Seeing Beyond Depression

There's new evidence that depression is not just a disorder of the mind—and blood tests for signs of inflammation promise treatment options precisely tailored to each patient's needs.

By Edward Bullmore M.D., published January 2, 2019 - last reviewed on January 3, 2019

I was a young doctor in 1990 when I met a patient with rheumatoid arthritis. Mrs. P told me quietly but in no uncertain terms that she ticked all the boxes for a diagnosis of co-occurring depression. When I reported this to the senior physician in charge of her case, he said: "Well, you would too, wouldn't you?" and changed the subject. He meant that her mood was obviously a reasonable reflection on her current state of disability and a future of inexorably deteriorating health and mobility. Mrs. P was "understandably" depressed because she was thinking about, and ruminating on, what it meant to have an inflammatory disorder. And so there was nothing we physicians could do about it. It was a matter of the mind, not of the body—the province of psychiatry.

Mrs. P's symptoms, which were intimately interconnected in her lived experience of arthritis, were split apart by doctors into mental and physical symptoms. Having diagnostically divided Mrs. P in two, we proceeded to treat her physical disease—her swollen joints—in completely different and disconnected way from her mental illness—her depression and fatigue. We used the medical language of immune cells to treat her inflammation, and a different team of doctors, in a different hospital, used the language of serotonin and psychotherapy to treat her depression.

Depression is a widely used word of many meanings. The mainstream clinical sense today is similar to what the ancient Greek physicians called melancholia—a syndrome of sadness or low mood, low energy, reduced capacity for pleasure (or anhedonia), reduced appetite for sex and food, pessimistic anticipation of the future, guilty rumination on the past, and a strongly self-critical bias in thinking that can lead to self-harming or suicidal behavior.

No question, it's depressing to be sick. But what if depression were not strictly a disorder of the mind? The notion that Mrs. P might be depressed because she was inflamed—not because she was thinking about being inflamed—did not cross my mind in 1990, and such an idea would have been medical bonkers even if I had been clever enough to conceive of it back then.
But the notion is very much a matter of investigation today, a centerpiece of the burgeoning science of neuroimmunology. And it not only reflects a new way of looking at the disorder but also promises new ways to treat it, to track it—even new measures to prevent it among those whose life experience puts them at risk for developing it.

**A New Path to Pathology**

Epidemiological data put the prevalence of depression at approximately 10 percent among the general population and significantly higher among patients with rheumatoid arthritis (25 percent), inflammatory bowel disease, psoriasis, chronic lung disease, or any number of other inflammatory or autoimmune disorders. Advocacy groups, like the National Rheumatoid Arthritis Society in the U.K., highlight psychological symptoms such as depression, fatigue, and "brain fog," as key areas of unmet need for many patients who have a physical disease.

Establishing that depression can be caused by inflammation somewhere — anywhere — in the body demands much evidence. But it also requires more: a radical shift in mindset, because it overrides one of the distinguishing features of Western thinking—the deep fault line that separates ideas about the workings of the body from those about the workings of the mind.

Even now, in 2019, Mrs. P's experience is not uncommon. Many patients with inflammatory disorders consult well-meaning specialist physicians, like rheumatologists, who may recognize the symptoms of depression but don't feel that they know how to treat them—or understand how they are linked to the swollen joints that they do feel qualified to treat. Physically disengagement from psychological symptoms is not surprising in view of the mind-body split of Western medicine, but it is surprising given that most physicians have some first-hand clinical experience of the mood-boosting effects of anti-inflammatory drugs.

Steroids are among the most powerful anti-inflammatory drugs available. They mimic the effects of cortisol, the body's own anti-inflammatory hormone, in counteracting the influence of immune activators called cytokines. Steroid treatment is well known to cause rapid and dramatic improvements in mood and energy (although such effects are generally not long-lasting, and chronic steroid use can be associated with depression and psychosis).

Antibodies against cytokines—one type is marketed as Remicade—have been a dramatic advance in the treatment of inflammatory disorders in the last 15 years. They very selectively target and disable inflammatory hormones and often have an antidepressant effect—called "the Remicade high"—within a few days of treatment.

An antidepressant effect of anti-inflammatory drugs in patients with comorbid depression—that's exactly what you'd expect if their depression was directly caused by their inflammation. But it is not usually explained that way. Instead, the Remicade high is seen as a placebo response: The patients would have been equally uplifted if they thought they were getting Remicade but got an innocuous substitute.

