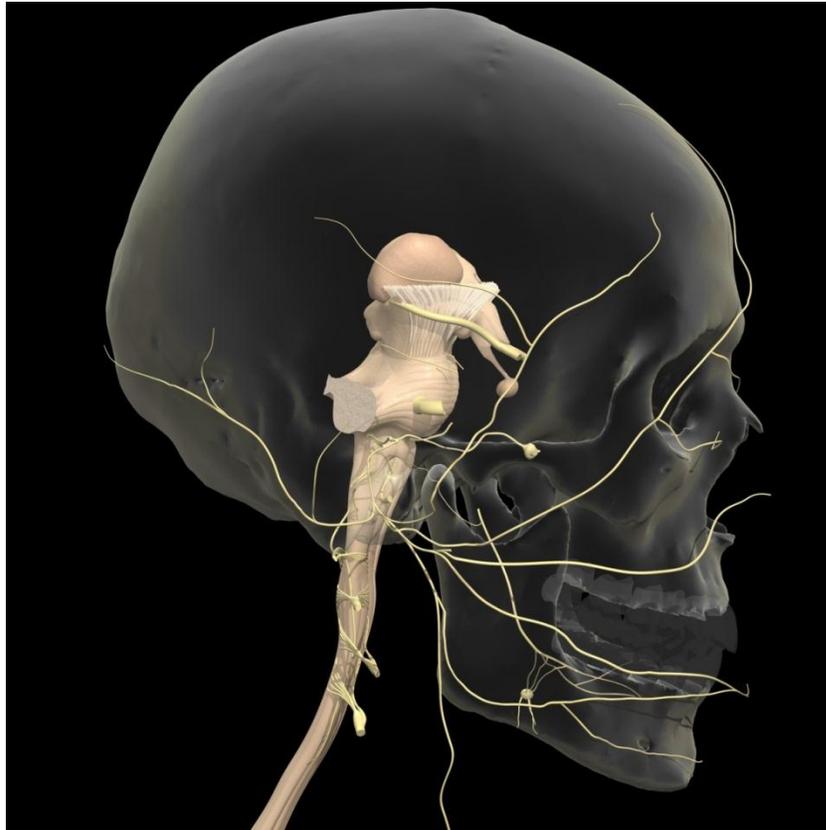


A New Approach to Rheumatoid Arthritis:
Treating Inflammation with Computerized Nerve Stimulation
By Ulf Andersson, M.D., Ph.D., and Kevin J. Tracey, M.D.



Cranial nerves with transparent skull. Primal Pictures/Photo Researchers, Inc.

Editor's note: Doctors currently treat rheumatoid arthritis, a crippling autoimmune disease, with an arsenal of drugs that, while often effective, can have serious side effects. Authors Ulf Andersson and Kevin J. Tracey describe a circuit between the immune system and the nervous system that enabled development of an implanted nerve stimulator to treat the disorder, now being tested by a patient in Bosnia. If further clinical trials show as much promise as this initial case, similar devices may be developed for a broad range of inflammation-related diseases, from diabetes to congestive heart failure.

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A few months ago one of us (Kevin Tracey) traveled to Mostar, Bosnia, to meet a very special patient, the first to receive a surgically implanted nerve stimulator to treat disabling rheumatoid arthritis. Eight weeks earlier, as a volunteer in a research study, the patient underwent a minor surgical procedure during which a neurosurgeon implanted a small pacemaker-like device and attached the electrode to a nerve in his neck. This vagus nerve, which runs from the brain, across the chest and thorax, and into the abdomen, sends branches into all of the major organs of the body. The implanted computer began delivering electrical signals that instructed his immune system to stop attacking his joints. As a result, after years of incapacitating pain in his hands, wrists, elbows, and legs, he is now in clinical remission. This comeback is remarkable, suggesting for the first time that it may be possible to replace powerful immune system-suppressing drugs with a computerized device to treat crippling inflammatory diseases.

Most people are comfortable with the concept that medical devices, ranging from cardiac stents to artificial hips and knees, can be used to treat broken hearts and broken bones. But the idea of using a nerve-stimulating medical device to treat inflammatory diseases is revolutionary. Its potential emerged from a breakthrough in neurophysiology revealing that electrical signals transmitted in the vagus nerve suppress inflammation. The potential therapeutic implications of this concept are far-reaching, because inflammation is a participant in many disease syndromes, including Alzheimer's and other neurodegenerative brain diseases, as well as inflammatory bowel disease, congestive heart failure, atherosclerosis, and diabetes.

Current Treatment Approaches

Rheumatoid arthritis, the first of these diseases to be studied in the clinic, is a crippling autoimmune disease that causes chronic inflammation in joints. Painful swelling can destroy the major and minor joints of the hands, feet, and extremities, leading to disability, fatigue, and immobility. It afflicts nearly one percent of the world's population, women more often than men, most frequently in the fifth and sixth decades of life (though all ages can be affected). The economic consequences to society from lost productivity and treatment costs are staggering, and currently there are no cures.

