REVIEW

# Inflammation, Sanitation, and Consternation

## *Loss of Contact With Coevolved, Tolerogenic Microorganisms and the Pathophysiology and Treatment of Major Depression*

*Charles L. Raison, MD; Christopher A. Lowry, PhD; Graham A. W. Rook, BA, MB, BChir, MD, FSB*

**Context:** Inflammation is increasingly recognized as contributing to the pathogenesis of major depressive disorder (MDD), even in individuals who are otherwise medically healthy. Most studies in search of sources for this increased inflammation have focused on factors such as psychosocial stress and obesity that are known to activate inflammatory processes and increase the risk for depression. However, MDD may be so prevalent in the modern world not just because proinflammatory factors are widespread, but also because we have lost contact with previously available sources of anti-inflammatory, immunoregulatory signaling.

**Objective:** To examine evidence that disruptions in coevolved relationships with a variety of tolerogenic microorganisms that were previously ubiquitous in soil, food, and the gut, but that are largely missing from industrialized societies, may contribute to increasing rates of MDD in the modern world.

**Data Sources:** Relevant studies were identified using PubMed and Ovid MEDLINE.

**Study Selection:** Included were laboratory animal and human studies relevant to immune functioning, the hygiene hypothesis, and major depressive disorder identified via PubMed and Ovid MEDLINE searches.

**Data Extraction:** Studies were reviewed by all authors, and data considered to be potentially relevant to the contribution of hygiene-related immune variables to major depressive disorder were extracted.

**Data Synthesis:** Significant data suggest that a variety of microorganisms (frequently referred to as the "old friends") were tasked by coevolutionary processes with training the human immune system to tolerate a wide array of nonthreatening but potentially proinflammatory stimuli. Lacking such immune training, vulnerable individuals in the modern world are at significantly increased risk of mounting inappropriate inflammatory attacks on harmless environmental antigens (leading to asthma), benign food contents and commensals in the gut (leading to inflammatory bowel disease), or self-antigens (leading to any of a host of autoimmune diseases). Loss of exposure to the old friends may promote MDD by increasing background levels of depressogenic cytokines and may predispose vulnerable individuals in industrialized societies to mount inappropriately aggressive inflammatory responses to psychosocial stressors, again leading to increased rates of depression.

**Conclusion:** Measured exposure to the old friends or their antigens may offer promise for the prevention and treatment of MDD in modern industrialized societies.

*Arch Gen Psychiatry. 2010;67(12):1211-1224*

**Author Affiliations:** Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, Georgia (Dr Raison); Department of Integrative Physiology and Center for Neuroscience, University of Colorado, Boulder (Dr Lowry); and Department of Infection, Windeyer Institute for Medical Sciences, University College London, London, England (Dr Rook).

ALTHOUGH RECOGNIZED since at least classical antiquity,[1] major depressive disorder (MDD) has grown in importance in recent years and is predicted to be the second leading cause of disease burden worldwide by 2030.[2] Following the famous Dobzhansky dictum that "nothing in biology makes sense except in the light of evolution,"[3] the current review applies evolutionary logic to the pathophysiology of MDD, focusing on how changes in environmental risks linked to modernity may provide new insights into basic pathogenic features of MDD. Such insights are likely to provide important first steps toward decreasing the risk of depression at a societal level, or preventing its onset altogether in individuals with identified vulnerability, an objective that has recently been put forward by the National Institute of Mental Health.[4]

### IN SEARCH OF THE PATHOPHYSIOLOGY OF ENVIRONMENTAL RISK: INFLAMMATION AS A SHARED MECHANISM

Most of the risk for MDD resides in environmental factors.[5] Moreover, rather than causing depression directly, genes that contribute to depression tend to do so by rendering individuals vulnerable to adversity factors in the environment, such as

**Table. Factors in the Modern World That Increase and Decrease Inflammation**

| Factors Associated With Depression That Increase Peripheral Inflammatory Markers | Factors That Decrease Peripheral Inflammatory Markers |
|---|---|
| Psychosocial stress[11-17] | Antidepressants[18-22] |
| Medical illness[23,24] | Psychotherapy[25-27] |
| Obesity[28-30] | Electroconvulsive therapy[31] |
| Sedentary lifestyle[32-34] | Exercise[18,32,35-38] |
| Diet (eg, low ω-3:ω-6 fatty acid ratio, high-fructose sugars)[39-41] | |
| Diminished sleep[18,42-45] | |
| Social isolation[18,46-49] | |
| Low socioeconomic status[18,50-54] | |
| Female sex[18,55] | |
| Smoking[18,56] | |

psychosocial stress and sickness, that are also known to strongly predict the development of MDD independently of genetic effects.[6-9] We suggest that better understanding of physiological processes that transduce these environmental risks into pathology may lead to novel therapeutic strategies for the treatment of MDD.[10] Herein, we focus on inflammation, a physiological process that is activated in a similar manner by a diverse range of reliably depressogenic environmental factors (**Table**).* Conversely, interventions that reduce depressive symptoms have been reported to lower inflammatory and/or increase anti-inflammatory, immunoregulatory activity in the body and brain (Table).[18-22,25-27,31,32,35-38]

## EVIDENCE THAT PSYCHOSOCIAL STRESS ACTIVATES INFLAMMATION AND THAT PROINFLAMMATORY PROCESSES CONTRIBUTE TO THE PATHOGENESIS OF MDD

In the last decade, numerous studies have demonstrated that psychosocial stress activates innate immune cytokines and intracellular inflammatory elements such as nuclear factor-κβ.[11-17,57-59] Psychosocial stress may also impair acquired immune processes that normally regulate inflammation. For example, acute laboratory stressors reduce plasma concentrations of the anti-inflammatory cytokine interleukin 10 (IL-10),[60] as well as circulating $CD4^+CD25^+$ regulatory T (Treg) cells that are an important source of IL-10.[60,61] Moreover, acute stress appears to downregulate Forkhead box 3 (Foxp3), an important T cell immunoregulatory transcription factor.[61] Chronic traumatic life stress has also been associated with reduced numbers and percentages of circulating $CD4^+CD25^+Foxp3^+$ Treg cells—a finding in line with many studies showing that posttraumatic stress disorder, like MDD, is associated with increased circulating levels of innate immune proinflammatory cytokines.[62-65]

In keeping with strong associations between stress and depression,[66] medically healthy individuals with MDD and a history of early life stress have been shown to mount larger IL-6 and nuclear factor-κβ responses to a laboratory psychosocial stressor than do nondepressed controls.[14] These findings are consistent with evidence that MDD is associated with a suite of stress system changes known to promote inflammation, including glucocorticoid resistance, sympathetic overdrive, and parasympathetic withdrawal (**Figure 1**).[32,67-75] Recent studies suggest that these changes are also capable of suppressing the number and activity of $CD4^+CD25^+Foxp3^+$ Treg cells.[76,77]

Given these alterations, it is not surprising that when compared with nondepressed individuals, both medically ill and medically healthy patients with MDD have been found to exhibit all of the cardinal features of inflammation, as well as reduced plasma/serum concentrations of the immunoregulatory, anti-inflammatory cytokines IL-10 and transforming growth factor β.[20,21,78-85] Reduced total numbers and percentages of $CD4^+CD25^+$ Treg cells in peripheral blood, as well as reduced expression of Foxp3, have also been observed in MDD.[81] In addition to these correlative data, both immediate and long-term administration of proinflammatory cytokines (or substances that induce these cytokines) cause behavioral symptoms that overlap with those found in MDD and respond to standard antidepressant therapy.[86-91] Consistent with evidence that proinflammatory cytokines promote depression (and do not just reflect its presence), plasma concentrations of the inflammatory biomarker C-reactive protein and the proinflammatory cytokine IL-1β predict the later development of depressive symptoms,[92,93] and plasma concentrations of IL-6 immediately after a motor vehicle accident predict the development of posttraumatic stress disorder within the subsequent 6 months.[63]

## INFLAMMATION, ENVIRONMENTAL RISK, AND THE CHANGING PREVALENCE OF MDD IN THE MODERN WORLD

Many proinflammatory environmental risk factors for MDD have increased markedly in prevalence and/or severity over the last half century in the industrialized world (Table).[94-102] If inflammation contributes to the pathogenesis of MDD, one might expect, therefore, to see a parallel rise in the prevalence of depression over the same period. Significant data do indeed point to an increase in MDD in the developed and developing world over the last 50 years. Multiple studies from the 1980s and early 1990s found that the prevalence of MDD was increased in younger compared with older cohorts in both sexes and in all countries examined.[103-107] These findings have been challenged more recently on methodological grounds[108,109]; however, recent studies with improved methods continue to suggest that rates of MDD are increasing in the United States and worldwide.[110-114] Studies also show that transitioning from the developing world to the United States increases the risk for MDD. For example, Mexican immigrants to the United States have rates of depression similar to those seen in Mexico, whereas individuals of Mexican descent born in the United States have higher rates of MDD that are equivalent to the US population at large, suggesting that it is American life itself, and not acculturation shock, that accounts for the increase.[115,116]

*References 11-18, 23, 24, 28-30, 32-34, 39-56.*

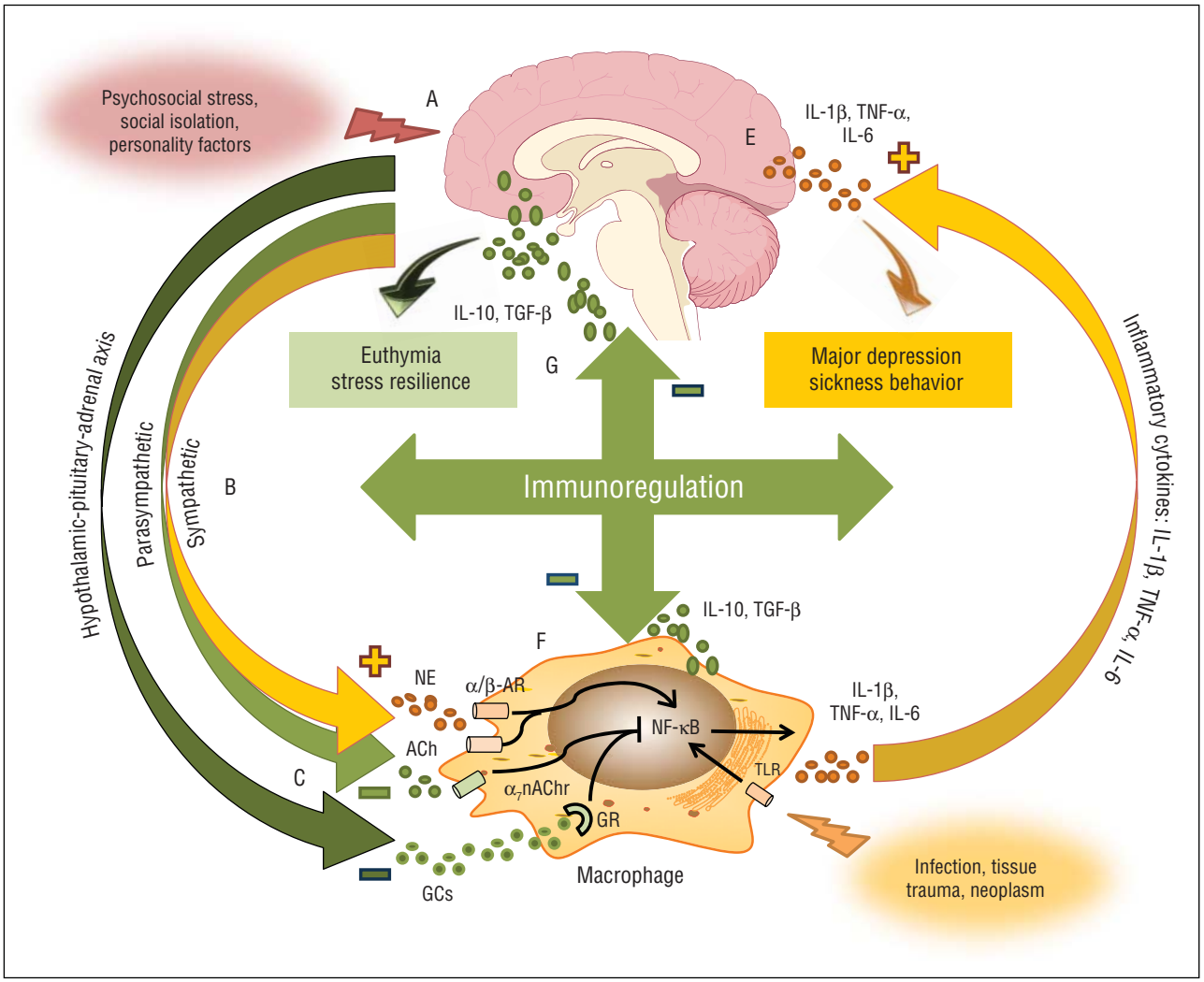


**Figure 1.** Psychosocial stress, inflammation, and immunoregulation in major depressive disorder (MDD). A, Psychosocial stress and factors that contribute to stress, such as social isolation and maladaptive personality, activate brain areas evolved to evaluate and respond to environmental danger. B, These brain areas contribute to activation of stress outflow pathways, including the sympathetic nervous system, with resultant norepinephrine (NE) production, and the hypothalamic-pituitary-adrenal axis, with resultant glucocorticoid (GC) release. In response to psychosocial stress, parasympathetic signaling is also withdrawn, leading to attenuated acetylcholine (ACh) release. C, In general, sympathetic activation promotes innate immune inflammatory processes, whereas parasympathetic signaling and glucocorticoids attenuate inflammation. D, Environmental adversity (whether via α- or β-adrenoreceptor [α/β-AR] stimulation in response to stress or via toll-like receptor [TLR] stimulation in response to infection, tissue trauma, or neoplasm) activates intracellular inflammatory signaling cascades (eg, nuclear factor-κβ [NF-κβ]) within innate immune cells (eg, macrophages and dendritic cells) leading to the production and release of inflammatory cytokines, including interleukin 1β (IL-1β), tumor necrosis factor α (TNF-α), and IL-6. $\alpha_7$ nAChR indicates $\alpha_7$ nicotinic acetylcholine receptor. E, These cytokines access the brain via leaky regions of the blood-brain barrier or active transport across the blood-brain barrier and can influence brain function via activation of afferent nerve fibers (ie, sensory vagus). Once in the brain, cytokine signals participate in processes known to be involved in the development of MDD, including alterations in monoaminergic neurotransmission, reduction in neurotrophic support, and increased production of excitotoxic/oxidative species that damage neurons and glial cells. F, Environmental adversities that activate inflammation (A and D) also stimulate immunoregulatory mechanisms that constrain inflammatory responses (F), in part via production of anti-inflammatory cytokines, including IL-10 and transforming growth factor β (TGF-β). G, Whereas inflammatory responses to psychosocial adversity are associated with MDD (E), immunoregulatory pathways antagonize these responses and by doing so promote psychosocial resilience, which enhances interpersonal functioning, contributing to euthymia (G). Immunoregulatory processes also likely contribute to euthymia by attenuating background levels of inflammatory activity that have been shown to be elevated in MDD.