Placebo-controlled, randomized trials of anticytokine antibodies in patients with arthritis, psoriasis, and inflammatory bowel disease have often demonstrated mood improvements. But it has still been argued...
that the mental health effects of anticytokine antibodies are a psychological reaction to their physical health benefits: Patients are less depressed because they have less joint pain and swelling and easier mobility. One way or another, the antidepressant effects of anti-inflammatory drugs in comorbid depression have been explained away as a function of the disembodied mind.

**The Berlin Wall in the Brain Is Crumbling**

Until relatively recently, the brain was considered to be "immune-privileged": The immune system couldn't get at it. The brain was protected behind the blood-brain barrier, formed by tight packing of the endothelial cells lining the blood vessels in the brain—and understood to be about as permeable as the Berlin Wall.

The wall in Berlin has since been broken through, and so too has the blood-brain barrier. It is increasingly clear that there are many channels of communication between the immune system and the nervous system. It is no longer absurd to think that they talk to each other; in fact, it is obvious that they do so all the time, and with significant implications for our health and survival in a hostile and competitive world.

The new science of neuroimmunology posits that the inflammatory response of the immune system includes changes in the way the brain works, leading to a behavioral response. Just as inflammation often causes an increase in body temperature, so it can often cause a decrease in energy levels and in pleasure-seeking behaviors.

Animal experiments show that if a rat or a mouse is infected with a germ, its behavior changes. It becomes less active, as if less energetic and less sociable, and demonstrates less of a positive preference for sweetened water, as if it found sweet taste sensations less pleasurable than usual. This syndrome, resembling the behavioral features of depression, is called illness or sickness behavior. It is seen in a wide range of species, including *Homosapiens*. Sickness behavior is not directly triggered by the infectious germ, but by the immune response to it. A rat injected with cytokines will typically show the same sickness behavior as a rat infected with germs.

Cytokines can pass through the blood-brain barrier quite easily, it turns out. There are big enough gaps between the endothelial "bricks" lining the walls of the blood vessels to allow proteins like cytokines to diffuse from the blood into the brain. Even white blood cells, the circulating immune cells, can be actively assisted to squeeze past the endothelial cells and enter the brain. And there are other channels of communication, like the vagus nerve, which is sensitive to changing cytokine levels in the body and can send electrical signals directly into the brain.

**It's Depressing Being Inflamed**

Depression is a common complaint of those with inflammatory disease, but among patients with major depressive disorder (MDD), it's not so clinically obvious that there's a link to inflammation. Confusingly, by DSM-5 definition, MDD can't be diagnosed in patients with a major inflammatory disorder. But studies starting in the 1990s have consistently found that levels of inflammatory proteins—including one known as C-reactive protein (CRP), as well as cytokines—are significantly increased in patients with MDD compared to healthy controls.

https://www.psychologytoday.com/us/articles/201901/seeing-beyond-depression
The difference in blood levels of inflammatory proteins between MDD patients and controls is not large, compared to the much higher levels of such proteins in patients with arthritis. And not every patient with MDD has cytokine or CRP levels outside the normal range. About a third of patients with MDD also have low-grade inflammation. There are many possible interpretations of this persistent fact: It could mean that depression causes inflammation, that inflammation causes depression, or that both are caused by some third, confounding factor.

If inflammation causes depression, we would expect to find evidence that it occurs first. Several studies have assessed patients repeatedly over time and confirmed that inflammation can indeed predict depression.

In southwest England, 14,000 people born in 1991 were repeatedly assessed from birth to study normal development. Nine-year-olds with blood cytokine levels in the upper third of the distribution had significantly increased rates of depression at age 18. Another study, of British civil servants older than 50, found that those who had higher levels of CRP but were not depressed when first assessed in 2004 and 2008 had significantly higher rates of depression when reassessed in 2012. In both cohorts, inflammation preceded depression by several years.

Other studies have investigated the sequence of events over shorter periods of time. For example, patients with hepatitis who were not depressed before receiving antiviral treatment with a cytokine called interferon had significantly increased risk of being depressed about six weeks after treatment. And healthy young people who were studied after a placebo injection and again after a typhoid vaccination experienced relatively mild and fleeting depressive symptoms 48 hours after vaccination. A clinically administered inflammatory shock like interferon treatment or a typhoid vaccination can predict subsequent depression over time periods ranging from days to decades.

