Fighting over fatigue

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In the summer of 1989, Leonard Jason fell ill with the worst sore throat of his life. He couldn't shake it. As the leaves turned red and gold that fall, his energy and weight dropped dramatically, eventually forcing him to stop teaching at DePaul University in Chicago. For 14 years, he had been a highly successful psychology professor, flush with research grants, president of the community psychology division of the American Psychological Association, and director of clinical training at DePaul. Now just a simple phone call was enough to leave him exhausted and bedbound.

The diagnosis? Chronic fatigue syndrome (CFS), a recently coined name for myalgic encephalomyelitis (ME). Jason preferred the original because it sounded less trivial. Confusion and disagreements over the disease's name – now usually a hybrid abbreviation, most often CFS-ME in the UK or ME-CFS in the USA – have long reflected wider confusion and misconceptions about it.

Jason's colleagues and friends were stumped. Perhaps most maddening were the well-meaning comments from people insisting they, too, had 'chronic fatigue'. "One colleague suggested I think about another job as a cook at a fast-food restaurant," he says. Others encouraged him to just "pull it together", as if this was simply mind over matter.

Indeed, for decades the medical community had largely agreed it was a psychosomatic disorder. A 1970 review of 15 historical outbreaks of 'benign myalgic encephalomyelitis' dismissed most of them as mass hysteria. Today physicians aren't sure what to call the illness, let alone

what to do about it. One of the few treatments to appear effective in clinical trials is rejected by many patients. Because it focuses on exercise and cognitive therapy, they say it presumes a psychological origin for their illness, which they consider as harmful as it is insulting. This has helped create one of the most disenfranchised, frustrated, fractious patient groups in history.

That may be about to change, though. In 2015, two US government-sponsored reports offered long-sought validation that this is a disease of the body, not the mind, and funding agencies have begun to offer more coordinated support and resources for research. For the first time, people with CFS-ME, their advocates, and the small band of researchers who study the disease have positive attention and momentum. It could be the start of a seismic shift in understanding. But if the momentum is lost, it would be a devastating blow to this fragile, yet increasingly activist group.

So can these fractured research and patient communities begin to engage constructively? As researcher and patient, Jason sees both sides of the coin: he thinks this is a crucial moment, an opportunity to finally start making real progress.

A 1990 Newsweek magazine article noted that an outbreak of CFS-ME near Lake Tahoe in the USA had been derisively dismissed as mass hypochondria, or 'Yuppie flu'. The mere mention of 'Yuppie flu' helped saddle the disease with this long-standing nickname. It has also been dubbed 'zombie sickness'. Hardly monikers that doctors would take seriously.

Jason took a leave of absence from DePaul and for the next year sought healing outside the mainstream medical establishment. He vacillated between alternative healers and warmer climes in Montana, Florida, Wisconsin and Mexico, searching in vain for improvement – finding

often only misleading claims and hype.

He began to comb through what little medical literature existed, and discovered that divisions between patients and doctors were being exacerbated by the widespread use of a flawed case definition. The medical view of CFS-ME did not match patients' experiences. The deepening divisions ruptured furiously in 2011, when results from a controversial trial were published in *The Lancet*.

The UK-based PACE trial had recruited 641 people with CFS-ME and compared four approaches to treating them: standard specialised medical care alone or in combination with either graded exercise, adaptive pacing (learning to avoid or reduce fatigue) or cognitive behavioural therapy. The published findings suggested that exercise and behavioural therapies to encourage a positive attitude could help people recover from CFS-ME, and these treatments have subsequently been widely adopted. But criticisms of the trial have festered in patient circles and among researchers ever since.

In October 2015, a 14,000-word critique of the PACE trial was published on Virology Blog. Among the most damning charges it comprehensively detailed was that the ways the PACE team had measured recovery were subjective; objective measures – physical, employment and financial – provided no evidence of recovery after any of the tested treatments.

A week later – amid calls from patients for the Lancet to retract the original study – the PACE team published a follow-up study, noting long-term benefits of cognitive behavioural and graded exercise therapies. The same old arguments and counter-arguments roared predictably back to life.

The rancour over PACE is understandable. For some, it is the only CFS-

ME trial to have found evidence of a treatment effect; for others it is the flawed cornerstone of treatments that many patients feel are harmful, and bolsters the notion that the disease is all in their heads, making it easier to dismiss.

"The psychological component is the issue," says Mary Dimmock, a former biotech executive who turned advocate after her son became bedridden with CFS-ME. Backers of graded exercise therapy believe that patients are simply afraid to move, she adds. But, she admits, patients have a reputation for overreacting to any suggestion of psychological underpinnings.

"To someone not familiar with it, the total objection to anything psychological, if it's not carefully articulated, shows how irrational these patients are – and that's used against them," she says. It's yet another cause of anger and frustration.