Taken together, these findings are consistent with the possibility that environmentally induced increases in immune dysregulation, resulting in heightened proinflammatory activity, may account for at least a portion of the increased prevalence of MDD observed in the developed world over the last half century.[117] But association does not establish causality,[118] and the plausibility of this hypothesis would be significantly strengthened if disease states in which immune dysregulation is known to be the primary pathogenic mechanism (and that are highly comorbid with MDD[23,24,119-127]) had also increased in the developed world over the same period. In this regard, overwhelming data demonstrate that the prevalence of helper T cell type 1 ($T_H1$)/$T_H17$–mediated autoimmune and inflammatory bowel and $T_H2$-mediated allergic/asthmatic conditions have increased dramatically in the developed world during the 20th century, with increases in immune-mediated disease incidence in the developing world during the same period closely paralleling the adoption of first-world lifestyles.[128-132] For example, the incidence of asthma, hay fever, type 1 diabetes mellitus, inflammatory bowel disease, and multiple sclerosis increased

an average of 2- to 3-fold in industrialized nations between 1950 and the present, with increases occurring earlier in the most developed countries and later in countries in the process of adopting western lifestyles.[130,133-142] As with MDD, the rate of increase in these disorders is too rapid to be accounted for by changes in the human genome.[143] Given this, it is likely that the incidence of these disorders has risen, at least in part, as a result of environmental changes that have increased the disease liability of genetic profiles that were previously benign. For example, the increasing incidence of type 1 diabetes between 1950 and 2005 can be attributed in large part to new cases with lower-risk HLA antigen genotypes (ie, HLA-DR4, HLA-DRX, HLA-DQ8, HLA-DQY/HLA-DQ2, and HLA-DR3).[144] Thus, recently operating environmental factors must be invoked to explain the increased penetrance of genes that previously conferred only moderate risk for type 1 diabetes. Data from the 1980s suggest a similar pattern of gene × environment interactions in mood disorders, with individuals from high–genetic risk families increasingly likely to manifest disease from mid–20th century onward, despite having roughly equivalent genetic risk as their immediate forbearers.[105]

## IMMUNOREGULATION, EVOLUTIONARY MISMATCH, AND THE CHANGING FACE OF HYGIENE: FROM INFECTION TO THE "OLD FRIENDS"

While inflammation-based etiologic theories for MDD have focused primarily on aspects of the modern world (such as diet, obesity, and stress) that are patently proinflammatory, a more comprehensive theory of evolutionary mismatch, focused on the loss of microbially modulated immunoregulation, has been articulated to account for recent increases in $T_H2$-mediated allergic/asthmatic disorders and $T_H1$-mediated inflammatory bowel and autoimmune diseases, all of which are highly comorbid with MDD.[117] As originally articulated, the "hygiene hypothesis" proposed that factors unique to industrialized societies, including improved sanitation, modern medicine, and reduced family size, reduce the prevalence and change the timing of childhood infections in a way that promotes the development of allergy and asthma.[145] Because infections typically mobilize $T_H1$-type inflammatory responses,[146] a necessary correlate of this idea—supported by immunologic understandings of the time—was that the loss of infection-induced $T_H1$ activation early in life released $T_H2$ processes from appropriate regulatory control with resultant increases in allergy/asthma.[143]

However, it soon became clear that, rather than decreasing (as would be predicted from the $T_H1$-$T_H2$ balance idea), $T_H1$-mediated autoimmune conditions and Crohn disease were also exploding in prevalence in exactly the same countries in which allergy was on the rise.[128,147] Moreover, allergies are most common in inner cities, where childhood infections are rife, and least common in isolated rural communities.[148] A Darwinian perspective also challenged the notion that sporadic childhood infections were the crucial factor in modernity-linked immune dysregulation. Most childhood viral infections derive from viruses transferred from domesticated animals within the last 10 000 years, which is too brief a period to credibly allow the emergence of the type of deep, coevolved interdependence between microbes and man suggested by the hygiene hypothesis, especially when it is considered that the population density required for these viruses to become endemic is even more recent.[149] Similarly, nonviral childhood infections are sporadic, making it highly unlikely that they provided the constant immunoregulatory input required within a coevolutionary framework.[150] Not surprisingly, therefore, most follow-up studies have failed to show an association between childhood infection and increased autoimmune and/or atopic conditions in the modern world,[151-153] while continuing, in general, to find correlations between a first-world lifestyle and increases in these conditions.

A potential resolution to this dilemma, implicating regulatory dendritic cells and Treg cells, began to emerge in the late 1990s.[154] In 2002, Rook and Brunet[150] put forth the "Old Friends" hypothesis, which posited that a disruption of ancient associations with microorganisms once ubiquitous in both the external and internal human environment might better explain the link between modernity and increased inflammatory/atopic disease. Rather than providing immune regulation/instruction via $T_H1$ activation, it was suggested that these microorganisms induced and maintained an adaptive level of immune suppression by stimulating T cells to differentiate along regulatory, rather than either $T_H1$ or $T_H2$, lines, with a resultant increased production of anti-inflammatory, immunoregulatory cytokines, especially IL-10 and transforming growth factor β (**Figure 2**).[143] It was hypothesized that these organisms took on the role of training the immune system in tolerance because they themselves needed to be tolerated, either because they were harmless but ubiquitous in the external environment in which mammals evolved or because they provided essential services for their hosts, as is the case with probiotic gut flora,[155] or because, although not harmless, they are not eradicable by inflammatory processes, which therefore inflict tissue damage to no good effect.[143,150] In essence, the Old Friends hypothesis suggested—quoting a recent article—that

> the mammalian genome does not encode for all functions required for immunological development, but rather that mammals depend on critical interactions with their microbiome (the collective genomes of the microbiota) for health.[156(p624)]

Said more simply, some factors required by the immune system to respond appropriately to the environment might have been "entrusted" over evolutionary time to microorganisms.[117,143]

Among organisms that were ubiquitous, but harmless, are a number of saprophytic mycobacterial species that are found in mud and untreated water/unwashed food. These organisms have been termed *pseudocommensals* because, while not colonizing the body, they historically passed through the body in large quantities.[117] Among organisms that colonized the body and provided essential services for their hosts are commensal and

probiotic members of the gut microbiota.[157] It is likely that numerous intestinal species contribute to immunoregulatory activities[158]; however, interest has focused primarily on 3 genera: *Bacteroides*, *Lactobacilli*, and *Bifidobacteria*. The final members of the old friends triad are helminthes, which are still highly prevalent in the third world but have essentially vanished as infectious agents in the last 50 years in the developed world.[117]

Significant in vitro and in vivo preclinical data indicate that all 3 classes of old friends have the potential to prevent/ameliorate pathology in animal models for autoimmune, allergic, and inflammatory bowel diseases, as well as neoplasms and certain infections, and do so via reductions in inflammatory activity.[117,159] As a striking example of this, a single polysaccharide (polysaccharide A) from a *Bacteroides* species largely corrected the subnormal and functionally distorted development of the immune system that occurs in germ-free mice and was protective against *Helicobacter hepaticus*–induced inflammatory colitis via induction of IL-10–producing Treg cells.[156,160] This and other basic science studies increasingly suggest that both gut microbiota and pseudocommensals that traditionally passed through the gut in high numbers have the potential to regulate "whole-body" immunoregulatory activity.[161-165] For example, intragastric administration of the pseudocommensal *Mycobacterium vaccae* was shown to induce an immunoregulatory cytokine profile in mesenteric lymph nodes and the spleen and to reduce eosinophilic infiltrates in the lung following an intragastric allergen challenge.[161] Prebiotics shown to increase *Bifidobacterium* species in the rodent gut markedly reduced plasma concentrations of IL-1β, TNF-α, IL-6, and monocyte chemoattractant protein 1,[162] and metabolic products from gut microbiota reduce inflammation in animal models of a variety of human autoimmune and allergic disorders, as well as in in vitro preparations of human peripheral blood mononuclear cells.[162] In addition to direct effects on immune functioning, recent evidence suggests that the gut microbiome profoundly impacts other whole-body physiological processes that are profoundly affected by activity in inflammatory signaling pathways and that are abnormal in MDD, including peripheral pain sensitivity, sleep, and metabolism.[166-168]

The tremendous variation that exists between different classes of old friends make it unlikely that common proximal molecular mechanisms will be identified by which all relevant species contribute to immunoregulation.[156,169] However, despite different proximal mechanisms (eg, production of polysaccharide A in *Bacteroides fragilis*, schistosome-specific phosphatidylserine in *Schistosoma mansoni*, and lipoteichoic acid in *Lactobacillus plantarum*[156,170,171]), a common denominator that differentiates old friends from primarily pathogenic microorganisms appears to be an ability to activate host production of anti-inflammatory and immunoregulatory, rather than proinflammatory, cytokines, while also promoting T cells (and in some instances B cells and macrophages) to differentiate along regulatory lines.[156,170,172-175] In addition to increasing anti-inflammatory cytokine production, the old friends also reduce proinflammatory signaling. For example, a recent study of humans with

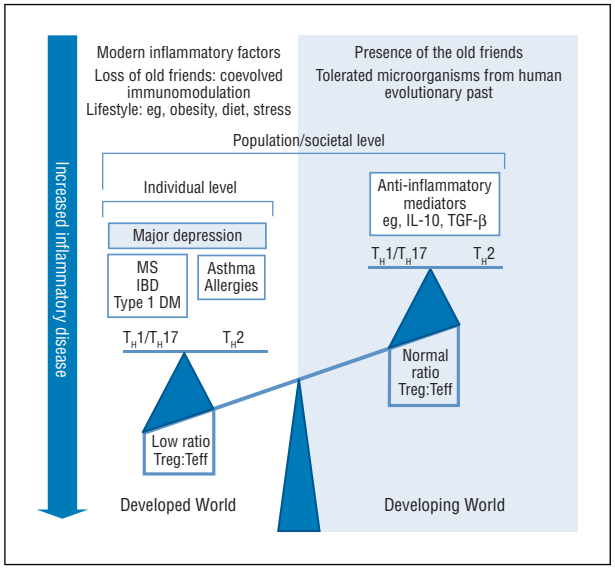


**Figure 2.** Loss of contact with the "old friends" and increased inflammatory conditions in the modern world. In populations adequately exposed to old friends, such as many societies in the developing world, priming of regulatory T cells (Treg) is sufficient to maintain an appropriate balance of Treg to effector T cells (Teff), with the result that inappropriate inflammation is generally constrained. When contact with the old friends is disrupted as a result of modern cultural practices (eg, sanitation, water and food treatment, modern medicines), priming of Treg is inadequate, with the result that the ratio of Treg to Teff is low. In this situation, the population as a whole is at risk for a variety of syndromes attributable to inadequate termination of inflammatory responses to any of a range of environmental stimuli. Consistent with this, although the prevalence of serious infections is significantly reduced in the industrialized world, rates of chronic inflammatory conditions (eg, autoimmune diseases, allergies, asthma, and cardiovascular disease) have been shown in many studies to be much higher than in the developing world. Some individuals have a genetic background and/or immunologic history that places them at risk for disorders, such as multiple sclerosis (MS), inflammatory bowel disease (IBD), and type 1 diabetes mellitus (DM), characterized by overactive/uncontrolled helper T cell type 1 ($T_H1$) and/or $T_H17$ activity. In other individuals, $T_H2$ responses are more liable to inadequate control, resulting in asthma and allergic disorders. While not developing gross immune-related pathology, a further group of individuals with inadequate termination of either $T_H1$ or $T_H2$ inflammatory responses is susceptible to central nervous system effects of cytokines, including major depressive disorder. However, conditions associated with $T_H1/T_H17$ and $T_H2$ dysregulation are highly comorbid with major depressive disorder. IL-10 indicates interleukin 10; TGF-β, transforming growth factor β.

tuberculosis showed that the pseudocommensal microorganism *M vaccae* markedly reduced serum and unstimulated peripheral blood mononuclear cell supernatant TNF-α concentrations over a 3-month period when compared with placebo (while also improving radiological findings).[176] Given multiple studies showing increased serum/plasma concentrations of TNF-α in MDD,[22,78,84,177-179] as well as evidence that antidepressants reduce TNF-α concentrations,[22,31] these findings raise the intriguing possibility that because *M vaccae* and other old friends have immunological activity similar to standard antidepressant medications, they may also demonstrate antidepressant behavioral effects.

