FEATURE

Signal Blues

Stress and cytokine levels underpin a provocative theory of depression

By Steve Bunk

In 1992, American writer Andrew Solomon, then in his late-20s, was about to publish his first novel when he unexpectedly slid into a major depression. In a subsequent book, he wrote that the experience is "almost unimaginable" to the uninitiated. Describing it, he likened himself to an oak being strangled by a vine, "a sucking thing that had wrapped itself around me, ugly and more alive than I." He called up the image of falling into an abyss: "You hit invisible things over and over again, until you are shredded." And he mentioned the fleeting terror anyone feels who trips and is about to fall: "I felt that way hour after hour after hour."[1]

Even as Solomon struggled with his demon, scientists were undertaking an effort to describe depression in terms of molecular biology. Evidence is growing that a key mechanism underlying major depression—a sometimes heritable, often lifetime illness, with repeated remissions and relapses—involves dysregulation of the signaling proteins called cytokines.[2]

"Depression can be induced by external or internal stressors," says psychiatry professor Michael Maes, University of Maastricht, Netherlands. "So, depression is probably a symptom or a syndrome of stress." A principal architect of the cytokine dysregulation hypothesis, Maes helped to establish the notion that overexpression of proinflammatory cytokines, in particular, can disrupt the stress response system's primary elements: the hypothalamic-pituitary-adrenal (HPA) axis and the monoaminergic system, including the hormones serotonin and norepinephrine. Among the stressors that can overstimulate these proinflammatory cytokines are infections and melancholy. Although the pathophysiology of depression remains unclear, Maes is among those researchers who assert that it is a psychoneuroimmunological disorder.

Others are not so sure. Robert Dantzer, a key figure in cytokine and mood research, rejects the exclusiveness of Maes' theory. "Cytokines can be at the origin of mood disorders, just like any other psychosocial life event that does not necessarily activate the brain cytokine system," says Dantzer, director of the Laboratory of Integrative Neurobiology at the National Institute for Health and Medical Research (INSERM) in Bordeaux, France.

Another school of thought: Cytokine dysregulation does not lead to mood disorders, but could increase the susceptibility of an already depressed patient to immunity-related illnesses.[3] The debate stems, in part, from animal studies upon which most of the cytokine data is based. Contradictory results, differing methodologies, and the nagging question of the relevance of animal depression models to the human experience keep the debate alive. (Try, for instance, to measure symptoms such as guilt or suicidal thoughts in a rodent.)

But human studies present their own challenges. Multiple factors, including genetic susceptibilities, body mass index, diet (ingested omega-3 polyunsaturated fatty acids, for example, can have anti-inflammatory effects), smoking, recent infectious diseases, and medications, can confound cytokine measurements. Yet, none of this complexity diminishes the attractiveness of focusing on stress mediators as potential targets to treat or prevent depression. And chief among those mediators are cytokines.

SICKNESS BEHAVIOR In 1988, Benjamin Hart unwittingly provided a thematic framework for investigations of depression and cytokine dysregulation. Hart, a professor in the School of Veterinary Medicine at the University of California, Davis, recognized that factors such as appetite loss, decreased grooming behavior, and lethargy in sick animals are evolved, adaptive strategies that save energy for recovery.[4] In 1992, INSERM's Dantzer put this concept into perspective for mood disorders by providing evidence that sickness behavior is mediated by brain cytokines.[5]

Another important contributor to this field, psychiatry professor Andrew Miller of Emory University in Atlanta, declares that Hart "got everybody thinking" about the possible connections between inflammatory responses to infection and behavioral changes, which are now well established. Hart, unaware until being interviewed for this article that his paper inspired an approach to studying depression, says his reading and observations led to the conclusion that the behavior of sick animals "increases their capability to meet demands of the fever response, which are costly."

Numerous inflammatory diseases, infectious and noninfectious, now have been associated with both cytokine dysregulation and depressive symptoms.[6] The infectious diseases include HIV and hepatitis C; the noninfectious conditions include stroke and autoimmune diseases such as diabetes mellitus and rheumatoid arthritis. Depression also is frequently comorbid with heart disease and cancer.

Most research to date has focused on depression in medically ill patients, in whom it is five to 10 times more prevalent than in healthy people, says Miller. In an experimental model that has been applied to hepatitis C and malignant melanoma, Miller has focused on the depressive symptoms caused by cytokines. For example, Miller says IFN (interferon)-α, which he has used to treat patients with hepatitis C and malignant melanoma, will induce depression in 30% to 50% of patients, depending on the dosage. Says Miller: "It's a wonderful model, where we have a tremendous amount of control over mood problems as they develop."

