic. July 1, 2014. http://www.mayoclinic.org/diseases-conditions/chronic-fatigue-syndrome/basics/treatment/con-20022009

[529] Gluckman, Stephen. "Patient information: Chronic fatigue syndrome (Beyond the Basics)." Edited by Weller, P. *UpToDate.*

- Last updated February 24, 2015. Last accessed March 31, 2015. http://www.uptodate.com/contents/clinical-features-and-diagnosis-of-chronic-fatigue-syndrome-systemic-exertion-intolerance-disease
- Last updated March 19, 2014 Lsat accessed March 31, 2015 http://www.uptodate.com/contents/treatment-of-chronic-fatigue-syndrome-systemic-exertion-intolerance-disease
- Last updated February 24, 201. Last accessed March 31, 2015. http://www.uptodate.com/contents/chronic-fatigue-syndrome-systemic-exertion-intolerance-disease-beyond-the-basics

[530] U.S. Centers for Disease Control and Prevention. "CDC CFS Toolkit." *CDC Chronic Fatigue Syndrome*. Last updated September 6, 2011. Last accessed April 8, 2015. http://www.cdc.gov/cfs/toolkit/index.html and http://www.cdc.gov/cfs/pdf/cfs-toolkit.pdf

[531] U.S. Department of Health and Human Services CFS Advisory Committee. CFSAC Meeting. *CFS Advisory Committee Website.* March 11, 2014 meeting. www.hhs.gov/advcomcfs/meetings/minutes/cfsac-minutes-march-11-a.pdf (P. 71)

Dr. Susan Levine (the chair of CFSAC and was the head of the CFSAC workgroup responsible for developing recommendations for education) stated, "We're not certain as to why a lot of these recommendations that we've made are lagging like for instance, you know, substitute the Canadian case definition for the outdated ones that appear and put a black box warning on there against physical exertion."

[532] Goudsmit E, Nijs J, Jason L, Wallman K. "Pacing as a strategy to improve energy management in myalgic encephalomyelitis/chronic fatigue syndrome: a consensus document." *Disability and Rehabilitation* June 2012; 34(13): 1140-1147. http://dx.doi.org/10.3109/09638288.2011.635746

[533] Action For ME. "M.E. 2008. What Progress? Initial findings of a national survey of over 2,760 people with M.E. focusing on their health and welfare." Action For ME. May 11-17, 2008. http://www.actionforme.org.uk/Resources/Action%20for%20ME/Documents/get-informed/ME%202008%20%20What%20progress.pdf

Eighty percent of patients found pacing to be helpful. (Page 12).

[534] Tucker, Miriam. "Addressing Fear of Exercise Cuts Chronic Fatigue…Perhaps." Medscape Medical News. January 21, 2015. Last accessed February 19, 2015. http://www.medscape.com/viewarticle/838452

[535] U.S. Centers for Disease Control and Prevention. "CDC CFS Toolkit." *CDC Chronic Fatigue Syndrome*. Last updated September 6, 2011. Last accessed April 8, 2015. http://www.cdc.gov/cfs/toolkit/get.html and http://www.cdc.gov/cfs/pdf/cfs-toolkit.pdf

[536] U.K National Institute for Health and Care Excellence (NICE). *Chronic fatigue syndrome/myalgic encephalomyelitis (or encephalopathy). Diagnosis and management of CFS/ME in adults and children.* (NICE clinical guideline 53). August 2007. http://guidance.nice.org.uk/CG53 Page 20,23

[537] U.S. Centers for Disease Control and Prevention. "CDC CFS Toolkit." *CDC Chronic Fatigue Syndrome*. Last updated September 6, 2011. Last accessed April 8, 2015. http://www.cdc.gov/cfs/toolkit/index.html and http://www.cdc.gov/cfs/pdf/cfs-toolkit.pdf

[538] Mayo Clinic staff. "Chronic Fatigue Syndrome." Mayo Clinic. July 1, 2014. http://www.mayoclinic.org/diseases-conditions/chronic-fatigue-syndrome/basics/treatment/con-20022009

[539] Some evidence suggests that some anti-depressants have anti-viral and anti-fungal properties, complicating the assessment of their therapeutic mechanism of action for this disease.
See Parker, W. "Antidepressants investigated for anti-viral, anti-fungal properties." *Scienceagog.com* McMurdo Media, Australia. July 28, 2012. http://www.scienceagogo.com/news/20120628185057data_trunc_sys.shtml
This topic was also cited in various articles in scientific literature

[540] Gluckman, Stephen. "Patient information: Chronic fatigue syndrome (Beyond the Basics)." Edited by Weller, P. *UpToDate.*

- Last updated February 24, 2015. Last accessed March 31, 2015. http://www.uptodate.com/contents/clinical-features-and-diagnosis-of-chronic-fatigue-syndrome-systemic-exertion-intolerance-disease
- Last updated March 19, 2014 Lsat accessed March 31, 2015 http://www.uptodate.com/contents/treatment-of-chronic-fatigue-syndrome-systemic-exertion-intolerance-disease
- Last updated February 24, 201. Last accessed March 31, 2015. http://www.uptodate.com/contents/chronic-fatigue-syndrome-systemic-exertion-intolerance-disease-beyond-the-basics

[541] Cunha, Burke. "Chronic Fatigue Syndrome." Chief editor Bronze, M. *Medscape*. Updated August 29, 2014. http://emedicine.medscape.com/article/235980-treatment and http://emedicine.medscape.com/article/235980-medication#showall

This site states "treatment is largely supportive and responsive to symptoms." It adds "Trials of antiviral agents have been ineffective in relieving the symptoms of chronic fatigue syndrome (CFS). Various medications have been shown to be ineffective, including steroids, liver extract, chelating agents, intravenous (IV) vitamins, vitamin B-12, and IV or oral vitamin or mineral supplements. Antidepressants have no major role to play in the treatment of CFS…. Antibiotics are used in patients with elevated immunoglobulin M (IgM)."

[542] Family Doctor.org. "Chronic Fatigue Syndrome." Family Doctor.org, operated by American Academy of Family Physicians (AAFP). Last updated February 2014. http://familydoctor.org/familydoctor/en/diseases-conditions/chronic-fatigue-syndrome/diagnosis-tests.html

[543] U.S. Centers for Disease Control and Prevention. "A Case Based Approach to Chronic Fatigue Syndrome." (CME). Centers for Disease Control and Prevention. Released April 19, 2013. http://www.cdc.gov/cfs/news/features/medscape-case-based.html and http://www.medscape.org/viewarticle/782106 and http://www.medscape.org/viewarticle/782106_slide (slides)

This CME discusses orthostatic intolerance and the use of drugs to treat it but this is often overlooked in most educational material, including other sections of the CDC site.

[544] U.K National Institute for Health and Care Excellence (NICE). *Chronic fatigue syndrome/myalgic encephalomyelitis (or encephalopathy). Diagnosis and management of CFS/ME in adults and children.* (NICE clinical guideline 53). August 2007. http://guidance.nice.org.uk/CG53 and http://www.nice.org.uk/guidance/cg53/evidence Chapter 1.4 "General management strategies after diagnosis" Page 18.

[545] On June 14, 2012, the CFSAC recommended that CFS Toolkit be removed from the CDC website. On Sept 10, 2012, the patient community submitted a position paper supporting the CFSAC recommendation and outlining the issues with the Toolkit and the negative impact the Toolkit has had on patients.

- U.S. Department of Health and Human Services CFS Advisory Committee. CFSAC Recommendations. CFS Advisory Committee. June 14, 2012. *CFS Advisory Committee Website* http://www.hhs.gov/advcomcfs/recommendations/06132012.html
- Patient Support Organizations and Advocates. "A Position Paper in Support of the CFSAC Recommendations on the Toolkit and Primer." Patient Support Organizations and Advocates. Sept 10, 2012. https://dl.dropboxusercontent.com/u/89158245/Position%20Toolkit%20IACFSME%20Primer%20Sept%2010.pdf

[546] U.K. Group on Scientific Research into Myalgic Encephalomyelitis (M.E.). "Inquiry into the status of CFS / M.E. and research into causes and treatment." (The Gibson Inquiry). U.K. Group on Scientific Research into Myalgic Encephalomyelitis (M.E.). Chaired by Dr. Ian Gibson. November, 2006.

- Report - www.erythos.com/gibsonenquiry/Docs/ME_Inquiry_Report.pdf and
- Press release - http://www.erythos.com/gibsonenquiry/Docs/Press_Release_26Nov06.rtf

The Press Release stated "NICE has just finished consulting on their draft guidelines for treating CFS/ME. These guidelines have been widely criticised by patient groups and by the APPG on ME. Chair Des Turner described them in a meeting last week as 'not fit for man nor beast' Dr Ian Gibson MP of the Inquiry described them as 'useless'."

[547] "Epidemic myalgic encephalomyelitis." *British Medical Journal* 3 June 1978; 1(6125): 1436–1437. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1604957/

This article was the lead article resulting from a symposium held in 1978 with the permission of the Council of the

Royal Society of Medicine. The full proceedings from the symposium were published later in the year in the Postgraduate Medical Journal as described below. As noted on page 1437 of the lead editorial "Epidemic myalgic encephalomyelitis", "Other terms that have been used to describe the disease were rejected as unsatisfactory for various reasons: the cardinal clinical features show that the disorder is an encephalomyelitis; "Iceland disease" is not specific enough; and "neuromyasthenia" suggests a relation to myasthenia gravis whereas the muscle fatigability is different, as are the electrophysiological findings. Indeed, the exhaustion and tiredness are similar to that described by patients with multiple sclerosis. From the patient's point of view the designation benign is also misleading, since the illness may be devastating. Originally the term was used because no deaths had been recorded from myalgic encephalomyelitis."

The full proceedings are available at:

- Postgraduate Medical Journal November 1978: 54(637): 709-774. http://pmj.bmj.com/content/54/637.toc#Articles

548 Ramsay, M. "Myalgic Encephalomyelitis: A Baffling Syndrome With a Tragic Aftermath." Published 1986. http://www.name-us.org/DefintionsPages/DefRamsay.htm#MYALGIC_ENCEPHALOMYELITIS_:_A_Baffling_Syndrome_With_a_Tragic_Aftermath

Ramsay stated, "The degree of physical incapacity varies greatly, but the dominant clinical feature of profound fatigue is directly related to the length of time the patient persists in physical effort after its onset; put in another way, those patients who are given a period of enforced rest from the onset have the best prognosis."

549 International Association for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis. "Chronic Fatigue Syndrome Myalgic Encephalomyelitis: A Primer for Clinical Practitioners 2014 Edition." International Association for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis. 2012, revised 2014. http://www.iacfsme.org/LinkClick.aspx?fileticket=iD3JkZAZhts%3d&tabid=509
The 2012 version was abstracted and placed onto Guidelines.gov - http://www.guideline.gov/content.aspx?id=38316

550 Carruthers BM, van de Sande MI, De Meirleir KL, Klimas NG, Broderick G, Mitchell T, Staines D, Powles ACP, Speight N, Vallings R, Bateman L, Bell DS, Carlo-Stella N, Chia J, Darragh A, Gerken A, Jo D, Lewis D, Light AR, Light K, Marshall-Gradisnik S, McLaren-Howard J, Mena I, Miwa K, Murovska M, Steven S. "Myalgic Encephalomyelitis – Adult and Paediatric: International Consensus Primer for Medical Practitioners." Co-editors B.M. Carruthers and M.I. van de Sande. Published by Carruthers and van de Sande, 2012. http://www.hetalternatief.org/ICC primer 2012.pdf

551 International Association for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis. "Chronic Fatigue Syndrome Myalgic Encephalomyelitis: A Primer for Clinical Practitioners 2014 Edition." International Association for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis. 2012, revised 2014. http://www.iacfsme.org/LinkClick.aspx?fileticket=iD3JkZAZhts%3d&tabid=509
The 2012 version was abstracted and placed onto Guidelines.gov - http://www.guideline.gov/content.aspx?id=38316

552 U.S. Department of Health and Human Services CFS Advisory Committee. CFSAC Meeting. October 4, 2012. *CFS Advisory Committee Website.* http://www.hhs.gov/advcomcfs/meetings/minutes/cfsac10042012.pdf

Mr. Krafchick asked three times if CDC intended to take the toolkit down. Dr. Belay of CDC stated "We have decided that we would still like to make it available." Krafchick said "So, despite our recommendation that it is not even close to perfect, you're keeping it up there?" Dr. Beth Unger's response was "Yes, I'm sorry."

553 The reason provided by CDC for not including a link to the IACFS/ME Primer is that CDC does not link to outside sources. But CDC has linked to St. Bartholomew's Hospital for information on GET in the CDC CFS Toolkit. St Bart's is a service associated with Peter White.

- U.S. Centers for Disease Control and Prevention. "CDC CFS Toolkit." *CDC Chronic Fatigue Syndrome*. Last updated September 6, 2011. Last accessed April 8, 2015. http://www.cdc.gov/cfs/toolkit/index.html and http://www.cdc.gov/cfs/pdf/cfs-toolkit.pdf
  The Toolkit states "The GET Guide 2008 by Chronic Fatigue Syndrome/ME Service at St. Bartholomew's Hospital can be helpful in structuring your graded exercise plan." (Page 12)

554 U.S. Department of Health and Human Services CFS Advisory Committee. CFSAC Meeting. CFS Advisory Committee Meeting. May 22, 2013. *CFS Advisory Committee Website* www.hhs.gov/advcomcfs/meetings/minutes/cfsacmay22_final_508.pdf
An example of CDC's resistance to input from CFSAC is on page 42.

Dr. Belay (CDC) stated, "We've revised the toolkit. It's not up on the website yet because it's going through a clearance process. That toolkit has been made consistent with rest of website, which has been reviewed by a subgroup of this committee." Mr. Krafchick (CFSAC member) stated, "Any chance we can see a copy of it when it's ready for publication or before it's ready for publication? "Dr. Belay stated, "We don't necessarily clear all information and content on the website through a committee." Mr. Krafchick stated, "I understand. I'm just asking if it would be possible for our review and comment as part of your process." Dr. Belay stated, "We haven't done that in the past. That's a very strange process for me to try to clear web content."

[555] U.S. Department of Health and Human Services CFS Advisory Committee. CFSAC Meeting. October 28-29, 2008. *CFS Advisory Committee Website.* https://wayback.archive-it.org/3919/20140324192720/http:/www.hhs.gov/advcomcfs/meetings/minutes/cfsac20081028min.pdf (Page 81)

[556] U.S. Department of Health and Human Services CFS Advisory Committee. CFSAC Meeting. October 28-29, 2008. *CFS Advisory Committee Website.* https://wayback.archive-it.org/3919/20140324192720/http:/www.hhs.gov/advcomcfs/meetings/minutes/cfsac20081028min.pdf (Page 81)

[557] Peterson TM, Peterson T, Emerson S, Regalbuto E, Evans M, Jason LA. "Coverage of CFS within U.S. Medical Schools." *Universal Journal of Public Health* 2013; 1(4): 177-179. http://www.hrpub.org/download/20131107/UJPH4-17600991.pdf

This paper stated, "Surveys were sent to personnel at 132 accredited U.S. medical schools and a total of 71 schools responded. The extent of coverage across the three domains was extremely limited. Only 29.6% of schools met the clinical criterion, 28.2% met the curricula criterion, and 15% met the research criterion. Only four of the 71 (5.6%) responding schools met criteria for all three domains. While the current study is preliminary, it points to significant gaps in the coverage of CFS among medical institutions, which is likely impacting the ability of physicians to fully acknowledge, understand, effectively treat, and find a cure for CFS."

[558] Taking ME Forward. "Medical Education in Scotland." Taking ME Forward. Sponsored by the 25% ME Group. 2014 http://www.25megroup.org/Campaignging/ME%20in%20Pariament/scottish/ME%20Education%20in%20Scotland37.doc

[559] Jutel A. "Medically unexplained symptoms and the disease label." *Social Theory & Health* Vol. 8, 3, 229–245 http://dx.doi.org/10.1057/sth.2009.21

[560] Brimmer D, Campbell C, Bonner, K, Lin J. "News from the CDC: chronic fatigue syndrome (CFS) and standardized patient videos — a novel approach to educating medical students about CFS." *Transl Behav Med.* December 2013; 3(4): 338–339. http://dx.doi.org/10.1007/s13142-013-0229-9 and http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3830016/

[561] M. Dimmock mailed CDC staff a number of times to determine whether PEM was presented as a required symptom in the standardized patients but did not get a response. In a private discussion with Dr. Unger at the IOM, Dr. Unger indicated that PEM was not a required symptom of the standardized patient, that PEM was not discussed in the video but that there would be supplemental material that would include info on PEM.

[562] Fayerman, Pamela. "Parting words – and hospital criticism – as Dr. Alison Bested leaves B.C., returns to Ontario." *Medicine Matters. Vancouver Sun.* Vancouver, Canada. July 22, 2014 http://blogs.vancouversun.com/2014/07/22/parting-words-and-hospital-criticism-as-dr-alison-bested-leaves-b-c-returns-to-ontario/

[563] Aetna. "Clinical Policy Bulletin. Chronic Fatigue Syndrome." Aetna. Created December 15, 1999. Last Review June 6, 2014. Number 0369. http://www.aetna.com/cpb/medical/data/300_399/0369.html
Policy discusses among other things, tilt table testing, which is considered experimental.

[564] Tricare. "Chronic Fatigue Syndrome Treatment." Tricare. Last updated October 9, 2014. http://www.tricare.mil/CoveredServices/IsItCovered/ChronicFatigueSyndrome.aspx

The policy states, "Benefits for Chronic Fatigue Syndrome (CFS) are limited by TRICARE, to relieving individual symptoms, such as prescription drugs for headaches or muscle pains. TRICARE doesn't cover tests used to diagnose CFS."

[565] My son's insurance company would only treat lab tests as in-network if they were ordered by a doctor in the state where the lab work was done. Tests ordered by his doctor from another state were treated as out-of-network.

[566] Ramsay, M. "Myalgic Encephalomyelitis: A Baffling Syndrome With a Tragic Aftermath." Published 1986. http://www.cfids-me.org/ramsay86.html

[567] International Association for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis. "Chronic Fatigue Syndrome Myalgic Encephalomyelitis: A Primer for Clinical Practitioners 2014 Edition." International Association for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis. 2012, revised 2014. http://www.iacfsme.org/LinkClick.aspx?fileticket=iD3JkZAZhts%3d&tabid=509

[568] Carruthers BM, van de Sande MI, De Meirleir KL, Klimas NG, Broderick G, Mitchell T, Staines D, Powles ACP, Speight N, Vallings R, Bateman L, Bell DS, Carlo-Stella N, Chia J, Darragh A, Gerken A, Jo D, Lewis D, Light AR, Light K, Marshall-Gradisnik S, McLaren-Howard J, Mena I, Miwa K, Murovska M, Steven S. "Myalgic Encephalomyelitis – Adult and Paediatric: International Consensus Primer for Medical Practitioners." Co-editors B.M. Carruthers and M.I. van de Sande. Published by Carruthers and van de Sande, 2012. http://www.hetalternatief.org/ICC primer 2012.pdf

[569] Tuller, David. "Chronic Fatigue Syndrome and the CDC: A Long, Tangled Tale." *Virology Blog About Viruses and Viral Disease,* November 23, 2011. http://www.virology.ws/2011/11/23/chronic-fatigue-syndrome-and-the-cdc-a-long-tangled-tale/

[570] Bonita R, Beaglehole R, Kjellström T. "Basic Epidemiology." *World Health Organzation.* Geneva Switzerland. 2006. Second Edition. whqlibdoc.who.int/publications/2006/9241547073_eng.pdf

[571] Tuller, David. "Chronic Fatigue Syndrome and the CDC: A Long, Tangled Tale." *Virology Blog About Viruses and Viral Disease,* November 23, 2011. http://www.virology.ws/2011/11/23/chronic-fatigue-syndrome-and-the-cdc-a-long-tangled-tale/

[572] Henderson D, Shelokov A. "Epidemic Neuromyasthenia—Clinical Syndrome?" *N Engl J Med* April 9, 1959; 260(15): 757-764. PMID: 13644582. http://dx.doi.org/10.1056/NEJM195904092601506

[573] Racaniello, Vincent. "A Tale of Two Viruses: Why AIDS Was Pinned to HIV, but Chronic Fatigue Remains a Mystery." *The Crux. Discover Blogs.* January 12, 2012. http://blogs.discovermagazine.com/crux/2012/01/12/hiv-in-xmrv-out-how-scientists-deduce-what-does-and-doesnt-cause-a-disease/

[574] Ibid.

[575] Tuller, David. "Chronic Fatigue Syndrome and the CDC: A Long, Tangled Tale." *Virology Blog About Viruses and Viral Disease,* November 23, 2011. http://www.virology.ws/2011/11/23/chronic-fatigue-syndrome-and-the-cdc-a-long-tangled-tale/

[576] Friedberg, F. Presentation at the U.S. Department of Health and Human Services CFS Advisory Committee Meeting. October 29-30, 2009. *CFS Advisory Committee Website.* https://wayback.archive-it.org/3919/20140324192910/http://www.hhs.gov/advcomcfs/meetings/presentations/fredfriedberg.pdf
Fred Friedberg is head of the IACFS/ME. In his presentation, Friedberg estimated that $100M had been spent by 2009. An estimated 4.7M/year was spent between 2010 and 2014 or 23.5M resulting in an estimate of $120-125M since the 1980s.

[577] The primary surveillance studies conducted by CDC include

- Gunn WJ, Connell DB, Randall B. "Epidemiology of chronic fatigue syndrome: the Centers for Disease Control study." *CIBA Foundation Symposium 1993;* 173: 83-101.PMID: 8387910. http://www.ncbi.nlm.nih.gov/pubmed/8387910.
  Also see "Chronic Fatigue Syndrome." CIBA Foundation Symposium. John Wiley & Sons. April 30, 2008. Symposium held in London, England on May 12-14, 1992. Available through Google Books. https://books.google.com/books?id=uXISpTK0mHMC&dq=gunn+Epidemiology+of+chronic+fatigue+syndrome&source=gbs_navlinks_s
- Reyes M, Gary HE, Dobbins JG, Randall B, Steele L, Fukuda K, Holmes GP, Connell DG, Mawle AC, Schmid DS, Stewart JA, Schonberger LB, Gunn WJ, Reeves WC. "Surveillance for chronic fatigue syndrome - four U.S. cities, September 1989 through August 1993." *Morbidity and Mortality Weekly Report, CDC Surveillance Summaries February 21, 1997.* 46. No. SS-2. Page 1-14.. http://www.cdc.gov/mmwr/PDF/ss/ss4602.pdf and http://www.cdc.gov/mmwr/preview/mmwrhtml/00046433.htm
  This paper stated that the objectives were to a) "collect descriptive epidemiologic information from patients who had unexplained chronic fatigue, estimate the prevalence and incidence of CFS in defined populations, and describe the clinical course of CFS."
  The approach used was a "physician-based surveillance for unexplained chronic fatigue" with followup assessment using Holmes criteria. Conducted between Sept 1989 to August 1993 in Atlanta, Georgia; Wichita, Kansas; Grand Rapids, Michigan; and Reno, Nevada.
  Results were: CFS patients were 98% white, 85% female, well educated, potentially high-income earners, half unemployed. Prevalence of 4.0 to 8.7 per 100,000. The overall annual incidence rate was estimated at less than 1 per 100,000.
- Steele L, Dobbins JG, Fukuda K, Reyes M, Randall B, Koppelman M, Reeves WC. "The epidemiology of chronic fatigue in San Francisco." *Am J Med* September 1998; 105(3): 83S-90S. PMID: 9790487. http://dx.doi.org/10.1016/S0002-9343(98)00158-2
- Dobbins JG, Randall B, Reyes M, Steele L, Livens EA, Reeves WC. "Prevalence of chronic fatiguing illness among adolescents in the United States." *Journal of Chronic Fatigue Syndrome* 1997 3(2):15-27. http://informahealthcare.com/doi/abs/10.1300/j092v03n02_03 ..
  The paper stated the following:
  - "Objective: To compare the prevalence of unexplained chronic fatigue (CF) and chronic fatigue syndrome (CFS) among adolescents."
  - "Design: The studies used the following three designs: (i) a physician-based CFS surveillance system, (ii) a random, cross-sectional community telephone survey and (iii) a cross-sectional survey of school nurses."
  - "Main Outcome Measures: The prevalence of unexplained chronic fatiguing illness was estimated in all three studies. The prevalence of CFS was estimated in one study, the prevalence of CFS-like illness was estimated in another, and the prevalence of a reported diagnosis of CFS was estimated in the third."
  - "Results. In general, the prevalence estimates of CF, CFS-like illness, and CFS for adolescents were lower than those for adults. One study also included children ages 2 to 11 years and found very little CF and no CFS. Cases of CFS among adolescents were evenly distributed across individual years of age."

  Speaking of this study in "Pediatric Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (2012), Jason stated. "As in other medical referral studies, the gatekeeper methodology, as well as reliance on previous diagnoses by physicians (rather than current evaluations), limited the validity of these findings."

- Reyes M, Nisenbaum R, Hoaglin DC, Unger ER, Emmons C, Randall B, Stewart JA, Abbey S, Jones JF, Gantz N, Minden S, Reeves WC. "Prevalence and incidence of chronic fatigue syndrome in Wichita, Kansas." *Arch Intern Med* Juy 14, 2003; 163(13): 1530-6. PMID: 12860574. http://dx.doi.org/10.1001/archinte.163.13.1530.
  - The study was conducted to "estimate the baseline prevalence and 1-year incidence of CFS" in Wichita.
  - The approach used included random digit dialing, screening interview, fuller interview and clinical examination Clinical exam used Fukuda and the Diagnostic Interview Schedule (DIS which Jason has reported as inappropriate for chronically ill patients). This was a longitudinal study with baseline and 3 year follow-up
  - The resulting prevalence was 235 per 100,000 with a prevalence rate about 4.5 times higher for women. Incidence reported as 180 per 100,000
  - Wichita data can be accessed through the *CDC CFS website*. http://www.cdc.gov/cfs/programs/wichita-data-access/index.html
- Bierl C, Nisenbaum R, Hoaglin D, Randall B, Jones AB, Unger ER, Reeves WC. "Regional distribution of fatiguing illnesses in the United States: a pilot study." *Population Health Metrics* February 2004; 2:1. PMID: 14761250.. http://dx.doi.org/10.1186/1478-7954-2-1
- Reeves WC, Jones JF, Maloney E, Heim C, Hoaglin DC, Boneva RS, Morrissey M, Devlin R. "Prevalence of chronic fatigue syndrome in metropolitan, urban, and rural Georgia." *Population Health Metrics* June 8, 2007; 5:5, 2007. PMID: 17559660. http://dx.doi.org/10.1186/1478-7954-5-5 and http://www.cdc.gov/cfs/programs/ga_study/index.html
  This is an Empirical definition study. The paper stated, "The primary objective was to obtain information that could be used as a basis for the development and evaluation of a control strategy for CFS."
  The study was conducted between Sept 2004 and July 2005 and focused on 18-59 year olds. Random digit dialing to perform an initial telephone screening interview for "unwellness" rather than just fatigue as in previous studies. Followed up by detailed telephone interviews using Fukuda to identify "CFS-line" subjects. Then followed up with clinical evaluations using approach/instruments recommended by empirical criteria. The study reported a prevalence of 2.54% for people 18 to 59 years of age. The study did not report significant differences in prevalence of CFS between metropolitan, urban or rural populations or between white and black residents of the three regions.

Other selected studies relevant to epidemiology include

- Reyes, M. Dobbins, J., Nisenbaum, R., Subedar, N., Randall, B. Reeves, W. "Chronic Fatigue Syndrome Progression and Self-Defined Recovery: Evidence from the CDC Surveillance System." *Journal of Chronic Fatigue Syndrome* 1999; 5(1): 17-27. http://informahealthcare.com/doi/abs/10.1300/J092v05n01_03?journalCode=wcfs
- Jones JF, Nisenbaum R, Solomon L, Reyes M, Reeves WC. "Chronic fatigue syndrome and other fatiguing illnesses in adolescents: A population-based study." *Journal of Adolescent Health* 2004. 35: 34-40. http://web.archive.org/web/20100311003721/http://www.cdc.gov/cfs/publications/clinical_4.htm
- Carmel L, Efroni S, White P, Aslakson E, Vollmer-Conna U, Rajeevan M. "Gene expression profile of empirically delineated classes of unexplained chronic fatigue." *Pharmacogenomics.* April 2006; 7(3): 375-86. PMID: 16610948. http://www.ncbi.nlm.nih.gov/pubmed/16610948
- Vollmer-Conna U, Aslakson E, White P. "An empirical delineation of the heterogeneity of chronic unexplained fatigue in women." *Pharmacogenomics.* Apr 2006; 7(3): 355-364. PMID: 16610946. http://dx.doi.org/10.2217/14622416.7.3.355
  The report concluded, "Chronic medically unexplained fatigue is heterogeneous. The putative syndromes were differentiated by obesity, sleep hypnoea, depression, physiological stress response, sleep disturbance, interoception and menopausal status."
- http://www.futuremedicine.com/doi/abs/10.2217/14622416.7.3.355
- Aslakson E, Vollmer-Conna U, Reeves WC, White PD. "Replication of an Empirical Approach to Delineate the Heterogeneity of Chronic Unexplained Fatigue" *Population Health Metrics*. October 5, 2009, **7**:17. http://dx.doi.org/10.1186/1478-7954-7-17

[578] Jason L, Porter N, Brown M, Anderson V, Brown A, Hunnell J, Lerch A. "CFS: A Review of Epidemiology and Natural History Studies." *Bull IACFS ME*. 2009 ; 17(3): 88–106. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3021257/

[579] Reeves WC, Jones JJ, Maloney E, Heim C, Hoaglin DC, Boneva R, Morrissey M, Devlin R. "Prevalence of CFS in metropolitan, urban and rural Georgia populations." *Population Health Metrics,* 2007; 5(5). PMID: 17559660 http://dx.doi.org/10.1186/1478-7954-5-5
This paper reported a prevalence rate of 0.0254 (2.54%) versus 0.0024 in the 2003 Reyes study (Prevalence and incidence of chronic fatigue syndrome in Wichita, Kansas).

[580] Publications for the Wichita Surveillance study include

- Reyes M, Nisenbaum R, Hoaglin DC, Unger ER, Emmons C, Randall B, Stewart JA, Abbey S, Jones JF, Gantz N, Minden S, Reeves WC. "Prevalence and incidence of chronic fatigue syndrome in Wichita, Kansas." *Arch Intern Med* Juy 14, 2003; 163(13): 1530-6. PMID: 12860574. http://dx.doi.org/10.1001/archinte.163.13.1530.

- Solomon L, Nisenbaum R, Reyes M, Papanicolaou DA, Reeves WC. "Functional status of persons with chronic fatigue syndrome in the Wichita population." *BMC Hlth Quality Life Outcomes* October 31, 2003, 1:48. PMID: 14577835. http://dx.doi.org/10.1186/1477-7525-1-48
- Nisenbaum R, Jones JF, Unger ER, Reyes M, Reeves WC. "A population-based study of the clinical course of chronic fatigue syndrome." *BMC Hlth Quality Life Outcomes* October 3, 2003, 1:49. http://dx.doi.org/10.1186/1477-7525-1-49
  This report stated, " About one-third of CFS subjects retained the classification after 1 year of follow-up (Table 6). At 2 and 3 years follow-up, only 21% of the subjects were classified as having CFS. Most transitioned into a non-CFS state because of insufficient symptoms or fatigue severity, absence of fatigue, or identification of an exclusionary condition. Overall, 23.1% (15 of 65) were eventually diagnosed with permanent exclusions."

[581] Ibid.

[582] The estimate for unemployment can be seen in

- Taylor R, Kielhofner G. "Work-related impairment and employment-focused rehabilitation options for individuals with chronic fatigue syndrome: A review." *Journal of Mental Health*. 2005, 14(3): 253-267 http://dx.doi.org/10.1080/09638230500136571
  The paper stated, "Few studies of work-related impairment and work-focused rehabilitation in CFS exist. Rates of unemployment ranged from 35–69% and rates of job loss ranged from 26–89%."
- Collin S, Crawley E, May M, Sterne J, Hollingworth W, UK CFS/ME National Outcomes Database. "The impact of CFS/ME on employment and productivity in the UK: a cross-sectional study based on the CFS/ME national outcomes database." *BMC Health Services Research* 2011, **11**:217. Last accessed February 14, 2015. http://dx.doi.org/10.1186/1472-6963-11-217
  The paper stated that 50.1% "had discontinued their employment 'because of fatigue-related symptoms'."
- Reynolds, K., Vernon, S., Bouchery, E. and Reeves, W. "The economic impact of chronic fatigue syndrome." Cost Effectiveness and Resource Allocation 2004, 2:4. PMID: 15210053. http://dx.doi.org/10.1186/1478-7547-2-4
  The paper stated, "For women and men, we estimated about a 27% reduction in employment attributable to CFS." The paper also stated, "We estimated a 37% decline in household productivity and a 54% reduction in labor force productivity among people with CFS.
- Chu L. "US ME/CFS Patient Survey – April to May 2013". Survey performed in preparation for the FDA Stakeholder Workshop April 25,26, 2013. Preliminary results submitted to FDA: http://iacfsme.org/LinkClick.aspx?fileticket=pMB2%2bjKy7EQ%3d&tabid=36 and http://iacfsme.org/LinkClick.aspx?fileticket=YkMRCzqkxnQ%3d&tabid=36.
  Final results submitted to IOM: http://www.iacfsme.org/LinkClick.aspx?fileticket=PuRykxCauTk%3D&tabid=36
  The report states, "Of 623 respondents, "Only 13% were employed, with almost all citing ME or CFS as the reason why they could not work."

[583] Few longitudinal studies have been done and to this author's knowledge, none have been done on patients characterized by the Canadian Consensus Criteria. The following sources provide information on prognosis. The 5-10% is for full recovery, not just improvement in some symptoms.

- International Association for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis. "Chronic Fatigue Syndrome Myalgic Encephalomyelitis: A Primer for Clinical Practitioners 2014 Edition." International Association for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis. 2012, revised 2014. http://www.iacfsme.org/LinkClick.aspx?fileticket=iD3JkZAZhts%3d&tabid=509
- Cairns R, Hotopf M. "A systematic review describing the prognosis of chronic fatigue syndrome." *Occup Med (Lond)*. January 2005; 55(1): 20-31. PMID: 15699087. http://dx.doi.org/10.1093/occmed/kqi013

[584] Brown M., Bell D, Jason L., Christos C., Bell D. "Understanding Long-Term Outcomes of Chronic Fatigue Syndrome." *Journal Of Clinical Psychology*. 2012; 68(9), 1028–1035. http://dx.doi.org/10.1002/jclp.21880
This study examined whether patients self-reported still having CFS after 25 years as compared to the 1 year increments in the CDC study. What is also notable is that although 80 percent said they no longer had a CFS diagnosis after 25 years, they showed significantly more impairment on 21 of 23 measures compared to controls and in fact, the pattern of their scores wasn't different than those who reported they still had CFS.

