

Transcript

Santa Fe Institute

“Medical, Scientific and Journalistic Pitfalls in the Study of Confusing Illnesses”

A Research Collaboration Seminar - February 26, 2014

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Background:

Julie Rehmeyer is an award-winning math and science journalist whose work has been published in *Science News*, *Wired*, *Discover*, *New Scientist*, *Science* and a variety of other publications. During her recent experience as a Miller journalism fellow at the Santa Fe Institute, she was invited to give a luncheon seminar about chronic fatigue syndrome (more properly known as myalgic encephalomyelitis).

The talk included presentation of basic information about ME/CFS; a description of Julie’s own experiences suffering from and then getting much better from the disease; consideration of the problems that the disease has faced in terms of getting appropriate recognition, understanding and study; and discussion about ways in which the disease might be effectively researched in the future. About 30 leading scientists and science journalists associated with the Santa Fe Institute attended the talk and contributed their thoughts.

The Santa Fe Institute is a prominent independent not-for-profit research institute that attracts eminent scientists from across the globe. It primarily focuses on theoretical scientific research and as well as complex systems research. SFI researchers, while well-trained in traditional fields, have a demonstrated ability to transcend the usual disciplinary boundaries in the pursuit of interesting and difficult scientific questions.

Julie says that she has a drive to improve people’s appreciation of the quantitative sciences and to clarify their understanding of misunderstood diseases. Since 2007 she has written the popular math column (“Math Trek”) in *Science News*, and since 2010 the occasional math column (“Equation”) in *Wired*. She recently was named a contributing editor for *Discover*, and her *Science News* article “Darwin: The Reluctant Mathematician” was included in the Best American Mathematics Writing 2010. She is a journalism fellow at the Santa Fe Institute; has a master’s degree (ABD Ph.D.) in mathematics from MIT; and previously taught math, science, philosophy, literature and music at St. John’s College in Santa Fe. She acquired ME/CFS in 1999 and for a time was mostly bedbound with it. She now is back to working full-time and exercising vigorously, and she describes herself as mostly recovered from the illness.

Introduction

So I have had chronic fatigue syndrome myself. I have had it for a long time. As a result of that, I've ended up doing a bunch of reporting about it.

It's kind of a grim story, really. A lot of bad things have happened on a lot of different levels with chronic fatigue syndrome.

As I've studied it and been part of this community more generally, I've seen that it's a fairly consistent pattern amongst illnesses that don't have a clear causation that are murky and confusing and often ill-defined.

I'm going to be talking mostly about chronic fatigue syndrome today, in detail.

But the lessons about it apply to lots of illnesses, such as chronic Lyme disease, fibromyalgia, Gulf War illness, multiple chemical sensitivity and autism.

Problems

Here are some of the problems that come up.

Government officials tend to minimize the severity and the importance of the illness.

An antagonistic relationship develops between the illness community as a whole -- including patient advocates, researchers who specialize in the illness, doctors who specialize in the illness -- and government agencies who are in charge of it.

The media does a terrible job, a terrible job. Most articles about chronic fatigue syndrome, I just cringe to see them.

There's very little research funding.

The definition is a particularly problematic thing. Not just with chronic fatigue syndrome, but with many of these illnesses, the definition ends up being a real battleground.

It's considered to be psychosomatic by some.

What research there is is poorly disseminated, so that the public and doctors and basically everybody doesn't really know what is going on.

I'm going to give you a quick primer on ME/CFS. I'm going to go through those problems in some detail.

What I really want to do is reflect on the significance and on what can be done about them.

And then if I have time, which I really hope I do, I want to brainstorm with all of you about some ideas of ways of going about research.

One of the good things about how pathetic things are at this point is that there is a lot of low-hanging fruit. There are a lot of questions that have not been researched at all.

And along the way, you'll hear a bit about my story.

Getting the Illness

This is a pretty good portrayal of what it feels like.



Image Credit: Daniel Horowitz for an NPR story.

In 1999, I ran a marathon. I built a house. I was strong and healthy.



Then after the marathon, I started feeling like something really wasn't quite right. I wouldn't have said that I was at the point where I was sick, but it didn't feel quite right. I wasn't able to exercise the way that I used to -- after the marathon, I really didn't run at all.

However, I looked at my house, and my house looked pretty much like that at the time. So I had a big project on my hands.



My personal life was also pretty much of a mess at that point, and I was working full-time as well as building this house.

So I pretty much figured: I need to finish the house, I need to straighten out my personal life and I need to get some rest, and then I'll be fine.

Here's my house now. So I did finish it. However, I didn't make it all fine.



I kind of went along for a few years.

It was in 2005 and 2006 where it got to the point where I thought: "I'm sick."

In particular, this convinced me. ([Click here to watch video.](#))



This happened very suddenly in late 2006. I had gotten a hepatitis A vaccine and the next day, I was walking like this.

That pretty well scared the crap out of me. I went to see doctors and the whole deal.

Doctors were pretty useless. I went to a neurologist who diagnosed me as having chronic fatigue syndrome.

I said, "What do I do? Are there tests or treatments? Or other doctors I should see?"

And he said, "I got nothing for you. Go home."

So then I looked for specialists. The only specialists I could find were semi-quacky people that I didn't have a lot of confidence in. They put me on lots of supplements that I tried for a while. They didn't seem like they did much, and eventually I stopped.

I got somewhat better, over time. It was up and down. I couldn't figure out any particular pattern for the ups and downs. They seemed more or less controlled by the Greek gods, capricious and irrational.

At times, I would try again with doctors, but I eventually concluded that they had pretty much nothing to offer and that I was better off saving my energy and money for living my own life, especially since energy and money were rather constrained at that point.

So I'm going to leave the story there.

That's pretty much the way that it was until 2011.

I will tell you more later.

Chronic Fatigue Syndrome

Let me tell you a bit more about ME/CFS.

Sudden onset is common. It was quite gradual for me, but it's probably more common for it to be sudden than gradual.

It's often triggered by some kind of virus, and it seems that almost any virus can do it.

The best estimate is that there are a million patients in the U.S.

It can be very disabling, though it varies quite substantially.

That video that I showed you at the time seemed really awful to me, but now it seems rather moderate on the basis of what I experienced later.

Even so, I would say that I had a moderately severe case. It can get a whole lot worse than what I experienced.