By administering antidepressants to such patients before they began IFN-α therapy, Miller discovered that depression did not develop.[7] However, there was little effect on the nonspecific or "neurovegetative" symptoms corresponding to sickness behavior that Miller colloquially refers to as feeling "blobbed." This suggests different pathways for the mood-related and neurovegetative symptoms, which Miller's team is currently exploring.[8]

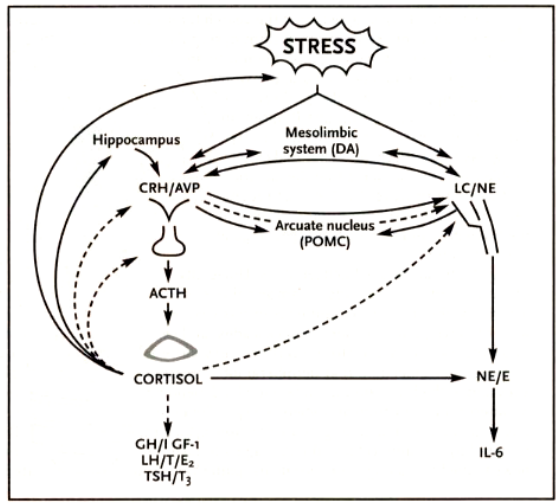
CANCER AND CYTOKINES For the past three years, Dantzer, Miller, and others have worked in a group led by Charles Cleeland, chairman of the Department of Symptom Research at the University of Texas' M.D. Anderson Cancer Center in Houston. The group has applied the sickness behavior concept to symptoms of various cancers, including melanoma, renal cell carcinoma, and chronic myelogenous leukemia, and to the side effects of cytokine treatment. Their hypothesis is that at least some symptoms of both the disease and its treatment stem from the same biological mechanism.[9] Accordingly, the group asserts that cytokine dysregulation can be a primary cause of cancer. "It's a simple idea and we've already been criticized for it, but you have to start somewhere," Cleeland says.

The group plans to perform initial studies that correlate tumor cell growth and disease symptoms to changes in cytokine levels, and then to mount the first placebo-controlled trial of a specific cytokine inhibitor to control a given cancer. "There are three [cytokines] that we would put our money on: IL-1, IL-6, and TNF-α," Cleeland says. Interleukin-1 is implicated in numerous cancers and in major depression, while interleukin-6 is a good predictor of survival and response in lung cancer. Tumor necrosis factor-α figures prominently in graft-versus-host disease, he explains.

Clinical trials have yet to be conducted for cytokine receptor antagonists, or to test anti-inflammatory agents (such as antalarmin, an inhibitor of corticotropin-releasing hormone, which stimulates HPA axis activity), or for blockers of cytokine-induced downstream mediators of depression, Cleeland says. The latter targets include prostaglandins, substance P, and nitric oxide. Another promising intervention involves the essential amino acid L-tryptophan, the precursor of serotonin. Its availability in the brain is controlled by an enzyme, indoleamine 2,3-dioxygenase, which is inducible by the cytokine interferon-γ.

FUZZY SYMPTOMS A major difficulty of fundamental research remains in matching clinical descriptions of depression to neurobiological functions, says Steven Maier of the multidisciplinary Center for Neuroscience at the University of Colorado, Boulder. "There may be nothing in the brain that corresponds to what the clinical psychiatrist describes as a major depression." He suggests that while a psychoneuroimmunological route to depression is likely, it probably is not the only one. He points to a line of thinking that downstream changes in molecules critical to neurotrophic signaling cascades, such as cyclic adenosine monophosphate (cAMP), could be important. Everyone might be right, he says. "It's not like talking about a medical condition that's clearly defined, like a lesion or an ulcer."

He and his colleagues showed that the psychological stressor of socially isolating rats causes a conditioned freezing behavior and raises IL-1 levels in some regions of the uninjured brain.[10] Although Maier concentrates on brain function rather than on a particular pathology, he declares that every aspect of human depression, including the different effects of acute and chronic stressors, which are just beginning to be studied, can be modeled



STRESS BY DESIGN: *This simplified schematic of the stress system's central and peripheral components shows the system's functional interrelations, and their connections, to other central systems involved in the stress response. (Redrawn from C.M. Pariante, A.H. Miller,* Biol Psychiat, *49:391-404, 2001.)*

in rodents, except for feelings such as guilt or worthlessness. "The only hurdle, really, is that you can't talk to animals."

Psychology professor Raz Yirmiya, Hebrew University of Jerusalem, has shown that activation of the immune system in rodents, when they are given an endotoxin, induces depression-like characteristics, including less interest in saccharine solutions. That behavior corresponds to human anhedonia (the inability to gain pleasure from normally pleasurable experiences), if controls are used to discard nonspecific effects on general activity and fluid intake. The animals exhibited a range of other depressive traits, such as reduced social interaction and psychomotor slowing, all of which were attenuated or eliminated by giving them antidepressants.[11] This work inspired Miller's clinical studies with IFN-α and antidepressants.