[585] Reeves W, Wagner D, Nisenbaum R, Jones J, Gurbaxani B, Solomon L, Papanicolaou D, Unger E, Vernon S, Heim C. "Chronic Fatigue Syndrome – A clinically empirical approach to its definition and study." *BMC Medicine* December 2005; 3:19. PMID: 16356178. http://dx.doi.org/10.1186/1741-7015-3-19
Patient classification over time according to this study report
Classification of the 227 patients at the time of the Wichita study as reported in the 2005 study.

able 1: General characteristics of subjects by recruitment classification. Patient Groups as originally classified in the Wichita Study	Total
CFS (includes any patients diagnosed with CFS at least once during 4 year surveillance) (1)	58
non-fatigued controls matched on sex, age, race and body mass	55
ISF (Insufficient fatigue) – medically unexplained fatigue not CFS	59
Met CFS criteria but also melancholic depression	27

MET ISF criteria but also melancholic depression	28
Total	227

1) it's unclear how many of these patients had CFS at every one of the study points, something that would be expected in the majority of ME patients.

[586] Ibid.

The report stated, "This study showed scant stability of CFS over time, when diagnosed by the usual algorithm (based on patients' subjective responses to direct questions as to whether they feel fatigued, if they perceive their fatigue causes substantial reduction in daily activities, and whether at least 4 case defining symptoms are present). There was poor correlation between illness classification during surveillance (recruitment classification) and classification by the same criteria during the clinical study. While this might reflect fluctuation in illness over time, illness categories (CFS, ISF, Remission, non-fatigued) defined by this surveillance classification scheme were not consistent with respect to overall illness severity."

[587] Jason L, Najar N, Porter N, Reh C. "Evaluating the Centers for Disease Control's Empirical Chronic Fatigue Syndrome Case Definition." *Journal of Disability Policy Studies* Published online October 2008, in print September 2009; 20(2): 93-100. http://dx.doi.org/10.1177/1044207308325995 and http://web.archive.org/web/20090816013354/http://www.co-cure.org/Jason-7.pdf

[588] U.S. Department of Health and Human Services CFS Advisory Committee. CFSAC Meeting. November 9, 2011. *CFS Advisory Committee Website.* http://www.hhs.gov/advcomcfs/meetings/minutes/cfsac_min-11092011.pdf (page 24)

Dr. Jason asked Dr. Unger about the continued publication of Empirical study results (the 2005 Empirical definition has been discredited) and how the CDC intended to evolve the criteria? Dr. Unger's response was that they had done a study comparing "the standardized approach to applying the Fukuda definition [Empirical definition] and the approach that we had used in the past in the Wichita studies. Everyone will find it very reassuring that the patient populations are quite comparable." According to Dr. Unger, a study was to have been published in early 2012 but so far, that study does not appear to have been published.

[589] Brurberg K, Fønhus A, Larun L, Flottorp S, Malterud K. "Case definitions for chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME): a systematic review." *BMJ Open* February 7, 2014; 4(2): e003973. PMID: 24508851. http://dx.doi.org/10.1136/bmjopen-2013-003973

Brurberg reported that one Fukuda study reported a 6..42% prevalence but compared to all the other studies, that is a very significant outlier.

[590] Data on population estimates..

a. United States Census Bureau, *Intercensal Estimates of the United States Population by Age and Sex, 1990-2000: All Months.* http://www.census.gov/popest/data/intercensal/national/index.html
b. United States Census Bureau, *National Intercensal Estimates (2000-2010)* http://www.census.gov/popest/data/intercensal/national/nat2010.html
c. United States Census Bureau, *National Totals: Vintage 2010-2013.* http://www.census.gov/popest/data/national/totals/2013/index.html and http://factfinder2.census.gov/bkmk/table/1.0/en/PEP/2013/PEPAGESEX

		Intercensal data - resident			
Year	Total	ME patients total (1)	Adults	ME Adults(1)	Children < 18
2012 Jul 1	313,873,685	1,324,547	240,165,506	1,013,498	73,728,088
2013	316,128,839	1,334,064	242,542,967	1,023,531	73,585,872

C 1) based on 0.422% prevalence rate. (Total population * 0.422%)

[591] Nacul L., Lacerda E, Pheby D, Campion P, Molokhia M, Fayyaz S, Leite J, Poland F, Howe A, Drachler M. "Prevalence of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) in three regions of England: a repeated cross-sectional study in primary care." *BMC Medicine* July 2011, 9:91 http://dx.doi.org/10.1186/1741-7015-9-91

[592] Reeves WC, Jones JJ, Maloney E, Heim C, Hoaglin DC, Boneva R, Morrissey, M., Devlin, R. "Prevalence of chronic fatigue syndrome in metropolitan, urban and rural Georgia." *Population Health Metrics,* 2007; 5:5. PMID: 17559660. http://dx.doi.org/10.1186/1478-7954-5-5

[593] Wessely S, Chalder T, Hirsch S, Wallace P, Wright D. "The prevalence and morbidity of chronic fatigue and chronic fatigue syndrome: a prospective primary care study." *Am J Public Health.* September 1997; 87(9):1449–1455. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1380968/

[594] Jason, L., Richman, J. "How Science Can Stigmatize: The Case of Chronic Fatigue Syndrome." *Journal of Chronic Fatigue Syndrome* 2007; 14(4): 85-103. http://informahealthcare.com/doi/abs/10.3109/10573320802092146 and http://web.archive.org/web/20120228222416/http://www.cfids-cab.org/cfs-inform/CFS.case.def/jason.richman.07.txt

[595] Bakken I, Tveito K, Gunnes N, Ghaderi S, Stoltenberg C, Trogstad L, Håberg S, Magnus P. "Two age peaks in the incidence of chronic fatigue syndrome/myalgic encephalomyelitis: a population-based registry study from Norway 2008–2012." *BMC Medicine* October 2014, 12:167 http://dx.doi.org/10.1186/s12916-014-0167-5

This study used ICD codes from medical records. In Norway, CFS and ME are both classified as neurological and either CCC or Fukuda are used for diagnosis. Records from mental health care facilities were not included. The study states incidence "of being diagnosed" as opposed to actual incidence recognizing that some are not diagnosed. The rate was roughly 3 times higher in women as in men and having two peaks, one at 10-19 years of age and another at 30-39 years of age

[596] Reyes M, Nisenbaum R, Hoaglin DC, Unger ER, Emmons C, Randall B, Stewart JA, Abbey S, Jones JF, Gantz N, Minden S, Reeves WC. "Prevalence and incidence of chronic fatigue syndrome in Wichita, Kansas." *Arch Intern Med* Juy 14, 2003; 163(13): 1530-6. PMID: 12860574. http://dx.doi.org/10.1001/archinte.163.13.1530.

[597] Nater U , Maloneya E, Lin J, Heim C, Reeves WC. "Coping Styles in Chronic Fatigue Syndrome: Findings from a Population-Based Study" Psychother Psychosom February 2012; 81(2): 127–129. http://dx.doi.org/10.1159/000329996

See also

- "Do patients with chronic fatigue syndrome have impairments in coping?" News release. Alpha Galileo News Service. http://www.alphagalileo.org/ViewItem.aspx?ItemId=121978&CultureCode=en.
  Requires login to get contact details but it appears to be the Journal of Psychotherapy and Psychosomatics

[598] Nater UM, Jones JF, Lina JS, Maloneya E, Reeves WC, Heim C. "Personality Features and Personality Disorders in Chronic Fatigue Syndrome: A Population-Based Study" in *Psychotherapy and Psychosomatics.* August 2010; 79(5): 312–318. PMID: 20664306. http://dx.doi.org/10.1159/000319312

This study stated, "Our results suggest that CFS is associated with an increased prevalence of maladaptive personality features and personality disorders. This might be associated with being noncompliant with treatment suggestions, displaying unhealthy behavioral strategies and lacking a stable social environment. Since maladaptive personality is not specific to CFS, it might be associated with illness per se rather than with a specific condition."

[599] Heim C, Nater UM, Maloney E, Boneva R, Jones JF, Reeves WC. "Childhood Trauma and Risk for Chronic Fatigue Syndrome." *Archives of General Psychiatry* January 2009; 66(1): 72-80.. PMID: 19124690. http://dx.doi.org/10.1001/archgenpsychiatry.2008.508

See also

- "Childhood Trauma and Chronic Fatigue Syndrome Risk Linked." Woodruff Health Sciences Center News, Emory University, Atlanta, Georgia. January 7, 2009. http://shared.web.emory.edu/emory/news/releases/2009/01/childhood-trauma-chronic-fatigue-syndrome-risk-linked.html#.UscXy_aE4YQ
  The press release stated "Results of the study confirm that childhood trauma, particularly emotional maltreatment and sexual abuse, is associated with a six-fold increased risk for CFS."

[600] Jason, L., Richman, J. "How Science Can Stigmatize: The Case of Chronic Fatigue Syndrome." *Journal of Chronic Fatigue Syndrome* 2007; 14(4): 85-103. http://informahealthcare.com/doi/abs/10.3109/10573320802092146 and http://web.archive.org/web/20120228222416/http://www.cfids-cab.org/cfs-inform/CFS.case.def/jason.richman.07.txt

Jason noted that a CDC study was able to effectively distinguish CFS patients on the basis of a depression score. However the biological factors were ineffective as they achieved little more than would be seen by chance. The study that Jason is referring to is:

- Gurbaxani BM, Jones JF, Goertzel B, Maloney EM. "Linear data mining the Wichita clinical matrix suggests sleep and allostatic load involvement in chronic fatigue syndrome." *Pharmacogenomics* April 7, 2006; 7(3): 455-465. PMID: 16610955. http://dx.doi.org/10.2217/14622416.7.3.455

[601] U.S. Centers for Disease Control and Prevention. "Early Life Stress and Adult CFS." *Chronic Fatigue Syndrome. Centers of Disease Control and Prevention.* Last updated October 31, 2011. Last Reviewed November 5, 2014. http://www.cdc.gov/cfs/news/features/childhood_adversity.html

[602] Besides for the Empirical definition childhood trauma study noted above, the CDC CFS page lists a number of other studies to support this including:

- Fuller-Thomson E, Sulman J, Brennenstuhl S, and Merchant M. "Functional Somatic Syndromes and Childhood Physical Abuse in Women: Data From a Representative Community-Based Sample." *Journal of Aggression, Maltreatment & Trauma* May 2011; 20(4): 445-469. http://dx.doi.org/10.1080/10926771.2011.566035
- Clark C, Goodwin L, Stansfeld SA, Hotopf M, White PD. "Premorbid risk markers for chronic fatigue syndrome in the 1958 British birth cohort." *Br J Psychiatry.* October 2011; 199(4): 323-9. PMID:21852302. http://dx.doi.org/10.1192/bjp.bp.110.083956

  The paper stated "Hypothesis testing of the individual risk markers identified similar premorbid risk markers for self-reported CFS/ME and CFS-like illness, suggesting aetiological roles for childhood adversity, adulthood physical inactivity, adulthood BMI and some childhood illnesses but not for childhood BMI or activity levels. Multivariable models, adjusted for premorbid and comorbid psychopathology identified parental physical

abuse, childhood gastrointestinal symptoms and reporting many colds as independent risk markers for self-reported CFS/ME."

[603] Taylor RR, Jason LA. "Sexual abuse, physical abuse, chronic fatigue, and chronic fatigue syndrome: a community-based study." *J Nerv Ment Dis* October 2001; 189(10): 709-15. PMID: 11708672. http://www.ncbi.nlm.nih.gov/pubmed/11708672

[604] Taylor RR, Jason LA. "Chronic fatigue, abuse-related traumatization, and psychiatric disorders in a community-based sample." *Soc Sci Med* July 2002; 55(2): 247-56. PMID: 12144139. http://www.ncbi.nlm.nih.gov/pubmed/12144139
This study stated, "These findings suggest that a history of abuse, particularly during childhood, may play a role in the development and perpetuation of a wide range of disorders involving *chronic fatigue* (emphasis added). Among individuals with chronic fatigue, PTSD and other anxiety disorders appear to demonstrate the strongest association with abuse history."

[605] U.S. Health and Human Services Chronic Fatigue Syndrome Advisory Committee. CFS Advisory Committee meeting, June 13, 2012. http://www.hhs.gov/advcomcfs/meetings/minutes/cfsac20120613.pdf (page 16)
Dr. Rowe stated, "One of the problems in case definition, as came up in one of the CDC studies, is if you define fatigue very broadly, that's a key symptom of depression. I think one of the least useful pieces of work that's been done was the one that suggested that childhood sexual abuse was a risk factor for CFS. It may be a risk factor for depression. That makes a tremendous amount of sense. But we just don't see high rates of physical or sexual abuse in the pediatric CFS population. They don't see it in Oslo, Norway, where they've been doing studies looking at this."

[606] Prins J, van der Meer J, Bleijenberg G. "Chronic fatigue Syndrome." *The Lancet* January 28, 2006; 367(9507): 346-355. PMID: 16443043. http://dx.doi.org/10.1016/S0140-6736(06)68073-2

[607] Burgess M, Chalder T. "PACE Manual for Therapists. Cognitive Behavioral Therapy for CFS/ME." MREC Version 2. November 2004. http://www.pacetrial.org/docs/cbt-therapist-manual.pdf
The manual states "It is important to include the precipitating factors, e.g., illness, life-events, working excessively hard, perfectionist personality etc. It is also important to discuss the maintaining factors, e.g., erratic or reduced activities, disturbed sleep patterns, unhelpful illness beliefs and any other unhelpful cognitions etc." (Page 81)

[608] Jason L, Porter N, Brown M, Anderson V, Brown A, Hunnell J, Lerch A. "CFS: A Review of Epidemiology and Natural History Studies." Bull IACFS ME. 2009 ; 17(3): 88–106. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3021257/
The paper stated, "Psychological functioning and coping have also been explored with this data set. Jason, Witter, and Torres-Harding explored psychological factors, such as coping styles, optimism, and perceived social support with the participants. Among the chronic fatigue groups, those with CFS had the highest levels of optimism and satisfaction with social supports, whereas those with ICF had the lowest scores. Among those with CFS, behavioral disengagement was related to decreased mental composite scores while maintaining activities and optimism was related to more positive mental composite scores. Those in the medically explained chronic fatigue group used the highest levels of venting and focusing on symptoms."

[609] Pharmacogenomics, April 2006; 7(3).Pharmacogenomics. http://www.futuremedicine.com/toc/pgs/7/3
Fourteen articles were released at once that report on the findings of this study. There was also a Perspective article that raised the issue of patient selection and outcome assessment.

- Demitrack, M. "Collaborative Study: chronic fatigue syndrome – Perspective." Pharmacogenomics. April 2006; 7(3): 521-528. http://dx.doi.org/10.2217/14622416.7.3.521
  The article stated, "A variety of operational case definitions based on symptom report have been developed that share some common clinical features. Patients often come to clinical presentation after months or, more typically, years of symptomatic distress. Comorbid presentation with psychiatric illnesses has been noted. Due to these fundamental issues, the impact of patient selection and the specification of the methods of outcome assessment loom large in therapeutic studies of CFS. While a substantial body of research has focused on increasing our understanding of the basic pathobiology of CFS, there have been comparatively fewer studies that have addressed the problems of patient characterization and outcome assessment. The role of clinical methodology in the study of the therapeutics of CFS is not trivial, and may confound our understanding of pragmatic recommendations for treatment."

[610] U.S. Centers for Disease Prevention and Control. "Genetic and Environmental Factors Impact CFS Patients." Centers for Disease Prevention and Control. April 20, 2006.

- Press Release:.*http://www.cdc.gov/media/pressrel/r060420.htm*.
- CDC Press Briefings Transcript. *http://www.cdc.gov/media/transcripts/t060420.htm*
  In addition to the quotes given in the body of the document, Dr. Reeves made the following statement at the end of the conference on CDC's position:.
  - "Our hypothesis that the HPA axis is involved in this, which is very clear in this allostatic load, is a physiologic marker of one's accumulated adaptation to stress."
  - "The working hypothesis is that the HPA axis and the brain is a plastic organ which changes its actual physical architecture depending on stresses that are accumulated over the lifetime."
  - "So as people experience stress, and that can be childhood abuse, it can be childhood infections, it can be multiple injuries--all the stresses that we experience as these are experienced throughout the lifespan, to

some extent the genetics determine how you are going to react to them, they determine how your allostatic load may accumulate, and more importantly, they actually determine your subsequent reaction to stress applied at a later time during the lifespan…"

[611] New York Times. "Genetics and Stress Are Found Linked To Fatigue Disorder." *New York Times*, New York, New York. April 21, 2006. http://query.nytimes.com/gst/fullpage.html?res=9F01E2DF153FF932A15757C0A9609C8B63

[612] Kaiser, J. "Genes and Chronic Fatigue: How Strong Is the Evidence?" Science. May 2006; 312(5774): 669-671. http://dx.doi.org/10.1126/science.312.5774.669

- Referencing Dr. Kerr, Kaiser stated "The gene-expression results, says Jonathan Kerr of Imperial College London, are "meaningless" because they don't demonstrate conclusively, using the polymerase chain reaction, that the genes' RNA is indeed expressed. After this step, says Kerr, 30% to 40% of genes could drop out."

Also see

- Friedberg, Fred. Testimony at U.S. Department of Health and Human Services Chronic Fatigue Syndrome Advisory Committee. October 29-30, 2009. *CFS Advisory Committee Wesbite.* https://wayback.archive-it.org/3919/20140324192910/http://www.hhs.gov/advcomcfs/meetings/presentations/fredfriedberg.pdf

  Friedberg, head of the IACFS/ME, quoted Kerr as saying "Research output on CFS from the CDC in the last 5 years has been principally in the areas of gene expression and mutation. These studies used patients who did not attend CFS clinics and were not diagnosed by recognised CFS clinicians. A microarray was utilised which did not represent the entire human genome (yet such an array was available at the time). But, at no time were the microarray gene profiles confirmed using real-time PCR, a standard procedure in microarray studies because the arrays are very sensitive but not very specific. The findings of these papers do not lead anywhere and were not followed up by CDC. They do not provide insights into pathogenesis, nor do they indicate candidate treatment targets. The authors made no effort to explain their work in context of the available CFS gene expression literature."
- BBC News. "Chronic fatigue gene signs found." BBC News. July 21, 2005. http://news.bbc.co.uk/2/hi/health/4702515.stm
  The story reports on work by Kerr into genomics linkage.

[613] Maupin, C. "CDC's Press Conference Generates Controversy." *The CFS Report. Undated. .* http://www.cfidsreport.com/News/06-CDC-CFS-Controversy.htm
Undated but appears to be from 2005 or 2006 shortly after the press conference.

[614] Nater UM, Jones JF, Lina JS, Maloneya E, Reeves WC, Heim C. "Personality Features and Personality Disorders in Chronic Fatigue Syndrome: A Population-Based Study" in *Psychotherapy and Psychosomatics.* August 2010; 79(5): 312–318. PMID: 20664306. http://dx.doi.org/10.1159/000319312

The paper stated, "Our results suggest that CFS is associated with an increased prevalence of maladaptive personality features and personality disorders. This might be associated with being noncompliant with treatment suggestions, displaying unhealthy behavioral strategies and lacking a stable social environment. Since maladaptive personality is not specific to CFS, it might be associated with illness per se rather than with a specific condition."

[615] Boneva RS, Lin JS, Unger ER. "Early menopause and other gynecologic risk indicators for chronic fatigue syndrome in women." *Menopause: The Journal of The North American Menopause Society.* February 2015; 22(8). Last accessed February 5, 2015. http://dx.doi.org/10.1097/gme.0000000000000411

[616] Joyce J, Hotopf M, Wessely S. "The prognosis of chronic fatigue and chronic fatigue syndrome: a systematic review." *Q J Med* March 1997; 90(3):223–233. 9093600. http://dx.doi.org/10.1093/qjmed/90.3.223 and http://qjmed.oxfordjournals.org/content/qjmed/90/3/223.full.pdf
Other examples include:

- Deale A, Chalder T, Wessely S. "Illness beliefs and treatment outcome in chronic fatigue syndrome." *J Psychosom Res.* July 1998; 45(1): 77-83. PMID: 9720857. http://dx.doi.org/10.1016/S0022-3999(98)00021-X

  This study concluded "In this study, good outcome is associated with change in avoidance behavior, and related beliefs, rather than causal attributions."
- Prins J, van der Meer J, Bleijenberg G. "Chronic fatigue Syndrome." *The Lancet* January 28, 2006; 367(9507): 346-355. PMID: 16443043. http://dx.doi.org/10.1016/S0140-6736(06)68073-2

  The paper states that inactivity is "caused by perceptions and expectations rather than by physical fitness," and that patients had "perception problems" for sleep and cognition. The paper further stated that other perpetuating factors were "social processes ranging from solicitous behaviour to lack of social support" and stated that partners, families and doctors could reinforce the patient's perception of being ill. Finally, the paper stated that "long-lasting illness can also have more desirable consequences, such as care, attention, disengagement, or even financial benefits, which might also be considered perpetuating factors."

[617] Two of the studies that reported on recovery include the following both of which found recovery is rare:

- Andersen M, Permin H, Albrecht F. "Nine-Year Follow-Up of Danish Chronic Fatigue Syndrome (CFS) Patients Impact on Health, Social, Vocational, and Personal Lives." *Journal of Chronic Fatigue Syndrome* 2007; 14(2): 7-23. http://informahealthcare.com/doi/abs/10.1300/J092v14n02_02 and http://www.me-foreningen.dk/filer/Nine_year_study.doc

- Cairns R, Hotopf M. "A systematic review describing the prognosis of chronic fatigue syndrome." *Occup Med (Lond)*. January 2005; 55(1): 20-31. PMID: 15699087. http://dx.doi.org/10.1093/occmed/kqi013
- Examples of CDC studies examining recovery:
  - Reyes, M. Dobbins, J., Nisenbaum, R., Subedar, N., Randall, B. Reeves, W. "Chronic Fatigue Syndrome Progression and Self-Defined Recovery: Evidence from the CDC Surveillance System." *Journal of Chronic Fatigue Syndrome* 1999; 5(1): 17-27. http://informahealthcare.com/doi/abs/10.1300/J092v05n01_03?journalCode=wcfs

[618] U.S. Centers for Disease Control and Prevention. "CFS Information." Centers for Disease Control and Prevention. Page last reviewed September 7, 2000. https://web.archive.org/web/20010405140050/http://www.cdc.gov/ncidod/diseases/cfs/info.htm.

The page contained information on the four-city surveillance study and states, "CDC continues to monitor the patients enrolled in the four-city surveillance study; recovery is defined by the patient and may not reflect complete symptom-free recovery. Approximately 50% of patients reported "recovery," and most recovered within the first 5 years after onset of illness."

[619] White PD, Goldsmith K, Johnson AL, Chalder T, Sharpe M, PACE Trial Management Group. "Recovery from chronic fatigue syndrome after treatments given in the PACE trial." Psychol Med. October 2013' 43(10): 2226-2235. PMID: 23363640. http://dx.doi.org/10.1017/S0033291713000020

The paper stated, "The SF-36 physical function subscale, rated by the participants, was the other primary outcome from the trial (McHorney et al. 1993)….We changed our original protocol's threshold score for being within a normal range on this measure from a score of >= 85 to a lower score as that threshold would mean that approximately half the general working age population would fall outside the normal range. The mean (S.D.) scores for a demographically representative English adult population were 86.3 (22.5) for males and 81.8 (25.7) for females (Bowling et al. 1999). We derived a mean (S.D.) score of 84 (24) for the whole sample, giving a normal range of 60 or above for physical function."

[620] Flo E, Chalder T. "Prevalence and predictors of recovery from Chronic Fatigue Syndrome in a routine clinical practice." *Behaviour Research and Therapy* December 2014; 63: 1-8..PMID: 25222752 http://dx.doi.org/10.1016/j.brat.2014.08.013

[621] Ibid.

The 2014 paper by Flo and Chalder noted that "Previous studies have indicated a CFQ score of below 18 and an SF-36 physical function score of 65 or higher are both within 1 SD of the normal population mean score (Deale et al., 2001 and Jenkinson et al., 1993)."

But critics have noted that this is based on an erroneous interpretation of "Normal."

- Matthees, A. Mees. "Re: Tackling fears about exercise is important for ME treatment, analysis indicates." *BMJ* January 21, 2015; 350 http://dx.doi.org/10.1136/bmj.h227
  Matthees stated that the lowering of the threshold to an SF-36 of 60 was "derived from an inappropriate statistical calculation using a non-representative population sample which included the elderly and disabled." Given that the vast majority of patients in the PACE trial were under 60, the author stated that the change "erroneously asserted that about half the general working age population score under 85, but it is actually 17.6%. Note that 92.3% of the 'healthy' working age English population score 85 to 100, and 61.4% score 100."

Its worth noting that the By comparison, the 2005 Empirical definition used a threshold of 70 or below on the SF-36 scale for a CFS diagnosis, somewhat higher than PACE's threshold

- Reeves W, Wagner D, Nisenbaum R, Jones J, Gurbaxani B, Solomon L, Papanicolaou D, Unger E, Vernon S, Heim C. "Chronic Fatigue Syndrome – A clinically empirical approach to its definition and study." *BMC Medicine* December 2005; 3:19. PMID: 16356178. http://dx.doi.org/10.1186/1741-7015-3-19 .

[622] Ibid.

The report stated, "This study showed scant stability of CFS over time, when diagnosed by the usual algorithm (based on patients' subjective responses to direct questions as to whether they feel fatigued, if they perceive their fatigue causes substantial reduction in daily activities, and whether at least 4 case defining symptoms are present). There was poor correlation between illness classification during surveillance (recruitment classification) and classification by the same criteria during the clinical study. While this might reflect fluctuation in illness over time, illness categories (CFS, ISF, Remission, non-fatigued) defined by this surveillance classification scheme were not consistent with respect to overall illness severity."

[623] Chang CM, Warren JL, Engels EA. "Chronic fatigue syndrome and subsequent risk of cancer among elderly US adults." *Cancer* December 2012, 118(23): 5929-36. PMID: 22648858. http://dx.doi.org/10.1002/cncr.27612

[624] Marcus, A. "Applying Venture Philanthropy to Chronic Fatigue Syndrome." *Wall Street Journal Health Blog*. Sept 15, 2011. http://blogs.wsj.com/health/2011/09/15/applying-venture-philanthropy-to-chronic-fatigue-syndrome/

[625] Carlson S, Hornig M, Klimas K, Ironson G, March D, Komaroff A. "The Chronic Fatigue Initiative (CFI)- Findings from the CFI Cohort Study and Pathogen Discovery & Pathogenesis Project." Presentation at International Association for CFS/ME. *Translating Science into Clinical Care.* International Association for CFS/ME Conference in San Francisco,

California. March 20-23, 2014. Conference Report by Dr. Rosamund Vallings - http://www.masscfids.org/resource-library/15-conference-reports/514-iacfsme-conference-2014-summary-rosamund-vallings-

[626] Jason L. Corrdai K, Gress S, Williams S, Torres-Harding, S. "Causes of Death Among Patients With Chronic Fatigue Syndrome." *Health Care for Women Internationa,* 2006; 27: 615–626. PMID: 16844674. http://dx.doi.org/10.1080/07399330600803766 and http://www.ncf-net.org/library/CausesOfDeath.pdf

Jason stated, "The median age of death for cancer in the United States is 72 (Reis et al., 2003, versus an average age of 47.8 for the CFS sample), the average age of death for suicide in the United States is 48 (Centers for Disease Control, 2003, versus an average age of 39.3 for the CFS sample), and the average age of heart failure is 83.1 (CDC, 2003, versus an average age of 58.7 years for the CFS sample)."

[627] Harding, L. "She went into a hellhole': A mother's candid account of her daughter's battle with ME." *Daily Mail: Mail Online.* Published by Associated Newspapers LTD. May 15, 2010. http://www.dailymail.co.uk/home/you/article-1277519/Criona-Wilson-recalls-daughters-losing-battle-ME-She-went-hellhole.html

Regarding Sophia Mirza's cause of death, Harding stated, "The coroner ruled that the 32-year-old had died of complications due to myalgic encephalomyelitis, a landmark verdict in the UK. A neuropathologist told the court that Sophia's spinal cord was inflamed, with three quarters of her sensory cells displaying significant abnormalities."

Regarding Sophia's sectioning into a psychiatric facility, Harding stated, "In July 2003, the bell of the flat rang, hands hammered on the door. 'Sophia had told me she wasn't going to a mental hospital willingly and they would have to break in. I was scared beyond belief. The door smashed down, two policemen came in, the psychiatrist, the doctor, the social worker. They went to Sophia's room and put on the light. She hadn't had the light on in years.' Within 13 days, the Mental Health Review Tribunal discharged her but, according to Criona, Sophia's ordeal in a psychiatric ward devastated her fragile health. 'She went into a hellhole, devoid of energy. She could never come back from that."

See also:

- Wilson, Criona. "Sophia's Story." Sophie and M.E. May 2006. http://www.sophiaandme.org.uk/sophia%20&%20m.e.%20her%20story.html
  Criona Wilson is Sophia's mother. A video of Sophia's mom talking about her daughter's condition is located at https://www.youtube.com/watch?v=7mZMpvtD3rg
- "The Story of Sophia and M.E." InvestInME. http://www.investinme.org/Article-050%20Sophia%20Wilson%2001.htm.
- Meridian Tonight TV News. Undated but broadcast after Sophia's death. Provided by InvestInME website. http://www.investinme.org/Mediatelevision2.htm
  This includes two reports – the first covers Sophia's condition, her sectioning and her death as reported by her mother while the second also covers the coroner's report, which had just been released.
- "Fatigue Syndrome Ruling Welcomed." BBC June 23, 2006. http://news.bbc.co.uk/2/hi/uk_news/5112050.stm
  Covers coroner's report.
- Barking, Havering and Redbridge Hospitals. Neuropathology Report. February 23, 2006. Last accessed April 25, 2015. http://www.sophiaandme.org.uk/neuropathologicalreport.html
- Additional information on the inquest and coroner's report can be found on the sites listed above. http://www.investinme.org/Article-050%20Sophia%20Wilson%2001-RIP.htm

[628] Schweitzer, Mary. "Casey Fero." Invest in ME. Undated. http://www.investinme.org/Article%20011-Casey%20Fero.htm

[629] Brown, Abigail. "Social Determinants of Health."NIH Pathways to Prevention: Advancing the Research on Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. December 9, 2015. Last accessed March 2, 2015. Time 2:04.

[630] Institute of Medicine of the National Academies. "Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness." Institute of Medicine of the National Academies. Prepublication copy. February 10, 2015. Last accessed February 16, 2015. https://www.iom.edu/Reports/2015/ME-CFS.aspx

[631] National Institute of Health. Office of Disease Prevention. "Pathways to Prevention Workshop: Advancing the Research on Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. Deccember 9-10, 2014. Draft Executive Summary." National Institute of Health. Office of Disease Prevention. Published on or about December 18, 2014. https://prevention.nih.gov/docs/programs/mecfs/ODP-MECFS-DraftReport.pdf

[632] 2014 AHRQ Evidence Review

- Executive Summary:
  U.S. Agency for Healthcare Quality and Research. "Executive Summary. Diagnosis and Treatment of Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome. Evidence Report/Technology Assessment Number 219." U.S. Agency for Healthcare Quality and Research. December 11, 2014. AHRQ Pub. No. 15-E001-1-EF
  http://effectivehealthcare.ahrq.gov/ehc/products/586/2005/chronic-fatigue-executive-141211.pdf
- Full report:
  U.S. Agency for Healthcare Quality and Research. "Research Review. Diagnosis and Treatment of Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome. Evidence Report/Technology Assessment Number 219." U.S. Agency for Healthcare Quality and Research. December 9, 2014. AHRQ Pub. No. 15-E001-EF
  http://effectivehealthcare.ahrq.gov/ehc/products/586/2004/chronic-fatigue-report-141209.pdf

[633] U.S. Department of Health and Human Services CFS Advisory Committee. CFSAC Recommendations. October 3-4, 2012. *CFS Advisory Committee Website*.
http://www.hhs.gov/advcomcfs/recommendations/10032012.html
One of the recommendations made was "Allocating specific funds to study patients with ME/CFS from past cluster outbreaks"

[634] U.S. Department of Health and Human Services. Response to CFS Advisory Committee Recommendation of October 2012. http://www.hhs.gov/advcomcfs/recommendations/response-from-ash-10-2012.pdf
Includes the original recommendation cited in the last reference. The website states that the Assistant Secretary of Health provided the response but does not explicitly state that it was Dr. Howard Koh.

[635] *PrimeTime Live.* Hosts Sam Donaldson and Nancy Snyderman. ABC News. Broadcast in 1996. http://www.youtube.com/watch?v=AW0x9_Q8qbo. Minute 11:12
In response to a question about Dr. Reeves statement that the Lake Tahoe cluster did not exist, Dr. Phillip Lee, Assistant Secretary of Health stated "CDC did investigate that. They reached certain conclusions, which many people disagree with."

[636] U.S. Centers for Disease Prevention and Control. "October 13, 1999 Meeting of CFS Patient Advocacy Group Representatives. Centers for Disease Control and Prevention. Summary Report." Centers for Disease Control and Prevention. October 13, 1999.
https://web.archive.org/web/20010126140500/http://www.cdc.gov/ncidod/diseases/cfs/hot_topics/10.99_update.htm
The summary stated, "CFS Cluster Investigations: CDC is able to investigate only a small proportion of all U.S. outbreaks for which states request assistance. Some clusters of CFS cases have not been investigated; others have been investigated by CDC, but have not been reported. Additionally, CDC cannot unilaterally decide to investigate illness clusters, as they must be invited to do so. One participant recommended that CDC write up the reports on these investigated clusters and publish them. Another participant requested that CDC develop reporting guidelines to assist hospitals and other institutions in recognizing clusters of CFS cases and in requesting CDC investigations of such clusters."

[637] *PrimeTime Live.* Hosts Sam Donaldson and Nancy Snyderman. ABC News. Broadcast in 1996. http://www.youtube.com/watch?v=AW0x9_Q8qbo. Minute 10:50
Defrietas said, "If they admit to a cluster, then they must say its infectious and I don't think the CDC wants CFS to be considered infectious."

[638] U.S. Centers for Disease Prevention and Control, Office of the Chief Financial Officer. "Budget Information." Office of the Chief Financial Officer, Centers of Disease Prevention and Control. Page last updated March 7, 2014. http://www.cdc.gov/fmo/topic/Budget Information/index.html Requests pulled from 2011-2014 budget operating plan summaries. During these years, funding for CFS was around 4.5-5.0 M.

DC Budget category	Funding in millions				
	2010 (1)	2011 (1)	2012 (2)	2013 (3)	2014 (3)
Total CDC Budget Authority (adjusted for ACL transfer)	6,389	5,649	5,656	5,430	5,793
CFS	4,824	4,737	4,707	5,360	5,400

Y1) from 2011 Operating Plan
2) from 2013 Operating plan.
3) From 2014 Operating Plan file

[639] Reeves, WC. "Agency Activities: Statement by Dr. William Reeves. Report of Erroneous Information from CDC on CFS Research Allocations 1996-98." Posted on *CFIDS Association of America*. Undated page copyright 2000. http://web.archive.org/web/20131413085500/http://www.cfids.org/advocacy/reeves-statement.asp
Dr. Reeves whistleblower statement reported that CDC had misused funds and had lied to Congress; this led to the GAO investigation.

[640] U.S. Department of Health and Human Services. Office of Inspector General. *Audit of Costs Charged to the Chronic Fatigue Syndrome Program at the Centers for Disease Control and Prevention* (CIN: A-04-98-04226). Department of Health and Human Services Office of Inspector General. May 10, 1999.
https://oig.hhs.gov/oas/reports/region4/49804226.pdf
This report and the subsequent 2000 GAO report were widely reported by a number of patient organizations and newspapers at the time. In his 2011 article, David Tuller also provides a useful summary.

