



Neuroinflammation—
literally inflammation
in the brain—may
be at the root of
depression and pain.

Brain On Fire

Scientists have hit on a theory about inflammation that could radically change the way we treat people with pain and depression. One doctor isn't waiting for proof.

BY KATE LOWENSTEIN

It's a riddle that vexes even the most lettered researchers—a widespread medical predicament affecting more people than cancer and heart disease combined, and yet there's no consensus on what's to blame. One hundred million Americans suffer from chronic pain, and they deal with it day after day with no clear fix. Twenty-one million have depression, and for many of them, medication and therapy help only so much. In this progressive medical age, doctors can transplant people's faces and manipulate genes, but they still can't seem to cure—or sometimes even effectively treat—these common conditions. Why? Gary Kaplan, DO, an osteopathic physician who's been dubbed the Doctor of Last Resorts, thinks he knows.

Patients arrive at the Kaplan Center for Integrative Medicine in McLean, VA, after having been turned away by doctors, sometimes dozens of them, who can't help. These people have been told in one way or another that their problems are all in their heads, and Dr. Kaplan agrees—just not in the way you'd think. He believes that unexplained depression and chronic pain result from a single thing: an overzealous immune reaction in his patients' brains.

Scientists refer to the immune response gone rogue as chronic inflammation and have identified it as a contributor to a wide range of

conditions, including heart disease, asthma, and joint pain. Since studies started making these links in the early 2000s, the term *inflammation* has become somewhat of a buzzword, bandied about by health nuts and doctors alike. Some physicians consider it such an important predictor of poor health that they monitor patients' blood for a marker of inflammation, called C-reactive protein, as part of a standard workup. This testing is still uncommon, and it's somewhat controversial, but more and more doctors are coming to see it as a tea-leaf reading of sorts: "How sick is my patient, really?" Meanwhile, scientists are still exploring what inflammation is and how it might be responsible for so many of our health problems.

We know it's necessary for our survival: When you slash open your shin or catch a virus, your immune system goes into combat mode, inflaming the area with an army of white blood cells. While this can show up in obvious ways—a swollen ankle, the raised edges of a wound—it can also happen inside your body without obvious outward signs. A healthy inflammatory response lasts a few hours or days and recedes when the threat is gone. But those white blood cells and potent virus-killing chemicals, called cytokines, can continue to proliferate long after their services are needed.

This longer-term version of inflammation—chronic inflammation—wreaks havoc on your body, because cytokines don't just stay at the site of

the insult; they can cruise through your bloodstream, ultimately damaging tissue, spurring plaque buildup in your arteries, and sometimes even causing the growth of tumors. It's a version of chronic inflammation—specifically, overactivity of microglia, immune cells in the brain—that Kaplan suspects is at the root of depression and pain.

He isn't the only one who thinks this. A raft of studies suggests that chronic inflammation in the brain may be an underlying cause of problems so widespread, we've come to think of them as normal, like anxiety, fatigue, depression, and pain. Research is mounting, but there remain holes in the evidence so large, you could drive a Mack truck through them. (Exhibit A: We still don't have brain-imaging tools sensitive enough to actually see the inflammation in most cases.) But he doesn't think there's time to wait for science to catch up, and neither do his patients.

Kaplan is 60 years old, with a boyish face and a tendency to launch into lengthy scientific explanations punctuated by bursts of laughter at his own jokes. His patients talk about him with gratitude and more than a hint of bewilderment. "At first I thought he was a charlatan," says Patricia Westpfahl, a 45-year-old attorney from Washington, DC, "and I still think half of what he does is pure voodoo. But he's the only one who was able to connect all the dots for me." Westpfahl made an appointment with Kaplan in late 2012 in hopes of finding relief from symptoms that



were slowly taking over her life. She had developed generalized pain so intense that combing her hair and putting on makeup sent searing pangs through her scalp and face, and depression and fatigue interfered with her ability to stay awake at work and while driving. Westpfahl had seen a sleep specialist, psychiatrists, and neurologists, but none could explain what she was experiencing. That afternoon in October, Kaplan sat with her for 2 hours, as he always does initially with patients, gathering details about her life starting from birth. He also ran a large panel of tests on her blood and stool. To him, the cause of her problem was utterly obvious.

