THIRTY YEARS OF DISDAIN

How HHS and
A Group of Psychiatrists
Buried Myalgic Encephalomyelitis

Mary Dimmock
Matthew Lazell-Fairman
December 2015

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

Thirty Years of Disdain: How HHS Buried M.E. December 2015. (M. Dimmock, M. Lazell-Fairman)  

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Preface
In 2010, I was nearing the end of a 31-year career in the pharmaceutical industry when my son, Matthew Lazell-Fairman, suddenly fell victim to myalgic encephalomyelitis (ME), a disease that causes profound neurological, immunological and energy production dysfunction and a level of debility worse than congestive heart failure, multiple sclerosis and end-stage renal disease. Since then, I have watched, helpless and heartbroken, as this disease has ripped his life to shreds, turning the promise of a vibrant and spirited future into a soul-crushing existence, at times so unrelentingly harsh and circumscribed, so brutal, so cornered, and with so little hope that I have wondered how he has managed to keep going.

Compounding the heartbreak, it has been disturbing to watch as the world around my son, including his own doctors, has not only dismissed his disease but also ridiculed him for believing that it is real and serious. Worst of all has been the realization that my son is paying this terrible price because the U.S. government has so badly mismanaged the ME crisis since before he was even born.

Everything I thought I understood about disease research, drug development, and the delivery of clinical care has been turned on its head. This isn’t science or medicine as I had come to know them but rather a parade of psychogenic bias, neglect, bad science, flawed public policy, and the political agendas of powerful people and institutions that have sentenced ME patients to the medical equivalent of the most squalid slum in the poorest country on earth. The political decisions taken over the last thirty years have polluted research, perverted clinical care, and shipwrecked ME patients with a life-threatening dose of stigma, disbelief and medically induced harm.

As a result of 2015 reports by the Institute of Medicine (IOM) and the National Institute of Health (NIH), the situation is beginning to change. But it is not yet known whether that change will be of a speed, magnitude, direction, and serious commitment that honors the weight of this crisis – the extreme debility of patients, the complete lack of approved diagnostics and treatments, the stagnation in research and epidemiology; the widespread medical disbelief in the disease; and the utter lack of appropriate medical care and patient support structures.

Band-aids, small point solutions, and incremental changes to business as usual are not acceptable substitutes for the sweeping changes that are needed to correct this medical tragedy. As a nation, we have the opportunity to make rapid change for ME patients but to achieve that, the U.S. Department of Health and Human Services (HHS) must exert its leadership position and finally takes the bold, committed, fully resourced, and urgently executed steps necessary to correct this terrible injustice. The medical community must learn about this disease and how to appropriately manage it and stop harming ME patients with inappropriate treatments and disbelief. And as a community, we must demand what we need, not accept what we are given.

About this document:
For anyone new to this disease, the story of what has happened to ME patients is difficult to understand as it is obscured by a mish-mash of disease labels, bad disease definitions, sloppy science, and misinformation. The objective in creating this manuscript was to compile a detailed reference that shines a light on how neglect, political agendas and bad science have impacted research, clinical care, and ME patients and what has to change to move forward. The focus is on the policy decisions and political and social forces that have held ME hostage since the mid-1980s, including how HHS and a group of psychiatrists have controlled the way in which this
disease has been viewed, studied, and treated.

Because this history is convoluted and open to interpretation, this manuscript may have unintentionally omitted or misinterpreted some key information. Any substantial errors or omissions will be corrected. Comments can be sent to medimmock@gmail.com

About the use of disease labels in this document: This field has been confounded by the adoption of overly broad and fatigue-focused “CFS” definitions that do not require key features of ME and are linked to psychogenic causes. Magnifying this muddle has been the interchangeable use of disease names (e.g. “CFS,” “ME,” ME/CFS,” and now “SEID”, etc) to refer to any of a set of twenty disparate ME and CFS definitions. Together, the bad definitions and sloppy naming practices have created confusion on the nature of ME, which has impeded not only research and medical care, but also even simple communication. To avoid this confusion, this manuscript uses only the term “myalgic encephalomyelitis” when referring to the neuroimmune disease with its characteristic post-exertional malaise. This name was chosen not because of a personal preference for the name but because ME is the historical name of this disease, adopted by the World Health Organization in 1969. The term “chronic fatigue syndrome” is used to refer to the fatigue-centered disease definitions that do not require the hallmark symptoms of ME. Other terms, such as “ME/CFS” and “CFS/ME” are used when the HHS agency uses that term, as with NIH’s Trans-NIH “ME/CFS” workgroup.

This document can be found at http://bit.ly/The_Burial_of_ME_Summary. A longer version with additional content and references is available at http://bit.ly/The_Burial_of_ME_B... 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 (December 2015) and the link. Many of the references cited in this document are available online and can be quoted directly. As this document may change, we ask that you link to it rather than posting it elsewhere.

I want to acknowledge the huge debt of gratitude that I owe to the many patients, researchers, and clinicians who have been fighting this battle for many years, sometimes decades, in spite of continued dismissal by HHS. Their painfully gained knowledge and experience has been and continues to be my teacher. I am honored to know them and to learn from them.

Finally and most of all, I want to thank my son for his inspiration and encouragement to pursue this project. In spite of his young age, he quickly and accurately sized up the institutional barriers and neglect that he and all ME patients have been up against. He understood the importance of telling this story even when he became unable to do so himself. The vision, the heart, and the soul of this project belong to him.

Mary Dimmock
Matthew’s Story

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 turn 18. When I asked why he was so disappointed, he said that he didn’t want to 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 Hanoi, 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. Then, without warning, he awoke on May 19, 2010 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.

Over the coming months, Matthew could feel his vitality draining away with each passing day as he desperately tried to understand the deluge of unimaginable symptoms that was 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 as the room swirled around him. He found that increasingly small amounts of activity would leave him feeling even worse for days after. Eight months into his illness, he had become so sick that when he stopped into a local museum to rest on his way home from work, he became so disoriented and confused that he stumbled from room to room, unable to find his way out.

This then 23-year-old man, who had managed to navigate solo across the panoramic breadth of Asia, was hopelessly lost in a familiar museum. 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 and needed to exercise more. At times, the change in the doctor’s behavior was so abrupt and their suggestions so ludicrous and dismissive of what he was actually experiencing that he didn’t know whether to laugh or to cry. Frustrated and browbeaten, he
sought support from family and friends. Many initially echoed his doctors’ sentiments, believing that if the problem was not immediately apparent, then it was all in his head. Others trivialized his health problems with suggestions that he needed to rest more, eat organic and meditate. One repeatedly insisted that he should look into electroshock therapy, as though he might “snap out of it.” An uncle said, “Oh, I think I had that once. 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 and the sense that his life force was draining out of his body. But within 10 months, he was no longer able to work and was seldom able to leave the house. He had become so sensitive to light and sound that if he went to stores and restaurants, watched television, listened to the music that he loved, or even just used a computer, 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. He learned that he would pay a severe penalty if he exceeded the diminishingly meager energy allowance that ME had left him. He darkened the windows of his bedroom, restricted himself to listening to audiobooks, and even began to shower sitting down in a hopeless gambit to avoid the crashes that would magnify his pain and suffering.

To save up enough energy to take his wife to a quiet restaurant for their first anniversary, he had to lay flat in the dark for three days before and then again after. At his worst, he became so cognitively challenged that he was unable to make sense out of a single written sentence and only had the physical capacity to walk 250-300 steps a day, enough to use the bathroom and get food that someone else had prepared. In weeks like that, he would lie in bed in a shuttered room for the entire day, unable to do anything, “lightheaded and zoned out, with [his] head aching, [his] eyes burning like fire, his muscles sore and weak, and exhausted to a degree that the healthy have never known, yet unable to sleep.” His “reality mediated by pain and incomprehensible fatigue.”

Yet, Matthew is very lucky in some ways. First, as sick as he has been, other ME patients are much sicker, so sick that they never leave their beds and may not be able to feed themselves or talk. They cannot tolerate a trip to a doctor, even if that doctor is local and even with months of planning. But even if they could physically tolerate a trip to see a doctor, they may not have the resources to pay out of pocket for the testing and the treatments that are largely not covered by insurance. Matthew is lucky to have had enough physical capacity and the financial resources to access a disease expert and pay tens of thousands of dollars out of pocket to try an experimental therapy. That treatment has resulted in some improvement in quality of life, allowing him to do two to three hours of activity two days a week and occasionally go to quiet stores and restaurants. Yet, he is still very sick, limited in what he can do physically. Worst of all, he still suffers such terrible cognitive dysfunction that he has never read this page. And he lives with the constant threat that at any point, he could go hurtling deeper into the hellhole of this disease and not be able to escape.

These physical limitations and suffering have been compounded by the tremendous emotional burden and financial loss. Almost overnight, his sense of boundless opportunity, his hunger for experience, his intellectual capacity, and his joy of life were crushed. Describing those losses when he was still able to write, Matthew said,

My wife and I will never be able to experience the joy of childbirth or first birthdays or graduations or watching as our children develop into adults. I have been rendered a spectator, a cruel witness to the atrophy of old friendships and the withering of my career...
ambitions. It is heartbreaking that I will never experience the challenges and frustrations of a career or the pride of providing for my family and giving to my community.\(^3\)

Like all ME patients, Matthew has had to grapple with finding meaning in what little life is left. This has been difficult for a young man who as a child saved his favorite childhood books for the day when he would read them to his own child. This has been especially difficult for a young man whose sense of value is grounded in being able to give back to the world, a world he is no longer part of.

But the physical and emotional burdens have not been the worst. The hardest thing to bear has been the treatment that he has received at the hands of his doctors and his own government. The terrible irony is that my son and all ME patients will only be believed and get proper medical care if they develop cancer or heart disease, diseases that studies have shown are the long term consequences of having ME.

This deadly combination of medical disbelief, stigma, and abuse along with governmental bias, disdain, and neglect has harmed his psyche, robbed him of the hope that he might one day recover, and sometimes left him dangling over the doorstep of suicide. In his words:

Perhaps I could adapt to a life where my dreams are off-limits and my ability to experience life’s pleasures has been nearly destroyed. What I cannot bear is experiencing such horrible, unending pain and suffering, every minute of every day, knowing that there is no hope of recovery, only the promise of premature death. Until our government begins to take this disease seriously, I will live every relentless, soul-crushing day knowing that my life will never improve. I will be the living dead, until I am dead. And because I am so sick, because we are all so sick, we cannot even advocate for our own futures.

To the extent that we do, we sacrifice what pitifully little quality of life we have. It is in this respect that suicide becomes a positive, life-affirming option. When your dreams are foreclosed, when your ability to appreciate life’s small moments is nearly eliminated, when all you know is pain, and you have no hope of recovery and no way of bettering your life, suicide ceases to be an attempt to escape reality, but becomes a conscious choice for a better future, even if that future is the deep black unknown. This is the unimaginable reality of ME/CFS. We struggle every moment of every day to face pain that knows no end and to cope with the loss of nearly everything meaningful and real in life, and we have absolutely no reason to hope that our future will be any better than our present, because our government has ignored our plight for the last twenty-five years and continues to do so, prioritizing protection of the twisted and broken status quo over creation of a framework capable of providing for our health and our dignity.”\(^4\)

Mathew is still here. But too many ME patients have given up in the face of such terrible debility, disbelief, stigma and neglect. And that is both the tragedy and the outrage of our nation’s response to myalgic encephalomyelitis.
Introduction

In 2015, the prestigious U.S. Institute of Medicine (IOM) published a report that confirmed what patients and disease experts have been saying for years—myalgic encephalomyelitis (ME), called "chronic fatigue syndrome" (CFS) in the U.S., is a debilitating, chronic, multisystem disease that has been neglected and stigmatized by the government and the research and medical communities for the last three decades. The IOM report noted “a paucity of research,” “remarkably little research funding,” and doctors who view patients with “hostile attitudes” and “recommend treatment strategies that exacerbate symptoms.” In parallel, the National Institutes of Health issued the 2015 Pathways to Prevention (P2P) Workshop report that found that “minimal progress has been made to improve the state of the science” and that patients are incorrectly “labeled as lazy, deconditioned, and disability-seeking.”

These are profoundly disturbing statements that stand as a serious indictment of the handling of this disease by the federal government and the medical community.

The inescapable question is why so little progress has been made in the last thirty years that news reports from the 1980s and 1990s still read like current events. Worse, how did a disease classified as neurological by the World Health Organization in 1969 become so widely misunderstood and mistreated? The answers are complex but the simplest explanation lies in the actions taken by staff at the U.S. Department of Health and Human Services (HHS) and by a group of psychiatrists, particularly in Britain, beginning in the mid to late 1980s. These powerful individuals leveraged their influence in the research and medical communities and access to money, top-tier scientific journals, the media, and other key institutions to reshape the dominant paradigm toward this disease in a way that reflected their own psychogenic bias, personal and professional agendas, and institutional priorities. In parallel, the establishment and persistence of this dominant paradigm has been enabled by bad science, medical attitudes about unexplained disease and “women’s” disease, and commercial interests in cost-containment, all of which have worked against efforts to change the status quo.

The fallout of this dominant paradigm—the way in which this disease has been viewed, studied and treated for the last thirty years—has been devastating. Disinterested researchers, conflicted research, no diagnostics or treatments, and abysmal, too often harmful medical care. ME patients experience such soul-crushing debility, disdain, and loss of hope that they too often commit suicide to escape.

ME is a complex disease. But ME is not an intractable scientific problem. To the contrary, significant advances in our understanding have already emerged from good science performed by caring and dedicated researchers. The real problem is the institutional bias and neglect, the personal and professional agendas, the bad science, a dismissive medical community, and a federal public health policy so misguided that not only did it fail to produce a single meaningful outcome in all these years, but it also buried ME in an unfathomable quagmire.

It is morally reprehensible that such terribly disabled patients have been discarded in this way. The medical community and especially HHS must finally act with the urgency, vigor, resources, and focused direction that have characterized the war on other diseases. And all of us, especially Congress, the media and the public, must hold them accountable to do so.
Myalgic Encephalomyelitis

The popular perception of CFS is one of tiredness, burnout, depression, and malingering. But for patients, ME can be said to feel like having the worst flu imaginable while simultaneously suffering from a hangover, being beat up, and/or not having slept in days. It can be so severe that patients can no longer take care of themselves. And it can take hold of anyone, often suddenly and with no apparent cause. ME crushes formerly vibrant lives, plunging its victims into a living hell from which they rarely escape.

Clinically, ME is an acquired, chronic, multi-system disease that causes a range of symptoms including severe memory impairment, confusion, dizziness, difficulty staying upright, sleep abnormalities, muscle weakness, whole body pain, ataxia, vision problems, profound exhaustion, and sensitivity to light, sound and touch.\textsuperscript{11} But the most notable symptom, and the one that has always defined this disease, is post-exertional malaise (PEM), in which even trivial physical or mental activity—for some, as little as talking or sitting up—can cause a severe exacerbation of all other symptoms to the point of incapacitation.

The IOM report stated that these patients are more functionally impaired than patients with congestive heart failure, multiple sclerosis, and end-stage renal disease.\textsuperscript{12} An estimated 25 percent of patients are bedbound or housebound, with up to 61 percent bedridden on their worst days.\textsuperscript{13} Many are unable to work and the sickest never leave their beds. In 1995, one disease expert, who also treated AIDS patients, told Congress that these patients could be “more sick and more disabled every single day” than his AIDS patients were until the last two months of life.\textsuperscript{14}

Given the neglect of the government and the research and medical communities, one might think that this disease is rare. But that is not the case. While uncertain because of sloppy disease definitions, the best estimates indicate that up to one million Americans\textsuperscript{15} and 17 million worldwide\textsuperscript{16} suffer from this disease. ME is more common in women than men and affects all races, socioeconomic groups, and ages with victims as young as five.\textsuperscript{17} There are no approved treatments and recovery is rare,\textsuperscript{18} as little as five to ten percent, leaving patients sentenced to decades of debility. Initial research suggests patients are more likely to die decades prematurely from cancer, cardiovascular disease, and suicide.\textsuperscript{19} The estimated annual economic impact in the U.S. alone is $19-24 billion dollars in lost productivity and direct medical costs.\textsuperscript{20} Given the lack of treatments, the lack of medical care, and the lost wages of caregivers who have had to leave their jobs to provide total care, this is likely a huge underestimate. And yet, even at that level, it dwarfs the $5 million in annual funding provided by NIH for research, funding that is orders of magnitude below that of other diseases of similar debility.\textsuperscript{21}

Skepticism in the medical community is widespread and there have been only “limited research efforts to study ME in fields other than psychiatry and psychology.”\textsuperscript{22} But enough biomedical research has been done, some going back to the 1970s and 1980s and before,\textsuperscript{23} to objectively demonstrate widespread impairment across multiple body systems, most notably in the neurological, immunological, and autonomic systems and in energy production/metabolism. For instance, as the IOM report noted, cardiopulmonary exercise testing has shown that the symptom of PEM (also referred to as post-exertional neuroimmune exhaustion or PENE) is associated with impairment in aerobic energy metabolism, in which the body shifts to anaerobic metabolism at pathologically low levels of exertion and heart rate.\textsuperscript{24} This is not only inefficient but, as one researcher said, is “associated with pain, reduced muscle function, altered enzyme activity, and ultimately cessation of activity.”\textsuperscript{25} As with the symptom of PEM, this energy
production impairment is worse on the second day of a 2-day exercise test, a finding so remarkable that some researchers at first questioned their equipment and so distinctive that experts have said it clearly differentiates ME from depression, deconditioning, and a number of other chronic conditions.

Researchers have also identified neurological and immunological impairment. An example is a 1992 study that noted neurological and immunological changes suggestive of a “chronic, immunologically mediated inflammatory process of the central nervous system.” Studies have demonstrated reduction in gray matter volume and blood flow, increases in brain lactate levels, changes on MRI and EEG, evidence of autonomic dysfunction, and the presence of abnormal proteins in the spinal fluid. Neuropsychiatric testing has demonstrated slowed information processing and limited working memory. A 2014 PET (a form of imaging) study demonstrated neurological inflammation, while a 2014 qEEG (quantitative electroencephalography) study demonstrated disrupted information transfer across networks in the brain. In both the PET and qEEG studies, the findings were correlated with severity of symptoms, further evidence of the relevance of the findings. Referencing the qEEG study, one veteran clinician stated that such changes demonstrate brain dysregulation seen “in a whole host of well-documented neurologic diseases.”

For decades, other studies have demonstrated lowered functioning of the natural killer cells (cells involved in fighting viruses and malignancies) and an increase in inflammatory cytokines. A 2006 study found that regardless of which of three pathogens was the initial trigger, about 11 percent of patients developed CFS, suggesting that the immune response was more important than the specific pathogen. More recently, a 2015 study noted “a markedly disturbed immune signature in the cerebrospinal fluid” that was consistent with central nervous system immune activation that was greater than in patients with multiple sclerosis. A separate study suggested immune exhaustion in longer duration patients. A 1999 study reported evidence of polyclonal B cell activation, while more recent studies reported that the B-cell depleting drug, Rituxan, produced a significant improvement in ME symptoms suggesting an autoimmune disease. A 2015 study by the same group suggested autoimmunity against neurotransmitter receptors in some of these patients. While perhaps less likely given these studies, some have suggested a pathogen resident in the B-cells. Finally, while evidence indicates that a variety of pathogens can trigger the disease, researchers continue to examine the role of pathogens in driving the disease.

Further insight on the nature of the biology comes from the improvement that some patients have seen with practices such as mold avoidance and therapies such as antiretrovirals. Unfortunately, the reports are largely empirical and there is little formal research into these approaches for this disease.

But descriptions of scientific evidence from research fail to convey the level of physical suffering and debility that ME patients experience. Patients wake up each day feeling like they have the most severe flu imaginable but haven’t slept in days. But unlike the flu, ME rarely goes away, leaving patients ill for the rest of their lives. They can have such severe cognitive impairment that previously articulate, educated people are unable to comprehend what they read, are unable to write more than a sentence or two, and are unable to find the words to express their thoughts. Lawyers and writers, people whose currency was once their words, struggle to turn stillborn thoughts into sentences or extract even simple words from a brain strangled by ME.

Patients can also experience profound disorientation; a history professor reported pouring an entire pot of coffee into a drawer, thinking it was a cup, while my son was unable to navigate
his way back out of that familiar museum. According to an FDA report on this disease, patients reported being unable to talk, unable to change clothes “more than every 7-10 days” and struggling with the “exertion of daily toileting.”\textsuperscript{46} Patients can experience constantly burning muscles\textsuperscript{47} and whole body pain for which there is little relief. They may spend much of their days lying in bed in the dark, doing little more than resting, just to avoid feeling worse. Even moderately ill patients can be made physically worse from the everyday light and sound of TV, computers, music, and stores—trivial stimulation that has suddenly become a weapon that assaults their bodies.\textsuperscript{48} The most severely ill patients never get out of bed. They may need to be fed by tube and can experience such extreme sensitivity to light, noise, and touch that they are sentenced to darkened, muffled rooms, cordoned off from life.

As bad as this level of suffering is, patients can experience an exacerbation of all these symptoms, referred to as post-exertional malaise (PEM), if they exceed the unyielding physical and mental activity limits imposed by ME. To combat this, patients use a practice called “pacing” to limit their activity to the level of energy (often referred to as their “energy envelope”) that their body is able to produce.\textsuperscript{49} The least ill may be able to work but often spend all their time away from work recovering from the effort. Moderately ill patients may tolerate a few hours of light activity around the house or may be able to go out for a quiet dinner but likely did little but rest for days before and after to have enough energy to do so. And as one severely ill group told the IOM panel, the most severely ill patients must use “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.”\textsuperscript{50}

One severely ill patient is 31-year-old Whitney Dafoe from California.\textsuperscript{51} Whitney was an accomplished, award-winning photographer who had traveled the world. He helped to build a monastery in India and a village in Jamaica and worked on President Obama’s 2008 campaign. But today, he is so severely ill that he is bedbound, cannot read or speak, cannot walk, and has to be fed intravenously. Whitney has severe pain and is extremely sensitive to light, sound, and touch—even the touch of his family. Whitney’s mom has left her career to provide the total care that he requires.

Another severely ill patient was Lynn Gilderdale, who became ill at 14. Like Whitney, she was confined to her bed and could not tolerate light or sound. She suffered from recurring infections and 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.” With the support of her mother, Lynn committed suicide at age 31. Her mother was charged with attempted murder but was eventually cleared.\textsuperscript{52}

All of these patients were healthy people with active, full lives until they contracted ME.

As with my son, such physical debility extracts a tremendous emotional toll because of the stunningly swift destruction of a once-vibrant life, the sense of vulnerability and worthlessness, the social isolation and loss of friends, and the heartrending evaporation of life’s dreams.\textsuperscript{53} Adding to the emotional loss is the financial uncertainty resulting from the loss of income, the lack of insurance coverage, and the difficulty of getting disability benefits, leaving some patients financially destitute. As a result of what one researcher described as “profound and multiple losses” in “jobs, relationships, financial security, future plans, daily routines, hobbies, stamina and spontaneity, and even their sense of self,” these patients have a significantly lower overall quality of life than patients with many other chronic diseases.\textsuperscript{54} For 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.

This disease is especially cruel on those who fall ill as children and adolescents. They may never be able to finish school or experience a first love, a first job, a first time driving a car, or the pleasure of just hanging out with friends. All of those formative moments that shape who we are and that help adult ME patients find the strength to deal with a life so stunted by disease, have been stolen.

But all chronic diseases can cause terrible debility and devastating emotional and financial losses. What makes ME especially cruel is the psychic damage caused by the widespread disbelief, neglect, mistreatment, and stigma by the public, their own doctors, and government health agencies. As noted by both the IOM and P2P reports, patients are blamed by a world that thinks they are malingers, depressed, or attention seeking. One doctor grilled my son on what made him think he was sick and why he “wanted to go on disability” as though that was preferable to the spirited life that he had lost. When Whitney Dafoe’s parents tried to get a feeding tube for their son, the gastroenterologist refused and said that their son needed acute psychiatric treatment instead.55 Such stories are widespread.

At its most extreme, this medical stigma and disbelief has resulted in the sectioning of ME patients into psychiatric facilities. One such patient is Denmark’s Karina Hansen.56 Karina was originally diagnosed with ME but then, in February 2013, was involuntarily removed from her home, committed to a psychiatric facility, and rediagnosed with “pervasive arousal withdrawal syndrome” (PAWS),57 a diagnosis in which the patient is said to have withdrawn socially and is refusing to walk, eat, talk or perform self-care.58 Karina has been detained in a psychiatric facility since 2013, despite legal challenges by her family to get her released to their guardianship. Another example is British ME patient Sophia Mirza. Sophia was confined to 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. Yet, she was sectioned into a psychiatric ward against her will, after doctors decided that she had made herself sick.59 She was released after thirteen days but, according to her mother, her treatment in that ward “devastated her fragile health.” She died a few years later at age 32. The post-mortem pathology report found dorsal root ganglionitis, inflammation of dorsal root ganglion at the entry point to the spinal column.60

While more prevalent in Europe, such cases have also occurred in the U.S., as evidenced by the 2010 case of North Carolina teen Ryan Baldwin.61 Baldwin, a CFS patient, was removed from his home for a year amidst accusations of medical neglect and Munchausen syndrome by proxy, a diagnosis in which the caretaker, usually a mother, is said to be feigning or inducing a child’s illness.

The disbelief and misunderstanding is not just an issue with the medical community but also with the response of the patients’ own families. 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.”62 A 2008 report for the Obama-Biden Transition team noted that patients are “cast out by spouses or parents, scolded and disdained by siblings, and even abandoned by their churches.”63

For ME patients, the medical mistreatment can cause great physical harm from inappropriate treatments. But the neglect, stigma, and disbelief they experience are crushing to the psyche. When a horrible disease has ripped your life to shreds, isolated you from your family and

Thirty Years of Disdain: How HHS Buried M.E. December 2015. (M. Dimmock, M. Lazell-Fairman)
friends, destroyed your career, left you destitute and grasping for a life you no longer have, it is deeply demoralizing and heartbreaking to have to fight off suggestions that you just want to be on disability or that you could overcome your ill health with "positivity" and exercise, as a 2015 news article declared. And it is deeply demoralizing to have to watch your government not just stand by and do nothing about it but actively pursue the misguided public policies that enabled this stigma, disbelief, and misunderstanding to begin with.

More than any other factor, this combination of disbelief, disdain, neglect, and even denial by the very people who should be helping, grinds the soul raw. As much as the disease itself, it is this mistreatment, stigma, and disbelief that puts ME patients at such risk of suicide.
The Burial of ME and the Birth and Perpetuation of CFS

Ample evidence exists to demonstrate the multi-system dysfunction of ME and the distinctive biological pathologies associated with symptoms such as PEM.65 And yet, beginning in the late 1980s, this disease was renamed by HHS to the trivializing “chronic fatigue syndrome,” redefined to be a vague condition of medically unexplained chronic fatigue, and recast as a psychogenic disease.

ME wasn’t always considered psychogenic. This disease surfaced in an outbreak at a Los Angeles hospital in the 1930s and has been seen in outbreaks and sporadic cases across the globe ever since.66 In 1955, one well-known outbreak at London’s Royal Free Hospital forced the closure of the hospital for over two months; 300 members of the staff fell ill and 200 were hospitalized.67 In 1959, Dr. Donald Henderson of the CDC and Dr. Alexis Shelokov of the NIH investigated a number of these outbreaks and published a review of twenty-three of them.68 The term “benign myalgic encephalomyelitis” was first coined in 195669 and formally classified as a neurological disease in 1969.70 The first international conference was held in 1978 to plan future research directions.71 The attendees endorsed the term “myalgic encephalomyelitis” (dropping the word “benign” as inappropriate) and described the characteristic muscle fatigability and protracted exhaustion following even trivial effort. The attendees also emphatically rejected a 1970 claim (made without interviewing a single patient) that the patients in the 1955 Royal Free Hospital outbreak had been suffering from mass hysteria.72 In 1986, Dr. Melvin Ramsay published the first ME case definition, which included essential features of cognitive impairment and delayed recovery after minor exertion—a description that reflects what is today called PEM or PENE—and suggested that the disease might be an “abnormal immune response” to a pathogen.73 Ramsay referred to the muscle fatigability after minor effort as the “sheet anchor” of the disease.74 He and other researchers were beginning to produce evidence of biological pathology, such as that suggestive of energy metabolism impairment,75 that still resonate today.

Then, in the 1980s, two large outbreaks occurred in Incline Village, Nevada and Lyndonville, New York, which brought increased national attention in the U.S. After repeated requests by Dr. Dan Peterson and Dr. Paul Cheney, the clinicians at Incline Village, the CDC reluctantly conducted an abbreviated investigation at Incline Village.76 But as documented in the 1996 book Osler’s Web by Hillary Johnson77 and a 1996 PrimeTime special, CDC dismissed the seriousness of the disease and the importance of the evidence of immunological and neurological problems provided by the treating physicians.76 CDC never investigated Lyndonville and did not return calls from Dr. David Bell, the Lyndonville clinician.79 In the mid 1980s, NIH’s Dr. Stephen Straus conducted a clinical trial of Acyclovir, based on a theorized connection between this disease and Epstein Barr Virus (EBV—a herpes virus), but dismissed the connection when the study failed to show efficacy.80 (Decades later, scientists would suggest the failure was due to inadequate duration and type of treatment.)81

Emergence of the Psychogenic View

Over the next few years, the way in which this disease was viewed and treated changed dramatically as a result of growing bias about the nature of this disease and the reemergence of the psychogenic explanations that had first surfaced in 1970.

One proponent of this psychogenic view was NIH’s Stephen Straus, who in a 1988 scientific publication said that patients with this disease had “histories of unachievable ambition, poor coping skills, and somatic complaints.”82 In the same year, he told The New York Times that
patients were “psychologically different long before they developed the syndrome.”\textsuperscript{83} CDC’s Dr. William Reeves would later characterize the 1984 Incline Village outbreak as “hysteria.”\textsuperscript{84} In 1988, Professor Simon Wessely, a British psychiatrist currently at Kings College in London, said that this disease was mainly characterized by fatigue and emotional disturbances,\textsuperscript{85} and would later compare it to neurasthenia, which he viewed as a “culturally sanctioned expression of distress.”\textsuperscript{86} Wessely and other psychiatrists, particularly in Britain, began to promote the “biopsychosocial” theory of CFS, in which the patient’s debility was said to be caused by psychological factors and deconditioning.\textsuperscript{87} As early as 1987 and probably earlier, \textit{The New York Times} and other mainstream press were reflecting these views and the dismissive term “Yuppie Flu” appeared.\textsuperscript{88}

Proponents of this biopsychosocial theory, still prominent today, have dismissed evidence of ongoing organic disease beyond an initial acute illness, which is said to have triggered a maladaptive, “activity avoidance”\textsuperscript{89} out of a presumed fear that activity will worsen symptoms. This maladaptive avoidance of activity is said to result in deconditioning, which in turn is said to cause the ongoing debility and symptoms that patients experience.\textsuperscript{90} In other words, patients’ beliefs, behaviors, and various social factors are keeping them sick (or as expressed in the theory, “maintaining” or “perpetuating” their illness), while their neuroticism, introversion and childhood inactivity “predisposed” them to the illness to begin with.\textsuperscript{91} The treatment recommended by the proponents of this theory is two pronged; cognitive behavioral therapy (CBT) to reverse patients’ presumed “fear of activity” and “false beliefs” that their disease is organic plus graded exercise therapy (GET) to reverse their presumed deconditioning.\textsuperscript{92} Poor response to treatment and poor prognosis overall are said to be linked to factors such as the patients’ believing they have an organic disease or being in receipt of a financial benefit in the form of a disability allowance.\textsuperscript{93}

The biopsychosocial theory has been touted as avoiding the “mind-body duality” that can lead to a discounting of social and emotional factors in human illness. 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 ME patients sick. The biopsychosocial theory for CFS has effectively excised the role of biology in its explanations of disease risk, causation, and persistence beyond acknowledging the possible existence of an initial triggering illness and deconditioning.

Together, Straus’s claims and the biopsychosocial theory for CFS put patients between a rock and a hard place: having to prove that they do not suffer from “unachievable ambition” while simultaneously having to prove that they do not have a fear of activity.

These psychogenic beliefs about the nature of the disease have been reinforced by numerous publications, some published since the 2015 IOM report,\textsuperscript{94} that directly equate this disease to a number of psychological diagnoses, particularly somatoform disorder, somatic symptom disorder, bodily distress disorder and functional somatic syndrome.\textsuperscript{95} Further, a 2014 U.K. National Health Service recommendation for “medically unexplained symptoms” includes chronic fatigue syndrome\textsuperscript{96} as does the 2015 protocol for a planned U.K. review of primary care treatments for “medically unexplained symptoms.”\textsuperscript{97} While the diagnostic criteria vary somewhat across these diagnoses, what is common is that all rely on psychosocial explanations for patients’ physical symptoms and debility\textsuperscript{98} and are most often associated with cognitive behavioral therapy and exercise as treatments.

Today, in mainstream clinical guidelines, CBT and GET remain the most commonly
recommended treatments for CFS, based on biopsychosocial studies and bolstered by the widely publicized and heavily funded but controversial 2011 U.K. PACE trial and subsequent publications. The controversies with the PACE trial are discussed further below.

Such psychogenic bias and unproven theories have had a profoundly negative influence on the way that HHS, the British government, and the research and medical community as a whole have viewed, studied and treated ME for the last thirty years. As the IOM report highlighted, “The proposed psychological etiology created great controversy and convinced health professionals that this was a plausible explanation for the condition.”

**Emergence and Broadening of the CFS Definitions**

These psychogenic theories didn’t flourish in a vacuum. They were enabled by the parallel establishment of overly broad CFS case definitions, which encompassed not only ME patients but also patients with mental illness and deconditioning that might be expected to respond to such psychological, behavioral, and exercise therapies.

A 1987 *JAMA* article by CDC’s Dr. Gary Holmes showed that the CDC was aware of both the earlier outbreaks going back to the 1930s and the use of the term “ME.” But in 1988, the CDC changed the name of the disease to chronic fatigue syndrome, reportedly to avoid unfounded explanations of causation. The CDC also published the Holmes definition; the first of what would become a series of overly broad CFS definitions that focused on medically unexplained chronic fatigue and included psychiatric illness. But the definition did not require the hallmark symptoms, such as the cognitive dysfunction or protracted fatigability after trivial exertion that Ramsay’s definition had required for a diagnosis. Even at the time, these decisions were controversial; two clinicians on the Holmes definition panel with experience in ME (NIH’s Dr. A. Shelokov and British clinician Dr. J. Gordon Parish), reportedly left the meeting because the emerging definition did not reflect the disease as they knew it.

In 1992, Peterson, Cheney, and other researchers published a study in the *Annals of Internal Medicine* that 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.” But CDC’s Reeves rejected these findings, stating that the disease described in the paper “is not the chronic fatigue syndrome or any other clinical entity.” HHS not only rejected the relevance of the disease in Incline Village to the “CFS” that the CDC was studying, but denied the reality of the disease seen at Incline Village.

Within a few years, researchers found that the Holmes definition was diagnostically unreliable, with the result that some psychiatric and medical illnesses were being misdiagnosed as CFS. Yet, remarkably, a 1991 NIH conference, attended by NIH’s Straus, British psychiatrist Professor Simon Wessely and several others with a psychogenic orientation, recommended that the disease definition be expanded to include more psychiatric illness. The stated rationale for this change was to allow an examination of the “possible common pathogenic pathways in patients with CFS and psychic stress” (emphasis added). The belief was that including psychiatric illness would “lead to a better understanding of factors underlying CFS.”