The basic problem in rheumatoid arthritis, and other autoimmune diseases, is that immune system cells begin to attack the body's own tissues.² Current therapies suppress the

attacking action of the immune cells with an armamentarium of drugs that includes aspirin-like substances, corticosteroids, and other so-called disease-modifying anti-rheumatic drugs. While such drugs can be effective, toxicity significantly limits their use in some cases, and treatment failure limits them in others. Another mainstay of therapy is drugs that target cytokines, molecules produced by white blood cells during inflammation. In a healthy immune response, cytokines ward off infection and promote tissue repair, but when the body produces these same molecules in excess, they are highly toxic. In rheumatoid arthritis, high cytokine levels accumulate in the cartilage and other inflamed joint tissues to produce pain and destroy tissues.

Treatments that specifically block the action of cytokines have shown major promise in alleviating the disease in some autoimmune patients. These advanced drugs have now been administered to millions of individuals, providing insight into the important role that cytokines play in the development of the disease. The downside, however, is that these drugs are powerful immune system-suppressing agents that impair defenses, which can leave the patient susceptible to major infection. Some of these therapies even carry a black box warning, a notice mandated by the FDA that immunosuppressive side effects can be extremely dangerous, or even fatal. Furthermore, the widespread adoption of these agents is hampered by cost, which may run as high as \$30,000 per patient annually. Even if patients undertake these risks and costs, 50 percent fail to achieve significant clinical benefit. So there obviously remains a major unmet medical need for the development of new treatment options for rheumatoid arthritis and other autoimmune diseases.

Healthy Nervous System Regulation

The origin of the device being tested in Bosnia came from studying body mechanisms that evolved to regulate one of the major toxic cytokines, termed TNF. The first cytokine that researchers successfully targeted to provide clinical benefit in rheumatoid arthritis patients (others have followed), TNF occupies a crucial role in triggering painful destruction of the joints.² In healthy people, the nervous system provides a precise mechanism of checks and balances that maintains the levels of TNF within a safe range. But in rheumatoid arthritis, like brake failure in a car barreling down a mountain, the neural control exerted by the vagus nerve fails and the production of TNF goes out of control. Very recent insights have revealed that it

may be possible to restore the vagus nerve signals that are missing in these patients and reestablish safe levels of TNF.³

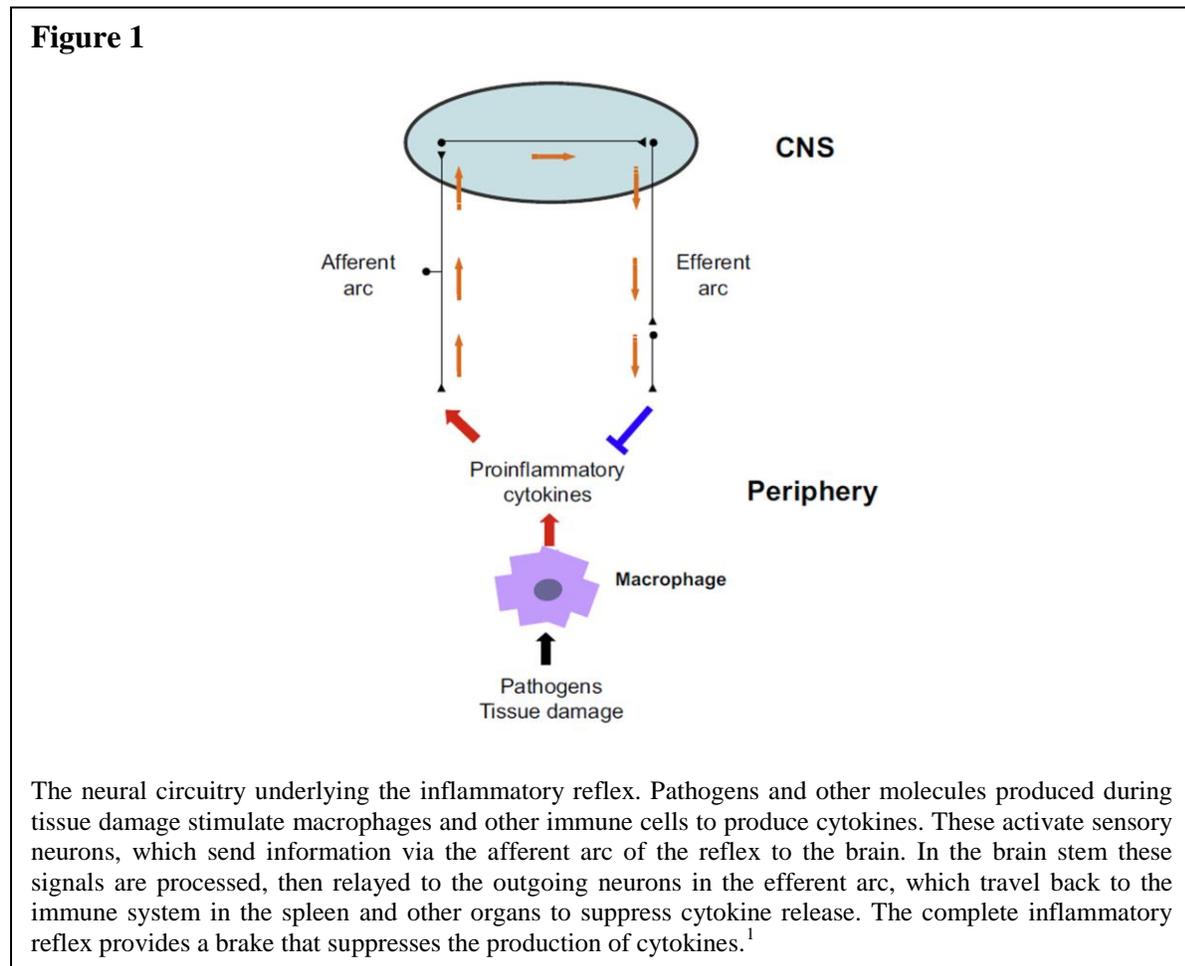
That the vagus nerve controls TNF production is quite consistent with long-known principles about how the body works: health is possible because the body regulates organ function within a narrow, optimal range. For example, body temperature is maintained at 37 degrees Celsius, and normal heart rate is 72 beats per minute. Healthy physiological systems adjust organ function around an ideal set point through a process called homeostasis, and the nervous system plays a critical role in regulating the activity of body organs within this healthy range.

