BIOMEDICAL RESEARCH

Biological underpinnings of chronic fatigue emerge

Gut bacteria and altered metabolic pathways are suspects in mysterious disease.

BY AMY MAXMEN

PRESTON GANNAWAY FOR *NATURE*

Ronald Davis holds the printed circuit he and his team developed to test for chronic fatigue syndrome.

Before his 33-year-old son became bedridden with chronic fatigue syndrome, biochemist Ronald Davis created technologies to analyse genes and proteins faster, better and more cheaply. Now he aims his inventions at a different target: the elusive inner workings of his son's malady.

In his office at the Stanford Genome Technology Center in Palo Alto, California, Davis holds a nanofabricated cube the size of a gaming die. It contains 2,500 electrodes that measure electrical resistance to evaluate the properties of human cells. When Davis exposed immune cells from six people with chronic fatigue syndrome to a stressor — a splash of common salt — the cube revealed that they couldn't recover as well as cells from healthy people could. Now his team is fabricating 100 more devices to repeat the experiment, and testing a cheaper alternative — a paper-thin nanoparticle circuit that costs less than a penny to make on an inkjet printer.

Davis's findings, although preliminary, are helping to propel research on chronic fatigue syndrome, also called myalgic encephalomyelitis (ME/CFS), into the scientific mainstream. Physicians used to dismiss the disease as psychosomatic, but studies now suggest that it involves problems in the chemical reactions, or pathways, within cells. "We now have a great deal of evidence to support that this is not only real, but a complex set of disorders," says Ian Lipkin, an epidemiologist at Columbia University in New York City. "We are gathering clues that will lead to controlled clinical trials."

A report released in February 2015 by the US Institute of Medicine (IOM) has helped to drive the shift. After reviewing more than 9,000 studies, an expert panel concluded that chronic fatigue syndrome was an understudied physiological illness. "They essentially said, 'Shame on you for not investigating this,'" says Zaher Nahle, vice-president of scientific programmes at the Solve ME/CFS Initiative, a non-profit group in Los Angeles, California.

The US National Institutes of Health (NIH) responded by doubling its planned spending on research into the condition, from around US$6 million in 2016 to $12 million in 2017. This month, Avindra Nath, a neurologist at the NIH's National Institute of Neurological Disorders and Stroke in Bethesda, Maryland, enrolled the first patients in a study to compare blood, spinal fluid, saliva and faecal samples from people with chronic fatigue to those without it. The scientists will analyse gut bacteria and proteins involved in metabolism and immune responses, among other things. "I call this a hypothesis-generating study," Nath says. "Researchers are thinking deeply about how to build the field."

FROM TESTS TO TREATMENTS

Elucidating the mechanisms behind the syndrome could lead to new treatments — and the first diagnostic tests. The US Centers for Disease Control and Prevention estimate that 1 million people in the United States have the illness, but the IOM report concluded that the number could be as high as 2.5 million. Physicians use a broad list of criteria to diagnose patients, including whether a person has experienced cognitive impairment and more than six months of profound fatigue — and whether other conditions have been ruled out.

"My son can't read. He can't listen to music. He can't talk. He can't write," Davis says. "But when the doctor does a battery of tests on him, they all come out normal." Having a test that could signal if something was wrong in such cases would be a big help, he adds.

Lipkin has identified a distinct set of intestinal bacteria in 21 people with chronic fatigue syndrome who also had irritable bowel syndrome — conditions that often occur together. His study, accepted for publication in the journal *Microbiome*, also links both diseases to changes in body processes influenced by gut microbes, such as the production of vitamin B6 (D. Nagy-Szakal *et al. Microbiome*; in the press). And a study by another team, published in December 2016, finds problems with the function of an enzyme that is crucial for the process by which cells create energy (Ø. Fluge *et al. JCI Insight* **1,** e89376; 2016).

Rather than seeing the thicket of metabolic, microbial and immunological data as adding to the confusion surrounding chronic fatigue, researchers are studying how the body's systems affect each other. The current consensus is that a variety of initial triggers might converge to alter similar metabolic pathways, which ultimately leads to life-changing fatigue.

Davis says that such metabolic disruptions could impair cells' ability to generate energy in response to stress, explaining the findings from his nanofabricated cube. First, however, he wants to ensure that his results are consistent, by comparing more data from people with chronic fatigue and those with and without other diseases.

"This is not an academic exercise," he says. "My son is in bad, bad shape." ■