It is hard to imagine that such conflation with mental illness would be recommended for the study of cancer, multiple sclerosis or any other organic disease. And not everyone agreed with doing so in this disease. In a discussion moderated by NIH’s Dr. Stephen Straus at a 1993 scientific meeting, Dr. H. James Wedner of Washington University, a clinician who treated CFS
patients, noted a “creeping movement” to include other conditions within “the rubric of CFS” and said that the inclusion of “somatoform disorders and panic disorder” would “broaden the scope of the clinical entity to the point at which it is no longer definable” (emphasis added).109

But perspectives like Dr. Wedner’s were unable to reign in the “creeping movement” seen in the CFS definitions. Predictably, given the 1991 conference, the next set of CFS definitions—U.K.’s 1991 Oxford definition110 and CDC’s 1994 Fukuda definition111—were even broader than Holmes.

The 1991 Oxford definition was developed in the U.K. under the key influence of the group of British psychiatrists who were promoting the biopsychosocial model of CFS, including Professor Simon Wessely; Michael Sharpe, of the University of Oxford; and Dr. Peter White, of Barts and The London School of Medicine. Demonstrating a stunning lack of specificity, the Oxford CFS definition requires nothing more than six months of debilitating and medically unexplained fatigue, which Oxford describes as subjective, not physiological.112 Oxford includes patients with psychiatric illness but does not require or even mention hallmark criteria like PEM for a CFS diagnosis. Oxford is little more than the symptom of chronic fatigue for which there is no current medical explanation.

Like Oxford, Fukuda also only explicitly requires six months of medically unexplained chronic fatigue but also requires any four of eight common symptoms. While the eight symptoms include hallmark criteria such as PEM and cognitive dysfunction, none are required for a diagnosis and a patient can easily meet Fukuda and not have ME. Like Oxford, Fukuda requires exclusion of medical causes of fatigue but allows psychiatric illness, such as anxiety disorders, somatoform disorders, neurasthenia, and nonpsychotic and non-melancholic depression.113 Fukuda justifies the inclusion of mental illness to “clarify the role that psychiatric disorders have in fatiguing illnesses.”114 Fukuda is self-described as a “conceptual framework” for studying fatiguing illnesses but notably only includes “medically unexplained” fatiguing illnesses. In fact, Professor Wessely, one of those who participated in the creation of Fukuda,115 suggested, without proof, that “medically unexplained” fatigue has a different etiology than “medically explained” fatigue.116 Structuring Fukuda in this way meant that potentially useful comparisons with organic diseases such as cancer or multiple sclerosis might not be pursued because such “explained” fatigue was considered different or somehow not relevant.

The Fukuda definition does acknowledge the importance of stratifying patients by factors such as coexisting psychiatric illness, level and duration of fatigue, level of functional performance, and other factors, although in practice, few studies did that.117 But even if studies had done that, it is difficult to imagine that such stratification could have compensated for the lack of definitional specificity or enabled sufficient cross-researcher consistency to allow comparison of studies.

This broad focus on unexplained fatigue and the failure to require ME’s hallmark criteria has had significant implications for the types of patients that are given a CFS diagnosis by either Oxford or Fukuda. At NIH’s 2014 Pathways to Prevention Workshop (P2P),118 conducted to identify gaps in research, Dr. Luis Nacul, of the London School of Hygiene and Tropical Medicine, pointed out that 80 percent of the allowable combinations of Fukuda’s eight symptoms do not include PEM.119 Dr. Leonard Jason of DePaul University has pointed out that some of these symptom combinations overlap with symptom profiles associated with depression.120 At the P2P Workshop, Jason also noted that in a review of 53 Fukuda studies, as few as 25 percent of the patients in a given study had PEM and as few as 16 percent had unrefreshing sleep, another ME hallmark.121 In both cases, the bottom line is that a substantial number of patients can be
diagnosed with CFS by Fukuda, whether they have hallmark symptoms of ME or not. The situation is likely much worse for Oxford since it requires no symptoms beyond fatigue.

For NIH’s Dr. Straus, Fukuda’s lack of specificity was apparently a good thing. In a letter (obtained by FOIA by advocate Chris Maupin) to CDC’s Dr. Keiji Fukuda, the Fukuda definition’s lead author, Straus praised the 1994 Fukuda definition. He referred to this disease as an “entity of dubious validity” and predicted that with a few years of use, the Fukuda definition would verify that there are no “differences between individuals who meet the full CFS criteria and those who can be said to suffer idiopathic Chronic Fatigue.” He went on to predict that the “notion of a discrete form of fatiguing illness [would] evaporate.”

An entity of dubious validity? The disease would “evaporate?” Straus’s attitude is disturbing. That he felt free to write this letter might suggest he wasn’t alone. A 1993 article in The CFIDS Chronicle (the newsletter of the CFIDS Association of America, now the Solve ME/CFS Initiative) stated that in a September 1993 CDC meeting regarding the establishment of the 1994 definition, Dr. Fukuda and others advocated for a criteria with no symptoms beyond fatigue (essentially chronic fatigue as defined in the 1991 Oxford definition), while others advocated for stratifying the existing criteria. As reported by advocate Roger Burns, the apparent compromise was to incorporate both views with a “broad category for chronic fatigue with many subsets,” one of which was CFS. In essence, Fukuda’s “conceptual framework” for medically unexplained fatiguing illnesses.

Further indication of Dr. Straus’s views can be seen in his response to the 1996 U.K. Royal Colleges of Physicians, Psychiatrists, and General Practitioners report on CFS. The U.K. report dismissed the relevance of findings of viruses and muscle dysfunction, discouraged the interpretation of immunological findings as being due to organic disease, emphasized psychological issues, rejected the term ME and the validity of an ME diagnosis, and endorsed the biopsychosocial theory and the use of CBT and GET as treatments. A Lancet editorial criticized the report as “haphazardly set-up, biased, and inconclusive.” But in a 1996 editorial in the British Medical Journal published at about the same time as the U.K. report, Straus enthusiastically endorsed the report as “the finest contemporary position statement” on CFS. He supported the emphasis seen in the biopsychosocial approach on the “complex interplay of social, behavioural and emotional factors,” notably not mentioning biological factors as contributing to the disease. U.S. Assistant Secretary of Health Dr. Phillip Lee adamantly disagreed with Dr. Straus’ position on the U.K. report and said that the biopsychosocial theory had gone too far. But in spite of the seniority of his position at HHS, Dr. Lee’s views appeared to have little influence on the direction taken by CDC and NIH as it played out in the coming years.

With use, the 1994 Fukuda definition, like Holmes, also turned out to be diagnostically unreliable. A 2005 paper by the CDC stated that a Fukuda CFS diagnosis showed “scant stability over time,” and noted that it is “essentially impossible to compare results between [Fukuda] studies critically.” But as with Holmes, CDC’s solution to this problem resulted in the even broader 2005 Empirical (Reeves) definition, which in a 2007 CDC study, resulted in a 10-fold increase in prevalence over CDC’s earlier Fukuda estimates and encompassed more mental illness. Remarkably, Dr. Peter White, one of the authors of the Oxford definition and a principle investigator in the PACE trial, embraced this increased prevalence seen with the Empirical definition and called for broadening CFS even further. He stated that the criteria for “diagnosing CFS are arbitrary” and need to be broadened 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). But how would stretching definitional boundaries to include all “chronically
tired and unwell” patients help either them or patients with ME? And in what other disease are the definitional criteria considered to be arbitrary? Such arbitrary broadening of the scope of the disease is exactly what Dr. Wedner had warned against in 1993.

Researchers outside of the CDC quickly rejected the 2005 Empirical definition. The 2015 IOM report concurred, stating that the Empirical definition resulted in “a biased sample with overrepresentation of individuals with depression and posttraumatic stress disorder (PTSD).” But CDC has said that their analysis (which CDC has not published) shows that the Empirical definition and accompanying approach selects the same group of patients as the approach used in earlier CDC studies, in spite of the 10-fold increased prevalence and the demonstrated inclusion of more patients with mental illness. Today, the CDC continues to publish Empirical definition studies and includes both Oxford and Empirical findings on its website and in its medical education, further muddying perceptions of the disease. As discussed further in the section on medical care, CDC has not yet formally stated whether it will continue to incorporate Empirical definition study findings in the new medical education for the IOM criteria.

It’s important to note that the 2005 Reeves definition (the Empirical approach) used Fukuda inclusion criteria but relaxed exclusion criteria and used an “unwellness” screening strategy and a different set of symptom assessment tools and cutoffs. Together, these could explain the increased mental illness and prevalence. The CDC refers to this definition as a “standardized approach” to Fukuda or as an operationalization of Fukuda. Some sources refer to the definition as the Reeves 2005 definition and others refer to it as a Fukuda definition. However, given the differences in prevalence and inclusion of mental illness, the 2005 Reeves definition and associated symptom assessment methods clearly encompass different patients than the 1994 Fukuda definition as applied by other researchers. To avoid ambiguity and confusion, this manuscript uses the term “Empirical definition” to refer to those studies, largely at CDC, that used the approach outlined in the 2005 Reeves paper.

For its part, the U.K. published the National Institute for Health and Care Excellence (NICE) Guidelines for CFS/ME in 2007. The NICE Guidelines, which also include management guidelines, require six months of medically unexplained fatigue characterized by post-exertional malaise (which is left undefined) and only one additional symptom out of a list of ten common symptoms. The NICE Guidelines have been poorly received by patient organizations. U.K.’s Dr. Ian Gibson, chair of the Group on Scientific Research into Myalgic Encephalomyelitis that had conducted the 2006 “Gibson Inquiry” into U.K. research and funding needs, called the NICE Guidelines “useless.” And as reported in the 2006 Gibson Inquiry report press release, Des Turner, chair at the time of the U.K. All Party Parliamentary Group on ME (a U.K. group of cross-party parliamentary officials) rejected the NICE Guidelines for CFS/ME as “not fit for man or beast.” Normally in Britain, clinical guidelines such as those for CFS would be reviewed every two years. But in early 2014, the NICE Guidelines for CFS/ME were placed on the static list, which means that they will not be reviewed for five years.

Reemergence of ME and Conflation of ME and CFS
Disease experts have authored definitions specific to ME since the 1986 Ramsay definition, most notably the 2003 Canadian Consensus Criteria (CCC) and the 2011 ME International Consensus Criteria (ME-ICC), published by 26 experts from 13 countries.

Unlike the Oxford, Fukuda, and Empirical CFS definitions, the CCC and ME-ICC require neurological dysfunction and hallmark symptoms such as PEM/PENE (PEM in the CCC and PENE in the ME-ICC). Also unlike the Fukuda, Oxford, and Empirical CFS definitions, the ME-
ICC and the CCC exclude primary psychiatric illness. Further, unlike the CFS definitions in which hallmark symptoms are neither defined nor explained, the ME-ICC and the CCC both provide extensive information about the nature of PEM and other hallmark criteria.\textsuperscript{149}

However, HHS and those promoting the biopsychosocial theory of CFS have not accepted these definitions. They have either questioned the evidence for the biological dysfunction associated with the required symptoms, or rejected the applicability of these ME definitions to “CFS” patients, while continuing to include patients described by these ME definitions within their “CFS” research. For instance, U.K.’s Wessely criticized the 2010 decision of the Scottish Public Health Network to split ME and CFS, with the Canadian Consensus Criteria for ME and the NICE Guidelines for CFS, in part because he felt the evidence for neurological impairment required by the Canadian Consensus Criteria was not supported by the evidence.\textsuperscript{150} In a 2010 paper, CDC’s Reeves stated, “the Canadian definition may signal the presence of a neurologic condition considered exclusionary for CFS.”\textsuperscript{151} The CDC website held this view until 2011, stating that CFS, ME and other terms were being incorrectly used interchangeably and that ME is “accompanied by neurological and muscular signs and has a case definition distinct from CFS.”\textsuperscript{152} Yet, the CDC CFS program had been established in response to an outbreak of a disease that even the CDC had linked to outbreaks of ME\textsuperscript{153} and CDC has never conducted a separate program for ME.

Given these positions, it is surprising that the CDC appeared to change its position on the relationship between CFS and ME in 2012. The statement about CFS and ME being different was removed from the CDC CFS website and the 2012 CDC medical education program (CME) started explicitly lumping Fukuda, Oxford, Empirical, CCC, and ME-ICC together as variants of “CFS” definitions. The CDC CME stated that all these definitions “identify similar pools of patients” and recommended the same diagnostic and treatment approaches for all of them.\textsuperscript{154} Further, in the 2013 CFSAC meeting, CDC’s Dr. Unger questioned the importance of PEM for a diagnosis of this disease, rhetorically asking “If a patient doesn’t have [post-exertional malaise], would you not manage them as a CFS patient?”\textsuperscript{155} In comments submitted in 2014 to the IOM panel charged with creating diagnostic criteria, CDC continued to embrace this broad umbrella of “CFS,” stating that the requirement for PEM in the Canadian Consensus Criteria and PENE in the ME International Consensus Criteria are limitations of these two definitions.\textsuperscript{156} More recently, in a discussion with this author at the August 2015 CFSAC, CDC’s Dr. Belay defended the continued use of findings from Empirical definition studies in CDC’s new medical education content being developed in response to the IOM. If this is indeed CDC’s intent, this is concerning given the problems with the Empirical definition noted most recently by the IOM.

Ironically, while CDC’s CME stated that all ME and CFS definitions represent the same group of patients, CDC separated CFS and ME into separate disease categories in the U.S. specific version of the World Health Organization’s international disease classification system, as discussed further below. CDC’s position on the relation of CFS and ME is at best inconsistent.

This question of whether the CFS and ME definitions represent the same set of patients or not has been the central issue since 1987 when those two ME experts left the Holmes definition meeting because the emerging definition did not reflect ME as they knew it.\textsuperscript{157} It was also raised in the U.K.’s 2006 Gibson Inquiry into CFS, which called for this question to be resolved.\textsuperscript{158} It remains a key issue today.

\textbf{The Debate over PACE}

Oxford studies in general have generated much controversy because of the use of overly broad
definitions that include mental illness; their focus on psychogenic factors for disease risk, persistence and prognosis; and their use of subjective measures to assess treatment effectiveness. No study better exemplifies that debate and controversy than the PACE trial.\textsuperscript{159}

The PACE trial, an Oxford “biopsychosocial” study of CFS, has studied the use of CBT and GET to reverse patients “fear of activity” and deconditioning. At £5 million (about $8 million),\textsuperscript{162} the PACE trial is the most expensive of any single study ever conducted for this disease. Since 2011, the PACE team has released a number of publications that have claimed that CBT and GET are helpful, are safe, and in fact have led to “recovery” in 22 percent of patients. These findings have been widely publicized through the media with headlines like “Chronic Fatigue Treatments Lead To Recovery.”\textsuperscript{161}

PACE and the biopsychosocial theory and treatment approach have also made their way into U.S. clinical guidelines as discussed further in the chapter on Clinical Care. In addition, a 2014 evidence review conducted by the Agency for Healthcare Quality and Research (AHRQ, part of HHS) ranked PACE as a good trial and recommended CBT and GET based on PACE and other Oxford trials, further enabling the proliferation of these recommendations in other published literature and in clinical guidelines globally.

However, Irish and British patient advocates have long disputed the conduct of PACE and have produced an extensive analysis and numerous letters to the publishing journals to highlight these concerns.\textsuperscript{162} Patient advocates have also filed FOIAs to access PACE trial raw data and information to enable a deeper analysis of these concerns. However, those requests have often been rejected and characterized as “vexatious” and having “the effect of harassing the public authority.”\textsuperscript{163}

Journalist David Tuller investigated these concerns and published his own findings in a series of articles in October 2015.\textsuperscript{164} The most obvious problem that affects all Oxford studies is the inclusion of patients who do not have the disease. Other concerns with PACE highlighted by Tuller include reliance on subjective measures to assess treatment outcomes, changes made to the outcome measures and planned analyses in the middle of the trial, the claim that the therapies are safe, the limited and clinically meaningless functional changes that were touted as improvement and “recovery,” and changes in the way in which “recovery” was assessed.\textsuperscript{165}

For example, as a result of the change to the way that recovery was assessed, patients could be deemed “recovered” and yet be at a lower level of functioning on some of the outcome measures than was required to enter the trial to begin with. Further, this assessment of recovery was based on subjective measures. Tuller noted that the investigators dismissed their own objective measures of recovery as unreliable and not relevant when those measures failed to show improvement. Speaking to one of PACE’s objective tests, the 6 minute walk test, Dr. Chris Snell, an expert in exercise-based functional assessments, told attendees at a 2013 FDA meeting that the level of functioning seen in PACE was so low that if these patients were being considered for a heart transplant, they would be rejected as unlikely to survive.\textsuperscript{166}

Regarding PACE’s claim that the therapies are safe, numerous patient surveys have reported harms from these therapies. According to a 2011 analysis of those surveys by advocate and patient Tom Kindlon, 51 percent of respondents did worse on GET in eight surveys while 20 percent did worse on CBT in five surveys.\textsuperscript{167} A 2014 survey of 1428 patients conducted by U.K.’s ME Association similarly reported adverse reactions to GET.\textsuperscript{168} This adverse reaction to GET is not surprising, given the negative reaction to exertion that is by definition part of the disease and was documented in numerous studies and by the IOM.
Another issue is the question of the scope of conditions and patients studied in PACE. PACE used the non-specific Oxford to select patients. But as Tuller noted, the PACE investigators said that they also then subgrouped patients with the "International (CDC) criteria" for CFS and the London criteria for ME. As a result, PACE investigators have claimed that PACE’s findings apply to patients meeting other definitions of CFS and also to ME. But Columbia University biostatistician Bruce Levin told Tuller that it was not reasonable to extrapolate from the CDC CFS and ME patients inside the Oxford CFS group to the full set of CDC CFS and ME patients. This is particularly true when ME definitions do not all require the fatigue required to select Oxford patients. But in addition, PACE used the seldom-used CDC Reeves 2003 criteria (the precursor to CDC’s Empirical definition) and then modified those criteria to only require symptoms for one week, not 6 months as required by the criteria. One of the PACE study publications itself acknowledged that the characterization of patients “may have been inaccurate” because of this change. For the ME criteria, PACE chose the unpublished and seldom used London criteria, which PACE apparently further modified. As a result of the issues raised by Levin and these modifications to the definitions, it is difficult to say anything about the applicability of the PACE findings to ME patients.

Tuller’s article focuses primarily on the conduct of the PACE trial. But his article also underscores the issues with the definitional gymnastics that has characterized this field and the controversies arising from focusing on psychogenetic theories to the exclusion of the biomedical pathologies seen in ME patients. Such blurring of definitional boundaries and single-minded focus on psychological issues to the exclusion of biological pathologies would not be tolerated in other organic diseases.

The Current Situation with the Definitions
To date, Fukuda, and to a lesser extent Oxford, have been the most commonly used definitions in research. Fukuda is the most commonly used in clinical guidelines in the U.S. But disease experts who view the disease as a biomedical disease have been using the CCC clinically and are increasingly using both the CCC and the ME-ICC in research.

In 2012, to resolve the definitional issues, the CFS Advisory Committee (CFSAC, the committee that advises HHS on this disease) recommended that HHS convene a meeting of stakeholders to reach consensus on the case definition for both research and clinical use beginning with the 2003 Canadian Consensus Criteria. The ensuing discussions between HHS and CFSAC members were so contentious that they led to allegations of intimidation of CFSAC members by the CFSAC DFO (designated federal official who is responsible for CFSAC), an issue discussed further in the chapter on HHS’s Stakeholder Engagement. Then, in a controversial move that generated strong negative community reaction, HHS rejected the CFSAC recommendation, and instead unilaterally announced that it intended to contract the Institute of Medicine to define new clinical diagnostic criteria. In response, fifty internationally renowned disease experts sent a letter to the Secretary of Health, calling on HHS to adopt the 2003 Canadian Consensus Criteria for both research and clinical care and to not engage the IOM to develop its own criteria because that was wasteful, unnecessary and risked setting the science backwards. But HHS rejected the experts’ recommendation and went forward with the IOM contract. In parallel, HHS progressed the Pathways to Prevention (P2P) Workshop, originally described as addressing the research case definition. (The IOM report also stated that P2P was “originally intended to complement the present study by developing a research case definition for ME/CFS.” But that did not happen.)
As originally defined, the P2P Workshop was also intended to examine the long-standing and critical issue of how ME and CFS differ and whether these illnesses are part of a spectrum or entirely separate.\textsuperscript{180} This was also a critical question that needed to be considered in the evidence review conducted by the Agency for Healthcare Research and Quality (AHRQ) in support of the P2P Workshop.\textsuperscript{181} AHRQ’s Dr. Beth Collins Sharpe, the ex-officio member of CFSAC at the time, told this author that she didn’t expect that the ME and CFS definitions would be lumped together for analysis in the review because that would be like “comparing Oxford apples to CCC oranges.”\textsuperscript{182} But that is what the AHRQ Evidence Review did—lumped together eight CFS and ME definitions as the same condition based solely on the symptom of unexplained chronic fatigue, in spite of substantial differences in inclusion and exclusion criteria across definitions.\textsuperscript{183} As a member of the Technical Expert Panel told the AHRQ Evidence Review authors, “The use of fatigue as the only criteria for [Diagnostic methods] diminishes the multi-system nature of the illness and is a limitation, perhaps even a fatal flaw of the report.”\textsuperscript{184} This “fatal flaw” of ignoring the hallmark symptom of PEM in its assessment of diagnostic methods is comparable to telling a doctor to diagnose a heart attack without considering the presence or absence of chest pain.

The final 2014 AHRQ Evidence Review focused on the symptom of fatigue. The evidence review did acknowledge that differences in the inclusion criteria meant that some definitions, particularly Oxford, could include people who did not have the disease. Further, in comments on one of the publications, the review authors acknowledged that improvement in function with CBT was seen in Oxford studies but not in Fukuda studies.\textsuperscript{185} Yet, the final evidence review graded the controversial PACE trial as a good study and recommended CBT and GET as treatments for all patients meeting any CFS or ME definitions.\textsuperscript{186} The review authors stated that they included the Oxford studies because excluding them “would limit the evidence” available for review,\textsuperscript{187} as though the quantity of evidence was more important than the relevance of that evidence to the disease under study. At the P2P Workshop, the AHRQ evidence review lead author defended the continued application of Oxford-based recommendations for all CFS and ME patients because they “may give us some clue as to where to go with things.”\textsuperscript{188} This is a remarkable statement that appears to be based on a mistaken belief that Oxford studies are relevant to ME. Would Oxford studies be considered relevant to any organic disease that has fatigue as a symptom?

Unfortunately, the AHRQ Evidence Review is not the only evidence review to take this approach. This practice of mixing and matching disparate definitions is the usual approach for “CFS” evidence reviews, most recently in the 2015 Cochrane evidence review for GET in CFS.\textsuperscript{189} Sometimes, these evidence reviews have included studies that only partially met a CFS definition or didn’t meet any CFS definition as long as patients had chronic fatigue of some length of duration.\textsuperscript{190} This practice has contributed to flawed evidence reviews that have in turn resulted in faulty “evidence based” recommendations for clinical care as discussed in the chapter on “Medical Care.” This has created a significant risk of harm for patients and can negatively impact insurance reimbursement decisions.

For its part, the P2P Workshop agenda also failed to examine the question of whether ME and CFS differ. The P2P workshop sessions that were held, particularly those describing the findings of the AHRQ Evidence Review, were presented as relevant to all ME and CFS patients.\textsuperscript{191} Further, the P2P workshop included a session on “Social Determinants of Health” but failed to include any sessions on the biological pathologies associated with PEM or the neurological symptoms that could have shed light on the question of whether the ME and CFS definitions represent the same disease.
The final 2015 P2P Workshop report stated that the disease was not psychological and called for Oxford to be retired. But it did not reject AHRQ’s recommendations for CBT and GET, recommendations, based largely on Oxford studies and on a psychological theory of disease. Beyond that, P2P called for future research to study symptoms beyond fatigue and noted, “The multiple case definitions for ME/CFS have hindered progress.” The report also called for a meeting of stakeholders to reach consensus on the case definition, a recommendation that looked remarkably like the 2012 CFSAC recommendation that HHS had already rejected.

In sharp contrast to the P2P Workshop and the AHRQ Evidence Review, the IOM report did examine the pivotal question of whether all of the ME and CFS definitions represent the same group of patients or not. The IOM report decisively concluded that they did not, stating, “a diagnosis of CFS is not equivalent to a diagnosis of ME.” The final IOM report emphasized that the disease is not a psychological illness, but rather a “serious, chronic, complex, multisystem disease” that can “consume the lives of those whom it afflicts.” The clinical diagnostic criteria proposed by IOM (for U.S. clinical use only) require a substantial decrease in function, post-exertional malaise, and unrefreshing sleep plus either cognitive impairment or orthostatic intolerance. The report recommended a set of tools and questions to aid diagnosis, recommended a positive diagnostic approach (as opposed to Fukuda’s diagnosis of exclusion), and recommended that these patients be pulled out of the Fukuda definition and not be called “ME/CFS” or “CFS.” The IOM also conducted an evidence review, recommended a new name (“systemic exertion intolerance disease” or “SEID”), and suggested a strategy to distribute the proposed criteria to the medical community.

The IOM’s evidence review, the most extensive review of the biomedical literature until that time, was generally well received. But Dr. Mary Ann Fletcher, a CFSAC member, raised concerns with missing and misinterpreted evidence in the immunological section of the IOM report. In addition, the neurological section is heavily focused on sleep, cognitive, and autonomic issues but is quite light in its review of other neurological symptoms and dysfunction. Regarding the name, many patients and some experts rejected the name “SEID” as trivializing and misleading. At the same time and reinforcing the concerns of the community, “SEID” has already been interpreted, in both published articles about the IOM report and in clinical guidelines published since the IOM report, as a simple renaming of CFS with UpToDate adopting the term “CFS/SEID.” More problematically and suggesting a misunderstanding of the nature of PEM and of the organic nature of the disease, UpToDate still recommends CBT and GET, using the 2014 AHRQ Evidence Review and PACE as references to support that recommendation.

Regarding the proposed IOM criteria themselves, some experts and patients have voiced concerns that the criteria will result in over-diagnosis and misdiagnosis because the criteria are subjective, are not “operationalized” (lack instructions on their use), fail to specify exclusionary conditions, do not include key neurological or inflammatory (flu-like) symptoms, and do not adequately cover early onset patients or the most severely ill patients. In a 2015 meeting, Incline Village’s Dr. Dan Peterson said that the SEID criteria might identify “another group of patients that is somewhat artificial and overlapping with other syndromes.” He added that this was likely a heterogeneous group but a different heterogeneous group than previously defined and one that might include patients with Lyme or Gulf War illness. Dr. Leonard Jason of DePaul University conducted a validation study of the IOM criteria that echoed Peterson’s comments. He found that the SEID criteria selected a larger group than the CCC; a group that was comparable in size to Fukuda and about 2.8 times bigger once the IOM criteria’s lack of exclusionary conditions was considered. Given the skepticism in the doctors who will be
expected to use the new diagnostic criteria, these issues could lead to significant misdiagnosis and overdiagnosis.

Because it was outside their remit, the IOM report did not address the issue of what to do with the Fukuda and Empirical definitions beyond stating that the remaining patients need to be cared for. The failure of the publicity surrounding IOM report to explicitly highlight the intent to separate patients meeting the IOM criteria from the broader CFS collection of conditions has led the medical community to see the IOM criteria as just another definition for “CFS.” Failure to explicitly address this issue going forward will exacerbate an already confusing situation.

Another significant issue is that while the IOM report stated that the IOM criteria were based on the CCC, the report did not define the intended relationship between the IOM criteria and the Canadian Consensus Criteria or the ME-ICC. Put another way, it is not clear whether the IOM criteria were intended to describe the same disease as the CCC and the ME-ICC. This creates a real dilemma because, as acknowledged by HHS staff, the 2003 Canadian Consensus criteria are widely embraced by disease experts and have been used and reported in some of the most significant research studies in 2014 and 2015. This disconnect between research and clinical criteria will complicate the translation of research to clinical care and create further confusion on the nature of the disease, confusion that will be amplified by using the same disease name for patient cohorts defined by both the IOM criteria and the Canadian Consensus Criteria. Adopting the IOM criteria for all research will perpetuate the current problems with conflicting research evidence because of the problems with the IOM criteria noted above.

This issue of whether the IOM criteria are intended to describe the same disease as the Canadian Consensus Criteria must be addressed. If the IOM criteria are intended to describe the same disease as the Canadian Consensus Criteria, then this should be clearly stated, and the Canadian Consensus criteria used as a standard to evaluate the diagnostic accuracy of the IOM criteria.

Finally, while the IOM recommendation was for clinical use in the U.S. only, this disease is international and is being researched across countries. Failure to drive for international agreement on the clinical and research criteria and what the disease is called will perpetuate the current muddle.

In August 2015, CFSAC made a number of recommendations to HHS to address some of the issues with IOM’s clinical diagnostic criteria and to target specific research and secure more research funding. CFSAC did not recommend follow-up on Jason’s validation study before rollout of the new criteria but instead called for validation within two years. As of October 2015, CDC is moving forward to develop new educational material but HHS has not yet responded to CFSAC’s recommendations.

The history of this disease is one of the sequential adoptions of a series of overly broad and unvalidated CFS definitions that have warped the understanding of ME, resulting in misdiagnosis and fueling medical skepticism and mistreatment. There is good reason to be concerned that this medical skepticism and misunderstanding continues today. For instance, the comments by doctors on an American Academy of Family Physicians article about the IOM report showed 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.” Similarly, in a September 2015
article in *NeurologyNow*, one doctor said that he recommends CBT to counter negative or inaccurate thoughts and said that it’s important to “avoid making the disease a lifestyle.”

ME is not a “lifestyle.” It is a life sentence and not one in which patients have any choice.

Given the subjectivity of the IOM criteria, the absence of key features, the lack of exclusionary criteria, the poor operationalization, and such ongoing skepticism and misunderstanding, the risk is significant that the IOM criteria will again result in continued misdiagnosis and overdiagnosis. This risk must be addressed.

**Bad Science and Questionable Medical Ethicality**

The interchangeable use of such disparate definitions, further confounded by interchangeable names and inappropriate medical dictionary classifications, demonstrates an inconceivable level of scientific ambiguity and sloppiness. It also suggests dubious medical ethicality in its unquestioning application of the findings from studies in one group of patients to patients with a different disease.

The first issue is that the CFS and ME definitions have been studied and treated as the same disease based solely on the symptom of medically unexplained chronic fatigue. Put another way, “CFS,” as a clinical entity described by the collection of CFS definitions, is constructed on the common but ill-defined symptom of fatigue plus the *current state* of medical knowledge. This has created what one researcher referred to as “a diagnosis of the undiagnosable.” Further, basing the clinical entity on the condition of being “medically unexplained” has fueled the idea that the disease is psychogenic because of the general tendency in the medical community to equate “medically unexplained” to “psychologically caused.” In the case of ME, that tendency is further fueled by this disease being more prevalent in women and the widespread publicity surrounding well-funded biopsychosocial studies such as the PACE trial. But no scientific rationale or evidence has ever been provided to demonstrate that all medically unexplained fatigue conditions suffer from the same underlying biological pathology and should be studied and treated in the same way. Simple logic and recognition of the limits of current scientific knowledge should be enough to demand that the validity of this construct be questioned.

The second issue is the long-standing, but never-proven, assumption that obviously disparate CFS and ME case definitions all represent the same or related diseases. A simple desktop comparison of the differences in inclusion and exclusion criteria across these definitions (Appendix 1), magnified by the operational differences in how the criteria are applied, demands that the validity of this assumption also be questioned. ME is undoubtedly complex and heterogeneous. But the heterogeneity of “CFS” is a man-made artifact of non-specific disease definitions that throw disparate diseases into the same wastebasket. Patient cohorts with primary psychiatric illness and fatigue but no hallmark symptoms such as PEM are not the same as cohorts with neurological symptoms and PEM but no primary psychiatric illness. Further, studies of biological markers, symptom profiles, and prevalence rates across the CFS and ME definitions have shown lower prevalence, more severe symptoms, and greater functional impairment in the CCC and the ME-ICC definitions when compared to CFS definitions. Other studies have shown that patients who meet CCC or ME-ICC or who have PEM show higher levels of inflammatory markers compared to those CFS patients who do not. Still other studies have provided objective evidence of the biological abnormalities associated with symptoms that are required by ME definitions but not by CFS definitions, as further documented in three scientific conferences in 2014 and in the IOM report itself. These nature of the biological abnormalities, especially the impairment in energy metabolism, that are associated
with symptoms only required by the ME definitions is evidence that the CFS and ME definitions do not represent a spectrum of one disease.

Other studies have shown that the overly broad CFS definitions are so diagnostically unreliable that in practice, they encompass a range of conditions. For example, a 2013 study found that over thirty percent of multiple sclerosis patients had first been misdiagnosed with CFS or chronic fatigue before being correctly diagnosed with multiple sclerosis,\textsuperscript{219} while a 2014 study found that 14 percent of MS patients also met the diagnostic criteria for Fukuda CFS.\textsuperscript{220} A British study showed that about 40 percent of the Fukuda CFS patients actually had another disease\textsuperscript{221} and a U.S. study showed that 38 percent of major depressive disorder patients could be given a CFS diagnosis using the Empirical definition.\textsuperscript{222} Finally, a 2003 study conducted by the CDC showed that only 7.5 percent of the patients maintained a Fukuda CFS diagnosis two years in a row\textsuperscript{223} while a 2005 study conducted by the CDC found only a 25 percent concordance between an Empirical CFS diagnosis and a CFS diagnosis by CDC’s 2003 study approach. Given that so few patients recover from ME or even improve enough to not qualify for a diagnosis two years in a row, these findings call into serious question the diagnostic reliability of CDC’s approach and suggest that whatever these “CFS” patients had, the overwhelming majority of them did not have ME with its hallmark PEM and cognitive dysfunction.

The third issue is the incompatibility of the proposed disease theories across the full range of CFS and ME definitions. For instance, the Oxford definition is most often used to study the biopsychosocial disease theory of CFS, in which the debility and symptoms are driven by patients’ fear of activity and subsequent deconditioning. Both the Fukuda and especially the Oxford definitions are broad enough to select patients who could be expected to have the presumed fear of activity and deconditioning and thus be helped by CBT and GET. But it is difficult to imagine that the disease described by the CCC and the ME-ICC, in which symptoms are the result of widespread organic dysfunction, not false cognitions, will respond to talk therapy intended to convince patients that they are not really sick, just deconditioned. Put another way, it is difficult to imagine that the disease that responds to Rituxan is the same disease that PACE claims can be effectively treated by reversing “fear of activity” and deconditioning. It is also worth noting that researchers have noted that CPET can differentiate this disease from deconditioning\textsuperscript{224} and Dr. Ellen Clayton, chair of the IOM panel, stated that the debility of this disease was too severe to be the result of deconditioning as the biopsychosocial theory purports.\textsuperscript{225}

The confusion created by the sloppy definitions is amplified by the interchangeable use of disease terms and the inappropriate classification of this disease in some medical dictionaries. For instance, the terms “CFS,” “CFS/ME,” “ME/CFS,” “ME,” “chronic fatigue,” and now “SEID” and even “CFS/SEID”\textsuperscript{226} are used interchangeably to refer to patients meeting any of these definitions.\textsuperscript{227} Yet, the Oxford definition clearly does not describe ME patients. This has created a linguistic Babel that thwarts the most basic communication and muddles the evidence base.

Equally muddled is the classification in medical terminology systems in which this disease is sometimes directly linked to chronic fatigue or psychiatric issues. This classification is important because it affects disease tracking, insurance reimbursement, and even doctor’s perceptions of the disease. The World Health Organization classifies both ME and CFS as neurological diseases in the International Classification of Diseases (ICD-10), used around the world. But in the U.S. specific ICD-10-CM, the CDC (responsible for the ICD-10-CM) has unilaterally reclassified CFS to be equivalent to the symptom of chronic fatigue (e.g. both use the same ICD code and thus can not be distinguished in tracking systems), while ME remains a neurological disease.\textsuperscript{228} This reclassification is against WHO standards and the recommendations of the
CFSAC.\textsuperscript{229} Ironically, CDC's reclassification is also in direct conflict with the position taken in the 2014 AHRQ Evidence Review and in CDC's medical education in which CFS and ME definitions are treated as representing the same disease.