- Tuller, David. "Chronic Fatigue Syndrome and the CDC: A Long, Tangled Tale." *Virology Blog About Viruses and Viral Disease,* November 23, 2011. http://www.virology.ws/2011/11/23/chronic-fatigue-syndrome-and-the-cdc-a-long-tangled-tale/

[641] U.S. Government Accountability Office. *CHRONIC FATIGUE SYNDROME: CDC and NIH Research Activities Are Diverse, but Agency Coordination Is Limited. (GAO Report* HEHS-00-98). U.S. Government Accountability Office, Washington, D.C.

June 2, 2000. http://www.gao.gov/assets/240/230415.pdf and http://www.gao.gov/products/HEHS-00-98 (Page 14, 17, 20)
Key findings included lack of coordination, inadequate communication, CDC misuse of funds
Other selected sources:

- "GAO Criticizes CDC, NIH Handling of Chronic Fatigue Research." Reuters. 2000. Reuters report accessed on the The National CFIDS Foundation website. http://www.ncf-net.org/library/GAOCriticizesCDC.htm
- CFIDS Association of America. "Agency Activities: CDC Scandal." Undated http://web.archive.org/web/20080829025914/http://cfids.org/advocacy/cdc-scandal.asp
- Enserik M. "Controversy Claims CDC Lab Chief." *Science* February 11, 2000. http://news.sciencemag.org/2000/02/controversy-claims-cdc-lab-chief
- CFIDS Association of America. "Congress directs CDC to restore full funding for misuse of chronic fatigue sydrome research money." CFIDS Association of America. Press release reposted on ProHealth. October 1999. http://www.prohealth.com/library/showarticle.cfm?libid=3263
- Strauss Valerie, "GAO to Probe Diversion Of CDC Research Funds." July 21, 1999 http://www.washingtonpost.com/wp-srv/WPcap/1999-07/21/009r-072199-idx.html
  Note this article is no longer available at this link as of December 2014.

642 Tuller, David. "Chronic Fatigue Syndrome and the CDC: A Long, Tangled Tale." *Virology Blog About Viruses and Viral Disease,* November 23, 2011. http://www.virology.ws/2011/11/23/chronic-fatigue-syndrome-and-the-cdc-a-long-tangled-tale/

643 U.S. Centers for Disease Prevention and Control. "October 13, 1999 Meeting of CFS Patient Advocacy Group Representatives. Centers for Disease Control and Prevention. Summary Report." Centers for Disease Prevention and Control. Page last updated September 7, 2000.
https://web.archive.org/web/20010126140500/http://www.cdc.gov/ncidod/diseases/cfs/hot_topics/10.99_update.htm

The report stated "CDC Director Dr. Jeffrey Koplan opened the meeting by acknowledging that the agency had made serious mistakes in the management of the CFS program, as described in the IG report. CDC did not spend CFS funds as they were intended to be spent, and the agency is taking several actions to rectify those mistakes and ensure that they do not recur. Dr. Koplan offered a personal apology to each of the participants. Personal apologies were also expressed by Dr. James Hughes, Director of the National Center for Infectious Diseases (NCID), and Dr. Brian Mahy, Director of the Division of Viral and Rickettsial Diseases (DVRD)."

The report also stated "CDC's response consists of corrective measures that will be carried out in two tracks. In the first track, which addresses the management of funds and program administration, CDC will do the following:

- "Restore $12.9 million in funding to the CFS program over the next 4 years;"
- "Place DVRD on probationary status through January 2001;"
- "Receive CFS funds as a separate apportionment from the Office of Management and Budget (OMB) and monitor the monies accordingly;"
- "Submit a CFS operating plan and budget to Congress;"
- "Require mandatory training for all CDC personnel involved in budget and accounting activities;"
- "Conduct an internal review of all CDC fiscal policies and practices; and"
- "Develop a new system for indirect program support costs."

Finally, the report stated, "The second track involves reinvigorating CDC's efforts to understand CFS and to prevent it. This reinvigoration includes development of a long-term research program that will be prepared with input from external peer-review scientists and CFS patient advocacy groups."

644 McCleary, Kim. Presentation and Testimony to the U.S. Department of Health and Human Services CFS Advisory Committee. CFSAC Meeting. October 28, 2008. *CFS Advisory Committee Website*. https://wayback.archive-it.org/3919/20140324192720/http:/www.hhs.gov/advcomcfs/meetings/minutes/cfsac20081028min.pdf (page 53). McCleary was the CEO of CFIDS Association of America at the time.

645 U.S. Centers for Disease Control and Prevention. "CDC Research Program Program Updates." *CDC Chronic Fatigue Syndrome*. Centers for Disease Control and Prevention. Last updated December 6, 2011.
http://www.cdc.gov/cfs/programs/cdc_research/index.html

The items listed are a composite of the program elements listed between 2001 and 2005 program updates. The most significant change over that time is that the question on whether CFS is a single illness or not was removed in the 2005 update as was the search for an etiological agent. However, the 2009 strategic plan included a focus on the causes and also added a focus in children and a focus on treatments and management.

646 U.S. Centers for Disease Control and Prevention. "External Peer Review Group Report Executive Summary. Chronic Fatigue Syndrome (CFS) Program." *CDC Chronic Fatigue Syndrome.* Centers for Disease Control and Prevention. Program Review conducted on November 15-16, 1999. Last updated September 7, 2000.
https://web.archive.org/web/20010312062722/http://www.cdc.gov/ncidod/diseases/cfs/reseach/research7.htm

647 U.S. Centers for Disease Control and Prevention. "Centers for Disease Control and Prevention CFS Public Health Research Program 5-year Strategic Plan (October 2009)." *CDC Chronic Fatigue Syndrome*. Centers for Disease Control

and Prevention. Page last updated December 6, 2011.
http://www.cdc.gov/cfs/programs/cdc_research/2009_5yr_research_plan.html
Also see Reeves presentation to CFSAC on the CDC CFS Research Program Strategic Plan

- Reeves, W. Presentation to U.S. Department of Health and Human Services CFS Advisory Committee. CFSAC Meeting. May 2009. *CFS Advisory Committee Website.*
  - CFSAC Minutes: https://wayback.archive-it.org/3919/20140324192913/http://www.hhs.gov/advcomcfs/meetings/minutes/cfsac052709min.pdf (page 30)
  - Presentation: http://web.archive.org/web/20100306133635/http://www.hhs.gov/advcomcfs/meetings/presentations/draft_strategic_plan_200905.pdf

[648] CFIDS Association of America. "Comments on draft Five-Year CFS Research Plan." Letter to CDC in response to the CDC 2009 Strategic Plan. CFIDS Association of America. June 26, 2009.
http://web.archive.org/web/20100616231508/http://cfids.org//temp/research-plan-response.pdf
The CFIDS Association response notes the following ten concerns with the plan

1. "Lacks meaningful innovation"
2. "Not actionable with present budget, staff, and leadership"
3. "Relies on flawed application of research definition ("empiric" definition) and is wholly dependent on just 113 CFS patients identified at baseline of the community-based study of CFS in Georgia"
4. "Bulk of activities described have already fallen behind previously reported timelines and have exceeded projected budgets, warranting closer examination of management's ability to execute plans"
5. "Overstates existing collaborations and branch's capacity for establishing and sustaining partnerships"
6. "Majority of projects are inconsistent with activities conducted in other branches within the division and coordinating center"
7. "Plan itself is laden with jargon and undefined terms; even the population to be studied is unclear (CFS vs. chronic unwellness)"
8. "Logic of plan is circular and does not leverage CFS research being conducted outside CDC or assets available within CDC"
9. "Plan does not clearly communicate priorities, weaknesses or contingencies"
10. "Threatens progress being made by other investigators in the field"

Speaking to CDC's leadership, the CFIDS response further stated, "It attempts to recreate several frameworks that presently exist within other centers at CDC, ignores the role of other HHS agencies (particularly NIH), and repeats CFS research already conducted and published by academic centers. While its language emphasizes collaboration and partnership, its design reinforces the isolated conduct of one small group of investigators, working at the direction of the branch chief without connection to colleagues inside the agency and at other institutions."

[649] U.S. Government Accountability Office. *CHRONIC FATIGUE SYNDROME: CDC and NIH Research Activities Are Diverse, but Agency Coordination Is Limited. (GAO Report* HEHS-00-98). U.S. Government Accountability Office, Washington, D.C. June 2, 2000. http://www.gao.gov/assets/240/230415.pdf and http://www.gao.gov/products/HEHS-00-98
Page 12

[650] U.S. Centers for Disease Control and Prevention. "External Peer Review Group Report Executive Summary. Chronic Fatigue Syndrome (CFS) Program." *CDC Chronic Fatigue Syndrome.* Centers for Disease Control and Prevention. Program Review conducted on November 15-16, 1999. Last updated September 7, 2000.
https://web.archive.org/web/20010312062722/http://www.cdc.gov/ncidod/diseases/cfs/reseach/research7.htm
The report stated, "One of the recurring themes during the presentations was the emphasis on CDC's work, coupled with the paucity of discussion about CFS research done in cooperation with others. There is clearly a need for more cooperation on CFS research both with outside groups and among research groups at CDC. To strengthen its collaborative efforts, CDC should aggressively pursue opportunities for collaborating with other CFS research groups and establish a cross-cutting group at CDC to focus on CFS research from various scientific and programmatic perspectives. The CFS program should also work with other parts of CDC in developing its education programs."

[651] U.S. Centers for Disease Prevention and Control. "CDC Chronic Fatigue Research Program External Peer Review." *CDC Chronic Fatigue Syndrome.* November 5-7, 2008.
http://www.cdc.gov/cfs/programs/cdc_research/external_peer_review.html

[652] U.S. Department of Health and Human Services CFS Advisory Committee. CFSAC Meeting. May 27-28, 2009. *CFS Advisory Committee Website.* https://wayback.archive-it.org/3919/20140324192720/http:/www.hhs.gov/advcomcfs/meetings/minutes/cfsac052709min.pdf
CFSAC members expressed their views to CDC on how it had engaged the experts in the community.

- Dr. Klimas stated (page 61) "I would encourage you now, before you start all of this, to really seriously consider how you're going to use the experts out there that are more than willing to lend a hand but really don't want to be given a piece and have you say, "You're a part of our team. Here's your piece" and not have any kind of input into the design or the priorities. That's really important…. The other thing was that you're doing it and you'll

involve the IACFS. That's not what we want. We want a partnership. The IACFS is going forward with management guidelines. They don't want to be members of the CDC process; they want to be full partners. The international community doesn't want to be hand-selected and told, "You're going to help inform the process." They want to be involved as a community, and there are ways to do that."

- Dr. Oleske stated (page 68): "But for some reason, with CFS, it does seem that you'd rather have a paternalistic relationship with us investigators. I think that's important. I think what you're hearing is that this group is trying to get the CDC to be what the CDC has always been. This paternalism is so out of character. I think that's what you're hearing from the panel. We just want to have an open partnership with the CDC."

[653] CFIDS Association of America. "Comments on draft Five-Year CFS Research Plan." Letter to CDC in response to the CDC 2009 Strategic Plan. CFIDS Association of America. June 26, 2009. http://web.archive.org/web/20100616231508/http://cfids.org//temp/research-plan-response.pdf

[654] Friedberg, Fred. Testimony at U.S. Department of Health and Human Services Chronic Fatigue Syndrome Advisory Committee. CFSAC Meeting. October 29-30, 2009. *CFS Advisory Committee Website.* https://wayback.archive-it.org/3919/20140324192910/http://www.hhs.gov/advcomcfs/meetings/presentations/fredfriedberg.pdf

Dr. Friedberg's text also included the following quote from Gudrun Lange, member of the distinguished external review panel that in 2008 evaluated the CFS program at CDC. "I am very disappointed that CDC has not been more proactive in implementing important suggestions made by peer reviewers. The committee recommended that CDC, as the lead health agency dealing with CFS, establish closer relationships with other traditional public health agencies to further promote CFS as a significant health concern."

[655] U.S. Centers for Disease Control and Prevention. "Multi-site Clinical Assessment of CFS." *CDC Chronic Fatigue Syndrome Website*. Centers for Disease Control and Prevention. Page last updated April 8, 2013. http://www.cdc.gov/cfs/programs/clinical-assessment/

[656] Tuller, David. "Chronic Fatigue Syndrome and the CDC: A Long, Tangled Tale." *Virology Blog About Viruses and Viral Disease,* November 23, 2011. http://www.virology.ws/2011/11/23/chronic-fatigue-syndrome-and-the-cdc-a-long-tangled-tale/

[657] Friedberg, Fred. Testimony at U.S. Department of Health and Human Services Chronic Fatigue Syndrome Advisory Committee. CFSAC Meeting. October 29-30, 2009. *CFS Advisory Committee Website.* https://wayback.archive-it.org/3919/20140324192910/http://www.hhs.gov/advcomcfs/meetings/presentations/fredfriedberg.pdf

In Friedberg's presentation, he estimated that $100M had been spent by 2009. An estimated 4.7M/year was spent between 2010 and 2014 or 23.5M resulting in an estimate of $120-125M since the 1980s.

[658] Carruthers BM, van de Sande MI, De Meirleir KL, Klimas NG, Broderick G, Mitchell T, Staines D, Powles ACP, Speight N, Vallings R, Bateman L, Baumgarten-Austrheim B, Bell DS, Carlo-Stella N, Chia J, Darragh A, Jo D, Lewis D, Light AR, Marshall-Gradisbik S, Mena I, Mikovits JA, Miwa K, Murovska M, Pall ML, Stevens S. "Myalgic Encephalomyelitis: International Consensus Criteria." *Journal of Internal Medicine* October 2011; 270(4): 327–338. PMID: 21777306. http://dx.doi.org/10.1111/j.1365-2796.2011.02428.x and http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2796.2011.02428.x/full

[659] In the early 1990s, researchers and clinicians were reporting a variety of immune abnormalities, neurological issues and evidence of viral infection. There were even reports of B- cell abnormalities at that time.. Margaret Williams from the U.K. has compiled documentation about the early research studies.

- Williams, Margaret. "'Grey' Information about ME/CFS." Part 1 covers 1956-1990. Compiled April 2011. http://www.investinme.org/Article422%20Grey%20Information%20About%20ME-CFS.htm
- Williams, Margaret. "'Grey Information about ME/CFS. Part 2 - 1991 – 1993." Compiled May 2011. http://www.investinme.org/Article422-2%20Grey%20Information%20about%20ME%20CFS%20Part%20II.htm
- Williams, Margaret. "'Grey Information about ME/CFS. Part 3 -1994." Compiled November 2011. http://www.investinme.org/Article422-3%20Grey%20Information%20about%20ME%20CFS%20Part%20III.htm

[660] Pharmaceutical Research and Manufacturers of America (PhRMA). "2014 Biopharmaceutical Research Industry Profile." Pharmaceutical Research and Manufacturers of America. Washington, D.C. April 2014. www.phrma.org/sites/default/files/pdf/2014_PhRMA_PROFILE.pdf

Also see

- Pharmaceutical Research and Manufacturers of America (PhRMA). "2013 Biopharmaceutical Research Industry Profile." Pharmaceutical Research and Manufacturers of America. Washington, D.C. July 2013. http://www.phrma.org/sites/default/files/pdf/PhRMA%20Profile%202013.pdf
- Milne C, Malins A. "Academic-Industry Partnerships for Biopharmaceutical Research & Development: Advancing Medical Science in the U.S." Tufts Center for the Study of Drug Development, Tufts University School of Medicine, Boston, MA. April 2012. http://csdd.tufts.edu/files/uploads/tuftscsdd_academic-industry.pdf
  Sponsored in part by a grant from the Pharmaceutical Research and Manufacturers of America (PhRMA)

[661] Milne C, Malins A. "Academic-Industry Partnerships for Biopharmaceutical Research & Development: Advancing Medical Science in the U.S." Tufts Center for the Study of Drug Development, Tufts University School of Medicine, Boston, MA. April 2012. http://csdd.tufts.edu/files/uploads/tuftscsdd_academic-industry.pdf

The Tufts paper stated, "the Coalition Against Major Diseases, which includes multiple biopharmaceutical companies, research institutions in the U.S. and Europe, and a range of foundations recognized that given the complexities associated with Alzheimer's and Parkinson's disease, extensive collaboration between public and private sectors would be necessary to facilitate the development of effective treatments."

[662] "The End ME/CFS Project." The Open Medicine Foundation. Last accessed February 3, 2015. http://www.openmedicinefoundation.org/the-end-mecfs-project/ and https://bos.etapestry.com/prod/viewEmailAsPage.do?databaseId=0MF&mailingId=29383841&personaRef=4933.0.8730658&jobRef=773.0.42856511&memberId=943741295&erRef=4933.0.8730656&key=1fc21404c9481e4c873e85323bfd4b

[663] Tuller, David. "Chronic Fatigue Syndrome and the CDC: A Long, Tangled Tale." *Virology Blog About Viruses and Viral Disease,* November 23, 2011. http://www.virology.ws/2011/11/23/chronic-fatigue-syndrome-and-the-cdc-a-long-tangled-tale/

[664] Summary of NIH Spending Trends from 1999 to 2013. Based on the 2000 GAO report, FIOA analysis done by Pat Fero and reported at 2011 NIH State of Knowledge Workshop, analyses done by Jennifer Spotila and information available on the NIH website. References listed below.

ear	Total NIH Budget (in M) (1)	Total NIH funding (In 1995 dollars (1, 2)	Total NIH spend (in 2014 dollars (2)	Total CFS funding as reported by NIH (3)	Total funding specifically for CFS from Fero and Spotila (4,5)	Total CFS funding (in 1995 dollars) (2)	Total CFS funding (in 2014 dollars) (2)
1987	$6,685	$8,968(2)	$13,931	$0.78		$1.1	$1.6
1988				$0.99		$1.3	$2.0
1989				$1.48		$1.8	$2.8
1990				$1.82		$2.1	$3.3
1991				$2.86			
1992				$3.49		$3.8	$5.9
1993				$5.75			
1994				$6.18			
1995	$11,300 (1)	$11,300 (2)	$17,533	$7.37		$7.4	$11.5
1996				$6.57			
1997	$12,740 (1)	$12,097 (2)	$18,791	$6.68		$6.3	$9.9
1998				$6.79			
1999	$15,000 (1-est)	$13,721 (2)	$21,315	$6.89		$6.3	$9.8
2000	$18,000 (1-est)	$15,930 (2)	$24,746	$5.8	$4.3 (4)	$5.1	$8.0
2001				$5.8	$4.6 (4)	$5.0	$7.8
2002				$7.2	$4.6 (4)	$6.1	$9.5
2003	$27,067 (1)	$22,419 (2)	$34,825	$6.9	$4.4 (4)	$5.7	$8.9
2004				$5.5	$2.9 (4)	$4.4	$6.9
2005				$5.5	$3.0 (4)	$4.3	$6.7
2006				$4.8	$4.0 (4)	$3.6	$5.6
2007				$4.5 (est)	$4.1 (4)	$3.3	$5.1
2008				$3.5	$2.5 (4) $3.2 (5)	$2.5	$3.8
2009	$35,745 (1-with ARRA)		$39,444	$4.8	$3.9 (4) $3.8 (5)	$3.4	$5.3
2010	$36,209 (1 – with ARRA)		$39,311	$6.2	$4.2 (5)	$4.3	$6.7
2011				$6.3	$5.0 (5)	$4.3	$6.6
2012	$30,860 (1)	$20,484 (2)	$31,820	$4.5	$3.7 (5)	$3.0	$4.6

2103	$29,151 (1)	$19,071 (2)	$29,624	$5.1	$5.0 (5)	$3.3	$5.2
2014	$30,070 (1)	$19,358 (2)	$30,070	$5.4		$3.5	$5.4
Total 1987-2014				$139.5 (avg: $5.0)			
2014 increase over 1999 (*)	100%	41%	41%	-22%		-44%	-45%
2014 increase over 1995	166%	71%	72%	-27%		-53%	-53%

* Calculated as (2014 budget – 1999 budget)/1999 budget. Increase over 1995 calculated same way

1) Garrison H, Drehman B. "NIH Research Funding Trends: FY1995 – 2013." Federation of American Societies for Experimental Biology. Produced by Federation of American Societies for Experimental Biology (FASEB). Office of Public Affairs. Last accessed February 20, 2015. http://www.faseb.org/portals/2/PDFs/opa/NIH%20Grant%20Slideshow.pptx
   - 2009 and 2010 include the Supplemental Appropriation (ARRA).
   - Also see FASEB website - http://www.faseb.org/Policy-and-Government-Affairs/Data-Compilations/NIH-Research-Funding-Trends.aspx
   - 2014 budget from http://www.nih.gov/about/budget.htm and http://www.faseb.org/Portals/2/PDFs/opa/2015/2.10.15%20NIH%20Funding%20Cuts%202-pager.pdf
   - 1987 and 1997 figures from
     - Brinkley W, Wood J, Garrison H. "Increased Funding for NIH, An Historical Perspective." *Federation of American Societies for Experimental Biology.* November 1998; 12(14): 1431-1435. http://www.fasebj.org/content/12/14/1431.long
2) U.S. Bureau of Labor Statistics. CPI Inflation Calculator. Undated. Calculated on February 21, 2015. http://146.142.4.24/cgi-bin/cpicalc.pl and http://data.bls.gov/cgi-bin/cpicalc.pl.
3) Sources:
   a. U.S. Government Accountability Office. *CHRONIC FATIGUE SYNDROME: CDC and NIH Research Activities Are Diverse, but Agency Coordination Is Limited. (GAO Report* HEHS-00-98). U.S. Government Accountability Office, Washington, D.C. June 2, 2000. http://www.gao.gov/assets/240/230415.pdf and http://www.gao.gov/products/HEHS-00-98 1987 to 1999 spending: GAO report, Appendix 7.
   b. 2000 – 2007: Pat Fero. "Inadequate National Institutes of Health funding for New Chronic Fatigue Syndrome grants." Wisconsin ME/CFS Association. September 27, 2010. http://www.investinme.org/Documents/NIH/Pat Fero CFSAC Oct 2010 NIH 9-27-10 11pm-1.pdf and personal correspondence related to the FOIA analysis. File "NIH SPend Total - OBM 00-10_PF 06.13.xls"
   c. 2008 – 2013: U.S. National Institutes of Health. "Estimates of Funding for Various Research, Condition, and Disease Categories (RCDC)." National Institutes of Health. Published March 7, 2014. http://report.nih.gov/categorical_spending.aspx and http://web.archive.org/web/20120401183252/http://report.nih.gov/categorical_spending.aspx (for 2008 -2010)
4) Pat Fero. "Inadequate National Institutes of Health funding for New Chronic Fatigue Syndrome grants." Wisconsin ME/CFS Association. September 27, 2010. http://www.investinme.org/Documents/NIH/Pat Fero CFSAC Oct 2010 NIH 9-27-10 11pm-1.pdf and http://www.wicfs-me.org/Pdf%20Files/NIH_CFS_funding_3_29_2011.pdf

   Note that there are slight discrepancies in these two versions. The table below contains the March 2011 numbers and has the September 2010 numbers in parentheses.

   Based on FOIA requests, Pat Fero analyzed funding between 2000 and 2009 and used that to assess whether the funding was used specifically for "CFS" or for other diseases not related to CFS. She found that the total funding for CFS specific research equals $38.3M as indicated below. This report states that NIH reported $60M was spent in 10 years but that figure appears to cover 11 years from 2000 to 2010. The amount spent through 2009 was is 54.3M. The amount spent on projects specifically related to this disease between 2000 and 2009 was $36.4M leaving $18M spent on other diseases.

   See Table 1 in Fero's above report: Inadequate Funding: A 10-year profile of ME/CFS science grant awards 2000 – 2009. (Discrepancies between the two sources in parentheses)

Year	New Studies	New Funding	Renewed Studies	CFS Centers Renewals	Renewal Funding	Total Funding

2000	2	$863,805	6	14	$3,414,202	$4,278,007 (*)
2001	3	$676,220	6	14	$3,876,723	$4,552,943
2002	1	$329,987	7	12	$4,269,156	$4,599,143
2003	3	$1,188,270	8	Discontinued	$2,034,241 ($3,222,511)	3,222,511
2004	1	$255,301	9		$2,667,530	$2,922,831
2005	1	$641,703	6		$2,344,369	$2,986,072
2006**	6	$1,736,061	4		$2,270,107	$4,006,168
2007	3	$809,875	9		$3,283,159	$4,093,034
2008	3	$795,041	5		$1,734,886	$2,529,927
2009	2	$355,600 ($1,037,421)	8		$2,852,214	$3,187,814
Totals	24	$7,631,863 ($8,333,684)			$28,746,585 ($29,934,857)	$36,378,448 ($38,268,541) (*)

Y Note: The original document had 4,278,005 in the first row and the total is 2 less. Corrected here.

5) Estimates for 2009 – 2013: Spotila, Jennifer. "2012 NIH Spending on CFS Studies." *OccupyCFS.* May 15, 2013. http://www.occupycfs.com/2013/05/15/2012-nih-spending-on-cfs-studies/ and Spotila, Jennifer. "2013 NIH Spending on CFS Studies." March 31, 2014. http://www.occupycfs.com/2014/03/31/2013-nih-spending-on-cfs-studies/
   - 2008 – one study in pain processing in FM and interstitial cystitis for $329K not related to CFS. The amount spent on this disease was $3.2K.
   - 2009 - one study in pain processing in FM and interstitial cystitis for $329K and a small grant for $2,692 for a total of $331K not related to CFS. The amount spent on this disease was $4.5M and if XMRV is excluded, then it is $3.8M
   - 2010 – Includes a stress response on TMJ and FM and one study in pain processing in FM and interstitial cystitis for a total of $407K not related to CFS. It also includes $1.54M for an XMRV study not related to CFS. The amount spent on the disease is $5.8KM and $4.2M if the unrelated XMRV is also excluded.
   - 2011 – All studies were related CFS with $1.7M on XMRV. Total was $6.3M
   - 2012: three studies, one on nausea and malaise after administration of a diabetes drugs and two on XMRV for a total of $822K. Spotila's rationale for excluding XMRV from the disease specific studies was that its focus was general and the 2011 study had already demonstrated contamination and the article in Science had been removed. This leaves $3.7M for studies into this disease.
   - 2013 – One study for $77K on nausea and malaise after administration of a diabetes drugs not CFS related.
6) Additional information on the grants given out by NIH between 1999 and 2005 can be found here: U.S. National Institutes of Health."NIH Funded CFS Research." Archived 2006. http://web.archive.org/web/20060907132224/http://orwh.od.nih.gov/cfs/cfsResearchNIH.html

[665] U.S. Department of Health and Human Services CFS Advisory Committee. "CFSAC Recommendations - June 16-17, 2014." CFS Advisory Committee. June 16-17, 2014. *CFS Advisory Committee Website.*

- Recommendation from CFSAC to Secretary Burwell. http://www.hhs.gov/advcomcfs/recommendations/06142014.html
  "CFSAC recommends that the NIH issue a Request for Applications (RFA) for ME/CFS by November 1st, 2014, or as soon as feasible, to address the gaps in ME/CFS knowledge and research. The RFA should consider current known gaps in knowledge for the following areas:"
  - "Provocation designs where symptoms are triggered through standardized challenges involving exercise, cognitive tasks, and mental stressors. These designs appear to be more likely to identify symptom to biology relationships in comparison to assessments done in resting states."
  - "Ambulatory monitoring of symptoms, activities, behaviors, and physiological states that identify associations between biological and behavioral measures, e.g., daily fatigue ratings and cytokine fluctuations."

- "Network analysis of dysregulation of multiple bodily systems, such as the neuroendocrine system, the central nervous system, the autonomic nervous system and the immune system."
- "Natural history studies aimed at identifying the genetic triggers and causal factors of ME/CFS."
- "Treatment trials that address both clinical and biologic outcomes. This RFA may also be informed by the gaps identified in the 2011 NIH State of the Knowledge Workshop, the Pathways to Prevention Program for ME/CFS research panel report or any relevant source, including but not limited to, the IACFS meeting summary. This RFA should encourage investigators to use the NIH data and biobank sharing platform (subject of an accompanying recommendation to this recommendation), if such a platform is established at the time of release or becomes available during the time awards are made on this RFA."

- Health and Human Services. "Responses to Recommendations from the Chronic Fatigue Syndrome Advisory Committee Ref: June 16-17, 2014, CFSAC Meeting." October 29, 2014. http://www.hhs.gov/advcomcfs/recommendations/letter-to-slevine-from-sburwell-june-2014-recommendations.pdf
  In HHS's response from Secretary Burwell to Dr. Susan Levine (Chair CFSAC), HHS stated "Unfortunately there remains a lack of definitive evidence regarding the etiology, diagnosis, and treatment for ME/CFS. As such, issuing a Request for Applications (RFA) would not be an effective strategy as RFAs generally encourage a narrowly defined research area that addresses more specific gaps in scientific knowledge. RFAs are designed to build upon recommendations that have been identified through cutting- edge research findings in the extant literature, that address unmet NIH Institute mission-specific objectives, or that incorporate findings from workshops and conferences on specific topics"

[666] Newby, Kris. "Immune System Disruption. The Search for Answers." *Stanford Medicine. Balancing Act.* Fall 2014. http://stanmed.stanford.edu/2014fall/immune-system-disruption.html

[667] Hornig M, Montoya J, Klimas N, Levine S, Felsenstein D, Bateman L, Peterson D, Gottschalk CG, Schultz A, Meredith X, Eddy L, Komaroff A, Lipkin I. "Distinct plasma immune signatures in ME/CFS are present early in the course of illness." *Science Advances* Feb 27, 2015; 1(1):e1400121 Last accessed March 29, 2015. DOI: 10.1126/sciadv.1400121 http://advances.sciencemag.org/content/1/1/e1400121

[668] Institute of Medicine of the National Academies. "Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness." Institute of Medicine of the National Academies. Prepublication copy. February 10, 2015. Last accessed February 16, 2015. https://www.iom.edu/Reports/2015/ME-CFS.aspx

[669] Dr. Leonard Jason of DePaul University has reported extensively on the impact of overly broad CFS definitions. Others concur. Selected articles include

- Kennedy G, Abbot N, Spence V, Underwood C, Belch J. "The Specificity of the CDC-1994 Criteria for Chronic Fatigue Syndrome: Comparison Of Health Status in Three Groups of Patients Who Fulfill the Criteria." *Ann Epidemiol* February 2004; 14(2): 95–100. PMID: 15018881. http://dx.doi.org/10.1016/j.annepidem.2003.10.004
  The study compared CFS, GWI and patients with exposure to Organophosphate insecticide and found that "Differences in simple, easily performed clinical outcome measurements can be observed between groups of patients, all of whom fulfill the CDC-1994 criteria for CFS. It is likely that their response to treatment may also vary. The specificity of the CFS case definition should be improved to define more homogeneous groups of patients for the purposes of treatment and research."
- Christley Y, Duffy T, Martin CR. "A review of the definitional criteria for chronic fatigue syndrome." *J Eval Clin Pract* February 2012;18(1):25-31. PMID: 21029269. http://dx.doi.org/10.1111/j.1365-2753.2010.01512.x
- Carruthers BM, van de Sande MI, De Meirleir KL, Klimas NG, Broderick G, Mitchell T, Staines D, Powles ACP, Speight N, Vallings R, Bateman L, Baumgarten-Austrheim B, Bell DS, Carlo-Stella N, Chia J, Darragh A, Jo D, Lewis D, Light AR, Marshall-Gradisbik S, Mena I, Mikovits JA, Miwa K, Murovska M, Pall ML, Stevens S. "Myalgic Encephalomyelitis: International Consensus Criteria." *Journal of Internal Medicine* October 2011; 270(4): 327–338. PMID: 21777306. http://dx.doi.org/10.1111/j.1365-2796.2011.02428.x and http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2796.2011.02428.x/full
  The paper stated, "Patient sets that include people who do not have the disease [ME] lead to biased research findings, inappropriate treatments and waste scarce research funds."
- Jason L, Najar N, Porter N, Reh C. "Evaluating the Centers for Disease Control's Empirical Chronic Fatigue Syndrome Case Definition." *Journal of Disability Policy Studies* Published online October 2008, in print September 2009; 20(2): 93-100. http://dx.doi.org/10.1177/1044207308325995 and http://web.archive.org/web/20090816013354/http://www.co-cure.org/Jason-7.pdf
  Dr. Jason stated, "Such blurring of diagnostic categories will make it even more difficult to identify biological markers for this illness, and if they are not identified, many scientists will be persuaded that this illness is psychogenic." In this paper, he also reported that the Empirical definition resulted in a tenfold increase over earlier prevalence estimates and led to 38% of major depressive disorder patients being misclassified as CFS.

[670] Institute of Medicine of the National Academies. "Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness." Institute of Medicine of the National Academies. Prepublication copy. February 10, 2015. Last accessed February 16, 2015. https://www.iom.edu/Reports/2015/ME-CFS.aspx

[671] U.S. National Institutes of Health. "NIH Budget. Research for the People." National Institutes of Health. Last updated March 11, 2014. http://www.nih.gov/about/budget.htm

[672] U.S. National Institutes of Health. "Estimates of Funding for Various Research, Condition, and Disease Categories (RCDC)." National Institutes of Health. Published March 7, 2014. http://report.nih.gov/categorical_spending.aspx
Provides NIH Estimates of funding by disease categories. Search by term chronic fatigue syndrome.

[673] New York Times. "Readers Ask: A Virus Linked to Chronic Fatigue Syndrome." *Consults. New York Times Blog.* October 15, 2009. http://consults.blogs.nytimes.com/2009/10/15/readers-ask-a-virus-linked-to-chronic-fatigue-syndrome/?_r=0

Dr. Klimas stated, "My H.I.V. patients for the most part are hale and hearty thanks to three decades of intense and excellent research and billions of dollars invested. Many of my C.F.S. patients, on the other hand, are terribly ill and unable to work or participate in the care of their families. I split my clinical time between the two illnesses, and I can tell you if I had to choose between the two illnesses (in 2009) I would rather have H.I.V. But C.F.S., which impacts a million people in the United States alone, has had a small fraction of the research dollars directed towards it."

[674] Solve ME/CFS Initiative. "P2P Draft Evidence Review. Can a Process that is Inappropriate for ME/CFS Inform the Research Path Forward?" Solve ME/CFS Initiative. October 20, 2014. http://solvecfs.org/p2p-draft-evidence-review/
Note that this article stated that $191.5M was spent between 1991 and 2014. However, as shown in the NIH spend reference further down on this page, spending in this time frame was $134.4M which was used instead as the cumulative figure for this disease.

[675] Kogelnik, A. "Money Matters. On a per-patient basis, ME/CFS is dead last on the NIH Roster." Provided by Ryan Prior, *Forgotten Plague.* March 30, 2014. https://www.facebook.com/CFSDocumentary/photos/pb.572661299431396.-2207520000.1419300020./733783573319167/?type=3&theater

Kogelnik, patient Ryan Pryor and Llewelyn King were guests on the Jim Bohannon Show, January 23, 2014 where this was discussed. The link to this show is here: https://m.soundcloud.com/ryan-prior-1/jimbo
Statement made by Dr. Kogelnik on the nationally syndicated Jim Bohannon radio show.

[676] U.S. National Institutes of Health. "Estimates of Funding for Various Research, Condition, and Disease Categories (RCDC)." National Institutes of Health. Published March 7, 2014. http://report.nih.gov/categorical_spending.aspx
The NIH budget information sourced directly from NIH.

