MEDICAL EXAMINER

Stolen Notebooks and a Biochemist in Chains

How did the study of chronic fatigue syndrome come to this?

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Chronic fatigue is a frustrating disease, and the scientific community isn't helping

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Two years ago, Judy Mikovits and the Whittemore-Peterson Institute for Neuro-Immune Disease were triumphant. Mikovits had just published a report in *Science* pointing to a retrovirus called XMRV as the possible cause of chronic fatigue syndrome, a little-understood illness characterized by debilitating flu-like symptoms that worsen with exertion. A wealthy woman whose daughter has the disease had started the institute in 2007 to study CFS, fibromyalgia, and Gulf War illness—and it wasn't long before its researchers appeared to have shown they could succeed where two decades of government-led research had produced little.

Best of all for many CFS patients, the work seemed to offer undeniable proof of what they had long hoped to establish: that their disease has a physiological cause, not a psychological one.

But as of mid-November, the XMRV retrovirus research had been discredited and was suspected of being fraudulent; Mikovits sat clad in a blue jumpsuit in a California jail, accused of stealing lab notebooks and computer files from her former employer; the research program at the Whittemore-Peterson Institute was in disarray; and CFS patients were as confused as ever about the source of their illness and how to treat it.

Mikovits and her employer share blame for this mess, having at the very least hugely oversold the certainty of their result and allowed an intellectual property dispute to get out of control. But a large share of the responsibility goes back to the National Institutes of Health, the Centers for Disease Control, and the researchers who engaged in the weak research those agencies funded. For decades, both agencies have propagated the idea that CFS probably isn't amenable to any physiological treatment, that psychologically healthy people aren't likely to get it, and hence that it isn't an important threat to the general public. Many CFS patients came to feel abandoned by the scientific establishment. This created a climate of mistrust that breeds hero-worship and conspiracy theories and that can cast a scientist simultaneously as a savior and a villain.

The Reno, Nev., institute itself was formed as a response to the despair CFS patients felt. Annette Whittemore, its co-founder, saw privately funded research as the only hope to save her daughter, who at times was homebound and was suffering from frequent seizures. Simply allowing the wheels of science to turn, she had concluded, was unlikely to lead to effective treatment anytime soon.

The first problem was funding: The NIH spends $5 per patient on CFS research each year, compared with $400 per multiple sclerosis patient and $3,000 per HIV patient. (Disclosure: I myself have CFS.) Even leading researchers have difficulty getting funding, especially for research on the hypothesis that CFS is caused by an infectious agent—which is exactly what Whittemore believed to be true. The CDC's reluctance to fund biological studies of chronic fatigue syndrome was so great that between 1995 and 1998, agency officials diverted half the funds allocated for the illness to other diseases and William Reeves, the head of the research program at the CDC, got whistle-blower protection when he testified that officials had lied to Congress to cover up the misappropriations.

Worse, much of that paltry funding has been wasted on questionable science. Soon after the outbreaks of CFS in the 1980s, government officials suspected that it was psychosomatic, because its manifestations were so bewilderingly diverse. Stephen Straus, head of the CFS research program at the NIH, said that he believed it was the same illness that was once called neurasthenia, "a neurosis characterized by weakness and fatigue." Officials stuck to that position even as a large body of evidence accumulated that CFS patients have characteristic patterns of immune, autonomic, neurological, and endocrine abnormalities.

Scientists funded by the CDC published a stream of research to support the idea that CFS is psychosomatic, but their work has some troubling flaws. Last year, for example, a study by the former director of the agency's CFS research program pointed out that 29 percent of diagnosed

patients have a personality disorder, compared with just 7 percent of healthy controls. The paper concluded that "this might be associated with being noncompliant with treatment suggestions, displaying unhealthy behavioral strategies and lacking a stable social environment." But the study ignored the fact that having a chronic illness, particularly a highly misunderstood one, itself takes a toll on mental health. In 2003, by contrast, a non-CDC study found no difference in neuroticism and depressive symptoms between patients with CFS and those with multiple sclerosis.

An additional problem with this study and many others was that they used a definition of the disease that most researchers consider overly broad. Because there is not yet a blood test or other clear diagnostic marker for the disease, any definition has to rely on a set of symptoms. A 1994 definition required that patients experience six months of fatigue that isn't helped by rest along with several of a set of other symptoms including concentration problems, sore throat, pain, and increased symptoms after exercise. Many researchers argued that the requirements needed to be tightened to ensure that the definition would capture only CFS patients, and not those with depression or some other ailment. In 2005, the agency offered a new "empirical" definition, but rather than tightening the criteria, the new definition quadrupled the number of people considered to have the disease. The included symptoms were unchanged, but the empirical definition required that the symptoms have lasted only one month rather than six and established a low threshold for the intensity and frequency of these symptoms. One study showed that 38 percent of people diagnosed with clinical depression qualified as having CFS under the new guidelines but not the old ones. But broadening the pool of patients in this way has only made it harder to find physiological abnormalities and easier to find psychological ones, and it casts into doubt whether any new results would apply to CFS patients as defined by a more specific definition.

