BY CARL ZIMMER

Can boosting immunity make you smarter?

The body's defense cells engage the brain in an intricate dialogue that may help raise IQ.

AFTER SPENDING A FEW DAYS IN bed with the flu, you may have felt a bit stupid. It is a common sensation, that your sickness is slowing down your brain. At first blush, though, it doesn't make much sense. For one thing, flu viruses infect the lining of the airways, not the neurons in our brains. For another, the brain is walled off from the rest of the body by a series of microscopic defenses collectively known as the blood-brain barrier. It blocks most viruses and bacteria while allowing essential molecules like glucose to slip through. What ails the body, in other words, shouldn't interfere with our thinking.

But over the past decade, Jonathan Kipnis, a neuroimmunologist in the University of Virginia School of Medicine's department of neuroscience, has discovered a possible link, a modern twist on the age-old notion of the body-mind connection. His research suggests that the immune system engages the brain in an intricate dialogue that can influence our thought processes, coaxing our brains to work at their best.

Kipnis got the idea of an immunity-intelligence link while earning his Ph.D. at the Weizmann Institute of Science in Israel. His adviser, Michal Schwartz, was performing experiments to understand how the brain repairs itself after an injury. She found that the brain depends on a type of immune cell known as the T cell, which normally kills infected cells or leads other immune cells in a campaign against foreign invaders. Her research suggested that T cells can also send signals that activate the brain's resident immune cells, microglia and blood-borne macrophages, telling them to protect the injured neurons from toxins released by the injury. Without T cells, Schwartz and other researchers have found, the brain does a bad job of healing itself.

If Kipnis's crazy idea was right, he reasoned, then he should be able to make the idiot mice smarter by giving them back their T cells.

Kipnis was fascinated by the discovery because he knew that T cells cannot get past the blood-brain barrier. Yet apparently they could significantly influence the brain from a distance. He wondered if T cells did more for the brain than just help heal wounds. "The crazy idea came to me: What if we needed T cells for healthy brain function?" Kipnis says.

'I've Never Seen Such Idiotic Mice'

To test the idea, Kipnis performed an experiment on mice. He reared two groups of the animals, one group that was normal and another that lacked T cells. Otherwise they were genetically identical. Kipnis then sent the mice to a colleague, Hagit Cohen at Ben-Gurion University of the Negev, to see how well they could learn a new trick.

Cohen subjected the mice to a learning test known as the Morris water maze. She put them in a pool of water, where they started to swim frantically. Just under the surface of the water was a hidden stand. If the mice could find the stand, they could climb onto it and stop their desperate swimming. Over several rounds, the mice learned where the stand was hidden and swam straight for it.

After testing the animals, Cohen—who didn't know the details of Kipnis's research—gave her colleague a call. "She said, 'One of the groups of the mice you sent me are real idiots. I've never seen such idiotic mice,'" Kipnis recalls. Those mice could not find the stand; they were also the ones without T cells.

If Kipnis's crazy idea was right, he reasoned, then he should be able to make the idiot mice smarter by giving them back their T cells. He injected the cells into the mice's bloodstream and gave the cells time to multiply and spread. Then he and his colleagues tested the mice again. With their T cells restored, they were idiots no more. They did almost as well as the mice born with normal immune systems.

Because the blood-brain barrier made it impossible for the T cells to affect the brain from the inside, Kipnis wondered whether they were maximizing their long-distance influence by getting as close as they could to the brain.

It has long been known that the membranes encasing the brain, called the meninges, are loaded with T cells and other immune cells. Kipnis and his colleagues wondered how smart mice would be if they

THINKSTOCK

Silverman had sequenced XMRV in seven of 11 CFS patient samples sent to him in March of 2009 by Mikovits. But when he reexamined those original samples again in the summer of 2011, Silverman discovered that all seven were contaminated, not with mouse DNA but with an infectious molecular clone originally made in his own lab in 2006. After researchers began using the Silverman clone for their experiments, it replicated "like crazy" and spread beyond the boundaries of those projects throughout the lab, Silverman now found. The discovery was even more troubling since Silverman had sent his synthetic clone to "about a hundred labs" around the world.

In September, Silverman and the other authors of the *Science* paper began working with the magazine's editors on the wording of a partial retraction of the data contributed by Silverman. (Silverman argued for a full retraction.) It was published in the online edition of *Science* on September 22, 2011, two years after the original study. Bruce Alberts, editor-in-chief of *Science*, unilaterally retracted the paper in full two months later.

Mikovits nevertheless remained deeply concerned that the prevalence of the Silverman clone in so many laboratories had prevented scientists from looking for greater virus sequence diversity that might have revealed additional MLV-like viruses, as Lo had done at the FDA. No one had yet disproved that a murine leukemia virus was spreading through human population, she insisted—an observation greeted with skepticism and occasional derision by scientists who were following the controversy.

entura County jail as a 'fugitive from justice.' She remained there for five days.