[677] U.S. Department of Health and Human Services. "HIV/AIDS 101. U.S. Statistics." Last revised December 2014. http://aids.gov/hiv-aids-basics/hiv-aids-101/statistics/
Note that this is a 2014 estimate.

[678] Estimate of 350,000 used based on following sources - Prevalence estimates for Lupus Prevalence

- U.S. Centers for Disease Control and Prevention. "Systemic lupus erythematosus (SLE or lupus)." Centers for Disease Control and Prevention. Page last updated July 22, 2014. http://www.cdc.gov/arthritis/basics/lupus.htm
  The site states "Prevalence estimates vary widely, and range as high as 1,500,000 (Lupus Foundation of America). A recent study estimated a 2005 prevalence of 161,000 with definite SLE and 322,000 with definite or probable SLE."
- Schur P, Hahn B. "Epidemiology and pathogenesis of systemic lupus erythematosus." Edited by Pisetsky D. UpToDate. Last updated September 15, 2014. http://www.uptodate.com/contents/epidemiology-and-pathogenesis-of-systemic-lupus-erythematosus
  This report stated "The reported prevalence of systemic lupus erythematosus (SLE) in the population is 20 to 150 cases per 100,000 which translates to 62,000 to 471,000 for a population of 314,000,000."
- American College of Rheumatology. "Prevalence Statistics." American College of Rheumatology. Undated. http://www.rheumatology.org/Research/Prevalence_Statistics/

The site stated that the prevalence of Systemic lupus erythematosus is 161,000 to 322,000 U.S. adults

[679] National Multiple Sclerosis Society. "MS Prevalence." National Multiple Sclerosis Society. Undated. http://www.nationalmssociety.org/About-the-Society/MS-Prevalence
Note that the 400,000 estimate of prevalence is based on a 2002 initiative by the Society that used 2000 census data.

[680] Autism Society. "Facts and Statistics. Autism Society. Undated. http://www.autism-society.org/about-autism/facts-and-statistics/
Based on a study by Buescher in 2014, autism spectrum is estimated at 3.5M Americans. This is significantly raised over earlier estimates.

[681] Summary of NIH Spending Trends from 1999 to 2013. Based on information in the 2000 GAO report, the FIOA analysis done by Pat Fero and reported at 2011 NIH State of Knowledge Workshop, analyses done by Jennifer Spotila and information available on the NIH website. Full list of references includes:

ear	Total NIH Budget (in M) (1)	Total NIH funding (In 1995 dollars (1, 2)	Total NIH spend (in 2014 dollars (2)	Total CFS funding as reported by NIH (3)	Total funding specifically for CFS from Fero and Spotila (4,5)	Total CFS funding (in 1995 dollars) (2)	Total CFS funding (in 2014 dollars) (2)
1987	$6,685	$8,968(2)	$13,931	$0.78		$1.1	$1.6
1988				$0.99		$1.3	$2.0
1989				$1.48		$1.8	$2.8
1990				$1.82		$2.1	$3.3
1991				$2.86			
1992				$3.49		$3.8	$5.9
1993				$5.75			
1994				$6.18			
1995	$11,300 (1)	$11,300 (2)	$17,533	$7.37		$7.4	$11.5
1996				$6.57			
1997	$12,740 (1)	$12,097 (2)	$18,791	$6.68		$6.3	$9.9
1998				$6.79			
1999	$15,000 (1-est)	$13,721 (2)	$21,315	$6.89		$6.3	$9.8
2000	$18,000 (1-est)	$15,930 (2)	$24,746	$5.8	$4.3 (4)	$5.1	$8.0
2001				$5.8	$4.6 (4)	$5.0	$7.8
2002				$7.2	$4.6 (4)	$6.1	$9.5
2003	$27,067 (1)	$22,419 (2)	$34,825	$6.9	$4.4 (4)	$5.7	$8.9
2004				$5.5	$2.9 (4)	$4.4	$6.9
2005				$5.5	$3.0 (4)	$4.3	$6.7
2006				$4.8	$4.0 (4)	$3.6	$5.6
2007				$4.5 (est)	$4.1 (4)	$3.3	$5.1
2008				$3.5	$2.5 (4) $3.2 (5)	$2.5	$3.8
2009	$35,745 (1-with ARRA)		$39,444	$4.8	$3.9 (4) $3.8 (5)	$3.4	$5.3
2010	$36,209 (1 – with ARRA)		$39,311	$6.2	$4.2 (5)	$4.3	$6.7
2011				$6.3	$5.0 (5)	$4.3	$6.6
2012	$30,860 (1)	$20,484 (2)	$31,820	$4.5	$3.7 (5)	$3.0	$4.6
2103	$29,151 (1)	$19,071 (2)	$29,624	$5.1	$5.0 (5)	$3.3	$5.2
2014	$30,070 (1)	$19,358 (2)	$30,070	$5.4		$3.5	$5.4
Total 1987-2014				$139.5 (avg: $5.0)			
2014 increase over 1999 (*)	100%	41%	41%	-22%		-44%	-45%
2014 increase over 1995	166%	71%	72%	-27%		-53%	-53%

* Calculated as (2014 budget – 1999 budget)/1999 budget. Increase over 1995 calculated same way

1) Garrison H, Drehman B. "NIH Research Funding Trends: FY1995 – 2013." Federation of American Societies for Experimental Biology. Produced by Federation of American Societies for Experimental Biology (FASEB). Office of Public Affairs. Last accessed February 20, 2015. http://www.faseb.org/portals/2/PDFs/opa/NIH%20Grant%20Slideshow.pptx
   - 2009 and 2010 include the Supplemental Appropriation (ARRA).

- Also see FASEB website - http://www.faseb.org/Policy-and-Government-Affairs/Data-Compilations/NIH-Research-Funding-Trends.aspx
- 2014 budget from http://www.nih.gov/about/budget.htm and http://www.faseb.org/Portals/2/PDFs/opa/2015/2.10.15%20NIH%20Funding%20Cuts%202-pager.pdf
- 1987 and 1997 figures from
  - Brinkley W, Wood J, Garrison H. "Increased Funding for NIH, An Historical Perspective." *Federation of American Societies for Experimental Biology.* November 1998; 12(14): 1431-1435. http://www.fasebj.org/content/12/14/1431.long

2) U.S. Bureau of Labor Statistics. CPI Inflation Calculator. Undated. Calculated on February 21, 2015. http://146.142.4.24/cgi-bin/cpicalc.pl and http://data.bls.gov/cgi-bin/cpicalc.pl.
3) Sources:
   a. U.S. Government Accountability Office. *CHRONIC FATIGUE SYNDROME: CDC and NIH Research Activities Are Diverse, but Agency Coordination Is Limited. (GAO Report* HEHS-00-98). U.S. Government Accountability Office, Washington, D.C. June 2, 2000. http://www.gao.gov/assets/240/230415.pdf and http://www.gao.gov/products/HEHS-00-98 1987 to 1999 spending: GAO report, Appendix 7.
   b. 2000 – 2007: Pat Fero. "Inadequate National Institutes of Health funding for New Chronic Fatigue Syndrome grants." Wisconsin ME/CFS Association. September 27, 2010. http://www.investinme.org/Documents/NIH/Pat Fero CFSAC Oct 2010 NIH 9-27-10 11pm-1.pdf and personal correspondence related to the FOIA analysis. File "NIH SPend Total - OBM 00-10_PF 06.13.xls"
   c. 2008 – 2013: U.S. National Institutes of Health. "Estimates of Funding for Various Research, Condition, and Disease Categories (RCDC)." National Institutes of Health. Published March 7, 2014. http://report.nih.gov/categorical_spending.aspx and http://web.archive.org/web/20120401183252/http://report.nih.gov/categorical_spending.aspx (for 2008 -2010)
4) Pat Fero. "Inadequate National Institutes of Health funding for New Chronic Fatigue Syndrome grants." Wisconsin ME/CFS Association. September 27, 2010. http://www.investinme.org/Documents/NIH/Pat Fero CFSAC Oct 2010 NIH 9-27-10 11pm-1.pdf and http://www.wicfs-me.org/Pdf%20Files/NIH_CFS_funding_3_29_2011.pdf

   Note that there are slight discrepancies in these two versions. The table below contains the March 2011 numbers and has the September 2010 numbers in parentheses.

   Based on FOIA requests, Pat Fero analyzed funding between 2000 and 2009 and used that to assess whether the funding was used specifically for "CFS" or for other diseases not related to CFS. She found that the total funding for CFS specific research equals $38.3M as indicated below. This report states that NIH reported $60M was spent in 10 years but that figure appears to cover 11 years from 2000 to 2010. The amount spent through 2009 was is 54.3M. The amount spent on projects specifically related to this disease between 2000 and 2009 was $36.4M leaving $18M spent on other diseases.

   See Table 1 in the above report: Inadequate Funding: A 10-year profile of ME/CFS science grant awards 2000 – 2009. (Discrepancies between the two sources in parentheses)

Year	New Studies	New Funding	Renewed Studies	CFS Centers Renewals	Renewal Funding	Total Funding
2000	2	$863,805	6	14	$3,414,202	$4,278,007 (*)
2001	3	$676,220	6	14	$3,876,723	$4,552,943
2002	1	$329,987	7	12	$4,269,156	$4,599,143
2003	3	$1,188,270	8	Discontinued	$2,034,241 ($3,222,511)	3,222,511
2004	1	$255,301	9		$2,667,530	$2,922,831
2005	1	$641,703	6		$2,344,369	$2,986,072
2006**	6	$1,736,061	4		$2,270,107	$4,006,168
2007	3	$809,875	9		$3,283,159	$4,093,034
2008	3	$795,041	5		$1,734,886	$2,529,927
2009	2	$355,600 ($1,037,421)	8		$2,852,214	$3,187,814

Totals	24	$7,631,863 ($8,333,684)			$28,746,585 ($29,934,857)	$36,378,448 ($38,268,541) (*)

1 Note: The original document had 4,278,005 in the first row and the total is 2 less. Corrected here.

5) Estimates for 2009 – 2013: Spotila, Jennifer. "2012 NIH Spending on CFS Studies." *OccupyCFS.* May 15, 2013. http://www.occupycfs.com/2013/05/15/2012-nih-spending-on-cfs-studies/ and Spotila, Jennifer. "2013 NIH Spending on CFS Studies." March 31, 2014. http://www.occupycfs.com/2014/03/31/2013-nih-spending-on-cfs-studies/

- 2008 – one study in pain processing in FM and interstitial cystitis for $329K not related to CFS. The amount spent on this disease was $3.2K.
- 2009 - one study in pain processing in FM and interstitial cystitis for $329K and a small grant for $2,692 for a total of $331K not related to CFS. The amount spent on this disease was $4.5M and if XMRV is excluded, then it is $3.8M
- 2010 – Includes a stress response on TMJ and FM and one study in pain processing in FM and interstitial cystitis for a total of $407K not related to CFS. It also includes $1.54M for an XMRV study not related to CFS. The amount spent on the disease is $5.8KM and $4.2M if the unrelated XMRV is also excluded.
- 2011 – All studies were related CFS with $1.7M on XMRV. Total was $6.3M
- 2012: three studies, one on nausea and malaise after administration of a diabetes drugs and two on XMRV for a total of $822K. Spotila's rationale for excluding XMRV from the disease specific studies was that its focus was general and the 2011 study had already demonstrated contamination and the article in Science had been removed. This leaves $3.7M for studies into this disease.
- 2013 – One study for $77K on nausea and malaise after administration of a diabetes drugs not CFS related.

6) Additional information on the grants given out by NIH between 1999 and 2005 can be found here: U.S. National Institutes of Health."NIH Funded CFS Research." Archived 2006. http://web.archive.org/web/20060907132224/http://orwh.od.nih.gov/cfs/cfsResearchNIH.html

682 Spotila, Jennifer. "2012 NIH Spending on CFS Studies." *OccupyCFS.* May 15, 2013. http://www.occupycfs.com/2013/05/15/2012-nih-spending-on-cfs-studies/
According to Spotila, $822K was dedicated to the following non-CFS activities:

- "A grant to Dr. Matthew Hayes for $80,000 is investigating the potential mechanisms that cause nausea and malaise after the administration of a class of drugs for diabetes in the hope of developing treatments for obesity."
- "Two grants relate to XMRV, and as such should also be excluded as non-CFS related. NIH's own study on XMRV (the Lipkin study) established that XMRV is not found in CFS patients or controls, and the original Science paper was retracted in December 2011. There is no reason to allocate XMRV spending to CFS research. Dr. Monica Roth received $293,436 as part of her ongoing study in the integration of murine retroviral vectors. Dr. Jeffrey Cohen received $448,678 in a new intramural NIH study that did not detect XMRV in CFS patients or patients with other chronic inflammatory diseases, and also tested use of a particular drug in a person with herpesvirus infection – although that patient does not appear to have CFS."
- "These three grants account for $822,114 or 18% of the total NIH claims to have spent on ME/CFS."

683 McCleary, K. Presentation to U.S. Department of Health and Human Services CFS Advisory Committee. CFSAC Meeting September 27, 2004. *CFS Advisory Committee Website.* http://www.hhs.gov/advcomcfs/meetings/minutes/cfsac_mins_092004_pdf.pdf page 5

McCleary presented a 45 page report to CFSAC entitled "Analysis of NIH-Funded Research on Chronic Fatigue Syndrome Shows a Trend of Decreased Support: Fiscal Years 1999–2003." She reported "the total five-year funding was $31.6 million.".She reported that of this, 5.24M + 0.5M was not related to CFS for a total of $5.74M or about 20% over the five-year period. Of those studies, she stated,

- "Twelve studies were found to have no support for CFS. These projects involved psychobiology of ethnicity, stress and disease, pathophysiology of neuroimmune communication, vascular disease, atherosclerosis, and chronic muscle diseases. The total value of these 12 projects was $5.24 million."
- "There were nine studies for "related" conditions. They involved muscle disorders, lime disease, orthostatic intolerance, delayed sleep phase syndrome, syncope, chronic multi-symptom illnesses, rheumatic diseases, fibromyalgia, and gulf war syndrome. This research totaled $1 million, which, when adjusted for direct CFS support, came out to be $502,866."

The full CFIDS Association of America report is listed here, along with a news story from ProHealth:

- CFIDS Association of America. "Steep Decline in NIH Funding for CFS Research!" CFIDS Association of America. 09/27/2004. http://web.archive.org/web/20041213171903/http://cfids.org/advocacy/2004/gac_09272004.asp

- ProHealth. "CFS NEWS - 35 Percent of NIH's Research Funding for CFS Being Diverted, Up from 18 Percent in 2004." ProHealth. July 25, 2006. http://www.prohealth.com/library/showarticle.cfm?libid=12053

[684] Fero, Pat. "Inadequate National Institutes of Health funding for New Chronic Fatigue Syndrome grants." Wisconsin ME/CFS Association. September 27, 2010. http://www.investinme.org/Documents/NIH/Pat Fero CFSAC Oct 2010 NIH 9-27-10 11pm-1.pdf and http://www.wicfs-me.org/Pdf%20Files/NIH_CFS_funding_3_29_2011.pdf
Note that there are slight discrepancies in these two versions. I used the September 2010 version.

[685] In a personal discussion, Pat Fero stated that her analysis had uncovered examples of where sleep studies and behavioral modification studies in mental health conditions were submitted to the CFS SEP. Also see previous footnote

[686] World Health Organization. "Global Burden of Disease." World Health Organization. Undated. http://www.who.int/topics/global_burden_of_disease/en/ and http://www.who.int/healthinfo/global_burden_disease/about/en/

The DALY (Disability Adjusted Life Years) provides "a framework for integrating, validating, analysing and disseminating such information is needed to assess the comparative importance of diseases, injuries and risk factors in causing premature death, loss of health and disability in different populations." The DALY was developed for the 1990 Global Burden of Disease (GBD) study. The DALY is a measure of the overall disease burden due to early death and also to disability over time. The DALY is a measure of years of life lost due to early death or disability. It considers factors like measures of mortality, incidence and duration of disease and disability.
Updated Disease burden is available in:

- US Burden of Disease Collaborators. "The State of US Health, 1990-2010. Burden of Diseases, Injuries, and Risk Factors" *JAMA.* August 14, 2013; 310(6):591-606. Last accessed February 22, 2015. http://dx.doi.org/10.1001/jama.2013.13805.
  DALY provided in Table 6 in the supplemental data. Link is http://jama.jamanetwork.com/data/Journals/JAMA/927436/JOI130037supp1_prod.pdf

A lay article on DALY related to this disease is available at

- Kewley A. "Measuring Disease Burden: How and Why." *Research 1st CFIDS Association of America.* October 13, 2011. https://web.archive.org/web/20140211222957/http://www.research1st.com/2011/10/13/disease-burden/

[687] Begg S, Vos T, Barker B, Stevenson C, Stanley L, Lopez A. "The burden of disease and injury in Australia 2003." Australian Institute of Health and Welfare. May 25, 2007. Overall summary: http://www.aihw.gov.au/publication-detail/?id=6442467990. Annex Tables: http://www.aihw.gov.au/WorkArea/DownloadAsset.aspx?id=6442459759 and http://www.aihw.gov.au/burden-of-disease/previous-studies/
DALY values were not calculated by the WHO for CFS but have been developed by the Australian government for CFS. Australian DALY levels includes calculated value for ME (CFS).

- Main paper reports a total population of 19,881,469M (page 4)
- Annex Table 24 reports "Prevalence per 1,000 population, by 5-year age groups, sex and cause, Australia, 2003." The prevalence reported for CFS is 1.483 per 1000 or 0.1483%. This translates to about 29,484 people affected.
- The report's Annex Table 10 reports "DALYs by 5-year age groups, sex and cause, Australia, 2003". The total DALY value listed for CFS is 8890. This translates to 44.67 per 100,000 (calculated as 8890 / (19,900,000/100,000)
- Other DALYs listed were 26.4 per 100,000 for MS, 33.5 per 100,000 for HIV/AIDS, 134.9 for Parkinson

The U.S. DALY was calculated by adjusting for the differences in reported prevalence. The most commonly accepted prevalence is 0.42% as reported by Jason. 126 per 100,000 people in the U.S. (calculated by 0.42%/0.148% * 44.67 per 100,000 people in Australia)

[688] Institute of Medicine of the National Academies. "Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness." Institute of Medicine of the National Academies. Prepublication copy. February 10, 2015. Last accessed February 16, 2015. https://www.iom.edu/Reports/2015/ME-CFS.aspx Page 31

[689] Gillum LA, Gouveia C, Dorsey ER, Pletcher M, Mathers CD, McCulloch C, Johnston SC. "NIH Disease Funding Levels and Burden of Disease." *PLoS ONE* February 24, 2011; 6(2): e16837. PMID: 21383981. http://dx.doi.org/10.1371/journal.pone.0016837

Gillum found that while a variety of disease burden measures, either alone or in combination, did not adequately account for differences in NIH funding levels, the DALY was the best predictor accounting for close to 40% of the differences.

[690] U.S. Department of Health and Human Services CFS Advisory Committee. "Recommendations to the Secretary of Health and Human Services." Last reviewed September 17, 2014. http://www.hhs.gov/advcomcfs/recommendations/index.html
Recommendations from 2004 to 2012 are summarized in an excel file on this page. Also see the itemized list of recommendations for research funding beginning on page 15.

- U.S. Department of Health and Human Services CFS Advisory Committee. "Comments from the HHS Chronic Fatigue Syndrome ADVISORY COMMITTEE. Subject: Draft Report. Pathways to Prevention: Advancing the

Research on Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. January 2015.
http://www.hhs.gov/advcomcfs/recommendations/cfsac-pathways-to-prevention-january-2015-updated.pdf

[693] Newby, Kris. "Immune System Disruption. The Search for Answers." *Stanford Medicine. Balancing Act.* Fall 2014.
http://stanmed.stanford.edu/2014fall/immune-system-disruption.html

[694] Garrison H, Drehman B. "NIH Research Funding Trends: FY1995 – 2013." Federation of American Societies for Experimental Biology. Produced by Federation of American Societies for Experimental Biology (FASEB). Office of Public Affairs. http://www.faseb.org/portals/2/PDFs/opa/NIH%20Grant%20Slideshow.pptx.
Also see FASEB website - http://www.faseb.org/Policy-and-Government-Affairs/Data-Compilations/NIH-Research-Funding-Trends.aspx.

[695] Spotila Jennifer. "2012 NIH Spending on CFS Studies." *OccupyCFS.* May 15, 2013.
http://www.occupycfs.com/2013/05/15/2012-nih-spending-on-cfs-studies/

Spotila stated, "NIH's Principal Deputy Director Dr. Lawrence Tabak stated that NIH spent $386 million in pain research in 2011. NIH now reports that $479 million was spent on pain research in 2012, an increase of $93 million or 24%. One contributing factor for this meteoric increase was that the Affordable Care Act of 2010 included specific requirements for pain research and care. But whatever the reasons, it's still a boatload of money. To me this reinforces the point that advocates have made over and over and over: there IS money available. It's just being allocated to "higher priorities" than ME/CFS."

Tabak's statement on "Pain Research & Care" before the Senate Committee on Health, Education, Labor, and Pensions United States Senate on Tuesday February 14, 2012 can be found here:
http://www.hhs.gov/asl/testify/2012/02/t20120214a.html

[696] Current ME and ME/CFS research/clinical centers include but are not limited to Dr. Peterson's Simmaron, Montoya's Chronic fatigue initiative at Stanford, Chronic fatigue initiative in New York, Klimas' Neuro-immune institute in Florida, Kogelnik's Open Medicine Institute in California, Lucinda Bateman's Fatigue Consultation Clinic, Enlander's Mt Sinai ME/CFS Center and the recently announced End ME/CFS Project.

[697] Newby, Kris. "Immune System Disruption. The Search for Answers." *Stanford Medicine. Balancing Act.* Fall 2014.
http://stanmed.stanford.edu/2014fall/immune-system-disruption.html

[698] Stanford University. *2014 Stanford Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Symposium. Advances In Clinical Care And Translational Research*. Stanford University School of Medicine and Stanford Hospital and Clinics. Conference at Stanford, California. March 19, 2014.

- Agenda - http://med.stanford.edu/chronicfatiguesyndrome/documents/2014StanfordME_CFSSymposiumBrochurefinal.pdf
- Videos - http://med.stanford.edu/chronicfatiguesyndrome/2014SymposiumVideo.html
- Conference report by Dr. Rosamund Vallings – https://www.masscfids.org/resource-library/15-conference-reports/534-2014-stanford-mecfs-symposium-advances-in-clinical-care-and-translational-research

[699] Open Medicine Foundation. "The End ME/CFS Project." Open Medicine Foundation. Page undated.
http://www.openmedicinefoundation.org/the-end-mecfs-project/

[700] Open Medicine Institute. "OMI-MERIT Priority Projects." Open Medicine Institute. June 2012.
http://openmedicineinstitute.org/research-initiatives/mecfs-merit/

[701] Delin G. "Discover Interview: The World's Most Celebrated Virus Hunter, Ian Lipkin." Discover. May 11, 2012.
http://discovermagazine.com/2012/apr/15-most-celebrated-virus-hunter-ian-lipkin

[702] U.S. Centers for Disease Control and Prevention. "CDC CFS Patient-Centered Outreach and Communication Activity (PCOCA) Conference Call." U.S. Centers for Disease Control and Prevention. September 10, 2013.
http://www.cdc.gov/cfs/meetings/cfspcoca-09-2013.html
Also see Phoenix Rising Patient Forum for more details and a transcript. http://phoenixrising.me/archives/19083 and https://docs.google.com/file/d/0B-NT-7M70igudmZVSVJUTnZVclU/edit?pli=1

[703] Kitei M. "Candid Conversation with Dr. Ian Lipkin." *CFSCentral.* May 11, 2014.
http://www.cfscentral.com/2014/05/candid-conversation-with-dr-ian-lipkin.html

[704] The Center for Infection and Immunity, Columbia University. "Chronic Fatigue Syndrome." Undated.
http://cii.columbia.edu/research.aspx?8Fo92f
Also see:
Microbe Discovery Project. https://giving.columbia.edu/giveonline/?schoolstyle=5881&alloc=21677 for the patient driven crowdsourcing effort to raise funds for Lipkin's Microbiome study.

[705] Maupin, C. "Scientific Review, CFS, and the NIH--- The CFS Special Emphasis Panel." *The CFS Report.* September 2005.
http://www.cfidsreport.com/Articles/NIH/NIH_CFS_3.htm
In 2005, Craig Maupin published an excellent article reviewing NIH grant review and approval process on the CFS Report, which includes Hoffeld's comments.

[706] Mangan, D. "Team Science: Playing in the Same Sandbox." *Research 1st*. CFIDS Association of America. August 21, 2012. https://web.archive.org/web/20130412234011/http://www.research1st.com/2012/08/21/team-science/

[707] U.S. Health and Human Services Advisory Committee. CFS Advisory Committee Meeting. May 2013. http://www.hhs.gov/advcomcfs/meetings/minutes/cfsacmay23_final_508.pdf (Page 39)

Dr. Mary Ann Fletcher, committee member stated "I think I mentioned yesterday that three of us went to NIH by invitation to present our idea for a P01 application. We were told that the field was not yet ready for this. Last fall I sent in an application. There was some disagreement. One of the reviewers really didn't like it and the other did. I was the primary investigator (PI) and Nancy Klimas was the co-investigator. For the P01, I was the co- investigator and Nancy Klimas was the PI. I don't know that there's a better recognized person in the field. So I'm not sure why the field is not ready for applications. Right now I'm writing another grant to be sent in on June 24. I send one in practically every time, but I'm only funded about one every go- round with the committee. I was told that the funding rate is about 6%. That's awful low."

[708] Institute of Medicine of the National Academies. "Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness." Institute of Medicine of the National Academies. Prepublication copy. February 10, 2015. Last accessed February 16, 2015. https://www.iom.edu/Reports/2015/ME-CFS.aspx

[709] NIH has held a number of conferences on CFS. These include

985 First NIH conference on CFS Held by NIAID	No direct documentation of this workshop found. But as reported in the report for the second conference, a key issue was "In 1985 at the first NIAID workshop, it was agreed that the greatest obstacle to CFS research was the lack of an objective case definition."
Second NIH Conference on CFS – March 1991 Held by NIAID. And National Institute of Mental Health	Purpose was to review the collective experience of investigators in the United States who have been using the CDC criteria for case definition in their research and, if necessary, to make recommendations concerning further modification and 2) to discuss approaches to assessment of illness severity for studies of natural history and intervention. Report: Schluederberg A, Straus S, Peterson P, Blumenthal S, Komaroff A, Spring S, Landay A, Buchwald D. "NIH Conference. Chronic Fatigue Syndrome Research Definition and Medical Outcome Assessment." *Annals of Internal Medicine* August 1992; 117(4): 325-31. PMID: 1322076. http://annals.org/article.aspx?articleid=705740 (abstract) and http://annals.org/data/Journals/AIM/19757/AIME199208150-00010.pdf (full text)
February 2000 Internal Science Consultation Held by NIAID	- Held in response to CFSCC recommendation but planned without CFSAC input - Stated purpose was to improve the quality, direction and extent of CFS research supported by NIH - Attendees – Originally planned to only include Simon Wessely, Michael Sharpe, Mark Demitrack and Stephen Straus. The revised meeting was attended by group of 11 people, including Gail Cassell (chair), Margaret Chesney, Mark Demitrack, Charles Engel, Helen Mayberg, Kevin McCully, William Reeves, Joan Shaver, Michael Sharpe, Simon Wessely, Stephen Straus, Lon White, Barry Wilson, Nancy Klimas. Patient Kathy Rabin. It is unclear who of these individuals were given the opportunity to speak and who wrote the final report. - Produced report and led to 2001 AHRQ evidence based review noted elsewhere - Report: National Institute of Health. "Chronic Fatigue Syndrome. State-of-the-Science Consultation." Report of the National Institutes of Health State of Science CFS Consultation. February 6-7, 2000. http://webharvest.gov/peth04/20041027092632/www.niaid.nih.gov/dmid/meetings/cfsreport.htm - Report from CFIDS Association of America Walker, V. "A monumentous week for CFIDS Pressure mounts for CDC, NIH." CFIDS Association of America. Winter 2000. http://web.archive.org/web/20130424133259/http://www.cfids.org/archives/2000/2000-1-article02.asp

October 2000 State of the Science workshop Organized by CFSCC, not NIH as the other conferences in this list were.	- Purpose - focus on CFS research areas in which information is both mature and exciting; summarize current knowledge and identify important gaps in knowledge; garner the perspective of expert investigators not currently working on the problem of CFS; and identify expert investigators who might be attracted to study CFS as a clinical problem. - Topics - neuroendocrinology; cognition; chronic pain; sleep; immunology; orthostatic intolerance/neurally mediated hypotension; and fatigue, functional status, and disability. - Sponsorship – according to the report, this was organized by the CFSCC with financial support from CDC and NIH - Led to program announcement - Conference Report – Department of Health and Human Services Chronic Fatigue Syndrome Coordinating Committee. "Chronic Fatigue Syndrome. State of the Science Conference" Report of the HHS Chronic Fatigue Syndrome Coordinating Committee (CFSCC) State of Science Conference October 22-23, 2000. http://web.archive.org/web/20111121094434/http://www.co-cure.org/SOS.pdf - CFIDS Association of America Summary Walker, V. "The D.C. Dispatch. Your CFIDS Public Policy Report." CFIDS Association of America. Spring 2000. http://web.archive.org/web/20131902341600/http://www.cfids.org/archives/2000/2000-2-dcd.asp - Maupin C. "The CFS program at the NIH – Past, present, and future." *The CFS Report*. September 2005. http://www.cfidsreport.com/Articles/NIH/NIH_CFS_2.htm
June 12-13 2003 Neuroimmune Mechanisms and chronic fatigue syndrome held by NIH	- Report has a focus on stress and allostatic load. - Sponsored by NIH Office on Women's Health and Trans-NIH Working Group on Research on CFS Conference Report – U.S. National Institutes of Health. "Neuroimmune Mechanisms and Chronic Fatigue Syndrome A Report of the Scientific Workshop." Co-Sponsored by the NIH Office of Research on Women's Health and the Trans-NIH Working Group for Research on Chronic Fatigue Syndrome. Workshop held on June 12-13, 2003. Chaired by Dr. Debra Buchwald and Dr. Leslie Crofford. https://web.archive.org/web/20060921064325/http://orwh.od.nih.gov/CFS_June03Report.pdf
April 2011 NIH State of Knowledge Workshop held by National Institutes of Health	National Institutes of Health. "State of the Knowledge Workshop Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Research. Workshop Report." National Institutes of Health. April 7-8, 2011. http://orwh.od.nih.gov/research/me-cfs/pdfs/ORWH_SKW_Report.pdf Sponsored by Office Research on Women's Health, National Institutes of Health and U.S. Department of Health and Human Services.

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[710] National Institute of Health. "Chronic Fatigue Syndrome. State-of-the-Science Consultation." Report of the National Institutes of Health State of Science CFS Consultation. February 6-7, 2000. http://webharvest.gov/peth04/20041027092632/www.niaid.nih.gov/dmid/meetings/cfsreport.htm

Following an uproar from the community, NIH modified the meeting to include 11 people, including Gail Cassell (chair), Margaret Chesney, Mark Demitrack, Charles Engel, Helen Mayberg, Kevin McCully, William Reeves, Joan Shaver, Michael Sharpe, Simon Wessely, Stephen Straus, Lon White, Barry Wilson, Nancy Klimas. Patient Kathy Rabin. It is unclear who of these individuals were given the opportunity to speak and who wrote the final report.

This meeting generated considerable controversy in the community. A few of the contemporary sources include:

- CFIDS Association of America. "CAA Response to the NIH "State of the Science" Meeting." CFIDS Association of America. January 24, 2000. http://www.co-cure.org/infoact2.htm
  Report on discussion with NIH prior to the meeting –
- Walker, V. "A monumentous week for CFIDS Pressure mounts for CDC, NIH." CFIDS Association of America. Winter 2000. http://web.archive.org/web/20130424133259/http://www.cfids.org/archives/2000/2000-1-article02.asp Report post meeting.
- Summary of events - After two months of requests by Kim Kenney (McCleary) of the CFIDS Association, Dr. David Morens, the CFS Program Officer at NIH finally stated the purpose of the conference was to help guide NIH's CFS research priorities" and there were four attendees - Professor Simon Wessely, Dr. Michael Sharpe, Dr. Mark Demitrack and Dr. Stephen Straus. The first three were psychiatrists and Wessely, Sharpe and Straus had

promoted or endorsed the "biopsychosocial" view of this disease. The CFSCC had not been involved in planning the conference even though CFSCC had recommended the meeting. As a result of vocal patient opposition, Dr. Klimas was invited to attend at short notice. Seven others also attended but the others were reported to not be expert in this disease. The resultant report discounted the importance of infectious agents. The report noted a higher prevalence of depression, generalized anxiety disorder, and panic in CFS and that the majority of CFS patients may have diagnosable psychiatric illnesses. It discussed chronic life stresses and the need to distinguish between predisposing, precipitating and perpetuating factors. Finally, the report stated "beliefs about illness should be explored as an aspect of CFS" and stated that CBT had been successfully used.

[711] U.S. National Institutes of Health. "Neuroimmune Mechanisms and Chronic Fatigue Syndrome A Report of the Scientific Workshop." Co-Sponsored by the NIH Office of Research on Women's Health and the Trans-NIH Working Group for Research on Chronic Fatigue Syndrome. Workshop held on June 12-13, 2003. Chaired by Dr. Debra Buchwald and Dr. Leslie Crofford. https://web.archive.org/web/20060921064325/http://orwh.od.nih.gov/CFS_June03Report.pdf

The workshop was chaired by Dr. Debra Buchwald of the University of Washington and Dr. Leslie Crofford of the University of Michigan Pain and Fatigue Clinic under Dr. Daniel Claaw. The final report stated that a model for this disease must address "the variability and clinical manifestations of CFS, including psychological distress" and "the altered perception or belief state for some of the crucial symptoms of CFS, such as exercise and cognition."

The NIH issued the following Science Series report in 2006, which reflected the 2003 conference and also noted the RFA that had been issued to address these issues.

- U.S. National Institute of Health. "Chronic Fatigue Syndrome." NIH Science Series 2006. National Institute of Health. 2006.
  https://web.archive.org/web/20060921064325/http://orwh.od.nih.gov/cfs/Chronic_Fatigue_Science_Series_FINAL.pdf
  The report stated:
  - "Any model of CFS must take into account a wide variety of published observations and findings. For instance, some experts believe that CFS is part of a family of disorders and thus is not a unique, identifiable disorder. Previous studies have detected a variety of biological abnormalities that are not specific for CFS and that are not consistently associated with severity or type of symptoms. The many meanings of "fatigue" also need to be addressed by investigators when designing studies that clarify a model for CFS; "fatigue" is a broad term that needs clearer definition and specification.
  - "Many researchers believe that changes in physical and mental functioning at the core of CFS are not well understood, but that most symptoms and findings can be explained by problems related to hormones that influence the activities of nerves. Researchers will need to design their studies to focus on models that can link mechanism and causation.
  - "Some areas ripe for investigation include whether neuroendocrine dysfunction is the cause or the result of physical inactivity, why significantly more women than men get CFS, what are the biological underpinnings of perception, and how perception is altered in individuals with CFS."

