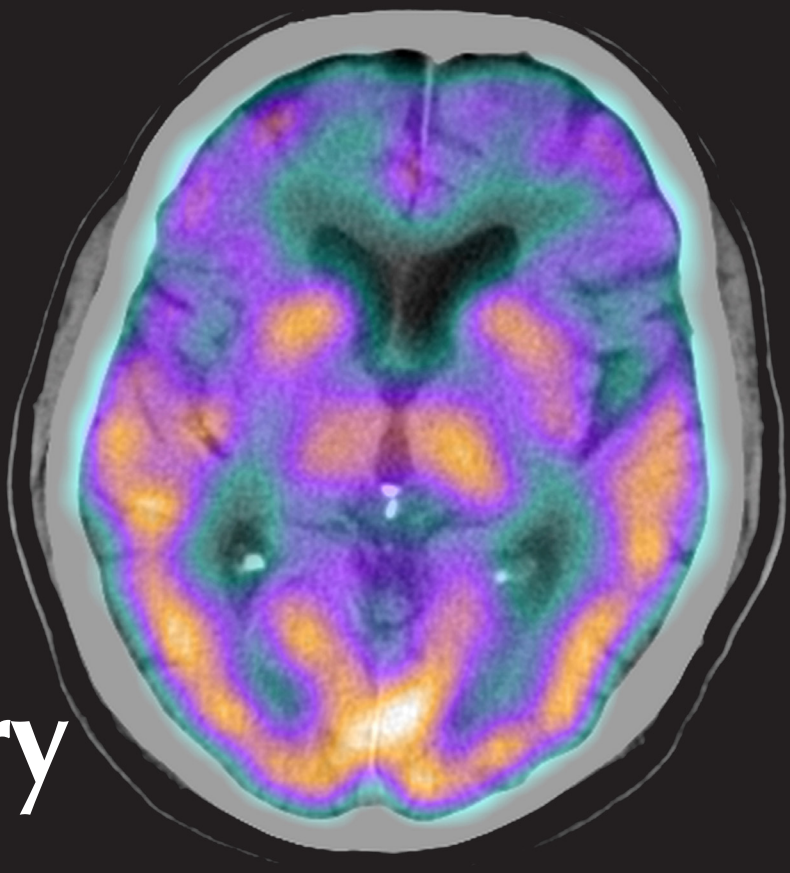

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Inflammatory illness:

Why the next wave of antidepressants may target the immune system

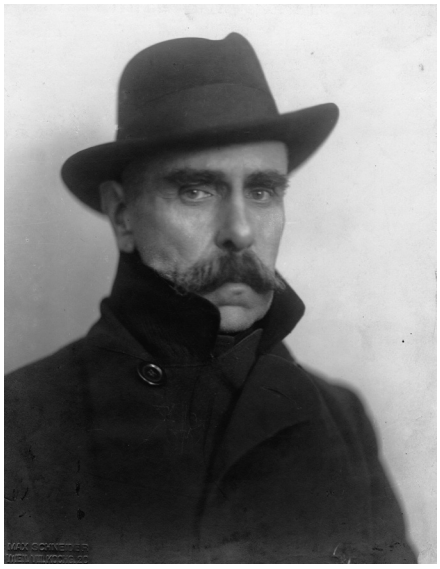
By Nicole Wetsman

In the winter of 1883, a psychiatric assistant named Julius Wagner-Jauregg was working in an Austrian asylum when he witnessed something curious. While making his rounds, Wagner-Jauregg encountered a woman with psychotic delusions who had caught a skin infection, which caused a high fever. But once her temperature resolved, she became coherent, and her symptoms of psychosis disappeared. Wagner-Jauregg spent the next decades of his career attempting to replicate that observation: he exposed people with mental illness to different types of infection to induce fever. But he had relatively little success until 1917, when he started injecting patients who had developed psychosis as a result of late-stage syphilis with blood from soldiers with malaria. The technique seemed to work, according to reports at the time; upwards of half of patients returned to normal life after they received it. The treatment, referred to as malariotherapy, was used in thousands of patients across the world during the 1920s and 1930s[1]. It was so well regarded at the time that Wagner-Jauregg won the Nobel Prize in Physiology or Medicine in 1927 for his development of the treatment.