THINGS WERE UNRAVELING BETWEEN ANNETTE Whittemore and Mikovits as well; earlier, on September 29, 2011, Whittemore had fired Mikovits as research director of the Whittemore Peterson Institute. In response to press inquiries, Whittemore offered "insubordination and insolence" as reasons for the dismissal. The dispute had to do with Mikovits's insistence that another scientist at WPI had improperly ordered a cell line for experiments that were beyond the purview of his authority. Whittemore roundly disagreed with her scientific director.

Three weeks later, Mikovits—who had returned to California to be with her husband—was served with a civil lawsuit by the WPI claiming she had "purloined" lab notebooks and other intellectual property belonging exclusively to the WPI, charges her attorney has vehemently denied. Finally, in a development that stunned even her harshest detractors, Mikovits was handcuffed in her home by police on December 4 and booked at the Ventura County jail as a "fugitive from [Nevada] justice." She remained there for five days, classified as a "flight risk," until her husband was able to obtain legal representation and have her released on bail.

But L'Affaire Mikovits and the search for retroviral infection in CFS has not come to an end. In January 2012, Ian Lipkin invited Mikovits and the NCI's Ruscetti to contribute to a rare, NIH-funded study to be orchestrated at Columbia. In fact, Lipkin braved the disapproval of his high-level friends at the NIH to insist that Mikovits be included in the study, which had Ruscetti and Mikovits, the CDC, and the FDA testing blood from nearly 150 CFS patients and an equivalent number of controls. Each of the three government teams was given blood samples from the same patients and controls. Lipkin asked each group to employ the lab methods they had used in their original papers. Lipkin and his staff broke the codes and analyzed the results.

None of the participants—including the NCI team—found evidence of XMRV in any samples. Given the definitive results and objective design of the study, the scientific world at last considers the XMRV case closed.

Mikovits is unqualified in her gratitude to Lipkin for insisting that unbiased science be done. XMRV "is one scary virus in the laboratory," she says today. "It seems to be ultra-stable and can spread through droplets in the air, like a mycoplasma. How could any of us have known?"

In spite of the disappointing results, Mikovits continues to believe a human retrovirus will be discovered eventually to lie at the heart of CFS. "I still see the footprints of a retrovirus there," she says. "In the Lipkin study, 3 percent of the controls and 3 percent of the CFS patients had an antibody cross-reactivity to something. It cannot be XMRV, since XMRV doesn't exist as a human infection. But it's very close."

The possibility that Mikovits's prediction is correct is being explored. A new, $10 billion research initiative to investigate CFS was launched in September 2011 at Lipkin's laboratory after multi-millionaire hedge fund manager Glenn Hutchins, a director of the Federal Reserve Bank of New York and vice chairman of the Brookings Institute, provided the cash and promised more money in the future should the investigation bear fruit. (Lipkin identified the brain infections Borna virus in 1990 and West Nile virus in 1999.)

"What's occurred in the last 30 years is criminal," Mikovits says today. "Mothers and fathers got sick, their children got sick." But with heightened attention, she adds, patients are likely to get help soon. Even lacking a causal pathogen, biomarkers in this patient population can be studied for clues. "We can find therapies for the CFS patient population even before we determine the exact cause," Mikovits says. For his part, Lipkin credits Mikovits with "opening Pandora's box. Right or wrong about this particular virus, she deserves credit for awakening interest in CFS."

For a disease that has languished in a kind of political never-never land for at least one human generation, leaving millions profoundly disabled, that is significant progress.

Hillary Johnson is the author of *Osler's Web: Inside the Labyrinth of the Chronic Fatigue Syndrome Epidemic* (Crown, 1996), which documented the CDC's squandering of millions of dollars meant for the study of CFS in the 1980s and 1990s.

had a normal supply of T cells everywhere in their bodies except the meninges, so he injected a compound into mice that prevented T cells from reaching the meninges. When those animals were put into a water maze, they, too, performed badly—just as Kipnis had predicted.