## OLD FRIENDS, IMMUNOREGULATION, AND TOLERANCE OF ENVIRONMENTAL ADVERSITY

Whatever other sources of inflammation are augmented by modernity, an unrestrained inflammatory drive due to reduced exposure to various classes of old friends seems

an inescapable consequence of the 20th century increase in hygiene and decrease in rates of parasitic infection. Although much interest in this regard has focused on potential diet- and medicinally induced (ie, antibiotic) changes in the gut microbiota,[180] helminthes and several species of saprophytic mycobacteria have also attracted widespread attention for their ability to induce not only direct immunotolerance toward themselves, but also what has been termed *bystander tolerance*, such that their presence in the immune environment promotes a wide-ranging and nonspecific immunoregulatory state that attenuates $T_H1/T_H17$, $T_H2$, and innate immune activity in general.[181-184] In some cases, these microbes also act as Treg adjuvants, resulting in Treg that specifically recognize allergens or autoantigens.[185] As noted earlier, failure of these immunoregulatory processes has been repeatedly linked to the development of both autoimmune and atopic/allergic conditions.

Thus, the Old Friends hypothesis provides a novel framework for understanding, at least in part, why living in the modern world may increase vulnerability to MDD. The same cultural practices that have decreased infectious morbidity have also deprived us of contact with a range of microorganisms, mostly derived from mud, animals, and feces, which had been entrusted through coevolutionary mechanisms with the task of modulating essential human immune regulatory systems. Lacking such tolerogenic training, vulnerable individuals in the modern world are at significantly increased risk of mounting inappropriate inflammatory responses to harmless environmental antigens (leading to asthma), benign food contents and commensals in the gut (leading to inflammatory bowel disease), or self-antigens (leading to any of a host of autoimmune diseases).[154] We suggest that loss of exposure to these coevolved benign microorganisms may also sensitize vulnerable individuals in industrialized societies to mount inappropriately aggressive inflammatory responses to psychosocial adversity, which may in turn serve as a mechanism by which stress promotes the development and/or maintenance of MDD (**Figure 3**). Said differently, just as recent studies suggest that the old friends may improve allergies by promoting tolerance to harmless environmental antigens,[184] it may be that exposing depressed individuals living in industrialized societies to immunoregulatory microbiota may improve the symptoms of depression by inducing Treg cells to downregulate inflammatory signaling in response to stress, thus promoting physiological and emotional tolerance to the types of psychosocial stressors that, like allergens, are frequently fairly harmless in the overall scheme of things but that have been repeatedly shown to predict the development and maintenance of MDD.[66] In addition to amplifying stress-induced inflammatory activation, loss of contact with the old friends may also promote a generalized increase in background inflammation as a result of insufficient Treg activity to completely shut off inflammatory responses, leading to depression in susceptible individuals, even in the absence of 1 of the $T_H1$- or $T_H2$-mediated organ-specific inflammatory disorders already attributed to the Old Friends hypothesis (Figure 3).

## OLD FRIENDS AND THE PATHOGENESIS AND TREATMENT OF MDD: SUGGESTIVE FINDINGS

Multiple lines of circumstantial evidence point to a potential role for the old friends in the pathogenesis and treatment of MDD. Relevant to the importance of psychosocial stress as a depressogenic risk,[66,186] in primates early life stress has been shown to reduce gut colonization by *Lactobacilli* and *Bifidobacteria* (both of which play important roles in maintaining gut endothelial barrier function) and promote colonization by pathogenic bacterial species.[187] Stress paradigms in adult animals produce similar changes in the microflora and reliably increase various measures of inflammation in the gut, as well as increased translocation of potentially pathogenic bacteria across the gut wall.[188,189] Interestingly, these changes are mediated in part by reduced vagal parasympathetic signaling and by the induction of glucocorticoid insensitivity,[190,191] both of which are classic neuroendocrine hallmarks of MDD.[67] Consistent with these observations, psychological stress in humans has been associated with reduced fecal *Lactobacilli* levels,[192] and a recent study found increased translocation of gram-negative gut bacteria with concomitant increases in plasma lipopolysaccharide in patients with MDD.[193] The study suggests that this type of "leaky gut" phenomenon (presumably caused, at least in part, by microflora disruption) might be a potential source for the increased inflammatory drive seen in many medically healthy individuals with depression.

Studies addressing potential antidepressant properties of the old friends in a rigorous manner in humans are few and are suggestive rather than conclusive. For example, a small double-blind, placebo-controlled trial found that treatment with trans-galactooligosacharide (a prebiotic that increases gut *Bifidobacteria*) reduced anxiety in patients with irritable bowel syndrome, although the degree to which reduced anxiety resulted from improved bowel function is unclear.[194] Similarly, 2 months of treatment with a *Lactobacillus* species reduced anxiety, but not depressive symptoms, in patients with chronic fatigue syndrome when compared with placebo.[195] A smaller open study in chronic fatigue syndrome found no effect of probiotic treatment on fatigue, but an improvement in the types of cognitive symptoms that are also core constituents of MDD was observed.[196]

Perhaps the most compelling data for any of the old friends come from 2 studies of *M vaccae* administration in patients with cancer. In a first study, the addition of *M vaccae* to IL-2 for renal cell carcinoma significantly reduced IL-2–induced sickness symptoms that resemble the symptoms of depression.[197] In a second and considerably larger study, *M vaccae* significantly improved quality of life in general—and depressive and anxiety symptoms in particular—in patients receiving chemotherapy for lung cancer.[198] These symptomatic effects are consistent with our emerging understanding of downstream effects of *M vaccae* and other old friends on non-immunological pathways of direct relevance to MDD. These effects include programming lifelong reductions in hypothalamic-pituitary-adrenal axis responses to psy-

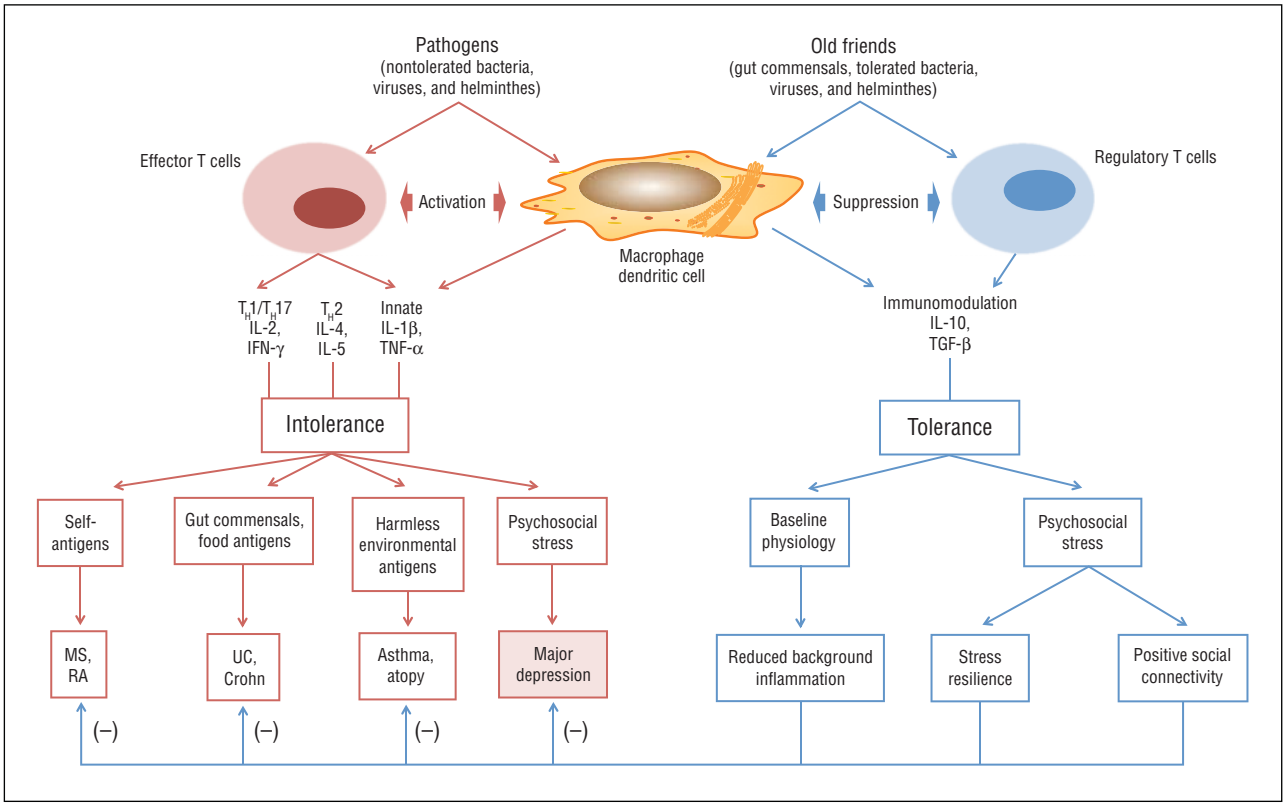


**Figure 3.** Microorganisms play important roles in shaping immune function in species over evolutionary time, and in individuals across the lifespan, to appropriately respond to a wide range of environmental threats and opportunities. When exposed to an optimal balance of immunostimulatory and immunoregulatory microorganisms during development, the immune system develops a finely honed ability to respond differentially to microorganisms that pose a threat to organismal integrity/survival vs those that are either neutral or may actually benefit the individual. When functioning appropriately, cells of the innate immune system (eg, macrophages, dendritic cells) respond to pathogens with activation of innate immune mechanisms, leading to the production of inflammatory cytokines, such as interleukin 1β (IL-1β) and tumor necrosis factor α (TNF-a). In addition to having pathogen-killing properties themselves, mediators of the innate immune response aid in the presentation of antigen to effector T cells and activation of cellular immunity. Viruses, bacteria, and protozoal pathogens elicit helper T cell type 1 ($T_H1$) and/or $T_H17$ responses from the cellular immune system, characterized by production of cytokines such as IL-2 and interferon γ (IFN-γ). $T_H2$ responses, mediated by cytokines such as IL-4 and IL-5, appear to be primarily directed toward combating acute helminth infection. These responses, combined with ongoing innate immune activity, lead to intolerance of the invading microorganism and attempts to contain and rid it from the body. This type of immunological intolerance is adaptive in contexts in which the organism in question poses significant danger and can be overcome by immunological mechanisms. However, as a result of reduced immunoregulatory activity in the modern world, due in part to loss of contact with the "old friends," vulnerable individuals may display inappropriate immune intolerance to an array of nonthreatening or actually beneficial factors in the self or environment, resulting in autoimmune and inflammatory bowel diseases when $T_H1$ and/or $T_H17$ responses are hyperactive and asthma and atopic conditions when $T_H2$ responses are hyperactive. In contrast, contact with old friends favors dendritic and T cells adopting an immunoregulatory profile characterized by production of anti-inflammatory cytokines such as IL-10 and transforming growth factor β (TGF-β). These cytokines suppress $T_H1/T_H17$, $T_H2$, and innate immune activity in an ongoing baseline fashion, but also in response to environmental adversities, such as psychosocial stress. These immunoregulatory processes lead to stress resiliency, which enhances psychosocial relationships in a positive feed-forward loop. Combined with reduced background inflammatory tone, these effects protect against autoimmune conditions such as multiple sclerosis (MS) and rheumatoid arthritis (RA), inflammatory bowel diseases such as ulcerative colitis (UC) and Crohn disease, asthma and atopy, and major depression.

chological stress in young animals, stimulating brain-derived neurotrophic factor activity in the central nervous system and producing a variety of neuroactive molecules that have been shown to be abnormal in MDD.[199] In this regard, gut microbiota are capable of increasing plasma concentrations of serotonin, and *M vaccae* activates specific serotonergic neural pathways that are implicated in mood regulation and cognitive function in animal models of depression.[165,200,201]

## TESTING AND APPLYING AN OLD FRIENDS HYPOTHESIS OF DEPRESSION

The hypothesis that disruptions in tolerogenic, coevolved relationships with microorganisms contribute to MDD by reducing our ability to cope effectively with adversity suggests a number of predictions that would, if true, greatly strengthen this hypothesis. These predictions include that (1) intolerance of psychosocial adversity should promote depression; (2) genetic risks for emotional intolerance of psychosocial adversity should also be associated with increased inflammatory responses to it; (3) exposure to proinflammatory cytokines (eg, IL-1β, TNF-α, IL-6) should decrease tolerance of psychosocial adversity; and (4) anti-inflammatory and/or immunoregulatory strategies should enhance tolerance of psychosocial adversity.