Although cytokine-induced depression affects both the monoaminergic system and the HPA axis, the question of which is the more critical dysregulation remains unresolved, Yirmiya thinks. "The neurochemistry of depression is very complex, and even without considering cytokines as a factor, it is not so clear what the specific role of any neurotransmitter or neuromodulator is, with respect to other mediators and with respect to the syndrome in general," he says.

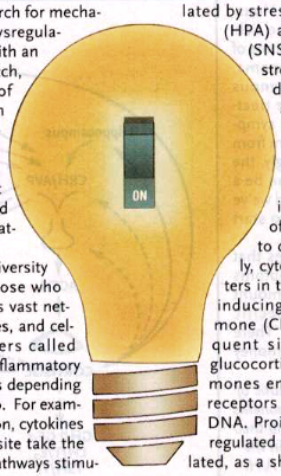
PREDICTING CHD Researchers say that to answer such questions, brain imaging and technologies in the genetics of risk, including single nucleotide polymorphisms, will be increasingly employed. Another approach being pursued by at least one scientist is the study of volunteers who are both physically and mentally healthy. Edward Suarez, a Duke University associate research professor of medical psychiatry, says he strove for 12 years before obtaining funds to measure cytokine levels and other stress-induced monocyte markers in healthy people. He attributes his change of fortune to the mounting evidence in the 1990s of a relationship between depression and cytokine dysregulation. Now starting the third year of a five-year study funded by the National Institutes of Health, he has several papers in press, he says. An overall goal is to discover if severity of depressive symptoms—a predictor of coronary heart disease (CHD)—will still foretell CHD onset in people who are neither clinically depressed nor physically sick.

His recruitment method involves screening thousands of potential participants for a wide range of confounding factors, such as cholesterol levels, obesity, hypertension, smoking, sports injuries, allergies, estradiol levels, and oral contraceptive use. Even people with a bruise are rejected, and no medications can be taken during the two weeks prior to the screening, including low-dose aspirin. His female recruits are premenopausal; Suarez says women are twice as likely as men to have depression and that significant changes in cytokine levels can follow menopause. He and colleagues have published a study of 53 apparently healthy men that demonstrates an association between increases in severity of depressive symptoms and in proinflammatory cytokine levels.[12] He is now asking subjects to recall stressful life events, in an attempt to determine how stress triggers these biochemical changes.

"A certain percentage of diseases can be promoted by the way we act and think, the way we struggle with ourselves," Suarez observes. For him, the boundaries of mood disorders are far wider than psychoneuroimmunological mechanisms. As he cast for a description of depression, he sounds like Andrew Solomon when he says, "It's like the unified theory of bad health." ⊗

Cytokines and Immunity: The Bulb or the Switch?

Esther Sternberg suggests that the search for mechanistic answers to immune system dysregulation is similar to solving a problem with an electric light. "It could be the bulb, the switch, or the wiring," says Sternberg, director of the Integrative Neural Immune Program in the National Institutes of Health. "Everything has to be checked." What makes the problem-solving harder is that the electricity travels both ways: Evidence of recent years shows that the immune system and the brain give and receive messages, regulating each other.[1]



Psychiatry professor Michael Maes, University of Maastricht, Netherlands, is among those who assert that the most important links in this vast network of nerve pathways, hormonal cascades, and cellular interactions are the signal carriers called cytokines.[2] Produced both at peripheral inflammatory sites and in the brain, they do different jobs depending on where they come from and where they go. For example, if someone is injured or gets an infection, cytokines secreted by immune cells at the damage site take the news to the brain along the major neural pathways stimulated by stressors: the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS). Most theories about the relationship of stress to behavioral responses such as anxiety or depression focus on these two pathways, according to psychiatry professor Andrew Miller, Emory University, Atlanta. "But you can get to cytokines from both those pathways," he says.

Brain cytokines respond to illness by inducing sickness behavior, a slowing down of various activities that allows the individual to direct resources toward recovery. Accordingly, cytokines can affect turnover of neurotransmitters in the brain. They also activate the HPA axis by inducing secretion of corticotropin-releasing hormone (CRH) from the hypothalamus, and a subsequent signaling cascade results in release of glucocorticoids from the adrenal glands. These hormones enter the circulation, eventually binding to receptors that then penetrate nuclei to interact with DNA. Proinflammatory cytokine production is downregulated and anti-inflammatory cytokines are upregulated, as a shift occurs from the cellular to the humoral