(One note: ICD-10 uses the term “CFS.” But in ICD-10-CM, the CDC adopted the term “chronic fatigue syndrome, NOS” where “NOS” means “not otherwise specified.” The American Academy of Professional Coders (AAPC) stated that in ICD-9, the added term “NOS” could result in the rejection of reimbursement because of a claimed lack of medical necessity and/or specificity.\textsuperscript{230} It is unknown how and whether this could affect reimbursement against ICD-10-CM.)

Issues have arisen with the classification of the term “CFS” in the U.K as well. The U.K.'s WHO Collaborating Centre, at Kings College in London, categorized CFS as a mental illness equivalent to neurasthenia in the 2001 U.K. specific “WHO Guide to Mental Health in Primary Care.”\textsuperscript{231} As a result, a number of authors and even textbooks have stated that CFS is classified as both a neurological and psychiatric illness, or else state it is only classified as a psychiatric illness.\textsuperscript{232} In 2001 and again in 2004, the World Health Organization ruled that this classification was incorrect.\textsuperscript{233} But this view has been remarkably persistent in other sources in the U.K even today.\textsuperscript{234} For instance, both the READ codes, used in clinical care,\textsuperscript{235} and the 2014 U.K Department for Work and Pensions (DWP) guidelines for disability analysts\textsuperscript{236} classify CFS as both a neurological disease and as neurasthenia. The DWP guidelines incorrectly state that ICD-10 classifies CFS as neurasthenia.

Finally, until August 2015, the \textit{Systematized Nomenclature of Medicine--Clinical Terms (SNOMED CT)}, important in electronic health records in the U.S. and likely elsewhere, classified CFS and ME as a multisystem disorder and also as a mental disorder.\textsuperscript{237} This has been corrected.

\textbf{The Impact of Bad Definitions}

The muddling seen across these definitions, names and classifications represent an astonishing level of scientific sloppiness and confusion that the authors of the 2011 ME International Consensus Criteria referred to as a “web of confusion,” a scientific Tower of Babel that has impeded forward progress in research and clinical care.

In research, it has resulted in flawed epidemiological studies, faulty prevalence numbers and erroneous claims of risk and prognosis.\textsuperscript{238} It has wasted precious dollars and time studying psychogenic issues and a disparate mix of “CFS” conditions with no proof that they have a biological relationship to each other or to ME. It has polluted research, making it impossible to replicate findings across studies, thereby casting doubt over all results. It has resulted in flawed evidence reviews that conflated disparate patient groups. It has impeded the development of diagnostic biomarkers, leaving the diagnosis one of subjectivity and exclusion.\textsuperscript{239} It has virtually stalled drug development and severely impacted the ability to attract private and commercial investment to this disease.\textsuperscript{240} It has generated such disdain and skepticism in the research community that researchers\textsuperscript{241} avoid the disease like leprosy out of a fear that it could kill their careers.\textsuperscript{242}

The definitional morass is also felt in clinical care where it has warped the physician’s understanding of the disease, leading to medical disbelief, hostility, and inappropriate treatments. It has enabled faulty evidence reviews to be churned into flawed “evidence based” clinical guidelines that include findings of maladaptive personalities and recommendations for CBT and GET that continue to hurt patients today. It has made it extremely difficult for patients
to get disability and to get insurance reimbursement, because most tests and treatments are considered experimental. It has stigmatized terribly disabled patients and sentenced them to abysmal clinical care. And worst of all, this definitional morass has directly enabled and nurtured psychogenic views. This has dramatically altered the perception of ME by the public at large, ensuring that neither the disease nor its victims are taken seriously by anyone.²⁴³ Sometimes not even by patients’ own families.

More than any other single factor, this definitional morass is at the heart of our country’s disgraceful failure to address the ME crisis since the 1980s. What is astonishing is that this “web of confusion” has been allowed to persist and even thrive for thirty years.
Abysmal Medical Care

Note: The statements about medical education were based on an analysis in September 2015.

By every measure imaginable, medical care for ME patients is appalling.\(^{244}\) Patients can go decades without a diagnosis and when they are diagnosed, they then face a medical community that is at best, ill prepared to care for them and at worst, unbelieving and abusive.\(^{246}\) Doctors routinely dismiss the disease as not real or else as deconditioning or a form of psychiatric or behavioral illness.\(^{246}\) Absurd stories of doctors telling patients they have conversion disorder or are on the “wrong life-path” are all too real. Doctors recommend inappropriate and potentially harmful treatments such as cognitive behavioral therapy and graded exercise therapy, even though those recommendations are based on studies such as PACE that use these therapies to reverse presumed faulty cognitions and deconditioning.\(^{247}\) Some doctors are so convinced that the problem is deconditioning that they insist that patients continue to exercise even when doing so makes patients crash.\(^{248}\) Doctors have also been known to dismiss other life-threatening diseases such as pneumonia because the patient is a “CFS” patient and therefore can’t really be sick.\(^{249}\) Doctors have humiliated patients for believing they have an organic illness and browbeat family members for refusing to accept that their loved one is not “just depressed.”\(^{250}\) One disease expert stated that some of her patients had experienced PTSD “where their trauma was their interaction with their physician around this illness.”\(^{251}\) This medical dismissal and haranguing is so severe and invalidating,\(^{252}\) that many patients intentionally withhold their diagnosis from doctors or else avoid doctors altogether.

Such treatment by their doctors is likely a significant factor contributing to the high rate of suicide in ME patients.

This is not just patient hyperbole. The 2015 Institute of Medicine report described medical “skepticism,” “hostile attitudes,” and the difficulties patients experience in getting diagnosis and medical care.\(^{253}\) One of the IOM panel members stated, “Many doctors mistakenly believe that chronic fatigue syndrome is a psychological problem—it is malingering; it is not real; there’s no objective evidence—and that patients should be dismissed as being not truly ill” (emphasis added).\(^{254}\)

NIH’s 2015 Pathways to Prevention (P2P) report reiterated these harsh criticisms, stating, “Both society and the medical profession often treat patients with ME/CFS with disdain, suspicion, and disrespect” and “negative interactions with the health care system are frequent.” The P2P report also noted that “clinicians have a poor understanding” of this disease that patients “usually have to make extraordinary efforts, at extreme personal costs” to find a doctor, and that patients are frequently harmed by the treatment they receive.\(^{255}\)

Bad Clinical Guidelines and Medical Education

The need for diagnostics and treatments is critical but unfortunately will require time, research and money to achieve what is needed. Until then, the issue that is causing the greatest medical confusion and harm to patients is the erroneous clinical guidance provided by mainstream medical education websites.

The CFS clinical guidelines provided by the CDC and other medical education providers are typically one-size-fits-all guidelines for a condition that is most typically described vaguely as “profound fatigue that is not improved by bed rest” or alternatively as “unexplained, persistent,
and sometimes debilitating fatigue. The clinical guidelines seldom describe the underlying organic nature of the disease with its infectious triggers, immune dysfunction and cognitive impairment; Medscape’s CFS guidelines (updated since the IOM report) are one of the few mainstream guidelines to do so. But much more typically, mainstream clinical guidelines focus on unexplained fatigue and either do not discuss or are dismissive of the evidence of biological dysfunction, often while emphasizing psychological issues. For instance, the Mayo Clinic’s CFS guidelines state that the condition is “characterized by extreme fatigue that can’t be explained by any underlying medical condition” and that the symptoms of the disease are often “linked to mood.” Clinical guidelines often cite personality disorders, a history of child abuse, and an inability to handle stress as risk factors. One clinical guideline cites both “high or low premorbid activity levels” as risk factors and recommends CBT to “modify thoughts, behaviors, and environmental contingencies that are perpetuating or exacerbating symptoms and impairments.” Even guidelines updated since the IOM hold this view. UpToDate refers to the disease as “CFS/SEID” and recommends the IOM criteria for diagnosis. But then it characterizes immune changes as minor or not different from controls. It then also notes a “close linkage of mood to perception of the symptoms” and states that a poorer prognosis may be related to a belief that the disease has an organic cause. It is remarkable that a guideline that was updated since the IOM report would take this stand.

It is important to note that when references are provided for such personality, abuse and stress-related factors, the references are largely Oxford and Empirical definition studies which are then being inappropriately applied to patients meeting any ME or CFS definition.

Regarding diagnosis, U.S. guidelines are based on Fukuda (unless updated to use the IOM criteria.) Thus, they most typically focus on medically unexplained fatigue as the identifying characteristic plus any four of eight symptoms. They do not require hallmark criteria like PEM while including patients with primary psychiatric illness, including somatoform illness. Only minimal lab tests are recommended and the ones that are recommended are almost always normal and are primarily used to exclude other causes of fatigue. One site recommends against extensive tests because of “the absence of known biological underpinnings.” Even simple and useful tests used by ME disease experts—e.g. tilt table tests to assess orthostatic intolerance—are almost never mentioned, even on CDC’s website. The U.K.’s NICE Guidelines specifically recommend against using a tilt table test.

Because CFS is often equated to a somatoform illness, it is likely that the clinical guidelines for somatoform illness come into play as well. For instance, as discussed by Dr. Allen Frances, chair of the DSM-IV, the American Association of Family Physicians advises doctors to make an early diagnosis of somatoform disorders “to save time and reduce costs.” As Laurie Endicott Thomas, medical writer and author of Not Trivial, told 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.” What she describes is exactly what happens to ME patients.

With regards to treatment, the vast majority of clinical guidelines recommend CBT and GET, based on PACE and other Oxford studies. One of CDC’s CMEs directly references the PACE trial in its recommendation for CBT and GET and states that “CBT is associated with significant improvement and possible full recovery from some symptoms,” a claim not supported by surveys of ME patients or a close examination of the PACE trial itself. MedPageToday’s KevinMD (not updated since the IOM), 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.” Epocrates (not updated since the IOM) recommends CBT to modify thoughts and behaviors thought to be “maintaining or exacerbating symptoms and impairment.” In its article announcing the 2015 IOM report, the American Academy of Family Physicians provided a link to a 2012 article that recommended CBT and GET (using PACE as a reference) and stated that poorer prognosis is associated with “poor social adjustment, a strong belief in an organic cause for fatigue, or some sort of sickness benefit.”

Even the medical education sources updated since the IOM report make similar statements. A 2015 Medscape article, entitled “Management of SEID,” referenced the PACE trial and recommended CBT and graded exercise. UpToDate (updated since the IOM) recommends CBT and GET, using PACE and the 2014 AHRQ Evidence Review as references. It also states that “increased rest is not recommended and should be strongly discouraged” and states that a poor prognosis may be “related to the patient's belief that the illness is due to a physical cause,” both statements that reflect the biopsychosocial theory of CFS. But remember that ME patients rest to avoid the exacerbation of symptoms that can occur with even trivial activity or even just being upright.

A 2015 Medscape CFS case study (issued after the IOM report) chose for their case a patient who had fatigue and other symptoms but not PEM. Medscape also noted that this patient had largely normal labs, was obese, had had multiple unprotected sexual encounters, had been to multiple doctors but remained unsatisfied with their workups and was stressed by her symptoms. The case study recommended CBT and GET and said that prolonged rest “showed no benefit and indirect evidence of harm.” There was nothing in this case study that indicated that this patient had ME as defined by the CCC or even the disease described by the IOM. Further, the recommendation for CBT and GET and the recommendation against rest could cause real harm in ME patients.

Across clinical guidelines, few medications are recommended and when they are, the recommendations are typically for depression, pain, and sleep. Treatment that is helpful for orthostatic intolerance is only rarely recommended; notably, one site to do so is CDC’s. Use of antivirals and immune modulators, successfully used by disease experts for some patients, is either not mentioned or rejected as unwarranted.

Medical education of this type can’t help but leave medical providers confused on the nature of the disease, convinced that it is psychological or malingering, and recommending inappropriate and harmful treatments such as CBT and GET. This confusion can be seen in a 2010 CDC study in which only 39 percent of doctors disagreed with the statement that “CFS is only in the patient’s head,” while 57 percent of doctors stated, “a diagnosis of CFS can inhibit a patient’s motivation to get better” (emphasis added). This last statement suggests that doctors believe that patients have control over their illness, an attitude reflected in a 2015 statement in a NeurologyNow statement on the need to “avoid making the disease a lifestyle.”

Such faulty medical education and the resultant medical confusion is inarguably the most likely reason why ME patients are dismissed, mistreated and, for up to 80 percent of patients, undiagnosed for years on end. And as noted earlier, these problems affect more than just ME patients. Patients with other diseases are too frequently misdiagnosed, as documented in the U.K. study where patients with sleep disorder, psychiatric illness, and cardiovascular disease were all misdiagnosed as CFS. And once patients are misdiagnosed with CFS, they then fail to get the treatments they need for whatever disease they have. Author and ME patient Toni Bernhardt described the story of one patient whose potentially fatal case of pneumonia was almost dismissed by doctors because he was a CFS patient. A physician friend warned Dr.
Vincent Racaniello (the host of “This Week in Virology”) when 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.”

The examples of *UpToDate* clinical guidelines and the *Medscape* case study, both updated since the IOM report, demonstrate the magnitude of the challenge that we face in changing the dominant paradigm of the medical community toward this disease. In both examples, and in other reports released since the IOM, the content includes a nonsensical mishmash of IOM findings, findings from Oxford biopsychosocial studies and Empirical studies, and the findings of flawed evidence reviews, such as the 2014 AHRQ evidence review, that were based on a conflation of disparate definitions. Such clinical guidelines are unhelpful at best and risk harming patients in their unethical application of recommendations from one group of patients to those with a different disease.

**Additional Challenges in Clinical Care**

While erroneous medical education has likely caused the greatest harm, other factors have degraded the quality of medical care as well. Insurance policies and medical office business practices lead to shorter visits, a significant problem in such a complex illness and one that the *Pathways to Prevention* report noted could impair “patient/clinician communication and quality of care.” The IOM report also noted the lack of information on the disease in medical school textbooks and curricula while a study in Scotland found that medical schools were equating CFS and ME to mental disorders such as functional somatic syndrome or somatoform illness. Other factors include the well-known tendency of doctors to assume psychological explanations when they can't find the cause, the failure of any medical society or specialty to take responsibility for ME, and the refusal of many insurance companies to provide coverage for most tests and treatments related to this disease. (As noted earlier, the ICD-10-CM code of “CFS NOS” could exacerbate this situation if insurance companies treat the NOS designation as medically unnecessary.)

In sharp contrast to the practices recommended in mainstream medicine education, ME disease experts have been successfully diagnosing patients and providing some relief with a set of diagnostic and treatment practices that have been compiled into primers for medical providers. The differences between these primers and mainstream clinical guidelines are stark. But because of a lack of research funding, the practices have not been formally replicated, validated, and published in peer-reviewed journals. As a result, the knowledge and experience of disease experts does not make it into mainstream clinical guidelines and evidence-based medicine. The lack of knowledgeable clinicians and appropriate clinical guidelines is already a crisis and is going to become more severe as the handful of disease experts, many of whom are older, retire and their knowledge is lost.

Over the years, the CFSAC, patients, and disease experts alike have made many recommendations to the CDC to fix its medical education by providing more accurate information and removing erroneous and at times harmful content from its website. This includes the removal of the controversial, one-size-fits-all CDC CFS Toolkit, the Oxford based recommendations for CBT and GET, and claims of child abuse as a risk factor based solely on an Empirical study. CFSAC has also recommended that the IACFS/ME Primer for Clinicians (produced by the International Association for CFS/ME) be made broadly available and that CDC use the Canadian Consensus Criteria (upon which the IACFS/ME Primer was based) as the basis of its medical education. While some changes have been made to the website, the CDC has rejected many of the formal and informal recommendations and has not...
incorporated content from the IACFS/ME primer or provided a link to it from the CDC CFS website. CDC also refused to remove its CFS Toolkit, as recommended by the CFSAC in 2012. In 2013, CDC resisted CFSAC’s request to have input on the new toolkit that CDC was developing. CDC finally listed the CFS Toolkit as archived in April 2015, although it is still available online.

One of the reasons given by CDC for not incorporating the practices of disease experts is that these practices have not been published in a peer-reviewed publication. This is admittedly a huge problem for this field, one that will require additional research funding from NIH to fix. However, it is impossible to escape the irony that the recommendations of disease experts cannot be provided in medical education in mainstream clinical guidelines, including CDC’s, but treatment recommendations and findings based on Oxford and Empirical studies—studies that even the IOM and P2P reports state have questionable relevance to ME patients—can be provided. The result is that ME patients don’t receive the care they should and are at risk of harm from receiving care that they should not. The medical ethicality of such clinical guidelines must be questioned, as must the scientific validity of “evidence-based” medicine when it is based on studies using non-specific definitions and on evidence reviews that conflate disparate definitions. For a disease with such a conflicted evidence base and so little research, a different approach to the establishment of clinical guidelines is essential, at least until the needed research is done and studies are published.

Following the IOM report, the CDC announced an initiative to work collaboratively with a range of stakeholders, including disease experts, patients, and also medical providers to create new medical education. The steering committee for this effort is internal to HHS, making it unclear whether and how disease experts will play a role in validating the final content of CDC’s new medical education material prior to its release. It is also not clear whether CDC intends to adopt the August 2015 CFSAC recommendations, which included a) working with disease experts to ensure that the criteria are properly operationalized before rollout, b) separating the IOM criteria with its mandatory PEM from the existing “CFS” definitions and website, c) not applying Oxford and Empirical study findings and recommendations to patients who meet the IOM criteria, and d) using the ICD-10-CM code for ME, not the ICD-10-CM code for CFS. Further, it is unclear how CDC intends to incorporate the unpublished practices of experts in its medical education.

CDC has announced that it is releasing “standardized patient videos” through the MedEd Portal to teach medical students about this disease. As noted above, the lack of medical school education on this disease is a critical issue. But these videos were developed in 2013-2014 using the Fukuda criteria in which only fatigue is required. In a 2014 discussion with this author, CDC staff indicated that PEM was not presented as a mandatory symptom in the videos themselves and that a discussion of PEM was relegated to supplemental material. If that is true, these videos may do little to dispel the misunderstanding of the disease.

The way in which all of these issues are addressed in CDC’s new medical education will have a profound influence on the way in which this disease is understood and treated clinically for the foreseeable future and will also influence the way it is researched. Given the current response of the medical community to the IOM, the subjectivity of the IOM criteria, and the questions related to CDC’s intent for its medical education plans, there is a substantial risk that the IOM criteria will not achieve the needed diagnostic reliability.
Flawed Epidemiological Research

In a 2011 article, 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. 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.”

For ME, the issues with bad CFS definitions and the psychogenic bias have perverted epidemiological research. As a result, in spite of an ongoing program at the CDC spanning thirty years and costing an estimated $120-125 million, we still know little about the etiology; the genetic, environmental and other biological risk factors; the progression and prognosis; the treatment and prevention; or even how many people really have the disease. Worse, as with the treatment recommendations made in the 2014 AHRQ Evidence Review, the statements made about prevalence, risk and prognosis are too often based on studies that focused on psychological explanations and included people who did not have the disease.

One example is the estimate of prevalence, which varies wildly as a result of disparate case definitions, how definitional criteria were evaluated, and other methodological differences. For instance, estimates based on Fukuda range from 0.07 to 2.60 percent, or somewhere between 170,000 and 6.3 million adults in 2014. The very breadth of this prevalence range highlights the diagnostic inconsistencies with Fukuda. Estimates using Oxford range from 0.43 to 3.73 percent and the prevalence estimate for the 2005 Empirical definition is 2.54 percent, ten times higher than CDC’s earlier Fukuda estimate. One study reported a Fukuda prevalence of 2.6 percent that decreased to 0.5 percent if psychiatric co-morbidities were removed. The most widely accepted prevalence rate, reported in a study by Dr. Leonard Jason of DePaul University, is 0.42 percent, which translates to an estimated 1.0 million adults in the U.S. today. In a large U.K. study of 143,000 people, Dr. Luis Nacul simultaneously estimated prevalence using both the Canadian Consensus Criteria and Fukuda and found that the Canadian prevalence was 0.11 percent, roughly 60 percent of the Fukuda estimate of 0.19 percent. While only a single study, this is a quantifiably significant difference between a Fukuda and a Canadian diagnosis.

As a result of the definitional problems, it is impossible to accurately say how many people have CFS, let alone ME. HHS has historically often used an upper limit of 4 million for CFS, an estimate that appears to be based on the higher prevalence reported in CDC’s 2007 Empirical definition prevalence study. The IOM report noted an upper prevalence limit of 2.5 million but the IOM reference for this number is a CDC prevalence estimate for “CFS-like” illness, not “CFS.” CDC has defined “CFS-like” illness as having chronic fatigue but not meeting the other criteria for Fukuda. As such, it is even broader than Fukuda. Such over-inflated estimates of disease prevalence hurt the credibility of the disease in the eyes of the medical community.

A second example of how the definitional issues and the researcher’s cognitive bias about the nature of the disease impacted epidemiological research is seen in the assessment of risk, prognosis, and disease pathology factors. Between 2006 and 2012, the CDC reported that patients had maladaptive coping, personality disorders, a history of childhood adversity and trauma, and that the single factor of depression could distinguish patients from controls. In a press conference on a 2006 CDC genetics study, CDC’s Reeves said that the study showed...
that people with CFS “were unable to deal with everyday challenges and adversity, including injuries, illnesses, divorce and stressful jobs.”

CDC’s 2009 study on childhood trauma reported that childhood trauma was associated with a 6-fold increased risk of CFS. Another CDC study noted that the observed personality disorders could result in a poorer response to treatment, while researchers outside of the CDC determined, largely based on Oxford studies, that a poorer prognosis is associated with membership in a support group, the receipt of disability benefits, and a belief that the disease is organic.

The very fact that these researchers chose to focus on these particular factors of risk and prognosis betrays a psychogenic bias about the disease. Further, it is important to note that these studies largely used overly broad definitions, which could include patients with mental disorders. For instance, the CDC studies listed above used the disputed 2005 Empirical definition. But the IOM report noted that the Empirical definition encompassed patients with depression and posttraumatic stress disorder (PTSD). Speaking about CDC’s 2009 childhood trauma study, the IOM report noted that the overrepresentation of patients with psychiatric issues “likely explains the study finding of an association between ME/CFS and adverse childhood experiences.” The IOM report further noted that no other studies supported such a finding. At the time of the study publication, one Psychology Today journalist perceptively asked if the real issue was not child abuse, but rather the abuse of research resulting from ill-defined disease definitions. But many news sources, including Science Daily, New Scientist, ABC News, and Medscape reported the link between childhood abuse and a 6-fold increase in risk of CFS without seeming to question the study. ABC News quoted CDC’s Reeves as saying that “about 60 percent of the people who have CFS have been badly abused as children.”

Today, CDC’s website still features childhood adversity as a risk factor for CFS, using this one Empirical definition study plus studies in other diseases, such as depression, to support this claim, while disregarding Dr. Leonard Jason’s study that showed that childhood trauma is not a risk factor. Such information biases the medical perceptions on the nature of ME.

Critics also raised concerns with CDC’s 2006 genetics study. In addition to patient selection problems because of the use of the Empirical definition, they also pointed out that the CDC used inadequate gene confirmation procedures and had focused only on a narrow set of genes that deal with stress. The authors noted that associations with other genes might have been found if CDC had looked for them. In other words, as with the focus on psychological issues in assessing risk and prognosis, you find what you look for.

The problems with CDC’s epidemiological approach have not only been in what studies were done and how, but in what studies were not done—most notably CDC’s failure to follow up on the patients from the Incline Village and Lyndonville outbreaks. This has been an exceptional missed opportunity since one of the Incline Village clinicians is still in practice there today. In response to a 2012 CFSAC recommendation to study patients from previous clusters, the CDC acknowledged the value of such a study. But CDC then stated, “CDC has not been able to confirm the occurrence of outbreaks of CFS.” Given the existence of Incline Village and Lyndonville, CDC’s response is frankly nonsensical.

In a 2011 article, journalist David Tuller summarized the critics’ view of the problems with CDC’s epidemiological research, stating,
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.342

Critics have noted other significant problems with CDC’s CFS program over the years. This includes the financial scandal reported by the U.S. Inspector General in 1999343 and the U.S. General Accounting Office in 2000344 in which the CDC misdirected about $12.9 million (55 percent of the total) between 1995-1998 and then lied to Congress about it. Critics also raised concerns with the program’s insularity (as seen by its failure to engage researchers outside its own agency345); its flawed 2009 epidemiological strategy (since archived),346 and the lack of accountability in how money was spent and the “bust of shameful scientific leadership”347 that led to the replacement of Dr. Reeves as head of CDC’s CFS program in 2010.348

To her credit, since taking over the leadership of the CDC CFS program, Dr. Beth Unger has decreased the program’s isolation by establishing, in 2012, a multi-site research program of disease experts to better characterize the disease and its subsets.349 No case definition has been used for this study because Dr. Unger said that they did not want to bias patient selection. The CDC has said that the sites were instructed to include patients diagnosed with “CFS, post-infective fatigue (PIF) or myalgic encephalomyelitis (ME);”350 diagnostic terms that are ill defined and/or could be used differently across the different sites, particularly PIF.351 The study has included adult and pediatric patients, healthy and illness controls, and some severely ill patients. It has focused largely on patient-reported outcomes but included some labs and a combined exercise-cognition test that utilized a single day exercise challenge.352

In the long run, the multi-site study could produce useful insight into the disease. But there are valid concerns with its design, particularly the lack of a common case definition to select patients,353 the lack of cross-site validation of patient diagnoses,354 and the choice of a single day exercise test when current research has demonstrated that a two-day exercise test is required to differentiate this disease from deconditioning and other chronic illnesses.355 Given the lack of a case definition, an IOM panel member asked Dr. Unger in 2014 if she intended to cross-validate diagnoses across the sites to which Dr. Unger said that she would leave it up to the sites to do that if they wanted to.356 Given the ambiguity on these terms and the decision to not use a case definition for patient selection in this study, it is surprising that this is not a planned part of the study. At the very least, the multi-site study should evaluate the patients in this study against the Canadian Consensus Criteria. Because the sites all use different approaches to diagnosing patients, this would allow validation against an external standard, the best “gold standard” that exists today. Further, that comparison would help highlight similarities and differences between the multi-site patient cohorts and the cohorts used internationally in research where the Canadian Consensus Criteria is increasingly being used. If CDC intends to use the multi-site data to revise the case definition used in both research and clinical care, this comparison will be essential.

Of course, the acknowledged widespread use of the Canadian Consensus Criteria by disease experts in their practices357 begs the question of why the Canadian was not incorporated into the multi-site study to begin, particularly since these clinicians are already using it in their practice and research. Does CDC accept these hallmark criteria as essential or are they still embracing the fatigue-focused CFS umbrella? A partial answer might be seen in CDC’s 2011 defense of the continued publication of Empirical studies, CDC’s questioning of the importance
of PEM at the 2013 CFSAC meeting,\textsuperscript{358} CDC’s 2014 IOM submission stating that a limitation of the Canadian Consensus Criteria was that it required PEM,\textsuperscript{359} CDC’s reclassification of CFS in the ICD-10-CM, and Dr. Belay’s August 2015 comments to this author supporting the continued use of Empirical definition findings in new medical education. Given CDC’s history and its most recent statements, it is both reasonable and essential to question whether CDC has let go of this disturbing thirty year legacy of bad definitions, sloppy naming and classification practices, tainted epidemiological research, and erroneous clinical guidelines that have been directly responsible for so much damage and harm to so many patients for so many years.
Lack of Research and Research Funding

On their own, the definitional confusion and psychogenic bias would have stalled forward progress in research by diluting patient cohorts and focusing efforts away from the biomedical pathologies. But NIH effectively crushed any hope of resolving these issues by providing only a paltry level of research funding, which was then too often siphoned off to other diseases. Further, what little NIH funding was available was difficult to access because of the bias and misunderstanding about the nature of the disease. Finally, this disease was dumped in the Office of Research on Women’s Health, exiled outside of all of the NIH institutes and centers that have money to spend on research and the authority to decide where to spend it. The lack of research funding, the institutional barriers, and NIH’s disregard and even bias have driven away all but the most tenacious biomedical researchers.

In concert with CDC’s muddling of the case definition and epidemiological research, this combination of bias, misunderstanding, institutional neglect, and the appalling lack of research funding are directly responsible for what the IOM report described as a “paucity of research” beyond psychiatry and psychology and a “CFS” evidence base so polluted that it is virtually unintelligible to everyone but the most experienced researchers who know where the tar pits are.

The CFSAC, disease experts, patients, and even congressional leaders have made numerous recommendations to the NIH over many years to address these issues. But the NIH has failed to take even the most remedial steps, claiming lack of evidence, lack of researcher interest and lack of quality applications. NIH’s lack of action has had a disastrous impact not only on research and drug development but also on medical care and ultimately the lives of patients.

Note that in the fall of October 2015, NIH announced that they were going to bring a renewed focus to this disease, including transferring leadership of the Trans-NIH ME/CFS Workgroup to the neurological diseases institute and initiating a clinical study to investigate disease etiology. But as of December 2015, few other details are available and the majority of issues outlined in this chapter have not yet been addressed.

Paltry NIH Funding

The most basic issue with NIH is the shameful lack of funding for research. In 2014, NIH provided only $5 million out of a total NIH budget of $30.1 billion. This is unreasonable by any standard. But it is especially deplorable when compared to the funding allocated to other similarly debilitating diseases or to this disease’s annual economic impact, conservatively estimated at $19-24 billion annually. For instance, in 2014, this disease ranked #226 out of 234 diseases funded by the NIH, below the $6M spent on hay fever in 2014 and well below the $9M spent in 2013. At $5 million, this disease received just four percent of that spent on multiple sclerosis, even though ME has greater prevalence and a similar if not worse disease burden as reported by the IOM. More dramatic is the 600-fold higher level of spending on HIV/AIDS, even though one expert who treats both HIV/AIDS and this disease has said that her HIV patients are doing well thanks to “three decades of research and billions of dollars invested” while her patients with this disease remain very ill and unable to work or care for their families.
Even from a strictly financial perspective, an annual NIH research budget that is only 0.03 percent of the annual economic impact of this disease is a bad financial decision for our country.

This low level of funding is not an historical anomaly. The highest budget for this disease was $7.4 million in 1995 and averaged about $5.8 million between 1995 and 2014. The CFS budget has decreased 27 percent since 1995 at a time when NIH’s total budget went up 166 percent. Yet, as demonstrated through FOIAs, even this miserly amount of money did not all go to this disease; an estimated 20 percent was apparently siphoned off to other diseases in most of the years between 1999 and 2012.

The lack of funding for biomedical research is not just a U.S. problem. For instance, in Canada, research funding reportedly averaged $0.52 per patient over three years compared to $66.46 per patient for multiple sclerosis in the same time period. In the U.K., the 2006 U.K. Gibson Inquiry reported that the U.K. government had provided £11 million for research for CFS by that point but the studies had focused on psychological factors and treatments. The authors were unable to identify any major biomedical studies. U.K. advocates have since reported that U.K.’s Medical Research Council (a government agency responsible for funding research) did not fund any biomedical research until 2012, when it provided £1.65 million for 5 small studies.

Bias, Misunderstanding, and Lack of Agency Interest
NIH has provided a variety of reasons for these low levels of research funding. Budgets are shrinking. The science isn’t ready and there is too little known about the disease. Researchers are not interested, are not asking the right questions, and are not submitting quality applications. Researchers are not submitting enough applications and NIH funding cannot rise until they do.

But these reasons ring as hollow excuses when examined against the facts.

First, shrinking budgets are not the issue as the budget for this disease went down at a time when the overall budget for NIH was increasing, a fact noted above and in the report that accompanied the 2000 Senate appropriations bill. But even if NIH’s total budget had not increased, there is still an issue of fairness. The funding allocated to this disease is far short of what would be considered a fair share of NIH’s total funding if that allocation had been based on the disease’s burden, its prevalence, and the scientific opportunity that exists to advance research. The issue is not shrinking NIH budgets but NIH’s priorities.

### 2014 NIH Funding and Prevalence for Selected Diseases

<table>
<thead>
<tr>
<th>Disease area</th>
<th>Funding (Millions)</th>
<th>Prevalence</th>
<th>Spend per patient</th>
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<tr>
<td>HIV/AIDS</td>
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<td>1,200,000</td>
<td>$2,482</td>
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<tr>
<td>Lupus</td>
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<tr>
<td>ME/CFS</td>
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</tr>
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</table>
Second, NIH’s claim that researchers are not interested is the direct result of NIH’s decades-long funding practices that have made it difficult for researchers to obtain grants for biomedical research for this disease. Researchers and the CFSAC have repeatedly told NIH that researchers are interested but are either not entering or are leaving the field because “the word is out” that there is so little money available and what funds are available are difficult to access. One of the difficulties is related to NIH’s grant review process used to make decisions on where to allocate research funds. The first step in that process is the ad hoc Special Emphasis Panel (SEP), while the second level of review is by the advisory councils of the NIH institutes. The CFS SEP has historically had many members who do not understand the disease, a point raised at CFSAC. Further, because it is ad hoc, the membership changes from one session to the next, making it difficult for researchers to respond to the review questions. The use of ad-hoc review panels are not unique to this disease. But the misperceptions on the nature of the disease by NIH reviewers magnify the challenges experienced by researchers with an ad hoc SEP. In 2008, CFSAC member Ron Glaser told NIH that the SEP and the hurdles in the review process are “just out of line with a fair review process.”

While the SEP members appear to be more knowledgeable today, bias still exists in the grant review process, as discussed below, and the final funding decisions are still ultimately made by institutes for whom this disease is not a priority. Challenges also still exist with requesting support for certain kinds of studies for this disease, such as clinical drug trials, and with getting a financial commitment from NIH in the form of an RFA (request for application) which comes with set aside funds. NIH has typically used R01s and similar mechanisms for ME/CFS, which do not provide set aside funds. The lack of set aside funds combined with bias and misinformed SEP reviewers has led to a record of rejections that has had a chilling effect on potential researchers. As one CFSAC member told NIH in 2011, “there is essentially something broken” when a small, private organization (the CFIDS Association, now Solve ME/CFS Initiative) can get more applications for a much smaller pot of money than the NIH can for their funding opportunities. To encourage more applications, the CFSAC has repeatedly recommended that NIH issue an RFA.

The NIH did issue one in 2006, for which it received 29 applications, an unusually high number that demonstrates the interest that exists when the NIH makes a commitment to provide funding. When CFSAC members requested another RFA in 2008, NIH’s Dr. Hanna said that NIH might issue a second RFA after NIH’s 2011 State of Knowledge (SOK) Workshop. But NIH did not do so then or in the four years since, in spite of numerous CFSAC recommendations and letters from congressional leaders to do so.