The prediction that intolerance of psychosocial adversity should promote depression hardly needs elaboration here, for although subsumed under a number of overlapping rubrics (ie, neuroticism, interpersonal sensitivity, perfectionism, hostility), emotional intolerance of life's challenges and imperfections has been repeatedly shown to predict the development and/or mainte-

nance of MDD.[202-207] Less well known are recent data that support the second prediction. Although a meta-analysis has cast some doubt on the association between the short form of the serotonin transporter–linked polymorphic region (5HTTLPR) of the serotonin transporter gene (*SLC6A4*) and MDD,[208] multiple lines of evidence suggest that this gene is associated with increases in a number of interrelated measures of emotional intolerance, including neuroticism, lack of resilience, hostility, and negative attentional bias.[209-214] Interestingly, the short form of the 5HTTLPR has been reported to predict the development of depression not just in response to psychosocial stress, but also in response to chronic inflammation resulting from interferon alfa therapy.[8,215] Consistent with these associations between the 5HTTLPR and reduced tolerance of various types of environmental challenge/adversity, the short allele of the gene has recently been shown to increase the ratio of proinflammatory to anti-inflammatory (ie, IL-6/IL-10) cytokines produced in response to a laboratory psychosocial stressor.[216] In a separate study, several single-nucleotide polymorphisms in the serotonin transporter associated with increased depressive symptoms were also associated with increased plasma IL-6 concentration measured at rest.[217] However, the physiological pathways by which these serotonin transporter alleles increase inflammatory activity remain to be elucidated.

In support of the third prediction, that proinflammatory cytokine exposure should decrease tolerance of psychosocial adversity, interferon alfa treatment markedly increases irritability, which is at least as common as, and frequently more destructive to, interpersonal relationships than depression and fatigue.[218,219] Indeed, clinical experience suggests that patients receiving interferon alfa are more often debilitated by a decreased ability to tolerate frustrations and interpersonal conflicts than by depression per se. Recent naturalistic studies provide preliminary support for these intuitions by reporting that both short- and long-term cytokine exposure increase sensitivity to interpersonal rejection and conflict.[87,220-222] Thus, inflammation does indeed appear to increase intolerance of psychosocial adversity at the phenomenological level. In tandem with these data, neuroimaging studies report that when compared with controls, individuals undergoing either short- or long-term cytokine exposure show increased activation of the dorsal anterior cingulate cortex,[223,224] a brain area critical for the detection and correction of errors.[225] In 1 study, subjects undergoing long-term interferon alfa treatment showed a strong correlation between amount of dorsal anterior cingulate cortex activation and increased number of errors on a target detection task, an association not seen in controls.[223] This pattern of heightened central nervous system sensitivity to minor task imperfections is also seen in individuals beset with various forms of environmental intolerance, including anxiety,[226] neuroticism,[227] and obsessive-compulsive disorder,[228] again consistent with the possibility that inflammatory processes contribute to cognitive/affective sets that make tolerance more difficult, in this case tolerance of one's own imperfections, a trait that powerfully associates with depression.[229,230]

To our knowledge, the fourth prediction (ie, that anti-inflammatory and/or immunoregulatory strategies should enhance psychosocial tolerance) has never been directly tested by examining whether cytokine antagonists/nonsteroidals/cyclooxygenase-2 inhibitors or immunoregulatory microorganisms (ie, the old friends) improve emotional tolerance in the face of psychosocial adversity. Nonetheless, other agents known to have anti-inflammatory properties in vivo provide indirect support and a rationale for future studies that address this issue directly. For example, pretreatment with cortisol, which is potently anti-inflammatory, reduced negative emotional reactions to a laboratory-based psychosocial stressor.[231] Most currently available data suggest that antidepressants reduce proinflammatory and augment anti-inflammatory signaling in humans[19] and reduce many metrics of emotional intolerance, including neuroticism, hostility, interpersonal and stress sensitivity, and perfectionism independently of effects on depressive symptoms.[232-240] It is not known, however, whether improvements in emotional tolerance of adversity correlate with antidepressant-induced changes in inflammatory activity. Behavioral strategies, such as exercise, that reduce inflammatory markers have also been shown to promote tolerance of psychosocial adversity. For example, physically fit individuals respond to psychosocial stress with reduced plasma concentrations of TNF-α when compared with sedentary individuals.[241]

Research into the role of the old friends in the pathogenesis of MDD is in its infancy. As such, at least 3 complementary lines of inquiry will likely emerge to test hypotheses put forward in this article. First, just as eradication of the old friends has been repeatedly shown to increase rates of autoimmune, inflammatory bowel, and atopic conditions, future studies will need to examine whether a similar uptick in the prevalence of MDD can be detected in populations that are in transition to living in modern industrialized conditions. Second, and perhaps most importantly, given that preparations derived from various old friends are available and being tested in formal clinical trials for a variety of illnesses linked to immune dysregulation in which depression is highly comorbid,[182-184] it will be important to directly test the efficacy of these compounds in medically healthy individuals with MDD.

Finally, should antidepressant efficacy be noted, it will be intriguing to examine whether administration of the old friends improves depression, at least in part, by reducing inflammatory responses to psychosocial stress and/or other relevant environmental adversities. Should the old friends impart this type of emotional and physiological tolerance to the challenges of daily life, the important public health question of whether we should encourage measured reexposure to benign environmental microorganisms will not be far behind.

**Submitted for Publication**: March 2, 2010; final revision received June 2, 2010; accepted July 4, 2010.
**Correspondence**: Charles L. Raison, MD, Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, 1365C Clifton Rd, 5th Floor, Atlanta, GA 30322 (craison@emory.edu).

**Financial Disclosure:** In the previous 5 years, Dr Raison has served as a speaker for Lilly, Wyeth, and Schering-Plough and as a consultant or an advisory board member for Lilly, Wyeth, Schering-Plough, Centocor, and Pamlab, LLC. He owns equity in ContemplativeHealth. In the previous 10 years, Dr Lowry has received research support from SR Pharma PLC (now Silence Therapeutics PLC). In the previous 5 years, Dr Rook has held (and still holds) equity in Silence Therapeutics PLC, and he acts as an unpaid ad hoc advisor to Immodulon, a biotech start-up that has licensed *M vaccae* technology from Silence Therapeutics PLC.

**Funding/Support:** Dr Raison receives research support from the National Institutes of Health (grants R01MH070553, R01AT004698, 3R01AT004698-01A1S1, 1RC1AT005728, R21MH0771172, UL1 RR025008, and M01RR0039), the Georgia Department of Human Services, and the Centers for Disease Control and Prevention. Dr Lowry receives research support from the National Institutes of Health (grants R01MH086539 and R01MH065702) and the National Science Foundation (grants IOS0845550 and IOS0921969). Dr Rook receives research support from the Bill and Melinda Gates Foundation Grand Challenge Explorations initiative and the GALTRAIN Marie Curie Early Stages Training Network, funded by the European Union.

## REFERENCES

1. Aretaeus. *The Extant Works of Aretaeus, the Cappadocian.* Boston, MA: Milford House, Inc; 1972.
2. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Med.* 2006;3(11):e442.
3. Dobzhansky T. Nothing in biology makes sense except in the light of evolution. *Am Biol Teach.* 1973;35:125-129.
4. Heinssen R, Insel TR. Prevention of mental disorders [published March 2, 2007]. *Annu Rev Clin Psychol.*
5. Kendler KS, Prescott CA, Myers J, Neale MC. The structure of genetic and environmental risk factors for common psychiatric and substance use disorders in men and women. *Arch Gen Psychiatry.* 2003;60(9):929-937.
6. Caspi A, Sugden K, Moffitt TE, Taylor A, Craig IW, Harrington H, McClay J, Mill J, Martin J, Braithwaite A, Poulton R. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. *Science.* 2003;301(5631):386-389.
7. Kendler KS, Kuhn JW, Vittum J, Prescott CA, Riley B. The interaction of stressful life events and a serotonin transporter polymorphism in the prediction of episodes of major depression: a replication. *Arch Gen Psychiatry.* 2005;62(5):529-535.
8. Bull SJ, Huezo-Diaz P, Binder EB, Cubells JF, Ranjith G, Maddock C, Miyazaki C, Alexander N, Hotopf M, Cleare AJ, Norris S, Cassidy E, Aitchison KJ, Miller AH, Pariante CM. Functional polymorphisms in the interleukin-6 and serotonin transporter genes, and depression and fatigue induced by interferon-alpha and ribavirin treatment. *Mol Psychiatry.* 2009;14(12):1095-1104.
9. Jabbi M, Kema IP, van der Pompe G, te Meerman GJ, Ormel J, den Boer JA. Catechol-o-methyltransferase polymorphism and susceptibility to major depressive disorder modulates psychological stress response. *Psychiatr Genet.* 2007;17(3):183-193.
10. Katz MM, Bowden CL, Frazer A. Rethinking depression and the actions of antidepressants: uncovering the links between the neural and behavioral elements. *J Affect Disord.* 2010;120(1-3):16-23.
11. Bierhaus A, Wolf J, Andrassy M, Rohleder N, Humpert PM, Petrov D, Ferstl R, von Eynatten M, Wendt T, Rudofsky G, Joswig M, Morcos M, Schwaninger M, McEwen B, Kirschbaum C, Nawroth PP. A mechanism converting psychosocial stress into mononuclear cell activation. *Proc Natl Acad Sci U S A.* 2003;100(4):1920-1925.
12. Kiecolt-Glaser JK, Preacher KJ, MacCallum RC, Atkinson C, Malarkey WB, Glaser R. Chronic stress and age-related increases in the proinflammatory cytokine IL-6. *Proc Natl Acad Sci U S A.* 2003;100(15):9090-9095.
13. Steptoe A, Hamer M, Chida Y. The effects of acute psychological stress on circulating inflammatory factors in humans: a review and meta-analysis. *Brain Behav Immun.* 2007;21(7):901-912.
14. Pace TW, Mletzko TC, Alagbe O, Musselman DL, Nemeroff CB, Miller AH, Heim CM. Increased stress-induced inflammatory responses in male patients with major depression and increased early life stress. *Am J Psychiatry.* 2006;163(9):1630-1633.
15. Miller GE, Rohleder N, Cole SW. Chronic interpersonal stress predicts activation of pro- and anti-inflammatory signaling pathways 6 months later. *Psychosom Med.* 2009;71(1):57-62.
16. Miller GE, Chen E, Sze J, Marin T, Arevalo JM, Doll R, Ma R, Cole SW. A functional genomic fingerprint of chronic stress in humans: blunted glucocorticoid and increased NF-kappaB signaling. *Biol Psychiatry.* 2008;64(4):266-272.
17. Fuligni AJ, Telzer EH, Bower J, Cole SW, Kiang L, Irwin MR. A preliminary study of daily interpersonal stress and C-reactive protein levels among adolescents from Latin American and European backgrounds. *Psychosom Med.* 2009;71(3):329-333.
18. O'Connor MF, Bower JE, Cho HJ, Creswell JD, Dimitrov S, Hamby ME, Hoyt MA, Martin JL, Robles TF, Sloan EK, Thomas KS, Irwin MR. To assess, to control, to exclude: effects of biobehavioral factors on circulating inflammatory markers. *Brain Behav Immun.* 2009;23(7):887-897.
19. Miller AH, Maletic V, Raison CL. Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. *Biol Psychiatry.* 2009;65(9):732-741.
20. Sutcigil L, Oktenli C, Musabak U, Bozkurt A, Cansever A, Uzun O, Sanisoglu SY, Yesilova Z, Ozmenler N, Ozsahin A, Sengul A. Pro- and anti-inflammatory cytokine balance in major depression: effect of sertraline therapy. *Clin Dev Immunol.* 2007;2007:76396.
21. Myint AM, Leonard BE, Steinbusch HW, Kim YK. Th1, Th2, and Th3 cytokine alterations in major depression. *J Affect Disord.* 2005;88(2):167-173.
22. Lanquillon S, Krieg JC, Bening-Abu-Shach U, Vedder H. Cytokine production and treatment response in major depressive disorder. *Neuropsychopharmacology.* 2000;22(4):370-379.
23. Moussavi S, Chatterji S, Verdes E, Tandon A, Patel V, Ustun B. Depression, chronic diseases, and decrements in health: results from the World Health Surveys. *Lancet.* 2007;370(9590):851-858.
24. Evans DL, Charney DS, Lewis L, Golden RN, Gorman JM, Krishnan KR, Nemeroff CB, Bremner JD, Carney RM, Coyne JC, Delong MR, Frasure-Smith N, Glassman AH, Gold PW, Grant I, Gwyther L, Ironson G, Johnson RL, Kanner AM, Katon WJ, Kaufmann PG, Keefe FJ, Ketter T, Laughren TP, Leserman J, Lyketsos CG, McDonald WM, McEwen BS, Miller AH, Musselman D, O'Connor C, Petitto JM, Pollock BG, Robinson RG, Roose SP, Rowland J, Sheline Y, Sheps DS, Simon G, Spiegel D, Stunkard A, Sunderland T, Tibbits P Jr, Valvo WJ. Mood disorders in the medically ill: scientific review and recommendations. *Biol Psychiatry.* 2005;58(3):175-189.
25. Zautra AJ, Davis MC, Reich JW, Nicassario P, Tennen H, Finan P, Kratz A, Parrish B, Irwin MR. Comparison of cognitive behavioral and mindfulness meditation interventions on adaptation to rheumatoid arthritis for patients with and without history of recurrent depression. *J Consult Clin Psychol.* 2008;76(3):408-421.
26. Thornton LM, Andersen BL, Schuler TA, Carson WE III. A psychological intervention reduces inflammatory markers by alleviating depressive symptoms: secondary analysis of a randomized controlled trial. *Psychosom Med.* 2009;71(7):715-724.
27. Doering LV, Cross R, Vredevoe D, Martinez-Maza O, Cowan MJ. Infection, depression, and immunity in women after coronary artery bypass: a pilot study of cognitive behavioral therapy. *Altern Ther Health Med.* 2007;13(3):18-21.
28. Simon GE, Von Korff M, Saunders K, Miglioretti DL, Crane PK, van Belle G, Kessler RC. Association between obesity and psychiatric disorders in the US adult population. *Arch Gen Psychiatry.* 2006;63(7):824-830.
29. Miller GE, Freedland KE, Carney RM, Stetler CA, Banks WA. Pathways linking depression, adiposity, and inflammatory markers in healthy young adults. *Brain Behav Immun.* 2003;17(4):276-285.
30. Suarez EC. C-reactive protein is associated with psychological risk factors of cardiovascular disease in apparently healthy adults. *Psychosom Med.* 2004;66(5):684-691.
31. Tuglu C, Kara SH, Caliyurt O, Vardar E, Abay E. Increased serum tumor necrosis factor-alpha levels and treatment response in major depressive disorder. *Psychopharmacology (Berl).* 2003;170(4):429-433.
32. Vieira VJ, Valentine RJ, McAuley E, Evans E, Woods JA. Independent relationship between heart rate recovery and C-reactive protein in older adults. *J Am Geriatr Soc.* 2007;55(5):747-751.
33. Moyna NM, Bodnar JD, Goldberg HR, Shurin MS, Robertson RJ, Rabin BS. Relation between aerobic fitness level and stress induced alterations in neuroendocrine and immune function. *Int J Sports Med.* 1999;20(2):136-141.

