

Can Infection Give You the Blues?

An overactive immune response can seed psychological illnesses

By Erich Kasten

ILLUSTRATIONS BY MANDY ROOT-THOMPSON

By the time she visited her doctor, Anne, a 28-year-old graduate student, had felt listless for months. Plagued by headaches, dizziness, anxiety and visual disturbances, she was struggling in her seminars and failed two exams. She also quit hobbies she enjoyed and stopped socializing. Her doctor diagnosed burnout, a depressive reaction to ongoing stress. He prescribed antidepressants and referred her to me for psychotherapy. Neither helped. A year later I suggested she

go for a routine checkup to rule out any underlying physical illness. Her doctor discovered that she suffered from chronic sinusitis. After two weeks on antibiotics, Anne's infection cleared. What is

more, her depression began to lift as well.

Anne's case is one of a growing number in my own practice and others to suggest that depression can be a symptom of something as simple as infection. Clinicians have long viewed depression as a complex disorder. Stress, neurochemical imbalances, physical pain and ill health can all precipitate an emotional collapse. Yet a flurry of research during the past 25 years has linked many of depression's contributing factors to a single root cause: inflammation.

In the short term, inflammation is an important part of our immune system's built-in ability to thwart disease and injury. But when prolonged, it can prompt fatigue and melancholy. In addition, investigations hint that an upset immune

system might underlie a host of other psychiatric illnesses, including obsessive-compulsive disorder, panic disorder and post-traumatic stress syndrome.

With these growing insights, scientists are testing new treatments to heal the psyche by tempering chronic inflammation. Even if the approach may help only some people with depression, the benefit could be enormous. About one in 10 individuals in the U.S. suffers from a serious spell of despondency at least once during their lives, and depression is the most prevalent mental illness among women.

Self-Defense in Overdrive

Our immune system deploys an arsenal of diverse cells to keep us healthy, choreographing their actions by way of messenger molecules called cytokines. Cells attacked by harmful bacteria, viruses, parasites or cancer secrete interferons, a class of cytokines that warn neighboring tissues to bolster their defenses and rally killer cells to engage. Cytokines called interleukins help to coordinate fever (which limits the spread of an infection) and inflammation (which rushes specialized immune cells to the scene). Tumor necrosis factors, yet another large family of cytokines, destroy abnormal cells and activate other cytokines. They also promote swelling, reddening and pain, which have both positive and negative effects.

Working together, these various proteins modulate the type, intensity and duration of an immune response. Across the blood-brain barrier, they also hold considerable sway over our emotional state. When we are unwell, interferons and interleukins announcing the start of an attack flood the brain. Numerous studies have revealed that these proinflammatory cytokines can disrupt the normal functioning of multiple neurotransmitters and dampen the production of serotonin, often called a happiness hormone for its ability to boost mood. As a result, even people with minor colds often lose their appetite, feel tired, seek warmth,

FAST FACTS

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- 1 Cytokines—the messenger molecules of our immune system—not only coordinate the body's defenses but also make us feel tired and listless when we are sick.
- 2 Stress may shift our immune system to a perpetual state of alert, causing higher levels of inflammation and increasing the risk of depression and other disorders.
- 3 Both medicines and dietary interventions that reduce inflammation appear to help some patients suffering from depression and anxiety disorders.

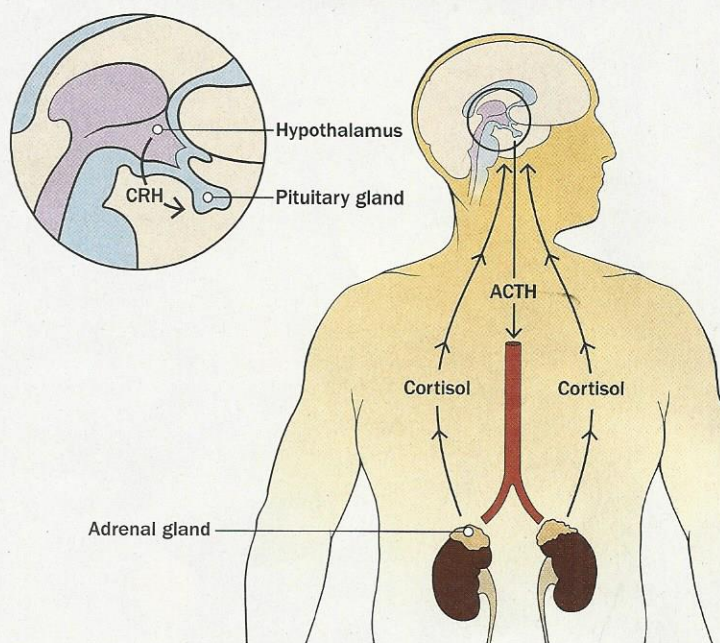
avoid others and struggle to concentrate.