Guarding the Brain

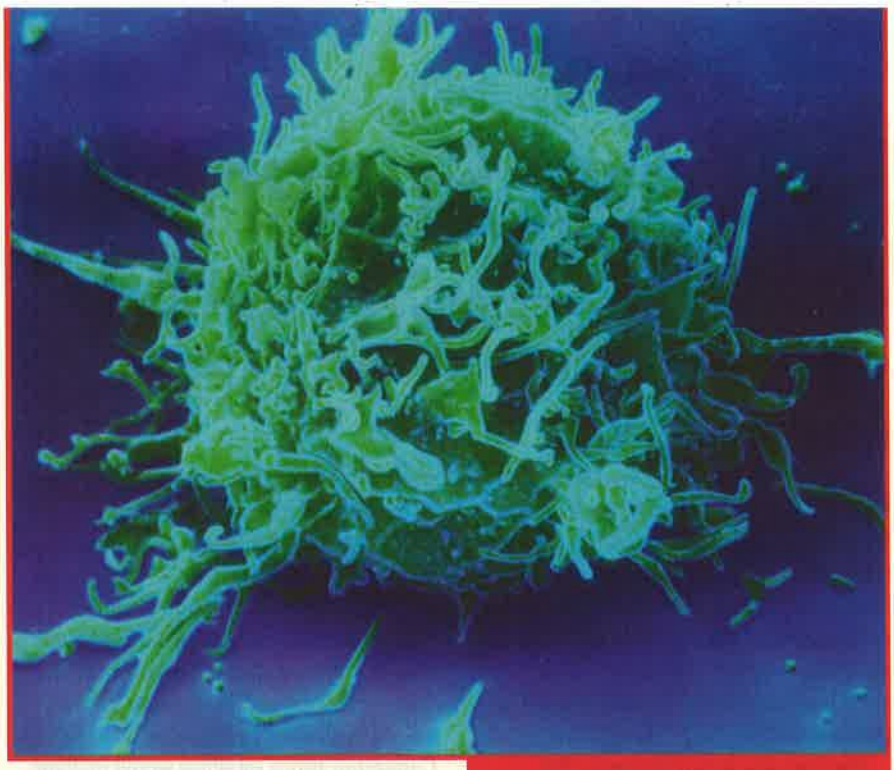
Kipnis is now investigating what exactly the T cells surrounding the brain are doing to make the brain work well. One strong possibility: They keep the rest of the immune system from inadvertently harming it.

When we learn something new, our neurons tear down old connections and build new ones. In the process they cast off lots of molecules. To the immune system, this waste may look like an infection or some other kind of trouble, resulting in inflammation and the release of harsh compounds that normally fight viruses but can also interfere with the brain and its function.

Kipnis suggests that T cells keep this process in check, differentiating between disease and ordinary stress and, when warranted, telling other immune cells to stand down by releasing antagonist molecules that prevent misguided inflammation.

The same T cells that protect the brain from inflammation also work to keep us sharp; and in what appears to be a feedback loop, the mere act of learning reinforces the effect. As mice learn something new, T cells in the meninges produce high levels of a molecule called interleukin 4 (IL-4). IL-4 is an immune system signal that curbs the inflammatory response and, according to research by Kipnis and others, also improves learning. Indeed, when mice lacking the gene for making IL-4 take the water maze test, they do badly, perhaps because their T cells lack a critical signal involved in fast learning.

This theory could explain why we lose our mental edge when we get sick, Kipnis says. When we're healthy, T cells keep the immune cells in the meninges from inflaming the brain. But when we get sick, the T cells loosen their hold to let the immune system attack invading pathogens. The resulting inflammation helps clear out the invaders, but it also blunts learning. When we're sick, Kipnis proposes, it's more important to launch a powerful immune attack than to have a sharp mind. "Everything in life is priorities," he says.



T cells, white blood cells that are a key part of the immune system, may also play an important role in cognitive function.

NIBSC/SCIENCE SOURCE

Kipnis has recently started to investigate what happens to people's brains when they start losing T cells. People with cancer, for example, often suffer a loss of T cells when they undergo chemotherapy. It may be no coincidence, he argues, that chemotherapy is notorious for causing "chemo brain"—a fuzzy mental state in which patients have trouble thinking clearly. Kipnis proposes that without T cells to keep inflammation in check, immune cells in the meninges pump harmful compounds into the brain.

Old age also strips us of our T cells. The thymus, a strawberry-size gland in the chest, produces a steady stream of T cell precursors in our youth. But over the decades it shrinks until it's barely visible. Kipnis proposes that with fewer T cells, older people cannot effectively suppress the inflammation around their brains—which could play a part in the cognitive decline that people experience as they age.

There are many other factors involved in how well we learn and remember things, but for the most part they are very hard to change. Drugs that might be able to rework neurons inside the brain and improve mental sharpness are often too big to get past the blood-brain barrier, for example. Dopamine, a molecule crucial for signaling between neurons, cannot cross this barrier, which is why its chemical precursor, L-dopa, is used instead to treat Parkinson's disease. But the immune system offers a new way of changing our cognition and treating illnesses affecting the brain.

An experiment Kipnis and his colleagues carried out recently on mice missing T cells foreshadows how future brain-immune medicine might work. The scientists drew blood from old mice, whose supply of T cells was depleted, and isolated immune cells. They added IL-4 to the flasks where they reared those immune cells. Then the scientists injected the IL-4-exposed cells back into the mice. Afterward, the mice were able to learn well—presumably because their brains were no longer suffering from inflammation.