34. Anton SD, Newton RL Jr, Sothern M, Martin CK, Stewart TM, Williamson DA. Association of depression with body mass index, sedentary behavior, and maladaptive eating attitudes and behaviors in 11 to 13-year old children. *Eat Weight Disord*. 2006;11(3):e102-e108.
35. Ghosh S, Khazaei M, Moien-Afshari F, Ang LS, Granville DJ, Verchere CB, Dunn SR, McCue P, Mizisin A, Sharma K, Laher I. Moderate exercise attenuates caspase-3 activity, oxidative stress, and inhibits progression of diabetic renal disease in db/db mice. *Am J Physiol Renal Physiol*. 2009;296(4):F700-F708.
36. Balducci S, Zanuso S, Nicolucci A, Fernando F, Cavallo S, Cardelli P, Fallucca S, Alessi E, Letizia C, Jimenez A, Fallucca F, Pugliese G. Anti-inflammatory effect of exercise training in subjects with type 2 diabetes and the metabolic syndrome is dependent on exercise modalities and independent of weight loss. *Nutr Metab Cardiovasc Dis*. 2010;20(8):608-617.
37. Kohut ML, McCann DA, Russell DW, Konopka DN, Cunnick JE, Franke WD, Castillo MC, Reighard AE, Vanderah E. Aerobic exercise, but not flexibility/resistance exercise, reduces serum IL-18, CRP, and IL-6 independent of beta-blockers, BMI, and psychosocial factors in older adults. *Brain Behav Immun*. 2006;20(3):201-209.
38. Blumenthal JA, Sherwood A, Babyak MA, Watkins LL, Waugh R, Georgiades A, Bacon SL, Hayano J, Coleman RE, Hinderliter A. Effects of exercise and stress management training on markers of cardiovascular risk in patients with ischemic heart disease: a randomized controlled trial. *JAMA*. 2005;293(13):1626-1634.
39. Tanskanen A, Hibbeln JR, Tuomilehto J, Uutela A, Haukkala A, Viinamäki H, Lehtonen J, Vartiainen E. Fish consumption and depressive symptoms in the general population in Finland. *Psychiatr Serv*. 2001;52(4):529-531.
40. Dai J, Miller AH, Bremner JD, Goldberg J, Jones L, Shallenberger L, Buckham R, Murrah NV, Veledar E, Wilson PW, Vaccarino V. Adherence to the Mediterranean diet is inversely associated with circulating interleukin-6 among middle-aged men: a twin study. *Circulation*. 2008;117(2):169-175.
41. Lee O, Bruce WR, Dong Q, Bruce J, Mehta R, O'Brien PJ. Fructose and carbonyl metabolites as endogenous toxins. *Chem Biol Interact*. 2009;178(1-3):332-339.
42. Breslau N, Roth T, Rosenthal L, Andreski P. Sleep disturbance and psychiatric disorders: a longitudinal epidemiological study of young adults. *Biol Psychiatry*. 1996;39(6):411-418.
43. Irwin MR, Wang M, Ribeiro D, Cho HJ, Olmstead R, Breen EC, Martinez-Maza O, Cole S. Sleep loss activates cellular inflammatory signaling. *Biol Psychiatry*. 2008;64(6):538-540.
44. Irwin MR, Wang M, Campomayor CO, Collado-Hidalgo A, Cole S. Sleep deprivation and activation of morning levels of cellular and genomic markers of inflammation. *Arch Intern Med*. 2006;166(16):1756-1762.
45. Vgontzas AN, Zoumakis M, Papanicolaou DA, Bixler EO, Prolo P, Lin HM, Vela-Bueno A, Kales A, Chrousos GP. Chronic insomnia is associated with a shift of interleukin-6 and tumor necrosis factor secretion from nighttime to daytime. *Metabolism*. 2002;51(7):887-892.
46. Steptoe A, Owen N, Kunz-Ebrecht SR, Brydon L. Loneliness and neuroendocrine, cardiovascular, and inflammatory stress responses in middle-aged men and women. *Psychoneuroendocrinology*. 2004;29(5):593-611.
47. Cacioppo JT, Hawkley LC. Social isolation and health, with an emphasis on underlying mechanisms. *Perspect Biol Med*. 2003;46(3)(suppl):S39-S52.
48. McDade TW, Hawkley LC, Cacioppo JT. Psychosocial and behavioral predictors of inflammation in middle-aged and older adults: the Chicago Health, Aging, and Social Relations Study. *Psychosom Med*. 2006;68(3):376-381.
49. Cole SW, Hawkley LC, Arevalo JM, Sung CY, Rose RM, Cacioppo JT. Social regulation of gene expression in human leukocytes. *Genome Biol*. 2007;8(9):R189.
50. Alley DE, Seeman TE, Ki Kim J, Karlamangla A, Hu P, Crimmins EM. Socioeconomic status and C-reactive protein levels in the US population: NHANES IV. *Brain Behav Immun*. 2006;20(5):498-504.
51. Howren MB, Lamkin DM, Suls J. Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. *Psychosom Med*. 2009;71(2):171-186.
52. Wolf JM, Miller GE, Chen E. Parent psychological states predict changes in inflammatory markers in children with asthma and healthy children. *Brain Behav Immun*. 2008;22(4):433-441.
53. Elenkov IJ, Iezzoni DG, Daly A, Harris AG, Chrousos GP. Cytokine dysregulation, inflammation and well-being. *Neuroimmunomodulation*. 2005;12(5):255-269.
54. Miller GE, Chen E, Fok AK, Walker H, Lim A, Nicholls EF, Cole S, Kobor MS. Low early-life social class leaves a biological residue manifested by decreased glucocorticoid and increased proinflammatory signaling. *Proc Natl Acad Sci U S A*. 2009;106(34):14716-14721.
55. Kessler RC, Berglund P, Demler O, Jin R, Koretz D, Merikangas KR, Rush AJ, Walters EE, Wang PS; National Comorbidity Survey Replication. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). *JAMA*. 2003;289(23):3095-3105.
56. Saules KK, Pomerleau CS, Snedecor SM, Mehringer AM, Shadle MB, Kurth C, Krahn DD. Relationship of onset of cigarette smoking during college to alcohol use, dieting concerns, and depressed mood: results from the Young Women's Health Survey. *Addict Behav*. 2004;29(5):893-899.
57. Kiecolt-Glaser JK, Loving TJ, Stowell JR, Malarkey WB, Lemeshow S, Dickinson SL, Glaser R. Hostile marital interactions, proinflammatory cytokine production, and wound healing. *Arch Gen Psychiatry*. 2005;62(12):1377-1384.
58. Rohleder N, Marin TJ, Ma R, Miller GE. Biologic cost of caring for a cancer patient: dysregulation of pro- and anti-inflammatory signaling pathways. *J Clin Oncol*. 2009;27(18):2909-2915.
59. Marin TJ, Chen E, Munch JA, Miller GE. Double-exposure to acute stress and chronic family stress is associated with immune changes in children with asthma. *Psychosom Med*. 2009;71(4):378-384.
60. Buske-Kirschbaum A, Kern S, Ebrecht M, Hellhammer DH. Altered distribution of leukocyte subsets and cytokine production in response to acute psychosocial stress in patients with psoriasis vulgaris. *Brain Behav Immun*. 2007;21(1):92-99.
61. Freier E, Weber CS, Nowottne U, Horn C, Bartels K, Meyer S, Hildebrandt Y, Luetkens T, Cao Y, Pabst C, Muzzulini J, Schnee B, Brunner-Weinzierl MC, Marangolo M, Bokemeyer C, Deter HC, Atanackovic D. Decrease of CD4(+)FOXP3(+) T regulatory cells in the peripheral blood of human subjects undergoing a mental stressor. *Psychoneuroendocrinology*. 2010;35(5):663-673.
62. Maes M, Lin AH, Delmeire L, Van Gastel A, Kenis G, De Jongh R, Bosmans E. Elevated serum interleukin-6 (IL-6) and IL-6 receptor concentrations in posttraumatic stress disorder following accidental man-made traumatic events. *Biol Psychiatry*. 1999;45(7):833-839.
63. Pervanidou P, Kolaitis G, Charitaki S, Margeli A, Ferentinos S, Bakoula C, Lazaropoulou C, Papassotiriou I, Tsiantis J, Chrousos GP. Elevated morning serum interleukin (IL)-6 or evening salivary cortisol concentrations predict posttraumatic stress disorder in children and adolescents six months after a motor vehicle accident. *Psychoneuroendocrinology*. 2007;32(8-10):991-999.
64. Spitzer C, Barnow S, Völzke H, Wallaschofski H, John U, Freyberger HJ, Löwe B, Grabe HJ. Association of posttraumatic stress disorder with low-grade elevation of C-reactive protein: evidence from the general population. *J Psychiatr Res*. 2010;44(1):15-21.
65. Hoge EA, Brandstetter K, Moshier S, Pollack MH, Wong KK, Simon NM. Broad spectrum of cytokine abnormalities in panic disorder and posttraumatic stress disorder. *Depress Anxiety*. 2009;26(5):447-455.
66. Cohen S, Janicki-Deverts D, Miller GE. Psychological stress and disease. *JAMA*. 2007;298(14):1685-1687.
67. Raison CL, Miller AH. When not enough is too much: the role of insufficient glucocorticoid signaling in the pathophysiology of stress-related disorders. *Am J Psychiatry*. 2003;160(9):1554-1565.
68. Lambert E, Dawood T, Schlaich M, Straznicky N, Esler M, Lambert G. Single-unit sympathetic discharge pattern in pathological conditions associated with elevated cardiovascular risk. *Clin Exp Pharmacol Physiol*. 2008;35(4):503-507.
69. Cizza G, Marques AH, Eskandari F, Christie IC, Torvik S, Silverman MN, Phillips TM, Sternberg EM; POWER Study Group. Elevated neuroimmune biomarkers in sweat patches and plasma of premenopausal women with major depressive disorder in remission: the POWER study. *Biol Psychiatry*. 2008;64(10):907-911.
70. Udupa K, Sathyaprabha TN, Thirthalli J, Kishore KR, Lavekar GS, Raju TR, Gangadhar BN. Alteration of cardiac autonomic functions in patients with major depression: a study using heart rate variability measures. *J Affect Disord*. 2007;100(1-3):137-141.
71. Moser M, Lehofer M, Hoehn-Saric R, McLeod DR, Hildebrandt G, Steinbrenner B, Voica M, Liebmann P, Zapotoczky HG. Increased heart rate in depressed subjects in spite of unchanged autonomic balance? *J Affect Disord*. 1998;48(2-3):115-124.
72. Lechin F, van der Dijs B, Orozco B, Lechin ME, Báez S, Lechin AE, Rada I, Acosta E, Arocha L, Jiménez V, et al. Plasma neurotransmitters, blood pressure, and heart rate during supine-resting, orthostasis, and moderate exercise conditions in major depressed patients. *Biol Psychiatry*. 1995;38(3):166-173.
73. Veith RC, Lewis N, Linares OA, Barnes RF, Raskind MA, Villacres EC, Murburg MM, Ashleigh EA, Castillo S, Peskind ER, et al. Sympathetic nervous system activity in major depression: basal and desipramine-induced alterations in plasma norepinephrine kinetics. *Arch Gen Psychiatry*. 1994;51(5):411-422.
74. Borovikova LV, Ivanova S, Zhang M, Yang H, Botchkina GI, Watkins LR, Wang H, Abumrad N, Eaton JW, Tracey KJ. Vagus nerve stimulation attenuates the systemic inflammatory response to endotoxin. *Nature*. 2000;405(6785):458-462.
75. Marsland AL, Gianaros PJ, Prather AA, Jennings JR, Neumann SA, Manuck SB. Stimulated production of proinflammatory cytokines covaries inversely with heart rate variability. *Psychosom Med*. 2007;69(8):709-716.