Even when researchers do persist and apply for the available grants, they run into a wall of bias, misunderstanding and disinterest. In 2014, Dr. Ian Lipkin, a world-renowned researcher referred to as “the most celebrated virus hunter” reported receiving abysmal scores on a grant proposal for this disease. Yet, Lipkin received $8.9M from NIH in 2014 for other diseases, suggesting he knows how to write a grant proposal. He was told by one reviewer 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” as he had planned. To secure the needed funds, Lipkin resorted to crowd funding and a “Chili ME Challenge,” in which he and his co-researcher, Dr. Mady Hornig, scorched their insides by eating hot chili peppers in order to raise money for their research into this disease. In 2015, another world-renowned researcher, Dr. Nancy Klimas, reported having had a proposal for a Phase 1 study of an already FDA-approved drug rejected six times in five years because the reviewers didn’t believe that this disease was “serious enough” to warrant a drug routinely prescribed for rheumatoid arthritis. She said she had little choice but to propose

Thirty Years of Disdain: How HHS Buried M.E. December 2015. (M. Dimmock, M. Lazell-Fairman)
a less optimal drug simply because it would be viewed as less “serious” and therefore more likely to be approved. A third example is Dr. Ron Davis of Stanford, famed geneticist and lead of the End ME/CFS Project, an impressive multi-disciplinary team that includes Nobel Laureates and members of the Academy of Sciences. Davis is also an expert in ME as his son is Whitney Dafoe, the severely ill man mentioned earlier. Yet, Davis’s team was not even allowed to apply for funding. One of NIH’s reasons for rejecting Davis’s request was that the NIH felt that Davis should focus on severely ill patients. But as Davis pointed out in his response to the NIH rejection, his entire proposal was focused on severely ill patients, suggesting that the reviewers had either not read his proposal or else failed to understand it.

The bias about the disease and NIH’s unwillingness to fund research has also infected academic research centers. Researchers at NIH’s 2011 SOK Workshop reported on the “stigma of ME/CFS research on faculty at academic institutions” and about being warned by colleagues not to enter the field because it would kill their careers. When Dr. Jose Montoya, ME clinician and Stanford researcher, told his mentor that he wanted to research this disease, his mentor predicted that doing so would leave him homeless. Montoya has been lucky; he has been able to secure private funding that has allowed him to pursue research even without NIH support.

A third issue is apparently the way in which NIH institutes award funds. According to the Stanford article on Montoya’s work, “NIH funding is awarded through medical specialty groups that tend to favor research that tests one narrow hypothesis about a disease” at a time, an approach that is slow and can take years to build on earlier work. Montoya credits part of the success of his work to the private funding that allowed him to take a more multi-disciplinary approach where experts work together across fields to identify underlying abnormalities. Stove-piped, narrow approach is an obvious problem for any complex, multi-system disease where such cross-discipline, cross-system integration is essential. But it is particularly challenging when that multi-system disease has been deprived of funding for thirty years, has a “paucity of research,” is believed to be psychogenic, and has been cast into the medical wasteland that exists outside of NIH institutes, academic centers, and medical societies.

The rejection of Davis’s proposal underscores some of these challenges. For instance, another reason for NIH’s rejection was the lack of a defined hypothesis. But as Davis stated, this work was intended to be hypothesis generating. Beyond that, NIH’s neurological diseases institute (NINDS) also suggested that the proposal should go to a different NIH institute because the study wasn’t collecting cerebrospinal fluid (CSF) or neurological outcomes but instead intended to look for markers in blood. Davis responded that these are severely ill, bedbound patients from whom collection of CSF or neurological outcomes would not be appropriate. Further, he noted that research in other neurological diseases supported by NINDS is looking at blood markers, begging the question of why looking for blood markers would be a problem in this disease.

In 2014, CFSAC made yet another recommendation for an RFA. In the same year, eleven congressional leaders also wrote to Dr. Collins calling for the NIH to issue an RFA for $7-10M, while the International Association for CFS/ME (IACFS/ME, the international professional organization) wrote to Dr. Collins calling for an RFA of $7-10M annually for five years. But NIH rejected these recommendations. NIH’s response to the congressional leaders did not even mention the requested RFA but instead called out the lack of trained researchers and recommended the existing R01s (the ones CFSAC has said were failing to attract researchers). Most disturbingly, in its response to the 2014 CFSAC recommendation, HHS stated, “there remains a lack of definitive evidence regarding the etiology, diagnosis, and
treatment” of this disease. This is a stunning statement, given the biomedical evidence dating back to the 1980s and the success of Rituxan in clinical trials.

What is especially frustrating about NIH’s rejection of the CFSAC’s 2014 recommendation for an RFA is that when NIH rejected Dr. Davis’s request to apply for funding, the rejection letter acknowledged that there was agreement that a biomarker study was needed but that “perhaps there needs to be an RFA that spells out what NIH would like to fund, with agreement between several institutes so that appropriately powered studies would be submitted and provided with sufficient funding to accomplish the studies.” Yes, multiple institutes should be involved in studying this disease. Yes, adequate funding needs to be provided. But when recommended by CFSAC, NIH has consistently refused to issue an RFA or provide adequate funding. Why is NIH now using the need for an RFA as one of the reasons to reject Dr. Davis’s proposal?

Sharply contradicting HHS’s claims that the science is not ready, that researchers are not interested, or that researchers are not producing quality applications, groundbreaking research is being done by privately funded initiatives. These initiatives are building on the base of what has been learned over the last thirty years despite a lack of NIH funding. Collectively, these initiatives have demonstrated the readiness of the science, the sophistication of the scientific approach, the caliber of the researchers and their interest, the significant demand for research dollars, and a focus on the most important research questions. Besides for the work at Stanford and Columbia, a grant of over $10 million from the Hutchins Family Foundation showed, among other things, both changes in the immune profile suggestive of immune exhaustion over time, and a disturbed immune signature in cerebrospinal fluid suggesting central nervous system immune activation. Other examples include Davis’s End ME/CFS Project, mentioned above, Dr. Nancy Klimas’ Institute for NeuroImmune Medicine, Dr. Dan Peterson’s Simmaron Research, and Dr. Andy Kogelnik’s Open Medicine Institute. Overseas studies such as the Norwegian work with Rituxan and the Japanese researchers’ demonstration of neuroinflammation have highlighted additional opportunities. These are exciting initiatives that are building on the scientific opportunity that has been available for years, opportunity that has not been pursued because of a lack of NIH research funding.

In an April 2015 U.S. Senate Appropriations hearing, Dr. Collins told the senators that in deciding where to allocate money, NIH looks at not only disease burden but also at scientific opportunity. How much more scientific opportunity is needed before the NIH finally decides to act?

Perhaps the most direct evidence that NIH’s reasons for low funding are just the excuses of a disinterested agency are the letters from the researchers themselves, such as Dr. Davis’s response to NIH’s rejection. Another example is the public comment submitted by the IACFS/ME on the 2014 draft of NIH’s P2P Workshop report, in which the IACFS/ME stated that NIH’s claims of a lack of knowledge and lack of researchers ignore the fact that “a critical reason why we have a dearth of researchers and knowledge is because of the poor funding situation, which has endured for the past 3 decades.” More pointedly, an August 2015 letter to Senator Mikulski from 27 disease experts (including Nobel Laureates and members of the Academy of Sciences) described the challenges they have had in getting research funding into this disease and stated that the disease is “massively underfunded.” In their letter, reported in an August 2015 Science article on community efforts to get more funding for this disease, these experts told Senator Mikulski that they would “eagerly submit grant proposals” for an RFA if NIH issued one.

Thirty Years of Disdain: How HHS Buried M.E. December 2015. (M. Dimmock, M. Lazell-Fairman)
And NIH’s response? The day after the *Science* article was released and just weeks after the NIH rejected Davis’s request to apply for funding, NIH’s Dr. Cheryl Kitt told attendees at the August 18, 2015 CFSAC meeting that the reason that NIH funding was so low was because the submitted applications were of poor quality and there were few interested researchers. This was an offensive dismissal of the well-known political realities at HHS and NIH that have buried this disease for decades.

**Exiled by NIH Institutes and Centers**

While the paltry research funding is the most visible issue, the placement of this disease in NIH’s Office of Research on Women’s Health (ORWH), outside of all the NIH institutes and centers, has probably been the most pivotal. At NIH, the institutes and centers are the organizational units that drive NIH’s strategies and priorities. They are also the groups with money to fund research and the authority to make the final decisions on what gets funded. Naturally, those final funding decisions are made in alignment with the priorities of the individual institutes.

CFS was originally placed in the National Institute of Allergy and Infectious Diseases (NIAID). But in 1999, the disease was moved out of NIAID to the Office of the Director and then to ORWH, where it has been exiled for the last fifteen years. Lacking a budget for this disease, ORWH has attempted to use the Trans-NIH ME/CFS Working Group to cobble together funds from the individual institutes to pursue research. The Trans-NIH ME/CFS Working Group appears to be the only disease-specific trans-NIH work group to not be headed by an institute. And no NIH institute has made this disease a priority. It’s not hard to imagine that the real reason that there has not been an RFA is because the institutes have been unwilling to dedicate the money to fund one.

And when institutes have expressed any interest, as seen in specific NIH funding opportunity announcements, that interest has typically been narrowly focused on the interests of that institute, not on the key needs of this disease. For instance, in a 2014 funding opportunity, one institute was interested in the overlap between this disease and tempo-mandibular joint disorder, another in the interaction between this disease and alcohol consumption, and a third in the relationship between this disease and urological chronic pelvic pain. Notably, of the $814,560 charged against the “CFS” program by the institute involved in chronic pelvic pain research between 2009 and 2013, none of the funded studies included CFS patients. This institute, along with three other institutes and one center, withdrew their support from the ME/CFS funding opportunity in October 2014. The only institute that expressed a disease-centered focus was NINDS. For its part, NIAID did not state any specific research interest, beyond stating that proposals for clinical trials “relevant to the mission of NIAID” needed to be submitted elsewhere. Given the well-known immunological dysfunction, this lack of an explicitly stated interest by NIAID is disconcerting. In 2014, NINDS and NIAID together contributed only $4 million for ME/CFS, nowhere near enough to even begin to address the most critical research gaps that have been known for years and reaffirmed in the 2015 IOM and P2P reports.

Such narrow slices of scientific interest are unlikely to produce keen insights into disease pathology or treatment. The institutes’ disinterest and self-interest has undoubtedly severely limited access to funds, resources and agency staff. Such narrow interests, particularly in combination with bias about the nature of the disease, has also likely restricted the kind of research that the NIH institutes have been willing to fund, as Dr. Davis, Dr. Lipkin, and Dr. Klimas have all seen. Finally, the placement in ORWH has left this disease outside of the
strategic planning and prioritization processes of the individual institutes\textsuperscript{441} and as a result, outside of the 2015 cross-institute strategic planning and prioritization effort that Dr. Collins described to the U.S. Senate Appropriations committee in April 2015.\textsuperscript{442} These institute-driven processes will also presumably be responsible for the allocation of any “new” money provided to NIH by Congress, including the proposed $2 billion increase in the NIH appropriation for 2016\textsuperscript{443} and an additional $1.75 billion for NIH for 2016 if the 21\textsuperscript{st} Century Cures Act is passed.\textsuperscript{444} Given that this disease is exiled outside of all the institutes, it is poorly positioned to get a reasonable share of the funds available in NIH’s baseline budget or the potential $3.75 billion in new funds for 2016.

These problems are well known and long-standing; in 2011, CFSAC member Dr. Nancy Klimas told NIH’s Dr. Cheryl Kitt that CFSAC had repeatedly told NIH that trying to use the trans-NIH workgroup “to patch together the funding has dramatically limited access” to grants.\textsuperscript{445} In August 2015, CFSAC recommended that this disease be moved to the neurological institute (NINDS) to try to rectify this situation. In October 2015, NIH announced that the director of NINDS would assume leadership for the Trans-NIH ME/CFS.\textsuperscript{446} (According to followup announcements, it appears that ME/CFS will not be moved to the NINDS but left as the responsibility of the Trans-NIH workgroup.) While this is a significant change, it is too early to say whether that change will be sufficient to address the barriers discussed in this chapter, particularly those on funding and strategy.\textsuperscript{447}

**Lack of a Strategy and Follow-up on Key Gaps**

Echoing this disinterest and lack of commitment, NIH has failed to develop a strategic plan for this disease, at least not one shared publicly. Further, it has ignored the strategic opportunities that could have changed the trajectory of research and of patients’ lives. As a result, critical research questions have remained unresolved for decades.

Following the 2011 State of Knowledge (SOK) Workshop, the Senate report accompanying the 2011 U.S. congressional appropriations bill asked the NIH to establish a “research plan outlining a coordinated strategy for intramural and extramural research” within one year.\textsuperscript{448} NIH has said that it has established a plan as a result of that workshop.\textsuperscript{449} But based on the limited information provided at a 2012 CFSAC meeting, NIH’s plan appeared to be a list of activities, not a “research plan” or “coordinated strategy” as requested by congressional leaders.\textsuperscript{450} Further, when asked by this author to share that plan publicly, NIH staff declined, stating that the plan was an internal working document and thus could not be shared because it might change.\textsuperscript{451} Of course the plan will change—plans always do. But NIH’s failure to share this plan makes it impossible for the community to understand NIH’s intent, to provide input or feedback on NIH’s plan, or to monitor progress in the plan’s implementation. But even without seeing it, it is obvious that NIH’s plan has lacked any sense of urgency as the highest priority issue identified in the 2011 SOK Workshop, the research case definition, has still not been addressed.

Over the years, NIH has held workshops that could also have been used to advance the field strategically.\textsuperscript{452} But the early NIH workshops were often controversial because of an overemphasis on psychological issues and/or the failure to include disease experts as seen in the 1991 and 2000 conferences.\textsuperscript{453} Other workshops, such as the 2011 State of Knowledge Workshop, failed to produce a timely and sufficient response from NIH.\textsuperscript{454} The most recent workshop, the 2014 NIH Pathways to Prevention Workshop, was controversial because it lacked clarity on the workshop goals, conflated ME and CFS definitions, inappropriately applied an evidence based approach to a disease with a controversial evidence base, relied heavily on those with no experience in the disease and no understanding of the controversies, and failed to
include sessions on key aspects of the disease biology (e.g. PEM and neurological impairment).\textsuperscript{455}

Even with those concerns, the final P2P report confirmed the IOM findings of paltry funding, the “paucity of research,” and the disbelief of the medical community. It also made numerous recommendations for research gaps that must be addressed. But the naked truth is that many of P2P’s recommendations had already been identified in earlier workshops and/or already formally recommended by the CFSAC over many years, a point made by the CFSAC in their 2015 comments on the draft P2P report.\textsuperscript{456} The problem has not been a lack of knowing what to do but a lack of doing anything about it.

One example of NIH’s failure to act is the P2P recommendation to address the research case definition. This need was highlighted in the 2011 NIH SOK Workshop\textsuperscript{457} and the 2012 CFSAC recommendation on the case definition. The 2013 letter from fifty experts called for the adoption of the Canadian Consensus Criteria to resolve this issue.\textsuperscript{458} NIH workshops have discussed the impact of poor definitions on research since the 1980s.\textsuperscript{459} In 2005, a CDC study highlighted the unreliability of Fukuda, which has been the most commonly used research definition to date.\textsuperscript{460} Yet, four years after the SOK Workshop identified this issue as the highest priority and ten years after the CDC study highlighted the problems with Fukuda, all we have is yet another recommendation, this time from P2P, that something needs to be done about it.

A second example is the need for a biomarker, also highlighted as a critical need in the 2011 SOK Workshop.\textsuperscript{461} Evidence for biomarkers such as impaired natural killer cell function has existed since at least 1987\textsuperscript{462} and was explicitly highlighted by the 2011 SOK Workshop. And yet, four years after the SOK Workshop, NIH has not yet targeted this need, despite many CFSAC recommendations to do so. Again, all we have is another recommendation. To its credit, the CDC is working with researchers in the multi-site study to evaluate commercial laboratory options to assess NK Cell function. But the broader need for specific biomarkers has not been addressed,\textsuperscript{463} a need that even NIH acknowledged in its rejection of Davis’s request to apply for a grant, as discussed earlier.

Other strategic opportunities have included studies to validate the outcome measures used to assess drug efficacy and preliminary clinical trials to assess drugs such as Rituxan and Kineret already being used off-label by disease experts. Such studies could have helped to sort through some of the study design issues that complicate the study of such a complex disease. As discussed by Dr. Peter Rowe at the 2013 FDA meeting, examples of study design issues include the type of trigger, the length of illness, severity, the presence of comorbid conditions, the use of concomitant medication, and the impact of the day to day differences in symptom severity, all factors that could complicate assessment of drug efficacy and harms.\textsuperscript{464}

Progress on any of these needs could have ignited further investment by academic research centers and pharmaceutical companies and advanced the needed diagnostics and treatments.

**A Failure in Leadership**

In 2000, the U.S. General Accounting Office (GAO, now called the General Accountability Office) investigated HHS’s handling of CFS.\textsuperscript{465} In that report, the GAO noted that the CFS Coordinating Committee (CFSCC, the HHS committee that preceded CFSAC) was intended to coordinate the federal response to this disease but had had “no effect on the direction of research at either CDC or NIH.” HHS’s response was that a “change in the direction of research generally occurs as a result of relevant scientific or technical breakthroughs.” HHS was waiting
for a change in the science. But this is clearly a case where the science—and these patients—have been waiting for a change in the actions and attitudes of this agency.

NIH drives the research that is at the heart of biomedical innovation, the development of new drugs, and the delivery of health care in this country. Academic centers depend on NIH funding to do the basic research, which in turn fuels investment by pharmaceutical companies on treatments. The resultant disease knowledge, biomarkers, and treatments revolutionize medical care. In the world of evidence-based medicine, little else will change the attitudes and actions of a skeptical medical community. For this disease, NIH’s paltry funding, the bias against the disease, and the neglect by the NIH institutes has spawned disinterested and disbelieving academic centers, pharmaceutical companies, and medical societies. The early bias of NIH leadership and the continued neglect and misunderstanding of the NIH institutes has also allowed inappropriate and harmful psychogenic disease theories and treatments to flourish.

At any point, NIH could have reestablished the research centers that they closed fifteen years ago as a way of jump-starting research and addressing the deplorable clinical care recognized for years and highlighted by both the IOM and P2P reports. NIH could have acted to resolve the obvious neglect by the institutes and the grossly unfair level of funding. NIH could have responded to any of the CFSAC recommendations, its own 2011 SOK report, and the 2014 letter from eleven congressional leaders to issue an RFA to overcome the well-known barriers to accessing funds. It could have fixed the problem with the NIH institutes or taken steps to resolve the definitional chaos.

But for thirty years, NIH has failed to exercise the leadership, commitment, and political will needed to purge the bias, break down the institutional barriers, and address the strategic needs that have held this disease hostage. It has abdicated its moral responsibility to do something to help these terribly disabled patients and instead responded with excuses, band-aids, blame, and misguided workshops that have failed to move the needle or worse, driven the needle backwards.

As a result of the 2015 Institute of Medicine report and NIH’s 2015 Pathways to Prevention report—and likely press coverage highlighting the impact of the disease on patients like Dr. Ron Davis’ son—NIH has recently shown greater interest in this disease. In an interview in the fall of October 2015, NIH’s Dr. Collins stated, “Given the seriousness of the condition, I don't think we have focused enough of our attention on this.” Collins has also stated that the research funding will be “substantially greater than the current five or six million a year” and added, “We are going to ramp this up.” But as of December 2015, one year after the Pathways to Prevention Workshop, few details are available and beyond the change in leadership of the Trans-NIH ME/CFS Workgroup, the majority of issues outlined in this chapter have not yet been addressed.

After thirty years, ME patients deserve more from our country’s premier health research agency. They deserve a serious, no-excuses, fully funded, and urgently executed commitment that is commensurate with the burden of ME and the scientific opportunities that have long existed to do something about it.
Stalled Drug Development

Given the size of the patient population, the level of their debility, the complete lack of approved treatments, and the fact that the disease is so unbearable that it drives some patients to suicide, this disease represents a significant unmet medical need. The magnitude of that unmet need represents a potentially huge commercial opportunity that would normally have fostered significant pharmaceutical investment. But it has not.

Under the best of circumstances, drug development is an expensive, risky proposition. At the most basic level, as noted by FDA’s Dr. Janet Woodcock and Dr. Sandra Kweder in meetings with patients, pharmaceutical companies need to know who the patients are (which requires a good case definition and/or a biomarker) and how to assess the effectiveness of the drug.\(^{471}\) A 2010 article on CFS in PharmExec, a magazine directed to the pharmaceutical industry, made the same points and referred to CFS as medicine’s “problem child” and described it as a “Gordian Knot” for the pharmaceutical industry.\(^{472}\) At FDA’s 2013 Drug Development meeting, Lily’s director of regulatory affairs also spoke to the challenges of recruiting properly diagnosed patients to trials, a challenge that Centers of Excellence could help address if they existed and included a clinical care component.\(^{473}\) Beyond those basics, in order to increase the odds of success, pharmaceutical companies rely on the deep knowledge of a disease’s biology that comes from academic centers typically heavily funded by the NIH. As a Tufts University study reported, extensive academic-industry collaborations are necessary to “facilitate the development of effective treatments” for complex diseases such as Alzheimer’s and Parkinson’s disease.\(^{474}\) ME is undoubtedly in this camp.

But in the case of ME, these collaborations have not happened because the bias and the lack of NIH funding for biomedical research has meant that academic centers have not studied ME. Additionally, even the basics—a good description of the patient population and an accepted way to measure treatment effectiveness—don’t exist. Compounding these factors are valid concerns about whether payers (e.g. insurance providers, Medicare, etc.) would pay for an approved drug. At a patient teleconference in 2013, FDA’s Dr. Theresa Michele said that pharmaceutical companies were concerned that “the definitions are so wishy-washy that insurers may not be willing to pay for a product.”\(^{475}\) Together, these factors have undoubtedly contributed to the dramatic underinvestment by the pharmaceutical industry in a disease where the significant commercial potential might be expected to spur investment.

The one exception in pharmaceutical investment in the U.S. has been the small biotech Hemispherx, whose drug, Ampligen, has been in clinical trials since 1988.\(^{476}\) In its 2013 review of the drug, the FDA’s advisory committee heard impassioned descriptions about the drug’s impact on patients’ quality of life.\(^{477}\) One of those patients was Dr. Mary Schweitzer, a former professor of history, who has described the dramatic Awakenings-type change that occurred when she went onto Ampligen, as well as the devastating and total relapse that occurred when she had to go off.\(^{478}\) However, in a split decision, the FDA review committee voted that the drug was safe but voted that Hemispherx had failed to demonstrate the drug’s efficacy, a vote that reflected in part the challenges of demonstrating efficacy in such a complex, under-researched and ill-defined disease. The FDA denied the application.\(^{479}\) Today, Ampligen is only available at a few treatment centers nationally and to a restricted number of patients through an open label (unblinded), “cost recovery” clinical trial in which patients have to pay out of pocket for the drug.\(^{480}\)

The FDA’s denial was a huge setback for patients who have experienced such dramatic
improvement while on Ampligen that they have been willing to relocate to another part of the country, sometimes without their families, and pay an estimated total cost of $20,000 or more a year out of pocket for twice-a-week infusions that keep them tethered to the treatment center.\textsuperscript{481} Heartbreakingly, a planned 267 percent price increase in the cost of Ampligen will likely force many patients off drug and leave them facing the kind of total relapse Schweitzer had previously experienced.\textsuperscript{482}

In marked contrast to the other agencies at HHS, the FDA has directly engaged the community through two-way teleconferences and a 2013 2-day Patient Focused Drug Development workshop.\textsuperscript{483} Predictably, given the current state of affairs, very few if any pharmaceutical companies attended beyond Hemispherx and those who were on the meeting panel. That workshop did result in the FDA’s \textit{Voice of the Patient} report, a patient-centered perspective on the nature of the disease and its impact on quality of life that could ultimately aid the drug development and approval process.\textsuperscript{484} It also resulted in a guidance document intended to encourage drug development.\textsuperscript{485} Unfortunately, the guidance document failed to address the issues related to the “wishy-washy” definitions and instead said that any definition can be used, leaving it up to the sponsor to decide. This might be understandable under normal circumstances but as the IOM pointed out, the CFS and ME definitions do not all diagnose the same group of patients.\textsuperscript{486} The failure to address this issue only perpetuates the confusion borne of the definitional morass. Further, the guidance document provided little guidance on how to address the known challenges with measuring treatment efficacy. These are key issues that will continue to impede pharmaceutical investment.

Given the IOM’s identification of post-exertional malaise as a mandatory criteria, the call for a single research case definition in the P2P report, CFSAC’s 2015 recommendation to use the CCC, and the increasing use of the CCC by the researchers themselves (as seen with the latest Norwegian Rituxan clinical trials),\textsuperscript{487} this issue needs to be addressed in the FDA’s drug development guidance document as well. Beyond that, while the FDA is downstream from the bottlenecks at CDC and NIH, the FDA is in a position to advance drug development and approval by partnering with NIH and disease experts to determine the best ways to assess treatment efficacy and to conduct the initial treatment trials necessary to encourage further pharmaceutical investment.
Inadequate Support Mechanisms

The disbelief and confusion surrounding this disease has not only impeded research and degraded medical care. It has also eroded other mechanisms of support, including support from the patient's family, accommodations at school and work, and the ability to obtain coverage through disability and health insurance plans. The lack of these critical support mechanisms creates significant and sometimes insurmountable challenges in patient's daily lives. A full analysis of these issues is outside of the scope of this manuscript but will be briefly discussed for context.

As already noted, insurance coverage for medical tests and treatment of symptoms is limited because everything is considered experimental. Patients also struggle to get approval for disability, made more difficult by the disbelief of both doctors and disability reviewers. Additionally, coverage for disability may be limited to two years if the patient is determined to have a mental illness. One example of how this might happen is seen in a 2012 article on CFS by Swiss RE, the insurance company. The article advised claims professionals that if a policy included functional somatic syndrome in addition to mental health in its exclusion, then “CFS may fall within that exclusion.” Further supporting a mental health classification, the article went on to state that CFS could also be classified as neurasthenia, another mental illness classification, even though, as noted earlier, CFS is not classified as neurasthenia in the World Health Organization’s ICD-10. In some recent cases, coverage is reportedly being limited when diagnosis is based on patient reported symptoms.

In the U.S., the American Medical Association’s Guides to the Evaluation of Work Ability and Return to Work provides physicians guidance on how to assess a patient’s ability to work. The 2011 edition of this guide states that there are no objective measures for this disease, 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. The guide states that it is not up to the doctor to certify disability but rather up to the patient to decide “whether or not the rewards of work outweigh the symptoms experienced.” This implies that these patients have a choice and could simply ignore their symptoms if they chose to do so. Clearly, this view ignores published evidence of functional impairment (i.e. by CPET and neuropsychiatric impairment) while minimizing the physical disability caused by ME.

These practices, the medical attitudes, and the limited availability of objective testing like cardiopulmonary exercise testing are some of the reasons why patients struggle to gain approval for disability. But even with these challenges, it is surprising that in 2009, the Social Security Administration (SSA) told CFSAC that only 14,000 people were receiving SSA disability for CFS. It is possible that patients are being approved for disability for other diseases but even with that, this is a remarkably low number for a disease that affects one million Americans and leaves a majority of them unable to work. Further analysis of the causes is required.

In April 2014, the Social Security Administration issued ruling SSR 14-1p. This references the CCC and the ME-ICC in its updated guidance, which should make it easier for patients who are unable to work to be approved for disability.

The misunderstanding surrounding the disease has also made it difficult for students to obtain school accommodations. School administrators have interpreted the ME child as school-phobic, malingering, or lying. One parent was told that her previously “straight-A” student was a “defiant, cheating liar.” Another parent said 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. A third example is U.K.’s Lynn Gilderdale, discussed earlier, who became ill at 14. Within a year of being struck down, Lynn “was bedridden, had difficulty swallowing, couldn’t recognize people,” and could only speak in whispers. And yet, as obviously sick as she was becoming, she was accused of pretending or of being school phobic.  

As a result of misperceptions of the disease, parents, particularly in Europe, have sometimes been charged with abuse or neglect. One British charity reported 121 cases in 25 years in which the family was being investigated by Child Protection over their handling of their child’s ME, typically to force school attendance or treatments such as CBT and GET. While more prevalent in Europe, these cases are not unique to Europe, as seen in the 2010 case of North Carolina Ryan Baldwin, discussed earlier. Ryan’s parents were charged with medical neglect and Ryan, seventeen years old at the time, was removed from his home for a year and was not allowed to see his parents or speak to them for five months. 

A more recent example is the 2013 case of Justina Pelletier, the Connecticut teen with a mitochondrial disease, who was rediagnosed with somatic symptom disorder, removed from her family, and placed in a psychiatric facility where she stayed for sixteen months. While Justina does not have ME, her case, like Ryan Baldwin’s, demonstrates just how vulnerable patients with contested, understudied illnesses, such as ME and mitochondrial disease, are to abuse by the medical community.
HHS’s Stakeholder Engagement And Cross-Agency Coordination

HHS’s Failure to Listen to the Key Stakeholders of its Action
As noted throughout this manuscript, the CFSAC, patients, the IACF/ME, and congressional leaders have all made repeated recommendations to HHS to dramatically change how this disease has been handled at the federal level. But HHS has largely ignored these recommendations.

The problems go back to the outbreaks of the 1980s when some HHS staff dismissed the findings of the clinicians treating these patients and instead began to promote a psychogenic view. It continued on through the 1990s, as noted in the 2000 GAO report, which found that the recommendations of the CFS Coordinating Committee (CFSCC) had not changed the direction of either CDC or NIH. HHS’s response was essentially that it was waiting for a scientific breakthrough. But like the dismissal of the outbreaks in the 1980s and NIH’s rejection of the 2014 CFSAC RFA recommendation because of a “lack of definitive evidence,” that claim was a pretense that covered up the neglect, the bias, and the disregard of patients and their doctors.

The CFSCC was disbanded in 2001, shortly after the GAO report was issued. When the CFSAC was finally established in 2003, it no longer had a role to coordinate the federal response, only to give advice. Since 2003, the CFSAC has given that advice in the form of seven recommendations to reestablish research/treatment centers; eight recommendations for increased funding (including through RFAs); four recommendations to address the definition; five recommendations for specific biomedical research; and seven formal recommendations plus numerous subcommittee and patient-driven recommendations to fix CDC’s medical education. In 2014, CFSAC recommended funding commensurate with the burden and prevalence of the disease. The CFSAC also recommended changes at NIH to address the bias against the disease, to use the novel approaches used in other disease areas to “jump-start” the field, and to resolve the problems resulting from exiling the disease outside of the NIH institutes and expecting to use a Trans-NIH working group headed by the Office of Research on Women’s Health to compensate.

In May 2013, CFSAC confirmed that HHS had not addressed the bulk of recommendations made by CFSAC since 2003. CFSAC reaffirmed this point again in its 2015 comments on the draft NIH Pathways to Prevention report, noting that it had already made many of P2P’s recommendations over the years.

The patients, often from their beds, have supported CFSAC recommendations and added their own through white papers, letters, petitions, and continued testimony at CFSAC. They have used Freedom of Information Act (FOIA) requests to obtain information about HHS’s activities and successfully sued when information was withheld. They have written letters to Public Citizen (a consumer advocacy organization) and HHS’s legal counsel to address FACA violations. They requested that HHS’s legal counsel investigate allegations that the designated federal official (DFO) had intimidated three CFSAC members during discussions of the federal response to CFSAC’s 2012 recommendation on the case definition. HHS’s response was that the DFO had the authority to engage in private conversations and provide information on FACA rules, a point that the community hadn’t questioned. HHS’s response did not mention the allegations of intimidation.

Despite all of these efforts, often made at great expense to patients’ fragile health, little has
changed.

For their part, congressional leaders have also made many recommendations for action through the reports accompanying the U.S. congressional appropriations bills going back to at least 1995 and apparently, based on the 2000 GAO report, back to 1988. For example, the 1995 report recommended increased funding, the expansion of the cooperative research centers that existed at the time, and the naming of a coordinator with institute wide authority to move the disease forward. (At the time, the disease was in the National Institute of Allergy and Infectious Diseases or NIAID.) In 2000, the report accompanying the appropriations bill noted NIH’s failure to increase funding, which it found “especially disturbing in light of past budget increases given to NIH overall” and “strongly encouraged” additional funding. In 2001, the report recommended treatment centers and in 2006, the report supported the CFSAC’s recommendation to establish centers of excellence (which include both research and also clinical care, a critical need). In 2011, the appropriations report called on NIH to develop a “CFS research plan outlining a coordinated strategy for intramural and extramural research” within one year of the 2011 State of Knowledge (SOK) Workshop. These are just a sampling of the requests directed at NIH; similar requests have been directed at the CDC and, to a lesser extent, other HHS agencies.

And what happened to these requests? Since 1995, the NIH funding for CFS (which covers ME) has decreased 27 percent while NIH’s overall budget increased 166 percent as noted earlier, despite numerous CFSAC and congressional recommendations for increased funding. Further, in 1999, rather than naming a coordinator with institute wide authority, NIH moved the disease out of NIAID and into the Office of the Director and then into NIH’s Office of Research on Women’s Health. In the early 2000s, the cooperative research centers were closed reportedly because the institutes were unwilling to provide the relatively tiny amount of funding that would have been required. The centers have remained closed, despite seven CFSAC recommendations and additional congressional requests since at least 2003 to reopen them. And as noted earlier, the “plan” that NIH developed after the 2011 SOK Workshop appears to fall far short of a “research plan outlining a coordinated strategy.” Most importantly, whatever is in NIH’s plan, it is obvious that it has no sense of urgency as it has failed to achieve the highest priority recommendation from the 2011 SOK workshop.

The advocacy efforts have resulted in some small successes; live-streaming of CFSAC meetings that allowed homebound advocates to watch the CFSAC, the FDA’s two-day Drug Development Workshop, achieved with the help of three senators, and the redress of a few FACA and FOIA violations. But in the areas that matter the most—in research, diagnostics, treatments, and medical care—none of these recommendations have produced any meaningful change in HHS’s actions and policies. Regardless of what recommendations have been made, who made them, what documentation was provided, and what allies were enlisted, HHS has essentially ignored the requests and recommendations of this community.

In its responses to those requests and recommendations, HHS has sometimes simply ignored the original request or recommendation, as it did in its response to the community request to investigate allegations of intimidation of CFSAC members by the DFO. Another example is its response to congressional leaders for an RFA, in which it never mentioned the request for an RFA. At other times, HHS’s responses have been disingenuous, as in its rejection of CFSAC’s 2014 recommendation for an RFA (because of a “lack of evidence”), its rejection of CFSAC’s recommendation to investigate previous clusters (to which CDC said it had not been able to confirm any clusters), and NIH’s stated reasons for why funding has remained so low for so many years.
Another disingenuous response is the one given in 2015 to journalist Miriam Tucker regarding the denial of Davis’s proposal. NIH stated, “Unfortunately, in challenging budget times, NIH turns away many potentially meritorious research applications.” That is undoubtedly true. But the problem with obtaining research funds for this disease is clearly not a problem of “challenging budget times.”

At other times, HHS’s responses have ignored key facts. For instance, in NIH’s response to the 2014 congressional letter asking for an RFA, Dr. Collins acknowledged the problems with multiple case definitions and stated that P2P would “address how to get ME/CFS researchers working together” on this issue. But HHS had already rejected the 2012 CFSAC recommendation for a stakeholder meeting to reach consensus on the definition and the 2013 letter from fifty international researchers stating they had reached consensus on the Canadian. Three years later, the P2P Workshop did nothing more than reiterate the 2012 CFSAC recommendation to hold a meeting to reach consensus on the definition.

HHS’s responses have at times also conflicted with its own statements. In a July 2012 letter to a patient advocate, President Obama said that Dr. Collins told him that HHS had established an Ad Hoc Workgroup to develop a “department-wide strategy” for the disease. But in the same time frame, HHS staff told advocates who had jointly requested a strategic, coordinated, and fully funded plan that HHS had no plans to develop a strategy because it already had too many strategies. The Ad Hoc Workgroup never produced a department-wide strategy, just a single agency-by-agency list of activities. Then the group disbanded.

Finally, HHS has at times responded by unilaterally implementing recommendations in ways that had little to do with the original recommendation, as it did when it unilaterally and controversially undertook the IOM initiative and the Pathways to Prevention Workshop as HHS’s response to the 2012 CFSAC case definition recommendation.