[712] Maupin C. "The CFS program at the NIH – Past, present, and future." *The CFS Report*. September 2005. http://www.cfidsreport.com/Articles/NIH/NIH_CFS_2.htm

[713] National Institutes of Health. "RFA: Neuroimmune Mechanisms and Chronic Fatigue Syndrome." National Institutes of Health. Release Date July 14, 2005. Part 1: Overview Information - http://grants.nih.gov/grants/guide/rfa-files/RFA-OD-06-002.html and Part II: Full Text of Announcement - http://grants.nih.gov/grants/guide/rfa-files/RFA-OD-06-002.html#PartII

Further information on NIH's activities on chronic fatigue syndrome at that time can be seen in NIH's 2007 biennial report.

- National Institutes of Health. *Biennial Report of the Director National Institutes of Health Fiscal Years 2006 & 2007*. National Institutes of Health. Undated.
  www.report.nih.gov/biennialreport0607/pdf/NIH_BR_Chapter2.pdf (page 52)
  The report stated, "Trans-NIH Chronic Fatigue Syndrome Research: NIH coordinates chronic fatigue syndrome research through a trans-NIH Working Group on Research on Chronic Fatigue. This working group developed an action plan to enhance the status of chronic fatigue syndrome research at the NIH and among the external and intramural scientific communities. The working group held a workshop on grantsmanship in FY 2007 to provide researchers with an overview of funding opportunities, an understanding of the NIH funding process, and an opportunity meet with program officials. In addition, the Office of Research on Women's Health and a subset of the work group ICs issued an RFA in FY 2006 to explicate how the brain, as the mediator of the various body systems involved, fits into the schema for understanding chronic fatigue syndrome. This RFA solicited proposals from multidisciplinary teams of scientists to develop an interdisciplinary approach to the study of chronic fatigue syndrome in men and women across the lifespan and resulted in seven new research projects on chronic fatigue syndrome."
  The report also provides a link to the grants awarded as a result of the RFA

– National Institutes of Health. "Chronic Fatigue Syndrome: 2006." National Institutes of Health. Undated. Archived June 2009. https://web.archive.org/web/20090604071957/http://orwh.od.nih.gov/cfs/2006NIHfundedCFSstudies.html

The list of grants awarded on this RFA can be found at:

– Trans-NIH Working Group on Chronic Fatigue Syndrome, National Institutes of Health. "NIH Announces Awards in Chronic Fatigue Syndrome Research." National Institutes of Health. Undated. Archived January 21, 2007. http://web.archive.org/web/20070121190839/http://orwh.od.nih.gov/cfs/awards2006.html

[714] Ibid. Link to grants awarded.

[715] Alter, Harvey. Testimony to the "Blood Products Advisory Committee Meeting." U.S. Food and Drug Administration. December 14, 2010. Page last updated February 14, 2014. http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/BloodProductsAdvisoryCommittee/ucm239304.htm

Harvey stated, "I'm absolutely convinced that when you define this disease by proper criteria, this is a very serious and significant medical disease, and not a psychological disease. It has the characteristics of a viral disease. It usually starts with a viral-like illness. If XMRV is not the causative agent — and it may well not be — there is still need by other groups to look for the next agent which may be the case."

[716] As observed by the author of this paper at the March 2014 Stanford Conference on ME/CFS where Dr. Lipkin also that he had received terrible scores on his submission. These statements were also reported on a number patient forums by other patients who attended the meeting, notably Phoenix Rising.

[717] Newby, Kris. "Immune System Disruption. The Search for Answers." *Stanford Medicine. Balancing Act.* Fall 2014. http://stanmed.stanford.edu/2014fall/immune-system-disruption.html

[718] U.S. Health and Human Services Advisory Committee. CFS Advisory Committee Meeting. November 9, 2011. http://www.hhs.gov/advcomcfs/meetings/minutes/cfsac_min-11092011.pdf (Page 46-47)
CFSAC discussion Between Dr. Klimas and Dr. Clayton of NIH.
Also see

- U.S. Health and Human Services Advisory Committee. CFS Advisory Committee Meeting. May 23, 2013. www.hhs.gov/advcomcfs/meetings/minutes/cfsacmay23_final_508.pdf (page 6)

  Dr. Maier of NIH stated "In order to increase the amount of funds that are spent on ME/CFS research, there needs to be an increase in the number of applications sent into NIH with well-crafted hypotheses, thoughtful and diligent experimental design, and careful attention to the science behind the application and the translational impact of the experimental outcome to the clinical realm."

[719] U.S. Health and Human Services Advisory Committee. CFS Advisory Committee Meeting. November 9, 2011 http://www.hhs.gov/advcomcfs/meetings/minutes/cfsac_min-11092011.pdf Page 30, 31
In a CFSAC exchange with Dr. Kitt of NIH. Dr. Kitt stated, "Another trend has developed in the past two years: if an individual is funded the first time, the person tends to not come back a second time. The CFS SEP is not getting competitive renewals very often." She also stated, "In the last two years, there were no new investigators in CFS that were reviewed. That is a problem for the field—that new investigators are not even submitting applications.

[720] Spotila Jennifer. "2012 NIH Spending on CFS Studies." *OccupyCFS.* May 15, 2013. http://www.occupycfs.com/2013/05/15/2012-nih-spending-on-cfs-studies/

Spotila stated, "Dr. Susan Maier, chair of the Trans-NIH ME/CFS Working Group, said at the October 2012 CFS Advisory Committee meeting that 18% of ME/CFS applications were funded in 2012, and that this represented a higher success rate than average at NIH." Spotila went on to say, "if 18% of grants were successful then this means that there may have been only 20 applications for ME/CFS research at NIH in 2012."

[721] Glaser, R. Presentation to U.S. Health and Human Services Advisory Committee. CFS Advisory Committee Meeting. May 2011. http://www.hhs.gov/advcomcfs/meetings/minutes/cfsac071128min.html

Includes discussion with Dr. Hanna of NIH during which Dr. Ronald Glaser stated, "The word is out that this issue exists with this study section. If I'm a young person with a good idea, I'm going to think carefully before I submit that proposal because I'm not sure if it's going to be worth the work. If I'm a senior person, it depends on the status of my laboratory and whether I have the resources. It's an issue that I hope would be addressed as NIH institutes its policy of multidisciplinary research."

[722] Newby, Kris. "Immune System Disruption. The Search for Answers." *Stanford Medicine. Balancing Act.* Fall 2014. http://stanmed.stanford.edu/2014fall/immune-system-disruption.html

[723] National Institutes of Health. "State of the Knowledge Workshop Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Research. Workshop Report." National Institutes of Health. April 7-8, 2011. http://orwh.od.nih.gov/research/me-cfs/pdfs/ORWH_SKW_Report.pdf

[724] U.S. Health and Human Services Advisory Committee. CFS Advisory Committee Meeting. May 23, 2013. www.hhs.gov/advcomcfs/meetings/minutes/cfsacmay23_final_508.pdf (Page 38).

Dr. Maier of NIH stated "I am begging you to go out and find people who will submit grants to NIH on this topic. I will personally help them. I can provide technical assistance with the grant application process. Any member of the

trans-NIH ME/CFS working group will provide applicants with technical assistance to get that application submitted. We can help you refine specific aims and we can help you determine which institute or center might be a better focus. I am begging you, please send in applications."

[725] National Institutes of Health. "Grants and Funding. Grant Process Overview." National Institutes of Health. Page last updated August 12, 2014. http://grants.nih.gov/grants/grants_process.htm and http://grants.nih.gov/grants/peer_review_process.htm#Initial

[726] Center for Scientific Review, National Institutes of Health. "Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) Special Emphasis Panel [ME/CFS SEP]." National Institutes of Health. Undated. http://public.csr.nih.gov/StudySections/IntegratedReviewGroups/IFCNIRG/CFSSEP/Pages/default.aspx

The website states, "The Myalgic Encephalomyelitis/Chronic Fatigue Syndrome recurrent Special Emphasis Panel [ME/CFS SEP] reviews applications in the multiple disciplines applied to studies of the potential causes, diagnosis, pathogenesis, clinical manifestations, epidemiology, and treatments of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. Of note, the members of this recurring SEP are recruited ad hoc each round based on expertise needed for the topic areas of the applications received."

[727] U.S. Health and Human Services Chronic Fatigue Syndrome Advisory Committee. CFS Advisory Committee Meeting. November 2011. http://www.hhs.gov/advcomcfs/meetings/minutes/cfsac_min-11092011.pdf Page 30

Dr. Kitt of NIH stated, "A standing committee usually reviews about 60-100 applications in a study section. CSR has 240 standing study sections and about 1,000 SEPs. The current number of CFS applications would not support a standing committee."

[728] The description of this disease used by the NIH Center for Scientific Review for the SEP varied over time as follows: November 2005 – SEP combined CFS, FM and other chronic polysystemic morbidity syndromes. The same text was used through from March 2009 through May 2011.

- National Institutes of Health, Center for Scientific Review. Chronic Fatigue Syndrome/ Fibromyalgia Syndrome Special Emphasis Panel [CFS SEP]. Last updated August 5, 2005. Archived November 13, 2005. https://web.archive.org/web/20051113160338/http://cms.csr.nih.gov/PeerReviewMeetings/CSRIRGDescription/MOSSIRG/CFSSEP.htm

  The website stated "The Chronic Fatigue Syndrome/ Fibromyalgia Syndrome [CFS SEP] continuing Special Emphasis Panel [SEP] reviews applications in the multiple disciplines applied to studies of the causes, manifestations and treatments of the Chronic Fatigue Syndrome, the Fibromyalgia Syndrome and other chronic polysystemic morbidity syndromes."

As of June 2011 – The site changed to be specific to CFS and then later to ME/CFS.

- Center for Scientific Review, National Institutes of Health. Chronic Fatigue Syndrome Special Emphasis Panel [CFS SEP]. Last updated June 1, 2011. Archived July 10, 2011. http://web.archive.org/web/20110710145002/http://cms.csr.nih.gov/PeerReviewMeetings/CSRIRGDescriptionNew/IFCNIRG/CFSSEP.htm

[729] Maupin, Craig. "The NIH and CFS." *The CFS Report,* September 2005. http://www.cfidsreport.com/Articles/NIH/NIH_CFS_1.htm

This article reviewed the NIH grant review and approval process. For the specific quotes, see

- Maupin, Craig. "Scientific Review, CFS, and the NIH--- The CFS Special Emphasis Panel." *The CFS Report,* September 2005. http://www.cfidsreport.com/Articles/NIH/NIH_CFS_3.htm
  Discusses Hoffeld's comments.

[730] Ibid.

Maupin's 2004 analysis of SEP roosters was reported in 2005 on The CFS Report.

[731] Glaser, R. Presentation to U.S. Health and Human Services Chronic Fatigue Syndrome Advisory Committee. CFS Advisory Committee Meeting. November 28-29, 2007. http://www.hhs.gov/advcomcfs/meetings/minutes/cfsac071128min.html

Dr. Glaser stated, "We found that over two years, only about 15 percent of study section members worked on anything related to CFS. There were no experts in etiology and maybe one in cytokines and the immune aspect of CFS."

Glaser also stated "I testified on a panel before Congress several years ago on the NIH budget. We were asked whether an influx of money would promote interdisciplinary research. We responded that money wouldn't make much of a difference without a change in the review process. If you have the same study sections with people who don't have the background in the appropriate area for the grant coming through, that grant's not going to get funded no matter how much money is there. The whole field doesn't move forward, not because there's no money, but because of the nature of the study sections."

[732] U.S. Health and Human Services Chronic Fatigue Syndrome Advisory Committee. CFS Advisory Committee Meeting. May 2008 Minutes http://www.hhs.gov/advcomcfs/meetings/minutes/cfsac080505min_pdf.pdf Page 74

[733] U.S. Health and Human Services Chronic Fatigue Syndrome Advisory Committee. CFS Advisory Committee Meeting. November 9, 2011. http://www.hhs.gov/advcomcfs/meetings/minutes/cfsac_min-11092011.pdf Page 31

Dr. Jason asked Dr. Kitt of NIH. "Your message to us repeatedly is how do we get more applications? What I hear from investigators is that because it is an SEP, sometimes the membership changes so that the reviewers are different

on the panel when the revisions come in. These reviewers sometimes have new sets of issues. I recognize that you cannot have a standing committee without more applications, but how do we deal with this issue of a different panel reviewing revised applications?"

[734] U.S. Health and Human Services Chronic Fatigue Syndrome Advisory Committee. CFS Advisory Committee Meeting. May 23, 2013. http://www.hhs.gov/advcomcfs/meetings/minutes/cfsacmay23_final_508.pdf Page 39

Dr. Mary Ann Fletcher stated, "I think I mentioned yesterday that three of us went to NIH by invitation to present our idea for a P01 application. We were told that the field was not yet ready for this. Last fall I sent in an application. There was some disagreement. One of the reviewers really didn't like it and the other did. I was the primary investigator (PI) and Nancy Klimas was the co-investigator. For the P01, I was the co- investigator and Nancy Klimas was the PI. I don't know that there's a better recognized person in the field. So I'm not sure why the field is not ready for applications. Right now I'm writing another grant to be sent in on June 24. I send one in practically every time, but I'm only funded about one every go- round with the committee. I was told that the funding rate is about 6%. That's awful low."

[735] Fero, Pat. "Inadequate National Institutes of Health funding for New Chronic Fatigue Syndrome grants." Wisconsin ME/CFS Association. September 27, 2010. http://www.investinme.org/Documents/NIH/Pat Fero CFSAC Oct 2010 NIH 9-27-10 11pm-1.pdf and http://www.wicfs-me.org/Pdf%20Files/NIH_CFS_funding_3_29_2011.pdf
Fero reported an approval rate of 7% for 2006-2008.

[736] Spotila Jennifer. "2012 NIH Spending on CFS Studies." *OccupyCFS.* May 15, 2013. http://www.occupycfs.com/2013/05/15/2012-nih-spending-on-cfs-studies/

Spotila stated, "Dr. Susan Maier, chair of the Trans-NIH ME/CFS Working Group, said at the October 2012 CFS Advisory Committee meeting that 18% of ME/CFS applications were funded in 2012, and that this represented a higher success rate than average at NIH." Spotila went on to say, "if 18% of grants were successful then this means that there may have been only 20 applications for ME/CFS research at NIH in 2012."

[737] U.S. National Institutes of Health. "Estimates of Funding for Various Research, Condition, and Disease Categories (RCDC)." National Institutes of Health. Published March 7, 2014. http://report.nih.gov/categorical_spending.aspx

NIH Funding for CFS in 2013 included two studies that do not appear to be CFS specific. One is "Neural mechanism of glucagon-like-peptide-1 receptor-mediated nausea /malaise" for $77,200 and the second is "Investigating Correlates and Therapeutics of Fatigue" for $83,921 for a total of $161K

[738] Spotila, Jennifer. "No Facts for You." *OccupyCFS*. June 6, 2013. http://www.occupycfs.com/2013/06/06/no-facts-for-you/

Spotila stated that she was told by NIH staff, "We no longer post this roster online due to threats some previous panel reviewers have received. Anyone who wishes to view the roster is advised to submit a Freedom of Information Act (FOIA) request to the NIH FOIA office."

[739] Newby, Kris. "Immune System Disruption. The Search for Answers." *Stanford Medicine. Balancing Act.* Fall 2014. http://stanmed.stanford.edu/2014fall/immune-system-disruption.html

[740] U.S. Health and Human Services Chronic Fatigue Syndrome Advisory Committee. CFS Advisory Committee Meeting. July 17, 2006. http://www.hhs.gov/advcomcfs/meetings/minutes/cfsac060717_min.html (page 18)
CFSAC discussion with Dr. Hanna of NIH.

Also see

- Letter from HHS to advocate Jill McLaughlin. April 6, 2001. https://listserv.nodak.edu/cgi-bin/wa.exe?A2=CO-CURE;52cbc044.0104E
  Letter regarding NIH's decision to move this disease to the Office Research on Women's Health.
- National Institutes for Health. "The Trans-NIH Working Group on Chronic Fatigue Syndrome." National Institutes for Health. November 2005.
  https://web.archive.org/web/20051110230137/http://orwh.od.nih.gov/cfs/cfsWG.html
  Provides basic background on the transfer to ORWH
- Maupin, Craig. "The CFS program at the NIH – Past, present, and future." *The CFS Report,* September 2005.
  http://www.cfidsreport.com/Articles/NIH/NIH_CFS_2.htm

[741] National Institute of Allergy and Infectious Disease. *Women's Health in the U.S. Research on Health Issues Affecting Women.* National Institute of Allergy and Infectious Disease, National Institutes of Health. February 2004. www.niaid.nih.gov/topics/womenshealth/documents/womenshealth.pdf

The Trans-NIH Workgroup was formed by at least 2001 based on this report on Women's Health. The report also discussed the Trans-NIH Work Group on CFS and the funding opportunity issued by Trans-NIG CFS workgroup in 2001. The report also discussed the three cooperative research centers that NIAID had been funding. Finally, the report also mentioned "a large-scale clinical trial of cognitive behavioral therapy and graded exercise in CFS patients" being sponsored by NIAID, along with the National Institute of Nursing Research.

[742] Trans-NIH ME/CFS Working Group, National Institutes of Health. "Trans-NIH Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome Research Working Group." *Trans-NIH ME/CFS Working Group Website*. Last revised June 5, 2014. http://orwh.od.nih.gov/research/me-cfs/

[743] Maupin, Craig. "The CFS program at the NIH – Past, present, and future." *The CFS Report,* September 2005. http://www.cfidsreport.com/Articles/NIH/NIH_CFS_2.htm

This report covered many facets of NIH approach to NIH including the rational for moving to the Office of Research on Women's Health. Maupin stated that Dr. Donna Dean stated that the intent in moving CFS was to make it easier to reach across institutes. She also said that she had been given the responsibility "of trying to straighten out, as much as I could, the mess that the NIH had gotten into with CFS (and the mess that DHHS had gotten into)." She further added "It was important to get the NIH CFS program leadership somewhere where people were focusing on scientific kinds of issues, on a scientific approach to medical conditions, without the encumbrances and biases of the past."

[744] U.S. Government Accountability Office. *CHRONIC FATIGUE SYNDROME: CDC and NIH Research Activities Are Diverse, but Agency Coordination Is Limited. (GAO Report* HEHS-00-98). U.S. Government Accountability Office, Washington, D.C. June 2, 2000. http://www.gao.gov/assets/240/230415.pdf and http://www.gao.gov/products/HEHS-00-98 (Page 70)

Findings included lack of coordination, inadequate communication, CDC misuse of funds

[745] Trans-NIH ME/CFS Working Group, National Institutes of Health. "Trans-NIH Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome Research Working Group." *Trans-NIH ME/CFS Working Group Website*. Last revised June 5, 2014. http://orwh.od.nih.gov/research/me-cfs/

As of December 2014, the Trans-NIH ME/CFS website included a funding opportunity announcement for the RO1 grant for "ME/CFS: Etiology, Diagnosis, Pathophysiology, and Treatment" http://grants.nih.gov/grants/guide/pa-files/PAR-12-032.html

[746] U.S. National Institutes of Health. "Estimates of Funding for Various Research, Condition, and Disease Categories (RCDC)." National Institutes of Health. Published March 7, 2014. http://report.nih.gov/categorical_spending.aspx

There are three records for the National Institute of Diabetes and Digestive and Kidney Diseases institute between 2010 and 2013

- Pain and Sensory Processing in IC/PBS and Fibromyalgia. Williams, David. $328,680. 2010
- Neural mechanism of glucagon-like-peptide-1 receptor-mediated nausea /malaise. Hayes, M. $80,000. 2012
- Neural mechanism of glucagon-like-peptide-1 receptor-mediated nausea /malaise. Hayes, M. $77,200. 2013

[747] Maupin, Craig. "The NIH and CFS." *The CFS Report,* September 2005. http://www.cfidsreport.com/Articles/NIH/NIH_CFS_1.htm

Maupin reported "On March 22, 2005, CAA Executive Officer Kim McCleary organized a conference call of advocacy leaders of 16 conditions funded by the NIH at less than 21 million dollars a year. According to McCleary, many of those leaders reported hearing the same comments from NIH staff, "We don't believe in this condition", "This is simply not a priority for our institute.", and "We don't get enough good fundable applications". McCleary also said "the challenge of funding multisystemic illnesses within the NIH's segmented structure" was also a topic of conversation among the conference call's participants."

[748] Division of Program Coordination, Planning and Strategic Initiatives, National Institutes of Health. "Trans-NIH Collaborations." National Institutes of Health. Last reviewed June 9, 2014. http://dpcpsi.nih.gov/collaboration/index

[749] U.S. Health and Human Services Chronic Fatigue Syndrome Advisory Committee. CFS Advisory Committee Meeting. November 9, 2011. http://www.hhs.gov/advcomcfs/meetings/minutes/cfsac_min-11092011.pdf (page 30)

[750] Hanna, E. Presentation to U.S. Health and Human Services Chronic Fatigue Syndrome Advisory Committee. CFS Advisory Committee Meeting. June 17, 2006. (Slide 2)

Dr. Hanna stated "It is only through an increase in meritorious proposals that funding can and will increase" - https://wayback.archive-it.org/3919/20140324192720/http:/www.hhs.gov/advcomcfs/meetings/presentations/presentation060717_ppt.ppt

[751] U.S. Health and Human Services Chronic Fatigue Syndrome Advisory Committee. CFS Advisory Committee Meeting. May 5, 2008. http://www.hhs.gov/advcomcfs/meetings/minutes/cfsac080505min_pdf.pdf (page 32)

Dr. Glaser stated: "The comments on pages 30-31 of the November 2007 CFSAC meeting minutes reflect how those of us on the Research Subcommittee feel about the review process, the SEP, and the hurdles that were just out of line with a fair review process."

[752] U.S. Health and Human Services Chronic Fatigue Syndrome Advisory Committee. CFS Advisory Committee Meeting. May 5, 2008. http://www.hhs.gov/advcomcfs/meetings/minutes/cfsac080505min_pdf.pdf (page 31, 98)

Discussion with Dr. Hanna of NIH on an RFA.

- Dr. Jason stated, "One thing that we think is important is Requests for Applications (RFAs) at NIH. When an RFA came out at NIH concerning CFS, there was a spike in applications and, particularly, grants that got funded. There were at least six grant applications that were funded. It seems that RFAs galvanize interest in applications and ultimately funded projects." (Page 31)
- Dr. Jason noted that there were 4 new grants in 2001, none in 2002, 3 in 2003, 1 in 2004, 2 in 2005, 6 in 2006 (with the RFA) and 3 in 2007." He went on to ask Dr. Hanna of NIH, "Given the enormity of the issues that we're

faced with, how do we get more grants submitted and funded? If this were another field such as HIV/AIDS, this would not be acceptable." (Page 98)

- Dr. Hanna responded, "I think the issue is what we try to do to interest people. We can only do so much. We will be having a meeting within the next two years on which we might base an RFA. But there are opportunities there for people to apply to and I'll have to echo what Cheryl said. A lot of it is up to your organizations to encourage your members to take advantage of the many funding opportunities that are available to them, especially in times of tight money. I know that the President finds money for what he wants to fund—money that isn't there. But the agencies are not able to do that. There is no appropriation for CFS research. The budget is what it is. What research we fund depends on what research you submit to us which we try to encourage with the RFAs and program announcements and by doing the work we all do together at the NIH." (Page 91)

Author's note: That meeting was the 2011 State of the Knowledge meeting. No RFA was issued after it.

Other stakeholders pointed out to NIH the positive impact of an RFA on applications.

- U.S. Health and Human Services Chronic Fatigue Syndrome Advisory Committee. CFS Advisory Committee Meeting. July 17, 2006. https://wayback.archive-it.org/3919/20140324192720/http:/www.hhs.gov/advcomcfs/meetings/minutes/cfsac060717min_pdf.pdf (Page 31)

  Kim McCleary stated, "As Dr. Hanna reported earlier, in 1999 there were zero CFS grants submitted to NIH for review. During the RFA round with $4 million in funding, there were 29 proposals submitted a short time after the announcement. This demonstrates that when there is the investment of financial resources, there is a response from the scientific community."

[753] Office of Extramural Research, National Institutes of Health. "Grants and Funding. Types of Grant Programs." National Institutes of Health. Last updated September 12, 2013. http://grants.nih.gov/grants/funding/funding_program.htm

[754] Solve ME/CFS Initiative. *Putting Research First.* Solve ME/CFS Initiative. Summer-Fall 2011 Report http://solvecfs.org/wp-content/uploads/2013/08/SummerFall2011.pdf

Summarizes the studies funded by Solve ME/CFS Initiative and the preliminary outcomes from those studies.

[755] U.S. Health and Human Services Chronic Fatigue Syndrome Advisory Committee. CFS Advisory Committee Meeting. November 9. 2011. http://www.hhs.gov/advcomcfs/meetings/minutes/cfsac_min-11092011.pdf (page 46-47)

In a CFSAC discussion between CFSAC members and Dr. Clayton of NIH, Dr. Klimas stated, "My following comment is directed toward NIH. When the CFIDS Association of American (CAA) had their call for proposals for their very small pot of money (about $120,000), they had 28 proposals. There is something essentially broken if the NIH is saying that it is getting 16 proposals. There are significant barriers there. When NIH had an RFA with a $4 million set-aside, the agency got more than 30 responses. I strongly urge NIH to put on its thinking cap and consider what is wrong when a small foundation can get more responses to an RFA than NIH can."

[757] IACFS/ME Board of Directors. "Open Letter to Dr. Francis Collins Director, National Institutes of Health." IACFS/ME Board of Directors. April 18, 2014. http://iacfsme.org/LinkClick.aspx?fileticket=tnCp3meyVmU%3d&tabid=36

Letter requested an RFA of 7-10M annually for 5 years

[758] Lofgren Z, Eshoo A, and 9 other U.S. congressmen and congresswomen. Letter to Dr. Francis Collins. March 19, 2014 https://dl.dropboxusercontent.com/u/57025850/Congressional%20letter%20-%20Dr.%20Collins%20-%20March%202014.pdf

[759] Health and Human Services. "Responses To Recommendations From The Chronic Fatigue Syndrome Advisory Committee: REF: October 3-4, 2012 CFSAC Meeting." Undated. Last accessed February 3, 2015. http://www.hhs.gov/advcomcfs/recommendations/response-from-ash-10-2012.pdf

[760] Collins, Francis. Response to Congresswoman Lofgren regarding request from eleven U.S. congressmen and congresswomen for an RFA. August 11, 2014. https://dl.dropboxusercontent.com/u/89158245/Dr%20Collins_Lofgren%20Ltr%20August%2011.pdf

Dr Collins stated, "Funding opportunities targeted to career development and enhancement will attract new investigators to the ME/CFS field, and funding opportunities targeted to training of students and postdoctoral fellows in ME/CFS research will contribute to the development of a sustainable biomedical workforce. This is a critical unmet need in the area since there are very few ME/CFS clinician-scientists pursuing this line of research (for example, the advocacy groups identify approximately 50 ME/CFS clinicians and scientists world-wide who are considered experts in this field.) This lack of sufficiently trained individuals applying for NIH research funds to conduct ME/CFS research projects contributes to the low number of applications received and subsequently the annual spending on ME/CFS research. We believe our commitment to targeted funding opportunities will increase the number of candidates who apply for funding and strengthen their skills, thereby resulting in an increase in the amount spent annually on ME/CFS research."

[761] U.S. Department of Health and Human Services. "Responses to Recommendations from the Chronic Fatigue Syndrome Advisory Committee. Ref: June 16-17, 2014, CFSAC Meeting." Undated. http://www.hhs.gov/advcomcfs/recommendations/hhs-cfsac-recommendations-response.pdf

The following text is part of the HHS Response to June 2014 CFSAC recommendation for an RFA (The CFSAC recommendation itself is listed on the previous page.

"Unfortunately there remains a lack of definitive evidence regarding the etiology, diagnosis, and treatment for ME/CFS. As such, issuing a Request for Applications (RFA) would not be an effective strategy as RFAs generally encourage a narrowly defined research area that addresses more specific gaps in scientific knowledge. RFAs are designed to build upon recommendations that have been identified through cutting- edge research findings in the extant literature, that address unmet NIH Institute mission-specific objectives, or that incorporate findings from workshops and conferences on specific topics"

[762] Links to the 2014 conferences on this disease

- Invest In ME. *Synergising Research into Myalgic Encephalomyelitis*. Invest In ME. Conference in London, England. May 2014
  - Conference Agenda - http://www.investinme.eu/IIMEC9.shtml#agenda
  - Conference report by Dr. Rosamund Vallings - http://www.investinme.eu/IIMEC9.shtml#report
  - Conference summary by Professor Edwards - http://www.investinme.org/Documents/Education/Invest%20in%20ME%20BRMEC4%20and%20IIMEC9%20Report%202014.pdf
  - Summary of conference by Phoenix Rising members - http://phoenixrising.me/archives/25516 and http://phoenixrising.me/archives/25447
- Stanford University. *2014 Stanford Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Symposium. Advances In Clinical Care And Translational Research*. Stanford University School of Medicine and Stanford Hospital and Clinics. Conference at Stanford, California. March 19, 2014.
- Agenda - http://med.stanford.edu/chronicfatiguesyndrome/documents/2014StanfordME_CFSSymposiumBrochurefinal.pdf
- Videos - http://med.stanford.edu/chronicfatiguesyndrome/2014SymposiumVideo.html
- Conference report by Dr. Rosamund Vallings – https://www.masscfids.org/resource-library/15-conference-reports/534-2014-stanford-mecfs-symposium-advances-in-clinical-care-and-translational-research
- International Association for CFS/ME. *Translating Science into Clinical Care.* International Association for CFS/ME Conference in San Francisco, California. March 20-23, 2014.
  - Agenda – http://www.iacfsme.org/Conferences/2014Conference/2014ProfessionalAgenda/tabid/535/Default.aspx
  - Conference Summary by Dr. Anthony Komaroff
    Video - http://www.prohealth.com/library/showarticle.cfm?libid=18864
    Transcript (provided by MECFS Forums)
    http://www.mecfsforums.com/wiki/Anthony_L._Komaroff,_MD;_Summary_3/23/2014
  - Conference Report by Dr. Rosamund Vallings - http://www.masscfids.org/resource-library/15-conference-reports/514-iacfsme-conference-2014-summary-rosamund-vallings-

[763] Institute of Medicine of the National Academies. "Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness." Institute of Medicine of the National Academies. Prepublication copy. February 10, 2015. Last accessed February 16, 2015. https://www.iom.edu/Reports/2015/ME-CFS.aspx Page 9 and page 225

[764] U.S. Health and Human Services Chronic Fatigue Syndrome Advisory Committee. CFS Advisory Committee Meeting. May 5, 2008. http://www.hhs.gov/advcomcfs/meetings/minutes/cfsac080505min_pdf.pdf (page 31, 98)

Discussion with CFSAC members and Dr. Hanna of NIH on an RFA. Dr. Hanna responded, "I think the issue is what we try to do to interest people. We can only do so much. We will be having a meeting within the next two years on which we might base an RFA." (Page 91)

[765] National Institutes of Health. "State of the Knowledge Workshop Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Research. Workshop Report." National Institutes of Health. April 7-8, 2011. http://orwh.od.nih.gov/research/me-cfs/pdfs/ORWH_SKW_Report.pdf

[766] Klimas, N. Presentation at Pandora Organization Research Report Series Webinar. February 24, 2015. https://www.youtube.com/watch?v=ldu843XAAHw. Minute 43:40
Dr. Klimas heads the Institute for Neuroimmune Research, Nova Southeastern

Dr. Klimas discussed the challenge with getting approval for the clinical trial from the reviewers. She said that to achieve that it requires the reviewers to "Buy into first that the illness is serious enough to use drugs that you would use in rheumatoid arthritis. Now for you and I, that's a no brainer. Of course, its serious enough… Of course you need biological response modifiers if they would work. But I couldn't get that past the review board. That's the sticking point. Are you sick enough to deserve serious therapy. So without phase 1 funding from private donations, I'm saying I lost 5 years here on this when I had an obvious target for treatment. And I've had to come around back at it using much less aggressive modalities and I think I will get those funded. But I have not been able to pick the obvious one,

the biolog response modifier that blocks IL-1. That makes so much sense, it exists, it's FDA approved. I am not allowed to touch it."

[767] U.S. Health and Human Services Chronic Fatigue Syndrome Advisory Committee. CFS Advisory Committee Meeting. November 9, 2011. http://www.hhs.gov/advcomcfs/meetings/minutes/cfsac_min-11092011.pdf (Page 30)

[768] U.S. Health and Human Services Chronic Fatigue Syndrome Advisory Committee. CFS Advisory Committee Meeting. May 5, 2008. https://wayback.archive-it.org/3919/20140324192720/http:/www.hhs.gov/advcomcfs/meetings/minutes/cfsac080505min_pdf.pdf (page 98)

[769] National Institutes of Health. "State of the Knowledge Workshop Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Research. Workshop Report." National Institutes of Health. April 7-8, 2011. http://orwh.od.nih.gov/research/me-cfs/pdfs/ORWH_SKW_Report.pdf
The SOK report made the following statements about the case definition:

- "These case definitions present a number of problems according to plenary presenters. For example, the lack of consistency in using one definition across the world is a major impediment to replicating findings in research and makes it exceedingly difficult to identify biomarkers for the disease. In addition, some of the case definitions lack explicit criteria for what meets threshold to be counted as one of the symptoms. As a consequence, some investigators use the occurrence of symptoms, rather than severity and frequency, to identify whether a person meets the threshold. More- over, the most commonly used definition across the world, CFS/Fukuda,6 is a "polythetic criteria," meaning that not all symptoms are needed to make a diagnosis. Rather, researchers and clinicians can select any four of eight symptoms instead of requiring a core common group of symptoms for a diagnosis. Finally, how a question is asked and how the data is collected can affect diagnosis."
- "The largest source of diagnostic unreliability is criterion variance. If the rules for identifying who is a patient and who is not differ, then problems will occur, not only for a patient seeking an accurate diagnosis, but for the entire scientific enterprise."

[770] Institute of Medicine of the National Academies. "Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness." Institute of Medicine of the National Academies. Prepublication copy. February 10, 2015. Last accessed February 16, 2015. https://www.iom.edu/Reports/2015/ME-CFS.aspx

[771] U.S. Health and Human Services Chronic Fatigue Syndrome Advisory Committee. CFS Advisory Committee Meeting. May 23, 2013. http://www.hhs.gov/advcomcfs/meetings/minutes/cfsacmay23_final_508.pdf (page 48)

In a discussion about the disposition of the October 2012 recommendation and the fact that P2P would not develop a case definition, Dr. Nancy Lee stated, "It may not be the goal of the workshop to come out with a research case definition, but there will be so much good evidence that that can be the next step."

[772] The IOM recommended criteria rely on a set of subjective criteria and does not specify objective tests. The report has recommended a number of symptom assessment tools but has not provided specific recommendations for threshhols of those tools; Jason has shown that differences in how the same tools are applied can cause issues. Additionally only two of the 25 tools recommended for assessing core symptoms have been validated for Fukuda and none for CCC. Eleven of the tools have never been used on this disease before and some of the tools, including those intended to be used to assess PEM, are marked as potentially hard to use clinically.
The list of assessment tools is found in the IOM report and also in the Guide for Clinicians

- Institute of Medicine of the National Academies. "Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness. Report Guide for Clinicians." Institute of Medicine of the National Academies. Undated. Last accessed April 9, 2015. http://www.iom.edu/~/media/Files/Report%20Files/2015/MECFS/MECFScliniciansguide.pdf

[773] Rowe, Peter. "Clinical Trial Design In CFS." Presentation to U.S. Food and Drug Administration, Center for Drug Evaluation and Research (CDER). "Drug Development For Chronic Fatigue Syndrome And Myalgic Encephalomyelitis: Public Workshop. Day Two. Scientific Drug Development Meeting." April 26, 2013. http://www.fda.gov/downloads/Drugs/NewsEvents/UCM355406.pdf (Page 170)

Dr. Peter Rowe stated, "And the design issues that come up the most are the careful selection of groups or subgroups which we've heard about before; the decisions on which groups of patients to include; at what point in the illness we include them -- early or with established symptoms; we need to look at how we include people with different levels of disease severity."