76. Bhowmick S, Singh A, Flavell RA, Clark RB, O'Rourke J, Cone RE. The sympathetic nervous system modulates CD4(+)FoxP3(+) regulatory T cells via a TGF-beta-dependent mechanism. *J Leukoc Biol*. 2009;86(6):1275-1283.
77. O'Mahony C, van der Kleij H, Bienenstock J, Shanahan F, O'Mahony L. Loss of vagal anti-inflammatory effect: in vivo visualization and adoptive transfer. *Am J Physiol Regul Integr Comp Physiol*. 2009;297(4):R1118-R1126.
78. Kim YK, Na KS, Shin KH, Jung HY, Choi SH, Kim JB. Cytokine imbalance in the pathophysiology of major depressive disorder. *Prog Neuropsychopharmacol Biol Psychiatry*. 2007;31(5):1044-1053.
79. Lee KM, Kim YK. The role of IL-12 and TGF-beta1 in the pathophysiology of major depressive disorder. *Int Immunopharmacol*. 2006;6(8):1298-1304.
80. Brietzke E, Stertz L, Fernandes BS, Kauer-Sant'anna M, Mascarenhas M, Escosteguy Vargas A, Chies JA, Kapczinski F. Comparison of cytokine levels in depressed, manic and euthymic patients with bipolar disorder. *J Affect Disord*. 2009;116(3):214-217.
81. Li Y, Xiao B, Qiu W, Yang L, Hu B, Tian X, Yang H. Altered expression of CD4(+)CD25(+) regulatory T cells and its 5-HT(1a) receptor in patients with major depression disorder. *J Affect Disord*. 2010;124(1-2):68-75.
82. Raison CL, Capuron L, Miller AH. Cytokines sing the blues: inflammation and the pathogenesis of depression. *Trends Immunol*. 2006;27(1):24-31.
83. Zorrilla EP, Luborsky L, McKay JR, Rosenthal R, Houldin A, Tax A, McCorkle R, Seligman DA, Schmidt K. The relationship of depression and stressors to immunological assays: a meta-analytic review. *Brain Behav Immun*. 2001;15(3):199-226.
84. Dowlati Y, Herrmann N, Swardfager W, Liu H, Sham L, Reim EK, Lanctôt KL. A meta-analysis of cytokines in major depression. *Biol Psychiatry*. 2010;67(5):446-457.
85. Dhabhar FS, Burke HM, Epel ES, Mellon SH, Rosser R, Reus VI, Wolkowitz OM. Low serum IL-10 concentrations and loss of regulatory association between IL-6 and IL-10 in adults with major depression. *J Psychiatr Res*. 2009;43(11):962-969.
86. Reichenberg A, Yirmiya R, Schuld A, Kraus T, Haack M, Morag A, Pollmächer T. Cytokine-associated emotional and cognitive disturbances in humans. *Arch Gen Psychiatry*. 2001;58(5):445-452.
87. Eisenberger NI, Inagaki TK, Mashal NM, Irwin MR. Inflammation and social experience: an inflammatory challenge induces feelings of social disconnection in addition to depressed mood. *Brain Behav Immun*. 2010;24(4):558-563.
88. Brydon L, Harrison NA, Walker C, Steptoe A, Critchley HD. Peripheral inflammation is associated with altered substantia nigra activity and psychomotor slowing in humans. *Biol Psychiatry*. 2008;63(11):1022-1029.
89. Raison CL, Borisov AS, Broadwell SD, Capuron L, Woolwine BJ, Jacobson IM, Nemeroff CB, Miller AH. Depression during pegylated interferon-alpha plus ribavirin therapy: prevalence and prediction. *J Clin Psychiatry*. 2005;66(1):41-48.
90. Musselman DL, Lawson DH, Gumnick JF, Manatunga AK, Penna S, Goodkin RS, Greiner K, Nemeroff CB, Miller AH. Paroxetine for the prevention of depression induced by high-dose interferon alfa. *N Engl J Med*. 2001;344(13):961-966.
91. Raison CL, Woolwine BJ, Demetrashvili MF, Borisov AS, Weinreib R, Staab JP, Zajecka JM, Bruno CJ, Henderson MA, Reinus JF, Evans DL, Asnis GM, Miller AH. Paroxetine for prevention of depressive symptoms induced by interferon-alpha and ribavirin for hepatitis C. *Aliment Pharmacol Ther*. 2007;25(10):1163-1174.
92. Gimeno D, Kivimäki M, Brunner EJ, Elovainio M, De Vogli R, Steptoe A, Kumari M, Lowe GD, Rumley A, Marmot MG, Ferrie JE. Associations of C-reactive protein and interleukin-6 with cognitive symptoms of depression: 12-year follow-up of the Whitehall II study. *Psychol Med*. 2009;39(3):413-423.
93. van den Biggelaar AH, Gussekloo J, de Craen AJ, Frölich M, Stek ML, van der Mast RC, Westendorp RG. Inflammation and interleukin-1 signaling network contribute to depressive symptoms but not cognitive decline in old age. *Exp Gerontol*. 2007;42(7):693-701.
94. Twenge JM. The age of anxiety? birth cohort change in anxiety and neuroticism, 1952-1993. *J Pers Soc Psychol*. 2000;79(6):1007-1021.
95. Reither EN, Hauser RM, Yang Y. Do birth cohorts matter? age-period-cohort analyses of the obesity epidemic in the United States. *Soc Sci Med*. 2009;69(10):1439-1448.
96. Wang Y, Beydoun MA. The obesity epidemic in the United States: gender, age, socioeconomic, racial/ethnic, and geographic characteristics: a systematic review and meta-regression analysis. *Epidemiol Rev*. 2007;29:6-28.
97. Nelson ME, Rejeski WJ, Blair SN, Duncan PW, Judge JO, King AC, Macera CA, Castaneda-Sceppa C; American College of Sports Medicine; American Heart Association. Physical activity and public health in older adults: recommendation from the American College of Sports Medicine and the American Heart Association. *Circulation*. 2007;116(9):1094-1105.
98. Sparling PB, Owen N, Lambert EV, Haskell WL. Promoting physical activity: the new imperative for public health. *Health Educ Res*. 2000;15(3):367-376.
99. Yashodhara BM, Umakanth S, Pappachan JM, Bhat SK, Kamath R, Choo BH. Omega-3 fatty acids: a comprehensive review of their role in health and disease. *Postgrad Med J*. 2009;85(1000):84-90.
100. Centers for Disease Control and Prevention (CDC). Prevalence of sedentary lifestyle: Behavioral Risk Factor Surveillance System, United States, 1991. *MMWR Morb Mortal Wkly Rep*. 1993;42(29):576-579.
101. Woolf SH, Johnson RE, Geiger HJ. The rising prevalence of severe poverty in America: a growing threat to public health. *Am J Prev Med*. 2006;31(4):332-341.
102. Weaver KL, Ivester P, Seeds M, Case LD, Arm JP, Chilton FH. Effect of dietary fatty acids on inflammatory gene expression in healthy humans. *J Biol Chem*. 2009;284(23):15400-15407.
103. Weissman MM, Bland RC, Canino GJ, Faravelli C, Greenwald S, Hwu HG, Joyce PR, Karam EG, Lee CK, Lellouch J, Lépine JP, Newman SC, Rubio-Stipec M, Wells JE, Wickramaratne PJ, Wittchen H, Yeh EK. Cross-national epidemiology of major depression and bipolar disorder. *JAMA*. 1996;276(4):293-299.
104. Joyce PR, Oakley-Browne MA, Wells JE, Bushnell JA, Hornblow AR. Birth cohort trends in major depression: increasing rates and earlier onset in New Zealand. *J Affect Disord*. 1990;18(2):83-89.
105. Klerman GL, Weissman MM. Increasing rates of depression. *JAMA*. 1989;261(15):2229-2235.
106. Weissman MM, Bland R, Joyce PR, Newman S, Wells JE, Wittchen HU. Sex differences in rates of depression: cross-national perspectives. *J Affect Disord*. 1993;29(2-3):77-84.
107. Wickramaratne PJ, Weissman MM, Leaf PJ, Holford TR. Age, period and cohort effects on the risk of major depression: results from five United States communities. *J Clin Epidemiol*. 1989;42(4):333-343.
108. Simon GE, VonKorff M, Ustun TB, Gater R, Gureje O, Sartorius N. Is the lifetime risk of depression actually increasing? *J Clin Epidemiol*. 1995;48(9):1109-1118.
109. Hawthorne G, Goldney R, Taylor AW. Depression prevalence: is it really increasing? *Aust N Z J Psychiatry*. 2008;42(7):606-616.
110. Collishaw S, Maughan B, Goodman R, Pickles A. Time trends in adolescent mental health. *J Child Psychol Psychiatry*. 2004;45(8):1350-1362.
111. Eaton WW, Kalaydjian A, Scharfstein DO, Mezuk B, Ding Y. Prevalence and incidence of depressive disorder: the Baltimore ECA follow-up, 1981-2004. *Acta Psychiatr Scand*. 2007;116(3):182-188.
112. Compton WM, Conway KP, Stinson FS, Grant BF. Changes in the prevalence of major depression and comorbid substance use disorders in the United States between 1991-1992 and 2001-2002. *Am J Psychiatry*. 2006;163(12):2141-2147.
113. Hasin DS, Goodwin RD, Stinson FS, Grant BF. Epidemiology of major depressive disorder: results from the National Epidemiologic Survey on Alcoholism and Related Conditions. *Arch Gen Psychiatry*. 2005;62(10):1097-1106.
114. WHO International Consortium in Psychiatric Epidemiology. Cross-national comparisons of the prevalences and correlates of mental disorders. *Bull World Health Organ*. 2000;78(4):413-426.
115. Vega WA, Sribney WM, Aguilar-Gaxiola S, Kolody B. 12-Month prevalence of *DSM-III-R* psychiatric disorders among Mexican Americans: nativity, social assimilation, and age determinants. *J Nerv Ment Dis*. 2004;192(8):532-541.
116. Vega WA, Kolody B, Aguilar-Gaxiola S, Alderete E, Catalano R, Caraveo-Anduaga J. Lifetime prevalence of *DSM-III-R* psychiatric disorders among urban and rural Mexican Americans in California. *Arch Gen Psychiatry*. 1998;55(9):771-778.
117. Rook GAW. 99th Dahlem conference on infection, inflammation and chronic inflammatory disorders: Darwinian medicine and the "hygiene" or "old friends" hypothesis. *Clin Exp Immunol*. 2010;160(1):70-79.
118. Popper KR. *The Logic Of Scientific Discovery*. London, England: Hutchinson; 1959.
119. Scott KM, Von Korff M, Alonso J, Angermeyer MC, Benjet C, Bruffaerts R, de Girolamo G, Haro JM, Kessler RC, Kovess V, Ono Y, Ormel J, Posada-Villa J. Childhood adversity, early-onset depressive/anxiety disorders, and adult-onset asthma. *Psychosom Med*. 2008;70(9):1035-1043.
120. Kojima M, Kojima T, Suzuki S, Oguchi T, Oba M, Tsuchiya H, Sugiura F, Kanayama Y, Furukawa TA, Tokudome S, Ishiguro N. Depression, inflammation, and pain in patients with rheumatoid arthritis. *Arthritis Rheum*. 2009;61(8):1018-1024.
121. Skilton MR, Moulin P, Terra JL, Bonnet F. Associations between anxiety, depression, and the metabolic syndrome. *Biol Psychiatry*. 2007;62(11):1251-1257.
122. Luppino FS, de Wit LM, Bouvy PF, Stijnen T, Cuijpers P, Penninx BW, Zitman FG. Overweight, obesity, and depression: a systematic review and meta-analysis of longitudinal studies. *Arch Gen Psychiatry*. 2010;67(3):220-229.
123. Rasmussen-Torvik LJ, Harlow BL. The association between depression and diabetes in the perinatal period. *Curr Diab Rep*. 2010;10(3):217-223.
124. Anderson RJ, Freedland KE, Clouse RE, Lustman PJ. The prevalence of comor-