After the first PACE trial research was published, some patients in the UK reportedly hurled death threats and verbal assaults at researchers who studied graded exercise or cognitive behavioural therapy as treatments for CFS-ME. Most of the ire targeted Peter White and Simon Wessely, leading advocates of graded exercise therapy, but it seemed that anyone studying the disease was at risk.

Esther Crawley received her share of threatening emails. Although the primary focus of her research is on rates and patterns of CFS-ME in children, she was also involved in a clinical trial of a behavioural therapy. She had to cope with numerous freedom of information requests from people with CFS-ME that were designed, she believes, to stop her work rather than gather information. Things got so unpleasant that she almost did stop. "I was accused of abusing children," she says.

Crawley was advised to go public about the harassment. Her story

appeared in medical journals, on television and radio. "Patients all over the world contacted me and asked that I not stop doing my work." Ultimately, she credits the Medical Research Council's interest in promoting CFS-ME research for helping her stay in the field, and she has been funded to investigate and describe the burden of the illness in young people in the UK. "My vision is to change what happens to kids with this illness."

Others, including Wessely, did leave the field. A 2011 Guardian story details how he installed panic buttons at police request and had his mail X-rayed. He's quoted saying that he felt safer studying combat-related post-traumatic stress disorder in war zones than working on CFS-ME.

Twenty-five years after his diagnosis, Jason, now 66, says he's at about 70 per cent of normal. Thin, but not gaunt, he cuts a Spartan figure in a blue pinstripe shirt and black trousers. Despite his illness, he has published over 690 scientific articles, written or edited 27 books and mentored over 150 graduate-level students; and also developed community-based efforts to prevent youth smoking and support substance abusers. "Seventy per cent for Lenny is about 140 per cent for the rest of us," says his longtime colleague Chris Keys.

Keys and Jason helped launch the field of community psychology in the 1960s. Their goal was to find ways to empower downtrodden groups. "Community psychologists are pissed off at everything that is not fair or right," says Jason. Pictures from that era show his transition from clean-cut college freshman to a wild-haired hippie graduate student. Understated and disarmingly tranquil, he's an unlikely rabble-rouser. "A gentle instigator," Keys says.

When Jason returned to work in 1991, it was only for about an hour a day at first. Over months and years, amid relapses, he slowly built that up to mornings and, eventually, to full eight-hour days. For him the key

was staying inside what he calls his "energy envelope": not overdoing it, slowly building stamina. He was always tactical, according to Keys, managing his own health while arguing that the name 'chronic fatigue syndrome' was tainted by stigma, and that the disease was more common than once thought and in need of much more study.

What most people don't understand about CFS-ME, says Jason, is that even though the body is exhausted, the mind is stimulated – making sleep difficult, despite the fatigue. "I describe it as 'tired but wired'," he says. To this day, he avoids noisy restaurants and keeps a strict sleep schedule (in bed by 9pm) to prevent disruption. "If I'm stressed out and pushed beyond my limits, I can deteriorate very quickly."

While most people balance family, personal and working sides of their lives, Jason dedicated his precious energy reserves solely to raising the profile of his disease in the biomedical research community.

He decided to start with finding out how common CFS-ME really was: "As long as people considered it a rare disorder… it would not get attention, resources or respect." He applied for grants for four years, finally securing funding in 1995.

"Yes, it was a long battle, with the odds against us," he says, chuckling at first, then becoming emotional as he recalls his relapse at that time because he'd used up so much energy pursuing the grant. "I was not coming into work, trying to assemble a team from home." He lets out a big sigh.

In the end, it took ten years. Jason and his colleagues called thousands of people at random and took them through a questionnaire of symptoms, eventually updating the official estimate of the number of people in the USA with CFS-ME from 20,000 to 800,000. (Due to population growth, estimates since have risen to 1 million in the USA and about 250,000 in

the UK.)

He next conducted the first non-drug trial, testing variations of cognitive, behavioural and relaxation therapies on over 100 patients. "We didn't find a cure, but we did find a very different reaction in the US patients from what was found in Great Britain." In direct contrast to PACE findings in favour of graded exercise, Jason found that people with CFS-ME needed to conserve their energy.

"We found that patients who were the sickest made the least improvement when pushing their activity levels," he says. "People who had learned to stay within their energy envelope had the best success."

Jason and other researchers studying the disease now think CFS-ME is an umbrella term that includes mild to severe cases. But there is no clear-cut way to distinguish different groups in order to identify underlying biological mechanisms or the most appropriate treatments. Even the patient groups spar bitterly over the definitions.