For some people, they are flat out in a darkened room, no sound, no light, no movement, can't feed themselves, nothing. Fortunately, I was never there.

It's not really clear how many people get better. It is clear that in severe cases, recovery is not common at all.

It hits people often in the prime of their life.

The financial impact on the country is quite large. \$24 billion is the best estimate. That's including direct and indirect costs.

The research budget is \$5 million.

Q: What is diagnosis like in other countries? Are there differential diagnosis rates across countries?

I just don't think it's been studied very much. There are a lot of cases in the UK and Denmark.

ME/CFS Symptoms

Typical symptoms.

Well, yeah, fatigue. It's in the name. It's a word that patients tend to be pretty stickly about. Laura Hillenbrand, who wrote *Seabiscuit* and has chronic fatigue syndrome herself, said, "This illness is to fatigue what a nuclear bomb is to a match."

Post-exertional malaise. This is probably the hallmark symptom. What it means is that if you exercise, you get much worse. It's not just that you feel sort of lousy. It's that whatever symptoms you have, they come up much much worse. Post-exertional relapse might be a better term for it. Effects can last from days to weeks to months to indefinitely.

Cognitive problems are probably what drive people craziest. Brain fog all the time, I've experienced that a lot. Memory problems and concentration problems are common. For me, I had a really hard time speaking at times. I would have this feeling that I knew what word I wanted to say, and it was right there, and somehow I had to spear down each one of those damn words before they ran away from me. And so each sentence was like -- I just can't keep doing this.

Q: I assume that the obvious kinds of blood workups don't reveal anything -- glucose levels are normal, insulin levels are normal?

Yes, that's right, the ordinary blood test levels are normal. There are a variety of objective abnormalities. That is kind of what is puzzling about it -- the kinds of tests your primary care doc would run all come out normal.

More symptoms. Pain. Sleep problems -- the biggest thing is that there is unrefreshing sleep, where you wake up feeling like you never went to bed, but other sleep problems are common too.

Autonomic problems are a big one. This is something that all primary care docs should know about, because it's easy to diagnose and easy to treat, at least partially.

ME/CFS patients usually have about a liter less blood than healthy patients do. The result is that when you stand up, your body can't handle it. POTS is that your heart

races when you've been standing up for a few minutes. NMH, neurally mediated hypotension, is that your blood pressure drops.

I didn't even know this was an issue for me until well into 2011. A test was done, slightly fancier than this, but it was basically just having me stand up and be completely still. Because usually you do a lot of moving when you stand, and that helps move blood around. If you stand completely still, that is the maximum orthostatic stress on the body. For me, after six minutes, I almost threw up and we had to stop the test. My blood pressure fell to 80/50 or something like that.

The first line of treatment for that is Gatorade, because it increases blood volume. There are a variety of medications that make a difference too.

Nobody knows about this, outside of the specialist community. It's shocking. Every primary care doctor, that should be the first thing that they test for when someone comes in and apparently has chronic fatigue syndrome.

And then part of what is confusing about it is that there are zillions of symptoms, and they vary hugely from patient to patient with chronic fatigue syndrome. This is only a partial list of the wide variety. There are lots of strange neurological symptoms. My walking thing is not particularly common, but you see all kinds of things in CFS patients.

Physiological Abnormalities

There are a lot of objective physiological abnormalities in CFS. They just aren't the ones that are usually tested for.

One of the biggies is natural killer cell function. Natural killer cells are the primary cancer assassins in your body. In most ME/CFS patients, it's almost zero, which was true for me.

There's also reactivation of a lot of common viruses that then start floating around in the blood again.

There are a lot of ways that the immune system is simultaneously overactive, which is why flu-like symptoms are common.

The two-day exercise test is a way of quantifying post-exertional malaise. If CFS patients exercise two days in a row, on the second day there are real changes that are not there in healthy patients or in any other illness that's been studied.

There are altered proteins in spinal fluid.

Tilt-table test is the fancier version of what I just described of standing still.

There's mitochondrial dysfunction.

There are these pathogens -- herpesviruses, enteroviruses, mycoplasma, parvovirus -- that are often reactivated.

This is a brand new thing that just came out: that there is an order of magnitude greater chromosomal damage in ME/CFS patients than in normal controls.

Causal Hypotheses

It goes on and on and on. There are hundreds of studies showing abnormalities.

The really bizarre thing is, they just don't seem related to one another. Like in almost every single system of the body, you can find some kind of abnormality in ME/CFS patients.

What on earth is going on here? What ties these together?

The answer is that we don't know. But as for ideas about causes, these are the leading contenders.

It's possible that there's some unknown pathogen. XMRV was the retrovirus that was thought to be the cause of ME/CFS a few years ago, and then it exploded spectacularly, it wasn't true. But it could be something else. It could be some other retrovirus or some other pathogen.

It could be that it's caused by some environmental trigger -- heavy metals, pesticides, flame retardants, mold, a variety of things. As some of you know, we'll be coming back to that in a big way.

It could be some kind of hit-and-run thing, where when you very first got sick, there was some virus that sent your immune system into going wacko, and the virus is long gone and we have no sign of it, but now your immune system is not working right.

Psychological factors. Some believe that's a key contender.

Or it could be some combination thereof.

It could vary from one person to another. It could be different in different people.

It's also possible that CFS is not a single illness, that you have different causes and that this creates similar physiological effects.

Early History

Now let's get into the problems, and for this I want to go through the early history.

There were a bunch of early outbreaks of a disease that has a similar description to this. Then in 1956, this term myalgic encephalomyelitis first appeared in the literature to describe these outbreaks, and that is the "M.E." in the term "ME/CFS."

Q: When you say outbreaks, that implies that there is some sort of localized cluster where the symptoms are there but nowhere outside a small geographic radius. Is that true now?

So that's one of the big mysteries and one of the things that I'm hoping to talk to you guys about. I do not know. You don't hear about outbreaks any more. You hear about just cases here and there. But the early history is definitely outbreaks. I don't know that anybody's even been looking into that. The epidemiological work that's been done is so minimal that it is entirely possible that there are outbreaks and we just don't see them. But you're absolutely right to ask that.

Q: We're more mobile now, so maybe if it's a longterm exposure, it's not something that would show up.

Q: Is this what some people call fibromyalgia?