[774] Ibid. PDF Transcript Page 187
Dr. Peter Rowe also shared his experiences on a Fluorinef trial, which was unable to show effect in the tested patients although he had seen it work clinically. One potential explanation was that patients who had tried and failed many treatments might be refractory to treatment and their inclusion could swamp a positive signal.

[775] Snell, C. "Repeated CPET Results as Clinical Endpoints for ME/CFS Research." Presentation to U.S. Food and Drug Administration, Center for Drug Evaluation and Research (CDER) "Drug Development For Chronic Fatigue Syndrome And Myalgic Encephalomyelitis: Public Workshop. Day Two. Scientific Drug Development Meeting." April 26, 2013. http://www.fda.gov/downloads/Drugs/NewsEvents/UCM355406.pdf (Page 267)

Dr. Snell stated: "because it's a multidimensional illness and the endpoints are likely to rely on expertise from

different individuals, coordinating the whole thing is a major task and a major economic problem."

[776] Milne C, Malins A. "Academic-Industry Partnerships for Biopharmaceutical Research & Development: Advancing Medical Science in the U.S." Tufts Center for the Study of Drug Development, Tufts University School of Medicine, Boston, MA. April 2012. http://csdd.tufts.edu/files/uploads/tuftscsdd_academic-industry.pdf sponsored in part by a grant from the Pharmaceutical Research and Manufacturers of America (PhRMA)

[777] Office of the Assistant Secretary for Planning and Evaluation. U.S. Department of Health and Human Services. "National National Alzheimer's Project Act." U.S. Department of Health and Human Services. Page last updated February 12, 2015. Page last accessed February 17, 2015.

[778] Committee On Energy And Commerce. U.S. House Of Representatives. "H.R. 4701, The "Tick-Borne Disease Research Accountability and Transparency Act of 2014." Committee on Energy and Commerce. U.S. House of Representatives. Bill passed, September 9, 2014. Page last accessed February 17, 2015.

The website states, "H.R. 4701 was introduced by Rep. Christopher Gibson (R-NY) on May 21, 2014. As amended at the Full Committee markup, the bill creates a new Interagency Lyme and Tick-Borne Disease Working Group. The group would have federal and non-federal members, including members appointed by the Speaker of the House of Representatives and the Majority Leader of the Senate. The working group would develop a summary of research and advances related to Lyme disease and other tick-borne diseases, monitor and make recommendations to the Secretary regarding federal activities on Lyme disease and other tick-borne diseases, and hold annual public meetings. The group would submit a report to Congress on its activities every two years. The bill also would require the Secretary of Health and Human Services to develop a strategic plan informed by the summary of research developed by the working group.

[779] National Institute of Neurological Disorders and Stroke. "Muscular Dystrophy Coordinating Committee." National Institute of Neurological Disorders and Stroke. Last updated October 6, 2014. http://www.ninds.nih.gov/about_ninds/groups/mdcc/

According to the website, "The MDCC has conducted two stages of planning. The first stage led to the Muscular Dystrophy Research and Education Plan for NIH, which was submitted to Congress in August 2004. This formed the basis for a subsequent, more intensive planning process that produced the MDCC Action Plan for the Muscular Dystrophies (approved by the MDCC in December 2005). The Action Plan contains specific research objectives that are appropriate to the missions of all MDCC member agencies and organizations and thus serves as a central focus for coordination of research in muscular dystrophy."

[780] NIH has held a number of conferences on CFS. These include

985 First NIH conference on CFS Held by NIAID	No direct documentation of this workshop found. But as reported in the report for the second conference, a key issue was "In 1985 at the first NIAID workshop, it was agreed that the greatest obstacle to CFS research was the lack of an objective case definition."
Second NIH Conference on CFS - March 1991 Held by NIAID. And National Institute of Mental Health	Purpose was to review the collective experience of investigators in the United States who have been using the CDC criteria for case definition in their research and, if necessary, to make recommendations concerning further modification and 2) to discuss approaches to assessment of illness severity for studies of natural history and intervention. Report: Schluederberg A, Straus S, Peterson P, Blumenthal S, Komaroff A, Spring S, Landay A, Buchwald D. "NIH Conference. Chronic Fatigue Syndrome Research Definition and Medical Outcome Assessment." *Annals of Internal Medicine* August 1992; 117(4): 325-31. PMID: 1322076. http://annals.org/article.aspx?articleid=705740 (abstract) and http://annals.org/data/Journals/AIM/19757/AIME199208150-00010.pdf (full text)

February 2000 Internal Science Consultation Held by NIAID	- Held in response to CFSCC recommendation but planned without CFSAC input - Stated purpose was to improve the quality, direction and extent of CFS research supported by NIH - Attendees - Originally planned to only include Simon Wessely, Michael Sharpe, Mark Demitrack and Stephen Straus. The revised meeting was attended by group of 11 people, including Gail Cassell (chair), Margaret Chesney, Mark Demitrack, Charles Engel, Helen Mayberg, Kevin McCully, William Reeves, Joan Shaver, Michael Sharpe, Simon Wessely, Stephen Straus, Lon White, Barry Wilson, Nancy Klimas. Patient Kathy Rabin. It is unclear who of these individuals were given the opportunity to speak and who wrote the final report. - Produced report and led to 2001 AHRQ evidence based review noted elsewhere - Report: National Institute of Health. "Chronic Fatigue Syndrome. State-of-the-Science Consultation." Report of the National Institutes of Health State of Science CFS Consultation. February 6-7, 2000. http://webharvest.gov/peth04/20041027092632/www.niaid.nih.gov/dmid/meetings/cfsreport.htm - Report from CFIDS Association of America Walker, V. "A monumentous week for CFIDS Pressure mounts for CDC, NIH." CFIDS Association of America. Winter 2000. http://web.archive.org/web/20130424133259/http://www.cfids.org/archives/2000/2000-1-article02.asp
October 2000 State of the Science workshop Organized by CFSCC, not NIH as the other conferences in this list were.	- Purpose - focus on CFS research areas in which information is both mature and exciting; summarize current knowledge and identify important gaps in knowledge; garner the perspective of expert investigators not currently working on the problem of CFS; and identify expert investigators who might be attracted to study CFS as a clinical problem. - Topics - neuroendocrinology; cognition; chronic pain; sleep; immunology; orthostatic intolerance/neurally mediated hypotension; and fatigue, functional status, and disability. - Sponsorship – according to the report, this was organized by the CFSCC with financial support from CDC and NIH - Led to program announcement - Conference Report – Department of Health and Human Services Chronic Fatigue Syndrome Coordinating Committee. "Chronic Fatigue Syndrome. State of the Science Conference" Report of the HHS Chronic Fatigue Syndrome Coordinating Committee (CFSCC) State of Science Conference October 22-23, 2000. http://web.archive.org/web/20111121094434/http://www.co-cure.org/SOS.pdf - CFIDS Association of America Summary Walker, V. "The D.C. Dispatch. Your CFIDS Public Policy Report." CFIDS Association of America. Spring 2000. http://web.archive.org/web/20131902341600/http://www.cfids.org/archives/2000/2000-2-dcd.asp - Maupin C. "The CFS program at the NIH – Past, present, and future." *The CFS Report*. September 2005. http://www.cfidsreport.com/Articles/NIH/NIH_CFS_2.htm
June 12-13 2003 Neuroimmune Mechanisms and chronic fatigue syndrome held by NIH	- Report has a focus on stress and allostatic load. - Sponsored by NIH Office on Women's Health and Trans-NIH Working Group on Research on CFS Conference Report – U.S. National Institutes of Health. "Neuroimmune Mechanisms and Chronic Fatigue Syndrome A Report of the Scientific Workshop." Co-Sponsored by the NIH Office of Research on Women's Health and the Trans-NIH Working Group for Research on Chronic Fatigue Syndrome. Workshop held on June 12-13, 2003. Chaired by Dr. Debra Buchwald and Dr. Leslie Crofford. https://web.archive.org/web/20060921064325/http://orwh.od.nih.gov/CFS_June03Report.pdf

April 2011 NIH State of Knowledge Workshop held by National Institutes of Health	National Institutes of Health. "State of the Knowledge Workshop Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Research. Workshop Report." National Institutes of Health. April 7-8, 2011. http://orwh.od.nih.gov/research/me-cfs/pdfs/ORWH_SKW_Report.pdf Sponsored by Office Research on Women's Health, National Institutes of Health and U.S. Department of Health and Human Services.

781 U.S. Health and Human Services Chronic Fatigue Syndrome Advisory Committee. CFS Advisory Committee meeting, November 9, 2011. http://www.hhs.gov/advcomcfs/meetings/minutes/cfsac_min-11092011.pdf Page 29.

782 National Institutes of Health. "State of the Knowledge Workshop Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Research. Workshop Report." National Institutes of Health. April 7-8, 2011. http://orwh.od.nih.gov/research/me-cfs/pdfs/ORWH_SKW_Report.pdf

The report stated that "a number of biomarkers have been described but need to be validated… including natural killer (NK) cell function, perforin, cell membrane dipeptidyl peptidase-4 (CD26 antigen), and levels of various individual cytokines."

783 Maier, S. Presentation to U.S. Health and Human Services Advisory Committee. CFS Advisory Committee Meeting. October 3 2012. http://www.hhs.gov/advcomcfs/meetings/minutes/cfsac10032012.pdf (Page 25) Presentation: http://www.hhs.gov/advcomcfs/meetings/presentations/nihupdate.pdf. (Slide 9).

The minutes stated, "We were working hard this summer as a group to produce a prioritized plan for implementing ME/CFS research based on the gaps in research that were identified from the April 2011 State of the Knowledge Workshop on ME/CFS. At this point in time, we are working on implementation of the prioritized plan, which involves:"

- "Assessment of the methods to collect information on the state of the field."
- "A needs assessment related to resources and tools that will facilitate the conduct of research in the gap areas."

Further information on this activity was provided in HHS response to these recommendations:

- U.S. Department of Health and Human Services. Response to CFS Advisory Committee Recommendation of October 3-4, 2012. http://www.hhs.gov/advcomcfs/recommendations/response-from-ash-10-2012.pdf

  The response stated, "As part of a broader approach to support ME/CFS research, the Trans-NIH ME/CFS Research Working Grouo recently completed a planning exercise to prioritize approaches to enhance ME/CFS research excellence identified by attendees of the 2011 State of the Knowledge Workshop, which included input from researchers, clinicians, patients and patient advocate groups. To address the highest priority identified, which was "case definition issues," the Working Group submitted a competitive application for an Evidence-based Methodology Workshop on ME/CFS coordinated by the NIH Office of Disease Prevention."

784 U.S. Health and Human Services Chronic Fatigue Syndrome Advisory Committee. CFS Advisory Committee meeting, October 13-14, 2010. Last accessed February 4, 2015. https://wayback.archive-it.org/3919/20140324192901/http://www.hhs.gov/advcomcfs/meetings/minutes/viewattachment.pdf Page 57

785 Personal email exchange between Dr. Susan Maier and Mary Dimmock. December 18, 2012.

In the email, Dr. Maier stated "Regarding the ME/CFS Research Plan. The prioritized plan for ME/CFS research is an internal document developed by the Trans-NIH ME/CFS Research Working Group from the State of the Knowledge Workshop recommendations, which provides a framework for engaging researchers, providing access to resources, and fostering the development of collaborations that will facilitate ME/CFS research overall. The first priority within that plan is to perform an evidence review of the ME/CFS case definitions and outcomes and hold a workshop (including researchers, clinicians, patients, patient advocate groups) to explore the extent to which the case definitions capture various sub-groups of individuals with the illness in order to guide future research direction."

The email also stated, "The prioritized plan is not published because it is an internal, dynamic working document open to changes in light of new discovery. The prioritized plan was developed with stakeholder input and participation in the State of the Knowledge Workshop meeting."

786 Caligiuri M, Murray C, Buchwald D, Levine H, Cheney P, Peterson D, Komaroff A, Ritz J. "Phenotypic and functional deficiency of natural killer cells in patients with chronic fatigue syndrome." *The Journal of Immunology* November 15, 1987; 139(10): 3306-3313.PMID: 2824604. http://www.jimmunol.org/content/139/10/3306.abstract

787 Klimas NG, Salvato FR, Morgan R, Fletcher MA. "Immunologic abnormalities in chronic fatigue syndrome." *J Clin Microbiol* June 1990; 28(6): 1403-10. PMID: 2166084. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC267940/

788 Brenu EW, Johnston S, Hardcastle SL, Huth TK, Fuller K, Ramos SB, Staines DR, Marshall-Gradisnik, SM. "Immune Abnormalities in Patients Meeting New Diagnostic Criteria for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis." J Mol Biomark Diagn November 14, 2013. 4: 152. http://dx.doi.org/10.4172/2155-9929.1000152 and http://www.omicsonline.org/immune-abnormalities-in-patients-meeting-new-diagnostic-criteria-for-chronic-fatigue-syndromemyalgic-encephalomyelitis-2155-9929.1000152.pdf

This paper examined immune markers for patients from an ME/CFS clinic in Australia. The patients were characterized as to whether they met ME-ICC versus Fukuda and their immunological markers were compared. The study found that NK Cell activity was reduced in both groups. Given Maes' study comparing markers for patients with PEM versus those without, it will be important to understand to what extent the Fukuda patients in this sample had PEM.

[789] Institute of Medicine of the National Academies. "Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness." Institute of Medicine of the National Academies. Prepublication copy. February 10, 2015. Last accessed February 16, 2015. https://www.iom.edu/Reports/2015/ME-CFS.aspx Page 221.

[790] Snell C, Stevens S. "Cardiopulmonary Exercise Testing (CPET) & Evaluating Functional Capacity." Presentation at U.S. Health And Human Services CFS Advisory Committee Meeting, October 12, 2010. https://wayback.archive-it.org/3919/20140324192901/http://www.hhs.gov/advcomcfs/meetings/minutes/viewattachment.pdf

- Slides - http://www.hhs.gov/advcomcfs/meetings/presentations/presentation_10132010_snell-stevens.pdf
- Video – starting at 4:38 - http://hhs.granicus.com/MediaPlayer.php?view_id=5&clip_id=99; http://media-02.granicus.com:443/ondemand/hhs/hhs_b947e197-a39c-4c51-8b89-077723983c8c.mp3

Includes references to statements by various medical societies including the American Heart Association, about the use of CPET as a gold standard

[791] Snell, C. "Repeated CPET Results as Clinical Endpoints for ME/CFS Research." Presentation to U.S. Food and Drug Administration, Center for Drug Evaluation and Research (CDER). "Drug Development For Chronic Fatigue Syndrome And Myalgic Encephalomyelitis: Public Workshop. Day Two. Scientific Drug Development Meeting." April 26, 2013. http://www.fda.gov/downloads/Drugs/NewsEvents/UCM355406.pdf (Page 225)

Dr. Snell stated, "I just put cardio-pulmonary exercise testing into clinicaltrials.gov and there are just under 400 clinical trials around the world that currently include cardio-pulmonary exercise testing in their protocol."

[792] CPET Replication studies by Keller and Vermeulen.

- Keller, B., Pryor, J., Giloteaux, L. Inability of myalgic encephalomyelitis/chronic fatigue syndrome patients to reproduce VO2peak indicates functional impairment. Journal of Translational Medicine April 2014, 12:104. PMID: 24755065. http://dx.doi.org/10.1186/1479-5876-12-104
- Keller B, Micale F. "Exercise Testing to Quantify Effects of Fatigue on Functional Capacity in Patients With CFS." Abstract of presentation given at IACFS/ME Biennial Conference; Translating Evidence Into Practice. 2011. Ottawa, Ontario, Canada. http://iacfsme.org/LinkClick.aspx?fileticket=%2BG6GTkbP33I%3D&tabid=499 Page 12
- Vermeulen RC, Kurk RM, Visser FC, Sluiter W, Scholte HR. "Patients with chronic fatigue syndrome performed worse than controls in a controlled repeated exercise study despite a normal oxidative phosphorylation capacity." *J Transl Med,* 2010. 8: p. 93. http://dx.doi.org/10.1186/1479-5876-8-93

[793] Keller, B., Pryor, J., Giloteaux, L. Inability of myalgic encephalomyelitis/chronic fatigue syndrome patients to reproduce VO2peak indicates functional impairment. Journal of Translational Medicine April 2014, 12:104. PMID: 24755065. http://dx.doi.org/10.1186/1479-5876-12-104

This paper stated, "ME/CFS patients currently represent a unique class of ill patients who do not reproduce maximal CPET measures, unlike individuals with cardiovascular disease, lung disease, end-stage renal disease, pulmonary arterial hypertension and cystic fibrosis."

[794] Racaniello V, Lipkin I. "TWiV Special: A paradigm for pathogen de-discovery." *This Week In Virology.* September 18, 2012. Webcast: http://www.twiv.tv/2012/09/18/twiv-special-a-paradigm-for-pathogen-de-discovery/ Transcript: http://www.twiv.tv/TWiV-Special-XMRV-091812.pdf

Audio of discussion between Dr. Vincent Racaniello and Dr. Ian Lipkin regarding the results of the XMRV study. September 18, 2012. Discussed the study that Lipkin performed to assess whether the XMRV finding was real or a contaminant. The patients were further well characterized by their level of functional capacity. The samples were obtained and handled in a consistent fashion to avoid extraneous variance.

[795] United States Senate,113th Congress. *Departments Of Labor, Health And Human Services, And Education, And Related Agencies Appropriation Bill, 2014.* Report 113-71. Washington, D.C. http://thomas.loc.gov/cgi-bin/cpquery/T?&report=sr071&dbname=113&

The report stated "Further, the Committee encourages NIH to issue a special funding opportunity to spur research into ME/CFS using the clinical specimens collected under an NIAID-funded study. This resource could help speed diagnostics and better understanding of the pathophysiology of this severely disabling condition."

[796] Comment about strategic use and first-come-first-served disposition based on an email exchange on October 10-12, 2012 between M. Dimmock and Dr. Maier and Dr. Eun-Chung Park.

- Questions that were asked of NIH were 1) Is there a strategy in place that could guide approval of which studies get selected? There are a variety of key research questions that these samples could help to answer? 2) in a first-come, first-serve approach, do you have a mechanism to ensure that these samples achieve their greatest impact in specifically understanding ME/CFS biopathophysiology, biomarkers, subsets, etc?

- NIH staff stated, "Thus, the intent of the program announcement is to supply samples to applicants, pending meritorious scientific review of the proposal, for any scientific purpose that helps advance understanding of the etiology and/or pathogenesis of CFS."
- NIH staff also stated, "We understand your concerns and do want to ensure that these clinical samples will be used to advance our knowledge base and ultimately benefit the CFS patient community. We believe we have addressed this issue by choosing our language carefully to reach and attract a wide group of researchers both already involved in and new to the ME/CFS field. Importantly, we have communicated with the review officer for the CFS SEP and she will make sure the review committee is aware of the announcement and its intent."

Also see

- Spotila, Jennifer. "Those Lipkin Samples." *OccupyCFS*. September 22, 2012. http://www.occupycfs.com/2012/09/22/those-lipkin-samples/ confirming that NIH would not provide set-aside funds for these samples.

[797] U.S. Government Accountability Office. *CHRONIC FATIGUE SYNDROME: CDC and NIH Research Activities Are Diverse, but Agency Coordination Is Limited. (GAO Report* HEHS-00-98). U.S. Government Accountability Office, Washington, D.C. June 2, 2000. http://www.gao.gov/assets/240/230415.pdf and http://www.gao.gov/products/HEHS-00-98(Page 66)

[798] NIH News. "NIAID Funds Three Chronic Fatigue Syndrome (CFS) Research Centers." October 20, 1999. Page last accessed February 5, 2015. http://www.niaid.nih.gov/news/newsreleases/Archive/1999/Pages/cfsrsch.aspx

[799] Hanna, Eleanor. Presentation at U.S. Department of Health and Human Services CFS Advisory Committee Meeting. September 29, 2003. https://wayback.archive-it.org/3919/20140324192720/http:/www.hhs.gov/advcomcfs/meetings/minutes/csfac_mins_2003.09.29r_pdf.pdf Page 11. The minutes stated, "Dr. Bell then asked about the status of the centers. Dr. Hanna explained that the NIAIDS Advisory Council recommended that the centers not be re-bid because they are located in Section 39, which was disbanded. Current centers will be funded until they close out their critical activities; they have been encouraged to submit RO1's."

[800] Maupin C. "The CFS program at the NIH – Past, present, and future." *The CFS Report*. September 2005. http://www.cfidsreport.com/Articles/NIH/NIH_CFS_2.htm

[801] Newby, Kris. "Immune System Disruption. The Search for Answers." *Stanford Medicine. Balancing Act.* Fall 2014. http://stanmed.stanford.edu/2014fall/immune-system-disruption.html

[802] Stanford University. *2014 Stanford Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Symposium. Advances In Clinical Care And Translational Research*. Stanford University School of Medicine and Stanford Hospital and Clinics. Conference at Stanford, California. March 19, 2014.

- Agenda - http://med.stanford.edu/chronicfatiguesyndrome/documents/2014StanfordME_CFSSymposiumBrochurefinal.pdf
- Videos - http://med.stanford.edu/chronicfatiguesyndrome/2014SymposiumVideo.html
- Conference report by Dr. Rosamund Vallings – https://www.masscfids.org/resource-library/15-conference-reports/534-2014-stanford-mecfs-symposium-advances-in-clinical-care-and-translational-research

[803] Goldman, Bruce. "Study finds brain abnormalities in chronic fatigue patients." Stanford Medicine News Center. October 28, 2014 http://med.stanford.edu/news/all-news/2014/10/study-finds-brain-abnormalities-in-chronic-fatigue-patients.html

[804] U.S. Department of Health and Human Services CFS Advisory Committee. "Comments from the HHS Chronic Fatigue Syndrome ADVISORY COMMITTEE. Subject: Draft Report. Pathways to Prevention: Advancing the Research on Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. January 2015. Last accessed February 4, 2015. Page 17 http://www.hhs.gov/advcomcfs/recommendations/cfsac-pathways-to-prevention-january-2015-updated.pdf

[805] National Institute of Health. Office of Disease Prevention. "NIH Pathways to Prevention Workshop: Advancing the Research on Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. Program Book. December 9-10, 2014. Draft Executive Summary." National Institute of Health. Office of Disease Prevention. Undated. Last accessed February 4, 2015. https://prevention.nih.gov/docs/programs/mecfs/ODP-MECFS-DraftReport.pdf

[806] Pharmaceutical Research and Manufacturers of America (PhRMA). "2014 Biopharmaceutical Research Industry Profile." Pharmaceutical Research and Manufacturers of America. Washington, D.C. April 2014. www.phrma.org/sites/default/files/pdf/2014_PhRMA_PROFILE.pdf Page 45

[807] U.S. Food and Drug Administration, Center for Drug Evaluation and Research. "Assignment of Drugs Developed to Treat Chronic Fatigue Syndrome (CFS)." Page last updated January 25, 2011. http://web.archive.org/web/20111028191041/http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm241014.htm

This announcement stated,

- "The Office of New Drugs (OND) recently announced a jurisdiction decision for products to treat chronic fatigue syndrome (CFS).
- "Applications for products being developed to treat chronic fatigue syndrome had previously been assigned to at least six different review divisions within OND. Across these applications, a variety of different endpoints have

been evaluated in assessing products for CFS. More recently there has been interest in the development of endpoints such as instruments that rely upon patient reported outcomes. Developing such tools may help facilitate development of new products to treat patients with CFS and allow for a better means for assessment of the benefits such products provide to patients."

- "In order to work effectively with internal and external stakeholders on developing clinical trial endpoints (e.g., PRO instruments designed for assessing patient symptoms and response in CFS) and clinical trial designs, OND leadership have agreed to assign all CFS applications to a single OND review division, the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP). This will allow for a coordinated and consistent process for review of products being developed for the treatment of CFS. In addition, consolidation to one division should allow for efficient and effective review, development of expertise within this area, and provide a single point of contact for CFS applications for stakeholders external to FDA."
- "Effective immediately, all new applications for drug and therapeutic biologic products for CFS, regardless of the proposed mechanism for the therapeutic product or primary endpoint, will be assigned to DPARP. Existing active applications (NDAs and INDs) will be transferred to DPARP in an orderly manner (timing to be mutually agreed between the DPARP and the currently assigned division)."

[808] U.S Food and Drug Administration. "Myalgic Encephalomyelitis and Chronic Fatigue Syndrome Webinar: Working Together for Change." U.S. Food and Drug Administration. Nov 15, 2012. Page last updated September 24, 2013. http://www.fda.gov/Drugs/NewsEvents/ucm369564.htm and https://collaboration.fda.gov/p75476335/?launcher=false&fcsContent=true&pbMode=normal (Video - Minute 18:1-20.56)

Dr. Kweder stated that there were 1800 new INDs total and 500 new INDs were from commercial companies and then said. "The ones that usually end up resulting in a marketing application are the ones that are commercial. (18.12)

Regarding ME/CFS, Kweder stated, "What we have been able to ascertain in house for ME or CFS, INDs that are for studies of treatments of ME or CFS. We have been able to locate evidence of nine INDs. Only four of those have had any active research ongoing within the past four years. Only four of the nine. One of those is a commercial IND, it is for the drug Ampligen by Hemispherix, and that has been open since 1990. And for that IND, the last randomized controlled trial ran from 1998 to 2004. So that is one of the four actives, the other three are much smaller research IND's of very small clinical trials of other things."

She went on to say that there had been only one new drug application for this disease.

[809] U.S. National Institutes of Health. "Clinical Trials.Gov". National Institutes of Health. Search on Sept 20, 2014. https://clinicaltrials.gov/ct2/results?term=chronic+fatigue+syndrome&Search=Search

Summary of search of Clinical Trials for CFS records

- Search conducted for chronic fatigue syndrome resulted in 67 records that targeted ME/CFS, either alone or in combination and an additional 106 records where ME/CFS not listed as the intervention in the title.
- Activity in last three years was judged by whether the clinicaltrials.gov record had been updated in three years.
- Of those, only 25 are for a trial of a drug, 14 are for behavioral therapy, 14 are for dietary supplements, activated charcoal or procedures, and 14 had no indication listed
- When filtered for those trials were not terminated and last updated in the last three years (Sept 1, 2011), there were only 17 trials of drugs. These included Rituxan (3), Ampligen (2), Sodium Oxybate (2) and single trials for drugs like Clonidine, Anakinra, Citalopram, Droxidopa, Etanercept, Interferon and ribavirin, and Methylphenidate.
- Of these 17 trials, 8 are listed as completed. The remaining 9 include include Rituxan. Ampligen, Anakinra, Duloxetine, Sodium Oxybate, Methyldopa and Methylphenidate.. Of these, only Ampligen and Methylphenidate are being conducted by a commercial interest. The rest are being conducted by universities and only three are U.S. based – 3 studies for Lisdexamfetamine Dimesylate, Duloxetine, L-NMMA trimethaphan/methyldopa

[810] Ampligen, which was apparently first used in 1988 according to this reference and then in trials since 1990. Today, Ampligen is provided under an open label, cost recovery trial and reportedly has been since 1997.

- The National Forum. "Appreciation: Nancy Kaiser." The National Forum. Undated. http://www.ncf-net.org/forum/fall-vol12-3-2.htm

[811] Relevant sources for the Ampligen review include:

- U.S. Department of Health and Human Services. Center for Drug Evaluation and Research (CDER). U.S. Food and Drug Administration. *ARTHRITIS ADVISORY COMMITTEE MEETING FDA Briefing Package.* Prepared for Ampligen Advisory Committee Meeting on December 20, 2012. http://www.fdatracker.com/2012/12/20/20121220-fda-arthritis-advisory-committee-meeting-webcast-audio-recording-heb-ampligen/ (2 hours 19 minutes) and www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/UCM345463.pdf
- SolveCFS Initiative (Formerly CFIDS Assoc). "FDA Panel Recommends Against Ampligen Approval." SolveCFS Initiative. December 2012. Last updated January 25, 2013. http://solvecfs.org/fda-panel-recommends-against-ampligen-approval/

- U.S. Food and Drug Administration. "FDA Response Letter Regarding Approval of Ampligen for ME/CFS." U.S. Food and Drug Administration. Page last updated February 5, 2013. http://www.fda.gov/Drugs/NewsEvents/ucm337750.htm
  FDA's notification to the public at the time of the Response Letter to Hemispherix.
- Simmaron Research. "Harsh FDA Report… Good Committee…Which Way Ampligen?" Simmaron Research. Undated but published prior to the Ampligen Advisory Committee meeting. http://simmaronresearch.com/simmaron-rising/harsh-fda-report-but-good-committee-which-way-ampligen-the-fda-advisory-meeting/
  Provides a summary of the trials conducted starting in 1990 and transfers across divisions of FDA

[812] Schweitzer, Mary. "Ampligen Diaries: Coda 1999-2007." Schweitzer, Mary. January 26, 2008. http://www.cfids-me.org/marys/ampcoda.html

[813] U.S. Department of Health and Human Services. Center for Drug Evaluation and Research (CDER). U.S. Food and Drug Administration. *ARTHRITIS ADVISORY COMMITTEE MEETING FDA Briefing Package.* Prepared for Ampligen Advisory Committee Meeting on December 20, 2012. http://www.fdatracker.com/2012/12/20/20121220-fda-arthritis-advisory-committee-meeting-webcast-audio-recording-heb-ampligen/ (2 hours 19 minutes) and www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/UCM345463.pdf (Page 122.)

Dr. Hennessey stated that Hemispherix had stated there were no approved therapies for CFS and then asked for someone "to summarize the data on cognitive behavioral therapy which I understand to be effective against chronic fatigue."

[814] U.S. Department of Health and Human Services. Center for Drug Evaluation and Research (CDER). U.S. Food and Drug Administration. *ARTHRITIS ADVISORY COMMITTEE MEETING FDA Briefing Package.* Prepared for Ampligen Advisory Committee Meeting on December 20, 2012. http://www.fdatracker.com/2012/12/20/20121220-fda-arthritis-advisory-committee-meeting-webcast-audio-recording-heb-ampligen/ (2 hours 19 minutes) and www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/UCM345463.pdf (Page 426)

[815] SolveCFS Initiative (Formerly CFIDS Assoc). "FDA Panel Recommends Against Ampligen Approval." SolveCFS Initiative. December 2012. Last updated January 25, 2013. http://solvecfs.org/fda-panel-recommends-against-ampligen-approval/

[816] U.S. Food and Drug Administration. "Drug Development for Myalgic Encephalomyelitis and Chronic Fatigue Syndrome (ME and CFS)." U.S. Food and Drug Administration. Last updated December 11, 2014. http://www.fda.gov/Drugs/NewsEvents/ucm319188.htm
FDA page of activities related to ME and CFS.

[817] U.S. Food and Drug Administration, Center for Drug Evaluation and Research (CDER). "FDA Workshop on Drug Development for Chronic Fatigue Syndrome (CFS) and Myalgic Encephalomyelitis (ME)" U.S. Food and Drug Administration, Center for Drug Evaluation and Research (CDER). Meeting April 25-26, 2013. Page last updated on December 11, 2014. http://www.fda.gov/Drugs/NewsEvents/ucm369563.htm

- Day 1: "Drug Development For Chronic Fatigue Syndrome And Myalgic Encephalomyelitis: Public Workshop. Day One. Patient-Focused Drug Development Meeting." http://www.fda.gov/downloads/Drugs/NewsEvents/UCM354951.pdf (Transcript.)
  This workshop was the first of a series of disease specific workshops held as part of the patient focused drug development initiative conducted as part of the Prescription Drug User Fee Act (PFUDA V).
- Day 2: "Drug Development For Chronic Fatigue Syndrome And Myalgic Encephalomyelitis: Public Workshop. Day Two. Scientific Drug Development Meeting." http://www.fda.gov/downloads/Drugs/NewsEvents/UCM355406.pdf (Transcript)

[818] U.S. Food and Drug Administration, Center for Drug Evaluation and Research (CDER). "Teleconference between FDA and Patients/Patient Advocates." U.S. Food and Drug Administration, Center for Drug Evaluation and Research (CDER). September 13, 2012.

- Website: Last updated September 24, 2013. http://www.fda.gov/Drugs/NewsEvents/ucm369565.htm
- Transcript: http://www.fda.gov/downloads/Drugs/NewsEvents/UCM320310.pdf

[819] Similar comments have been made by multiple speakers

- Kweder, Sandra speaking at "Teleconference between FDA and Patients/Patient Advocates." U.S. Food and Drug Administration, Center for Drug Evaluation and Research (CDER). September 13, 2012. http://www.fda.gov/downloads/Drugs/NewsEvents/UCM320310.pdf. Page 16
- Munos, B. at "Drug Development For Chronic Fatigue Syndrome And Myalgic Encephalomyelitis: Public Workshop. Day Two. Scientific Drug Development Meeting." April 26, 2013. http://www.tvworldwide.com/events/fda/130425/globe_show/default_go_archive.cfm?gsid=2249 (Video: Minute 8:00)

  Mr. Munos said that data is needed to characterize outcome measures but that the industry will not collect this data because the disease is so ill defined.

[820] U.S. Food and Drug Administration, Center for Drug Evaluation and Research (CDER). "Drug Development For Chronic Fatigue Syndrome And Myalgic Encephalomyelitis: Public Workshop. Day Two. Scientific Drug Development Meeting." April 26, 2013. http://www.fda.gov/downloads/Drugs/NewsEvents/UCM355406.pdf (Page 26)

[821] U.S. Food and Drug Administration, Center for Drug Evaluation and Research (CDER). "Drug Development For Chronic Fatigue Syndrome And Myalgic Encephalomyelitis: Public Workshop. Day Two. Scientific Drug Development Meeting." April 26, 2013. http://www.fda.gov/downloads/Drugs/NewsEvents/UCM355406.pdf (Page 302, 304, 330)

Jody L. Roth, MS, RAC, Director Regulatory Affairs, Biomedicines Eli Lilly and Company stated, "I think there are several questions I guess I would like to pose kind of to this question back, which is what are the criteria by which we need to have in place to register for a CSF (sic) indication? And we've already talked about regulatory path, but also then what might that look like? What are the claims or indications that might be associated with it? As we've heard over the last couple days, those can be anything from signs and symptoms to maintenance, and like one time I heard the word "cure." So what is that going to look like, and what do we need to make sure the clinical trials are set up to do?"

[822] U.S. Food and Drug Administration, Center for Drug Evaluation and Research (CDER). "Chronic Fatigue Syndrome and Myalgic Encephalomyelitis (CFS and ME) Stakeholder Teleconference". U.S. Food and Drug Administration, Center for Drug Evaluation and Research (CDER). October 16, 2013. Page last updated October 21, 2013 http://www.fda.gov/Drugs/NewsEvents/ucm370166.htm and http://www.fda.gov/downloads/Drugs/NewsEvents/UCM371482.pdf (Transcript Page 37 and 40)

Dr. Michele stated "I think that you outlined that beautifully because one of the concerns that I've heard from companies is that they may have difficulty getting reimbursement for approved products because the definitions are so wishy-washy that insurers may not be willing to pay for a product. So I think anything that we can do to facilitate definitions and importantly, to facilitate widespread uptake of these definitions by the medical community and a group with the status of the Institute of Medicine putting their shoulder to wheel on this, I think really does help augment those efforts of the patient community." (page 40)

[823] Ibid.