bid depression in adults with diabetes: a meta-analysis. *Diabetes Care*. 2001; 24(6):1069-1078.
125. Paparrigopoulos T, Ferentinos P, Kouzoupis A, Koutsis G, Papadimitriou GN. The neuropsychiatry of multiple sclerosis: focus on disorders of mood, affect and behaviour. *Int Rev Psychiatry*. 2010;22(1):14-21.
126. Ghaffar O, Feinstein A. The neuropsychiatry of multiple sclerosis: a review of recent developments. *Curr Opin Psychiatry*. 2007;20(3):278-285.
127. North CS, Alpers DH. A review of studies of psychiatric factors in Crohn's disease: etiologic implications. *Ann Clin Psychiatry*. 1994;6(2):117-124.
128. Bach JF. The effect of infections on susceptibility to autoimmune and allergic diseases. *N Engl J Med*. 2002;347(12):911-920.
129. Fleming JO, Cook TD. Multiple sclerosis and the hygiene hypothesis. *Neurology*. 2006;67(11):2085-2086.
130. Eder W, Ege MJ, von Mutius E. The asthma epidemic. *N Engl J Med*. 2006;355 (21):2226-2235.
131. The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. *Lancet*. 1998;351(9111): 1225-1232.
132. Butland BK, Strachan DP, Lewis S, Bynner J, Butler N, Britton J. Investigation into the increase in hay fever and eczema at age 16 observed between the 1958 and 1970 British birth cohorts. *BMJ*. 1997;315(7110):717-721.
133. Asher MI, Montefort S, Björkstén B, Lai CK, Strachan DP, Weiland SK, Williams H; ISAAC Phase Three Study Group. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. *Lancet*. 2006;368(9537):733-743.
134. Upton MN, McConnachie A, McSharry C, Hart CL, Smith GD, Gillis CR, Watt GC. Intergenerational 20 year trends in the prevalence of asthma and hay fever in adults: the Midspan family study surveys of parents and offspring. *BMJ*. 2000; 321(7253):88-92.
135. Anderson HR, Gupta R, Strachan DP, Limb ES. 50 years of asthma: UK trends from 1955 to 2004. *Thorax*. 2007;62(1):85-90.
136. Green A, Brutti G, Patterson CC, et al; EURODIAB ACE Study Group. Variation and trends in incidence of childhood diabetes in Europe. *Lancet*. 2000;355 (9207):873-876.
137. Gale EAM. The rise of childhood type 1 diabetes in the 20th century. *Diabetes*. 2002;51(12):3353-3361.
138. Sawczenko A, Sandhu BK, Logan RFA, Jenkins H, Taylor CJ, Mian S, Lynn R. Prospective survey of childhood inflammatory bowel disease in the British Isles. *Lancet*. 2001;357(9262):1093-1094.
139. Lindberg E, Lindquist B, Holmquist L, Hildebrand H. Inflammatory bowel disease in children and adolescents in Sweden, 1984-1995. *J Pediatr Gastroenterol Nutr*. 2000;30(3):259-264.
140. Armitage E, Drummond H, Ghosh S, Ferguson A. Incidence of juvenile-onset Crohn's disease in Scotland. *Lancet*. 1999;353(9163):1496-1497.
141. Poser S, Stickel B, Krtsch U, Burckhardt D, Nordman B. Increasing incidence of multiple sclerosis in South Lower Saxony, Germany. *Neuroepidemiology*. 1989; 8(4):207-213.
142. Rosati G, Aiello I, Mannu L, Pirastru MI, Agnetti V, Sau G, Garau M, Gioia R, Sanna G. Incidence of multiple sclerosis in the town of Sassari, Sardinia, 1965 to 1985: evidence for increasing occurrence of the disease. *Neurology*. 1988; 38(3):384-388.
143. Rook GA. Review series on helminths, immune modulation and the hygiene hypothesis: the broader implications of the hygiene hypothesis. *Immunology*. 2009; 126(1):3-11.
144. Fourlanos S, Varney MD, Tait BD, Morahan G, Honeyman MC, Colman PG, Harrison LC. The rising incidence of type 1 diabetes is accounted for by cases with lower-risk human leukocyte antigen genotypes. *Diabetes Care*. 2008;31(8): 1546-1549.
145. Strachan DP. Hay fever, hygiene, and household size. *BMJ*. 1989;299(6710):1259-1260.
146. Abbas AK, Lichtman AH. *Cellular and Molecular Immunology*. 5th ed. Philadelphia, PA: WB Saunders Co; 2003.
147. Bernstein CN, Shanahan F. Disorders of a modern lifestyle: reconciling the epidemiology of inflammatory bowel diseases. *Gut*. 2008;57(9):1185-1191.
148. Riedler J, Braun-Fahrländer C, Eder W, Schreuer M, Waser M, Maisch S, Carr D, Schierl R, Nowak D, von Mutius E; ALEX Study Team. Exposure to farming in early life and development of asthma and allergy: a cross-sectional survey. *Lancet*. 2001;358(9288):1129-1133.
149. Armelagos GJ, Brown PJ, Turner B. Evolutionary, historical and political economic perspectives on health and disease. *Soc Sci Med*. 2005;61(4):755-765.
150. Rook GA, Brunet LR. Give us this day our daily germs. *Biologist (London)*. 2002; 49(4):145-149.
151. Bremner SA, Carey IM, DeWilde S, Richards N, Maier WC, Hilton SR, Strachan DP, Cook DG. Infections presenting for clinical care in early life and later risk of hay fever in two UK birth cohorts. *Allergy*. 2008;63(3):274-283.
152. Matricardi PM, Rosmini F, Riondino S, Fortini M, Ferrigno L, Rapicetta M, Bonini S. Exposure to foodborne and orofecal microbes versus airborne viruses in relation to atopy and allergic asthma: epidemiological study. *BMJ*. 2000; 320(7232):412-417.
153. Benn CS, Melbye M, Wohlfahrt J, Björkstén B, Aaby P. Cohort study of sibling effect, infectious diseases, and risk of atopic dermatitis during first 18 months of life. *BMJ*. 2004;328(7450):1223.
154. Rook GA, Stanford JL. Give us this day our daily germs. *Immunol Today*. 1998; 19(3):113-116.
155. Collins SM, Bercik P. The relationship between intestinal microbiota and the central nervous system in normal gastrointestinal function and disease. *Gastroenterology*. 2009;136(6):2003-2014.
156. Mazmanian SK, Round JL, Kasper DL. A microbial symbiosis factor prevents intestinal inflammatory disease. *Nature*. 2008;453(7195):620-625.
157. Marchesi J, Shanahan F. The normal intestinal microbiota. *Curr Opin Infect Dis*. 2007;20(5):508-513.
158. Lundgren A, Strömberg E, Sjöling A, Lindholm C, Enarsson K, Edebo A, Johnsson E, Suri-Payer E, Larsson P, Rudin A, Svennerholm AM, Lundin BS. Mucosal FOXP3-expressing CD4+ CD25high regulatory T cells in *Helicobacter pylori*-infected patients. *Infect Immun*. 2005;73(1):523-531.
159. Rook GAW. The Hygiene Hypothesis and Darwinian medicine. In: Parnham MJ, ed. *Progress in Inflammation Research*. Boston, MA: Birkhauser; 2009.
160. Mazmanian SK. Capsular polysaccharides of symbiotic bacteria modulate immune responses during experimental colitis. *J Pediatr Gastroenterol Nutr*. 2008; 46(suppl 1):E11-E12.
161. Hunt JR, Martinelli R, Adams VC, Rook GA, Brunet LR. Intragastric administration of *Mycobacterium vaccae* inhibits severe pulmonary allergic inflammation in a mouse model. *Clin Exp Allergy*. 2005;35(5):685-690.
162. Cani PD, Possemiers S, Van de Wiele T, Guiot Y, Everard A, Rottier O, Geurts L, Naslain D, Neyrinck A, Lambert DM, Muccioli GG, Delzenne NM. Changes in gut microbiota control inflammation in obese mice through a mechanism involving GLP-2-driven improvement of gut permeability. *Gut*. 2009;58(8):1091-1103.
163. Maslowski KM, Vieira AT, Ng A, Kranich J, Sierro F, Yu D, Schilter HC, Rolph MS, Mackay F, Artis D, Xavier RJ, Teixeira MM, Mackay CR. Regulation of inflammatory responses by gut microbiota and chemoattractant receptor GPR43. *Nature*. 2009;461(7268):1282-1286.
164. Monagas M, Khan N, Andrés-Lacueva C, Urpí-Sardá M, Vázquez-Agell M, Lamuela-Raventós RM, Estruch R. Dihydroxylated phenolic acids derived from microbial metabolism reduce lipopolysaccharide-stimulated cytokine secretion by human peripheral blood mononuclear cells. *Br J Nutr*. 2009;102(2):201-206.
165. Desbonnet L, Garrett L, Clarke G, Bienenstock J, Dinan TG. The probiotic *Bifidobacteria infantis*: an assessment of potential antidepressant properties in the rat. *J Psychiatr Res*. 2008;43(2):164-174.
166. Amaral FA, Sachs D, Costa VV, Fagundes CT, Cisalpino D, Cunha TM, Ferreira SH, Cunha FQ, Silva TA, Nicoli JR, Vieira LQ, Souza DG, Teixeira MM. Commensal microbiota is fundamental for the development of inflammatory pain. *Proc Natl Acad Sci U S A*. 2008;105(6):2193-2197.
167. Brown R, Price RJ, King MG, Husband AJ. Are antibiotic effects on sleep behavior in the rat due to modulation of gut bacteria? *Physiol Behav*. 1990; 48(4):561-565.
168. Vijay-Kumar M, Aitken JD, Carvalho FA, Cullender TC, Mwangi S, Srinivasan S, Sitaraman SV, Knight R, Ley RE, Gewirtz AT. Metabolic syndrome and altered gut microbiota in mice lacking toll-like receptor 5. *Science*. 2010;328(5975): 228-231.
169. Forsythe P, Bienenstock J. Immunomodulation by commensal and probiotic bacteria. *Immunol Invest*. 2010;39(4-5):429-448.
170. van der Kleij D, Latz E, Brouwers JFHM, Kruize YC, Schmitz M, Kurt-Jones EA, Espevik T, de Jong EC, Kapsenberg ML, Golenbock DT, Tielens AG, Yazdanbakhsh M. A novel host-parasite lipid cross-talk: schistosomal lyso-phosphatidylserine activates toll-like receptor 2 and affects immune polarization. *J Biol Chem*. 2002;277(50):48122-48129.
171. Grangette C, Nutten S, Palumbo E, Morath S, Hermann C, Dewulf J, Pot B, Hartung T, Hols P, Mercenier A. Enhanced antiinflammatory capacity of a *Lactobacillus plantarum* mutant synthesizing modified teichoic acids. *Proc Natl Acad Sci U S A*. 2005;102(29):10321-10326.
172. Adams VC, Hunt JR, Martinelli R, Palmer R, Rook GA, Brunet LR. *Mycobacterium vaccae* induces a population of pulmonary CD11c+ cells with regulatory potential in allergic mice. *Eur J Immunol*. 2004;34(3):631-638.
173. Zuany-Amorim C, Sawicka E, Manlius C, Le Moine A, Brunet LR, Kemeny DM, Bowen G, Rook G, Walker C. Suppression of airway eosinophilia by killed *Mycobacterium vaccae*-induced allergen-specific regulatory T-cells. *Nat Med*. 2002; 8(6):625-629.

