Six times a day, Katrin pauses whatever she’s doing, removes a small magnet from her pocket and touches it to a raised patch of skin just below her collar bone. For 60 seconds, she feels a soft vibration in her throat. Her voice quavers if she talks. Then, the sensation subsides. The magnet switches on an implanted device that emits a series of electrical pulses — each about a milliamp, similar to the current drawn by a typical hearing aid. These pulses stimulate her vagus nerve, a tract of fibres that runs down the neck from the brainstem to several major organs, including the heart and gut.

The technique, called vagus-nerve stimulation, has been used since the 1990s to treat epilepsy, and since the early 2000s to treat depression. But Katrin, a 70-year-old fitness instructor in Amsterdam, who asked that her name be changed for this story, uses it to control rheumatoid arthritis, an autoimmune disorder that results in the destruction of cartilage around joints and other tissues. A clinical trial in which she enrolled five years ago is the first of its kind in humans, and it represents the culmination of two decades of research looking into the connection between the nervous and immune systems.

For Kevin Tracey, a neurosurgeon at the Feinstein Institute for Medical Research in Manhasset, New York, the vagus nerve is a major component of that connection, and he says that electrical stimulation could represent a better way to treat autoimmune diseases, such as lupus, Crohn’s disease and more.

Several pharmaceutical companies are investing in ‘electroceuticals’ — devices that can modulate nerves — to treat cardiovascular and metabolic diseases. But Tracey’s goal of controlling inflammation with such a device would represent a major leap forward, if it succeeds.

He is a pioneer who “got a lot of people onboard and doing research
in this area”, says Dianne Lorton, a neuroscientist at Kent State University in Ohio, who has spent 30 years studying nerves that infiltrate immune organs such as the lymph nodes and spleen. But she and other observers caution that the neural circuits underlying anti-inflammatory effects are not yet well understood.

Tracey acknowledges this criticism, but still sees huge potential in electrical stimulation. “In our lifetime, we will see devices replacing some drugs”, he says. Delivering shocks to the vagus or other peripheral nerves could provide treatment for a host of diseases, he argues, from diabetes to high blood pressure and bleeding. “This is the beginning of a field.”

SHOCK VALUE
It was only by accident that Tracey first wandered down the path of neuroimmunity. In 1998, he was studying an experimental drug designated CNI-1493, which curbed inflammation in animals by reducing levels of a potent immune protein called tumour-necrosis factor-α (TNF-α). CNI-1493 was usually administered through the bloodstream, but one day, Tracey decided to inject it into a rat’s brain. He wanted to see whether it would lower TNF-α in the brain during a stroke. But what happened surprised him.

CNI-1493 in the brain reduced production of TNF-α throughout the animal’s body. Other experiments showed that it did this about 100,000 times more potently than when injected straight into the bloodstream1. Tracey surmised that the drug was acting on neural signals.

His follow-up experiments supported this idea. Minutes after he injected CNI-1493 into the brain, Tracey saw a burst of activity rippling down the rat’s vagus nerve2. This neural highway regulates a handful of involuntary functions, including heart rate, breathing and the muscle contractions that push food through the gut. Tracey reasoned that it might also control inflammation. When he severed the nerve and the drug’s potent effect disappeared, he was convinced. “That was a game-changer,” says Tracey. The finding meant that if one could stimulate the vagus nerve, the drug wouldn’t even be necessary.

And so he tried a pivotal experiment. He injected a rat with a fatal dose of endotoxin, a component of the bacterial cell wall that sends animals into a spiral of inflammation, organ failure and death. The drug’s effects roughly mirror septic shock in humans. Then, Tracey stimulated the animal’s vagus nerve using an electrode. The treated rats had only one-quarter as much TNF-α in the bloodstream as untreated animals, and they didn’t go into shock3.

Tracey instantly saw medical potential for vagus-nerve stimulation as a way to block surges in TNF-α and other inflammatory molecules. Companies were already selling implantable stimulators to treat epilepsy. But to extend the technique to inflammatory conditions, it should be moderating. As the disease progresses, these nerves advance back into the tissues that they abandoned — but they do so in abnormal ways, making connections with different subsets of immune cells. These rearranged neural pathways actually maintain inflammation rather than dampen it4. It happens in places such as the spleen, lymph nodes and joints, and is causing a lot of pathology, says Bellinger.

But she, Lorton and others are sceptical of Tracey’s account of the pathway by which vagus-nerve stimulation lowers inflammation. Robin McAllen, a neuroscientist at the University of Melbourne in Australia, has searched for connections between the vagus nerve and the nerve that stimulates T cells in the spleen — but so far, he has found none.

Vagal stimulation “is acting indirectly” through other nerves, says Bellinger. It’s important that these neural circuits are properly mapped before moving onto treatment in people, she says. “The anatomy makes a big difference in what kind of side effects you might see.”

Yet, even these sceptics see potential in Tracey’s methods. Bellinger points out that in many autoimmune diseases, not only do sympathetic nerves become overactive as they rearrange themselves into proinflammatory circuits, but also the vagus nerve, which opposes them, becomes underactive. Vagal stimulation might partially restore the balance between these two neural systems. “It’s a first step,” she says. “I believe that they will introduce it to the clinic, and they will show remarkable effects.”

A PATIENT APPROACH
People given vagus-nerve stimulation for seizures or depression experience some side effects — pain and tightening in the larynx, or straining in their voice, for example; Katrin feels a minor version of this when she stimulates her vagus. Shocking this nerve can also lower the heart rate or increase stomach acid, among other effects.

In this respect, Tracey has cause for optimism. The human vagus nerve contains around 100,000 individual nerve fibres, which branch out to reach various organs. But the amount of electricity needed to trigger neural activity can vary from fibre to fibre by as much as 50-fold.

Yaakov Levine, a former graduate student of Tracey’s, has worked out that the nerve fibres involved in reducing inflammation have a low
A shock to the immune system

The vagus nerve, which connects the brainstem to several organ systems in the body, has a putative connection with the splenic nerve, part of the sympathetic nervous system. It is through this connection that a technique called vagal-nerve stimulation is thought to reduce inflammation.

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CORRECTION

The News Feature ‘The electric cure’ (Nature 545, 20–22; 2017) erroneously stated that Kevin Tracey initiated the first trial for vagus nerve stimulation in humans. In fact, the trial was started by SetPoint Medical. And Paul-Peter Tak, who ran the trial, first joined GlaxoSmithKline in 2011, not 2016.