Jason explains that one group believes ME and CFS are different diseases – and that the people with CFS have psychological problems. Another group believes they are more or less extreme versions of the same disease. "Boy, what a clash of those two groups. They are fighting it out," he says. "Viciously."

Amid the divisions and the infighting, two separate reports published in the USA in 2015 called for more coordinated research on CFS-ME and huge hikes in funding (in 2014, CFS-ME received about $5 million in research funding in the USA; many think $250m would be more appropriate). Significantly, one of the reports was from the National Institutes of Health (NIH) – an organisation that some claim has contributed to the low funding levels and lack of coordination, since research on the disease has always been spread among different NIH

institutes.

The other report was from the Institute of Medicine (IOM), which also offered a new case definition, based on a person having four out of five proposed fundamental symptoms, and yet another name – systemic exertion intolerance disease, or SEID.

Jason predicts that SEID will go unadopted. Indeed, four recent surveys found little support for the name, and a petition against it was quickly set up. He is also deeply concerned that the proposed diagnostic criteria weren't tested with actual patient data, and that people with psychiatric disorders weren't excluded. Not taking these steps to systematically define the CFS-ME patient population will, he says, further "complicate efforts to identify biological markers for this illness".

Jason has also criticised the process behind the two reports – much to the chagrin of those who desperately want the field to move forward but who also value his judgement. His issue? Neither involved patients. "The problem with both is they are exclusionary at heart," he says.

Ironically, the NIH Pathways to Prevention report specifically states that "Patients must be at the center of the research efforts and their engagement is critical." But during the teleconference to launch the report in June 2015, no effort was made to acknowledge their concerns, and only questions from the media were permitted. Despite repeated solicitations, only one journalist asked a question and opportunities to hear from patients instead were ignored. Jennie Spotila, a former lawyer who has CFS-ME, says she called six times with well-articulated questions about both the content of the report and the public comment process.

Spotila thinks NIH views patients as "a pain in the ass". "Maybe we are, but are we more of a pain in the ass than other groups waiting 30 years

for improvements?" she asks. "I've been sick for over 20 years, my entire productive time of life is gone. I'm stuck in my house and couldn't have kids. But that's just me and I'm not even the sickest person.

"The pain, disillusionment, anger and frustration comes from watching the government not deal with this problem for 30 years," she says. "If they listened to what people have been through, it would change opinions."

Vicky Whittemore is an epilepsy researcher recently tasked with overseeing CFS-ME research at the National Institute of Neurological Disorders and Stroke, and a member of a CFS-ME working group drawn from across NIH. She agrees that NIH must start listening.

"We need to hear the concerns of the community," she says. "At different meetings, I've seen these patients get cut off; people be rude to them, roll their eyes. It's so disrespectful."

Jason suspects the recent reports and media coverage may prompt a modest funding boost. But he believes patients, advocates, NIH and others will have to work together to find the right name, diagnostic criteria and treatment options that this disease so desperately needs.

Following the 2011 PACE trial controversy, hostilities between researchers and patients in the UK were so fierce it was unclear how to move forward at all. The situation was desperate, says Stephen Holgate, an immunopharmacologist at Southampton General Hospital. He had never studied CFS-ME before, but believed he could bring some much-needed impartiality to the field.

He knew the community had to start afresh. He wooed several charities to join a new CFS-ME research collaborative, and secured more than £1.6m from the Medical Research Council to fund five grants. The

collaborative wants to raise the profile of CFS-ME research, talk to patients and professionals about priorities, and review the UK and international research landscape.

"Part of the problem has been that patients have been seeking a single treatment for a single problem, but, as the recent IOM report points out, these are complicated interactions in different patients," Holgate says.

His approach sounds a lot like what Jason wants in the USA: a collective of medical practitioners, researchers, patient groups and funders working to strategically improve the evidence base for this disease. Unlike Jason's emphasis on transparency and patient participation, however, the secret to the UK collaborative's success, according to Holgate, is a membership charter that forbids harassment or abuse of researchers. In effect, patient groups are banned from whipping up a media frenzy over research findings.

The charter has already been tested a couple of times, says Holgate, who gave the aggressors a choice: apologise or leave. He's even suggested that he'll disband the collaborative completely if all parties don't play by the rules.

"We set up the charter to protect researchers; anybody who joins us can't abuse or upset that trust," he says. "There is power in this to stop silly publicity which is quite destructive."

One influential charity, Invest in ME, balked at the charter, as well as the stipulation that patients can't be members. "This [charter] is specifically to block patients who might be critical… critical in the same way I would be," says Jonathan Edwards, Emeritus Professor of Connective Tissue Medicine at University College London, who is advising the charity. "As far as I can see," he says, "the harassment referred to is legitimate criticism of bad science."

