disrupts the inflammatory response, however, remains unknown. One possibility is that, as in some autoimmune disorders, T cells mistakenly become alarmed by one of the body's own proteins, rather than by an invader, and B cells secrete self-reactive antibodies.

An accidental finding has lent support to this idea. In 2008, Øystein Fluge, an oncologist at Haukeland University Hospital in Bergen, Norway, treated a lymphoma patient with rituximab, an antibody therapy that kills B cells. The patient told him that the drug resolved their ME/CFS. Fluge and his colleagues then conducted a placebo-controlled trial with 30 people who had the condition (and not cancer), and found that rituximab improved their symptoms[10]. As word spread, Fluge was flooded with hundreds of e-mails from people asking to take part in his trials, and doctors around the world fielded desperate requests for the experimental therapy.

Yet any hopes that Fluge dared to have were dashed last October, as he assessed data from an as-yet unpublished 151-person clinical trial and found that rituximab proved no better than the placebo. Fluge says the finer details of the trial might yet reveal whether a small subset of participants benefited. Like many others, he suspects that ME/CFS might turn out to be several diseases, with different causes and underlying mechanisms. Therefore, what helps some people might not help others. This effect might not be discernible until researchers can tease out how patients differ from one another. Still, the trial's overall failure suggests that autoimmunity is not the main cause of ME/CFS, says Derya Unutmaz, an immunologist at the Jackson Laboratory for Genomic Medicine in Farmington, Connecticut. Rather, he speculates that inflammation seen in ME/CFS might result from a problem on the regulatory side of a person's immune system, which normally reins in the T-cell response to innocuous viruses, mould particles or other non-threatening stimuli. "Rituximab's failure is very disappointing for patients, but the fact that such a trial was done is a very important thing in the field," Unutmaz adds. "By ruling this out, we can focus on other directions." This is the kind of scientific response that patient advocates have been fighting for since the 1990s.

METABOLIC SYSTEM AND MICROBIOME

Newsletters dating back decades document how activists have struggled to be recognized by scientists. In one column from 1998, the co-founder of an ME/CFS organization reports on a conference on the ailment in Boston. She notes that someone from ACT UP, a group known for driving research on HIV, was in attendance, "and may show us how to get more attention for the disease".

Through the 2000s, advocates accused the NIH of favouring grant proposals focused on psychiatric and behavioural studies, as opposed to those exploring physiological pathways. A sea change occurred in 2015, however, with the IOM's review[5] of more than 9,000 scientific articles. "The primary message of this report," concluded the IOM, "is that ME/CFS is a serious, chronic, complex and systemic disease." Soon afterwards, NIH director Francis Collins said that the agency would support basic science to work out the mechanisms of the syndrome.

In September last year, the NIH announced the winners of new grants in support of research hubs looking into ME/CFS. Some of the projects sound as if they duplicate each other, but that's by design. Walter Koroshetz, head of the NIH's National Institute of Neurological Disorders and Stroke in Bethesda and chair of the Trans-NIH ME/CFS Working Group, explains that the NIH sees strength in replication. "There has not been a coordinated effort to follow up on publications and to figure out which findings are most important, which can be reproduced and which fall away when you look at a different patient population," he says. For this reason, one of the NIH grants goes towards a centre at Research Triangle Institute in North Carolina that will merge ME/CFS data.

A $10-million, 5-year grant is also going to Unutmaz, who is studying the interplay between the immunological, metabolic and nervous systems of people with ME/CFS. As part of this, he will collaborate with microbiologists to assess the bacteria living in patients' bodies, and to see how shifts in those populations alter metabolites, such as glucose, that may in turn affect inflammation. Unutmaz admits that his studies are at an early stage, and says the point is to generate data to form sharper hypotheses. "We don't know what we don't know in this disease," he says. Researchers at Columbia University in New York City and Cornell University in Ithaca, New York, have won NIH grants to explore some of the same themes, and to delve into inflammation in the brain.

Some CFS researchers argue that the NIH's contribution remains too lean. "A real problem is that funders want to see papers coming out in a short time period, but this is a complex disease that requires long-term studies that are expensive to conduct," says Eleanor Riley, an immunologist at the University of Edinburgh, UK. Beginning in 2013, Riley helped to launch and maintain an NIH-supported biobank of ME/CFS samples at the London School of Hygiene and Tropical Medicine. But the bank has been limited by funding constraints.

Ronald Davis, a biochemist who directs Stanford's Genome Technology Center, says that he too struggles to fund his lab's work on ME/CFS. He points out that although HIV affects roughly the same number of people in the United States — about 1.2 million — it received 200 times as much funding from the NIH as ME/CFS did in 2017.

In December, the Open Medicine Foundation in Agoura Hills, California, a research charity that Davis advises, announced its support for an ME/CFS collaborative centre led by him. In one project, the team intends to finish analysing the complete genomes of 20 people severely ill with ME/CFS, along with the genomes of their family members, to look for a genetic predisposition to the disease. Another project involves the development of what could be the first diagnostic test for ME/CFS.

"I'VE LEARNED THAT IF IT'S EXCITING, IT'S PROBABLY WRONG."

That test uses a small device containing 2,500 electrodes that measure electrical resistance in immune cells and plasma from blood. When Davis exposed blood samples from people with ME/CFS to a stressor — a splash of salt — the chip revealed that the blood did not recover as well as samples from healthy adults. Davis is holding out on pronouncements, however, until he has conducted a study large enough to show clear and statistically significant effects — including a difference between people with ME/CFS and those with other conditions. "With XMRV, the problem was that people jumped to conclusions," Davis says. "I've learned that if it's exciting, it's probably wrong."

Davis knows the pain of disappointment personally. He started studying ME/CFS in 2008, when his son, Whitney Dafoe, became incapacitated by the disease. Dafoe volunteered to be studied at his father's centre. A member of the team, Laurel Crosby, recalls exchanging e-mails with Dafoe, discussing the research. But as Dafoe's condition got worse, he stopped replying in sentences, and began answering text messages with just a 'Y' or an 'N'. Then those, too, stopped coming. Dafoe, now 34 years old, can no longer speak. He communicates with his parents through small motions, such as ripping holes in the shape of hearts in paper towels.

A poster of Dafoe hangs in his father's office. In it, he is standing on a beach in northern California with his arms raised towards the sky. Davis took the photo on one of the last days his son could walk. "Now he cannot talk, he can't listen to music, he can't write, he lays in bed all day, and there are thousands of patients like this, patients who are embarrassed to be told that nothing is wrong with them," Davis