Fibromyalgia is actually different, but they are related. Fibromyalgia is another example of this kind of confusing illness where you get this same dynamic going on. But it's technically a different illness. And I don't know enough about it to say what the distinctions are exactly.

So in 1984, there was an outbreak in Lake Tahoe. This was a big deal, because this is what brought it to CDC attention for the first time. There are a couple of doctors who studied the patients around there quite intensively, and the CDC came in and studied it.

There were outbreaks around the same time in a bunch of other places too.

Q: When you say outbreaks, how many patients were there?

In Lake Tahoe, it was several hundred. I'm not sure about the other areas.

In 1987, this CDC investigation resulted in them developing a definition of this new thing, “chronic fatigue syndrome.” It was the first time that that term had been used.

They defined it in a rather broad way. It didn’t include any of the objective findings that the doctors in Lake Tahoe had found. It was intending to encompass all of these different outbreaks, and the definition was pretty vague.

The result was that it included a lot of different kinds of patients.

Myalgic encephalomyelitis kind of got absorbed, implicitly, into chronic fatigue syndrome. The kinds of things that had been seen in these previous outbreaks, the kind of specific symptoms, got absorbed into this much broader category.

In 1992, these doctors that I mentioned who had focused on Lake Tahoe came out with a study in the *Annals of Medicine*, and it documented a variety of abnormalities -- abnormal MRI brain scans, lowered white blood cell counts and functioning, HHV6 and more.

The CDC didn’t like it very much. They immediately responded with vociferous criticism.

They said, “We conclude that the disease described is not chronic fatigue syndrome or any other clinical entity and that they showed no association with HHV6 activation.”

HHV6 is human herpes virus 6, which had recently been discovered at that point.

Fatigue

The other thing that happened was that there was a lot of controversy around the name. “Fatigue” -- everybody’s tired, right? We’re all chronically fatigued. We’re busy and we work hard.

Also, there have been studies that have been done, where if you go into a doctor and say that you are fatigued, the doctor will be like, “I am so not worried.”

So it was an extremely trivializing name. Patients really really didn’t like it. Specialists really really didn’t like it.

So the CDC responded with a public awareness campaign about chronic fatigue syndrome.

This is an ad they had as part of a public awareness campaign in the early 2000’s.



Q: Are you saying that this disease had never been noticed or that it didn't exist before these first episodes?

Well, as I say, there were outbreaks going back some time that had been documented in the medical literature. So at least those outbreaks had occurred. How widespread it was, I don't know.

Antagonistic Relationship with Government

So an antagonistic relationship developed between the illness community and government agencies. You can see some of the roots of it already, but it kind of goes on from there.

In 1996, the head of the CFS program at the CDC became a whistleblower. He pointed out that the CDC had spent \$13 million that was specifically allocated for CFS research on other programs and consequently lied to Congress about it.

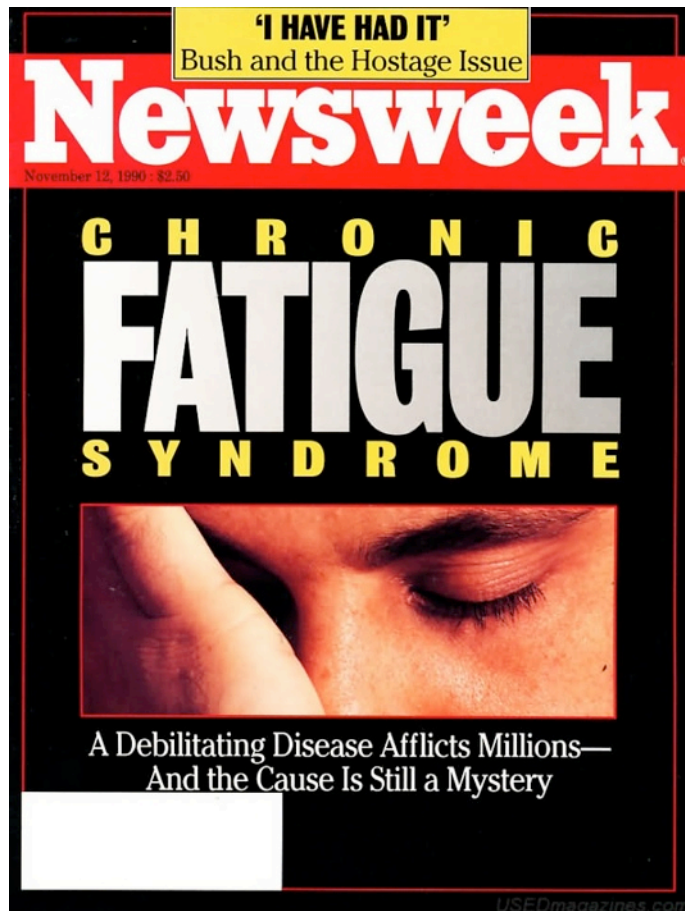
The relationship between officials and the CFS community continued to decline, and it's continued to be highly fraught. Recently there was a meeting of this committee where

the head of the CFS program for the government yelled at patient activists for not being nice enough. It was really astonishing. It's not a good relationship.

Other Challenges

Media.

Here's a early example of how bad the media coverage was. In 1990 it was on the cover of *Newsweek*. This is where "yuppie flu" got coined.



The reality is that CFS has been shown to be more prevalent in lower income communities. It's just less diagnosed.

There's little research funding.

There is \$5 million a year for CFS funding, which means five bucks a patient. There are about the same number of HIV/AIDS patients in the U.S. We spent \$3 billion on AIDS research, so that is \$3,000 a patient.

Definition

Arguments over the definition.

This is a biggie. When I was describing it at the beginning in terms of symptoms, I was going off of experience but also based on the Canadian Consensus Criteria. This was developed by ME/CFS specialists. It's never been officially endorsed by any government agency though.

The one that is officially used is this one called Fukuda. This is related to the initial definition from the CDC. It says that you have to have fatigue that lasts for at least six months, along with four of the following eight symptoms: memory or concentration problems, sore throat, tender lymph nodes, muscle pain, multi-joint pain, headaches, unrefreshing sleep, and post-exertional malaise.

In particular, post-exertional malaise is listed on there, but you only need to have four of the symptoms, so you don't necessarily have to have post-exertional malaise. This is a big problem because that is actually the hallmark symptom of the disease.

There are other problems too. It doesn't include any of the objectively verifiable signs of it.

Q: Is it seen more often in women than men?