But Esther Crawley credits the collaborative for improving the relationship between patient groups and researchers. "You can question or debate, but no coordinated attacks," she explains. And because of its ability to secure external funding, everyone sees it as worthwhile to work together.

That said, it's not clear the collaborative is yet on solid footing. "We're still building a foundation and it's important to spend the time getting that right," says Sonya Chowdhury, Chief Executive of the Bristol-based charity Action for ME. Sensitivities, she adds, run deep.

"Building trust should take a long time," acknowledges Crawley, adding that no one is at fault. "If you think about fatigue, the core symptom, we all experience this, but [CFS-ME] is something different and it's difficult for clinicians and researchers to see it as something different."

The collaborative has not healed all the rifts. Invest in ME has created a separate European ME Research Group (EMERG) to work directly with patients, and while researchers can be involved in both efforts, it isn't always easy. EMERG and the CFS-ME research collaborative each held important meetings in October 2015, but they ran on overlapping dates.

After the collaborative's meeting, Chowdhury wrote that "the excitement, energy and desire from researchers at the conference was overwhelming". While he disagrees with the collaborative's approach, Edwards does agree that this is a critical moment for CFS-ME research. He thinks resolution between the factions will come "when PACE washes out of the story", and is equally encouraged by the number of scientists now showing an interest, eager to dive into a disease area so ripe for discovery: "People from other disciplines see something exciting is going on."

Despite the relative pittance of funding available to date, researchers are

finding intriguing clues that regulation of the immune and nervous systems goes wrong in CFS-ME. But it's unclear whether the brain or the immune system – or both – go haywire. For example, tests of heart-rate variability in CFS-ME patients suggest that one part of the nervous system gets stuck in a hyper-vigilant state while another is, essentially, asleep. Together, this results in the cognitive impairment often experienced.

Hugh Perry at the University of Southampton has shown that microglia, immune cells in the brain that cause inflammation, can be primed to generate exaggerated signals that make the brain feel sick. He thinks this could shed light on CFS-ME, particularly how the brain perceives symptoms. "We're interested in the circuitry of sickness," he says.

Jason's team, working with multiple sclerosis researcher Matthew Sorenson, are also pursuing new clues. After they discovered that levels of an important inflammatory protein are unusually high in CFS-ME patients, Sorenson found that when patients' immune systems are stimulated, the pattern of immune regulation is askew. "There are three distinct groups of proteins that typically turn on and off immune systems," he says. "With CFS-ME patients, those groups blur." This means proteins that normally turn the immune system off are not coming into play when they should.

And most interesting to those eager for new treatments, two small trials testing rituximab, a drug that wipes out a person's ability to make antibodies, have found that some patients experience long periods of remission.

Many scientists agree that the most pressing challenge for CFS-ME research now is to find a way to separate the disease into the range of conditions it encompasses. "We have an umbrella term – CFS-ME – and call it all one thing, but it is almost inconceivable that this is one simple

disease," says Perry. "It wasn't that long ago when we referred to breast cancer as one disease. We now know many different types of tumours exist that require different treatments."

Breaking down CFS-ME in a similar way will require funding, large sample sizes and coordinated effort. Such an effort, adds Perry, will require compassion from medical professionals towards patients and tolerance from patients for the medics.

Few disease areas are so ripe for big breakthroughs and much-needed clues to treatments. Researchers desperately want to tease apart what's going on. But can disgruntled patients, academics promoting behavioural therapy and exercise, wary government officials and cautious medical professionals finally bury the hatchet?

Jason says the only way forward is to bring in all the voices, even the strident ones, and let them have a say in any process to identify a name and a case definition that will get research on the right footing. "Failure to do that will lead to the same type of bad feelings and struggles that have divided this field." More than funding, he says, any indication that the culture is changing to one that engages with patients would be "monumental".

Such a culture shift looks increasingly possible. On 29 October 2015, NIH announced that a new research programme for CFS-ME would soon get underway and the disease would be the responsibility of the National Institute of Neurological Disorders and Stroke, where it would finally have a single home within NIH. Perhaps most tellingly, though, NIH director Francis Collins and his staff reached out to patients and advocacy groups, seeking input.

Collins telephoned Brian Vastag, a former journalist with CFS-ME, who had written an open letter to Collins making the case for greater

investment in CFS-ME. Touched by the letter, Collins sought Vastag's opinion on how best to engage patients and advocates. "For 30 years, there has been police tape around this disease at NIH. Nobody could touch it," says Vastag. "That changed today. Collins says he wants to start fresh with the patient-advocacy community."

Jason is delighted. "Sometimes," he says, "there needs to be a furore to make changes that are necessary." The furore has been raging for decades – now might just be the moment for the changes to begin.

More information: PD White et al. Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): a randomised trial, *The Lancet* (2011). DOI: 10.1016/S0140-6736(11)60096-2