Biologically, this sickness behavior, as it is called, makes sense. Our immune system works more efficiently and we can recuperate faster if we stay in bed. We are also less likely to infect our co-workers and friends. Once an illness has cleared, anti-inflammatory cytokines see to it that our bodies and our brain chemistry reset. But what if an illness drags on and the immune system continues to pump out proinflammatory signals? In that case, sickness behavior begins to look a lot like depression. Tooth decay, urinary tract infections and sinusitis are all examples of infections that do not always produce obvious symptoms or pain but might perpetuate sickness behavior for a long period.

To test the idea that depression can sometimes be a kind of extended sickness behavior, psychology researcher Yekta Dowlati of the University of Toronto and her colleagues evaluated 24 studies in a paper published in 2010, looking at measurements of proinflammatory cytokines in about 400 depressed individuals. Overall, these subjects showed significantly heightened blood levels of tumor necrosis factor alpha (TNF-alpha) and interleukin-6, hallmarks of an ongoing immune reaction. Two years later researcher Simon Gray and psychiatrist Michael Bloch of Yale University conducted another meta-analysis of 12 studies of obsessive-compulsive disorder, often diagnosed alongside depression. They, too, reported elevated blood levels of TNF-alpha in individuals suffering from both depression and obsessive-compulsive disorder.

An overcooked immune response may also trigger anxiety disorders. In 2009 psychiatrist Elizabeth Hoge of Harvard Medical School and her co-workers compared the immunological status of 48 patients suffering from panic disorder or post-traumatic stress disorder with that

STRESS RESPONSE SYSTEM



When we are threatened, the hypothalamus releases corticotropin-releasing hormone (CRH), causing the pituitary gland to secrete adrenocorticotropic hormone (ACTH), which reaches the adrenal gland via blood circulation. The adrenal cortex produces cortisol, which suppresses the immune system so we focus all our energies on any immediate dangers. Long-term stress can permanently damage this feedback and kick the immune system dangerously into overdrive.

of 48 age- and gender-matched healthy control subjects. The team tested blood serum levels of 20 different inflammation markers and found 18 of them to be higher in the psychiatric patients. To look for a generalized inflammatory state—indicative of an underlying injury or infection—they measured how many participants had detectable levels of at least six out of nine common proinflammatory cytokines. Some 87 percent of the anxiety sufferers met the criterion, compared with only 25 percent of the controls.

The Role of Stress

There seems to be little doubt that protracted low-grade inflammation can engender depression and other emotional disorders in some people. Whether or not a person succumbs may depend in part on how aggressive their immune system is to begin with. In 2013 psychiatrists Charles L. Raison of the University of Arizona and Andrew H. Miller of Emory University conducted a meta-analysis examining data on genes that predispose

humans to depression. They noted that many of these genes are present in individuals with an especially vigorous immune response—which might explain why the genes have persisted in the human population even though they can have a detrimental effect.

Until the advent of good hygiene and antibiotics, infection was arguably the greatest threat to staying alive, so having an overactive immune system conferred a real advantage. Raison and Miller speculate that today, when most of us are not routinely exposed to hazardous microbes, some people's immune systems habitually overreact to harmless stimuli, leading to a persistent increase in proinflammatory cytokines. This may account for an increased prevalence of not only depression and other emotional disorders but also allergies, autoimmune diseases, cardiovascular disease, stroke, cancer, diabetes and dementia.