Inflammatory precedence in time is compatible with inflammation's causing depression but not conclusive. It's still not understood how an inflammatory signal in the blood triggers changes in the brain that could, in turn, cause the mood and behavioral changes of depression. Animal experiments indicate that such a chain of events is conceivable in humans, but it is much trickier to measure the status of immune cells or nerve cells in the living human brain than in the rat brain.

Brain-scanning methods, like functional magnetic resonance imaging (fMRI), show that MDD patients with higher levels of CRP in their blood have reduced strength of connectivity between components of the brain circuits or networks known to be important for emotional processing and mood disorders. Peripheral inflammation, occurring in far-flung parts of the body, disrupts the coherent function of the emotional brain in depression. Marvelous though fMRI is, it cannot provide information about individual nerve cells or tell us anything specific about the inflammatory status of the brain's immune cells. In fact, there is no good way of measuring human brain inflammation at the moment; it is one of the current roadblocks to working out exactly how inflammation of the body begets inflammation in the human brain, which in turn begets changes in mood and behavior.
Sparked by Stress
There are many possible sources of inflammation that could cause MDD in a patient. The immune system is responsive to many internal and external factors that can influence its state of inflammation. For example, cytokine levels increase in winter months and decrease in the summer. Aging and postmenopausal hormone changes are associated with increased inflammation. Obesity is strongly correlated with inflammation—fatty tissue is rich in macrophages. All these factors and others known to increase inflammation are also known to increase the risk of depression.

But the most significant source of inflammation causing MDD is likely stress. Social stress is the single biggest risk factor for depression. Major life events like bereavement, divorce, and loss of employment, as well as burdensome adult social roles, like caring for a dependent loved one, increase the risk of depression weeks, months, or years later. Childhood stresses, like early separation from parents, are also predictive of depression decades later.

Intriguingly, there is growing evidence that the relationship between stress and depression could be mediated by inflammation—that stress causes inflammation, which in turn causes depression. In a large long-term study of a birth cohort in New Zealand, children who had experienced abuse or adversity by age 8 had increased levels of inflammatory proteins in their blood at age 21. A study of stressed and resilient teachers found that the burnt-out teachers produced more cytokines than the resilient ones—and all the teachers pumped out more cytokines within an hour of the acutely stressful task of public speaking. There is much more evidence of stress causing inflammation in animals.

Why Does the Immune System Make Us Depressed?
Like all "Why?" questions in biology, the answer goes back to Darwin. There must be some way depressive behavior as part of the inflammatory response boosts our fitness for survival.

It is not glaringly obvious that depression is good for survival or reproduction. Patients with MDD are typically poorer, have fewer stable partnerships and children, and have lower life expectancy than the nondepressed. In the British National Health Service in 2016, serious mental illness—MDD, bipolar disorder, schizophrenia—cut life expectancy by 12 years. Clearly MDD has not been selected because it makes us fitter to survive in the 21st century. But depression-like behaviors in response to inflammation could have helped our ancestors survive in the distant past, when they were much more vulnerable to infectious disease.

Reduced energy and activity might have conserved energy to fight infection. Social withdrawal might have protected the "patient" from competitive stress and protected the rest of the tribe from the possibly contagious infection. Anxiety and interrupted sleep might have made a patient more vigilant, less vulnerable to opportunistic predation.

It could even be that our ancestors evolved to become inflamed not just in response to infection but in anticipation of the threat of infection. Social situations like conflict or competition for resources, which would likely lead to violence and trauma—with a high risk of infection—could have triggered a preemptive inflammatory response, including sickness behavior.
If so, the genes that increase the risk for MDD today should include genes that produce cytokines or other proteins of the immune system. Ideally, the genes would control the behavioral response to inflammation and infection in animals and humans. Unfortunately, our understanding of the genetics of depression is not this advanced—yet.

We do know that depression runs in families and is genetically heritable. Not until 2018 were the first really solid data published identifying 44 "genes for depression," although collectively they account for less than 10 percent of the total risk for MDD. The work of gene discovery for MDD has been slow because, it turns out, there are likely thousands of genes involved, each having a tiny effect. And scientists must look at DNA from very large numbers of patients and controls to spot the significant MDD genes from among all the other genes on the genome.