But a year after Wagner-Jauregg received his Nobel Prize, a discovery occurred in London that would ultimately cause malariotherapy to fall out of style: Alexander Fleming struck upon penicillin, and within three decades, it became the go-to treatment for syphilis. Malariotherapy became a historical footnote, and Wagner-Jauregg's psychiatric legacy was quickly overshadowed by the dubious ethics of his experiments and his support of Nazism and eugenics.

Wagner-Jauregg had no clear sense of why malariotherapy worked—and he said as much in his Nobel Prize acceptance speech. It's only now that researchers have any sort of explanation of why he might have witnessed such change in the individuals whom he treated. In the past 10 years, scientists began to recognize that the body's inflammatory response has a role in mental illness, which may explain why manipulating the immune system seemed to help Wagner-Jauregg's patients. Whereas a fever, such as the one he induced in his patients, causes inflammation, it also increases the production of certain anti-inflammatory proteins[2]. It's this second, anti-inflammatory component that may have brought into balance an out-of-whack inflammatory system that could have been contributing to his patients' mental illness.

These insights didn't just function to explain the possible mechanism of the century-old malariotherapy protocol—which would never fly in modern-day psychiatric care, for a range of reasons—but paved the way for a new line of inquiry in psychiatry. The underlying principle that the immune system is important in mental illness is regaining momentum, particularly in depression. A study published in July looking at blood samples from 113 patients with severe depression reported that of 90 genes that were found to be overexpressed in this group of individuals, many were linked to the immune system and the body's response to infection[3]. Scientists are narrowing in on inflammatory proteins to use as biomarkers that could help to predict which antidepressant treatment will work best for an individual patient. And there are at least a half-dozen ongoing clinical trials that are testing anti-inflammatory drugs to treat depression, bipolar disorder or schizophrenia. Some evidence goes as far as to



Imagno/Contributor

Inflammatory idea: Julius Wagner-Jauregg, who treated psychiatric illness with malaria.

suggest that inflammation is perhaps not only a contributor to mental illness, but a cause in and of itself: "You're going right after the heart of the matter if you go after inflammation itself," says psychiatrist Andrew Miller, director of the Behavioral Immunology Program at the Emory University School of Medicine.

Interferon insight

There are well-documented structural and molecular changes in the brain that accompany mental illness, but there are also shifts throughout the rest of the body that are associated with illnesses such as depression. For example, evidence suggests that patients with depression have elevated levels of certain proteins involved in inflammation, such as interleukin 6, tumor necrosis factor-alpha and interleukin 1-beta[4]. These inflammatory proteins have the ability to pass into the brain, where they can disrupt the action of neurotransmitters, such as serotonin, that are implicated in depression and mood disorders[5]. Although the cause-and-effect relationship between depression and inflammation levels is still uncertain, some studies show that increased levels of inflammatory proteins can predict an increased risk of developing a mood disorder[6,7].

In the late 1990s, doctors began to notice that individuals with cancer who were treated with a drug called interferon-alpha, which increases the inflammatory response in the body, were anxious and had depressed moods. The patients lacked motivation, had difficulty concentrating and were fatigued[8]. Other drugs used to treat cancer can affect mood and cognition, but to Miller, the reaction to interferon-alpha was out of the ordinary. "I interviewed a patient on interferon-alpha and said, 'This is not your everyday toxicity.' These patients were meeting all the symptom criteria for major depression," says Miller.

The work on interferon-alpha, taken together with early research on inflammation in the brain, indicated to Miller that reducing inflammation using drugs that worked in the immune system could be a viable option for the treatment of depression. Within psychiatry, this area of research was still on the fringe, but the data were still sufficient to lead him to initiate a clinical trial in 2007 involving 60 patients. Miller and his team at Emory began giving people with depression infusions of an antibody typically used to treat autoimmune disorders such as Crohn's disease and rheumatoid arthritis. The drug, called infliximab, reduces the levels of tumor necrosis factor-alpha.

The infliximab clinical trial, the results of which were published in 2013, did not find that the treatment lowered depression any more than a placebo treatment did. However, a subset of patients in the trial, who had the highest blood levels of an inflammatory molecule called C-reactive protein (CRP), did experience a statistically significant improvement. CRP increases in response to elevated levels of other inflammatory proteins, and is often measured to track overall inflammation in the body[9]. Half of those patients saw a 50% reduction in their scores on a depression assessment scale, as compared to only one-third of those who received a placebo[10].

Miller's study laid the foundation for future work at the intersection of psychiatry and immunology. "The team at Emory deserves kudos," says Roger McIntyre, the head of the Mood Disorders Psychopharmacology Unit at the University Health Network in Toronto. "They had the vision, they got this on the map and really got this going."