Kaplan believes that treatments like acupuncture, diet changes, and the sparing use of drugs can tamp down chronic inflammation and potentially reverse major depression, chronic pain, and a host of other pernicious physical and psychological ills. If the theory is right, it could one day change the way doctors handle these difficult diseases, allowing them to treat the underlying problem—the inflammation itself—rather than just the symptoms. (It could also explain why centuries of alternative medicine have been effective while other solutions have remained elusive.) “Until now, our best options were to mask the symptoms—to give morphine to temporarily dull pain, for instance, or an antidepressant to modulate

depression,” he writes in his forthcoming book, *Total Recovery* (Rodale, May 2014). “For the first time in history, we are on the threshold of knowing how to cure them.”

America’s best-known vices—sedentary behavior, poor diet, smoking, and alcohol abuse—can cause chronic inflammation. The body responds to these modern irritations by launching a prolonged immune response that sticks around as long as the bad habit does. Another culprit: psychological stress, which can cause an increase in these unhealthy habits but also independently increases inflammation. It’s a vicious circle: Stress triggers inflammation, which can cause ills ranging from heart disease to pain and depression. Those diseases are stressors themselves, which in turn can lead to more inflammation.

Emotional or physical trauma early in life might be a particularly potent cause. “People who have very

“Old wounds left

difficult childhoods have higher rates of chronic inflammation,” says Aoife O’Donovan, PhD, an assistant adjunct professor of psychiatry at the University of California, San Francisco, School of Medicine. In a 2012 study of nearly 1,000 people ages 45 to 90 with cardiovascular disease, those who had encountered major stressors, like surviving a natural disaster or serious car accident, had increased

rates of inflammation (as measured by markers in their blood) later in life. Other research shows that people with stress in early life have higher rates of chronic pain and inflammatory diseases in adulthood.

Kaplan sees a pattern among patients with unexplained chronic pain and depression: Each person's past, he says, is dotted with physical or psychological traumas. One woman experienced the death of her father, immediately followed by a serious car accident. Another patient developed an allergic reaction to a mold infestation in his house, and then tore his anterior cruciate ligament (ACL) while snowboarding. Westpfahl, as Kaplan learned during her initial session, was abused as a child, and years later she became infected by a Lyme-disease-carrying tick.

If research shows that childhood stress could lead to inflammation in adulthood, then each of these traumas, he suspects, has the capacity to trigger

the body," he writes. "So it makes sense that a woman who was raped as a child and gets a concussion in her 20s could develop fibromyalgia and clinical depression. These events may seem unrelated, but all of them result in chronic neuroinflammation."

It may sound farfetched, but preliminary science bears out the theory. We've long known that a hard blow to the skull or a severe neurological illness can cause the brain to launch an acute inflammatory response via microglia, the central nervous system's immune cells. But more recent research suggests that inflammation from elsewhere in the body can go to the brain, also spurring microglial activity. Long-term stimulation of these immune cells can make them hypersensitive, causing the brain to become chronically inflamed.

Still, most scientists agree that the data is not far enough along to inform the way patients are treated.

unresolved build up inside the body."

an immune reaction, bringing on an internal, invisible inflammatory state that lasts well beyond the point of outward healing. In cases like these, he says, chronic inflammation has spread to the brain, setting off changes in neurons that result in uncontrolled, unpredictable pain, along with symptoms of depression.

"When remnants of old wounds are left unresolved, they build up inside

"Hundreds of investigators have proposed that there's a relationship between immune activity and symptoms like fatigue, pain, and depression, but, in terms of treatment, we're not there yet," says Andrew H. Miller, MD, a professor of psychiatry and behavioral sciences at Emory University and a pioneer in research on the effects of inflammation on the brain. "I believe there is a subgroup of

Turn Down the Heat

Stress is an unavoidable part of life, but there are things you can do to keep the effects from becoming chronic.