Now that we have DNA from hundreds of thousands of patients, we can identify with certainty some of the genes linked to MDD. Many are genes that code proteins in the brain; some are genes related to the immune system. The single gene most strongly associated with MDD—called olfactomedin 4—is known to control the inflammatory response of the stomach to infection. This is the kind of thing you might expect if the evolutionary explanation is to be believed. But it will require much more rigorous analysis of the data to be sure.

One Size Does Not Fit All
What difference could it make to treatment and prevention if further research continued to validate and refine the idea that depression can sometimes be caused by inflammation?
One obvious innovation could be the use of anti-inflammatory drugs as antidepressants for patients with MDD and comorbid depression. Many clinical trials of anti-inflammatory drugs have served up circumstantial evidence of antidepressant efficacy. But far fewer effectiveness. There have been a handful of small studies of nonsteroidal anti-inflammatory drugs for the treatment of MDD, but when all the data are analysed, there's no clear evidence that they work as antidepressants.

Still, the studies suggest something potentially important—not to get overexcited about the prospect of a panacea. The history of antidepressant drug development has been dominated by the search for a magic bullet that will work for everyone with depression. The antidepressant drugs already available, like Prozac and related serotonin-tweaking SSRIs, are licensed for use in everyone with depression, and they work moderately well on average. But MDD would not be on track to become the single biggest cause of disability in the world if SSRIs worked well for everyone with depression. Evidently, one size does not fit all.

Anti-inflammatory interventions will never be the answer for all patients with depression. Currently under development are new alternative antidepressant treatments: dietary regimens to alter the microbiome, electromagnetic stimulating devices designed to change the function of emotional brain circuits, and drugs, like ketamine, that work primarily on glutamate rather than on serotonin receptors. The future promises a spectrum of treatment choices. But how to know which treatment is likely to work best for each patient?

A Therapeutic Revolution?
When the scientists running one of the antidepressant trials of an anti-inflammatory drug—the nonsteroidal agent Remicade—dissected their data, they found that some patients responded better than
others. The beneficial effects of treatment were greater in those MDD patients who had the highest levels of the inflammatory protein CRP in their blood before they started treatment. That is, the anti-inflammatory treatment for depression worked best for the depressed patients who were most inflamed—not surprising. What is surprising is the improved way of approaching depression that the results point to for the future.

They suggest that blood tests will become much more important in psychiatry than they have been in the past. The next wave of clinical trials of anti-inflammatory drugs for depression are more likely to measure biological markers of inflammation to predict which patients are most likely to respond.

Numerous interventions of varying efficacy and invasiveness are now in use to reduce depression. They range from the purely psychological, like mindfulness training, to the surgical, such as vagal nerve stimulation, in which a device is implanted under the skin to deliver electrical impulses to the vagus nerve, which mediates an anti-inflammatory reflex. The procedure is risky and reserved for patients who have not responded to other therapies. Biomarkers of immune system status could not only indicate which people are most likely to respond to a given approach but also guide treatment progress.

This is standard practice in other areas of medicine. It would be a major advance if psychiatry could do likewise.

I predict that in the future, we will be using biomarkers of the immune system—CRP, cytokines, and more—to identify those patients whose depression is caused by inflammation. That will allow us to offer them a more customized treatment plan with targeted anti-inflammatory interventions. It may even be possible to leverage the immune system not just to treat depression but to prevent it as well.

Childhood abuse or adversity is a strong predictive risk factor for depression, sometimes decades later. It's long been known that the immune system has a remarkable memory of exposure to biological threats, like infection, in childhood. For example, survivors of a potentially fatal childhood infection like measles retain an immune memory that enables them to respond aggressively if they are exposed again to the virus later in life. Could it be similar for social threats to survival in childhood?

There is growing evidence that a history of childhood adversity is associated with increased inflammatory proteins in adults. In animal experiments, there is detailed evidence that early life stress—like separation from a parent—can leave a mark on the genome that biases the animal's inflammatory response to later stresses. In other words, a rat's immune system can hold a long-term memory of being exposed to stress in childhood that could make it more likely to become inflamed (and depressed) as an adult.

