

Reprogramming the Immune System by Charlene Laino, MSNBC.com

Jan. 23 — It's like pouring gasoline on a fire to put it out. Yes, you read correctly: that's the best way to describe a novel approach that shows promise for treating multiple sclerosis. Using an extremely large dose of the very substance that is causing the disease will help cure it.

For the first time, scientists have shown that the experimental approach works in non-human primates with multiple sclerosis. There's every reason to believe, they say, that the same tactic could help stomp out symptoms in humans suffering not only from MS, but also from other autoimmune diseases, such as rheumatoid arthritis and diabetes.

Researchers have known for years that autoimmune diseases result when a malfunctioning immune system mistakenly recognizes certain cells in the body as the enemy and launches an all-out attack. In multiple sclerosis, the myelin sheath — the protective covering that surrounds nerve cells in the brain and spinal cord — is the target.

More recently, experiment showed that specialized immune-system cells called T-helper cells are the key players, the culprits that produce substances that attack and damage the myelin sheath. The result is devastating for the millions of Americans with the disease: fatigue, dim or blurred vision, disturbed speech, memory loss, muscle weakness, even paralysis.

Like soldiers, T-helper cells sit ready for invasion from a foreign invader, be it a flu bug, food-borne bacteria or other pathogen. Then, as soon as they recognize the enemy, these T cells turn into commanding officers of sorts and begin multiplying until an entire army is set to fight.

“But like any potent weapon, you want to control how much is deployed,” says the National Institutes of Health's Dr. Michael Lenardo. “If the cells just kept multiplying ... you'd have a surfeit of T cells, very potent activators that can actually kill you — as happens in toxic shock syndrome.”

Programmed for Destruction

Fortunately, every cell has a built-in suicide mechanism. “When there are too many soldiers, they are programmed to self-destruct,” he says. “A healthy immune system doesn't let your T cells grow uncontrolled and kill you.”

Several years ago, Lenardo, a researcher at the National Institute of Allergy and Infectious Diseases' laboratory of immunology, decided to put the new knowledge about the immune system in general and MS in particular to a test. Since MS is an autoimmune disease in which T-helper cells are activated that shouldn't be, Lenardo reasoned that he could thwart the disease if he could just activate T-helper cells' built-in suicide mechanism.

Working at first in the lab, Lenardo proved his point. As expected, T-helper cells exposed to small amounts of the proteins making up the myelin sheaths were stimulated to attack the sheaths.

Paradoxically, when these activated T-helper cells were exposed to large amounts of the same proteins, they died off. “Instead of robust proliferation, which is what we expected, we got self-destruction,” says Lenardo. “We observed negative feedback.”

Next, Lenardo tried the experiments in mice, “with very dramatic results. Not only did the MS mice become healthy, but the disease-causing T cells were actually eliminated,” he says.

Monkey Business

In the latest test, nine male marmoset monkeys were injected with just enough myelin proteins to stimulate their T cells to attack myelin sheaths, inducing a disease very similar to MS in humans. Three monkeys then received additional large doses of myelin proteins, three got moderate doses, and three received nothing.

About three months later, all three of the untreated monkeys showed symptoms of the disease. In contrast, none of the primates who got large doses of myelin had symptoms. The moderate-dose group didn't fare as well, with two showing symptoms, though less severe ones than their untreated counterparts. The report appears in the February issue of the *Journal of Immunology*.

Imaging scans of the animals' brains further validated the observations. Magnetic resonance images revealed severe damage to the myelin sheaths in two of the untreated monkeys and one of the moderate-dose monkeys. Minor damage did occur in the large-dose group, indicating the disease process had not been completely thwarted although it had been greatly suppressed, Lenardo says.

One of the most exciting aspects of the new work is that it marshals the body's own, nontoxic resources to fight off the disease. Similar to chemotherapy for cancer, current treatments for MS and other autoimmune diseases are atom bombs of sorts, killing or suppressing everything in their wake, good or bad.

"Conceptually, we have a very powerful new tool," Lenardo says. "It selectively homes in only on those cells causing the disease rather than shutting down the entire immune system."

There are even advantages over other immune-based approaches to autoimmune diseases, he says. "The others just paralyze T cells, but they could wake back up. This actually gets rid of them." With human testing still on the horizon, it's too early to say whether Lenardo's approach is best. But with one in 20 Americans victim of one autoimmune disease or another, at enormous personal cost in pain and suffering and at monetary costs topping \$100 billion each year, it's certainly worth a shot.