It does so through a network of involuntary, or autonomic, nerves, which, as the name implies, act without conscious input. These neurons project to all of the body's major organs, including heart, lungs, kidneys, spleen, and digestive tract. We don't have to think about digesting our food or accelerating our heart rate during exercise because these processes are regulated by the involuntary nervous system. The basic mechanism underlying homeostasis is set in motion when sensory nerves send minute-to-minute information about the status of the organs back to the brain. The brain processes the incoming data in neural feedback loops, resulting in return instructions being sent back to the organs to maintain function within a healthy range.

Neurons in these networks communicate with other cells by transmitting information as small electrical spikes, called action potentials. These propagate very quickly along nerve axons to stimulate the release of neurotransmitters from the nerve ending. The release of these molecules converts the electrical signal into a chemical one; the neurotransmitters travel a short distance away from the nerve ending and then bind to receptors on adjacent cells, acting like drugs to change the behavior of the cell. The receiving cell can be another neuron, a muscle cell, or a white blood cell, and binding of the neurotransmitter to the specific receptor signals the receiving cell to modify its metabolism, biochemical activity, and gene-expression patterns.

The fundamental guiding principles by which autonomic neural circuits regulate organ function have been known for decades. For example, to regulate heart rate, sensory nerve fibers detect the resting heart rate and relay that information to the brain stem, which in turn sends instructions via nerves traveling from the brain stem to the heart, causing heart rate to either slow or accelerate. The net effect of this closed-loop circuit is like the thermostat on the wall of your home, in which deviation from a set point activates a signal to compensate for the change.

Autonomic nerve reflex circuits operate continuously to and from the principal organs, below the level of normal consciousness. Despite this advanced knowledge, only quite recently did studies surprisingly reveal that similar principles apply to the immune system.



In this nervous-system-to-immune-system circuit, sensory nerves detect the presence of molecules produced during inflammation, initiating a report to the brain. This is the first step in a reflexive circuit that maintains immunological homeostasis (See Figure 1). The resultant outbound neural signals to the immune system are carried in the vagus nerve to slow down the inflammatory response. Some of these signals travel to the spleen, a spongy blood-filled organ adjacent to the stomach, where immune cells are a major source of TNF in the body. Thus, cytokine-blocking signals originating in the brain stem travel down the vagus nerve until they reach the abdomen, where they terminate upon neurons that in turn travel in the splenic nerve,

the only nerve to enter the spleen. This is the basic anatomy of the inflammatory reflex, enabling the vagus nerve to shut down TNF release from the spleen and confer a braking action against damaging inflammation.³ For unknown reasons, in rheumatoid arthritis these vagus nerve signals fail, and the resulting brake failure causes an excessive production of TNF.