The magnitude of the wall that the ME community has faced in trying to change HHS policy is also seen in HHS’s response to the 2014 CFSAC recommendation for research funding commensurate with the disease burden. HHS responded, “Agencies have the responsibility for determining funding for all diseases and conditions, unless directed by Congress” (emphasis added). But as noted earlier, when asked at the 2015 Senate Appropriations hearing, Dr. Collins assured the senators that NIH’s processes could fairly allocate funding across diseases without congressional intervention. As a result, congressional leaders are largely unwilling to intervene on the allocation of NIH dollars to specific diseases, leaving it up to NIH to do that. A game of tossing responsibility, leaving terribly disabled patients with no options to resolve the situation.

The issue with HHS’s engagement of the community is not just in what HHS has done but also in how HHS has chosen to engage the community. For instance, as noted above, the plan that NIH developed after the 2011 State of Knowledge Workshop was not developed in collaboration with the community or shared with them once developed to get their input and allow them to monitor its execution. Another example is seen in HHS’s plans to have the Ad Hoc Workgroup develop a “department-wide strategy.” HHS staff said that the Ad Hoc Workgroup’s charge was “inherently internal” to HHS, but that the Workgroup would get community input because some of its members were ex-officio members of CFSAC “where they hear the stakeholder perspective.” In parallel, advocates were told that CFSAC was their mechanism to provide input to HHS.
CFSAC meets twice a year for at most two days each time. The interactions are largely one-way and limited, and the meetings have recently been held by teleconference about half the time. There is typically little direct interaction between ex-officio members and meeting attendees. Researchers rarely attend in person unless they are on CFSAC and most patients are too sick to attend. CFSAC met in August 2015 and will not meet again until spring of 2016, a long lapse at a critical time for this disease. Such limited interaction is completely inadequate as a mechanism to engage the key stakeholders in the development of a department-wide strategy.

Over the last thirty years, HHS has acted with blatant disregard of those whose lives have been trampled by its actions. It has provided limited transparency on its activities, as with the NIH plan. It has marginalized the input of the community. It has failed to be accountable to the patients to make progress on the disease. And it has stubbornly pursued its own agenda and clung to its own erroneous conceptions of this disease, as with NIH’s failure to fix the institute and funding issues and CDC’s continued embrace of faulty case definitions, flawed epidemiological studies, and bad medical education, even when those actions were so obviously misguided.

Ironically, potential insight into HHS’s modus operandi came from the inside—from the resignation letter of Dr. David Wright, who resigned in 2014 from a position in the Office of the Assistant Secretary of Health (OASH). In a scathing resignation letter, Dr. Wright stated the culture of OASH (the office in which the Office of Women’s Health and CFSAC are housed) was “secretive, autocratic and unaccountable” and “intensely political,” with decisions often made for “political expediency and to obtain favorable ‘optics’.”

Secretive, autocratic, and unaccountable. HHS’s approach to engaging this community has left a legacy of mistrust and has isolated HHS from the very expertise it needs to fix this muddle.

**Lack of Interagency Coordination and Planning**

HHS’s disregard and marginalization of the key stakeholders of its actions are bad enough. But when HHS has acted, its actions have appeared to be inadequately planned and coordinated across its own agencies. This has resulted in significant waste and misaligned, misdirected initiatives. This problem was highlighted in the 2000 GAO report, which found “little evidence of coordination between CDC and NIH on CFS research” and “few mechanisms for interagency coordination.” The report also stated that while the CFSCC had helped keep federal agencies and the public informed of current activities, it had not been successful in its goal of ensuring interagency coordination.

This lack of coordination appears to have persisted. For instance, in her 2008 CFSAC testimony, Kim McCleary, then CEO of the CFIDS Association of America (now Solve ME/CFS Initiative), noted an apparent lack of coordination and lack of alignment between the CDC’s and the NIH’s mission as evidenced by the overlap between CDC’s 2009 strategic plan and the funding opportunities provided by the NIH at that time. She also voiced concerns that the differences between CDC’s Empirical definition and that being used by researchers funded by NIH would make it impossible to compare research studies. One only has to examine the CFS research evidence base to know that her concerns were well placed. This issue still exists today as CDC has continued to publish Empirical studies while researchers funded by NIH have largely referenced Fukuda in their published papers. Notably, in the last few years, some of the most significant research papers have reported using Fukuda together with either the CCC or the ME-ICC, while one announcement of a clinical trial indicates it will use the CCC.
The coordination, planning, and alignment issues are apparently also an issue in the conduct of the 2014 IOM initiative, the Pathways to Prevention Workshop, and the AHRQ Evidence Review. Most obviously, uncoordinated timelines across these initiatives resulted in duplication of efforts and made it difficult if not impossible to share information between the IOM initiative on the one hand and the P2P Workshop and the AHRQ Evidence Review on the other, a fact explicitly noted in the IOM report.\textsuperscript{549} And P2P’s imprecise and/or shifting goals resulted in misaligned expectations, as seen in the IOM’s expectation that the P2P workshop was intended to complement its work by developing a research case definition, something P2P did not do.\textsuperscript{550} But most critically, these initiatives failed to align on how the disease was characterized, what definitions were used, what parts of the evidence base were included and excluded, and how the expertise of disease experts and patients was incorporated. Failure to even explicitly agree on the scope of the disease being investigated across concurrent initiatives is particularly alarming.

As a result, the IOM emphatically stated that this disease is not psychological, that there is evidence of neurological, immunological, and energy metabolism impairment, and that the disease is characterized by exacerbation of all symptoms following trivial activity. The IOM report explicitly noted the differences in CFS and ME definitions and stated, “A diagnosis of CFS is not the same as a diagnosis of ME.”

But the AHRQ Evidence Review ignored the differences in ME and CFS case definitions, focused on fatigue to the exclusion of PEM and other hallmark ME criteria, and treated ME and CFS definitions as the same disease, diagnosable and treatable in the same way. By embracing the overly broad Oxford definition and the associated psychogenic CFS theories and studies, the AHRQ Evidence Review implicitly accepted the psychogenic theories that the IOM report had emphatically dismissed. Further, the AHRQ Evidence Review recommended treatments that are potentially harmful for patients with the post-exertional malaise that the IOM report declared to be the hallmark of the disease.

One only needs to look at how clinical guidelines updated since the IOM report have mixed and matched IOM diagnostic criteria with AHRQ Evidence Review treatment recommendations to see the confusion that HHS’s continued misalignment and muddling has fostered. Such a lack of coordination across HHS agencies and initiatives on something as fundamental as the nature and scope of the disease being studied is inexcusable and has squandered the opportunity to resolve this chaos.
CFS as a Social and Political Creation

Sociologists study the social construction of diseases—the ways in which social and political factors shape the understanding of disease and how that understanding then shapes the policies and attitudes toward the disease. For instance, as sociologist Dr. Peter Conrad noted, a disease is not inherently stigmatizing. Instead, it is society’s response to that disease that is stigmatizing as seen with leprosy. Similarly, the tendency to associate women’s disease with mood, to blame the patient for lung cancer, or to equate unexplained illness to psychological disorder are social, cultural, and political responses. Such responses can cause diseases to be taken less seriously and can negatively impact the clinical care, the money available for research, and the type of research done. As journalist Carolyn Johnson pointed out in a 2015 article discussing NIH’s analysis of how it allocates research funds across diseases, “we tend to underfund things where we blame the victim.”

When one looks closely at what has happened to ME, it is obvious 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 objective evidence of ME’s biological pathologies or with the disease as experienced by its victims. As Dr. Wedner noted in 1993, “CFS” is not a disease or a syndrome, but an entity created to solve clinical, social and political problems. Expressedly differently, the way in which this disease has been defined, classified, studied, and treated for the last thirty years—its dominant paradigm—is a social and political construction that has warped the identity of this disease beyond recognition and resulted in a clinical entity that, in Dr. Wedner’s words, is undefinable.

The question is not whether this happened to ME but how and why. What social and political forces were at play in the creation of “CFS” to begin with and what enabled it to persist for so long, in spite of the obvious debility of these patients and the just as obvious inadequacies of our nation’s response?

In Contested Illnesses: Citizens, Science and Health Social Movements, Dr. Phil Brown of Brown University examined the parallel controversies that have swirled around Gulf War Illness (GWI) for the last twenty plus years. Like CFS, GWI is defined by self-reported symptoms and has been mired in scientific disputes over whether the debility is due to an organic pathology or to a psychological reaction, perhaps to the stress of war. The Veteran’s Administration has generally adopted psychological explanations for GWI. Notably, as he has done with CFS, U.K.’s Professor Wessely has also promoted psychological explanations for GWI. Also notable is that CDC’s Dr. Keiji Fukuda and Dr. William Reeves were involved in the creation of one of the most commonly used GWI definitions—the overly broad 1998 definition for “chronic multisymptom illness,” which GWI advocates have stated was “defined so broadly as to include nearly any human health condition.”

As Brown noted, some have suggested that progress on Gulf War Illness has been slow because “science takes time.” Brown acknowledged that science can indeed take time but emphasized that the length of time needed to make progress, to change the dominant paradigm toward a disease is also dependent on the political power of those institutions and persons involved in the creation and maintenance of the dominant paradigm and on the “institutional, political, social, and other barriers” that “impede challenges to it.” In other words, non-scientific issues may control the rate of scientific progress more than the scientific issues do.

When myalgic encephalomyelitis gained widespread national attention following the outbreaks
in the 1980s, the disease had the unfortunate coincidence of being a complex, chronic illness that affected primarily women and had a wide range of unexplained symptoms. Standard lab tests at the time were all normal and what abnormalities were seen appeared to be inconsistent or of unknown importance. Early theories of a potential viral etiology lost whatever institutional support there might have been when Straus’s anti-viral treatment trial failed to deliver the expected efficacy. And the U.S. research and medical community was dealing with the AIDS crisis, at the time a death sentence.

The Architects of the Dominant Paradigm
Whatever the specific combination of circumstances, this disease was quickly relegated to the medical wasteland that exists outside of the traditional scientific disciplines, research institutes, academic centers, and medical societies that drive research and clinical care in this country. In this vacuum, the players with the power and vested interest to do so—those within HHS responsible for this disease along with a small group of psychiatrists, particularly in Britain—were able to reshape the dominant paradigm for this disease according to their own cognitive biases, personal agendas, and vested interests. And by at least 1987, key players in these groups had decided that the disease was psychogenic. Since that time, HHS and this group of psychiatrists have been hugely influential in maintaining and evolving a fatigue-focused, psychogenic dominant paradigm through their position in the research and medical communities and their access to money, top-tier scientific journals, the media, and key institutions.

Beginning with that very first visit to Incline Village, HHS has played an oversized role. HHS established the trivializing name “chronic fatigue syndrome” and authored increasingly broad and fatigue-focused “CFS” definitions that effectively obscured this neuroimmune disease and produced the conflicted evidence base that exists today. CDC ignored the standards of the World Health Organization and reclassified CFS to be equivalent to the symptom of chronic fatigue. CDC’s epidemiological research efforts focused on ill-defined patient populations that encompassed psychiatric illness and emphasized risk factors like child abuse and maladaptive personalities, while downplaying findings of organic impairment and failing to follow up on the patients from the Incline Village or Lyndonville outbreaks. CDC’s definitions and epidemiological studies bolstered the perception of the disease as a psychological problem.

For its part, NIH has consistently starved research funding and has provided little institutional support, orphaning this disease outside of all NIH institutes. Combined with the biased views of NIH leaders like Dr. Straus, the disease stigma and the lack of funding and institutional support has had a chilling effect on the field, driving away researchers. The bias, misperceptions, and the lack of interest in the disease on the part of those involved in reviewing and funding NIH grants likely shaped what kinds of research were done and not done. Lack of NIH support for basic research chilled the investment by pharmaceutical companies needed for the development of treatments. Both NIH and CDC have allowed funds allocated to this disease to be redirected to research in other diseases.

Through its flawed medical education efforts and its influence on the content of secondary medical education providers, CDC has warped the understanding of the disease in the medical community, resulting in medical confusion and the resultant disbelief and hostility toward patients that the IOM report noted. Finally, through HHS’s ready access to the mainstream media, HHS was able to impact the perception of the disease by the public at large with statements such as Straus’s statement to the New York Times that patients were “psychologically ‘different’ long before they developed the syndrome” and Reeves’s 2009 quote to ABCNews that “about 60 percent of the people who have CFS have been badly
abused as children. These statements were the product of personal beliefs and bad definitions, not of the rigorous science that is expected of these agencies.

But HHS did not act alone. The group of psychiatrists who promoted the CFS biopsychosocial theory were also influential.

At a 2015 presentation at the Royal Society of Medicine, the Countess of Mar, a member of the U.K. House of Lords and a longtime advocate for this disease, summed up their role as follows:

It was when a small group [sic] psychiatrists from the UK, Europe and the USA purloined ME and renamed it CFS in the mid-1980s that the real problems began. They insisted that it was a psychosocial behavioural problem that could readily be overcome with a course of cognitive behavioural therapy and graded exercise. From their earliest beginnings, they managed to attract the attention of the media and of their medical colleagues with their assertions. They found their way onto government advisory committees and research organisations; onto the boards of medical publications and into insurance companies...

Members of this group were key drivers of the Oxford definition and have been the architects and key proponents of psychosocial disease theories and treatments. They were able to influence the U.K. government research agenda as evidenced by what appeared to be a singular focus on psychological issues and treatment and the apparent lack of funding for biomedical research in the U.K until 2012. Over the last three decades, they have heavily influenced and supported HHS’s definitional evolution and the direction of CDC’s and NIH’s research through participation in NIH workshops, their role in the creation of Fukuda and the Empirical definitions, and their occasional editorial support and co-authorship of CDC epidemiological papers.

Further, these individuals had strong support from major journals, which not only published their studies but also appeared to actively promote their view of the disease. For instance, in a 2004 article, Goudsmit pointed out that between 1995 and 2000, the articles published in the prestigious British Medical Journal “leaned towards the psychological and psychiatric aspects” of the disease, while there was “a lack of papers on the immunological or virological aspects of CFS.” The Countess of Mar told attendees at the 2015 Royal Society of Medicine meeting that in the previous year, the British Medical Journal had described CFS as “a culturally driven disorder with no known organic cause” (emphasis added). And in 2011, The Lancet editor-in-chief Richard Horton staunchly defended the PACE trial, stating, “We were delighted to get this trial,” which he described as a “remarkable study.” Horton’s comments were dismissive of the view that the disease “is an organic disease which is not reversible by changes in behaviour.” But Horton went further and denounced the criticisms of disease advocates as “vexatious,” and “an orchestrated response” by “a fairly small, but highly organised, very vocal and very damaging group of individuals who have…hijacked this agenda and distorted the debate...” This is a remarkable statement for the editor of a premier scientific journal to make.

Like HHS, the members of this group of psychiatrists have also been successful at getting extensive, positive international publicity for their own research findings and theories about the disease. In 2013, when the PACE investigators published the recovery paper, claims that CBT and GET could lead to recovery reverberated around the world. Yet few if any news outlets probed the concerns that critics were raising with the PACE trial and how PACE had assessed recovery. The U.K. Science Media Center, a group whose “aim is to get scientific voices into media coverage and policy debates,” provided quotes from six scientists regarding the 2011...
PACE trial, all overwhelmingly positive. Notably, when scientists from Columbia, Harvard, and Stanford reported a distinctive immune profile that provided “robust evidence” that this was a biological illness, the responses provided by the Science Media Center were generally more skeptical. A call for further investigation of scientific findings is warranted. But the difference in response to the two trials is notable, especially when one considers the controversy surrounding PACE and that four of the seven individuals responding on the Columbia immunological study were psychiatrists or those pursuing the psychosocial model of CFS. It is important to ask to what extent the skepticism was a product of this research conflicting with their own theories about the disease.

The breadth of influence of this group of psychiatrists can also be seen in the widespread international adoption in clinical guidelines of the biopsychosocial treatment approaches and ideas about risk and prognosis. This is seen in the U.K.’s NICE Guidelines but also in mainstream U.S. clinical guidelines, including the CDC’s, which recommend CBT and GET. Even in the face of the 2015 IOM report, these psychogenic views on the nature of the disease and how to treat it have been remarkably persistent, as evidenced by UpToDate’s 2015 recommendations for CBT and GET based on the PACE trial and NeurologyNow’s 2015 statement about the need to “avoid making the disease a lifestyle.”

This group’s influence appears to have been felt in other key institutions as well. U.K. lawyer and patient Valerie Eliot Smith used FOIA to obtain documents from the U.K. Department of Work and Pensions (DWP, formerly called the Department of Social Security) that included exchanges between staff at DWP and members of this group. In one exchange, Professor Wessely advocated against this disease being listed as a neurological disease, even though the WHO classified it as such. But beyond presenting his view that there was a lack of scientific evidence to support such a classification, Wessely went further and delegitimized patients by stating that the main difference between this disease and mental disease was “the existence of a powerful lobby group that dislikes association with psychiatry.” He framed the community’s concerns as “partisan views put forward by pressure groups as a basis for making medical decisions.”

It is not hard to imagine that such exchanges over the years might have influenced the categorization of CFS as neurasthenia, a mental illness, in the 2001 U.K. specific “WHO Guide to Mental Health in Primary Care” or in the U.K.’s 2014 Department of Work and Pensions Guidelines for Disability Analysts. It could also have led to the statement in the disability analysts’ guidelines that predisposing factors of CFS include “personality factors of neuroticism and introversion” and that a “strong belief in the physical cause” perpetuates the disease.

But perhaps more important than their direct impact on science and public policy, comments such as those of Professor Wessely and The Lancet’s Horton noted above have negatively impacted the public and research community perception of the motivations and rationality of ME patients. Patients, many too disabled to leave their homes, have been called extremists and as “dangerous and uncompromising as animal rights activists.” They have been accused of harassing researchers and issuing death threats. Such charges continue to be reported in the media today, particularly in the U.K. Death threats are a serious charge and even one death threat is unacceptable. But it’s not clear how many people were involved originally and whether the death threats are a current problem or just a recycling of old news. Regarding charges of harassment, it’s important to note that the vague label of “harassment” is being applied to parliamentary questions, FOIA requests, and requests for data by other researchers.

These are all legal actions undertaken because of valid scientific concerns with these studies.
and the characterization of this disease as a psychogenic illness. Characterizing these actions as harassing and vexatious has had the effect of marginalizing the ME patient community while drawing attention away from the legitimate concerns that have been raised. Such charges have made it difficult to gain the attention of the broader research community and to challenge the status quo.

Two powerful groups. Collectively, the level of influence and power wielded by both HHS and this group of psychiatrists have had a profoundly negative impact on how this disease—and these patients—have been understood, defined, studied, and treated, not only by researchers and the medical community but also by the public at large.

The “Enablers”
As Dr. Brown pointed out, it is not just the political power wielded by the groups that created and have maintained this dominant paradigm. It is also the social, institutional, and political factors that have worked to resist change to the status quo. In the case of ME, such factors have likely included social and cultural attitudes about diseases that affect women, the attitudes of the medical community toward diseases for which they have no explanation, commercial interests in cost containment, the limits of evidence-based medicine, and especially the controversy and confusion created by the definitional, naming, and classification muddle.

The first factor that has made it difficult to challenge the dominant paradigm is the “web of confusion”\textsuperscript{588} borne of the scientifically sloppy naming, definition, and classification practices. Multiple names used interchangeably to refer to any of a set of disparate definitions that describe different conditions. The disease reclassified as a mental illness or a form of chronic fatigue, in direct conflict with the standard set by the World Health Organization. At the most fundamental level, these practices impede even the most basic communication because the same name is used to refer to different conditions and groups of patients. One advocacy organization astutely pointed out that it is like all the characters in a book have been named “John,”\textsuperscript{589} making it is impossible to know what character—or in this case what disease—is being discussed. As Brown noted, “When the science on a contested illness is in disarray and unable to advance toward a shared understanding of a disease or condition, other forces may steer the evolution” of the dominant paradigm.\textsuperscript{590} The naming, definition, and classification practices adopted for this disease have fostered confusion and controversy, which have stalled scientific and medical progress, while creating fertile ground for the proliferation of psychogenic explanations.

The second factor is how the research and medical communities respond to “women’s” diseases and to conditions for which there is no medical explanation. Dr. Thomas Szasz, psychiatrist and author of “The Myth of Mental Illness,” noted that if a physician “cannot diagnose organic illness, he is expected to diagnose mental illness.”\textsuperscript{591} And indeed, according to a survey of the American Autoimmune Diseases Association, “a staggering forty-five percent of autoimmune disease patients have reported being denied medical care because doctors mistakenly diagnosed patient symptoms as somatoform,” when they were unable to identify organic illness.\textsuperscript{592} The medical community similarly often dismisses women’s illness as not serious. For instance, a 2000 study in the New England Journal of Medicine found 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.\textsuperscript{593} Together, medical attitudes toward a disease that affects primarily women and toward medically unexplained conditions have created a receptive audience for the psychogenic theories of CFS.
In the case of this disease, Dr. Judith Richman, of the Department of Psychiatry at the University of Illinois, pointed out that the failure of Straus’s 1988 Acyclovir study to demonstrate a link to a viral etiology coincided with a “substantial shift in the dominant research paradigm.” According to Richman, this shift resulted in an increased focus on psychological and psychosocial factors, with the disease being framed as “a flight into the sick role in order to escape from cultural expectations.” Straus’s views about “unachievable ambitions” and “poor coping skills” and Wessely’s comments about the disease being a “culturally sanctioned expression of distress” likely fueled this transition. Further, as Richman pointed out, some CFS researchers adopted a decidedly gender-based view toward this disease, suggesting that the “problematic cultural expectations” of women (e.g. of having both careers and families) were leading some “women to unconsciously seek refuge in the sick role.” In other words, women were believed to be feigning sickness because they couldn’t cope. The tendencies of the medical community to recast both women’s symptoms and unexplained disease as psychological are well-documented problems that still exist today.

A third factor often cited as a cause of slow progress is the reported complexity of the disease. In an article comparing the progress made in AIDS to that made in this disease over the same thirty years, Dr. Vincent Racaniello pointed out that “in retrospect, it is clear that the properties of AIDS made it an easy disease to understand.” In contrast, while acknowledging the impact of non-scientific issues, Racaniello said, “the main reason why we do not understand this disease is because it is extraordinarily complex.”

It is true that ME is biologically complex and will not be solved by the simple models of disease used in the past. But its biological complexity does not explain the rapid proliferation of a psychogenic view in the 1980s. Nor can it account for the persistence of psychogenic theories, the lack of biomedical research, and the ongoing dismissal of the evidence of biological pathologies that has dogged the field ever since.

To really understand the impact of complexity and heterogeneity on the rate of scientific progress in ME, it is important to distinguish between the biological complexity of the disease itself and the manmade complexity and artificial heterogeneity that has resulted from lumping together such disparate definitions as though they represent the same disease. The manmade complexity resulting from grouping all medically unexplained fatiguing conditions together under the “CFS” umbrella has mired scientific progress much more than the biological complexity of ME.

A fourth factor is the business and commercial interests in cost containment. In the Handbook of Medical Sociology, Dr. Kristen Barker of Oregon State University noted that managed care organizations could play a role in influencing “the type and amount of conditions discovered.” Barker pointed out that diagnosing a contested illness, as CFS is, in patients who have medically unexplained symptoms typically limits costs for tests and referrals because the most commonly recommended treatments are comparatively cheap—“pain, sleep, and antidepressant medications, as well as behavioral and exercise therapies.” She noted that managed care organizations might use such diagnoses for cost containment.

In her 2015 comments at the Royal Society of Medicine, the Countess of Mar spoke explicitly of the role of commercial interests in this disease. So did the U.K.’s 2006 Gibson Inquiry, which stated, “There have been numerous cases where advisors to the DWP [U.K. Department of Work and Pensions] have also had consultancy roles in medical insurance companies. Particularly the Company UNUM Provident (sic). 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.\textsuperscript{602}

For example, in the 2011 PACE trial publication, one of the PACE trial investigators, Dr. Peter White, declared a conflict of interest because of his consultancy work for the “U.K. Departments of Health and Work and Pensions” and also for “Swiss Re (a reinsurance company.)”\textsuperscript{603} In 2012, according to a Swiss RE website, White led a web-based discussion for Swiss RE on the management of this disease.\textsuperscript{604} Swiss Re’s summary of this discussion included recommendations for CBT and GET, discouraged pacing (the method that patients favor), and encouraged claims professionals to “Check that private practitioners are delivering active rehabilitation therapies, such as those described in [PACE], as opposed to sick role adaptation”\textsuperscript{605} Further, the Swiss Re article correctly noted that ME was classified as neurological in the ICD-10 but incorrectly stated that “CFS can alternatively be defined as neurasthenia,” the mental health disorder. This claim could have a significant impact on ME disability claims as some disability policies limit coverage for a mental health disorder.

Like all businesses, insurance companies are concerned with containing costs. But even ignoring the factual error regarding the classification of the disease, Swiss Re’s article appears to be a remarkable level of endorsement of a disease theory and treatment approach that is controversial and fails to account for the biomedical evidence that counters the theory. Further, as journalist David Tuller noted in a November 2015 article, the article raises questions regarding potential conflicts of interest of some of the PACE investigators.\textsuperscript{606}

A fifth factor is the way in which “evidence-based” practices, when applied to such a controversial and muddled evidence base, have served to maintain the status quo. For instance, evidence-based reviews inappropriately assume that all “CFS” and “ME” definitions represent the same disease for which one set of diagnostic and treatment recommendations is appropriate. This has been done in spite of substantial differences in inclusion and exclusion criteria across those definitions, which demonstrate that these definitions encompass different conditions. Similarly, evidence-based clinical guidelines have inappropriately combined the IOM diagnostic criteria with risk and prognosis theories and treatment recommendations based on PACE and other Oxford psychogenic studies, recommendations that are medically inappropriate for the disease described by the IOM. In both cases, the products of these “evidence-based” practices have not considered the controversies within the evidence base and whether the different parts of the evidence base should be combined. Instead, they appear to rely on superficial features such as the name of the disease or the ill-defined symptom of medically unexplained chronic fatigue in deciding what to combine. Such evidence-based practices perpetuate the medical confusion about the nature of the disease and the iatrogenic harm experienced by patients.

The final factor that has impeded progress is the role of the media, mentioned earlier but important to highlight in its own right. For many years, journalists have reported difficulties with getting articles about this disease and its impact on patients published in mainstream journals. In sharp contrast, HHS and this group of psychiatrists have often had broad coverage of their study reports. Most recently, when the PACE trial mediation and followup studies were published in 2015, even mainstream journals such as The Economist\textsuperscript{607} and U.S. News and World Report\textsuperscript{608} covered the studies. In the U.K., a 2015 article in The Telegraph declared that CFS “is not actually a chronic illness and sufferers can overcome by increasing exercise and thinking positively.”\textsuperscript{609} The situation has started to change in the U.S. with the publication of the IOM report and articles about Whitney Dafoe and the research at Stanford but is still mixed.
Changing the Dominant Paradigm

A dominant paradigm based on “medically unexplained” chronic fatigue and psychogenic explanations and treatments may have helped busy doctors faced with hard-to-diagnose patients. It likely gave cover to NIH institutes who had priorities in other diseases that they deemed more important and more deserving. And it undoubtedly advanced the agenda of those with a vested interest in psychological treatments and commercial cost containment. But this dominant paradigm has had a profoundly deleterious impact on ME research and medical care and on the lives of ME patients. It has created medical disbelief and confusion on the nature of the disease and fostered inappropriate and harmful treatment recommendations. It has created scientific controversy and confounded research with irreconcilable findings and nonsensical evidence reviews. And as the U.K.’s 2006 Gibson Inquiry pointed out, it has fostered beliefs about the disease that are based on studies that include patients who do not have the disease. Most tragically, this dominant paradigm has caused stigma and irreparable physical, financial and emotional harm to ME patients for the last three decades.

The history of the last thirty years is littered with reports—both in the U.S. and internationally—that have been shouting out that we have a problem, that the emperor’s clothes are not doing the job. Given the difficulties that politically powerful veterans have faced in changing the dominant paradigm around Gulf War Illness, it is not surprising that disabled, powerless, and stigmatized ME patients have struggled for so long with so little success.

Perhaps the most important thing that the IOM report achieved is that a voice with political and scientific clout has finally said that the dominant paradigm is wrong and must change. Perhaps in combination with the indisputable scientific evidence that continues to emerge, the recent Tuller articles on the problems with the PACE trial, the more favorable coverage in the U.S. press, and the initial commitments from NIH, it may finally be enough to chart a new course. But achieving that will require two key steps. First, HHS and the medical community must let go of the outdated and wrong-headed ideas about the nature of ME. And secondly, HHS must finally respond with the serious commitment, focus, resources, and sense of urgency that this disease and these patients have always deserved.
Advancing ME Research and Clinical Care

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, time has stood still for ME patients, with so little progress made that a 1990 Newsweek article still reads 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 turning ME patients into pariahs, untouchable by the very people who should have been helping them.

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 agendas and politics, the bad science, the questionable medical ethicality, the neglect and arrogance, the commercial and professional self-interests, and the outright refusal to listen to patients or to the experts trying to help them. It is the story of what happens to a disease when it is exiled outside of the research institutes, the academic centers, and the medical specialties that drive biomedical innovation and delivery of health care in this country. It is the story of a federal response that was so neglectful and wrong-headed that it not only failed to achieve a single meaningful outcome in thirty years but also drove the field to such an unfathomable state of disarray and confusion that science itself has been held hostage. It is the story of ME patients left with such soul-crushing debility, disdain, and loss of hope that they have too often committed suicide to escape.

What makes this situation so tragic is that these patients were ignored simply because they were so easy to ignore. Their lives had been ripped to shreds because they were too disabled, too powerless, and too stigmatized to do anything about it. It is disturbing to think about the political calculations and mental gymnastics that allowed all of us to turn a blind eye to what was happening. It is morally unacceptable that up to one million disabled Americans—and seventeen million worldwide—have been mistreated and disbelieved in this way for so long.

Myalgic encephalomyelitis is not an intractable scientific problem. It is a social and political problem that can be solved if the medical community and especially HHS exert the commitment and political will needed to combat the political agendas, scientific confusion, and neglect that created this problem to begin with. Given HHS’s key role in the genesis of this situation and in the research and medical communities, HHS must take a leadership role to resolve it. HHS’s plan to do this will need to be developed in true collaboration with key stakeholders (including ME patients and disease experts) but will likely need to include components such as the following:

1. **Revamp Engagement:** Establish a truly open, collaborative, and transparent model of engagement to ensure that disease experts, patients, and patient advocates are fully involved in the public health policy discussions and decisions toward ME.

2. **Establish a Strategic Plan and Monitor its Execution:** Implement a fully funded, urgently executed, cross-agency strategy, developed in full collaboration with stakeholders to drive the national response to ME. Establish congressional oversight and monitor implementation of the strategic plan to ensure rapid progress.

3. **Fix the Definition:** Separate the neuroimmune disease from the broader collection of CFS conditions in disease name, research and clinical criteria, medical education, and disease classification. Drive for the international adoption of a common, diagnostically accurate case definition, such as the Canadian Consensus Criteria for all ME research. Ensure that criteria adopted for clinical use encompass the same disease as the
research criteria and are diagnostically sensitive and specific for ME at all levels of severity and disease duration.

4. **Invigorate ME Research and Drug Development:** Move the disease into an NIH institute. Provide funding for research that is commensurate with the disease burden and prevalence—estimated to be $250 million annually from NIH with an additional appropriate amount for epidemiological research by CDC—and use it to aggressively advance biomedical research into disease etiology, pathology, diagnostics, treatment, natural history, risk, prognosis, and prevention across the spectrum of disease severity, disease duration, and patient age, race and socioeconomic status.

5. **Establish Regional Centers of Excellence:** Fully fund regional Centers of Excellence with both a clinical and research component to address both the need for integrated, multi-disciplinary, bench to bedside research and the crisis in clinical care as a result of lack of knowledgeable doctors and the aging of the existing disease experts.

6. **Fix Medical Care:** Adopt expertly authored, ME disease-specific clinical guidelines for CDC’s planned medical education program, website and other medical education materials. Partner aggressively with medical societies and medical education providers to re-educate the medical community and to establish medical specialties for needed referrals to disease experts.

7. **Fix Health Insurance, Disability, and Accommodations:** Work with the appropriate agencies to address gaps and challenges in health insurance and disability coverage and in employment and school accommodations.

8. **Provide Cross-Department Leadership:** Provide the cross-agency leadership needed to resolve internal and external institutional barriers, to address the disbelief, stigma, and neglect by academic centers and the medical community so that forward progress can be made.

More than any moment in the past, this moment is the time for change. Our government and medical providers must embrace this illness with all the seriousness and vigor that characterized the fight against HIV/AIDS. For that to happen, public officials responsible for ME/CFS must take seriously the trust implicit in their position, for it is their moral responsibility to break down the doors that these sick patients cannot reach. Medical providers must honor their oath to first do no harm and provide the compassionate care that these patients deserve. And all of us—HHS, families, the medical and research communities, congressional leaders, the media, and the public at large—must refuse to allow the neglect, bias, sloppy science, and political agendas of the past dictate the future of ME patients.
### 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, CCC, ME-ICC and Pediatric. Ramsay was first definition. Nice Guidelines are used in Britain. Holmes is seldom if ever used today.