Yes. About two-thirds women.

This definition doesn't require very extreme symptoms. It doesn't focus on immune, endocrine or autonomic problems. Many times, depressed people will qualify. That's a really big problem.

But it's not the worst definition out there by far!

In 2005, the CDC developed a new empirical definition. It's basically the same thing as Fukuda, but they wanted to set specific levels so they had a long questionnaire. They were trying to make everything very objective and empirical.

Chronic Fatigue Syndrome – A clinically empirical approach to its definition and studyWilliam C Reeves*¹, Dieter Wagner¹, Rosane Nisenbaum^{1,2}, James F Jones¹, Brian Gurbaxani¹, Laura Solomon^{1,3}, Dimitris A Papanicolaou^{4,5}, Elizabeth R Unger¹, Suzanne D Vernon¹ and Christine Heim⁶

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Abstract

Background: The lack of standardized criteria for defining chronic fatigue syndrome (CFS) has constrained research. The objective of this study was to apply the 1994 CFS criteria by standardized reproducible criteria.

Methods: This population-based case control study enrolled 227 adults identified from the population of Wichita with: (1) CFS (n = 58); (2) non-fatigued controls matched to CFS on sex, race, age and body mass index (n = 55); (3) persons with medically unexplained fatigue not CFS, which we term ISF (n = 59); (4) CFS accompanied by melancholic depression (n = 27); and (5) ISF plus melancholic depression (n = 28). Participants were admitted to a hospital for two days and underwent medical history and physical examination, the Diagnostic Interview Schedule, and laboratory testing to identify medical and psychiatric conditions exclusionary for CFS. Illness classification at the time of the clinical study utilized two algorithms: (1) the same criteria as in the surveillance study; (2) a standardized clinically empirical algorithm based on quantitative assessment of the major domains of CFS (impairment, fatigue, and accompanying symptoms).

Results: One hundred and sixty-four participants had no exclusionary conditions at the time of this study. Clinically empirical classification identified 43 subjects as CFS, 57 as ISF, and 64 as not ill. There was minimal association between the empirical classification and classification by the surveillance criteria. Subjects empirically classified as CFS had significantly worse impairment (evaluated by the SF-36), more severe fatigue (documented by the multidimensional fatigue inventory), more frequent and severe accompanying symptoms than those with ISF, who in turn had significantly worse scores than the not ill; this was not true for classification by the surveillance algorithm.

Conclusion: The empirical definition includes all aspects of CFS specified in the 1994 case definition and identifies persons with CFS in a precise manner that can be readily reproduced by both investigators and clinicians.

But the result was that the levels were set very low. So, “I had a sore throat a year ago” qualifies. Not quite, I’m exaggerating. But the levels are low enough that lots of people qualify.

Depending on where you started from, it multiplied the people who qualified either by four or by ten. They said that by this definition, there were 4 million patients in the U.S. By the previous CDC study, there were only 400,000. By a study done by an actual expert in the disease, there were a million.

Later, a study was done where 38% of those with major depressive disorder were misclassified as having ME/CFS, according to this definition. This definition basically has not been used, it’s been pretty much ignored.

Having a lot of definitions floating around makes a real mess of the research literature. You’re not talking about the same thing, even though you’re using the same words for it. That’s a big problem.

Pace Study

The next problem is that some people think it appears to be psychosomatic. There are a lot of different forms of this belief.

A good example of this is the “PACE Study,” which is especially atrocious especially because it is especially big.

It was a 5 million pound study financed by the National Health Service in the UK. It had 640 ME/CFS patients plus controls. This is the biggest study ever on ME/CFS. It was published in February 2011 in *The Lancet*.



It compared GET (graded exercise therapy) and CBT (cognitive behavioral therapy) with Adaptive Pacing.

Graded exercise therapy means that you'll exercise each day, and every day you do a little bit more. It doesn't matter how you're feeling, you do a little bit more anyway, even if you're having a crummy day. This is really really not a good idea, if you have chronic fatigue syndrome. It's quite a dangerous thing to do, actually.

Cognitive behavioral therapy, you probably already know.

Adaptive pacing. It's a funny thing. It sounds exactly like what you should do, where you should stay within what you can do. But they defined it in a very conservative way, where you stay within 70% of your energy envelope, which basically means you do almost nothing.

Also, they used yet another definition, even worse.

You need to have six months of unexplained fatigue.

There were no other symptoms required.

In fact, if you have other symptoms like neurological or cardiac symptoms, which you probably do if you have ME/CFS, then you're disqualified.

Their theory, the theory driving this, was that the patients once were sick, that they got a bug and they got sick, and they got deconditioned while they were sick. And then they just got freaked out! They're deconditioned, and so it doesn't feel the way it used to, and so they're afraid, and so they don't exercise, and it perpetuates itself.

That's their theory.

Q: Have there been any prior examples of deconditioning leading to fear of exercise?

Not as far as I know.

So their conclusion was that it was an effective treatment for ME/CFS and that a significant percentage of patients "recovered."

It got worldwide press coverage.

It is endorsed to this day on the Mayo Clinic site and the CDC site. And it is in fact the only treatment that is endorsed on those sites.



Diseases and Conditions

Chronic fatigue syndrome

Therapy

The most effective treatment for chronic fatigue syndrome appears to be a two-pronged approach that combines psychological counseling with a gentle exercise program.

- **Graded exercise.** A physical therapist can help determine what types of exercise are best for you. Inactive people often begin with range-of-motion and stretching exercises for just a few minutes a day. If you're exhausted the next day, you're doing too much. Your strength and endurance will improve as you gradually increase the intensity of your exercise over time.
- **Psychological counseling.** Talking with a counselor can help you figure out options to work around some of the limitations that chronic fatigue syndrome imposes on you. Feeling more in control of your life can improve your outlook dramatically.

As bad as the study itself was, the press coverage was even worse.

For instance:

“It may sound counterintuitive to patients suffering with fatigue, but scientists have found encouraging people with ME to push themselves *to their limit* gives the best hope of recovery.”

Got ME? Fatigued patients who go out and exercise have best hope of recovery, finds study

By DAILY MAIL REPORTERS
UPDATED: 06:32 EST, 18 February 2011

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It may seem counter-intuitive to patients suffering with fatigue, but scientists have found encouraging people with ME to push themselves to their limits gives the best hope of recovery.