In response to a question on whether FDA is lumping ME and CFS together, Janet Maynard of FDA stated, "So currently FDA is using the term CFS, ME and CFS and ME interchangeably in describing these conditions and at this time the FDA does not endorse any particular definition. We're hoping that drug developers will focus on the measures of benefit in a defined patient population. We're sort of leaving it up to pharmaceutical companies to define which patient population they would like to study and establish that." (Page 37)

[824] U.S. Food and Drug Administration (FDA), Center for Drug Evaluation and Research (CDER). *The Voice of the Patient. Chronic Fatigue Syndrome and Myalgic Encephalomyelitis.* Report Date: September 2013. Report based on public testimony submitted at the Patient-Focused Drug Development Initiative Meeting for Chronic Fatigue Syndrome and Myalgic Encephalomyelitis held on April 25, 2013. http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM368806.pdf
Meeting agenda, transcript and video can be found at:

- U.S. Food and Drug Administration, Center for Drug Evaluation and Research (CDER). "FDA Workshop on Drug Development for Chronic Fatigue Syndrome (CFS) and Myalgic Encephalomyelitis (ME)" U.S. Food and Drug Administration, Center for Drug Evaluation and Research (CDER). Meeting April 25-26, 2013. Page last updated December 11, 2014. http://www.fda.gov/Drugs/NewsEvents/ucm369563.htm

[825] U.S. Food and Drug Administration (FDA), Center for Drug Evaluation and Research (CDER). *Guidance for Industry Chronic Fatigue Syndrome/Myalgic Encephalomyelitis: Developing Drug Products for Treatment DRAFT GUIDANCE.* U.S. Food and Drug Administration, Center for Drug Evaluation and Research (CDER). March 2014. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM388568.pdf .
The guidance states:

- "For this guidance, the terms CFS, ME, and CFS/ME are used interchangeably. The term CFS/ME is used in the singular to refer to a disease or set of diseases. The term CFS/ME is intended to be inclusive and does not infer the cause of different symptom complexes. Currently, the FDA does not recognize a particular definition or name as appropriate for use in clinical trials of drug products for CFS/ME." (Page 2)
- "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. Sponsors should provide justification for the chosen case definition or criteria and should provide sufficient details of the enrollment criteria. Consequently, any case definition or criteria for CFS/ME can be used to define the patient population. Sponsors should provide justification for the chosen case definition or criteria and should provide sufficient details of the enrollment criteria." (Page 3)

Note: The draft guidance leaves it up to the sponsor to choose what definition they want to use and how to select patients. Such an approach perpetuates the current problems by allowing the possibility that each sponsor defines the disease differently. And while the draft guidance does describe the types of efficacy endpoints (symptoms, exercise capacity/post-exertional malaise and health-related quality of life) that could be used, it is very general in its

statements and acknowledges that the tools that might be used to assess these endpoints have not been validated for this disease.

826 Comeford, Barbara. Presentation to U.S. Health and Human Services Chronic Fatigue Syndrome Advisory Committee. CFS Advisory Committee meeting, October 28, 2009. www.njcfsa.org/wp-content/uploads/2010/08/5-2-Presentation-to-the-Chronic-Fatigue-Syndrome-Advisory-Committee1.pdf

827 Van Hoof E, De Becker P, De Meirleir K. "Pediatric Chronic Fatigue Syndrome and Munchausen-By-Proxy: A Case Study." *Journal of Chronic Fatigue Syndrome* 2006; 13(2-3): 45-53. http://informahealthcare.com/doi/abs/10.1300/J092v13n02_02
Pediatric Chronic Fatigue Syndrome. Edited by De Meirleir K, McGregor N, Van Hoof E. February 7, 2007. According to title page, was co-published simultaneously as The Journal of Chronic Fatigue Syndrome. Volume 13 2/3. 2006. https://books.google.com/books?id=MrcUN2k91IMC&dq=Pediatric+Chronic+Fatigue+Syndrome.&source=gbs_navlinks_s

828 Colby, Jane. "False Allegations of Child Abuse in Cases of Childhood Myalgic Encephalomyelitis (ME)." *Argument and Critique*. July, 2014. http://www.argumentcritique.com/publications.html and http://www.tymestrust.org/pdfs/falseallegations.pdf

829 Holder, Nelda. "Home for the holidays". *Mountain Xpress* (Asheville, North Carolina). Jan 6, 2010. http://www.mountainx.com/article/26040/Home-for-the-holidays and http://www.bringingryanhome.com/

830 For information on the kinds of accommodations that can help students, see

- Mass CFIDS/ME and FM Association. "Pediatric ME/CFS: Resources for Patients, Parents, Schools and Clinical Practitioners." Mass CFIDS/ME and FM Association. August 2012. Last accessed February 17, 2015
  Mass CFIDS has delivered this program to various schools.
  http://www.masscfids.org/privatefiles/pediatricresourcecd2012/TABLE_OF_CONTENTS.html
- Newton, F. "Improving academic success for students with myalgic encephalomyelitis/chronic fatigue syndrome." *Fatigue: Biomedicine, Health & Behavior*. February 6, 2015. Last accessed February 19, 2015. http://dx.doi.org/10.1080/21641846.2015.1004831

831 U.S. Department of Labor. "Disability Resources. Job Accommodations." U.S. Department of Labor. Last accessed February 17, 2015. http://www.dol.gov/dol/topic/disability/jobaccommodations.htm
Also see:
Job Accommodation Network (JAN). "Accommodation and Compliance Series: Employees with Chronic Fatigue Syndrome (CFS)." Job Accommodation Network (JAN). Updated March 6, 2013. https://askjan.org/media/cfs.html
The website states that "JAN is one of several services provided by the U.S. Department of Labor's Office of Disability Employment Policy (ODEP)."

832 U.S. Health and Human Services Chronic Fatigue Syndrome Advisory Committee. CFS Advisory Committee meeting, October 4, 2012. http://www.hhs.gov/advcomcfs/meetings/minutes/cfsac10042012.pdf. Page 18.

833 U.S. Social Security Administration presentation at U.S. Health and Human Services Chronic Fatigue Syndrome Advisory Committee. CFS Advisory Committee meeting, November 9, 2011.
Meeting presentation materials provided by U.S. Social Security Administration.

- "Social Security Disability Programs."
  http://www.hhs.gov/advcomcfs/meetings/presentations/ssa_disability.pdf
- "Title II And Title XVI Disabled Beneficiaries In Current Pay For Impairment 9330 - Chronic Fatigue Syndrome As Of May 2009." http://www.hhs.gov/advcomcfs/meetings/presentations/data-2009cfs_current_pay_table.pdf
- Other meeting materials provided by Social Security Administration -
  http://www.hhs.gov/advcomcfs/meetings/presentations/11082011.html
- Meeting minutes http://www.hhs.gov/advcomcfs/meetings/minutes/cfsac_min-11092011.pdf (Page 25)

Also see:

- Spencer, Arthur. "Myalgic Encephalomyelitis/Chronic Fatigue Syndrome." U.S. Social Security Administration presentation at U.S. Health and Human Services Chronic Fatigue Syndrome Advisory Committee. CFS Advisory Committee meeting, October 4, 2012.
  http://www.hhs.gov/advcomcfs/meetings/presentations/ssapresentation.pdf

834 The estimate for unemployment can be seen in

- Taylor R, Kielhofner G. "Work-related impairment and employment-focused rehabilitation options for individuals with chronic fatigue syndrome: A review." *Journal of Mental Health*. 2005, 14(3): 253-267 http://dx.doi.org/10.1080/09638230500136571
  The paper stated, "Few studies of work-related impairment and work-focused rehabilitation in CFS exist. Rates of unemployment ranged from 35–69% and rates of job loss ranged from 26–89%."
- Collin S, Crawley E, May M, Sterne J, Hollingworth W, UK CFS/ME National Outcomes Database. "The impact of CFS/ME on employment and productivity in the UK: a cross-sectional study based on the CFS/ME national outcomes database." *BMC Health Services Research* 2011, **11**:217. Last accessed February 14, 2015. http://dx.doi.org/10.1186/1472-6963-11-217
  The paper stated that 50.1% "had discontinued their employment 'because of fatigue-related symptoms'."

- Reynolds, K., Vernon, S., Bouchery, E. and Reeves, W. "The economic impact of chronic fatigue syndrome." Cost Effectiveness and Resource Allocation 2004, 2:4. PMID: 15210053. http://dx.doi.org/10.1186/1478-7547-2-4
  The paper stated, "For women and men, we estimated about a 27% reduction in employment attributable to CFS." It also stated, "We estimated a 37% decline in household productivity and a 54% reduction in labor force productivity among people with CFS.
- Chu L. "US ME/CFS Patient Survey – April to May 2013". Survey performed in preparation for the FDA Stakeholder Workshop April 25,26, 2013. Preliminary results submitted to FDA: http://iacfsme.org/LinkClick.aspx?fileticket=pMB2%2bjKy7EQ%3d&tabid=36 and http://iacfsme.org/LinkClick.aspx?fileticket=YkMRCzqkxnQ%3d&tabid=36.
  Final results submitted to IOM: http://www.iacfsme.org/LinkClick.aspx?fileticket=PuRykxCauTk%3D&tabid=36
  The report states, "Of 623 respondents, "Only 13% were employed, with almost all citing ME or CFS as the reason why they could not work."

[835] U.S. Social Security Administration. "Social Security Ruling, SSR 14-1p; Titles II and XVI: Evaluating Claims Involving Chronic Fatigue Syndrome (CFS)." April 3, 2014. https://www.federalregister.gov/articles/2014/04/03/2014-07465/social-security-ruling-ssr-14-1p-titles-ii-and-xvi-evaluating-claims-involving-chronic-fatigue

[836] Krafchick S, Vernon S. "Social Security Ruling Rescinded and Replaced for ME/CFS." Undated but published after the April 3, 204 ruling cited in last reference. http://solvecfs.org/ss-ruling-rescinded-and-replaced-for-mecfs/
The article stated, "The presentations by the FDA's Dr. Sandra reminded us of the lack of consensus and confusion regarding ME/CFS definition and the need to define the core signs, symptoms and decrements in specific functioning. It is apparent from this revised ruling that the important clinical observations included in the CCC and ICC are helping to clarify these core signs and symptoms."

[837] Institute of Medicine of the National Academies. "Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness." Institute of Medicine of the National Academies. Prepublication copy. February 10, 2015. Last accessed February 16, 2015. https://www.iom.edu/Reports/2015/ME-CFS.aspx Appendix C

[838] Talmage J, Melhorn JM, Hyman MH, and American Medical Association *AMA Guides to the Evaluation of Work Ability and Return to Work.* Published by the American Medical Association. Second Addition, 2011.
The section focused on CFS stated (Chapter 8): "These patients experience symptoms, like pain and fatigue, with activity; however, the increase in subjective symptoms without any detectable objective correlate is not significant harm." The chapter went on to state that the best choice for the doctor is to state that there is "no need for physician imposed restrictions and no basis for physician described activity limitations" and that its up to the patient to decide if the rewards of work outweigh the symptoms experienced". The article went on to state "It is not the physicians decision to certify or not certify disability. It is the patient's decision to work or not to work."

[839] U.K. Department for Work and Pensions. *Continuing Medical Education Programme. Chronic Fatigue Syndrome / Myalgic Encephalomyelitis (CFS/ME) - Guidelines for the Disability Analyst.* Version 7, Module 6, Published May 28, 2014. http://www.actionforme.org.uk/Resources/Action%20for%20ME/dwp-training-doc-for-assessors-on-me.pdf
On pages 14-16, the manual incorrectly states that ICD lists CFS as both a neurological disease and as a subtype of neurasthenia. The ICD does not list CFS as a subtype of neurasthenia. The manual also equates CFS to the controversial somatic symptom disorder in the DSM-5 and states that the DSM 5 "emphasizes that the diagnosis of Somatic Symptom Disorder depends on the distressing somatic symptoms PLUS the abnormal thoughts or behaviours in response to the symptoms (i.e. maladaptive thoughts)"

[840] One example is ChampVA which denies all coverage if CFS is the only diagnosis.

- U.S. Department of Veterans Affairs. "Chapter 2, Section 16.2 CFS (Chronic Fatigue Syndrome)." in *ChampVA Policy Manual.* U.S. Department of Veterans Affairs. Accessed on line December 26, 2014. http://www.va.gov/PURCHASEDCARE/pubs/champva_policy.asp
  The policy for CHS is listed as
  - "A. Services or diagnostic testing and supplies required to rule out other causes of protracted fatigue are covered when appropriate based on benefit policy.
  - B. Benefits are limited to relieving individual symptoms, such as prescribing analgesics for headache or muscle pains. In those cases where there are irregular lab findings, treatment is covered for the identified causes.
  - The listed exclusions are:
  - CFS ICD (International Classification of Diseases)-9-CM (Clinical Modification) 780.71, when listed as the sole diagnosis on the claim.
  - Experimental/investigational (unproven) procedures used to diagnose or manage CFS.

[841] Aetna Insurance Company. "Clinical Policy Bulletin: Chronic Fatigue Syndrome." Aetna Insurance Company. Effective date: December 12, 1999. Last June 6, 2014. http://www.aetna.com/cpb/medical/data/300_399/0369.html
Regarding Neurasthenia, the policy includes the following statement on conditions that do not exclude a diagnosis of CFS: "Any condition defined primarily by symptoms that can not be confirmed by diagnostic laboratory tests, including fibromyalgia, anxiety disorders, somatoform disorders, non-psychotic or melancholic depression,

neurasthenia, and multiple chemical sensitivity disorder." Note that WHO ICD-10 excludes neurasthenia from G93.3, the code used for CFS in ICD-10.

[842] President Obama's Administration. *Open Government Initiative.* President Obama's Administration. Open Government Initiative. Undated. http://www.whitehouse.gov/open

The website stated, "On December 8, 2009, the White House issued an unprecedented Open Government Directive requiring federal agencies to take immediate, specific steps to achieve key milestones in transparency, participation, and collaboration. Agencies have set forth those steps in biennial Open Government Plans available on each agency's Open Government website."

[843] U. S. Health and Human Services. "HHS.gov Open Initiatives." U. S. Health and Human Services. Undated. http://www.hhs.gov/open/initiatives/

[844] U.S. Government Accountability Office. *CHRONIC FATIGUE SYNDROME: CDC and NIH Research Activities Are Diverse, but Agency Coordination Is Limited. (GAO Report* HEHS-00-98). U.S. Government Accountability Office, Washington, D.C. June 2, 2000. http://www.gao.gov/assets/240/230415.pdf and http://www.gao.gov/products/HEHS-00-98(Page 9)

[845] Ibid. Page 25.

The report stated, "CFSCC's five goals are (1) provide advice to the Secretary of HHS and others to ensure interagency coordination and communication regarding CFS research and other related issues, (2) develop complementary research programs that minimize overlap, (3) facilitate increased department and agency awareness of CFS research and educational needs, (4) identify collaborative and coordination opportunities in research and education, and (5) develop informed responses to constituency groups regarding agency efforts and progress."

[846] Ibid. Page 27.

The GAO report stated that the five goals of the CFSCC were to "(1) provide advice to the Secretary of HHS and others to ensure interagency coordination and communication regarding CFS research and other related issues, (2) develop complementary research programs that minimize overlap, (3) facilitate increased department and agency awareness of CFS research and educational needs, (4) identify collaborative and coordination opportunities in research and education, and (5) develop informed responses to constituency groups regarding agency efforts and progress"

[847] Ibid. Page 28.

The report stated, "At each of the committee's biannual meetings, representatives from each agency have described their recent CFS activities, but there has been little discussion about how to coordinate these activities. Moreover, according to agency officials, the meetings have had no effect on the direction of research at either CDC or NIH. However, agency officials stated that a change in the direction of research generally occurs as a result of relevant scientific or technical breakthroughs."

Note: given the context of the discussion, "agency" appears to apply to both CDC and NIH.

[848] U.S. Health and Human Services Chronic Fatigue Syndrome Advisory Committee. CFS Advisory Committee Meeting Recommendations. June 16-17, 2014. http://www.hhs.gov/advcomcfs/recommendations/06142014.html
Health and Human Services. "Responses to Recommendations from the Chronic Fatigue Syndrome Advisory Committee Ref: June 16-17, 2014, CFSAC Meeting." October 29, 2014.
http://www.hhs.gov/advcomcfs/recommendations/letter-to-slevine-from-sburwell-june-2014-recommendations.pdf

[849] Institute of Medicine of the National Academies. "Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness." Institute of Medicine of the National Academies. Prepublication copy. February 10, 2015. Last accessed February 16, 2015. https://www.iom.edu/Reports/2015/ME-CFS.aspx

The report made a number of recommendations for additional research and stated, "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."

[850] See the following sources:

- Sterling J, Kenney K. posted by Brehio, R. "Statement about the CFSCC." Co-Cure. May 21, 2002. https://listserv.nodak.edu/cgi-bin/wa.exe?A2=CO-CURE;b1c53d51.0205C
  Jon Sterling was chairman of The CFIDS Association of America and member of the DHHS CFS Coordinating Committee. Kenney (later McCleary) was the president and CEO. The letter concerns with the fact that the CFSCC had not met since January of 2013.
- CFIDS Association of America. "CFS Advisory Committee Status. Advocacy Alert." June 27, 2002. https://web.archive.org/web/20021019165735/http://www.cfids.org/advocacy/c-act_06272002.asp
  This was an advocacy alert on the failure of HHS to call for a CFSCC meeting in 18 months. Called for congressional action to ensure the CFSCC meetings were reinstituted.
- Letter from Assistant Secretary for Health Eve Slater to Jill McLaughlin regarding transition to advisory committee. August 30, 2002. Posted by McLaughlin on *Co-Cure*. September 14, 2002. https://listserv.nodak.edu/cgi-bin/wa.exe?A2=CO-CURE;4713084e.0209B

[851] Hanna, Eleanor. Presentation at U.S. Department of Health and Human Services CFS Advisory Committee Meeting. September 29, 2003. https://wayback.archive-it.org/3919/20140324192720/http:/www.hhs.gov/advcomcfs/meetings/minutes/csfac_mins_2003.09.29r_pdf.pdf

On page 11, The minutes stated, "Dr. Bell then asked about the status of the centers. Dr. Hanna explained that the NIAIDS Advisory Council recommended that the centers not be re-bid because they are located in Section 39, which was disbanded. Current centers will be funded until they close out their critical activities; they have been encouraged to submit RO1's."

[852] Hanna, Eleanor. Presentation at U.S. Department of Health and Human Services CFS Advisory Committee Meeting. September 29, 2003. https://wayback.archive-it.org/3919/20140324192720/http:/www.hhs.gov/advcomcfs/meetings/minutes/csfac_mins_2003.09.29r_pdf.pdf

The minutes provide a good summary information on the history of the CFSCC and the formation of the CFSAC (Page 10). Donna Dean, who headed the CFSCC when it was disbanded in January 2001, also discusses CFSCC background. Regarding the transition to CFSAC as discussed by Dean, the minutes note "An outcome of the GAO report was to bring the CFSCC in line with other HHS committees, where federal members would be ex officio non-voting members." (Page 6)

Note that when CFSAC was first created, it was managed by the Office of Public Health and Science.[852] In 2008, administrative support for CFSAC was moved to the Office of Women's Health in the Office of the Assistant Secretary for Health, reportedly to "provide more logistical support". See Dr. Parekh's comments in:

- U.S. Health and Human Services Chronic Fatigue Syndrome Advisory Committee. CFS Advisory Committee meeting, October 28, 2008. https://wayback.archive-it.org/3919/20140324192916/http://www.hhs.gov/advcomcfs/meetings/minutes/cfsac20081028min.html

Also see the 2006 charter.

- U.S. Department of Health and Human Services. "Charter. Chronic Fatigue Syndrome Advisory Committee." Charter in place through September 5, 2006. http://fido.gov/facadatabase/docs_charters%5C5136_Charter_(2002-10-23-17-41-21).doc

[853] Jason, L. "What's in a Name: Public Policy implications of Language." The Community Psychologist. Fall 2007; 40(4); 35-39.

[854] Letter from Assistant Secretary for Health Eve Slater to Jill McLaughlin regarding transition to advisory committee. August 30, 2002. Posted by McLaughlin on *Co-Cure*. September 14, 2002. https://listserv.nodak.edu/cgi-bin/wa.exe?A2=CO-CURE;4713084e.0209B

[855] Jason, L. "What's in a Name: Public Policy implications of Language." The Community Psychologist. Fall 2007; 40(4); 35-39.

[856] U.S. Health and Human Services. "Charter. Chronic Fatigue Syndrome Advisory Committee." Approved September 5, 2014. http://www.hhs.gov/advcomcfs/charter/

[857] Letter from Dr. Howard Koh, Assistant Secretary for Health and Human Services to patient advocates in response to a June 5, 2012 letter requesting a coordinated, fully funded, strategic federal response to this disease. Sept 11,2012. https://dl.dropboxusercontent.com/u/89158245/Dr%20Koh%20response%20Sept%2011.pdf

Dr. Koh stated, "HHS is working diligently to address ME/CFS using a multi- pronged approach. An ad hoc workgroup comprised of senior agency representatives has been assembled to increase and better coordinate the efforts of individual HHS components related to ME/CFS. This workgroup was instituted to address many of the concerns expressed in your letter including developing a strategic, coordinated response and providing evidence of a greater sense of urgency and focus. While the workgroup and its charge are inherently internal to HHS, some of the members are also ex officio members of the CFS Advisory Committee (CFSAC) where they hear the stakeholder perspective. CFSAC provides a mechanism to ensure stakeholders are engaged and have opportunities to provide input."

This letter was in response to

- Letter to U.S. Health and Human Services Secretary Sebelius, Assistant Secretary Dr. Howard Koh, Deputy Assistant Secretary Nancy Lee and the CFS Advisory Committee from patient advocates requesting a coordinated, fully funded, strategic federal response to this disease. June 5, 2012. https://dl.dropboxusercontent.com/u/89158245/Joint%20Request%20from%20the%20MECFS%20Community%20-%20June%202012%20Extended.pdf

[858] U.S. Centers for Disease Control and Prevention. "Patient-Centered Outreach and Communication Activity (PCOCA) teleconference." *CDC Fatigue Syndrome Website.* January 14, 2013. http://www.cdc.gov/cfs/meetings/cfspcoca-01-2013.html

At this call, the one question beyond those directed to the speaker was "Should CFS patients get the flu shot?"

[859] U.S. Department of Health and Human Services CFS Advisory Committee. CFS Advisory Committee recommendations. October 3-4, 2012 http://www.hhs.gov/advcomcfs/recommendations/10032012.html

The recommendation stated, "CFSAC recommends that you will promptly convene (by 12/31/12 or as soon as possible thereafter) at least one stakeholders' (Myalgic Encephalomyelitis (ME)/Chronic Fatigue Syndrome (CFS)experts, patients, advocates) workshop in consultation with CFSAC members to reach a consensus for a case definition useful for research, diagnosis and treatment of ME/CFS beginning with the 2003 Canadian Consensus Definition for discussion purposes."

[860] U.S. Department of Health and Human Services CFS Advisory Committee. CFS Advisory Committee Meeting. May 23, 2008. https://www.youtube.com/watch?v=GEAqwVmPpBE&list=PLrl7E8KABz1FGfzllYcomOoI9agz8-6QL&index=1 (video minute 35.20) and http://www.hhs.gov/advcomcfs/meetings/minutes/cfsacmay23_final_508.pdf (transcript page 48)

In a discussion on HHS's response to the CFSAC recommendation for a case definition. Dr. Lee stated, "Let me also say that the department took the recommendation which asked for research and clinical definitions and let that be advice from the committee. The original recommendation said something about working on both clinical and research definitions. What we decided to do with that amidst a good bit of controversy among the subcommittee calls—which I don't think we have the time to revisit—we discussed that NIH had the wonderful and already funded process to think about the research case definition. It may not be the goal of the workshop to come out with a research case definition, but there will be so much good evidence that that can be the next step. We are now actively pursuing methods to address the clinical research definition part. I think we should not discuss this anymore because I don't want to take up the rest of the day."

Author's note: This is not the first time that Dr. Lee reminded the committee that their role was to give advice. At the December 2013 CFSAC discussion on HHS's decision to engage the IOM, Dr. Lee stated "I just want to remind everyone that the Chronic Fatigue Syndrome Advisory Committee is an advisory committee; it is not an oversight committee. It is an advisory committee. We took the advice and we put it through our public health experience.".

- U.S. Department of Health and Human Services CFS Advisory Committee. CFS Advisory Committee Meeting December 11, 2013 http://www.hhs.gov/advcomcfs/meetings/minutes/cfsac-minutes-dec-11-b.pdf (Page 14)

[861] U.S. Department of Health and Human Services CFS Advisory Committee. CFS Advisory Committee Meeting. May 23, 2008. https://www.youtube.com/watch?v=GEAqwVmPpBE&list=PLrl7E8KABz1FGfzllYcomOoI9agz8-6QL&index=1 (Video at 41.30) and http://www.hhs.gov/advcomcfs/meetings/minutes/cfsacmay23_final_508.pdf (Minutes, page 49)

Allegations of intimidation of CFSAC members by the DFO

[862] Letter from Dr. Howard Koh, Assistant Secretary for Health to patient advocates in response to an June 12, 2013 request to the General Counsel that he investigate allegations of intimidation. October 31, 2013 https://dl.dropboxusercontent.com/u/89158245/KohResponse103113.pdf

Dr. Koh stated, "In providing direction and guidance for the Committee's activities, every effort is made to ensure that all the members are given equal opportunity to express their viewpoints and opinions. The concerns that have been expressed by the members will be taken into consideration as the Committee moves forward in working to accomplish its mission. However, it is important to understand that the Designated Federal Officer for CFSAC, Dr. Nancy C. Lee, has authority to engage in private conversations with individual members of CFSAC. These discussions may be confidential in nature and also may involve providing information about rules and regulations of the Federal Advisory Committee Act as they relate to managing CFSAC and the roles and responsibilities of the Committee members."

Dr. Koh's letter closed, stating "Thank you for your interest in the work being performed by CFSAC. The Committee is vital to the Department in its efforts to properly address the issues and concems of the CFS community. All engaged in this activity should conduct themselves in a manner that is conducive to respectful and candid discussions."

The original letter sent to HHS' General Counsel and a followup letter after Dr. Koh failed to address the allegations of intimidation.

- Letter from patient community to U.S. Health and Human Services General Counsel William Schulz requesting investigation of allegations of intimidation made at CFS Advisory Committee Meeting. Letter dated June 12, 2013. https://dl.dropboxusercontent.com/u/89158245/Letter%20to%20General%20Counsel%20June%2012.pdf
- Letter from patient community to U.S. Health and Human Services General Counsel William Schulz stating that Dr. Koh's response was non-responsive to our original request to investigate allegations of intimidation. Letter dated November 24, 2013. https://dl.dropboxusercontent.com/u/89158245/GeneralCounsel112413FINAL.pdf

[863] HHS first announced its IOM plans publicly through a solicitation on FedBizOps on August 27, a solicitation that originally had a September 3 response date later that was updated to September 11. HHS cancelled its solicitation request on September 4 after overwhelming patient opposition, stating that it intended to "pursue mechanisms to accomplish this work." On September 12, HHS announced that it intended to continue with the IOM contract. HHS did not release any information on the contract, saying that it could not until the contract had been signed. On September 23, HHS announced that the IOM would begin conducting its study by the end of September. On the same day, 35 disease expects sent a letter to Secretary Sebelius calling for her to adopt the CCC both both research and clinical work and not proceed with efforts like the IOM

The FedBixOps announcement can be found here

- U.S. Government's FedBizOppps. "Study on Diagnostic Criteria for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. Solicitation Number: 13-233-SOL-00686." FedBizOpps. First issued August 27, 2013. Cancelled on September 4, 2013. Last accessed February 20, 2015.

https://www.fbo.gov/index?s=opportunity&mode=form&tab=core&id=7fafc35816ee932dc44d6c319937b366&_cview=1

[864] Letter from Dr. Christopher Snell on behalf of fifty ME/CFS experts to Secretary Sebelius, Department of Health and Human Services. Originally sent on September 23, 2014. Resent on October 25, 2014. https://dl.dropboxusercontent.com/u/89158245/Case%20Definition%20Letter%20Sept%2023%202013.pdf

The letter stated "We strongly urge the U.S. 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. In addition, we strongly urge you to abandon efforts to reach out to groups such as the Institute of Medicine (IOM) that lack the needed expertise to develop "clinical diagnostic criteria" for ME/CFS. Since the expert ME/CFS scientific and medical community has developed and adopted a case definition for research and clinical purposes, this effort is unnecessary and would waste scarce taxpayer funds that would be much better directed toward funding research on this disease. Worse, this effort threatens to move ME/CFS science backward by engaging non-experts in the development of a case definition for a complex disease about which they are not knowledgeable."

[865] U.S. Department of Health and Human Services CFS Advisory Committee. "Comments from the HHS Chronic Fatigue Syndrome ADVISORY COMMITTEE. Subject: Draft Report. Pathways to Prevention: Advancing the Research on Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. January 2015. Last accessed February 6, 2015. Page 15 summarizes recommendations made to date by category http://www.hhs.gov/advcomcfs/recommendations/cfsac-pathways-to-prevention-january-2015-updated.pdf
Also see:

- U.S. Department of Health and Human Services CFS Advisory Committee. "Recommendations to the Secretary of Health and Human Services." U.S. Department of Health and Human Services CFS Advisory Committee. Page last updated February 9, 2015. Page last accessed April 7, 2015. http://www.hhs.gov/advcomcfs/recommendations/index.html
- U.S. Department of Health and Human Services CFS Advisory Committee. CFS Advisory Committee. "CFSAC Recommendations Since September 2004 Sorted by Focus Area, Agency, and Progress Last Updated: February 4, 2013." https://wayback.archive-it.org/3919/20140324192829/http://www.hhs.gov/advcomcfs/recommendations/cfsac_recommendationschart.pdf

  This chart marked some of these recommendations as completed but its important to assess what that really means. For instance, one example was to provide adequate funding to carry out the five year plan including identification of biomarkers, creation of guidelines done in partnership with CFS expertise. The recommendation is marked completed but we don't have biomarkers, the experts are routinely ignored by CDC and the five year plan was retired before it was completed and was never replaced.

[866] Schweitzer, Mary, Moderator. "Obama-Biden Transition Project, Health Care Community Discussion Report." December 30, 2008. http://www.cfids-me.org/dhhs/longreport.pdf
Advocates have directly petitioned and submitted a report to President Obama's transition team in 2008 that detailed the long-standing issues with this disease.

[867] U.S. Department of Health and Human Services CFS Advisory Committee. CFS Advisory Committee. "CFSAC Recommendations Since September 2004 Sorted by Focus Area, Agency, and Progress Last Updated: February 4, 2013." https://wayback.archive-it.org/3919/20140324192829/http://www.hhs.gov/advcomcfs/recommendations/cfsac_recommendationschart.pdf

- One example of where marked completed when it was not is the November 2006 CFSAC recommendation "Based on the positive response to the NIH's Request for Applications issued in July 2005 (funded in 2006), the Committee recommends equivalent funding for a second RFA. (11/06)". The recommendation was marked as completed with a note that NIH has issued 2 PA funding announcements. But the recommendation was specifically for an RFA and there has been extensive discussion at CFSAC that a regular program announcement is not achieving what an RFA will.

HHS has also indicated that certain recommendations were not doable when that appears to be incorrect. For instance, in HHS response to the 2012 CFSAC recommendation to investigate clusters, CDC said they were unable to identify clusters. But Incline village is a well-known cluster. The cluster recommendation response is here:

- U.S. Department of Health and Human Services. Response to CFS Advisory Committee Recommendation of October 2012. http://www.hhs.gov/advcomcfs/recommendations/response-from-ash-10-2012.pdf

[868] U.S. Department of Health and Human Services CFS Advisory Committee. "Highest Recommendations from the Chronic Fatigue Syndrome Advisory Committee." Voted on at the May 2013 CFS Advisory Committee Meeting. Undated. https://wayback.archive-it.org/3919/20140324192829/http://www.hhs.gov/advcomcfs/recommendations/cfsac-recs513.pdf

Note that the list was to be updated with new recommendations but it has not been updated since it was originally approved.

[869] U.S. Department of Health and Human Services CFS Advisory Committee. CFS Advisory Committee Meeting, Mar 11, 2014. www.hhs.gov/advcomcfs/meetings/minutes/cfsac-minutes-march-11-a.pdf (Page 71)

The reference to the recommendation for the Canadian Consensus Criteria was

- U.S. Department of Health and Human Services CFS Advisory Committee. CFSAC Recommendations. CFS Advisory Committee. June 14, 2012. *CFS Advisory Committee Website* http://www.hhs.gov/advcomcfs/recommendations/06132012.html

[870] U.S. Department of Health and Human Services CFS Advisory Committee. CFS Advisory Committee Meeting, May 5, 2008. http://www.hhs.gov/advcomcfs/meetings/minutes/cfsac080505min_pdf.pdf (page 22)

In an exchange between Dr. Jason and Dr. Reeves, Dr. Jason stated, "Do you both feel that you have adequately responded to the five recommendations made by this CFSAC at its last meeting?" Dr. Reeves stated: "I would point out that those are recommendations to the Secretary of Health and Human Services, not the CDC. As I have pointed out at multiple meetings, with respect to the research program, with respect to public awareness, we take this very seriously. I believe we have responded programmatically to the majority of suggestions when we can, but this committee exists to make recommendations to the Secretary of Health and Human Services, not to the Deputy Director of Science for CDC."

[871] "Yuppie Flu is Dead." *Listening to CFID.* Editor Sue Boetcher. Page undated, copyrighted 1996-1999. Page last accessed April 25, 2015. http://wwcoco.com/cfids/yuppieflu.html
Loveless was an infectious disease specialist and head of the CFS and AIDS Clinic at Oregon Health Sciences University. This statement is often quoted. This is one source from that time.

[872] Dimmock, M. "Appropriations Request History. 1995 to 2013 and GAO report." January 2014. https://dl.dropboxusercontent.com/u/89158245/Appropriations%20report%20language%20for%20MECFS.pdf

[873] Harrison, J. "Video cast [PODcast] of CFSAC Meetings." May 16, 2009. Mombu The Medicine Forum. http://www.mombu.com/medicine/medicine/t-act-video-cast-of-cfsac-meetings-down-14401034-last.html
Report on accommodations for live-streaming secured by the MAME organization.
Also see:

- Cambridge, Mass Commission for Persons with disabilities. "MAME Advocates Fight for Access to Meetings." Cambridge, Mass Commission for Persons with disabilities. April/May 2010. www.cambridgema.gov/cityofcambridge_content/documents/access0410.doc
- Harrison, J. "Mothers against Myalgic Encephalomyelitis (MAME) Issues Reminder of Forthcoming Meeting of the Chronic Fatigue Syndrome Advisory Committee now Accessible to People with CFS." *Co-Cure.* October 27, 2009. https://listserv.nodak.edu/cgi-bin/wa.exe?A2=CO-CURE;b7dc4326.0910D

[874] Spotila, J. "A Public Citizen." *OccupyCFS.* February 18, 2013. http://www.occupycfs.com/2013/02/18/a-public-citizen/

[875] Letter from President Obama to ME patient's wife Courtney Miller following up on Miller's question at a town hall. July 26, 2012. https://dl.dropboxusercontent.com/u/89158245/President-Obama-Letter-on-CFS.pdf

[876] June 2012 joint patient advocates for a strategic, coordinated, fully-funded plan for this disease, Dr. Lee's initial response, follow-up letter from patient advocates and Dr. Koh's Sept 2012 response.

