exploratory studies are now under way. Scientists entering the field are using the powerful tools of modern molecular biology to search for any genes, proteins, cells and possible infectious agents involved. They hope the work will yield a laboratory test to diagnose ME/CFS — which might have several different causes and manifestations — and they want to identify molecular pathways to target with drugs.

The US National Institutes of Health (NIH) in Bethesda, Maryland, bolstered the field last year by more than doubling spending for research into the condition, from around US$6 million in 2016 to $15 million in 2017. Included in that amount are funds for four ME/CFS research hubs in the United States that will between them receive $36 million over the next five years.

The stakes are high because the field's scientific reputation has been marred by controversial research. A 2009 report[1] that a retrovirus called XMRV could underlie the disease was greeted with fanfare only to be retracted two years later. And in 2011 and 2013, a British team reported that exercise and cognitive behavioural therapy relieved the symptoms of ME/CFS for many people in a large clinical study called the PACE trial[2,3]. US and UK health authorities had made recommendations based on the findings, but, starting around 2015, scientists and patient advocates began publicly criticizing the trial for what they saw as flaws in its design. The organizers of the trial deny that there were serious problems with it, but health officials in both countries have nevertheless been revising their guidelines.

**"LAST YEAR, I WENT TO 117 DOCTOR APPOINTMENTS AND PAID $18,000 IN OUT-OF-POCKET EXPENSES."**

Patients, meanwhile, are adrift in a vacuum of knowledge about the condition, says Jose Montoya, an infectious-disease specialist at Stanford Medical School in California and one of Allen's physicians. "ME/CFS has suffered from scientists applying the usual approaches," he says. He hopes that sophisticated analyses of genomics, proteomics, metabolomics and more will help to change that. "It wasn't until the microscope became available that an Italian microbiologist could link cholera to the bacteria that caused it," he says. "In the same sense, we have not had the equivalent to the microscope until now."

## EARLY DAYS

In 1984 and 1985, an epidemic of persistent fatigue broke out in Lake Tahoe, Nevada. The US Centers for Disease Control and Prevention (CDC) tested people for Epstein–Barr virus, one cause of the fatigue-inducing illness called mononucleosis or glandular fever, but the results were inconclusive and the investigation was dropped. Around 1987, researchers coined the name chronic fatigue syndrome. But the media snidely called it 'yuppie flu'. Doctors often told people their symptoms were caused by neuroses and depression.

But a small fraction of clinicians listened closely to patients — who insisted that their debilitating exhaustion was not just in their minds. And whereas a little exercise might temporarily uplift someone with depression, individuals with ME/CFS would be bedridden for days after exertion. Some people also struggle with chronic impairment, some with intestinal disorders, and others completely lose the ability to walk. Anthony Komaroff, a physician-scientist at Harvard Medical School in Boston, Massachusetts, began conducting studies on the disease in the mid-1980s despite being discouraged by his colleagues. "I was emboldened by the fact that when I asked my colleagues why they were sceptical, they could not articulate a reason," he says.

In the 1990s, Leonard Jason, a psychology researcher at DePaul University in Chicago, Illinois, started questioning basic epidemiological information on ME/CFS. For one thing, the CDC described the syndrome as rare and predominantly affecting white women. But Jason reasoned that clinicians could be missing many cases. Those who were diagnosed were the ones most likely to return for a second, third or fourth medical opinion. And people who felt stigmatized, were confined to bed, were poor or had little social support might not go to such lengths to get a diagnosis.

So, Jason's team called almost 30,000 random Chicago phone numbers to ask whether someone in the household had symptoms of the disorder. If they did, the team brought them into clinics for evaluation. As a result of the findings from this[4] and other studies, the CDC removed the word 'rare' from its description of the syndrome. In 2015, a report[5] from the US Institute of Medicine (IOM) estimated that 836,000 to 2.5 million Americans have the disorder. Another study[6] estimated that more than 125,000 people in the United Kingdom are living with ME/CFS. And a report[7] from Nigeria suggests that the prevalence of the disease might be even higher there, perhaps exacerbated by other infectious diseases and poor nutrition. But these tallies are fraught, owing to the different ways in which doctors diagnose the condition.

In many ways, people with ME/CFS remain invisible. Most have been dismissed by at least one physician. And society often ignores them, too. In the United States, financial pressures are common because health insurers might consider experimental treatments unnecessary, and employers might not feel that disability payments are justified. Even in countries where health care is a right, the situation has been dire. Many patient advocates say that UK government agencies have essentially treated ME/CFS as if it were a strictly psychological condition, a conclusion that they argue was bolstered by the PACE trial's findings that exercise and cognitive behavioural therapy relieve symptoms. The National Health Service (NHS) recommended these interventions, even after many patients complained that exercise dramatically worsens their condition.

Epidemiologists have suggested[8] that the anguish of contending with the disorder and society's general dismissal of it contribute to an up to sevenfold increase in the rate of suicide for people with ME/CFS.

Montoya will never forget one such tragedy. A decade ago, he opened an ME/CFS clinic for half a day each week at Stanford. One afternoon, he received a call from a crying woman whose 45-year-old daughter had returned home to California after falling ill with ME/CFS. The daughter had read about Montoya's clinic online and wanted an appointment, but Montoya was booked for a couple of years. In her suicide note, he says, the daughter asked that her brain be donated to him for research. "I feel so guilty, since those were the years with hundreds of patients on the waiting list," he says.

## IMMUNE SYSTEM

Today, Montoya's clinic is open five days a week. And in his research, he's exploring several avenues. The hormone study in which Allen is participating is looking for changes in how the endocrine system is regulated among people with ME/CFS, a factor that might explain why the disorder is more common in women than in men. But Montoya's leading hypothesis is that ME/CFS begins with an infection that throws the immune system out of whack.

Infections generally lead to inflammation when protein receptors on T cells, a kind of immune cell, recognize corresponding proteins carried by bacteria, parasites or viruses. The T cells multiply and catalyse an inflammatory attack that includes the replication of antibody-producing immune cells, called B cells. In the past few years, researchers have revealed hints of an unusual immune response in ME/CFS. Most recently, last June, Montoya and his colleagues revealed[9] abnormalities in the levels of 17 immune-system proteins called cytokines in people with severe cases of the syndrome. What