British researchers conducted the largest trial to date of people with the mysterious and debilitating condition and found that up to 60 per cent of patients improved if therapists encouraged them gradually to do more.



Wow.

It got an enormous amount of press coverage, actually. And really worldwide.

This was the story in *The New York Times*.

It was February 2011, when I read this. At the end of 2010, I just collapsed. I thought at the time that it was a downturn and that I would have an upturn again, but I was out. Basically, I ended up being pretty much out for a year. Sometimes I was too weak to turn over in bed. I was bedbound about half the time. I ended up flying to Florida to go to a specialist, which helped a bit but not that much. I kind of ran out of standard medical options at that point.

I read this article while bedbound. I was horrified and frankly humiliated. I was juggling my deadlines trying to keep my career alive at the time, and I imagined my editors reading this and was really horrified.

It was kind of a galvanizing moment for me at that point. Before that, I had ignored all of this political stuff. This article changed it for me.

Psychotherapy Eases Chronic Fatigue Syndrome, Study Finds

By DAVID TULLER
Published: February 17, 2011

A new study suggests that psychotherapy and a gradual increase in [exercise](#) can significantly benefit patients with [chronic fatigue syndrome](#).

Related

Health Guide: [Chronic Fatigue](#)

Exhausted by Illness, and Doubts
(January 4, 2011)


While this may sound like good news, the findings — published Thursday in *The Lancet* — are certain to displease many patients and to intensify a fierce, long-running debate about what causes the illness and how to treat it.

Many patients, citing two [recent high-profile studies](#), believe the syndrome may be caused by viruses related to mouse leukemia viruses, and they are clamoring for access to antiretroviral drugs used to treat the virus that causes [AIDS](#). That treatment is very expensive and would be expected to continue indefinitely, and health insurers are not generally willing to pay for untested drug regimens.

The new study, conducted at clinics in Britain and financed by that country's government, is expected to lend ammunition to those who think the disease is primarily psychological or related to stress.

The authors note that the goal of cognitive behavioral therapy, the type of psychotherapy tested in the study, is to change the psychological factors "assumed to be responsible for perpetuation of the participant's symptoms and disability."

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Now, I should say that David Tuller, who is the author of this, he has done some of the very best press coverage around. This particular article was not very good, but it is the best article out there on this study. And he did some follow-up articles that improved things greatly. So he's actually kind of a journalist hero in this world. I don't want to give him too hard of a time.

PACE Study Problems

How did this happen? What was the deal with this study?

They had only one objective test. Everything else was subjective, asking patients if they were feeling better.

The objective test was only semi-objective. What they did was to put patients on a treadmill and tell them to go as fast as you can for six minutes. There's a lot of squishiness there in terms of effort and what-not.

At the beginning of the study, patients were able to go just under 2 mph. That's worse than cardiac patients. That's a leisurely, very leisurely pace. That was as fast as they could go. So these were really sick patients.

After treatment, "recovered": just over 2 mph.

Halfway through the study, they changed the criteria for recovery.

They had some scale with a questionnaire about how ill you are, and the standard for daily functioning was 85. This is to measure how functional you are.

To enter the study, you had to be 65 or below. But after they changed it, to count as recovered, you could be at 60 or above.

You could have gotten worse and be said to have recovered. So not surprisingly, patients were not very happy.

They also didn't point out that the types of improvements that they saw were similar to what you see with graded exercise therapy in heart disease and multiple sclerosis.

They excluded patients who were too sick to get to a clinic.

Finally -- and this was not pointed out in the news coverage, and I think this actually is the key. They did an incredibly gentle form of graded exercise therapy.

It took me a long time to figure this out. I thought, "My God, they did exercise, that's the worst thing you can do for these patients. Why weren't these patients all completely falling apart?"

The answer is that they did an incredibly low level of exercise, and they increased it incredibly slowly. They didn't report very much about adverse outcomes, and I think this is why.

Contrasting Exercise Studies

There is in fact good research on this topic.

Here is a friend of mine, having the two-day exercise test that I described done, where patients exercise to exhaustion two days in a row. She showed me a video of her doing this, and for me, as an ME/CFS patient, it was just horrifying to watch someone exercising to exhaustion knowing what the consequences of that would be. It was like watching someone slice their arm open, really horrible.



CFS patients can do much less on the second day than on the first. This is not true of healthy people or of all kinds of other patients.

What came out of that were recommendations about ways that patients can exercise that's careful enough that they're not going to make themselves sick.

Exercise is a good thing. Deconditioning is not a good thing. But you have to be super super careful about it.

And the key thing is -- hardly anybody knows about this. Doctors don't know about this. Basically nobody outside the specialist community knows about this.

It's an important thing, particularly the recommendations about how to exercise.

Patients need to know that. But the only way to find out is if you go to one of the dozen or so ME/CFS specialist docs in the country.

So that's the last thing I keep talking about -- poor dissemination of the good research.

What Causes These Problems?

So, what's going on here? How does this happen?

In the case of PACE in particular, I think it was a case of seeing what you want to see. It was mostly psychiatrists who did the study. It was funded by the National Health Service. I think they had a strong agenda.

I don't really know how they could have justified these kinds of things to themselves. I'm guessing that they were well-intentioned. My best guess is that they were driven by seeing what they want to see.

I'm asserting without proof that this is a pattern amongst all these confusing illnesses, not just this one.

So why does this happen?

It's pretty appalling. It's not what anybody wants. Everybody involved wants to have decent medical care for sick people. So what's going on?

I think it really has to do with the complexity of the illness and that it doesn't fit within our model.

We want a disease that we have a simple story about that we can put in our heads, where we can say, "Okay, there's this virus." Things got much better in AIDS research when we had an identified virus.

M.S. is an interesting example. These same kinds of things happened in multiple sclerosis, until we had scans that showed demyelination.

Now, when you start looking hard at that, it doesn't actually answer very many questions. Because what causes the demyelination? We don't know. There's also the problem that the degree of demyelination and the degree of disability don't necessarily correlate all that well. Improvements in functioning don't necessarily correlate with improvements in demyelination.

So it seems to be playing a role and to be important, but what does it mean to say it's "the cause"? What it is is a tidy story, something we can put in our minds and have something to hold on to, and that we then can attach other things to. We can ask those questions as elaborations of this basic story that we have in our heads.

But with these other kinds of illnesses, we don't have a story that makes any sense and that is compelling.