174. Wilson MS, Taylor MD, O'Gorman MT, Balic A, Barr TA, Filbey K, Anderton SM, Maizels RM. Helminth-induced CD19+CD23hi B cells modulate experimental allergic and autoimmune inflammation. *Eur J Immunol*. 2010;40(6):1682-1696.
175. Smits HH, Engering A, van der Kleij D, de Jong EC, Schipper K, van Capel TM, Zaat BA, Yazdanbakhsh M, Wierenga EA, van Kooyk Y, Kapsenberg ML. Selective probiotic bacteria induce IL-10-producing regulatory T cells in vitro by modulating dendritic cell function through dendritic cell-specific intercellular adhesion molecule 3-grabbing nonintegrin. *J Allergy Clin Immunol*. 2005;115(6):1260-1267.
176. Dlugovitzky D, Fiorenza G, Farroni M, Bogue C, Stanford C, Stanford J. Immunological consequences of three doses of heat-killed *Mycobacterium vaccae* in the immunotherapy of tuberculosis. *Respir Med*. 2006;100(6):1079-1087.
177. Vaccarino V, Brennan ML, Miller AH, Bremner JD, Ritchie JC, Lindau F, Veledar E, Su S, Murrah NV, Jones L, Jawed F, Dai J, Goldberg J, Hazen SL. Association of major depressive disorder with serum myeloperoxidase and other markers of inflammation: a twin study. *Biol Psychiatry*. 2008;64(6):476-483.
178. Huang TL, Lee CT. T-helper 1/T-helper 2 cytokine imbalance and clinical phenotypes of acute-phase major depression. *Psychiatry Clin Neurosci*. 2007;61(4):415-420.
179. Eller T, Vasar V, Shlik J, Maron E. Pro-inflammatory cytokines and treatment response to escitalopram in major depressive disorder. *Prog Neuropsychopharmacol Biol Psychiatry*. 2008;32(2):445-450.
180. Sachs JS. *Good Germs, Bad Germs: Health and Survival in a Bacterial World*. New York, NY: Hill and Wang; 2007.
181. Rook GA. The hygiene hypothesis and the increasing prevalence of chronic inflammatory disorders. *Trans R Soc Trop Med Hyg*. 2007;101(11):1072-1074.
182. Summers RW, Elliott DE, Urban JF Jr, Thompson R, Weinstock JV. Trichuris suis therapy in Crohn's disease. *Gut*. 2005;54(1):87-90.
183. Summers RW, Elliott DE, Urban JF Jr, Thompson RA, Weinstock JV. Trichuris suis therapy for active ulcerative colitis: a randomized controlled trial. *Gastroenterology*. 2005;128(4):825-832.
184. Ricklin Gutzwiller ME, Reist M, Peel JE, Seewald W, Brunet LR, Roosje PJ. Intradermal injection of heat-killed *Mycobacterium vaccae* in dogs with atopic dermatitis: a multicentre pilot study. *Vet Dermatol*. 2007;18(2):87-93.
185. Correale J, Farez M. Association between parasite infection and immune responses in multiple sclerosis. *Ann Neurol*. 2007;61(2):97-108.
186. Kendler KS, Thornton LM, Gardner CO. Stressful life events and previous episodes in the etiology of major depression in women: an evaluation of the "kindling" hypothesis. *Am J Psychiatry*. 2000;157(8):1243-1251.
187. Bailey MT, Lubach GR, Coe CL. Prenatal stress alters bacterial colonization of the gut in infant monkeys. *J Pediatr Gastroenterol Nutr*. 2004;38(4):414-421.
188. Bailey MT, Engler H, Sheridan JF. Stress induces the translocation of cutaneous and gastrointestinal microflora to secondary lymphoid organs of C57BL/6 mice. *J Neuroimmunol*. 2006;171(1-2):29-37.
189. Bailey MT, Dowd SE, Parry NMA, Galley JD, Schauer DB, Lyte M. Stressor exposure disrupts commensal microbial populations in the intestines and leads to increased colonization by *Citrobacter rodentium*. *Infect Immun*. 2010;78(4):1509-1519.
190. Ghia JE, Blennerhassett P, Collins SM. Impaired parasympathetic function increases susceptibility to inflammatory bowel disease in a mouse model of depression. *J Clin Invest*. 2008;118(6):2209-2218.
191. Reber SO, Birkeneder L, Veenema AH, Obermeier F, Falk W, Straub RH, Neumann ID. Adrenal insufficiency and colonic inflammation after a novel chronic psycho-social stress paradigm in mice: implications and mechanisms. *Endocrinology*. 2007;148(2):670-682.
192. Knowles SR, Nelson EA, Palombo EA. Investigating the role of perceived stress on bacterial flora activity and salivary cortisol secretion: a possible mechanism underlying susceptibility to illness. *Biol Psychol*. 2008;77(2):132-137.
193. Maes M, Kubera M, Leunis JC. The gut-brain barrier in major depression: intestinal mucosal dysfunction with an increased translocation of LPS from gram negative enterobacteria (leaky gut) plays a role in the inflammatory pathophysiology of depression. *Neuro Endocrinol Lett*. 2008;29(1):117-124.
194. Silk DBA, Davis A, Vulevic J, Tzortzis G, Gibson GR. Clinical trial: the effects of a trans-galactooligosaccharide prebiotic on faecal microbiota and symptoms in irritable bowel syndrome. *Aliment Pharmacol Ther*. 2009;29(5):508-518.
195. Rao AV, Bested AC, Beaulne TM, Katzman MA, Iorio C, Berardi JM, Logan AC. A randomized, double-blind, placebo-controlled pilot study of a probiotic in emotional symptoms of chronic fatigue syndrome. *Gut Pathog*. 2009;1(1):6.
196. Sullivan A, Nord CE, Evengård B. Effect of supplement with lactic-acid producing bacteria on fatigue and physical activity in patients with chronic fatigue syndrome. *Nutr J*. 2009;8:4.
197. Patel PM, Sim S, O'Donnell DO, Protheroe A, Beirne D, Stanley A, Tourani JM, Khayat D, Hancock B, Vasey P, Dalgleish A, Johnston C, Banks RE, Selby PJ. An evaluation of a preparation of *Mycobacterium vaccae* (SRL172) as an immunotherapeutic agent in renal cancer. *Eur J Cancer*. 2008;44(2):216-223.
198. O'Brien ME, Anderson H, Kaukel E, O'Byrne K, Pawlicki M, Von Pawel J, Reck M; SR-ON-12 Study Group. SRL172 (killed *Mycobacterium vaccae*) in addition to standard chemotherapy improves quality of life without affecting survival, in patients with advanced non-small-cell lung cancer: phase III results. *Ann Oncol*. 2004;15(6):906-914.
199. Forsythe P, Sudo N, Dinan T, Taylor VH, Bienenstock J. Mood and gut feelings. *Brain Behav Immun*. 2010;24(1):9-16.
200. Sudo N, Chida Y, Aiba Y, Sonoda J, Oyama N, Yu XN, Kubo C, Koga Y. Postnatal microbial colonization programs the hypothalamic-pituitary-adrenal system for stress response in mice. *J Physiol*. 2004;558(pt 1):263-275.
201. Lowry CA, Hollis JH, de Vries A, Pan B, Brunet LR, Hunt JR, Paton JF, van Kampen E, Knight DM, Evans AK, Rook GA, Lightman SL. Identification of an immune-responsive mesolimbocortical serotonergic system: potential role in regulation of emotional behavior. *Neuroscience*. 2007;146(2):756-772.
202. Ormel J, Oldehinkel AJ, Vollebergh W. Vulnerability before, during, and after a major depressive episode: a 3-wave population-based study. *Arch Gen Psychiatry*. 2004;61(10):990-996.
203. Kendler KS, Gatz M, Gardner CO, Pedersen NL. Personality and major depression: a Swedish longitudinal, population-based twin study. *Arch Gen Psychiatry*. 2006;63(10):1113-1120.
204. Davidson J, Zisook S, Giller E, Helms M. Symptoms of interpersonal sensitivity in depression. *Compr Psychiatry*. 1989;30(5):357-368.
205. Zuroff DC, Blatt SJ, Sotsky SM, Krupnick JL, Martin DJ, Sanislow CA III, Simmens S. Relation of therapeutic alliance and perfectionism to outcome in brief outpatient treatment of depression. *J Consult Clin Psychol*. 2000;68(1):114-124.
206. Soenens B, Luyckx K, Vansteenkiste M, Luyten P, Duriez B, Goossens L. Maladaptive perfectionism as an intervening variable between psychological control and adolescent depressive symptoms: a three-wave longitudinal study. *J Fam Psychol*. 2008;22(3):465-474.
207. Reinherz HZ, Giaconia RM, Hauf AM, Wasserman MS, Silverman AB. Major depression in the transition to adulthood: risks and impairments. *J Abnorm Psychol*. 1999;108(3):500-510.
208. Risch N, Herrell R, Lehner T, Liang KY, Eaves L, Hoh J, Griem A, Kovacs M, Ott J, Merikangas KR. Interaction between the serotonin transporter gene (5-HTTLPR), stressful life events, and risk of depression: a meta-analysis. *JAMA*. 2009;301(23):2462-2471.
209. Caspi A, Hariri AR, Holmes A, Uher R, Moffitt TE. Genetic sensitivity to the environment: the case of the serotonin transporter gene and its implications for studying complex diseases and traits. *Am J Psychiatry*. 2010;167(5):509-527.
210. Rutter M, Thapar A, Pickles A. Gene-environment interactions: biologically valid pathway or artifact? *Arch Gen Psychiatry*. 2009;66(12):1287-1289.
211. Wray NR, James MR, Gordon SD, Dumenil T, Ryan L, Coventry WL, Statham DJ, Pergadia ML, Madden PA, Heath AC, Montgomery GW, Martin NG. Accurate, large-scale genotyping of 5HTTLPR and flanking single nucleotide polymorphisms in an association study of depression, anxiety, and personality measures. *Biol Psychiatry*. 2009;66(5):468-476.
212. Stein MB, Campbell-Sills L, Gelernter J. Genetic variation in 5HTTLPR is associated with emotional resilience. *Am J Med Genet B Neuropsychiatr Genet*. 2009;150B(7):900-906.
213. Gonda X, Fountoulakis KN, Juhasz G, Rihmer Z, Lazary J, Laszik A, Akiskal HS, Bagdy G. Association of the s allele of the 5-HTTLPR with neuroticism-related traits and temperaments in a psychiatrically healthy population. *Eur Arch Psychiatry Clin Neurosci*. 2009;259(2):106-113.
214. Fox E, Ridgewell A, Ashwin C. Looking on the bright side: biased attention and the human serotonin transporter gene. *Proc Biol Sci*. 2009;276(1663):1747-1751.
215. Lotrich FE, Ferrell RE, Rabinovitz M, Pollock BG. Risk for depression during interferon-alpha treatment is affected by the serotonin transporter polymorphism. *Biol Psychiatry*. 2009;65(4):344-348.
216. Fredericks CA, Drabant EM, Edge MD, Tillie JM, Hallmayer J, Ramel W, Kuo JR, Mackey S, Gross JJ, Dhabhar FS. Healthy young women with serotonin transporter SS polymorphism show a pro-inflammatory bias under resting and stress conditions. *Brain Behav Immun*. 2010;24(3):350-357.
217. Su S, Zhao J, Bremner JD, Miller AH, Tang W, Bouzyk M, Snieder H, Novik O, Afzal N, Goldberg J, Vaccarino V. Serotonin transporter gene, depressive symptoms, and interleukin-6. *Circ Cardiovasc Genet*. 2009;2(6):614-620.
218. Constant A, Castera L, Dantzer R, Couzigou P, de Ledinghen V, Demotes-Mainard J, Henry C. Mood alterations during interferon-alfa therapy in patients with chronic hepatitis C: evidence for an overlap between manic/hypomanic and depressive symptoms. *J Clin Psychiatry*. 2005;66(8):1050-1057.

219. Kraus MR, Schäfer A, Faller H, Csef H, Scheurlen M. Psychiatric symptoms in patients with chronic hepatitis C receiving interferon alfa-2b therapy. *J Clin Psychiatry*. 2003;64(6):708-714.
220. Dieperink E, Leskela J, Dieperink ME, Evans B, Thuras P, Ho SB. The effect of pegylated interferon-alpha2b and ribavirin on posttraumatic stress disorder symptoms. *Psychosomatics*. 2008;49(3):225-229.
221. Lotrich FE, Rabinovitz M, Gironda P, Pollock BG. Depression following pegylated interferon-alpha: characteristics and vulnerability. *J Psychosom Res*. 2007;63(2):131-135.
222. Sgorbini M, O'Brien L, Jackson D. Living with hepatitis C and treatment: the personal experiences of patients. *J Clin Nurs*. 2009;18(16):2282-2291.
223. Capuron L, Pagnoni G, Demetrashvili M, Woolwine BJ, Nemeroff CB, Berns GS, Miller AH. Anterior cingulate activation and error processing during interferon-alpha treatment. *Biol Psychiatry*. 2005;58(3):190-196.
224. Harrison NA, Brydon L, Walker C, Gray MA, Steptoe A, Dolan RJ, Critchley HD. Neural origins of human sickness in interoceptive responses to inflammation. *Biol Psychiatry*. 2009;66(5):415-422.
225. Carter CS, Braver TS, Barch DM, Botvinick MM, Noll D, Cohen JD. Anterior cingulate cortex, error detection, and the online monitoring of performance. *Science*. 1998;280(5364):747-749.
226. Paulus MP, Feinstein JS, Simmons A, Stein MB. Anterior cingulate activation in high trait anxious subjects is related to altered error processing during decision making. *Biol Psychiatry*. 2004;55(12):1179-1187.
227. Eisenberger NI, Lieberman MD, Satpute AB. Personality from a controlled processing perspective: an fMRI study of neuroticism, extraversion, and self-consciousness. *Cogn Affect Behav Neurosci*. 2005;5(2):169-181.
228. Ursu S, Stenger VA, Shear MK, Jones MR, Carter CS. Overactive action monitoring in obsessive-compulsive disorder: evidence from functional magnetic resonance imaging. *Psychol Sci*. 2003;14(4):347-353.
229. Teasdale JD, Cox SG. Dysphoria: self-devaluative and affective components in recovered depressed patients and never depressed controls. *Psychol Med*. 2001; 31(7):1311-1316.
230. Longe O, Maratos FA, Gilbert P, Evans G, Volker F, Rockliff H, Rippon G. Having a word with yourself: neural correlates of self-criticism and self-reassurance. *Neuroimage*. 2010;49(2):1849-1856.
231. Het S, Wolf OT. Mood changes in response to psychosocial stress in healthy young women: effects of pretreatment with cortisol. *Behav Neurosci*. 2007; 121(1):11-20.
232. Tang TZ, DeRubeis RJ, Hollon SD, Amsterdam J, Shelton R, Schalet B. Personality change during depression treatment: a placebo-controlled trial. *Arch Gen Psychiatry*. 2009;66(12):1322-1330.
233. Du L, Bakish D, Ravindran AV, Hrdina PD. Does fluoxetine influence major depression by modifying five-factor personality traits? *J Affect Disord*. 2002; 71(1-3):235-241.
234. Knutson B, Wolkowitz OM, Cole SW, Chan T, Moore EA, Johnson RC, Terpstra J, Turner RA, Reus VI. Selective alteration of personality and social behavior by serotonergic intervention. *Am J Psychiatry*. 1998;155(3):373-379.
235. Bagby RM, Levitan RD, Kennedy SH, Levitt AJ, Joffe RT. Selective alteration of personality in response to noradrenergic and serotonergic antidepressant medication in depressed sample: evidence of non-specificity. *Psychiatry Res*. 1999; 86(3):211-216.
236. Kamarck TW, Haskett RF, Muldoon M, Flory JD, Anderson B, Bies R, Pollock B, Manuck SB. Citalopram intervention for hostility: results of a randomized clinical trial. *J Consult Clin Psychol*. 2009;77(1):174-188.
237. Hunter AM, Ravikumar S, Cook IA, Leuchter AF. Brain functional changes during placebo lead-in and changes in specific symptoms during pharmacotherapy for major depression. *Acta Psychiatr Scand*. 2009;119(4):266-273.
238. Wichers MC, Barge-Schaapveld DQ, Nicolson NA, Peeters F, de Vries M, Mengelers R, van Os J. Reduced stress-sensitivity or increased reward experience: the psychological mechanism of response to antidepressant medication. *Neuropsychopharmacology*. 2009;34(4):923-931.
239. Santonastaso P, Friederici S, Favaro A. Sertraline in the treatment of restricting anorexia nervosa: an open controlled trial. *J Child Adolesc Psychopharmacol*. 2001;11(2):143-150.
240. Fava M, Abraham M, Clancy-Colecchi K, Pava JA, Matthews J, Rosenbaum JF. Eating disorder symptomatology in major depression. *J Nerv Ment Dis*. 1997; 185(3):140-144.
241. Hamer M, Steptoe A. Association between physical fitness, parasympathetic control, and proinflammatory responses to mental stress. *Psychosom Med*. 2007; 69(7):660-666.