Among U.S. scientists who work primarily on this disease, essentially no one argues for a psychosomatic cause. Nor do any researchers use the 2005 definition, besides the ones whose work is paid for by the CDC. Nevertheless, the agency has had a huge influence on the opinion of doctors and the general public, creating an attitude of skepticism and even condescension toward the disease. Rather than focusing on treatments, the majority of research has gone toward providing evidence, in one form or another, that patients had some kind of psychological problem long before they developed the syndrome. Although public officials have acknowledged that the disease may have a number of different causes, including physiological ones, their public statements have alienated the patient community, without offering any clear path to treatment or prevention.

So when Whittemore opened her institute, many patients saw it as their hope for salvation. Whittemore used her own wealth (reportedly contributing $5 million initially) and connections (raising $10 million from the state of Nevada, and $1.4 million from patients and other private donors) to fund research that would be free of the federal government's apparent bias toward psychiatric explanations. Eventually, the NIH got behind Whittemore's effort, too, supplying a $1.5 million grant for her institute's CFS research.

Just a few years after its founding, the retrovirus finding seemed to justify all the high hopes. Because retroviruses can spread through blood transfusions, the risk to the general public was obvious. CFS was catapulted out of the backwaters of science and into the land of big money.

When other groups' first attempts to replicate Mikovits' finding failed, some patients waited for more rigorous studies, but some rallied harder to defend Mikovits, sending money from their disability checks to support the institute. (A few were said to have levied death threats against scientists who questioned the retroviral link.) Mikovits was deluged with emails from patients expressing their desperation for a cure, proclaiming her a hero and pledging to stand by her no matter what. And Mikovits herself combatively defended her result. She even fanned the skepticism by making wildly irresponsible claims, tying the retrovirus to autism, Parkinson's disease, MS, Lou Gehrig's disease, and dementia. The Whittemores also went way beyond the evidence, selling an unvalidated XMRV test to patients for around $500 apiece through a separate lab that they owned.

Eventually, though, major studies came in showing that the infectious agent she'd discovered was almost certainly a laboratory contaminant and not the cause of CFS at all. And that turned out to be only the beginning of the bad news for Mikovits and the institute. The commercial lab stopped selling its XMRV test, but it had taken many thousands of dollars from patients for an illegitimate test. Questions emerged about whether Mikovits had faked data in her *Science* paper. Whittemore fired Mikovits in a dispute over who controlled her lab samples, putting into limbo the institute's $1.5 million grant, for which she is the principal investigator. Soon after, Mikovits' former research assistant said that he had secreted critical lab notebooks out of the building to her and the WPI pressed charges against her for theft, leading to her manacled appearance in a California courtroom. She is now out on bail and the notebooks have been returned.

How did this once-promising effort to understand and treat CFS go so far off the rails? The intoxicating effect of being lauded as the sole defender of the theory that might rescue more than a million desperately ill Americans probably contributed. Some CFS patients felt so mistreated that for them, Mikovits wasn't just a researcher whose theory wasn't yet validated; she was their redeemer. For those patients, the legitimacy of the retrovirus research became conflated with public acceptance of CFS as a "real" disease. Their fervor may well have fueled that of both Mikovits and the institute, leaving each feeling that they were the only ones left standing up for patients and supercharging their initial enthusiasm for the work into self-righteous certainty. For now, it's unclear whether Mikovits is a fraud; an overambitious, careless, and irresponsible scientist; or just a researcher who temporarily lost all perspective. But it's easy to imagine how her sense of obligation to produce results quickly for desperate patients, and the polarized atmosphere around CFS research, could have greased the slide she and the institute took from cautious science into reckless overreaching.

The failings of Mikovits, Whittemore, or the patients who trusted them aren't the point, though. With a disease this debilitating and marginalized, some patients are bound to make leaps of faith; some researchers might start to believe their own press; and a mother may overextend herself in her quest to save her child. But the alienation of the patient community only arose because of the mishandling of CFS by the public agencies. The best way to avoid this kind of fiasco would be

for researchers and public health officials to follow their obligation to protect public health, be faithful to the science from the beginning, and fund and pursue the many promising avenues for research on CFS that have recently emerged.

Remarkably, despite the minimal funding, such avenues *have* emerged. Researchers are making progress toward developing a test that could definitively determine who has the disease and who doesn't—by using either proteins in spinal fluid or alterations in gene expression after exercise. Such "biomarkers" for CFS would show whether CFS is a single disease or a cluster of related ones. An experimental drug treatment has been remarkably effective and has provided evidence that CFS is an autoimmune disease, opening a whole new area of treatment possibilities. These scientists aren't selling testing kits or making dramatic statements about their devotion to their patients. They're just doing their jobs. And they need a lot more government support in getting them done.