Personalizing care

One of the biggest challenges of treating mental illness is identifying a medicine that will work for a given patient. There's hope that knowing more about the immune system's role in these disorders will help doctors to be able to recommend treatments with more confidence. Interestingly, evidence suggests that people who have treatment-resistant depression that does not respond to commonly used antidepressant medication are more likely to have higher levels of inflammation than people who benefit from these drugs[11].

Carmine Pariante, who researches biological psychiatry at King's College London, saw the potential of leveraging these differences for treatment. In a study published in September 2016, his team was able to use the number of mRNA molecules of two inflammatory proteins, interleukin-1-beta and macrophage migratory inhibitory factor, to predict which patients would respond to standard antidepressant treatments and which would not. In a total of 142 patients between two sample groups, the predictions based on that analysis were almost all accurate: 100% of the 27 patients predicted to be nonresponders were actually nonresponders, and 83% of the 115 patients predicted to be responders were actually responders[12]. "We're confirming this overall picture that if you're depressed and have high levels of inflammation, you're less likely to respond to a standard antidepressant treatment," Pariante says.

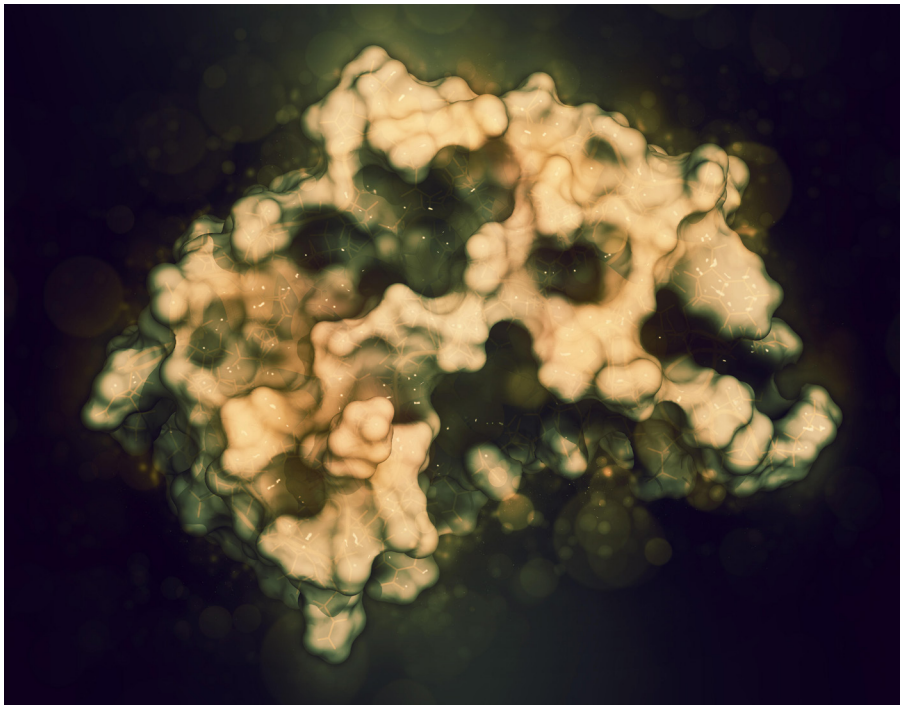
Pariante is now involved in a clinical trial mapping immune system biomarkers in three groups of people who have depression: those who respond well to treatment, those who don't and those who have not yet received any treatment for their disorder. He is also including a control group of people without depression. The trial is being conducted through a collaboration between a number of universities in the UK and the drug companies GlaxoSmithKline, Janssen and H. Lundbeck A/S. It is expected to conclude by the end of this year. The researchers are using brain scans, protein analysis, mRNA sequencing and other molecular tools to closely examine the inflammatory profile of each study participant.

"All of these techniques are the contemporary standard of immunology … they just haven't yet been translated to psychiatry," says Ed Bullmore, head of the Department of Psychiatry at the University of Cambridge, UK, and another researcher collaborating on the study. "There's an opportunity in taking these extraordinary techniques in immunology and using them for the first time in psychiatry."

The goal, Pariante says, is to develop a biomarker-based blood test that psychiatrists could use to pick the best treatment regimen for a patient: "For those who have high level of inflammation, those would move on much more quickly to a more assertive antidepressant strategy," or could one day even be a candidate for an alternative treatment targeting inflammation, Pariante explains. He and Bullmore say that a blood test for immunological biomarkers has the potential to dramatically change the practice of psychiatry. "If we can predict who will respond to particular treatments," Bullmore says, "That [would be] quite a seismic shift."