Take the right supplements.

Gary Kaplan, DO, recommends magnesium (work up to 150 to 350 mg), vitamin D (2,000 IU), probiotics (10,000 to 25,000 CFU), and omega-3s (2.5 g).

Drink green tea. It's been shown to lower so-called bad LDL cholesterol, which is associated with inflammation in the cardiovascular system.

Exercise regularly. Working out can lower the activation of microglia, the immune cells in the brain that cause neuroinflammation.

Get mindful daily. Meditation of any type lowers inflammation—and studies show that it can have a measurable impact on heart disease, back pain, insomnia, arthritis, and other conditions.

For more, look for Dr. Kaplan's forthcoming book, **Total Recovery: Solving the Mystery of Chronic Pain and Depression** (Rodale, May 2014).

depressed patients whose increased inflammation is causing their disease. But these ideas remain theories."

Kaplan isn't waiting for validation. Take Jada Peric, a woman who came to his clinic after years of unexplained pain and gastrointestinal trouble. Other doctors had diagnosed her with fibromyalgia and irritable bowel syndrome, but the drugs she was prescribed were getting progressively less effective and the side effects more unbearable.

Kaplan noted that Peric had had malaria as a child and again as an adult. The illnesses had run their course but, he thought, might have left her brain inflamed in the years that followed. This neuroinflammation set her up to be hypersensitive to physical assaults that came later, including whiplash from a fender bender that resulted in unexplained whole-body pain. Kaplan thinks that if doctors had understood the precarious state Peric

Anti-inflammatory

was in before her symptoms set in, her years of physical misery could have been curbed.

So far there's no satisfying explanation for why many people have inflammation in, say, their joints that never spreads to the brain. (Kaplan and others suspect it likely depends on a person's genes.) What

is clear, says Charles Raison, MD, an associate professor of psychiatry at the University of Arizona and a longtime researcher in the field, is that these conditions are interrelated. For instance, people with major depression have an increased risk of heart attack, stroke, and dementia – conditions all thought to arise from inflammation.

For inflamed, depressed patients, anti-inflammatory drugs could help. In several studies, adding the anti-inflammatory drug celecoxib (Celebrex, commonly used to treat arthritis) to traditional antidepressants decreased symptoms of major depression more effectively than when antidepressants were given with a placebo. But so far, there are no FDA-approved drugs for inflammation-related mental-health conditions. (And no, you can't just take an aspirin.) "It will take really targeted anti-inflammatories to be effective," says Dr. O'Donovan, "and these have yet to be identified."

and psychotherapy. Admittedly, integrative doctors have recommended these treatments for years, and even Kaplan allows that they might be working via mechanisms other than the brain's immune system. Regardless, they seem to help people.

Westpfahl is one of them. After treating her Lyme disease with antibiotics, Kaplan prescribed acupuncture, craniosacral therapy, and psychotherapy to calm down her activated brain immune cells. After about 7 months, she reports, her pain started to recede, and she began to see glimpses of the high-energy woman she'd once been.

Dr. Miller and Dr. Raison are skeptical of this kind of broad application of the theory. But whether or not Kaplan's techniques are based on mainstream science, there's no doubt that he stands as a model alternative for millions of people who have been given no other option. "We're not going to help people who are depressed and in

drugs could one day treat depression.

Kaplan sidesteps this problem by using a variety of drugs off-label, including Celebrex and low-dose naltrexone, normally used to treat narcotic and alcohol addiction. He also calls upon a host of alternative practices, including elimination diets (in which patients ditch allergens like gluten, soy, and dairy), acupuncture, craniosacral therapy (manipulation of the head and neck to relieve tension),

pain if we don't spend time finding out about them as whole people with histories that greatly influence their health," he says. "Neuroinflammation is not the answer to everything, but understanding it is extremely important. It will eventually change how we treat these reversible diseases." If he's right, a lot of people stand to gain. ■

Additional reporting by Carrie Arnold