If this turns out to also be true for humans, then perhaps biomarkers of the immune memory of childhood abuse or adversity could be used to identify children likely at risk of mental health disorders in later life—and therefore most likely to benefit from preventative programs. Eventually, perhaps scientists will find ways of reprogramming the immune memory of abuse so that survivors don't carry the risk of depression for the rest of their lives.
Immune Warriors: Macrophages and Microglia

The high-level mission of the immune system is to defend the self against the nonself. The classic example is the immune response to infection. We live in a world teeming with germs—microscopic particles of nonself—that can damage or kill us. If we are infected by a dangerous germ—a bacterium or virus—the immune system is on call to deal with the situation. Bacteria are detected and destroyed by immune cells called macrophages, a made-up word meaning "big eater."

The first immune response to infection is typically inflammation. When macrophages detect the presence of an infectious germ, they get "angry," or activated. They move towards the germ, trying to make contact with it, and then ingest and digest it. Effective as macrophages are, germs can proliferate very rapidly and outnumber them. To aid in the battle against potentially overwhelming numbers of nonself agents, activated macrophages summon support: They release into nearby blood vessels signaling proteins called cytokines, which circulate throughout the body, attracting other macrophages to reinforce the immediate immune response to attack.

In the days and weeks following infection, other specialized immune cells and systems get involved. For example, lymphocytes, a type of white blood cell, may ramp up production of antibodies, the proteins that can help macrophages recognize and kill the same type of germ more quickly if it reappears in future.

Once inflammatory signals from the body reach the brain, they are often picked up and amplified by the brain's resident macrophages, called microglia. Microglial cells are activated by cytokines to produce more cytokines—a positive feedback loop that can have adverse effects on the function of neighboring nerve cells. Cytokines make the nervous system less plastic; the synaptic connections between nerve cells don't adapt so rapidly to changing patterns of stimulation. They also make nerve cells less likely to reproduce and more likely to die. What's more, inflammation makes some nerve cells cut back production or release of serotonin, the neurotransmitter that is thought to play a key role in depression. Combined, the changes wrought by inflammation lead to behavioral inflexibility, a hallmark of depression.

How to Factor Inflammation Into Your Treatment for Depression

Recognize that you're not alone. Being depressed tends to make people withdraw socially. In fact, depression is very common: about one in four people experiences an episode of major depression sometime in life. It touches every family on the planet.

1. If you know that you have an inflammatory disorder, like rheumatoid arthritis or Crohn's disease, and are also depressed or fatigued, talk to your physician about your psychological symptoms as well as your physical ones. Standard treatments for depression—SSRIs and psychotherapy—can help with comorbid depression, but many patients with physical illness do not access them. Your physician may refer you to a clinical psychologist or psychiatrist. Consider any antidepressant treatment options suggested by clinicians. And consider making contact and sharing experiences with others, perhaps through relevant patient advocacy groups.

2. If you are depressed but don't have a major inflammatory disorder, low levels of inflammation might still be contributing to your depression. A simple blood test for C-reactive protein or white blood cell count can "take the temperature" of your immune system and indicate your level of bodily inflammation. If blood tests are positive, try to work out the cause of the inflammation and eliminate it. Common possibilities include unrecognized periodontitis, obesity, and social stress.
3. Many anti-inflammatory drugs are already on the market but none has yet been shown to have significant antidepressant effects. Of the many nondrug approaches to depression—from yoga and meditation to diet and vagal nerve stimulation—none has yet been approved for treating depressive symptoms of inflammation. So proceed with caution. Ask critical questions about the evidence for and against any treatment. The risks of attending a yoga retreat or cutting food items from your diet are low. But it is still worth asking for proof that doing so will change the levels of inflammatory proteins or cells in your body.

4. The presence of inflammation does not mean that conventional treatments for depression (such as SSRIs and psychotherapy) have no role. They do. Do not stop or start any medication for depression except in consultation with a psychiatrist or other physician.

5. Whatever therapeutic course you choose, keep track of your levels of inflammation with repeated blood tests. Review your approach if the inflammatory temperature of your immune system stays high.

6. Talk about it. Being depressed makes people self-critical and guilty, but don't be ashamed of your symptoms. Seek social or therapeutic contacts that can support you in recovering from depression.

Sources of Increased Inflammation
- Obesity
- Sedentary lifestyle
- Disordered sleep
- Childhood maltreatment
- Emotional and physical trauma
- Medical illness such as cardiovascular disease, diabetes, autoimmune and inflammatory disorders
- Bacterial or viral infection
- Medical treatments such as surgery, radiation, and chemotherapy
- Antidepressant treatment resistance