- June 5, 2012 letter to HHS
  Letter to U.S. Health and Human Services Secretary Sebelius, Assisant Secretary of U.S. Health and Human Services Dr. Howard Koh, Deputy Assistant Secretary Nancy Lee and the CFS Advisory Committee from patient advocates requesting a coordinated, fully funded, strategic federal response to this disease. June 5, 2012. https://dl.dropboxusercontent.com/u/89158245/Joint%20Request%20from%20the%20MECFS%20Community%20-%20June%202012%20Extended.pdf
- July 17, 2012 response from Dr. Lee to patient advocates. See second half of the document. https://dl.dropboxusercontent.com/u/89158245/Response_to_Dr_Sebelius%20August%208.pdf
- August 8, 2012 Letter to HHS
  Letter to U.S. Health and Human Services Secretary Sebelius from patient advocates in response to Dr. Lee's response stating that the response was not acceptable. August 8, 2012. https://dl.dropboxusercontent.com/u/89158245/Response_to_Dr_Sebelius%20August%208.pdf
- September 11, 2012 response from Dr. Koh
  Letter from Dr. Howard Koh, Assistant Secretary of U.S. Health and Human Services to patient advocates in response to a June 5, 2012 letter requesting a coordinated, fully funded, strategic federal response to this disease. Sept 11,2012.
  https://dl.dropboxusercontent.com/u/89158245/Dr%20Koh%20response%20Sept%2011.pdf

  Dr. Koh stated, "Despite budgetary constraints, HHS is working diligently to address ME/CFS using a multi-pronged approach. An ad hoc workgroup comprised of senior agency representatives has been assembled to increase and better coordinate the efforts of individual HHS components related to ME/CFS. This workgroup was instituted to address many of the concerns expressed in your letter including developing a strategic, coordinated response and providing evidence of a greater sense of urgency and focus. While the workgroup and its charge are inherently internal to HHS, some of the members are also ex officio members of the CFS Advisory Committee (CFSAC) where they hear the stakeholder perspective. CFSAC provides a mechanism to ensure stakeholders are engaged and have opportunities to offer input."

[877] In a discussion on Oct 18, 2012 between patient advocates and Dr. Nancy Lee in response to a June 5, 2012 patient request to meet with key DHHS officials to address our concerns and to begin to formulate a strategic, coordinated and fully funded plan, both Dr. Lee and Dr. Woods iterated that DHHS would not be developing a strategy for ME.

- June 5, 2012 letter from patient advocates to HHS
  Letter to U.S. Health and Human Services Secretary Sebelius, Assisant Secretary Dr. Howard Koh, Deputy Assistant Secretary Nancy Lee and the CFS Advisory Committee from patient advocates requesting a coordinated, fully funded, strategic federal response to this disease. June 5, 2012.
  https://dl.dropboxusercontent.com/u/89158245/Joint%20Request%20from%20the%20MECFS%20Community%20-%20June%202012%20Extended.pdf
- July 17, 2012 response from Dr. Lee to patient advocates.. See second half of the document.
  https://dl.dropboxusercontent.com/u/89158245/Response_to_Dr_Sebelius%20August%208.pdf
- August 8, 2012 letter from patient advocates to HHS
  Letter to U.S. Health and Human Services Secretary Sebelius from patient advocates in response to Dr. Lee's response stating that the response was not acceptable. August 8, 2012.
  https://dl.dropboxusercontent.com/u/89158245/Response_to_Dr_Sebelius%20August%208.pdf
- September 2012 response from Dr. Koh
  Letter from Dr. Howard Koh, Assistant Secretary for Health and Human Services to patient advocates in response to a June 5, 2012 letter requesting a coordinated, fully funded, strategic federal response to this disease. Sept 11,2012.
  https://dl.dropboxusercontent.com/u/89158245/Dr%20Koh%20response%20Sept%2011.pdf
- October 18, 2012 meeting with Dr. Nancy Lee and Dr. Caira Woods, Advisor for Health and Science Policy, Office on Women's Health.

[878] U.S. Department of Health and Human Services, HHS Ad hoc Workgroup on ME/CFS. "HHS Department Actions Addressing Myalgic Encephalomyelitis/Chronic Fatigue Syndrome." HHS Ad hoc Workgroup on ME/CFS. Report on HHS 2011, 2012 Accomplishments. Published in 2013. Last updated in December 2014.
http://www.hhs.gov/advcomcfs/notices/mecfs-accomplishments.pdf
The following agencies were reported to be members

ACF – Administration for Children and Families
AHRQ – Agency for Healthcare Research and Quality
ASPE – Office of the Assistant Secretary for Planning and Evaluation
CDC – Centers for Disease Control and Prevention
CMS – Centers for Medicare and Medicaid Services
FDA – Food and Drug Administration
HRSA – Health Resources and Services Administration
NIH – National Institutes of Health
OASH/OWH – Office of the Assistant Secretary for Health/Office on Women's Health
SAMHSA – Substance Abuse and Mental Health Services Administration

On January 22, 2015, Barbara James, designated federal official for CFSAC confirmed that the group had been disbanded two years ago and had only compiled the one report listed above

[879] Letter from Dr. Howard Koh, Assistant Secretary of U.S. Health and Human Services to patient advocates in response to a June 5, 2012 letter requesting a coordinated, fully funded, strategic federal response to this disease. Sept 11,2012.
https://dl.dropboxusercontent.com/u/89158245/Dr%20Koh%20response%20Sept%2011.pdf

Dr. Koh stated, "While the workgroup and its charge are inherently internal to HHS, some of the members are also ex officio members of the CFS Advisory Committee (CFSAC) where they hear the stakeholder perspective. CFSAC provides a mechanism to ensure stakeholders are engaged and have opportunities to offer input."

[880] U.S. Government Accountability Office. *CHRONIC FATIGUE SYNDROME: CDC and NIH Research Activities Are Diverse, but Agency Coordination Is Limited. (GAO Report* HEHS-00-98). U.S. Government Accountability Office, Washington, D.C. June 2, 2000. http://www.gao.gov/assets/240/230415.pdf and http://www.gao.gov/products/HEHS-00-98 *(*Page 28)

The report stated, "Patient advocates serving on CFSCC have voiced their dissatisfaction with the committee's ability to get information from the agencies. Specifically, they have been unable to obtain timely information from CDC and NIH necessary to carry out their advisory function and to be responsive to constituents. According to some of the patient advocate members, they repeatedly requested from each agency, over separate time periods, information on funding and research activities but did not receive the information in a timely fashion."

[881] Spotila, Jennifer. "Not so FOIA." *OccupyCFS.* March 17, 2014. http://www.occupycfs.com/2014/03/17/not-so-foia/

Spotila has said that when she requested documents regarding voting member appointments to CFSAC, she was told the Office of Women's Health did not keep such records. But a FOIA request showed that they did keep such documentation. Spotila pointed out that advocates asked to see the CFS SEP rosters and were told this information – public for other NIH grant review panel – could not be released due to undisclosed security concerns.

[882] Jeannette Burmeister's FIOA lawsuit against U.S. Department of Health and Human Services.

- Burmeister, J. "US District Court: HHS/NIH Violated Federal Law in Response to FOIA Request for IOM Documents." *ThoughtsAboutME.* September 3, 2014. http://thoughtsaboutme.com/2014/09/03/us-district-court-hhsnih-violated-federal-law-in-response-to-foia-request-for-iom-documents/
- Burmeister, J. "Federal Court awards $139,147 in Attorneys' Fees Against HHS and NIH in IOM FOIA Case." *ThoughtsAboutME.* November 7, 2014. http://thoughtsaboutme.com/2014/11/07/federal-court-awards-139147-in-attorneys-fees-against-hhs-and-nih-in-iom-foia-case/

[883] Center for Effective Government. "Making the Grade: Access to Information Scorecard 2014." Center for Effective Government. March 10, 2014. http://www.foreffectivegov.org/access-to-information-scorecard-2014 and http://www.foreffectivegov.org/access-to-information-scorecard-2014-agencies (summary by agencies)

[884] The following three blog entries detail information on the content of the so-called "Secret Files of ME/CFS." Smith stated that there were two files - "*one from the Department of Work and Pensions (DWP)_and one from the Medical Research Council (MRC)" – that were held in The National Archives in London. The files were closed to until 2072 (DWP) and 2071 (MRC). Smith filed FOIA in 2011 to gain access*

- Smith, Valerie Elliott. "Update on the "Secret" Files on ME/CFS + Wessely and the Wok?" *Valerie Elliott Smith Blog.* November 19, 2012. Last accessed March 3, 2015. https://valerieeliotsmith.wordpress.com/2012/11/19/update-on-the-secret-files-on-mecfs-wessely-and-the-wok/
- Smith, Valerie Elliott. "The Secret Files Unwrapped: Part I – the importance of fair and accurate records." *Valerie Elliott Smith Blog.* January 15, 2015. Last accessed March 3, 2015. https://valerieeliotsmith.wordpress.com/2015/01/20/the-secret-files-unwrapped-part-i-the-importance-of-fair-and-accurate-records/ and link for DWP file https://valerieeliotsmith.files.wordpress.com/2015/01/natarchbn141dss.pdf
- Raising a concern that CFS might be listed as a neurological illness, Professor Wessely stated, "The main difference between CFS and the major psychiatric disorders is neither aetiological, nor symptomatic, but the existence of a powerful lobby group that dislikes association with psychiatry."
- Wessely also stated, "It is also a most unfortunate message to send sufferers. It colludes with the erroneous belief that this is a severe disorder of neurological functioning… As we, and now many other groups, have shown that the only determinant of outcome in this condition is strength of belief in a solely physical cause, then it will also itself contribute to disability and poor outcome."
- Finally, Wessely stated, "I believe that the Department is making an error if it accepts the partisan views put forward by pressure groups as a basis for making medical decisions."
- Smith, Valerie Elliott. "The Secret Files Unwrapped: Part 2 – Control, not Collaboration." *Valerie Elliott Smith Blog.* March 2, 2015. Last accessed March 3, 2015. https://valerieeliotsmith.wordpress.com/2015/03/02/the-secret-files-unwrapped-part-2-control-not-collaboration/ and link for MRC file https://valerieeliotsmith.files.wordpress.com/2015/02/natarchfd234553.pdf

[885] Spotila, J. "Will the Real P2P Please Stand Up." OccupyCFS. May 19, 2014 - http://www.occupycfs.com/2014/05/19/will-the-real-p2p-please-stand-up/
Spotila described the different statements from NIH about the purpose of P2P. The following text is quoted from her blog.

1. "NIH statements that P2P would address the research case definition
    a. The NIH has made a commitment to conduct an evidence-based review of the status of ME/CFS research and also convene a dedicated workshop to address the research case definition for ME/CFS. Dr. Howard Koh, October 3, 2012 CFSAC Minutes, p. 5."
2. "Dr. Maier of NIH told CFSAC that it would not address the research case definition and that it was about identifying gaps
    a. This will not create a research case definition in the end, but will inform anyone who wants to do research in this area about what aspects of the case definition are really strong, which are really lacking, and how those holes might be filled. Dr. Beth Collins-Sharp, May 23, 2013 CFSAC Minutes, P. 16.
    b. The purpose of the Pathways to Prevention Program and the ME/CFS workshop is not —and I repeat, not—to create a new case definition for research for ME/CFS. Dr. Susan Maier, December 11, 2013 CFSAC Minutes, p. 16.
    c. The purpose of an evidence-based methodology workshop is to identify methodological and scientific weaknesses in a scientific area and move the field forward through the unbiased and evidence-based assessment of a very complex clinical issue. Dr. Susan Maier, May 23, 2013 CFSAC Minutes, p. 6.
    d. The takeaways from a systematic review are answers to the key questions that identify where there's strong evidence, where there are gaps, and some ideas about how those gaps may be filled. Those are called research recommendations. Dr. Beth Collins-Sharp, May 23, 2013 CFSAC Minutes, p. 13."
3. "Dr. Maier told CFSAC that it was about the research case definition
    a. The purpose of the Pathways to Prevention Program for ME/CFS is to evaluate the research evidence surrounding the outcome from the use of multiple case definitions for ME/CFS and address the validity,

reliability, and ability of the current case definitions to identify those individuals with or without the illness or to identify subgroups of individuals with the illness who might be reliably differentiated with the different specific case definitions. Dr. Susan Maier, December 11, 2013 CFSAC Minutes, p. 16."

[886] Burmeister, J. "P2P FOIA Documents, Part 7—Collins, Murray and Maier: Trouble in NIH Paradise." *ThoughtsAboutME*. November 23, 2014. http://thoughtsaboutme.com/2014/11/23/p2p-foia-documents-part-7-collins-murray-and-maier-trouble-in-nih-paradise/ and https://www.dropbox.com/s/ak305vlb9367kq8/FOIA_P2P_Batch%237.pdf?dl=0 (Page 18)

In an email to Dr. Francis Collins, Dr. David Murray stated, "Our P2P workshop will review the various definitions for ME/CFS that have been used in research studies to clarify the type of patients that are captured under each definition and how those patients respond to various therapeutic options. This will inform future research by providing a better understanding of the implications of choosing one definition over another…"

[887] Institute of Medicine of the National Academies. "Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness." Institute of Medicine of the National Academies. Prepublication copy. February 10, 2015. Last accessed February 16, 2015. https://www.iom.edu/Reports/2015/ME-CFS.aspx Page 20.

[888] Kaiser, J. "Top U.S. Scientific Misconduct Official Quits in Frustration With Bureaucracy." *ScienceInsider. Science.* March 12, 2014. http://news.sciencemag.org/people-events/2014/03/top-u.s.-scientific-misconduct-official-quits-frustration-bureaucracy

Dr. David Wright made the following points in his resignation letter to Dr. Howard Koh:

- "The organizational culture of OASH's immediate office is seriously flawed, in my opinion." Wright went on to state that best practice of organizations included transparency, "shared decision-making and accountability" but that OASH "secretive, autocratic and unaccountable."
- "One [drawback of bureaucracy] is that public bureaucracies quit being about serving the public and focus instead on perpetuating themselves. This is exactly my experience with OASH. We spend exorbitant amounts of time in meetings and in generating repetitive and often meaningless data and reports to make our precinct of the bureaucracy look productive."
- Wright stated that OASH is an "intensely political environment," where "decisions are often made on the basis of political expediency and to obtain favorable "optics."

[889] U.S. Health and Human Services Chronic Fatigue Syndrome Advisory Committee. CFS Advisory Committee meeting, June 13, 2012. http://www.hhs.gov/advcomcfs/meetings/minutes/cfsac20120613.pdf (page 16)

CFSAC exchange between Dr. Rowe and a CFSAC member, the CFSAC member stated, "Thanks for an enlightening discussion. I'm interested to find out if there's any evidence of childhood depression as a marker, as a precursor, as part of the natural history of this disease that would help identify different categories at a potentially early stage." Dr. Rowe responded, "One of the problems in case definition, as came up in one of the CDC studies, is if you define fatigue very broadly, that's a key symptom of depression. I think one of the least useful pieces of work that's been done was the one that suggested that childhood sexual abuse was a risk factor for CFS. It may be a risk factor for depression. That makes a tremendous amount of sense. But we just don't see high rates of physical or sexual abuse in the pediatric CFS population. They don't see it in Oslo, Norway, where they've been doing studies looking at this."

[890] U.S. Health and Human Services Chronic Fatigue Syndrome Advisory Committee. CFS Advisory Committee Rooster. http://www.hhs.gov/advcomcfs/roster/index.html

[891] U.S. General Services Administration. "The Federal Advisory Committee Act." U.S. General Services Administration. Last updated December 1, 2014. Last accessed February 20, 2014. http://www.gsa.gov/portal/content/100916

[892] Spotila, J. "A Public Citizen. *OccupyCFS*. February 18, 2013. http://www.occupycfs.com/2013/02/18/a-public-citizen/

[893] U.S. Department of Health and Human Services CFS Advisory Committee. "CFSAC Recommendations – March 11, 2014." CFS Advisory Committee. March 11, 2014. Content last reviewed January 16, 2015. Page last accessed January 2015. http://www.hhs.gov/advcomcfs/recommendations/03112014.html

Note that these recommendations are the ones approved by the committee in March. But they are NOT the same as the recommendations originally reported to Secretary Sebelius as reported by Spotila. See the previous footnote for the comparison of what was approved by CFSAC and what was originally forwarded.

[894] The original response by HHS to the modified CFSAC recommendations has been removed from the CFSAC website. The response to the updated recommendations can be found here:

- U.S. Department of Health and Human Services CFS Advisory Committee. "Responses To Recommendations From The Chronic Fatigue Syndrome Advisory Committee. Ref: March 11, 2014 CFSAC Meeting." Content last reviewed January 16, 2015. Last accessed January 2015. http://www.hhs.gov/advcomcfs/recommendations/03112014.html and http://www.hhs.gov/advcomcfs/recommendations/recommendations-responses-march-2014-final-jan-14-2015.pdf

[895] U.S. Government Accountability Office. *CHRONIC FATIGUE SYNDROME: CDC and NIH Research Activities Are Diverse, but Agency Coordination Is Limited. (GAO Report* HEHS-00-98). U.S. Government Accountability Office, Washington, D.C. June 2, 2000. http://www.gao.gov/assets/240/230415.pdf and http://www.gao.gov/products/HEHS-00-98(Page 23)

[896] Ibid.(Page 28)

[897] Ibid. Page 5
The GAO report stated, "Coordination between CDC and NIH and their use of input from external researchers and patient advocates in developing agency research programs have been limited. CDC and NIH have not jointly conducted research, although CDC's advisory panel and external peer reviewers have recommended that CDC undertake such a collaboration. CFSCC, chartered to encourage federal coordination, has helped to facilitate some interagency communication, but it has not provided an effective forum for developing coordinated research programs."

[898] Ibid. On page 26 and 30, the GAO report stated:

- "However, there is little evidence of coordination between CDC and NIH on CFS research... we identified no specific efforts to ensure that CFS research does not overlap or leave important gaps…..We also identified no activities intended to build on the results of studies at the other agency, beyond generally reading the scientific literature."
- "Further, there have been no joint CFS research projects undertaken by CDC and NIH scientists. While CDC's peer review and Board of Scientific Counselors both recommended that there be more collaboration, projects of this type have not been initiated to date. CDC has indicated that it will share blood and serum samples with NIH intramural and extramural scientists when appropriate".
- "CFSCC has not been successful in meeting its goal: to ensure interagency coordination. While the committee has been useful in keeping both federal agencies and the public informed of current developments at the agencies and allowing the public an opportunity to raise issues that the committee might want to consider, it has yet to stimulate much discussion about how CDC and NIH could coordinate their programs."
- "Much of the committee's meeting time is spent presenting reports from each agency on recent CFS activities. Minutes from the meetings show that, during CDC and NIH agency updates, the agencies' representatives rarely, if ever, questioned or discussed information in each other's updates. Meeting minutes also reflect no discussion of the issues raised during the public testimony portion of the meeting."

[899] U.S. Health and Human Services Chronic Fatigue Syndrome Advisory Committee. CFS Advisory Committee Meeting. May 27, 2009 CFSAC Minutes. https://wayback.archive-it.org/3919/20140324192720/http:/www.hhs.gov/advcomcfs/meetings/minutes/cfsac052709min.pdf

Reeves presented to CFSAC on CDC's strategic plan (Page 30). McCleary also gave a presentation (page 56). Kim McCleary, CEO of CFIDS Association of America, stated, "One of the central topics seems to be a lack of clarity about where the mission of NIH begins and ends and where the mission of the CDC begins and ends. A lot of the studies that were included in that presentation [CDC's strategic plan] sound like they would be responsive to the NIH's neuroimmune PA."

Regarding the differences in case definition and measurement, McCleary spoke to the fact that CDC was using the empirical definition but no one else was. She stated, "A lot has been made of the empiric definition. While it continues to be clarified that this does not represent a new definition of CFS, I think that most people would agree at this point that it circles a different patient group than the '94 utilized in a more traditional way without the instruments and the cutoff points that have been established. If CDC continues to use the empiric definition and everybody else in academia, around the world, and in pharmaceutical and biotech companies uses the '94 definition without those same instruments applied, I think that Dr. Cavaille-Coll is correct—it changes everything. It would make things totally incomparable. We won't be able to compare one thing to the next."

"I think that's something that this committee [CFSAC] has a unique ability to help sort out, because the other agencies of HHS are not using the same definition or the same measurements to define CFS as the CDC is. Subsets of the disease were discussed, but there was no mention of how they will be consistent among agencies."

[900] The description of this disease used by the NIH Center for Scientific Review for the SEP varied over time as follows:

- November 2005. SEP combined CFS, FM and other chronic polysystemic morbidity syndromes (The same text was used through from March 2009 through May 2011.)
  National Institutes of Health, Center for Scientific Review. Chronic Fatigue Syndrome/ Fibromyalgia Syndrome Special Emphasis Panel [CFS SEP]. Last updated August 5, 2005. Archived November 13, 2005. https://web.archive.org/web/20051113160338/http://cms.csr.nih.gov/PeerReviewMeetings/CSRIRGDescription/MOSSIRG/CFSSEP.htm
  The website stated, "The Chronic Fatigue Syndrome/ Fibromyalgia Syndrome [CFS SEP] continuing Special Emphasis Panel [SEP] reviews applications in the multiple disciplines applied to studies of the causes, manifestations and treatments of the Chronic Fatigue Syndrome, the Fibromyalgia Syndrome and other chronic polysystemic morbidity syndromes."
- June 2011 – The site changed to be specific to CFS and then later to ME/CFS.
  Center for Scientific Review, National Institutes of Health. Chronic Fatigue Syndrome Special Emphasis Panel [CFS SEP]. Last updated June 1, 2011. Archived July 10, 2011.
  http://web.archive.org/web/20110710145002/http://cms.csr.nih.gov/PeerReviewMeetings/CSRIRGDescriptionNew/IFCNIRG/CFSSEP.htm

Also see the description in the 2006 RFA by the National Institutes of Health.

- National Institutes of Health. "RFA: Neuroimmune Mechanisms and Chronic Fatigue Syndrome." National Institutes of Health. Release Date July 14, 2005. Part 1: Overview Information - http://grants.nih.gov/grants/guide/rfa-files/RFA-OD-06-002.html and Part II: Full Text of Announcement - http://grants.nih.gov/grants/guide/rfa-files/RFA-OD-06-002.html#PartII
  The RFA states, "It has been proposed that CFS is one of a family of disorders that include fibromyalgia (FM), irritable bowel syndrome (IBS), posttraumatic stress disorder (PTSD), temporomandibular disorder (TMD), chemical sensitivities and others."

[901] Letter from President Obama to ME patient's wife Courtney Miller following up on Miller's question at a town hall. July 26, 2012. https://dl.dropboxusercontent.com/u/89158245/President-Obama-Letter-on-CFS.pdf

[902] U.S. Department of Health and Human Services. Response to CFS Advisory Committee Recommendation of October 2012. http://www.hhs.gov/advcomcfs/recommendations/response-from-ash-10-2012.pdf
HHS response to October 2012 definition recommendation. HHS stated,,"The National Institutes o f Health (NIH) is convening an Evidence-based Methodology Workshop process (outlined in recommendation 3b) to address the issue of case definitions appropriate for ME/CFS research. However, it will not cover in detail a clinical case definition. The Office of the Assistant Secretary for Health, Department of Health and Human Services, is actively pursuing options for a separate effort that would work in coordination with the NIH process, but result in a case definition useful for clinicians who see patients with symptoms that may be ME/CFS."

[903] U.S. Health and Human Services Chronic Fatigue Syndrome Advisory Committee. CFS Advisory Committee Meeting. October 28-29, 2008. https://wayback.archive-it.org/3919/20140324192720/http:/www.hhs.gov/advcomcfs/meetings/minutes/cfsac20081028min.pdf (Page 53)

[904] Racaniello, Vincent. "A Tale of Two Viruses: Why AIDS Was Pinned to HIV, but Chronic Fatigue Remains a Mystery." *The Crux. Discover Blogs.* January 12, 2012. http://blogs.discovermagazine.com/crux/2012/01/12/hiv-in-xmrv-out-how-scientists-deduce-what-does-and-doesnt-cause-a-disease/
Racaniello states, "In retrospect, it is clear that the properties of AIDS made it an easy disease to understand. While the path to understanding CFS has been clouded by non-scientific issues, in the end the main reason why we do not understand this disease is because it is extraordinarily complex. But that never stopped a good scientist."

[905] Wikipedia. "War on Cancer." *Wikipedia* http://en.wikipedia.org/wiki/War_on_Cancer

[906] Rolak, Loren. "The Basic Facts. The History of MS." *National Multiple Sclerosis website.* National Multiple Sclerosis Society. Undated. www.nationalmssociety.org/NationalMSSociety/media/MSNationalFiles/Brochures/Brochure-History-of-Multiple-Sclerosis.pdf (Page 10)

[907] According to figures in the table above in the section on NIH funding, NIH reported spending $139.5M between 1987 and 2014 on this disease. But that figure is inflated as advocates have demonstrated that some of that funding was used to fund research on other diseases.

[908] National Institute of Health. "NIH-supported clinical trials to evaluate long-acting, injectable antiretroviral drugs to prevent HIV infection." National Institute of Health. February 19, 2015. Last accessed February 21, 2015. http://www.nih.gov/news/health/feb2015/niaid-19c.htm

[909] New York Times. "Readers Ask: A Virus Linked to Chronic Fatigue Syndrome." *Consults. New York Times Blog.* October 15, 2009. http://consults.blogs.nytimes.com/2009/10/15/readers-ask-a-virus-linked-to-chronic-fatigue-syndrome/?_r=0
Dr. Klimas stated, "My H.I.V. patients for the most part are hale and hearty thanks to three decades of intense and excellent research and billions of dollars invested. Many of my C.F.S. patients, on the other hand, are terribly ill and unable to work or participate in the care of their families. I split my clinical time between the two illnesses, and I can tell you if I had to choose between the two illnesses (in 2009) I would rather have H.I.V. But C.F.S., which impacts a million people in the United States alone, has had a small fraction of the research dollars directed towards it."

[910] U.S. Burden of Disease Collaborators. "The State of US Health, 1990-2010 Burden of Diseases, Injuries, and Risk Factors. *JAMA.* August 14, 2013, 310(6): 591-606. Last accessed May 14, 2014. http://dx.doi.org/10.1001/jama.2013.13805.
The referenced information is found in Table of the Supplemental Information on page 170 of Webappendix Table 6. "DALYs and median percent change in the United States by cause for both sexes combined in 1990 and 2010."

[911] U.S. News and World Report. "Women Still Left Out of Medical Research: Report" *U.S. News and World Report*. March 3, 2014. http://health.usnews.com/health-news/articles/2014/03/03/women-still-being-left-out-of-medical-research-report
Also see
- Kotz, Deborah. "Medical research still lags on women, study says." *Boston Globe,* Boston Massachusetts. March 3, 2014. http://www.bostonglobe.com/lifestyle/health-wellness/2014/03/03/research-lacking-gender-differences-disease-study-finds/HV1QWeYEm8J1Lu6KTrIW1H/story.html
- Kotz stated that twice as many women as men suffer from depression but only 45% of animal studies use female animals. At the same time, only one third of participants in clinical trials are women.[911]

[912] *Contested Illnesses. Citizens, Science and Health Social Movements*. Edited by Brown P, Morello-Frosch R, Zavestoski S, and the Contested Illnesses Research Group. University of California Press. 2012.

Brown stated, "Although science does indeed take time, it takes varying lengths of time depending on who the stakeholders are in the formation of the dominant epidemiological paradigm and what sorts of institutional, political, social and other barriers impede challenges to it… The dominant epidemiological paradigm is both a belief system and a process and as such is subject to change. But the prevailing systems of scientific, government and military power have made it difficult to challenge."

[913] Institute of Medicine of the National Academies. "Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness. Report Guide for Clinicians." Institute of Medicine of the National Academies. Undated. Last accessed April 9, 2015. http://www.iom.edu/~/media/Files/Report%20Files/2015/MECFS/MECFScliniciansguide.pdf

[914] Holmes G, Kaplan J, Gantz N, Komaroff A, Schonberger L, Straus S, Jones J, Dubois R, Cunningham-Rundles C, Pahwa S, Tosato G, Zegans L, Purtilo D, Brown N, Schooley R, Brus I. "Chronic Fatigue Syndrome: A Working Case Definition." *Annals of Internal Medicine.* March 1, 1988; 108(3): 387-389. PMID: 2829679. http://dx.doi.org/10.7326/0003-4819-108-3-387 *and http://www.ncf-net.org/patents/pdf/Holmes_Definition.pdf*

[915] Arpino C, Carrieri MP, Valesini G, Pizzigallo E, Rovere P, Tirelli U, Conti F, Dialmi P, Barberio A, Rusconi N, Bosco O, Lazzarin A, Saracco A, Moro ML, Vlahov D. "Idiopathic chronic fatigue and chronic fatigue syndrome: a comparison of two case-definitions." *Ann Ist Super Sanita.*1999; 35(3): 435-41. PMID: 10721210 http://www.ncbi.nlm.nih.gov/pubmed/10721210?dopt=Abstract

The paper states "In conclusion, the 1994 criteria increased the number of patients classified as CFS (compared to Holmes); however, those who fit only the 1994 criteria were less likely to have an acute symptomatic onset and signs and symptoms suggestive of an infectious process."

[916] Sharpe M, Archard L, Banatvala J, Borysiewicz L, Clare A, David A, Edwards R, Hawton K, Lambert H, Lane R, McDonald E, Mowbray J, Pearson D, Peto T, Preedy V, Smith A, Smith D, Taylor D, Tyrrell D, Wessely S, White P. "A report—chronic fatigue syndrome." *J Roy Soc Med* February 1991; 84(2): 118-121. PMID: 1999813. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1293107/

The criteria for Oxford CFS are:

a) "A syndrome characterized by fatigue as the principal symptom"
b) "A syndrome of definite onset that is not life long"
c) "The fatigue is severe, disabling and affects physical and mental functioning"
d) "The symptom of fatigue should have been present for a minimum of 6 months during which it was present for more than 50% of the time"
e) "Other symptoms *may* be present, particularly myalgia, mood and sleep disturbance"

[917] Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A and the International Chronic Fatigue Syndrome Study Group. "The chronic fatigue syndrome: a comprehensive approach to its definition and study." *Ann Intern Med* 1994; 121(12): 953-9. PMID: 7978722. http://www.ncf-net.org/patents/pdf/Fukuda_Definition.pdf and http://dx.doi.org/10.7326/0003-4819-121-12-199412150-00009

[918] Jason, L, Torres-Harding, S, Jurgens, A, Helgerson, J. "Comparing the Fukuda et al. Criteria and the Canadian Case Definition for Chronic Fatigue Syndrome, Journal of Chronic Fatigue Syndrome 2004; 12(1): 37-52. http://informahealthcare.com/doi/abs/10.1300/J092v12n01_03?src=recsys and http://web.archive.org/web/20120216181206/http://www.cfids-cab.org/cfs-inform/CFS.case.def/jason.etal04.pdf

Also see

- Jason, L. "Defining CFS: Diagnostic Criteria and Case Definition". Presented at CFIDS Association webinar, April 14, 2010..http://web.archive.org/web/20120425130843/http://www.cfids.org/webinar/jason-slides041410.pdf
  On slide 12, Jason describes how fatigue plus 4 Fukuda symptoms are equivalent to the symptoms of depressed patients

[919] Carruthers BM, Jain AK, De Meirleir KL, Peterson DL, Klimas NG, Lerner 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." *Journal of Chronic Fatigue Syndrome* 2003; 11(1): 7-117. http://mefmaction.com/images/stories/Medical/ME-CFS-Consensus-Document.pdf

Also see the following overview of the CCC, produced in 2005.

- Carruthers B, van de Sande M. "Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: A Clinical Case Definition and Guidelines for Medical Practitioners. An Overview of the Canadian Consensus Document" Published by Carruthers B, can de Sande M. 2005. http://www.name-us.org/DefintionsPages/DefinitionsArticles/ConsensusDocument%20Overview.pdf

[920] Reeves W, Wagner D, Nisenbaum R, Jones J, Gurbaxani B, Solomon L, Papanicolaou D, Unger E, Vernon S, Heim C. "Chronic Fatigue Syndrome – A clinically empirical approach to its definition and study." *BMC Medicine* December 2005; 3:19. PMID: 16356178. http://dx.doi.org/10.1186/1741-7015-3-19

[921] Jason L, Najar N, Porter N, Reh C. "Evaluating the Centers for Disease Control's Empirical Chronic Fatigue Syndrome Case Definition." *Journal of Disability Policy Studies* Published online October 2008, in print September 2009; 20(2):

93-100. http://dx.doi.org/10.1177/1044207308325995 and http://web.archive.org/web/20090816013354/http://www.co-cure.org/Jason-7.pdf

[922] Jason L, Jordan K, Miike T, Bell DS, Lapp C, Torres-Harding S, Rowe K, Gurwitt A, DeMeirleir K, Van Hoof EA. "A Pediatric Case Definition for Myalgic Encephalomyelitis and Chronic Fatigue Syndrome." *J Chronic Fatigue Syndr*. 2006; 13(2-3): 1-44. http://informahealthcare.com/doi/abs/10.1300/J092v13n02_01 and http://solvecfs.org/wp-content/uploads/2013/06/pediatriccasedefinitionshort.pdf

[923] U.K National Institute for Health and Care Excellence (NICE). *Chronic fatigue syndrome/myalgic encephalomyelitis (or encephalopathy). Diagnosis and management of CFS/ME in adults and children.* (NICE clinical guideline 53). August 2007. http://guidance.nice.org.uk/CG53 and http://www.nice.org.uk/guidance/cg53/evidence

[924] Carruthers BM, van de Sande MI, De Meirleir KL, Klimas NG, Broderick G, Mitchell T, Staines D, Powles ACP, Speight N, Vallings R, Bateman L, Baumgarten-Austrheim B, Bell DS, Carlo-Stella N, Chia J, Darragh A, Jo D, Lewis D, Light AR, Marshall-Gradisbik S, Mena I, Mikovits JA, Miwa K, Murovska M, Pall ML, Stevens S. "Myalgic Encephalomyelitis: International Consensus Criteria." *Journal of Internal Medicine* October 2011; 270(4): 327–338. PMID: 21777306. http://dx.doi.org/10.1111/j.1365-2796.2011.02428.x and http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2796.2011.02428.x/full

[925] U.S. Department of Commerce, U..S. Census Bureau. "Annual Estimates of the Resident Population by Single Year of Age and Sex for the United States: April 1, 2010 to July 1, 2012. 2012 Population Estimates." American Fact Finder. U.S. Census Bureau. Release Date June 2013. http://factfinder2.census.gov/bkmk/table/1.0/en/PEP/2012/PEPSYASEXN Population statistics broken down by single age years. total from 18-59 is 179,226,911 or roughly a prevalence of 4,552,364 for Reeves 2.54% rate.

[926] Acheson,E.D. "The clinical syndrome variously called benign myalgic encephalomyelitis, Iceland disease and epidemic neurasthaenia." *JAMA* April 1959; 26(4): 569- 595. PMID: 13637100. http://dx.doi.org/10.1016/0002-9343(59)90280-3 and www.name-us.org/DefintionsPages/DefinitionsArticles/Acheson1959.pdf