<table>
<thead>
<tr>
<th>Definition Name</th>
<th>Label Used (1)</th>
<th>Key Symptoms in the definition</th>
<th>Psychiatric Illness allowed?</th>
<th>PEM Required</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1986 Ramsay612</td>
<td>ME</td>
<td>Muscle weakness and fatigability after trivial exertion, cognitive impairment, pain, circulatory issues/temperature sensitivity, other autonomic</td>
<td>States is not mental illness but that there can be emotional lability</td>
<td>Yes as fatigability after exertion</td>
<td>PEM term not used but muscle fatigability after trivial exertion is central to PEM</td>
</tr>
<tr>
<td>1988 CDC Holmes613</td>
<td>CFS</td>
<td>6 months chronic fatigue plus any 8 symptoms out of eleven. No PEM, but e.g. muscle weakness, pain</td>
<td>Prior chronic psychiatric illness excluded but a 1989 clarification allowed</td>
<td>No</td>
<td>Replaced by Fukuda. Patients show more signs of infectious process than Fukuda614</td>
</tr>
<tr>
<td>1991 Oxford615</td>
<td>CFS</td>
<td>6 months severe fatigue that affects mental or physical function.</td>
<td>No Schizophrenia, manic-depressive illness. Anxiety, depression allowed</td>
<td>No</td>
<td>Myalgia, sleep, mood disturbance may be present but not required. PEM not mentioned</td>
</tr>
<tr>
<td>1994 CDC Fukuda616</td>
<td>CFS</td>
<td>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</td>
<td>Major depressive &amp; bipolar disorder, schizophrenia excluded. Anxiety somatoform &amp; other types of psych disorder allowed</td>
<td>No</td>
<td>PEM one of optional symptoms but not required. Fukuda includes more depressed and less symptomatic patients than CCC617</td>
</tr>
<tr>
<td>2003 Canadian Consensus Criteria (CCC)618</td>
<td>ME/CFS</td>
<td>PEM plus two neurological/cognitive plus 1 of autonomic, immunological &amp; neuroendocrine symptoms</td>
<td>Primary psychiatric illness excluded</td>
<td>Yes</td>
<td>Requires PEM plus combination of these symptoms. 6 month wait</td>
</tr>
<tr>
<td>2005 CDC Empirical (Reeves) Criteria 619</td>
<td>CFS</td>
<td>Operationalization of Fukuda</td>
<td>Depression, anxiety, somatoform disorders not exclusionary</td>
<td>No</td>
<td>Led to ten-fold prevalence increase. Jason has shown 38 percent of patients with depression fit criteria.620</td>
</tr>
<tr>
<td>Pediatric Case Definition for ME &amp; CFS (2006) Jason et al 621</td>
<td>ME/CFS</td>
<td>3 months of fatigue, PEM, unrefreshing sleep, neurocognitive, pain plus one of autonomic, neuroendocrine, immune</td>
<td>Schizophrenia, Bipolar, depressive disorders exclusionary. May have concomitant anxiety, depression, somatoform</td>
<td>Yes</td>
<td>3-month waiting period.</td>
</tr>
<tr>
<td>NICE Clinical Guideline (2007)622</td>
<td>CFS</td>
<td>4 months chronic fatigue plus any one of 10 symptoms</td>
<td>Appears to allow primary psychiatric illness</td>
<td>Consider CFS if PEM exists</td>
<td>Pain, cognitive and sleep difficulties considered key. 3 months duration in child</td>
</tr>
<tr>
<td>2011 ME International Consensus Criteria (ME-ICC)623</td>
<td>ME</td>
<td>PENE and neurological, plus immunological, GI/GU plus energy metabolism/transport</td>
<td>Primary psychiatric illness excluded</td>
<td>Yes</td>
<td>Requires PENE (expansion of PEM) plus symptoms from each of other categories. No waiting period</td>
</tr>
</tbody>
</table>

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

http://bmjopen.bmj.com/content/4/2/e003973.long#T1

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Thirty Years of Disdain: How HHS Buried M.E. December 2015. (M. Dimmock, M. Lazell-Fairman)
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. Calculated for adults only.624

<table>
<thead>
<tr>
<th>Author</th>
<th>Rate</th>
<th>2012 estimate</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fukuda</td>
<td>0.0019</td>
<td>456,000</td>
<td><a href="http://dx.doi.org/10.1186/1478-7954-5-5">http://dx.doi.org/10.1186/1478-7954-5-5</a></td>
</tr>
<tr>
<td>Fukuda w PEM</td>
<td>0.00026 (36% of Fukuda)</td>
<td>62,400</td>
<td><a href="http://www.mayoclinicproceedings.org/article/S0025-6196(12)00923-8">http://www.mayoclinicproceedings.org/article/S0025-6196(12)00923-8</a></td>
</tr>
</tbody>
</table>

Appendix 3: Key Resources

Videos
3. News story about two sisters with ME. *Menschen - das Magazin.* April 2014. (subtitled in English). [https://www.youtube.com/watch?v=XgZ1ayl7J6w](https://www.youtube.com/watch?v=XgZ1ayl7J6w) and [https://www.youtube.com/watch?v=fws-oAEvAS](https://www.youtube.com/watch?v=fws-oAEvAS)
4. **Voices from the Shadows.** Produced by Natalie Boulton and Josh Natalie. 2011 Trailer [http://www.youtube.com/watch?feature=player_embedded&v=fxZG4VtK02k](http://www.youtube.com/watch?feature=player_embedded&v=fxZG4VtK02k)
Web site - [http://voicesfromtheshadowsfilm.co.uk/](http://voicesfromtheshadowsfilm.co.uk/)
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](http://www.youtube.com/watch?v=KGFVXacPuho)
   - Part 2 - [http://www.youtube.com/watch?v=Q0EjR2yepHg](http://www.youtube.com/watch?v=Q0EjR2yepHg)
   - Part 3 - [http://www.youtube.com/watch?v=1stOT72UCQw](http://www.youtube.com/watch?v=1stOT72UCQw)
   - Part 4 - [http://www.youtube.com/watch?v=bGphVlRKovY](http://www.youtube.com/watch?v=bGphVlRKovY)
   - Part 5 - [http://www.youtube.com/watch?v=wD363vqG38U](http://www.youtube.com/watch?v=wD363vqG38U)
   - Part 6 - [http://www.youtube.com/watch?v=1SteyLtnxOo](http://www.youtube.com/watch?v=1SteyLtnxOo)
12. Larry King. “Living Hell.” *McNeil Lehrer.* 1992. King interviews patient and advocate Tom Hennessy. [https://www.youtube.com/watch?v=SyB49g_i959&list=UUaCAv_xLayn32wR9cXjHSTQ](https://www.youtube.com/watch?v=SyB49g_i959&list=UUaCAv_xLayn32wR9cXjHSTQ)

Books and Articles on ME and on the History


This article documents the early outbreaks and gives a perspective on what was known at the time. Unfortunately, it reads like its current events.


Congressional requests made through appropriations reports.
1. Compilation of congressional requests in appropriations report language for ME/CFS from 1995 to 2013 and for 1988 to 2000 as reported by the GAO.

Summary of pre-1980 ME epidemics and review articles.

References on the Politics of ME and CFS


Compilation and Summaries of Published Scientific Literature


3. Margaret Williams. Grey information about ME/CFS

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

5. NHS Services for people with Chronic Fatigue Syndrome/Myalgic Encephalitis. The National Task Force on CFS/ME 1998 (link unavailable)
   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)
Bibliography
This document is a summary of a longer document, which contains additional information and references.

  The May 2015 version can be found here. [https://dl.dropboxusercontent.com/u/89158245/Thirty%20Years%20of%20Distain%20How%20HHS%20Buried%20Myalgic%20Encephalomyelitis%20May%202015.pdf](https://dl.dropboxusercontent.com/u/89158245/Thirty%20Years%20of%20Distain%20How%20HHS%20Buried%20Myalgic%20Encephalomyelitis%20May%202015.pdf)

All online references listed below were last accessed in December 2014 unless otherwise noted. Where required, translations were done with Google Translate.

   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 FOIA 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](https://dl.dropboxusercontent.com/u/89158245/Straus%20to%20Fukuda%20letter%201994.docx)
   Matthew spoke anonymously in this testimony
   Matthew spoke anonymously in this testimony
   Reflecting the concerns raised by patients for years, the IOM report found that the name chronic fatigue syndrome was trivializing and recommended it no longer be used.
6 Ibid. Page 1
   Journal article
   This Newsweek article reports on the neurological and immunological impairment that IOM reported and also on the medical community dismissal
   Also see:
     This reports on the 1980s investigation of the Incline Village and Lyndonville outbreaks by the CDC, the evidence of impairment that was found and the medical dismissal
   Last accessed August 30, 2015
10 Most notable were a group of British psychiatrists, a group in the Netherlands and to a lesser extent, individuals within the U.S. They have promoted what they refer to a “biopsychosocial” or “psychosocial” model of CFS. The following two articles discuss these theories. The Harvey article discusses the “biopsychosocial” approach, while the Vercoulen article discussed by Maes uses the term “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
Further details in the following source:
See "The Growing Focus on Psychological Issues" in the “What is CFS” chapter.

The best descriptions of ME can be found in two case definitions and the associated clinical guidelines.

### Definitions


This is the most recently developed ME case definition and gives extensive information with references regarding the nature of the abnormalities.


The CCC discusses neurological and cognitive manifestations that include confusion, difficult concentrating, disorientation, trouble with processing information, trouble with locating words, perceptual and sensory disturbances, difficulty focusing, ataxia, muscle weakness, and overload (noise, light, etc.)

### Primers


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


This primer is based on the ME International Consensus Criteria.

### Videos


Discussion starts at minute 6:38, during which Dr. Komaroff summarized key biological findings across systems


This presentation was given on the last day of the conference and summarized the highlights seen in the presentations given at the conference.


13 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:
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.

- 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:

- Dr. Mark Loveless, who was an infectious disease specialist and head of the CFS and AIDS Clinic at Oregon Health Sciences University. In a May 1995 briefing sponsored by John Porter (R-IL) and Senator Harry Reid (D-NV), Loveless 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” This statement is often quoted but the original source is not available. This is one source from that time.


16 No official source exists for this number but this is the commonly reported worldwide prevalence. As with all prevalence numbers, it is at best a rough estimate because of the definitional issues that have always plagued these studies.


18 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.”

Also see papers by Snell, Stevens, Van Ness, Davenport, Keller and Vermeulen. For instance:


Starts at minute 48.30 Snell discussed aerobic and anaerobic energy production at minute 58 and how CPET can distinguish between deconditioning and ME at minutes 75-84.

One of the researchers talked about this in a presentation but the exact source could not be identified.


The paper stated, “ME/CFS participants were unable to reproduce most physiological measures at both maximal and ventilatory threshold intensities during a CPET performed 24 hours after a prior maximal exercise test. Our work confirms that repeated CPETs warrant consideration as a clinical indicator for diagnosing ME/CFS. Furthermore, if based on only one CPET, functional impairment classification will be mis-identified in many ME/CFS participants.”

The paper also 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.”


The authors 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. The active replication of HHV-6 most likely represents reactivation of latent infection, perhaps due to immunologic dysfunction.”


Reviews neurological changes along with the role of infection as a triggering event.


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


The text notes dominant features of “Abnormal muscular fatigability and weakness.” With muscle power returning after rest. It also noted severe pain in the legs and back, along with spasms and often numbness of lower legs. It also noted Circulatory impairment... coldness of the extremities and acute sensitivity to alterations in temperature” and impairment of memory and ability to concentrate.

PETIs positron emission tomography, which uses imaging techniques to show functional processes.


Speaking to the Zimm’s 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.”


Summarizes key biological findings across systems

Also see the following review which cites many of the studies done over the years


The paper stated “Profiles of ME/CFS subjects also differed from those of MS subjects, with ME/CFS cases showing a markedly greater degree of CNS immune activation as compared with those with MS.”


41 Response to B cell eradication by Rituxan could be related to a pathogen resident in the B cells or else the depletion of antibodies. EBV, which has high titers in some patients, can be resident in B cells. But the response to Rituxan therapy is typically delayed for a number of months after the beginning of treatment. This delayed response to Rituxan is more indicative of an autoimmune response, in which time is required to deplete the antibodies.


Includes a report on High Throughput Sequencing/Pathogen Discovery that stated, “Through our continued partnership with Holden Maecker PhD at Stanford and W. Ian Lipkin MD and Mady Horning MA, MD at Columbia University, our effort of looking for pathogens present or abundant in ME/CFS patients has yielded exciting results. We are in the process of preparing a manuscript for submission to a peer-reviewed journal.”

The following report is one source for the patient’s experience of this disease.


Meeting agenda, transcript and video can be found at:

Another source is:

- **Voices from the Shadows.** Produced by Natalie Boulton and Josh Natalie. 2011
  - Trailer [http://www.youtube.com/watch?feature=player_embedded&v=fxZG4Vlk02k](http://www.youtube.com/watch?feature=player_embedded&v=fxZG4Vlk02k)
  - Web site - [http://voicesfromtheshadowsfilm.co.uk/](http://voicesfromtheshadowsfilm.co.uk/)


Also see the IOM report noted above, and the following two 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](http://www.iacfsme.org/LinkClick.aspx?fileticket=iD3JkZAZhts%3d&tabid=509)


- **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](http://www.iacfsme.org/LinkClick.aspx?fileticket=iD3JkZAZhts%3d&tabid=509)


Also see


Also

- Swain, Gill. ”Trapped in bed for 14 years with chronic fatigue.” *Daily 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](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.”


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/](http://voicesfromtheshadowsfilm.co.uk/2013/karina-hansen-is-a-severely-ill-danish-patient-who-was-forcibly-taken-from-her-home-update-may-2013-9th/)

Karina has been treated by staff from the Research Clinic for Functional Disorders and Psychosomatics, which is run by Dr. Per Fink. 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 Guidelines for CFS/ME as evidence to support the use of CBT and GET in his treatment regimen.


The Research Clinic for Functional Disorders at Aarhus University Hospital in Denmark. The website for that clinic is at [www.functionaldisorders.dk](http://www.functionaldisorders.dk)


Also see:


Also see:

- 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%201-RIP.htm](http://www.investinme.org/Article-050%20Sophia%20Wilson%201-RIP.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.


Reticuloendothelial system that the disease was characterized by a) signs of brain damage b) muscle pain c) emotional disturbance d) reticuloendothelial system involvement in some cases e) protracted disease course
Note that by benign, the author meant that death did not occur immediately after onset. The author stated that the disease was not hysteria.


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


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?”

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.”

Also see:


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Also see:


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.”

Ramsay issued two articles on the definition, one in 1986 and one in 1988.


Extract provided by Connie Nelson to Mary Schweitzer who provided it on http://www.cflds.me.org/ramsay86.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."


The text notes dominant features of "1) Abnormal muscular fatigability and weakness. Muscular power was restored by a period of rest but recurred following further activity. "The study suggested a role that "intracellular energy mechanisms" might play."

Also see:


This study reported abnormal acidosis from exercise. Arnold postulated that this could "represent excessive lactic acid formation resulting from a disorder of metabolic regulation."


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.


See also the following sources for Straus's reaction to the disease.


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, "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."

Note that a 2013 paper suggested the Acyclovir failure could have resulted from inadequate duration of treatment and/or the failure to treat a potentially co-existing virus.


Straus stated that educated white women were more likely get the disease which could either reflect the resources to access evaluations or “some unique constitutional frailty of such individuals.” He also said that most had excellent health and said that some were competitive athletes or “at least aggressively maintained physical conditioning.” He went on to state “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.”


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The PACE trial, done in patients that met the Oxford definition, tested cognitive behavioral therapy (CBT) and graded exercise therapy (GET) which, according to the study publication, 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.”
Etiology of Chronic Fatigue Syndrome: Testing Popular Hypotheses Using a Systematic Review and Dissemination. PROSPERO Register CRD42015025520 Available from http://www.crd.york.ac.uk/PROSPERO/display_record.asp?id=CRD42015025520

This review is assessing behavioral modification interventions for medically unexplained symptoms. Regarding the condition being studied, the publication stated, “The term MUS may be applied to patients presenting with single symptoms, multiple symptoms, or clusters of symptoms that are related to one another and are specific to a certain organ system or medical specialty.” The examples given were CBS, FM and IBS which the paper stated were terms typically referred to functional somatic syndromes and references a 1995 Wessely paper. 


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. Examples of CFS being referred to as Somatoform illness include:


Referring to the IOM report and CFS, IBS and other diseases often grouped together, this article stated that “None of these conditions have common, overlapping features that usually consist of both fatigue and pain, and, in the absence of definitive objective confirmation, might be best classified under one heading such as somatic symptom disorder.”


The article 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 therapy.”


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. Examples of CFS being referred to as Somatoform illness include.


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


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NHS is the National Health Service in the U.K.


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The article states that CFS “represents one of a cluster of functional somatic syndromes, which all share similar psychosocial etiological and maintaining factors,”


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chronic fatigue syndrome” that “assume that the syndrome is perpetuated by reversible physiological changes of deconditioning and avoidance of activity.”

The protocol and 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, Sharpe M, Chalder T, DeCesare J, Walwyn R. “Protocol for the PACE trial: A randomised controlled trial of adaptive pacing, cognitive behaviour therapy, and graded exercise as supplements to standardised specialist medical care versus standardised specialist medical care alone for patients with the chronic fatigue syndrome/myalgic encephalomyelitis or encephalopathy.” BMC Neurology. March 8, 2007. 7:6
  http://dx.doi.org/10.1186/1471-2377-7-6
  http://www.plosone.org/article/info:doi/10.1371/journal.pone.0040808
  http://www.trialsjournal.com/content/14/1/386
  http://www.jpsychores.com/article/S0022-3999(14)0007-3

Information on the cost of the PACE trial can be found here
  http://www.rae.ac.uk/submissions/ra5a.aspx?id=176&type=hei&subjid=3181

The Research Assessment Exercise was conducted jointly by the Higher Education Funding Council for England (HEFCE), the Scottish Funding Council (SFC), the Higher Education Funding Council for Wales (HEFCW) and the Department for Employment and Learning, Northern Ireland (DEL).

This quote was made in the context of discussing the 1970 psychogenic theories of Beard and McEvedy, which is the precursor to the later theories that manifested in the biopsychosocial theory.

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 polyomylitis,” benign myalgic encephalomyelitis, epidemic neuromyastenia, encephalomyelitis, and postviral syndrome.”

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.” Prior to this, the disease had started to be referred to as chronic Epstein Barr Virus or chronic Epstein Barr virus syndrome.

Also see the following for the loosening of the exclusions against mental illness in 1989


Komaroff et al stated that mood disorders preceding the onset of the disease should not be considered exclusionary, in part because such neuropsychiatric problems "could be viewed as contributing to the emergence of biochemical responses that perpetuate many of the syndrome's somatic features."

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 reportedly on the CDC-sponsored panel that worked on the development of Holmes. But according to Dr. Byron Hyde, a Canadian clinician who attended the meeting, 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."

See:


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


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."


The quotes are from the Tuller article, which references the following study:


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:


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.


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 agoraphobia), generalized anxiety disorder, and somatiform 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 psychiatric 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 (beyond the authors) included Susan E. Aubrey, 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.


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, stated:

“...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.”


As listed in the Oxford CFS definition, the criteria include a) fatigue as the main symptom b) definite onset, not lifelong, c) fatigue is disabling and affects both physical and mental functioning d) has lasted for 6 months and was present for 50 percent of the time and e) may be accompanied by other symptoms including pain, sleep disturbance and mood. The criteria then list exclusions of medical conditions known to cause fatigue and certain psychiatric illness including schizophrenia, manic depressive illness, substance abuse, eating disorder or proven organic brain disease. The Oxford definition describes fatigue as subjective and not physiological failure to sustain muscle power.


112 Subjective fatigue was defined in a talk given by Professor P.K. Thomas and Professor Simon Wessely on February 11, 1993 and obtained by Valerie Elliot Smith by FOIA. In the summary, Thomas was noted as stating, “Subjective fatigue refers to the situation where the delivery of the required force cannot be maintained because of uncomfortable sensations, not in the muscles themselves but in an indefinable way that affects drive and motivation.”

According to Smith, 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. References include


Also see

115 Fukuda listed the "International Chronic Fatigue Syndrome Study Group" as one of its authors. Wessely was a member of this group.


The authors noted that current definitions called for CFS to not be diagnosed when there was an active medical or mental cause for the fatigue. They went on to state "This implies that the etiology of 'unexplained' CFS is different to that of the 'explained' fatigue seen in those with a diagnosed medical condition."


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."

Also see the following - discusses the need for stratification on factors that also include medication: P 332-335


At P2P, Nacul stated 163 combinations of Fukuda symptoms of which only 35 (20%) require PEM. Nacul said:
- "If we use the Fukuda criteria, CDC 1994, which is probably the most widely used criteria, it's 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 that make a diagnosis would drop to about 35."


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.


Jason noted that a review of 53 Fukuda CFS studies found that 25-100 percent of patients reported PEM while 16-100 percent reported unrefreshing sleep.


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 FOIA 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%20%201994.docx

Straus stated, "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 "shill 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)


The panel consisted of Dr. Susan Abbey, Dr. Keiji Fukuda, Dr. Nelson Gantz, Dr. Gary Holmes, Dr. James Jones, Dr. Heidi Johnson, Dr. Anthony Komaroff, Dr. Ben Natelson, Dr. William Reeves, Dr. Ann Schlueterberg and Dr. Stephen Straus. A request by CFIDS Association of America to have Dr. David Bell, Dr. Nancy Klimas, Dr. Susan Levine and Dr. Leonard Jason was rejected.

CFIDS wrote that Fukuda was the "first to advocate for a case definition free of symptom criteria."


The follow-up case definition meeting was held on November 19, 1993. In his newsletter, Burns, who attended the meeting wrote, "CDC’s Dr. Keiji Fukuda proposed a scheme that would incorporate both views. There might be a broad category for chronic fatigue with many subsets, one of which would be "core" chronic fatigue syndrome."


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 Colleges of Physicians of London, Royal College of Psychiatrists, Royal College of General Practitioners. According to the report, the Chief Medical Officer requested the report to "advise on matters such as diagnosis, clinical practice, aetiology and service provision" of chronic fatigue syndrome.


http://dx.doi.org/10.1016/S0140-6736(05)64917-3 and http://www.thelancet.com/journals/lancet/article/PII%0007.pdf

The editorial stated "Psychiatry has it 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".


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 evidenced 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."


The report stated, “This study showed scant stability of CFS over time, when diagnosed by the usual algorithm” which the paper described as using patients responses to questions on fatigue and symptoms.
This report also 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."

Ibid.


http://dx.doi.org/10.1186/1478-7954-5-5

This paper reports a prevalence rate of 0.0254 versus 0.0024 found in a CDC Reyes study ("Prevalence and incidence of chronic fatigue syndrome in Wichita, Kansas").


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.

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

White 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)


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 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.


Jason stated, "The present study investigated this new definition with 27 participants with a diagnosis of CFS and 37 participants with a diagnosis of a Major Depressive Disorder…. Findings indicated that 38% of those with a diagnosis of a Major Depressive Disorder were misclassified as having CFS using the new CDC definition.”

CDC referral to the Empirical definition as Fukuda or as the "standardized approach to applying Fukuda" creates substantial confusion on what patients are being studied.

One recent example is:


The paper stated that about 20,000 residents were "screened for unwellness among household members for whom at least one CFS symptom was reported [fatigue, impaired cognition, un-refreshing sleep, muscle or joint pain].”

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


  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 [the 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.


  Note this is CFS course WB1888. Origination Date: 06/27/2012. Expiration Date: 06/27/2016

  Note that the description of Fukuda definition states that recommendations for standardized measures were made in 2003. These recommendations were used for the 2005 Empirical definition. The 2005 Empirical definition is not listed separately.


Examples of concerns raised by patient organizations with the NICE Guidelines for CFS/ME:


  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."


• Report - www.erythos.com/gibsonenquiry/Docs/ME_Inquiry_Report.pdf and

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'."

• Website - http://erythos.com/gibsonenquiry/Index.html Includes index of materials
• Evidence Review created by BRAME


Includes extensive comments from stakeholders raising concerns with the decision to place a disease on the static list.


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 fatigue 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.


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.

For instance in the CCC

PEM is defined as “There is an inappropriate loss of physical and mental stamina, rapid muscular and cognitive fatigability, post exertional malaise and/or fatigue and/or pain and a tendency for other associated symptoms within the patient’s cluster of symptoms to worsen. There is a pathologically slow recovery period—usually 24 hours or longer.”


The article criticizes the CCC because they were “developed without reference to any standard methodology,” published in a journal that is no longer in existence, received funding from a pharmaceutical company, had “not been operationally defined or validated,” and the statements made were “not supported by published or peer-reviewed evidence, and the report holds an open stance of a neurological view of ME/CFS, also not referenced or supported by the evidence.”

Author’s note: These criticisms are remarkable given the lack of operationalization of Oxford, the ties to the insurance companies of some proponents of the biopsychosocial approach and the evidence for neurological dysfunction.


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 neurological condition considered exclusionary for CFS.”


The “Overview of CFS” in this expired CME stated “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 was available through at least 2011 and 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.


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 Akureyi disease, Iceland disease, atypical poliomyelitis, benign myalgic encephalomyelitis, epidemic neuromyasthenia, encephalomyelitis, and postviral syndrome.”


Note this is CFS course WB1888. Orignation Date: 06/27/2012. Expiration Date: 06/27/2016

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.

Note that this does not specifically call out the Empirical definition but CDC refers to Empirical as an operationalization of Fukuda. The Fukuda definition page lists a study that led to the Empirical definition.

U.S. Department of Health and Human Services CFS Advisory Committee. CFSA May 22-23, 2013 meeting. https://www.youtube.com/watch?v=VJ7VqYJTsW8&list=P LtL7EBKAbz1PFzedYComOolI9agz8-6QL&index=12 (minutes 25-45 for exchange, Minute 28:15 for quote)

Exchange between Dr. Unger and CFSA 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?”

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_1%2628%2614

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 reportedly on the CDC-sponsored panel that worked on the development of Holmes. But according to Dr. Byron Hyde, a Canadian clinician who attended the meeting, 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."

See:

  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
  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


- Website - http://erythos.com/gibsonenquiry/Index.html Includes index of materials
- Evidence Review created by BRAME

  http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(11)60096-2/fulltext
Other publications include:


  http://www.plosone.org/article/info:doi/10.1371/journal.pone.0040808
  http://www.trialsjournal.com/content/14/1/386
  http://www.jpsychores.com/issue/S0022-3999(14)00073-3
  http://dx.doi.org/10.1016/S2215-0366(15)00317-X

Information on the cost of the PACE trial can be found here.


The Research Assessment Exercise was conducted jointly by the Higher Education Funding Council for England (HEFCE), the Scottish Funding Council (SFC), the Higher Education Funding Council for Wales (HEFCW) and the Department for Employment and Learning, Northern Ireland (DEL).

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Example includes


A list of published comments on PACE trial papers can be found here:


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


• Part 1: http://www.virology.ws/2015/10/21/trial-by-error-i/

• Part 2: http://www.virology.ws/2015/10/22/trial-by-error-ii/


PACE recovery was based in part on achieving a score on one scale that was lower than the entrance criteria. Other criteria included no longer meeting the CFS definitions. These are not clinically meaningful definitions of recovery for patients. Comments on issues with the conduct of the PACE trial can be found in published comments on the above trials and in the following sources:

- Comments submitted on PACE Trial protocol. BMC Neurology. 2010. [link]
- Hooper, Malcolm. “MAGICAL MEDICINE: HOW TO MAKE A DISEASE DISAPPEAR.” InvestInME. February 2010. [link]
- Provides an extensive review of PACE and related issues.

Selected issues highlighted by Petrisor 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 starts at minute 48.30. He made this 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.”


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As noted by ME patient and advocate Tom Kindlon, “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.” He found that 51 percent of respondents said that GET (8 studies) made them worse while 20% said CBT (5 studies) made them worse.


Tucker quoted Levin as saying “I would not accept an extrapolation to people diagnosed with alternative criteria from a subgroup comprising people satisfying both sets of criteria rather than just the alternative set of criteria,”


According to comments made by CDC’s Dr. Reeves at a May 2009 CFSAC discussion, 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 defining cases of CFS.

CFSAC discussion can be found here.


• 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 that they evaluated whether participants met the “International (CDC) criteria for CFS at 52 weeks.” The paper stated “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 months.”


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.”

• The paper lists the criteria as: “(1) exercise-induced fatigue precipitated by trivially small exertion, (2) impairment of short-term memory and loss of powers of concentration, (3) fluctuations of symptoms usually precipitated by physical or mental exertion, (4) symptoms present for at least 6 months, and (5) no ‘primary’ depressive illness and no anxiety disorder present (which we interpreted as no co-morbid mood disorder of any kind).”

• However, while using the same reference, on page 824, the 2011 PACE trial publication states that it used version 2 of the London Criteria. Goudsmit has stated that Version 2 of the London criteria is a looser criteria.

For further information on the London Criteria


Describes both version 1 and version 2 where version 2 is the looser criteria.


The article on ShoutAboutMe stated, “Two versions of the London Definition appeared around 1993/94. Version 1 was devised for APME. A truncated and inaccurate revision, Version 2, published in the 1994 National Task Force Report did not include the exclusion diagnoses and the physical examination findings.”

Also see
NIH Pathways to Prevention Workshop: Advancing the

Letter from Secretary Kathleen Sebelius, U.S. Department of Health and Human Services

Includes summary of patient advocates concerns with the IOM

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.”

Patients submitted petitions and also a white paper advocating for the adoption of the CCC.

One example is

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.

Includes summary of patient advocates concerns with the IOM

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.

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’S response to the October 2012 CFSAC recommendation to convene a meeting to reach consensus on the case definition.


The response to the CFSAC recommendation stated “The National Institutes of 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.”

Also see the IOM report, which noted the change in the goal of the P2P workshop.

Reference:
Provides additional information on the events surrounding HHS’S decision to engage the IOM.

Also see

- 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
- The NIH Pathways to Prevention Initiative was originally called the Evidence based Methodology Workshop.
In a personal email on 6/4/2014, Dr. Beth Collins-Sharp had stated that she didn’t “think that the different diagnoses will be lumped together for analysis. You’re right that it would be comparing Oxford apples to CCC oranges.” Dr. Collins-Sharp was ex-officio at the time that the AHRQ Evidence Review protocol was published.


The inclusion criteria for the diagnosis question is “symptomatic adults... with fatigue” and excludes “patients with other underlying diagnosis.”
On page 192, in response to a question on why the focus on fatigue, the disposition stated, "During topic refinement, the questions were developed with the NIH working group and AHRQ. Given the breadth of symptoms that patients with ME/CFS experience, we could not have tackled all of these within the scope of this one report. In consultation with the technical expert panel, the working group and AHRQ, the key questions were set on the syndrome of ME/CFS and the universally experienced symptom of fatigue. We will recommend areas of future research including a systematic review on PEM diagnosis and treatment which would be a topic unto itself."

Regarding input from the Technical Expert Panel

- On page 25, the disposition stated, "The advice of the Technical Expert Panel was that the most meaningful and helpful to focus on the syndrome of ME/CFS and the universally experienced symptom of fatigue."
- But on page 28, the comments of the Technical Expert Panels comments indicated that this was not true. The panel member stated, "The use of fatigue as the only criteria for Key Question 1 diminishes the multi-system nature of the illness and is a limitation, perhaps even a fatal flaw of the report. Please consider expanding the criteria for Key Question 1 to include other important symptom features of the syndrome." The response to this was, "A priori, we were commissioned to review the evidence on diagnosing the syndrome of ME/CFS rather than methods used to diagnose specific symptoms such as orthostatic hypotension, PEM, etc. Identifying diagnostic tests for specific symptoms was beyond the scope of this report."

The authors stated "Dr. Chu’s comment regarding the importance of analyzing data based on case definitions used for inclusion to trials is consistent with our approach. For example, in the trials of cognitive behavioral therapy (CBT) using the SF-36 physical function item as an outcome measure, the two studies using Oxford criteria indicated improvement, while the two using CDC criteria reported no improvement."

The review stated "Fourteen trials compared counseling or behavioral therapy versus usual care, no treatment, or other types of counseling or behavioral therapy (Table D) in ME/CFS patients diagnosed primarily by the Oxford (Sharpe, 1991) or CDC (Fukuda, 1994) case definitions.68-89 Results were mixed for most outcomes, but when considering all studies comparing any type of counseling with a control, counseling improved fatigue (7 of 11 trials showed positive effect), measures of functioning (4 of 11 trials showed positive effect; 2 of 11 showed mixed results on different measures), quality of life (2 of 4 trials showed positive effect), and global improvement (2 of 2 trials showed positive effect). Treatment effectiveness may not be generalizable to all patients because no study used a case definition that selected for more disabled patients (i.e., case definition for ME)." (ES-6)

The review stated "Six trials evaluated exercise therapies, including graded exercise therapy (GET), qigong, and home orthostatic training compared with no treatment or several other types of therapies in ME/CFS patients diagnosed primarily by the Oxford (Sharpe, 1991) or CDC (Fukuda, 1994) case definitions (Table E).57,89-93 "GET improved measures of fatigue, function, and clinical global impression of change compared with controls. Treatment effectiveness may not be generalizable to all patients because no study used a case definition that selected for more disabled patients (i.e., case definition for ME)." (ES-7)

The disposition of comments notes "We appreciate that the case definitions are very different and that some are more inclusive than others and may reflect less severe cases or non-cases of ME/CFS as is outlined in the Key Question 1 results in the report. After consultation with the Working Group and Technical Expert Panel, we elected to include all case definitions in the report a priori for several reasons. First, there are very few trials; excluding some of these definitions would limit the evidence even further than is already outlined. Second, the intent was that this could at least provide a foundation to determine what interventions may be effective. Where available, we compared findings using different case definitions to determine if findings were consistent or not across studies."


Advocate Jennifer Spotila asked why the Oxford studies should not be retired as they retire to the ME/CFS population since Dr. Smith’s recommended that Oxford criteria be retired. Smith stated that the methodology of the trial was good and warranted a good rating and that the issue of the inclusion criteria used in the trial (the Oxford) was a different question than the quality of the trial. Regarding retiring all studies based on Oxford, she went on to state, “I'm not sure that this is the best way to move the research forward because again, sometimes as they spoke about this morning or was it earlier this afternoon on the MAPP network, sometimes it’s important to spread, to put out a wider net, to get some information before drawing it to a narrower spectrum and I think that some of the Oxford studies may give us some clues as to where to go with things.”


The paper stated that patients feel less fatigued and there was no evidence of harm.

The protocol can be found here:


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 is prominent, is unexplained, is significantly disabling or distressing and has lasted for 6 months or more. 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.

190 Some evidence reviews include not only any CFS and ME definition, but also studies that do not use a specific definition, as long as the patients have some duration of chronic fatigue. One example is One example is:


The study included Oxford, Fukuda, and Australian definition studies, but also included studies where the symptom requirements of Fukuda were dropped, or where patients could have had just three or four months of fatigue even if no CFS definition was met.


The P2P workshop used the AHRQ Evidence Review as input, which lumped together definitions, while the P2P agenda excluded broad swaths of research, an approach described by advocate Jennifer Spotila as “science-lite.” For instance, the workshop included sessions on “Social Determinations of Health” and “Self-Management.” But none of the workshop sessions focused on neurological, autonomic, or energy production dysfunction, key areas of research. In addition, the speakers selected to speak at the session on fostering innovative research, arguably the most important session, have had a research focus on psychosocial theories, perceptual issues and pain research. These topics are far from the mainstream biomedical focus of research in this disease.”

As discussed later, the review authors defended the recommendation for CBT and GET for all patients, even though based on Oxford studies.

See also


194 Ibid. Page 5.

195 Ibid. Page 210. “The committee recognizes that some patients diagnosed by other criteria, such as the Fukuda definition (Fukuda et al, 1994), will not fulfill all of the criteria proposed here, but emphasizes that all patients should receive appropriate care.”

Page 227 - “The committee recommends that this disorder be renamed “systemic exertion intolerance disease” (SEID). SEID should replace myalgic encephalomyelitis/chronic fatigue syndrome for patients who meet the criteria set forth in this report.”

The summary of neurological evidence beyond cognitive, sleep and autonomic issues only occupies two pages (87-88). Two sources that list a number of other neurological studies:


Auwaerter stated, "What do I do in my office? Simon Wessely and colleagues, 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."

Two examples include:


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.” However, such therapy has been shown to produce harm in patients with the systemic intolerance to exercise described by the IOM report.

The following articles deal with concerns on the IOM criteria include:


Dolan, Darrach. "Beyond Tired: Is chronic fatigue syndrome a real medical condition? Yes, according to a report from the Institute of Medicine, which urges physicians to treat it accordingly." NeurologyNow. October/November 2015; 11(5):60-63. http://journals.lww.com/neurologynow/fulltext/2015/11050/Beyond_Tired__Is_chronic_fatigue_syndrome_a_real.31.aspx

In reality, the ME-ICC does not specify chronic fatigue but rather fatigability so it is incorrectly lumped into this group.

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 Jutel was referring to medically unexplained symptoms in general, not specifically to CFS but the description is apt here. This paper is an interesting review of how MUS symptoms are handled in general.
Ibid. 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." Also see Dalen, Per. "Somatic medicine abuses psychiatry — and neglects causal research" Copyright 2003. Available on http://www.art-bin.com/art/dalen_en.html

This paper discusses the issue of presuming a psychological explanation for diseases in which there is not yet 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."

Examples of PACE publicity include

  Horton, editor-in-chief of Lancet, said "But one sees a fairly small, but highly organised, very vocal and very damaging group of individuals who have, I would say, actually hijacked this agenda and distorted the debate so that it actually harms the overwhelming majority of patients."


Also see the AHRQ Evidence Review publication for a table comparing definitions, although their analysis did not focus on exclusionary criteria


For a fuller discussion, see


Ibid. Also see

- 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.pscychres.2012.03.031

While not complete, the IOM report contains the most extensive review of the studies of biomedical pathologies associated with some of the symptoms that has been done to date.