I think that is the kind of fundamental thing that then also triggers the other problems. There's a sort of escape valve in the medical world that, "Oh, it must be psychosomatic." And what goes along with that is a lot of disrespect, and that starts feeding on itself.

A Loser of an Issue

And in fact, CFS is a real loser of an issue for everyone involved.

Obviously it's a loser of an issue for patients.

It's also a loser of an issue for doctors, because they need respected medical organizations to tell them what to do. And they don't have it. So they have these patients come in, they're sick, they're whining, they're complaining, and the doctors have nothing to offer them. And it sucks.

For researchers who get involved in this illness, it's a total loser. They can't get funding. It's really really hard to get funding.

They're not likely to get big dramatic results, partly because it's hard to get funding, but also because they're complicated illnesses. You're not going to say, "I found the cause," because it probably doesn't work that way. Probably there is not one single cause that is going to provide that kind of tidy story. They have a really hard time getting tenure.

It sucks to be an ME/CFS researcher. The people who do it are heroic.

It's also the case that whatever they do, they're likely to piss patients off somehow. There will be a group of patients who view them as absolute heroes, and then there will be a group of patients who hate their guts and spew horrid stuff on the Internet about them. So even though they're doing it for the patients, it still sucks for them.

Government officials.

I kind of portrayed them as villains in my story. But they're middlemen. To do anything, they've got to persuade their superiors. Their superiors have the same attitudes about ME/CFS that the general public does. It's really hard to get anything done, and when you step into the job, the patients hate you from the beginning because there's this long history.

So it's really horrible. If you want to have a good career in government service, do not go into ME/CFS. It's really awful.

Journalists.

I can tell you from experience that it's extremely hard to get stories on ME/CFS into papers or magazines because editors, not unreasonably, perceive that the general public really isn't all that interested. They have the same kinds of conceptions that everybody else does. So it's very hard to get articles published.

For me, because I'm a patient, that adds another layer of complexity. But if you're not a patient, do you really care enough to dive into this?

And they're also really complicated stories. You can't take things at face value at all. It takes a lot of time and effort to research all of these things.

Q: These last few days, there's been a lot of press on this new virus that is in southern California that is impacting a certain population. Do you think that that press is related to the population that is being impacted? I hate to be that crass about it, but there are 8- and 12-year-old kids becoming partially paralyzed from this unknown virus. Somehow that seems to be better videoed than a 24-year-old.

Sure. Yes. It's true.

All of these things feed into one another. It's a complex system working badly.

Death Valley and Lake Tahoe

So now, let's go back to my story for a minute.

At the end of 2011, I had this one little window where I was a little more functional and I managed to write a story about ME/CFS for *Slate*.

As a result, I got contacted by a patient who argued that mold was actually a big part of the problem for many, maybe most, maybe even all ME/CFS patients.

And she linked me to a blog post about someone who was trying mold avoidance -- extreme mold avoidance -- and he was able to exercise again. This just blew my mind.

So I contacted her and ended up following her advice.

I went to the desert, to Death Valley, for two weeks with none of my own belongings, because my belongings were potentially contaminated with mold.

So that was a way to get completely clear of mold.

The prediction was that I might or might not feel better when I was there, but that when I came back I would be able to tell when I was exposed to mold -- that I hadn't been able to tell previously because I was basically stewing in it all of the time.

So I did that.

This is where I camped in Death Valley. This was my view. I spent two weeks there.



Then I did a slight elaboration. I actually went to Lake Tahoe where this outbreak had occurred back in the 1980's.

There's a guy who lives near there who was one of the patients in that outbreak and who was the person who kind of figured this out.

So I went on a mold tour with him. He took me to some of the famously bad places.

And I reacted to them.

While I was there, it was hard to tell and I could explain it all away.

But then I woke up in the middle of the night and couldn't walk.

I fired off emails to all of my friends: "Oh my God, I can't walk!" That hadn't been happening lately.

So I came back and I did react to my own living space.

I got rid of all of my stuff and moved, and I quickly got very much better.

That's two years ago. I'm not totally well at this point, but I'm here.

So that's my story.

Mold

The science of mold. There's stuff suggesting that mold can do bad things. But there's been no systematic study of what mold might be doing.

Here again, we get into issues of complexity. There's the mold itself. There's the toxins the molds emit when they kind of go to war with one another. They also emit volatile organic compounds. All of those can have effects.

In water-damaged buildings, you also have particulates released and there are bacteria, and you've got the interactions between all of these things.

Also, molds produce different toxins and different volatile organic compounds depending on what they're eating.

So if you've got mold growing on the Drano that spilled in the bottom of your kitchen cabinet, then it's going to produce different things than mold that's growing on your drywall.

So it's really complicated.

The other thing about mold is that it's kind of come into awareness in a legal context, because of lawsuits about water-damaged buildings. That introduces a whole additional layer into the mix.

A Complex System

What do we do about all of this?

One thing that I think is that there is the possibility of studying the medical system itself as a complex system and to think about ways that it could be intervened in or changed so that this is not the default thing that occurs.

There's also the potential for more complex systems thinking in the medical research itself. Systems biology seems to be one possibility for that. Personalized medicine is another area.

Another big thing is that I think we really need more humility in science. There's kind of an attitude with this kind of thing that, "Well, we don't have good science about it, so we don't have anything to say, so let's turn away and go some other direction."

There's also a certain way that because it's complex, there's a middle ground that one lives in when there is not good science.

I think we have this idea not just that all questions can be answered with science but that all questions will be answered given enough time. And so we'll get to the point where we have evidence-based medicine for chronic fatigue syndrome. And that in the meantime, that patients should just hang in there, because we can't do anything until we've got that. I think that tends to be the kind of default attitude.

But it's not clear to me, frankly, that we're going to get to that point with something like chronic fatigue syndrome. It may well be that there is too much individual variation, that it's too complex.

In any case, I don't think we're going to get there anytime soon. And certainly not if we're spending \$5 million a year. And even if we started spending more, it's a complex illness. It's going to take a while to unravel it.

When Medicine Can't Help

So it seems to me that there's potential for really thinking seriously about what to do with patients when we don't have that kind of knowledge at the level that we want. The way that we do it now is that basically we say, you're on your own. But I don't think that's necessary.

For me, for a long time, I just figured -- well, if doctors don't have anything to offer me, then I will just use what energy I have for living my life and make the best of it.