Stress probably plays a crucial role in this nexus of cause and effect. In the short term, the mere anticipation of injury can

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amplify inflammation. Several experiments have confirmed that animals experiencing moments of acute stress crank out higher levels of proinflammatory cytokines, and prolonged stress can eventually elicit depressionlike behavior in these same creatures. In 2009 psychiatrist Lisa Christian and her co-workers at Ohio State University demonstrated a similar phenomenon in humans. They studied 60 women during pregnancy and found an association between depression and blood levels of TNF-alpha and interleukin-6. Proinflammatory cytokines rise during any pregnancy, but the researchers found elevated levels of both cytokines and de-

prone to overreact and add stress. The chance of physical illness skyrockets, proinflammatory cytokines surge and sickness behavior becomes the new normal. Further investigations reveal that trauma in any form primes this pathway. In 2007 psychiatrist Andrea Danese of King's College London and his colleagues conducted a longitudinal study of people who were rejected or mistreated by their parents during childhood. They found that even 20 years after the abuse, many study participants had greatly elevated blood levels of inflammation biomarkers.

Several other studies suggest that disturbing childhood experiences may per-

to more inflammation and depression.

Indeed, so complex is the interplay of contributing factors that it may be impossible to determine the degree to which immune reactivity, personality, general physical health and life experiences contribute to depression in any one person. Chronic inflammation in and of itself almost certainly accounts for only a subset of patients with emotional disorders. Yet several trials have shown that patients who do not respond to traditional antidepressants frequently begin to improve when they take anti-inflammatory medications, from everyday ibuprofen to cytokine inhibitors, on top of their other prescriptions. Interestingly, the reverse is also true. Patients suffering from skin cancer or hepatitis C frequently take the cytokine drug interferon-alpha, which causes inflammation, and many develop symptoms of depression as a side effect.

Practitioners are thus pursuing a variety of approaches—from medications to dietary interventions—to tackle unwanted inflammation in psychiatric patients. For instance, in 2011 psychiatrist Janice Kiecolt-Glaser and her colleagues at Ohio State reported that omega-3 fatty acids, which curb inflammation, alleviated anxiety in medical students before an exam. Scientists are hopeful that drugs aimed at blocking cytokine receptors in the brain might also help quell emotional disorders. Several initiatives are under way to develop effective cytokine antagonists. Meanwhile more studies on the role of stress and trauma may reveal better ways to keep inflammation in check, lessening the risk that a chance infection will lead to an intractable disease. **M**

Prolonged low-grade infection can engender depression and other emotional disorders in some people.

pression in women under stress and the highest levels of depression in women under presumably the greatest stress—those with unwelcome pregnancies and those who received the least support.

Chronic stress is even more deleterious. Faced with some threat, the body prepares for fight or flight. A hormonal cascade along the so-called stress axis—from the hypothalamus to the pituitary gland to the adrenal gland—jump-starts the production of cortisol. Among other functions, this hormone temporarily suppresses the immune system to guarantee that we focus all of our energy on external dangers. If the stress endures, though, cortisol keeps the immune system offline, and we are more susceptible to illness. Over the course of several years, stress can permanently damage signaling along the axis, and we begin to release too little cortisol—in which case, the immune system reawakens and kicks into overdrive, with proinflammatory cytokines flowing freely.

Stacking the Deck

The sum of this research is a rough mechanism by which inflammation can seed depression: take an immune system

manently unbalance the stress axis and alter the sensitivity of cortisol receptors in the brain. Miller and his colleagues have discovered that compared with emotionally healthy control subjects, depressed men who were distressed as children mount much stronger immune responses when they take a test designed to cause psychosocial stress. Physical pain can also overload the immune system. Scientists have documented especially high levels of TNF-alpha in depressed women who also exhibit an increased sensitivity to pain—itsself a symptom of sickness behavior. Constant pain is a stress factor, creating a vicious circle: pain begets inflammation and stress, leading

FURTHER READING

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- From Our Archives
- **Inflammation Brings on the Blues.** Corey Binns, Head Lines; September/October 2009.