"Today we can't really get inside the brain and fix things. But we can take the immune system out of the body, we can put it back in, we can do almost anything we want to it," Kipnis says. "We could target the immune system and get benefits in the brain. It could be an amazing therapeutic tool."

BY COREY S. POWELL

Beware: Superflare

Getting ready for a devastating solar storm just might require some impossible-seeming physics.

SEPTEMBER 2, 1859, WAS A TERRIBLE day to be working in the information industry. Telegraph machines around the world behaved as if possessed. They spat out electric shocks and set telegraph paper on fire. Some of the machines continued to send and receive messages even after they were disconnected from the batteries that powered them.

One man saw how it all began. The day before, Richard Carrington, a British brewer's son who rose to be the foremost solar astronomer of the time, had observed an extraordinary event. He was examining an 11-inch-wide projected image of the sun, part of his routine monitoring of the solar surface, when he noted the eruption of "two patches of intensely bright and white light ... the brilliancy ... fully equal to that of direct sun-light." Carrington knew he was witnessing an enormous explosion, nearly as bright as all the rest of the sun put together. It was the first time anyone had observed a solar flare, and the first time anyone had seen a solar event produce such tangible consequences on Earth.

Fortunately, those consequences were modest, since the telegraph pretty much defined the beginning and the end of high tech in the middle of the 19th century. If the same event happened today, the story would be drastically different. Flares and the broader solar eruptions associated with them unleash storms of charged particles, emit flashes of energetic X-rays, and temporarily mangle our planet's magnetic field. Even for regular-strength flares, those effects can fry electronics in space and overload power transformers on the ground.

But the eruption that Carrington witnessed—now known as the Carrington Event—was hardly ordinary. It is now recognized as the most powerful solar storm ever documented. Such superflares seem to occur once every few centuries. Half-Carringtons (which are still terrifyingly potent) strike every half century or so. The most recent one happened in 1960.

A National Research Council panel recently examined the likely impact of a present-day solar superstorm. GPS signals and radio transmissions would be disrupted by the radiation blasting Earth's upper atmosphere. Communications satellites would malfunction. Most unnerving, the electrical grid in the U.S. (and potentially much of the world) could collapse as transformers overload, leading to a wide-scale blackout that could take 10 years to repair in full. Health care, sanitation, and transportation would be crippled. The Council's estimated price tag: up to $2 trillion during the first year alone. Or in the words of Ephraim Fischbach, a physicist at Purdue University, "The damage from a solar storm would vastly overwhelm the damage from Hurricane Sandy. Literally millions of people could die."

The best scientists can do right now is watch the sun for signs of trouble and monitor space weather—the flow of particles and fields—between the sun and Earth. Fischbach has a better idea. He may have figured out a way to forecast the next Carrington Event far enough in advance to allow meaningful action: putting satellites in standby mode, reconfiguring critical services that rely on GPS, shutting down or decoupling key parts of the grid—things that could make the difference between short-term inconvenience and long-term disaster.

Unfortunately, Fischbach's plan puts him squarely at odds with much of the scientific community.

A Seasonal Link?

Fischbach is the epitome of the curious soul, constantly poking around at the edges of known physics in search of something that other people overlooked: a fifth force of nature, for instance, or a flaw in Einstein's theory of relativity. About a decade ago he noticed a juicy oddity buried in a pair of overlooked papers, one from Brookhaven National Laboratory, the other from a German measurement institute. The two teams were watching the decay of certain radioactive elements. This is a routine bookkeeping style of research: According to known physics, this type of radioactive decay is a fundamental process that unfolds at an unchanging rate, and all the researchers were aiming to do was to measure that rate and record it for reference. Instead, both teams got a rude surprise. The rate of decay in their samples was not steady but varied according to the season. That fluctuation was small, about 0.3 percent, but it was consistent and—Fischbach noted happily—very, very weird.

Most scientists dismissed the two papers as flukes and moved on. Fischbach decided to take the results at face value. "We had two experiments on two different continents seeing essentially the same thing," he says. What effect, he wondered, could make a lump of radioactive silicon decay faster or slower?

In conjunction with his Purdue colleague Jere Jenkins, Fischbach realized that the seasonal nature of the variation might provide the crucial clue. Earth follows a slightly oval path around the sun, closest in January and farthest in July. The changes in radioactive decay rate tracked that pattern, rising and falling on cue over the course of the year. It seemed as if it affected the way atoms decayed on Earth, 93 million miles away.

Sensing they were onto something big, Fischbach and Jenkins scoured the literature and found more reports of radioactive decay enigmatically slowing down and speeding up, results so contrary to expectation that they, too, had largely been tossed into the dust bin of odd results and equipment error. Even more intriguing, these experiments also seemed to show a seasonal variation. The only way to determine if the effect was real, Fischbach decided, was to run an experiment of his own. So his group acquired a sample of radioactive man-