But what ended up working was actually listening to patients and trying the things that they said.

This requires a kind of time-consuming and elaborate process of getting to know them individually. And trying to figure out -- okay, who should I pay attention to? Who seems crazy and who seems sane? Who seems crazy about what in what way?

So if I heard a recommendation from someone who seemed reliable, like the person who initially recommended mold to me, then that was really worth paying attention to. If I hear something from a number of people who seem medium reliable, and I think about the ways that they're reliable, and it seems like with respect to that they're kind of reliable, then maybe that's worth listening to too.

For that kind of process, I think we could put some real thought into how we can do that in a more rigorous and systematic way.

One thing that's being developed along those lines is a project called HealClick. Actually, it's being developed by the very guy who wrote the blog post that so inspired

me, where he could exercise again. He's just launching this social network site to link patients on the basis of their symptoms, where they can put in information about the treatments that they've tried and lab results and all of that kind of thing and learn from one another.

What he wants to do is to make that information available to researchers as well.

Mold avoidance has come out as a really effective treatment on this website so far. Maybe that has the potential to attract some researcher's attention.

Mold Reactivity

Q: What kind of environment were you in when you had your worst malady?

That's a good question. When I first got really sick in 2006, I was living in Berkeley. I think that was actually really key. There seem to be particular locations that are really bad for people who are sensitive to mold. Berkeley is one of them.

Q: So you discovered that at the source?

Yeah. I was initially really skeptical because I'd lived in lots of different places and it never seemed to matter. I'd never gone into a building or something and gotten much sicker. It didn't seem like this applied to me at all.

Q: Is there a chart that shows where the worst mold is?

Actually, the patient who turned me on to this is here, and she knows more about this than anybody else does. She's got some information about that. There's a website that she started that collects patients' experiences in different locations.

Q: So you found there was a big difference between locations where there were notorious molds and other locations?

Yeah. Yeah. And then after I got clear of mold, I started having incredibly dramatic reactions. Like at the Regal 14 movie theater. I walked in there and -- splat, on the floor. I literally collapsed.

Before I started mold avoidance, I was kind of steeped in it, and so I never noticed anything. But afterwards, I had really dramatic responses.

Q: So you could be a useful tool!

Yes, I have many friends who say, "Can you come to my house and see?"

Q: Did you eat the popcorn first?

No, I just walked in the door, took two steps and went down!

Minimization

Q: You kind of mentioned this but maybe it would be worth pushing it a bit further, for the cultural modelers in the room. Maybe the reason that the minimization occurs is because we live in a society that's sleep deprived, so that anybody who's just a little bit different than that seem like whiners and get culturally denied. If we lived in a society that was actually healthy, if we got enough sleep and took care of ourselves and exercised, then the CFS people really would look like outliers.

Yes, that's true, although severe cases of ME/CFS are far from ordinary experience. When you can only be in a darkened room and not move and have no light and no sound and you can't feed yourself and can barely lift your arm at all, that's pretty far.

Q: Even people who have reduced activity levels in a healthy population would seem unusual. Whereas in our culture now, we're all kind of like that half the time.

That's true.

Crowdsourcing

Q: Julie, you've taught me more about this than reading six or seven years' worth of press releases and studying this. I know more after listening to this than I have had in my entire experience. It occurred to me as you were describing this is that the most effective research that you seem to have run across is basically crowdsourcing. It seems to sort of trump science. Is it producing results for more people? Are more people getting well?

Julie: Yeah, you bet.

Q: Are researchers doing anything with it?

Julie: Nope. Not yet. There are sort of little nibbles of interest. But not yet.

ME/CFS Doctors

Q: Where are these 12 experts located and what connection do they have with the research if any?

So I went to Miami, Florida, to see Nancy Klimas. North Carolina. New York. Utah. Lake Tahoe. There are others as well.

Q: Are those locations related to mold?

They vary quite substantially.

Q: Is there more mold in Florida, for instance?

I can't really address that question. I do think that different doctors see somewhat different versions of CFS in their location because there are different kinds of mold in different areas. But honestly, that's pretty speculative.

Q: What I'm trying to get at is, are the experts located in a place where there are more patients?

I just don't know.

Psychosomatic Medicine

Q: Julie, you probably know the power of psychosomatic medicine. You can be paralyzed from psychosis. Have you met any patients who.... Do you believe that every single patient you've met with CFS..... Or do you think that some patients are psychosomatic, in your experience?

Well, I don't know that I would put it in such stark terms. I think that psychology plays a role in more or less all illnesses, and that it also plays a role in CFS. It plays a role, from my own experience. There's definitely a psychological component, and I've got various bizarre stories to tell about that. Is that all that's going on for some patients? I have absolutely no idea. I have no way of knowing that.

Q: Because that's what the doctors think.

But what is clear to me is that there is a there there. It's not just psychosomatic. What role that is playing, I don't know. Actually that is something that I am interested in looking into and reading the science literature.

Explaining the Illness

Q: I just wanted to point to two things that have come up. But let me preface it with the fact that I have since the early 1980's been told that I had fibromyalgia. My experience was that fibromyalgia and chronic fatigue syndrome are very blurry, and that you get one set of symptoms if you push and go mountain climbing. You're tired and in pain. There's a classic continuum there. And I've been through all the experiences you talk about, being sent off to the shrink. One thing is that when you're steeped in it and you're already sick, you wouldn't know if you're in a location that's causing you to react or not. Only when you feel better are you able to say, "Oh, I walked into Target and then I felt horrible and wanted to lie on the floor. Okay. What's in there?" The other is that the symptoms are just normal human symptoms, like, my body's not doing well today. If you say to someone, "I feel like I'm coming down with the flu." And they go, "Oh, that, yes, I know that." Except that I've felt that way for 12 years. So if you just say, "I'm really tired," then 90% of the people in any room will say, "Yeah, me too." Or if you say, "I get these headaches," people say, "Yes, me too." They overlap with normal human experience. So it's a matter of locating the four or five things that if you have all of them, all long enough and hard enough, then you're talking about something.

Crowdsourcing

Q: With regard to crowdsourcing -- that seems like a really great idea of getting a lot of information from a lot of places, quite independent, and try to get a pattern. But the problem is: Who extracts that pattern and how? How do you avoid suggestion? There are issues of what matters and what doesn't matter.