Restoring the Brakes on Inflammation with Computerized Nerve Stimulation

The stimulator being tested by the Bosnian patient is a direct method to restore the brakes on inflammation. Instead of drugs to block inflammation, a small computer generates an electrical pulse, which is relayed through an electrode connected to the patient's vagus nerve. This stimulates the production of action potentials in the vagus nerve that travel to the spleen. There are theoretical advantages to this approach as compared with using immunosuppressive drugs. The effects of drugs entering the body are not restricted to the spleen: they can also produce unwanted or unnecessary effects in other organs. But selective stimulation of the neural circuit to the spleen should make it possible to restrict the treatment effects of the device to specific organs, and to control the immune system regionally without adversely affecting other body organs.

Researchers are studying whether it may be possible to modulate the inflammatory reflex for treating a number of diseases, since the basic mechanisms of dysregulated inflammation (as described above) also contribute to the pathogenesis of inflammatory bowel disease, congestive heart failure, arthritis, shock, sepsis, and other syndromes.⁴ Our studies have revealed that vagus nerve stimulation leads to the release of significant quantities of the neurotransmitter acetylcholine in the spleen. We identified an acetylcholine-producing, memory phenotype T-cell population in mice that is integral to the inflammatory reflex.⁵ These T-cells are required for the inhibition of cytokine production by vagus nerve stimulation. Thus, action potentials originating in the vagus nerve regulate specialized T-cells, which in turn produce the neurotransmitter acetylcholine, required to control TNF production and other innate immune responses. Moreover, white blood cells are constantly passing through the spleen, and upon exiting it, these inflammatory cells have a role in the onset and progression of arthritis and other forms of tissue injury in areas that the vagus nerve does not reach. The net effect of this arrangement is that vagus nerve signals can significantly limit the ability of these cells to cause damage when they travel to distant tissues, like the joints in patients with rheumatoid arthritis.

Hope for the Future

Eight weeks after his surgery, this first patient returned to work, performed manual labor, and drove a delivery truck. When asked about how he felt before and after the surgery, he made it very clear that the vagus nerve stimulator therapy had alleviated the severe pain in his joints. A review of his laboratory test results indicated that his serum levels of CRP, a marker of inflammation that is often elevated in arthritis patients, had fallen from an abnormally high value (more than 20 milligrams per liter), to a normal level (1.2 milligrams per liter). His quality-of-life measures and the number of joints that were swollen, painful, and tender were all significantly improved. His face wore an expression of unbridled joy, gratitude, and relief.

Obviously, his story represents but a single case, and in today's world of highly regulated, comprehensive clinical trials, it serves as an important step down the path to additional work that must be done in large-scale studies to replicate and validate the results. Future studies may reveal subgroups of patients who are particularly sensitive to this therapeutic approach, and others who may fail to respond. It is likely that important new clinical information about optimal stimulation methods and treatment responses will come from larger controlled studies with prolonged follow-up periods. Researchers will have to extensively explore and understand the possible risks of this approach, including wound infections and unanticipated consequences on the cardiac, respiratory, or neurological systems. But this single case is also a quantum leap, because the clinical, symptomatic, and biochemical evidence of this treatment response was predicted by more than a decade of preclinical laboratory work that successfully used devices to stimulate the vagus nerve to suppress damaging inflammation.³

The next few years promise to be a busy and exciting time in this field, since preclinical studies in laboratory settings indicate that this approach may be effective in diseases ranging from arthritis to inflammatory bowel disease, psoriasis, diabetes, heart disease, sepsis, Alzheimer's, and other neurodegenerative diseases. Today we are witnessing the clinical testing of a new concept in treating inflammation, and already the first critical steps have been taken to determine whether surgically implanted nerve-stimulating devices can successfully modulate an inflammatory disease. If this approach also offers advantages in efficacy, safety, cost, and compliance over drugs, then it is not difficult to imagine that devices may replace immunosuppressive agents as a therapeutic mainstay for inflammatory diseases.

Ulf Andersson, M.D., Ph.D., has worked for 35 years as a pediatric rheumatologist at the Karolinska Institute in Stockholm, Sweden. During this period, he has performed parallel basic studies in immunology in the context of inflammation in order to develop novel therapy for arthritis. He has authored some 200 original publications and reviews. At present, he is a professor of pediatric rheumatology at the Karolinska University Hospital and chairman of the Pediatric Unit at the Department of Women's and Children's Health at the Karolinska Institute.

Kevin J. Tracey, M.D., is president of the Feinstein Institute for Medical Research and Jacobson professor and head of the Laboratory of Biomedical Science. He is a member of the American Society for Clinical Investigation and the Association of American Physicians, and holds a doctorate *honoris causa* from the Karolinska Institute. He is a neurosurgeon by training, and his laboratory's contributions to science include discovering HMGB1, a pivotal mediator of sterile and infectious inflammation, and delineating the molecular and neurophysiological basis of neural circuits that control immunity. Dr. Tracey is the author of *Fatal Sequence* (Dana Press, 2005).

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