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 Summary by Dr. Anthony Komaroff
  - Transcript (provided by MECFS Forums)

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220 Gaber T, Oo W, Ringrose, H. "Multiple Sclerosis/Chronic Fatigue Syndrome overlap: When two common disorders collide.” *NeuroRehabilitation*; 2014; 35(3): 529-34 http://dx.doi.org/10.3233/NRE-141146


This study was of 260 patients in the November 2008 to December 2009 timeframe. The paper evaluated patients meeting Fukuda and an alternative fatigue diagnosis, stating “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).”


Jason stated, “The present study investigated this new definition with 27 participants with a diagnosis of CFS and 37 participants with a diagnosis of a Major Depressive Disorder. Findings indicated that 38% of those with a diagnosis of a Major Depressive Disorder were misclassified as having CFS using the new CDC definition.”


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.”

The paper also stated, “We found that 20%-33% of the originally identified CFS subjects remained in the CFS state at any subsequent visit, and only 7.5% remained in the CFS state for two consecutive periods.


The paper stated, “ME/CFS participants were unable to reproduce most physiological measures at both maximal and ventilatory threshold intensities during a CPET performed 24 hours after a prior maximal exercise test. Our work confirms that repeated CPETs warrant consideration as a clinical indicator for diagnosing ME/CFS. Furthermore, if based on only one CPET, functional impairment classification will be mis-identified in many ME/CFS participants.”

The paper also 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.”
The National Center for Health Statistics (NCHS) actions goes against recommendations by CFSAC, a recommendation by CDC. Dr. Clayton noted, “The level of response is much more than would be seen with deconditioning,” with reference to the belief voiced by some clinicians that physical abnormalities in these patients are merely a result of their lack of activity.


CDC and Fukuda use the term “CFS,” NIH and the CCC use the term “ME/CFS,” FDA and NICE use the term “CFS/ME,” the ME-ICC and many in other countries use the term “ME,” and many speakers use the term “chronic fatigue” as a short-hand for any of these other terms.

The current version of the U.S. version of ICD-10 is ICD-10-CM, which is intended to be rolled out in October, 2015


• CFS is listed as follows under “chronic fatigue” which is under “Malaise and Fatigue” in the Symptoms chapter. Note that CFS and CF both use the code R53.82
  R53.82 Chronic fatigue, unspecified
  Chronic fatigue syndrome NOS
  Excludes1: postviral fatigue syndrome (G93.3)

• ME is listed as follows under “Other disorders of the brain” in the Neurological chapter
  G93.3 Postviral fatigue syndrome
  Benign myalgic encephalomyelitis
  Excludes1: chronic fatigue syndrome NOS (R53.82)

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.


• Formal proposals by patient advocates to National Center for Health Statistics
  o 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/data/icd/Coordination_and_Maintenance_Committee_Meeting_Sep2011.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/data/icd/Coordination_and_Maintenance_Committee_Meeting_Sep2012.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%26tabi%3D516&via=aoyRYODCvP9sATr-YCACw&vde=0CBgQFjAB&sig2=TE3jR6ca_tZcTVN40GLXQ&usg=AFQjCNHfRYvgNfkaOtP24WdmEFYluTPQw 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
  o 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

States that CFS is “Known internationally as Neurasthenia, may be referred to as ME”

It is not clear exactly when this was first published but it was on the May 9, 2001 version of this page.

This article by Prins had even stated, “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.

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.

  - Website - http://www.erythos.org/gibbonenquiry/Index.html

  Hooper states, that the WHO response on January 23, 2004 was that it was not allowed to have the same condition in two locations (Page 8)


This was from a Royal Society of Medicine conference on CFS. Note that White discusses classification of CFS in ICD-10, the various definitions that exist and also the view that the term ME refers to epidemics, not episodic occurrences. At minute 17:00, he discusses a collaboration done with the CDC.

A partial transcript can be found here: https://dxrevisionwatch.files.wordpress.com/2015/11/rspeterwhiteitranscript5.pdf

The agenda of the conference is here: https://meagenda.wordpress.com/2007/12/14/royal-society-of-medicine-conference-april-28/


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:

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.”


The page discusses the use of NOS in ICD-9-CM and states, “Within ICD-9-CM, you may select codes defined as “Not Otherwise Specified” (NOS) when there isn’t enough documentation to select a more specific code. In other words, a deficiency in documentation prevents you from coding to a higher level of specificity. NOS codes are never favored, and claims submitted with such diagnoses may be rejected for lack of medical necessity and/or specificity.”


Note that White discusses classification of CFS in ICD-10, the various definitions that exist and also the view that the term ME refers to epidemics, not episodic occurrences. At minute 17:00, he discusses a collaboration done with the CDC.

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The Read Codes, Clinical Terms Version 3 (CTV3) can be viewed at:

106
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.


According to this description, G93.3 only gets used when there is a viral trigger or where the symptoms do not meet Neurasthenia criteria. 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)."


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.

Note that SNOMED CT - International version at the link above originally had both Mental Health and Multi-system disease as parents for CFS. As of August 2015, the Mental Health parent was dropped. But the U.S. version still contains both. It is unclear when this will be updated.

Other sources include:


Jason noted that this “blurring of diagnostic categories” makes it harder to identify biological markers.

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.


Tuller stated that Dr. Racaniello, Higgins Professor of Microbiology & Immunology, Mt. Sinai School of Medicine of CUNY said that he would ask colleagues about CFS but they would dismiss it as not real. He said “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.” Tuller also said that he said that “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.


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.


Personal experience of these authors. A doctor at a major medical center insisted that Matthew continue to exercise even though doing so caused him to crash. Two other doctors recommended aerobic exercise and refused to even look at the results of his CPET testing that showed his aerobic energy metabolism impairment. One of those would not consider signing for him to receive a disability-parking pass until he undertook an aerobic exercise program.

The following articles speak to patient difficulties with getting treatment and are discussed more fully in the chapter on medical care.


In the second article, 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 x-ray, although he seemed most concerned with the expense of it. The x-ray showed that his lungs were full of pneumonia 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.

Many family members have reported having doctors try to convince them that the patient has a mental disorder, a problem experienced with three different doctors by this author.


Dr. Klimas’s comments were based on the following study


This article further discussed the issue of physician induced PTSD


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.”


The guidelines referred to the disease as “CFS/SEID” and stated “Chronic fatigue syndrome (CFS), also called systemic exertion intolerance disease (SEID), is a disorder that causes unexplained, persistent, and sometimes debilitating fatigue.”


The article states “The cause of CFS is unknown, but the disorder is probably an infectious disease with immunologic manifestations.”

The article also states, “Chronic fatigue syndrome (CFS) is a disorder characterized by a state of chronic fatigue that persists for more than 6 months, has no clear cause, and is accompanied by cognitive difficulties.”

Both Fukuda and the IOM criteria are provided.

One example is


This source recommends against tests because of the “absence of known biological underpinnings.”


References include:


CDC’s CFS website highlights child abuse as a risk factor, even though the study that demonstrated this was done with the Empirical definition.


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.”


This article states “Childhood trauma (for example, physical or sexual abuse) may raise the risk of getting it.”


Epocrates states that ‘psychological disturbance’ and ‘emotional instability’ are risk factors.”


For a discussion and additional references on medical education, see the chapter on Medical Care.

Examples of diagnostic recommendations in various information sources:

  
  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.

  The Appendix notes that the following conditions are not exclusionary "Fibromyalgia, anxiety disorders, somatoform disorders, nonpsychotic or nonmelancholic depression, neurasthenia, and multiple chemical sensitivity disorder."


  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."


  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."


  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."


CDC’s website does not list tilt table test. The following webinar does mention standing test but not tilt table test.


  Transcript archived – Need to click on "Continue to Activity" to see full

  The CME, developed by CDC, was released on April 19, 2013 and is valid for credit through 4/19/2014 but is still listed on the CDC website as of October 24, 2015. Note that Medscape has produced its own guideline, which is significantly different from this one. This one recommends CBT and GET while the other Medscape CFS guideline does not.

For a discussion and additional references on medical education, see the chapter on Medical Care.

The CME states: “Having patients briefly track symptoms and function in a diary may more clearly illuminate this association for the patient and the healthcare provider. Adaptive pacing therapy, cognitive behavioral therapy (CBT), or graduated exercise therapy (GET), along with specialist medical care appear to be beneficial for some patients [26].”

Reference # 26 is the PACE trial

Ibid. Chapter 4, page 5

The CME states: “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. 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 again, and so on.

The page also states “CBT is associated with significant improvement and possible full recovery from some symptoms of the syndrome. Acceptance of both the illness and particular modes of therapy positively impacted the outcome.”


As noted by ME patient and advocate Tom Kindlon, “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.” He found that 51 percent of respondents said that GET made them worse (8 surveys- 28-82%) while 20% said CBT made them worse (5 surveys – 7-38%).


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."


This page includes a link to:

  The article 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 therapy. Unlike with many other illnesses, membership in a CFS support group was associated with worse outcomes."


The article stated, "What do I do in my office? Simon Wessely and colleagues, 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."

UpToDate

  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. However, such therapy has been shown to produce harm in patients with the systemic intolerance to exercise described by the IOM report.


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,” is “stressed by her symptoms,” has had unprotected sex with numerous partners, and has gone to multiple doctors “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 patient snores and can’t stay asleep. She doesn’t abuse drugs or alcohol.

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.

See the chapter on Medical Care for a discussion on medical education literature in place before the IOM report.

Table 6

Dolan, Darrach “Beyond Tired: Is chronic fatigue syndrome a real medical condition? Yes, according to a report from the Institute of Medicine, which urges physicians to treat it accordingly.” October/November 2015; 11(5):60–63 [http://dx.doi.org/10.1097/01.NNN.0000472913.82545.7a]


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

This study was of 260 patients in the November 2008 to December 2009 timeframe. The paper evaluated patients meeting Fukuda and an alternative fatigue diagnosis, stating “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).”


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 pneumonia 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.


Other examples include:


  Auwaerter stated, “What do I do in my office? Simon Wessely and colleagues,12 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.”


  Recommends classifying CFS and its new name SEID, FM, IBS, etc. under the one diagnosis, somatic symptom disorder. States that these are all associated with fatigue and another label to replace CFS will not help. States that “All these conditions have common, overlapping features that usually consist of both fatigue and pain” and should be classified as SSD. Finally states that “these diagnoses are indistinguishable from “medically unexplained physical symptoms”


The report stated “Limited time during the clinical encounter has impaired patient/clinician communication and quality of care for patients with ME/CFS.”


The report stated, “Less than one-third of medical schools include ME/CFS-specific information in the curriculum (Peterson et al., 2013), and only 40 percent of medical textbooks include information on the disorder (Jason et al., 2010).”


The study examined the curricula of medical schools in Scotland and found that when CFS is mentioned, it is equated to “Medically Unexplained Symptoms” or “Functional Somatic Syndrome” as has been done in the planned York review of primary care interventions of “medically unexplained symptoms." When ME is mentioned, it is equated to CFS, or described as a "Somatoform Disorder.

Also see the following U.S. analyses


  This paper discussed a survey of 132 accredited U.S. medical schools, of 71 replied. Across schools, the coverage was extremely limited. The paper stated, “Only 29.6% of schools met the clinical criterion, 28.2% met the curriculum criterion, and 15% met the research criterion. Only four of the 71 (5.6%) responding schools met criteria for all three domains.”

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One example is in the reaction to CFSAC recommendations and discussions on the CFS Toolkit. 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.


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M. Dimmock mailed CDC staff a number of times to determine whether PEM was presented as a symptom of the standard patient. References for historical position include:

- U.S. Department of Health and Human Services CFS Advisory Committee. CFSAC May 22-23, 2013 meeting. [http://www.youtube.com/watch?v=VJ7VqYITsWl&list=PLr17E8KAByz1FG6lYcom0oI9a9g8-6OL&index=12](http://www.youtube.com/watch?v=VJ7VqYITsWl&list=PLr17E8KAByz1FG6lYcom0oI9a9g8-6OL&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?”

- Institute of Medicine. "Diagnostic Criteria for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome." (Activity Description) Public File requested by advocate Jennifer Spotila. The IOM public file contains the following document, 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](https://dl.dropboxusercontent.com/u/89158245/IOM%20submission%20from%20CDC%20CFS%20Case%20Definition%20Issues%20with%20Appendices%201_28_14)

  in its August 2015 meeting, CFSAC recommended that Empirical and Fukuda represent the same group of patients, as discussed elsewhere in this document. At the August 2015 CFSAC meeting in a personal conversation with this author, CDC staff indicated continued support for Empirical studies and stated that 80 percent of them have PEM (given Empirical’s prevalence of 2.5%, this would translate to about 5M adults experiencing PEM, far greater than ME prevalence estimates.)


- 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 in 2014, 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.


  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.


- Ibid. The CDC has previously rejected PEM as a distinguishing characteristic in both CFSAC discussion and in its submission to the IOM, in which CDC stated requirement for PEM was a weakness of the CCC. References for historical position include:

  • U.S. Department of Health and Human Services CFS Advisory Committee. CFSAC May 22-23, 2013 meeting. [https://dl.dropboxusercontent.com/u/89158245/IOM%20submission%20from%20CDC%20CFS%20Case%20Definition%20Issues%20with%20Appendices%201_28_14](https://dl.dropboxusercontent.com/u/89158245/IOM%20submission%20from%20CDC%20CFS%20Case%20Definition%20Issues%20with%20Appendices%201_28_14)

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Note that CDC has stated that the Empirical definition is really just an operationalization of Fukuda, meaning that it uses Fukuda's symptom criteria but uses a specific set of tools to assess those symptoms in patients. However, there are differences in some of the exclusionary diagnoses and additionally, the tools that are used have biased what patients were included.

For further information, see Appendix 2.

United States Census Bureau, National Totals: Vintage 2014
http://www.census.gov/popest/data/national/totals/2014/index.html
http://factfinder.census.gov/faces/tableservices/jsf/pages/productview.xhtml?src=bkmk

Numbers from XLS sheet “Annual estimates of the resident population.”

<table>
<thead>
<tr>
<th>Year</th>
<th>Total</th>
<th>Adults</th>
<th>Children &lt; 18</th>
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<tbody>
<tr>
<td>2014</td>
<td>318,857,056</td>
<td>241,047,848</td>
<td>77,809,208</td>
</tr>
</tbody>
</table>

1) 0.07 percent prevalence equates to 168,733 adults (Total population * prevalence)
2) 2.6 percent prevalence equates to 6,267,244 adults


Note that CDC has stated that the Empirical definition is really just an operationalization of Fukuda, meaning that it uses Fukuda’s symptom criteria but uses a specific set of tools to assess those symptoms in patients. However, there are differences in some of the exclusionary diagnoses and additionally, the tools that are used have biased what patients were included.

For more information on this topic, see the following which discuss the inflated prevalence and that 38% of patients with major depressive disorder can be given a CFS diagnosis by Fukuda.


http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1380968/

Multiple criteria were used. Prevalence was reported as Oxford - 2.2%, Fukuda - 2.6% and Holmes - 1.2%. If psychiatric comorbidity was removed, Oxford - 0.7%, Fukuda - 0.5% and Holmes - 0.1%.

United States Census Bureau, National Totals: Vintage 2014
http://www.census.gov/popest/data/national/totals/2014/index.html
and http://factfinder.census.gov/faces/tableservices/jsf/pages/productview.xhtml?src=bkmk

Numbers from XLS sheet “Annual estimates of the resident population.”

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<th>Adults</th>
<th>ME Adults (1)</th>
<th>Children &lt; 18</th>
</tr>
</thead>
<tbody>
<tr>
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<td>1,345,577</td>
<td>241,047,848</td>
<td>1,012,401</td>
<td>77,809,208</td>
</tr>
</tbody>
</table>

1) 0.422 percent prevalence equates to 1,012,401 adults (Total population * 0.422%)
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.


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.


Meeting agenda, transcript and video can be found at:


The IOM report used Jason’s 1999 study and a 2006 study as reference. The 2006 paper lists a CFS-like prevalence of 2.5M, which appears to be the source of the IOM upper limit. The paper states, “The CDC currently estimates there are up to 900,000 Americans with CFS and another 2.5 million with CFS-like illness.


The CDC CFS Toolkit has defined “CFS-like” illness as 6 months of fatigue but failing to meet the other symptom requirements for CFS.


See also


Requires login to get contact details but it appears to be the Journal of Psychotherapy and Psychosomatics


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."


See also


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.”

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


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:


These statements are made in a number of sources. One source is:


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.”

Another example is the PACE trial, which stated that a perfectionist personality is a precipitating factor for CFS.

One of the referenced studies to support this claim is:


This paper stated “Poor outcome was predicted by membership of a self-help group, being in receipt of sickness benefit, claiming a disability-related benefit, low sense of control, a strong focus on symptoms, and a pervasively passive activity pattern.”


See also Jason’s study which used stricter case selection criteria and reported that a history of abuse was not a significant predictor of this disease.


Also see


Besides the Empirical definition childhood trauma study noted above, the CDC CFS page lists a number of other studies to support this including:


The criteria used was a modification of the Fukuda criteria and required “requiring a self-report of ‘feeling tired most of the time’” plus 4 of headaches, difficulty falling asleep, backache, “rheumatism/fibrositis” and problems concentrating.


Using stricter disease criteria, Jason reported that a history of child abuse was not a significant predictor of chronic fatigue syndrome. 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.


- 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, 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.”


The story reports on work by Kerr into genomics linkage.

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"


Includes the original recommendation cited in the last reference. The website states that the Assistant Secretary of Health provided the response.


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.


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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.”


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.”

McClean, Kim. Presentation and Testimony to the U.S. Department of Health and Human Services CFS Advisory Committee. CFSC Committee Meeting. October 28, 2008. CFS Advisory Committee Website. https://wayback.archive-it.org/3919/20140324192720/http://www.hhs.gov/advcom/cfs/meetings/minutes/cfsac20081028min.pdf (page 53). McClean was the CEO of CFIDS Association of America at the time. She described CDC research as a “bung of shameful scientific leadership, zero accountability, invisible outcomes, and millions and millions of dollars stuck in suspended animation, if not wasted... only accountability contractors seem to be benefiting from millions spent for which there are no worthwhile outcomes for American taxpayers or CFS patients.


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.”


See also:


Dr. Unger stated “And I am using the term CFS but we made it clear to the clinicians participating in this study that patients that they managed as CFS or myalgic encephalomyelitis, as post-infectious fatigue, any of these synonyms or possibly related illnesses were eligible to participate.”

Post-infective fatigue (PIF) 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.

The term PIF itself is not defined and implies no duration of illness or set of specific symptoms as defined by CCC or even by Fukuda. It is unknown to what extent patients with PIF were included that would not have met definitions for CFS or ME.


The minutes state that the study has enrolled 471 CFS patients, healthy controls and ill comparison groups and included saliva for wakening cortisol profile and blood for DNA and RNA, adolescent/pediatric CFS cohort at some sites and a combined cognition and exercise study. The next stage will include severely ill patients.

No case definition is being used to guide patient selection; instead, the clinicians have been asked to use their expert judgment. They have been instructed to include patients diagnosed with CFS, ME, and also post-infective fatigue. This is potentially concerning because the terms “CFS” and “post-viral fatigue syndrome” are ill-defined, do not require hallmark symptoms, and may be used differently by different clinicians in the study. The closest case definition for post-infectious fatigue syndrome found during research for this review is 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.

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_GKtxhl#t=810 Time 4:20 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.

Spotila discusses the decision to not use the two-day exercise test to demonstrate the change in energy metabolism. The combination of a one day exercise test with cognitive testing follow-up has not to this author’s knowledge been validated in any studies.

356 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_GKtxhl#t=810 Q&A:  http://www.youtube.com/watch?v=U9D59TU-JIY  
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Dr. Lee stated, “the 2003 Canadian Consensus criteria are widely embraced by many ME/CFS experts and patients.”

358 U.S. Department of Health and Human Services CFS Advisory Committee. CFSAC May 22-23, 2013 meeting.  
https://www.youtube.com/watch?v=VI7VqYITsW&list=PLrI7BKBABz1FGfEvYcomOol9agg8-60Q&index=12 (minutes 25-45 for exchange, Minute 28:15 for quote  
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?”

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. PEM was stated as a limitation of the Canadian Consensus Criteria.  
https://dl.dropboxusercontent.com/u/89158245/IOM%20submission%20from%20CDC%20Case%20Definition%20Issues%20With%20Appendices%201-28.14-under%20NCEZID%20Review.docx


Provides NIH Estimates of funding by disease categories. Search by term chronic fatigue syndrome.


Provides NIH Estimates of funding by disease categories. Search by term chronic fatigue syndrome.
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:

<table>
<thead>
<tr>
<th>Year</th>
<th>Total NIH Budget (in M) (1)</th>
<th>Total NIH funding (in M in 1995 dollars (1, 2)</th>
<th>Total NIH spend (in M in 2014 dollars (2)</th>
<th>Total CFS funding in M as reported by NIH (3)</th>
<th>Total funding in M specifically for CFS from Fero and Spotila (4, 5)</th>
<th>Total CFS funding in M (in 1995 dollars) (2)</th>
<th>Total CFS funding in M (in 2014 dollars) (2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1987</td>
<td>$6,685</td>
<td>$8,968(2)</td>
<td>$13,931</td>
<td>$0.78</td>
<td>$1.1</td>
<td>$1.6</td>
<td></td>
</tr>
<tr>
<td>1988</td>
<td></td>
<td>$0.99</td>
<td></td>
<td></td>
<td>$1.3</td>
<td>$2.0</td>
<td></td>
</tr>
<tr>
<td>1989</td>
<td></td>
<td>$1.48</td>
<td></td>
<td></td>
<td>$1.8</td>
<td>$2.8</td>
<td></td>
</tr>
<tr>
<td>1990</td>
<td></td>
<td>$1.82</td>
<td></td>
<td></td>
<td>$2.1</td>
<td>$3.3</td>
<td></td>
</tr>
<tr>
<td>1991</td>
<td></td>
<td>$2.86</td>
<td></td>
<td></td>
<td>$3.8</td>
<td>$5.9</td>
<td></td>
</tr>
<tr>
<td>1992</td>
<td></td>
<td>$3.49</td>
<td></td>
<td></td>
<td>$3.8</td>
<td>$5.9</td>
<td></td>
</tr>
<tr>
<td>1993</td>
<td></td>
<td>$5.75</td>
<td></td>
<td></td>
<td>$7.37</td>
<td>$7.4</td>
<td>$11.5</td>
</tr>
<tr>
<td>1994</td>
<td></td>
<td>$6.18</td>
<td></td>
<td></td>
<td>$7.4</td>
<td>$11.5</td>
<td></td>
</tr>
<tr>
<td>1995</td>
<td>$11,300 (1)</td>
<td>$11,300 (2)</td>
<td>$17,533</td>
<td>$7.37</td>
<td>$7.4</td>
<td>$11.5</td>
<td></td>
</tr>
</tbody>
</table>

Note that the 400,000 estimate of prevalence is based on a 2002 initiative by the Society that used 2000 census data.


Based on a study by Buescher in 2014, autism spectrum is estimated at 3.5M Americans. This is significantly raised over earlier estimates.

As reported above, the IOM gave a prevalence of 1-2.5M. But this paper uses a prevalence of 1M because the 2.5 M appears to be based on "CFS-like" illness.

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:
<table>
<thead>
<tr>
<th>Year</th>
<th>Budget (1)</th>
<th>Budget (2)</th>
<th>Budget (3)</th>
<th>Budget (4)</th>
<th>Budget (5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1996</td>
<td>$12,740</td>
<td>$12,097</td>
<td>$18,791</td>
<td>$6.57</td>
<td>$6.3</td>
</tr>
<tr>
<td>1997</td>
<td>$15,000 (1-est)</td>
<td>$13,721 (2)</td>
<td>$21,315</td>
<td>$6.89</td>
<td>$6.3</td>
</tr>
<tr>
<td>1998</td>
<td>$18,000 (1-est)</td>
<td>$15,930 (2)</td>
<td>$24,746</td>
<td>$5.8</td>
<td>$4.3 (4)</td>
</tr>
<tr>
<td>1999</td>
<td>$27,067 (1)</td>
<td>$22,419 (2)</td>
<td>$34,825</td>
<td>$6.9</td>
<td>$4.4 (4)</td>
</tr>
<tr>
<td>2000</td>
<td>$35,745 (1-with ARRA)</td>
<td>$39,444 (2)</td>
<td>$39,311</td>
<td>$6.2</td>
<td>$4.2 (5)</td>
</tr>
<tr>
<td>2001</td>
<td>$36,209 (1-with ARRA)</td>
<td>$31,820 (2)</td>
<td>$30,070</td>
<td>$3.5</td>
<td>$3.7 (5)</td>
</tr>
<tr>
<td>2002</td>
<td>$29,151 (1)</td>
<td>$19,071 (2)</td>
<td>$29,624</td>
<td>$4.5</td>
<td>$5.0 (5)</td>
</tr>
<tr>
<td>2003</td>
<td>$30,070 (1)</td>
<td>$19,358 (2)</td>
<td>$30,070</td>
<td>$5.4</td>
<td>$3.5</td>
</tr>
<tr>
<td>Total 1987-2014</td>
<td>$139.5 (avg: $5.0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2014 increase over 1999 (*)</td>
<td>100%</td>
<td>41%</td>
<td>41%</td>
<td>-22%</td>
<td>-44%</td>
</tr>
<tr>
<td>2014 increase over 1995</td>
<td>166%</td>
<td>71%</td>
<td>72%</td>
<td>-27%</td>
<td>-53%</td>
</tr>
</tbody>
</table>

* Calculated as (2014 budget – 1999 budget)/1999 budget. Increase over 1995 calculated same way

http://www.faseb.org/portals/2/PDFs/opa/NIH%20Grant%20Slideshow.pptx

   o 2009 and 2010 include the Supplemental Appropriation (ARRA).
   o 1987 and 1997 figures from

http://www.fasebj.org/content/12/14/1431.long

http://146.142.4.24/cgi-bin/cpicalc.pl and http://data.bls.gov/cgi-bin/cpicalc.pl

Sources:


http://www.investinme.org/Documents/NIH/Pat%20Fero%20CFSAC%20Oct%202010%20NIH%2

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)

<table>
<thead>
<tr>
<th>Year</th>
<th>New Studies</th>
<th>New Funding</th>
<th>Renewed Studies</th>
<th>CFS Centers Renewals</th>
<th>Renewal Funding</th>
<th>Total Funding</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>2</td>
<td>$863,805</td>
<td>6</td>
<td>14</td>
<td>$3,414,202</td>
<td>$4,278,007 (*)</td>
</tr>
<tr>
<td>2001</td>
<td>3</td>
<td>$676,220</td>
<td>6</td>
<td>14</td>
<td>$3,876,723</td>
<td>$4,552,943</td>
</tr>
<tr>
<td>2002</td>
<td>1</td>
<td>$329,987</td>
<td>7</td>
<td>12</td>
<td>$4,269,156</td>
<td>$4,599,143</td>
</tr>
<tr>
<td>2003</td>
<td>3</td>
<td>$1,188,270</td>
<td>8</td>
<td>Discontinued</td>
<td>$2,034,241</td>
<td>(3,222,511)</td>
</tr>
<tr>
<td>2004</td>
<td>1</td>
<td>$255,301</td>
<td>9</td>
<td></td>
<td>$2,667,530</td>
<td>$2,922,831</td>
</tr>
<tr>
<td>2005</td>
<td>1</td>
<td>$641,703</td>
<td>6</td>
<td></td>
<td>$2,344,369</td>
<td>$2,986,072</td>
</tr>
<tr>
<td>2006**</td>
<td>6</td>
<td>$1,736,061</td>
<td>4</td>
<td></td>
<td>$2,270,107</td>
<td>$4,006,168</td>
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<tr>
<td>2007</td>
<td>3</td>
<td>$809,875</td>
<td>9</td>
<td></td>
<td>$3,283,159</td>
<td>$4,039,034</td>
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<tr>
<td>2008</td>
<td>3</td>
<td>$795,041</td>
<td>5</td>
<td></td>
<td>$1,734,886</td>
<td>$2,529,927</td>
</tr>
<tr>
<td>2009</td>
<td>2</td>
<td>$355,600 ($1,037,421)</td>
<td>8</td>
<td></td>
<td>$2,852,214</td>
<td>$3,187,814</td>
</tr>
<tr>
<td>Totals</td>
<td>24</td>
<td>$7,631,863 ($8,333,684)</td>
<td>8</td>
<td></td>
<td>$28,746,585 ($29,934,857)</td>
<td>$36,378,448 ($38,268,541) (*)</td>
</tr>
</tbody>
</table>

Note: The original document had 4,278,005 in the first row and the total is 2 less. Corrected here.

4) Estimates for 2009 – 2013:

- 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.

5) Additional information on the grants given out by NIH between 1999 and 2005 can be found here:


See chapter on Research and Drug Development. Contains a discussion of the NIH spend over the years, including a discussion on budget siphoned off to other diseases.

Note that different groups have done similar analyses and found similar results. This includes Jennifer Spotila who found 18% spent on other diseases in 2012, a 2004 report by the CFIDS Association that showed about 20% being spent on other diseases between 1999 and 2003 and a report by advocates Pat Fero and Charlotte von Salis that showed similar redirection between 2000 and 2009

http://www.lawyersweekly.ca/articles/2414


- Website - http://erythos.com/gibsonenquiry/Index.html Includes index of materials
- Evidence Review created by BRAME

http://www.mrc.ac.uk/documents/pdf/cfsme-current-projects/

Also see


Dr. Neil Abbott of ME Research UK (a U.K. ME charity) told advocate Craig Maupin of CFIDS Report that the Medical Research Council (MRC) had rejected 30 applications for biomedical research prior to 2008.


Countess of Mar noted, “Funding for biological causes and treatments is miniscule against the funding for psychiatric or psychological ones.”


In response to the 2014 CFSA recommendation for an RFA, 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.

The response also stated, “Given the current limited researcher pool, a complementary approach might be to stimulate and enhance the base of ME/CFS investigators who can successfully compete for an NIH award.”

Both advocates and CFSAC have historically raised this issue of the inadequate expertise of SEP members. 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 six, three were focused on behavioral issues. Dr. Ronald Glaser raised similar issues at 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 wasn’t emphasizing too early because of the nature of the study sections.

See also


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.”

NIH uses an ad-hoc Special Emphasis Panel, created anew for each review cycle, to review grants prior to passing them onto the relevant institutes for the final decision on funding. Historically, the SEP was composed of dentists and other who didn’t understand the disease. That problem appears to be less of an issue now although there are still reports of reviewers having misconceptions of the disease. The other issue is that researchers have said that SEP members raise one set of issues one time but the next SEP has different members who raise different concerns making it difficult for those submitting grants to get their grants approved.

See also


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 applications?”


Dr. Kitt stated, “A standing committee usually reviews about 60-100 applications in a study section. CSR has 240 study sections and about 1,000 SEPs. The current number of CFS applications would not support a standing committee.”


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.”


See discussion on the SEPs in chapter on Research and Development.


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.”


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.”


RFA announced in 2005 and awarded in 2006. See the following for the grants made


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.”


Discussion with Dr. Hanna of NIH on an RFA.

- 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.”

- The meeting that Dr. Hana referred to was the 2011 SOK


Appendix A provided a list of recommendations provided by CFSAC to HHS. This included 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)


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 she had submitted it 6 times to funding agencies and it has not been funded. 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 no a brainer. Of course, it’s 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. You are 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 biology response modifier that blocks IL-1. That makes so much sense, it exists, it’s FDA approved. I am not allowed to touch it.”


and [https://bos.etapstry.com/prod/viewEmailAsPage.do?databaseId=OMF&emailingId=29383841&personaRef=4933.0.8730658&jobRef=773.0.42856511&memberId=943741295&erRef=4933.0.8730656&key=1fc21404e94814e873e85323bf4d4]


- One reason recommended that Davis “narrow the focus of the application to focus on the very ill population” to which Davis replied that the application already was focused on the most severely ill.

Also see:


407 Ibid.

408 Ibid.

409 Ibid.


- The letter questioned whether this was in NINDS’ purview since there was “no mention of collection of CSF or of analysis of cognitive or other nervous system function.” Davis’s response was that these were severely ill, bedbound patients and collection of CSF was not appropriate and that further, blood markers of a neurological disease was more appropriate.

Also see:


130
The recommendation states “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.

Congressional letter to Dr. Collins for an RFA from 11 congressional leaders, spearheaded by Representatives Lofgren and Eshoo. March 19, 2014.
https://dl.dropboxusercontent.com/u/89158245/Dr%20Collins%20to%20Lofgren%20letter%20April%2016%202014.pdf

Collins response to the Eshoo letter
https://dl.dropboxusercontent.com/u/89158245/Dr%20Collins%20to%20Lofgren%20letter%20April%2016%202014.pdf

A second letter was sent from just Congresswoman Lofgren to Dr. Collins on July 29, 2014 iterating the need for an RFA and asking for transparency on the P2P workshop.

https://dl.dropboxusercontent.com/u/89158245/Dr%20Collins%20to%20Lofgren%20letter%20July%2029%20%202014.pdf

https://dl.dropboxusercontent.com/u/89158245/Dr%20Collins%20to%20Lofgren%20Ltr%20August%202011.pdf


https://dl.dropboxusercontent.com/u/89158245/Dr%20Collins%20to%20Lofgren%20letter%20April%20%202014.pdf

Recommendations from CFSAC to Secretary Burwell and HHS’s response

http://www.hhs.gov/advcomcfs/recommendations/06142014.html

The CFSAC recommendation stated:
“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.”

• Response to Dr. Levine from Secretary Burwell Health and Human Services. “Responses to Recommendations from the Chronic Fatigue Syndrome Advisory Committee Ref: June 16-17, 2014, CFSAC Meeting.” October 29, 2014.

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.

The response also stated, “Given the current limited researcher pool, a complementary approach might be to stimulate and enhance the base of ME/CFS investigators who can successfully compete for an NIH award.” While its admittedly necessary to attract new researchers, the problem is not lack of people capable of submitting quality grants as the refusal of Ron Davis’s grants show.


Current ME and ME/CFS research/clinical centers include but are not limited to: Dr. Peterson’s Simmaron Research in Incline Village, Dr. Montoya’s ME/CFS initiative at Stanford, the Hutchins family Chronic fatigue initiative in New York, Dr. Klimas’s Neuro-immune institute in Florida, Dr. Kogelnik’s Open Medicine Institute in California, Dr. Lucinda Bateman’s Bateman Horne Center in Utah, Enlander’s Mt Sinai ME/CFS Center, Dr. Lipkin’s Chronic Fatigue Syndrome program at Columbia, Dr. Snell’s and Staci Stevens Foundation and Dr. Ron Davis’s End ME/CFS Project.


This study was picked up by the Science Daily and mainstream media. Two examples include:


“The End ME/CFS Project.” The Open Medicine Foundation. Last accessed February 3, 2015. http://www.openmedicinefoundation.org/the-end-mefs-project/ and https://bos.etapesty.com/prod/viewEmailAsPage.do?databaseId=OMF&emailId=29383841&personaRef=4933.0.8730658&jobRef=773.0.42856511&memberId=493741295&erRef=4933.0.8730656&key=1f1c2140e9481e4c873e85323bf4d4

Institute for Neuro Immune Medicine. NOVA Southeastern University. http://www.nova.edu/nim/


The response to therapy is typically delayed for a number of months after the beginning of treatment. This delayed response to Rituximab is more indicative of an autoimmune response, in which time is required to deplete the antibodies.


PET is positron emission tomography, which uses imaging techniques to show functional processes.

It’s important to note the findings of early studies. As noted in the text, Ramsay suggested it could be an abnormal immunological response to a pathogen. Examples include:


The two doctors at Incline Village ordered 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,329 which led Cheney and Peterson to question whether the illness involved immunodeficiency or general immune dysfunction.

- Ramsay AM, Rundle A. “Clinical and biochemical findings in ten patients with benign myalgic encephalomyelitis.”
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.”