And it's not independent at all, because these patients are talking to one another.

Q: Exactly. These are the kinds of issues that you see often with studying complex systems. The problem then shifts to that issue. We have more means to get information in this way, which is great. The question is then, how are we able to extract something that is more objective and useful from that pattern? Do you have any insights from your experiences? When you go online, you see a lot of

blogs about people sharing experiences about their conditions, but it's very hard to get at.

The only thing that occurs to me to say about that at the moment is from personal experience is with this really labor-intensive process of getting to know people. Getting to know people relatively deeply and talking to them at length about their illness and how they think about their illness. With the psychosomatic thing -- how are they doing on a psychological level? How are they dealing with it? Do they freak out? Do they tend to be the type of person who tries something and it makes a difference just because they're trying something? How discerning are they? How skeptical are they of their own responses? All those kinds of things -- then I take that into account as I'm judging it. I don't know how we could do that in any kind of systematic way.

Epidemiology

Q: There's a science that studies the causes of disease, epidemiology. A way that you could use a lot of these ideas is that you come up with an adequate case definition. That's hard. You start by identifying true cases and matched controls, and you can go through and create hypotheses. For instance, about mold exposure. Where you've lived in the past ten years. Then you come up with nice identifiable risk factors for this disease. Like with the AIDS epidemic. You had this collection of individuals who had Kaposi's sarcoma and pneumocystis, but you had no idea what caused it. They sat down and had this clear case definition that you can try to tease apart from there. It's surprising to me, and I guess it's because it's such a nebulous thing, that no one's ever sat down and done this.

There's no money.

Q: We know that. The question is, how do you do that?

Q: Well, you have to go to experts and get the case definition.

Research in Complex Systems

Q: This is a question that arises in complex systems. If you're dealing with a complex system, whether it be about public health or whatever, it's very hard for you -- the scientist or the urban planner or the economic planner -- to know everything you need to know to do a good job, and then to know how to put all those things together to get a pattern or mechanism, so that you can act on it. So

how might you do that better? I think this is an interesting example of how people could do this.

But I also would say that there is a lot of research that just hasn't been done. In fact, I would love to have a more extended conversation with some of you about that, and about ways that standard scientific tools that have not been employed with any intelligence yet could be used.

Q: I think that is key. I would flip this around. I wouldn't sort of say, oh, science is bad. Or doctors, they are not precisely the same thing, that doctors are bad because they don't take these patients seriously and so on. I would almost flip it. Given that it is somewhat straightforward in terms of the scientific tools needed, the kind of expertise needed and so on -- if there's a million patients out there, presumably some of them could actually have the resources to dedicate a lot of time and so on. So we could push this to the next level. Have the crowd become the scientists, rather than sit there and outsource it to some existing scientific community. Have people like yourself -- I'm not saying you do it! -- but there are going to be people with typical training, if you've got a million out there, there must be many such. I don't know how to get from here to there, but given that you're not getting research dollars, and that's a problem with Congress and so on that nobody in this room's going to be able to solve, given that, maybe this needs to be completely ground up, not just the data generation but also hypothesis generation, the actual testing and so on, and get it to the stage where you would then elicit the interest of the funders and the more standard community.

There are definitely efforts along those lines. That's why I'm interested in talking to you all about this. I have some nascent ideas about research that could be done that I would love to kind of tease out with you.

Parkinson's Disease

Q: Alternatively, aren't many of these symptoms similar to what you see in Parkinson's, for which there is no definitive test or diagnostic tool now either. But there is a lot of money and recognition of Parkinson's disease. That perhaps is something that you can hang off of it as a subset.

I don't know that much about Parkinson's. I don't know that much about how it's come to be seen as a legitimate thing and hasn't fallen in this slough. One thing that's interesting that I do know about Parkinson's in particular is that there's been a fair amount of research that it's caused by toxins of various kinds. And in fact, there's a recent study about how it can be caused by mold volatile organic compounds. So that's an interesting example to bring up.

Knowledge from Patient Peers

Q: Maybe push it over to treatment. There are some other chronic diseases that are considered to be complex, such as diabetes and obesity. Who's better at treating you -- your peers or a doctor?

Diabetes is an interesting case because there actually is quite a bit of evidence-based medicine. So in that case, I would say the doctor.

Q: It's actually not. In a health care clinic here that's primarily targeted toward the poor, it has one of the best diabetes programs in the country. The reason is that the ex-diabetes patients are the ones who help the new diabetes patients, not the doctors.

Julie: That's fascinating.

Q: I think the same is true for obesity. I would believe the same is true for CFS.

The Legal Community

Q: I just wondered. I had a couple of people who were close to me who had epilepsy and were given Dilantin. Both of them experienced personality disorders, and one committed suicide. In both cases, their wives, noodling around on the Internet, were the people who could tell that this medicine was causing the personality disorder. And it was my friend who died's wife was the leader in a class action lawsuit. So when you start to say toxins, if someone can be made responsible, you can soon find a legal community of everyone's favorite ambulance-chasing lawyers. But within that kind of thing, I would think in the legal world, but you would have to monetize it somehow.

Lack of Funding

Q: Just one small point, about it not being funded. If it were taken seriously and it were funded by the NIH and CDC, all of the things that people have talked about here would be done. It's just that simple. So the problem is the funding. Why isn't it funded? I have talked over the past 25 years with people from Massachusetts General, Mayo, NIH, National Institute of Aging, National Cancer Institute, about this very problem and asked the question, "Why isn't it taken seriously and funded?"

About CFS in particular?

Q: Yes, in particular, about part of syndromes that tend to be undefinable. And one of the reasons is what you say, that they claim is the minor reason, that it is difficult to define. The biggest reason they give is that it is not perceived as life-threatening. Everything else that you've talked about, including diabetes and obesity and AIDS and cancer and cardiovascular, are all not only perceived to be but actually are life-threatening. This may well be life-threatening. But it is not perceived that way. So until you can make a link to death, I think it's going to be extremely difficult to get it funded. If it's just a quality of life issue that you feel shitty all the time, frankly no one gives a flying fuck. It's that simple. And I say that from deep personal experience.

There's a terrible joke about CFS. A patient goes to a doctor and gets diagnosed with CFS and he says, "Well, the good news is you're not going to die. The bad news is you're not going to die."

Thank you everybody, and I'd love to talk more about this.

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