Tomorrow's treatments

Ever since reading Miller's paper[10] in 2013, McIntyre wondered whether it would be possible to build on the finding that a small



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Problem protein: An illustration of interleukin-6, one of the inflammatory proteins implicated in depression.

group of participants with depression in that trial did benefit from anti-inflammatory treatment. In 2015, McIntyre and his team in Toronto initiated a clinical trial using the same drug, infliximab, to treat depression. However, in this study, one of the criteria for participation is a CRP level above the value that predicted a reduction in depression in response to the antibody drug in the 2013 trial. "We designed our study informed by the results of the Emory study," McIntyre says.

Another ongoing clinical trial, run by Janssen Pharmaceuticals, is dosing patients who have depression with an antibody called sirukumab, which acts to neutralize the inflammatory protein interleukin-6. The experimental new drug, which is not yet approved for any illness, was originally developed to treat rheumatoid arthritis. Janssen's depression study is focused on how this drug will work in participants who have high CRP levels. The company made this decision on the basis of Miller's findings, says Wayne Drevets, a psychiatrist and disease-area leader in mood disorders at Janssen. Another antibody to interleukin-6, tocilizumab, is being used in a clinical trial by a team at Brigham and Women's Hospital to treat depression. Tocilizumab, marketed under the brand name Actemra, is currently indicated to treat rheumatoid arthritis.

These anti-inflammatory treatments might also have applications for other mental illnesses, such as schizophrenia. Ragy Girgis, a psychiatrist at the Columbia University Medical Center, saw Miller's 2013 study and immediately noted its potential use for schizophrenia. "I read it and said, 'We have to be able to do something like this in schizophrenia,'" Girgis says. Research shows that interleukin-6 levels are elevated in people with this condition, so Girgis used tocilizumab in a clinical trial that finished collecting data in February. The results are not yet available. Girgis is hopeful that the findings will be positive. There's already a large amount of overlap between existing treatments for depression and treatments for schizophrenia, he adds. "Chances are that treatments for one could very well be effective for the other."

But once the clinical trials researching depression and schizophrenia finish, even assuming the response is good, getting approval to use an anti-inflammatory medication for these disorders could take years. Drevets says that it could be almost a decade or longer. Moreover, in their current form, immunosuppressants are expensive: in the US, a single dose of infliximab can cost thousands of dollars per infusion.

Cost is one of the reasons that the treatment isn't intended as a one-size-fits-all drug, Drevets says. Instead, the drugs could specifically target the subset of people with depression who don't respond to other treatments, or who have results on future inflammatory-biomarker tests that indicate immunosuppression might work for them. Most researchers are working under the assumption that these treatments are not going to benefit everyone. "We're thinking about developing drugs that might work particularly well for a particular subgroup," Bullmore says. "I think that a lot of people in industry would think that is the right thing to do."

Even Miller doesn't think the immunosuppressant therapies are ready for prime time just yet. "Don't play with fire unless you really know what you're dealing with," Miller says. "The immune system is very complicated." His current work focuses on the role that the neurotransmitters glutamate and dopamine have in inflammation and depression. He thinks that the way dopamine interacts with inflammatory pathways in the brain could make it a potential treatment target.

Scientists in this field remark that the landscape has changed dramatically in the past ten years. "Now, if you go to a psychiatry meeting, there are tons of mainstream talks on inflammation, and the place is packed," McIntyre says. The crowded rooms are a good thing, Miller notes, despite the extra pressure the attention brings: "It's easier to work in the shadows, sometimes, than it is to work in full sunlight. People get more competitive. But I think it makes the science better."

Nicole Wetsman is* Nature Medicine*'s news intern in New York.

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Correction

In the August 2017 issue, the story "Breaking through: How researchers are gaining entry into barricaded bacteria" (*Nat. Med.* **23**, 907–910, 2017) misstated that the pharmaceutical company Achaogen would be filing a New Drug Application with the FDA in 2018. The company will be filing an Investigational New Drug application. The article was also unclear in wording the progress of siderophore-conjugated antibiotics. Such antibiotics have made it to clinical trials, but none so far have made it to market. The errors have been corrected in the HTML and PDF versions of the article as of 23 August 2017.