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.”

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In public comment submitted to the P2P initiative, the IACFS/ME discussed NIH’s refusal to implement a specific CFSAC recommendation and stated, “The essential message conveyed is that the US government does not want to invest additional funds because not enough is known about the disease and there are not enough researchers. Yet a critical reason why we have a dearth of researchers and knowledge is because of the poor funding situation, which has endured for the past 3 decades.”


This article includes a link to an August 17, 2015 letter from 27 disease experts stating their interest in research in this disease. [http://news.sciencemag.org/sites/default/files/ScientistLetterAugust179am.pdf](http://news.sciencemag.org/sites/default/files/ScientistLetterAugust179am.pdf)

The letter stated, “Many of us have had a very difficult time securing adequate funding. Others have been unable to determine even how to apply for funding as no institute within the NIH has responsibility for researching ME/CFS. The NIH has responded to requests for increased funding by stating that few researchers are interested in studying the illness.”

The letter went on to state, “ME/CFS is massively underfunded compared to other diseases of similar severity and number of patients... It is imperative to increase research funding for ME/CFS. If invited to apply for NIH funding via a new Request for Applications (RFA), we would eagerly submit grant proposals.”


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


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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.

Also see


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, 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.


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

The funding announcement lists the particular priority or interest of each of the institutes, offices, and centers that are participating in the funding opportunity. For instance, 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.

NINDS said “NINDS is particularly interested in encouraging multi-PI interdisciplinary research directed at the pathogenesis of ME/CFS affecting the brain, autonomic, and the peripheral nervous system. Examples of topics for which there are gaps in knowledge and research opportunities are: 1. Differences in CNS-related biomarkers between new onset and established ME/CFS patients and appropriate comparison groups. 2. Identification of biomarkers in cerebrospinal fluid, blood, urine, etc. that can identify physiologically relevant subgroups of ME/CFS. 3. Studies elucidating the characteristic autonomic abnormalities seen in the central or peripheral nervous system of patients with ME/CFS.”


Of the $815K funded between 2009 and 2013, 81 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.” According to the grant announcement in the previous footnote, this institute withdrew its support of this grant in 2014 along with 3 other institutes

- Pain and Sensory Processing in IC/PBS and Fibromyalgia. Williams, David. $328,680. 2009, Proj# 5U01DK082345-02
- Pain and Sensory Processing in IC/PBS and Fibromyalgia. Williams, David. $328,680. 2010, Proj# 5U01DK082345-03
- Neural mechanism of glucagon-like-peptide-1 receptor-mediated nausea/malaise. Hayes, M. $80,000. 2012. Proj# 1R03DK093874-01

Ibid.

NIAID only said “The NIAID will not support clinical trials under this Program Announcement. Applicants interested in conducting clinical trials relevant to the mission of NIAID are encouraged to review NIAID’s Policy on Investigator-Initiated Clinical Trials…”


Collins presentation at minute 8:30 on their overall efforts at stewardship and the development of the cross-institute strategic plan.
Senator Cassidy at 1:12:00 – he asked about the document due in December 2015 that would address rebalancing spending priorities and how NIH makes funding decisions within and across portfolios


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:


The response 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 on ME/CFS coordinated by the NIH Office of Disease Prevention.”


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.”

Note that while NIH has claimed extensive input of disease experts and patients, the reality is far different. One strong case in point is that the community submitted hundreds of comments on the Draft P2P report and yet, very few changes were made as a result of those suggestions. Another example is the extensive feedback that was received on the AHRQ Evidence Review and yet there was little change. Finally, NIH’s response to CFSAC recommendations reflects an agency that is not listening to the community.

NIH has held a number of workshops on CFS. These include:

<table>
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<tr>
<th>Workshop</th>
<th>Description</th>
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<tr>
<td>1985 First NIH conference on CFS Held by NIAID</td>
<td>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.”</td>
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<tr>
<td>Conference/Consultation</td>
<td>Purpose</td>
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| 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. Led to loosening of the disease boundaries and greater overlap with mental illness as described by Dr. Wedner in the chapter on CFS.  
| 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 from CFIDS Association of America  
| 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; 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  
- CFIDS Association of America Summary  
Examples include:


  This conference was initially designed to include just 4 participants - 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 Lilly. At least Dr. Straus, Professor Wessely, and Professor Sharpe promoted the biopsychosocial view of the disease. Advocates objected and disease experts were invited to observe and the panel was expanded. None of the panel was disease experts.


  Also see the following, which summarize the findings and the needs. The majority of these have not been acted on.

    The report stated that a number of critical needs including the need for a single research case definition and 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.”

    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.

http://www.occupycfs.com/2014/06/02/collins-please-cancel-p2p/

The P2P Workshop agenda included sessions on "social determinants of health" and "self management" but did not to include sessions on PEM, autonomic dysfunction and neurological impairment. The full letter submitted to Dr. Collins on May 28, 2014 details the full set of concerns and can be found at:  

Also see comments from Solve ME/CFS Initiative regarding the P2P initiative  


The report stated, "Many of the observations highlighted in the draft executive summary support recommendations made to the Secretary by this Committee. (See Appendix A)."  
Appendix A provided a list of recommendations provided by CFSAC to HHS that targeted the same needs identified by P2P.

A partial list of CFSAC recommendations and the dates included are:  
- 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 out dated 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)


The 2000 workshop sponsored by the predecessor to CFSAC,459 the 2001 AHRQ Evidence Review,459 and the 2003 NIH workshop459 had also discussed the issues with patient selection in research  

  - This paper summarized future research needs to include “How should CFS be defined such that the definition is reliable, valid, discriminatory from related conditions, and acceptable to both the lay and scientific community?”


Also see


Kweder said “One of the things that we've learned from experience is you've got to be able to define the condition well and they need to - they want to know where are the rules about studying it. What am I going to have to show in order to
get a drug approved? Because I don’t want to invest in a drug that I’m ultimately not going to get approved for marketing. That’s not good business for me.”

See also: FDA’s director Janet Woodcock made similar comments

Woodcock stated that the lack of clarity on endpoints and patient selection creates challenges in drug development.

http://www.pharmexec.com/race?id=&sk=&date=&pageID=2


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 exist 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?”


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.”

http://www.fda.gov/Drugs/NewsEvents/ucm370166.htm and

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)

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.


Relevant sources for the Ampligen review include:

www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/UCM345463.pdf


http://www.fda.gov/Drugs/NewsEvents/ucm337750.htm

FDA’s notification to the public at the time of the Response Letter to Hemispherix.


Provides a summary of the trials conducted starting in 1990 and transfers across divisions of FDA
Hunter

Relevant sources for the Ampligen review include:


FDA’s notification to the public at the time of the Response Letter to Hemispherix.


- Provides a summary of the trials conducted starting in 1990 and transfers across divisions of FDA


- Dr. Lapp, whose site this is, is one of the doctors providing Ampligen on a cost recovery basis. This site describes the infusion schedule and the costs, stating, "The cost of Ampligen is about $150 per dose, or $1200 per month. Infusion costs, medical visits, and laboratory add approximately $1000 monthly, thus the total cost may exceed two thousand dollars per month."


- Cost of drug increasing from an estimated $15,600 to $41,600 annually. Other infusion costs above and beyond that.


- FDA page of activities related to ME and CFS including the two-day conference in 2013. The meeting agenda, transcript and video can be found at:


  - "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.


The IOM report noted “a diagnosis of CFS is not equivalent to a diagnosis of ME.”


One example is ChampVA which denies all coverage if CFS is the only diagnosis.


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.

Swiss Re. “Managing claims for chronic fatigue the active way.” Swiss Re. September 11, 2012 (date listed in index of searched items). Last accessed October 11, 2015.

http://www.swissre.com/clients/newsletters/Managing_claims_for_chronic_fatigue_the_active_way.html

The article discusses the issue of whether “CFS would fall in a mental health exclusion” and states that depends on the wording. The article states, “If the policy refers to functional somatic syndromes in addition to mental health, then CFS may fall within the exclusion.” The document went on to state that ME is “considered a neurological condition” according to the ICD whereas “CFS can alternatively be defined as neurasthenia, which is in the mental health chapter of the ICD10.”

Swiss RE removed this page sometime in December 2015 following the release of the following article by Tuller, discussing the Swiss RE article in his series on the PACE trial.


A copy of the original Swiss RE document can be found here.


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.”

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.
• 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/cfsc_min-11092011.pdf] (Page 25)

Also see:


Swain, Gill. "Trapped in bed for 14 years with chronic fatigue." Daily 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.”

[http://informahcarehealthcare.com/doi/abs/10.1300/1092v13n02_02]


Other stories that cover the March 2014 decision to grant permanent custody to the state


Decision to release Justina in June 2014.


The report noted lack of coordination and lack of impact on direction of research at CDC and NIH, stating “Overall, however, CFSCC has made only limited progress in meeting the goals established by the Secretary to better coordinate CFS efforts. For example, CFSCC has not been a particularly useful forum for developing complementary research programs. 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.”

143
For instance, as noted in the discussion on research and the NIH, there has been evidence for NK Cell function as a biomarker going back to the 1980s. Given the importance of establishing a biomarker, this should have been followed up.


See the Chapter on HHS Commitment and Engagement. The recommendations include the following:

- Case Definition: (Dated recommended: 10/09, 10/12, 3/14, 8/15)
- 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, 8/15)
- 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, 8/15)
- 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, 8/15 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)
- Funding commensurate with burden and prevalence

Also see:

- CFSAC has had numerous discussions on medical education and the CDC website. These include:
  - U.S. Health and Human Services Advisory Committee. CFS Advisory Committee Meeting, November 9, 2011. Last accessed August 31, 2015. http://www.hhs.gov/advcomcfs/meetings/minutes/cfsac_min-11092011.pdf - Page 15. Discussion of a set of teleconferences to update the CDC CFS website. CFSAC members stated that there was good information on the site but also harmful information.


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.”


In November of 2011, Dr. Klimas told NIH’s Dr. Cheryl Kitt, Deputy Director of the Center for Scientific Review, “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.”


Note that the list was to be updated with new recommendations but it has not been updated since it was originally approved.


Also see:
  - Videos – see “IOM P2P Report and Discussion” https://www.youtube.com/playlist?list=PLr7E8KAbz1GQ61Y44NmuLjJj9jXk2MqA
  - Minutes – not available as of August 28, 2015
  - Recommendations – not available as of August 28, 2015


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.


A number of these patient led initiatives are covered in this paper and range from medical education, to funding for research, the definitional issues including widespread support for the adoption of the Canadian Consensus Criteria and also issues with the execution of the AHRQ Evidence Review.

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. Jeannette Burmeister’s FIOA lawsuit against U.S. Department of Health and Human Services.


Letter from Dr. Howard Koh, Assistant Secretary for Health to patient advocates in response to a 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 concerns 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’s General Counsel and a followup letter after Dr. Koh failed to address the allegations of intimidation.

The patient community rewrote 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


This report includes extracts of the requests made in reports accompanying the appropriations bills from 1995 to 2013 and also requests from 1988 to 2000 as reported in the 2000 GAO report.

Ibid.


“The Committee commends NIH for holding a state of the knowledge workshop on CFS in 2011. Within 1 year following that 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.

NIH’s response to this request is on slide 39.

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:

<table>
<thead>
<tr>
<th>Year</th>
<th>Total NIH Budget (in M)</th>
<th>Total NIH funding (In 1995 dollars)</th>
<th>Total NIH Spend (in 2014 dollars)</th>
<th>Total CFS funding as reported by NIH</th>
<th>Total CFS funding specifically for CFS from Fero and Spotila</th>
<th>Total CFS funding (in 1995 dollars)</th>
<th>Total CFS funding (in 2014 dollars)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1987</td>
<td>$6,685</td>
<td>$8,968 (2)</td>
<td>$13,931</td>
<td>$0.78</td>
<td>$1.1</td>
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<td>$0.99</td>
<td></td>
<td>$1.3</td>
<td>$2.0</td>
<td></td>
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<tr>
<td>1989</td>
<td></td>
<td></td>
<td>$1.48</td>
<td></td>
<td>$1.8</td>
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<td></td>
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<tr>
<td>1990</td>
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<td>$1.82</td>
<td></td>
<td>$2.1</td>
<td>$3.3</td>
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<tr>
<td>1991</td>
<td></td>
<td></td>
<td>$2.86</td>
<td></td>
<td>$3.8</td>
<td>$5.9</td>
<td></td>
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<tr>
<td>1992</td>
<td></td>
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<td>$3.49</td>
<td></td>
<td>$3.8</td>
<td>$5.9</td>
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<tr>
<td>1993</td>
<td></td>
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<td>$5.75</td>
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<td>$3.8</td>
<td>$5.9</td>
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<td>1995</td>
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<td>$7.4</td>
<td>$11.5</td>
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<td>$6.57</td>
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<td>$6.3</td>
<td>$9.9</td>
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<tr>
<td>1997</td>
<td>$12,740 (1)</td>
<td>$12,097 (2)</td>
<td>$18,791</td>
<td>$6.68</td>
<td>$6.3</td>
<td>$9.8</td>
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<tr>
<td>1998</td>
<td></td>
<td></td>
<td>$6.79</td>
<td></td>
<td>$6.3</td>
<td>$9.8</td>
<td></td>
</tr>
<tr>
<td>1999</td>
<td>$15,000 (1-est)</td>
<td>$13,721 (2)</td>
<td>$21,315</td>
<td>$6.89</td>
<td>$6.3</td>
<td>$9.8</td>
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<tr>
<td>2000</td>
<td>$18,000 (1-est)</td>
<td>$15,930 (2)</td>
<td>$24,746</td>
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<td>$5.1</td>
<td>$8.0</td>
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<tr>
<td>2001</td>
<td></td>
<td></td>
<td>$5.8</td>
<td></td>
<td>$5.0</td>
<td>$7.8</td>
<td></td>
</tr>
<tr>
<td>2002</td>
<td></td>
<td></td>
<td>$7.2</td>
<td></td>
<td>$6.1</td>
<td>$9.5</td>
<td></td>
</tr>
<tr>
<td>2003</td>
<td>$27,067 (1)</td>
<td>$22,419 (2)</td>
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<td>$5.7</td>
<td>$8.9</td>
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<tr>
<td>2004</td>
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<td></td>
<td></td>
<td></td>
<td>$6.4 (4)</td>
<td></td>
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<tr>
<td>2005</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>$5.0 (4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2006</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>$4.3 (4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2007</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>$3.6 (4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2008</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>$4.1 (4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2009</td>
<td>$35,745 (1-with ARRA)</td>
<td>$39,444</td>
<td>$4.8</td>
<td>$3.9 (4)</td>
<td>$3.4 (5)</td>
<td>$5.3</td>
<td></td>
</tr>
<tr>
<td>2010</td>
<td>$36,209 (1-with ARRA)</td>
<td>$39,311</td>
<td>$6.2</td>
<td>$4.2 (5)</td>
<td>$4.3 (5)</td>
<td>$6.7</td>
<td></td>
</tr>
<tr>
<td>2011</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>$6.3 (5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2012</td>
<td>$30,860 (1)</td>
<td>$20,484 (2)</td>
<td>$31,820</td>
<td>$4.5</td>
<td>$3.0 (5)</td>
<td>$4.6</td>
<td></td>
</tr>
<tr>
<td>2103</td>
<td>$29,151 (1)</td>
<td>$19,071 (2)</td>
<td>$29,624</td>
<td>$5.1</td>
<td>$3.3 (5)</td>
<td>$5.2</td>
<td></td>
</tr>
<tr>
<td>2014</td>
<td>$30,070 (1)</td>
<td>$19,358 (2)</td>
<td>$30,070</td>
<td>$5.4</td>
<td>$3.5 (5)</td>
<td>$5.4</td>
<td></td>
</tr>
<tr>
<td>Total 1987-2014</td>
<td></td>
<td></td>
<td>$139.5 (avg: $5.0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2014 increase over 1999(*)</td>
<td>100%</td>
<td>41%</td>
<td>41%</td>
<td>-22%</td>
<td>-44%</td>
<td>-45%</td>
<td></td>
</tr>
<tr>
<td>2014 increase over 1995</td>
<td>166%</td>
<td>71%</td>
<td>72%</td>
<td>-27%</td>
<td>-53%</td>
<td>-53%</td>
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</tr>
</tbody>
</table>
   http://www.faseb.org/Portals/2/PDFs/opa/NIH%20Grant%20Slideshow.pptx
   o 2009 and 2010 include the Supplemental Appropriation (ARRA).
   o 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%202015-pager.pdf
   o 1987 and 1997 figures from
     http://www.fasebj.org/content/12/14/1431.long
   http://146.142.4.24/cgi-bin/cpicalc.pl and http://data.bls.gov/cgi-bin/cpicalc.pl
8) Sources:
      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”
      http://report.nih.gov/categorical_spending.aspx and
9) Pat Fero. “Inadequate National Institutes of Health funding for New Chronic Fatigue Syndrome grants.”
   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 $4.3M. 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)

<table>
<thead>
<tr>
<th>Year</th>
<th>New Studies</th>
<th>New Funding</th>
<th>Renewed Studies</th>
<th>CFS Centers Renewals</th>
<th>Renewal Funding</th>
<th>Total Funding</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2000</td>
<td>2</td>
<td>$863,805</td>
<td>6</td>
<td>14</td>
<td>$3,414,202</td>
<td>$4,278,007 (*)</td>
</tr>
<tr>
<td>2001</td>
<td>3</td>
<td>$676,220</td>
<td>6</td>
<td>14</td>
<td>$3,876,723</td>
<td>$4,552,943</td>
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<tr>
<td>2002</td>
<td>1</td>
<td>$329,987</td>
<td>7</td>
<td>12</td>
<td>$4,269,156</td>
<td>$4,599,143</td>
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<tr>
<td>2003</td>
<td>3</td>
<td>$1,188,270</td>
<td>8</td>
<td>Discontinued</td>
<td>$2,034,241</td>
<td>$3,222,511</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>($3,222,511)</td>
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<tr>
<td>2004</td>
<td>1</td>
<td>$255,301</td>
<td>9</td>
<td></td>
<td>$2,667,530</td>
<td>$2,922,831</td>
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<tr>
<td>2005</td>
<td>1</td>
<td>$641,703</td>
<td>6</td>
<td></td>
<td>$2,344,369</td>
<td>$2,986,072</td>
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<tr>
<td>2006**</td>
<td>6</td>
<td>$1,736,061</td>
<td>4</td>
<td></td>
<td>$2,270,107</td>
<td>$4,006,168</td>
</tr>
</tbody>
</table>

147
<table>
<thead>
<tr>
<th>Year</th>
<th>Grant Count</th>
<th>Amount</th>
<th>CFS Count</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>2007</td>
<td>3</td>
<td>$809,875</td>
<td>9</td>
<td>$3,283,159</td>
</tr>
<tr>
<td>2008</td>
<td>3</td>
<td>$795,041</td>
<td>5</td>
<td>$1,734,886</td>
</tr>
<tr>
<td>2009</td>
<td>2</td>
<td>$355,600</td>
<td>($1,037,421)</td>
<td>8</td>
</tr>
<tr>
<td>Totals</td>
<td>24</td>
<td>$7,631,863</td>
<td>($8,333,684)</td>
<td>$28,746,585</td>
</tr>
</tbody>
</table>

Note: The original document had 4,278,005 in the first row and the total is 2 less. Corrected here.

10) Estimates for 2009 – 2013:

http://www.occupycfs.com/2013/05/15/2012-nih-spending-on-cfs-studies/

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 related to CFS.

- 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.  


See chapter HHS’s Commitment and Engagement


Excellent series that covers many facets of NIH approach to CFS 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

http://www.hhs.gov/advcomcfs/meetings/minutes/cfsac060717_min.html (page 18)

Dr. Hanna’s presentation - https://waybackarchive-it.org/3919/20140324192720/http://www.hhs.gov/advcomcfs/meetings/presentations/presentation060717_ppt.ppt

Page 10

Current centers will be funded until they close out their critical activities; they have been encouraged to submit RO1’s.”


http://www.cfdsreport.com/Articles/NIH/NIH_CFS_2.htm

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.”

According to a 1999 NIAID press release, the first-year cost for three centers at that time was $1.9 million. The estimated NIH budget at the time was probably around $25 billion, based on the available information


https://dl.dropboxusercontent.com/u/89158245/Congressional%20Requests%20for%20MECF5.pdf

This report includes extracts of the requests made in reports accompanying the appropriations bills from 1995 to 2013 and also requests from 1988 to 2000 as reported in the 2000 GAO report.


Report on accommodations for live streaming secured for the MAME organization.

Also see:


• 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;h7dc4326.9910D


Senators Richard Blumenthal, Robert Casey, and Kay Hagan wrote a letter to HHS in support of this meeting.


Spotila investigated a FACA violation in which NIH staff changed six medical education recommendations approved at the March 2014 CFSAC meeting by eliminating the requirement for compliance with the Canadian Consensus Criteria

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


In 2013, HHS requested that CFSAC work in workgroups to develop fuller recommendations that would have a better change of approval. To date, substantial effort has been put into medical education recommendations and a recommendation for a data-sharing platform. Neither was advanced by HHS.


http://www.hhs.gov/advcomcfs/recommendations/06142014.html
Letter from Dr. Howard Koh, Assistant Secretary for Health to patient advocates in response to a June 12, 2013 request to the General Counsel that he investigate allegations of intimidation. October 31, 2013

Dr. Collins response to Lofgren et al never mentioned the RFA:
https://dl.dropboxusercontent.com/u/89158245/Dr%20Collins%20to%20Lofgren%20letter%20April%2016%202014.pdf

Lofgren et al sent a second letter on July 29, 2014 to follow up on the RFA and share advocacy concerns about the P2P. Collins response was:

Includes the original recommendation “Allocating specific funds to study patients with ME/CFS from past cluster outbreaks.”

http://www.paloaltoonline.com/morguepdf/2015/2015_07_10.paw.section1.pdf and

Also see

https://www.washingtonpost.com/national/health-science/with-his-son-terribly-ill-a-top-scientist-takes-on-chronic-fatigue-syndrome/2015/10/05/c5d6189c-4041-11e5-8d45-d815146f81fa_story.html

https://dl.dropboxusercontent.com/u/89158245/Dr%20Collins%20to%20Lofgren%20letter%20April%2016%202014.pdf

Dr. Collins acknowledged that “one of the troubling issues in this research field is the use of multiple case definitions, which may contribute to inconsistent inclusion criteria and outcome results” and stated that the intent was to hold the Pathways to Prevention Workshop to “get ME/CFS researchers working together on this issue.” Given that the researchers had already reached consensus on the CCC, the P2P also seemed unnecessary, at least if it was intended to address the research case definition.

https://dl.dropboxusercontent.com/u/89158245/Dr%20Collins%20to%20Lofgren%20letter%20April%202014.pdf

In a July 2012 letter to President Obama, Dr. Collins stated that HHS had launched a cross-agency “Ad Hoc Workgroup” to develop a “Department-wide strategy” for the disease. But the Ad Hoc Workgroup did not deliver a department-wide strategy. It delivered one report—a listing by agency of the tactical activities being conducted—and then disbanded.535
Sources:
• 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
This letter was sent from President Obama to a patient’s wife as a follow-up to a question asked at a town hall about how this disease was being handled. President Obama stated, “Dr. Collins also advises that the Department of Health and Human Services (HHS) has launched an Ad Hoc Workgroup on CFS and is working to develop a Department-wide strategy to address the disease.”

On June 5 2012, patient advocates submitted a letter to HHS patient requesting a meeting with key DHHS officials to address our concerns and calling for a strategic, coordinated, fully funded response to this disease. On October 18, 2012, advocates met with Dr. Nancy Lee and Dr. Caira Woods, Advisor for Health and Science Policy, Office on Women’s Health, at which time Dr. Lee and Dr. Woods stated that HHS was not developing a strategy for this disease. Additional references include:

• June 5, 2012 letter from patient advocates to HHS
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
The joint request for a strategic fully funded plan also included a request to meet with key leaders at HHS. Dr. Collins Presentation at Senate appropriations hearing on NIH budget. April 30, 2015. Last accessed in July 2015.

On January 22, 2015, Barbara James, designated federal official for CFSAC confirmed by personal email with this author that the group had been disbanded two years ago and had only compiled the one report listed above


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Exchange with Senator Moran who is asking for assurance that NIH has processes in place so that congressional leaders can rely on NIH to allocate the funds.


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.”

The joint request for a strategic fully funded plan also included a request to meet with key leaders at HHS. The advocates

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 also stated that OASH was “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.”


The report stated, “However, there is little evidence of coordination between CDC and NIH on CFS research. While the missions of the two agencies are somewhat distinct, we identified no specific efforts to ensure that CFS research does not overlap or leave important gaps. For example, while CDC and NIH-funded researchers have shared preliminary manuscripts of their surveillance studies, both agencies have separately funded community-based surveillance research. We also identified no activities intended to build on the results of studies at the other agency, beyond generally reading the scientific literature.”

Ibid. Page 28

Kim McCleary 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. Cavielle-Coll is correct—it changes everything. It would make things totally incomparable. We won’t be able to compare one thing to the next.”

In the last few years, some of the most important studies in this disease have started to report the use of Fukuda together with the CCC and one clinical trial record has reported the use of the CCC alone. Examples include:

- Fluge O, Risa K, Lunde S, Alme K, Rekeland IG, Sapkota D, Kristoffersen EK, Sørland K, Bruoland O, Dhal O, Melia O. “B-Lymphocyte Depletion in Myalgic Encephalopathy/ Chronic Fatigue Syndrome. An Open-Label Phase II Study with Rituximab Maintenance Treatment.” *PLoS ONE* July 1, 2015. 10(7): e0129898. [http://dx.doi.org/10.1371/journal.pone.0129898](http://dx.doi.org/10.1371/journal.pone.0129898) This study stated that patients met both Fukuda and CCC
- 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 on February 10, 2015. Final release by May 2015. Last accessed May 19, 2015. [https://www.iom.edu/Reports/2015/ME-CFS.aspx](https://www.iom.edu/Reports/2015/ME-CFS.aspx) (page 20) AHRQ did an evidence review to support P2P. But this evidence review was not done in time to be used by the IOM initiative. The IOM report stated, Dr. Maier of NIH “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.”
- 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 on February 10, 2015. Final release by May 2015. Last accessed May 19, 2015. [https://www.iom.edu/Reports/2015/ME-CFS.aspx](https://www.iom.edu/Reports/2015/ME-CFS.aspx) (page 20) The IOM report stated, “The NIH P2P workshop was originally intended to complement the present study by developing a research 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 research case definition but to suggest a research agenda for ME/CFS based on an unbiased review of the evidence.”


The article referenced NIH’s funding analysis

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.


Note that Brown uses the term “dominant epidemiological paradigm.” This paper uses the more general “dominant paradigm.”

Ibid. Brown summarizes a variety of evidence for biomedical issues in GWI patients. For a recent study, see


Requires one or more symptoms from at least two of the three following categories: 1) fatigue 2) mood and cognition (symptoms of feeling depressed, difficulty in remembering or concentrating, feeling moody, feeling anxious, trouble in finding words, or difficulty in sleeping) 3) musculoskeletal (symptoms of joint pain, joint stiffness, or muscle pain)


In the conclusion of the chapter “A Narrowing Gulf of Difference?” (Page 105) on Gulf War Illness, 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 prevailing systems of scientific, government and military power have made it difficult to challenge.”


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, “many patients were psychologically ‘different’ long before they developed the syndrome.” Brody noted that Straus said some were anxious or depressed or had neurotic symptoms before they got sick while others were driven and motivated, while some were stressed by their lives.


Straus stated, "The demography of this syndrome reflects an excessive risk for educated adult white women... may reflect... [those] who can best afford a sophisticated medical evaluation or some unique constitutional frailty of such individuals... A less casual appraisal, however, often uncovers histories of unachieviable ambition, poor coping skills, and somatic complaints... It is difficult and at times unpleasant to address the demands of such patients.”


Dr. Straus was interviewed for this report, in which he emphasized psychological issues at the root of the disease. Brody stated that Dr. Straus noted, “many patients were psychologically “different” long before they developed the syndrome.” Brody noted that Straus said some were anxious or depressed or had neurotic symptoms before they got sick while others were driven and motivated, while some were stressed by their lives.


For example, Wessely participated in the 1991 and 2000 conferences. The 2000 conference was originally scheduled to include only Simon Wessely, Michael Sharpe, Mark Demitrack and Stephen Straus.


566 Ibid. Through their participation in the 1991 conference which led to a loosening of the criteria for the disease and the inclusion of more mental illness. Michael Sharpe was one of the listed Fukuda authors and Simon Wessely was a member of the "International Chronic Fatigue Syndrome Study Group," which was also listed as an author.

567 The Empirical definition was based on a series of workshops that was reported in 2003. Peter White, one of the Oxford authors was an author on this paper.


Also see the following editorial supporting the 2007 CDC paper that increased prevalence 10-fold. Also see


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.”


This was from a Royal Society of Medicine conference on CFS. Note that White discusses classification of CFS in ICD-10, the various definitions that exist and also the view that the term ME refers to epidemics, not episodic occurrences. At minute 17:00, he discusses a collaboration done with the CDC.

A partial transcript can be found here: https://dxrevisionwatch.files.wordpress.com/2015/11/rsmptwhitetranscript5.pdf

The agenda of the conference is here: https://meagenda.wordpress.com/2007/12/14/royal-society-of-medicine-conference-april-28/


Includes interview of Richard Horton, editor-in-chief at The Lancet

Horton stated that the investigators compared treatments like CBT “against a treatment which was very much endorsed by parts of the patient community, but very sceptically received by the more scientific community.” He went on to state that these were “two philosophies of what chronic fatigue syndrome was” and that patients believed that “chronic fatigue is an organic disease which is not reversible by changes in behaviour.”


Includes interview of Richard Horton, editor-in-chief at Lancet

573 Example includes


Further information on the U.K. Science Media Center, including pros and cons, can be found in the following articles:


http://www.sciencemediacentre.org/expert-reaction-to-biomarkers-for-cfme/


See also
  http://www.cdc.gov/cfs/education/diagnosis/index.html (Chapter 4, Page 4)  
  The CME stated “Having patients briefly track symptoms and function in a diary may more clearly illuminate this association for the patient and the healthcare provider. Adaptive pacing therapy, cognitive behavioral therapy (CBT), or graduated exercise therapy (GET), along with specialist medical care appear to be beneficial for some patients [26].” Reference # 26 is the PACE trial


579 Dolan, Darragh “Beyond Tired: Is chronic fatigue syndrome a real medical condition? Yes, according to a report from the Institute of Medicine, which urges physicians to treat it accordingly.” October/November 2015; 11(5):60–63  
http://dx.doi.org/10.1097/01.NNN.0000472913.82545.7a

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.”


The following statements come from page 17-18 of the Department for Work And Pensions FOIA file

• On page 18, in a letter to Dr. Mansel Aylward at the Department of Social Security (now called the Department for Work and Pensions according to Smith), Professor Wessely raised a concern that CFS might be listed as a neurological illness and 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.”

Further information on his views of the biology of the disease is found on page 8.


States that CFS is “Known internationally as Neurasthenia, may be referred to as ME”

It is not clear exactly when this was first published but it was on the May 9, 2001 version of this page.


According to this document, G93.3 gets used when there is a viral trigger or where the symptoms do not meet Neurasthenia to begin with. 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).” The document states that the Association of British Neurologists rejects CFS as a neurological condition.

See page 12 for predisposing and perpetuating factors.
The document states, “Predisposing factors identified include personality factors of neuroticism and introversion.3 Inactivity in childhood has also been identified.”

It also states, “Psychological and social factors appear to be involved in perpetuating the symptoms of the illness. Factors associated with increased fatigue and severity of the condition include: a strong belief in the physical cause of the illness, a focus on bodily sensations and a poor sense of control over the complaints.”

Author’s note: There are many organic diseases that cause psychiatric issues but they are not similarly treated.


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.

Also see

  
  Full article available at https://cfsresearch.wordpress.com/2011/06/30/dangers-of-research-into-chronic-fatigue-syndrome/

  For another article that includes the patient perspective see:
  


According to Tymes Trust, the discussion included freedom of information requests and parliamentary questions as examples of harassment.

Also see

  
  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.”


Frances noted that 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."

This psychologization of disease and of everyday experience has resulted in broad criticism of DSM. 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:


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."


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).


Straus stated that educated white women were more likely get the disease which could either reflect the resources to access evaluations or "some unique constitutional frailty of such individuals." He also said that most had excellent health and said that some were competitive athletes or "at least aggressively maintained physical conditioning." He went on to state "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."


Frances references Dr. Thomas Szasz, psychiatrist and author of "The Myth of Mental Illness," who 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."

Some articles citing treatment of women in medical care and research

0’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.


- Website - http://erythos.com/gibsonenquiry/Index.html Includes index of materials
- Evidence Review created by BRAME

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.


That article by Bass 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. As with Swiss Re’s article, this is a remarkable level of endorsement for the biopsychosocial approach.


This article was removed by Swiss RE following the release of the following article by Tuller discussing the Swiss RE article in his series on the PACE trial.

Also see

This is a point made by in the following inquiry:

    “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).
  - Website - http://erythos.com/gibsonenquiry/Index.html Includes index of materials
  - Evidence Review created by BRAME


This Newsweek article reports on the neurological and immunological impairment that IOM reported and also on the medical community dismissal
Also see:
  http://www.youtube.com/watch?v=AW0x9_Q8qbo.
  This reports on the 1980s investigation of the Incline Village and Lyndonville outbreaks by the CDC, the evidence of impairment that was found and the medical dismissal

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.
  http://www.meactionuk.org.uk/ramsey.html and http://www.name-us.org/DefinitionsPages/DeRamsay.htm#MYALGIC_ENCEPHALOMYELITIS:_A_Baffling_Syndrome_With_a_Tragic_Aftermath
  Extract provided by Connie Nelson to Mary Schweitzer who provided it on http://www.cfids-me.org/ramsay86.html
  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 recurrent 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.”


See also: Letter recommending preceding mood disorder not be considered exclusionary


Note that the 1991 NIH conference noted that the following were allowed. “Nonpsychotic depression: concurrent, 1 month post onset or 6 months or more before onset: recurrent or non-recurrent, somatoform disorders, anxiety disorders: generalized or panic disorder.”


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.”


As listed in the Oxford CFS definition, the criteria include a) fatigue as the main symptom, b) definite onset, not lifelong, c) fatigue is disabling and affects both physical and mental functioning d) has lasted for 6 months and was present for 50 percent of the time and e) may be accompanied by other symptoms including pain, sleep disturbance and mood. The criteria then list exclusions of medical conditions known to cause fatigue and certain psychiatric illness including schizophrenia, manic depressive illness, substance abuse, eating disorder or proven organic brain disease.

The Oxford definition describes fatigue as subjective and not physiological failure to sustain muscle power.


http://dx.doi.org/10.7326/0003-4819-121-12-199412150-00009


Also see


On slide 12, Jason describes how fatigue plus 4 Fukuda symptoms are equivalent to the symptoms of depressed patients


Also see the following overview of the CCG, produced in 2005.


8.1 The diagnosis of CFS/ME should be reconsidered if none of the following key features are present: post-exertional malaise or fatigue (typically delayed, for example by at least 24 hours, with slow recovery over several days).

“The diagnosis of CFS/ME is characterised by post-persistent and/or recurrent; unexplained by other conditions; has resulted in a substantial reduction in activity level; cognitive difficulties, sleep disturbance, or chronic pain.”


NICE requires “fatigue with all of the following features: new or had a specific onset (that is, it is not lifelong); persistent and/or recurrent; unexplained by other conditions; has resulted in a substantial reduction in activity level; [and is] characterised by post-exertional malaise and/or fatigue (typically delayed, for example by at least 24 hours, with slow recovery over several days)”


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