

# Inflammation, Sanitation, and Consternation

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

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**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 non-threatening 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.

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**A**LTHOUGH RECOGNIZED since at least classical antiquity,<sup>1</sup> 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.<sup>2</sup> Following the famous Dobzhansky dictum that “nothing in biology makes sense except in the light of evolution,”<sup>3</sup> 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.<sup>4</sup>

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

Most of the risk for MDD resides in environmental factors.<sup>5</sup> 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 <sup>11-17</sup>	Antidepressants <sup>18-22</sup>
Medical illness <sup>23,24</sup>	Psychotherapy <sup>25-27</sup>
Obesity <sup>28-30</sup>	Electroconvulsive therapy <sup>31</sup>
Sedentary lifestyle <sup>32-34</sup>	Exercise <sup>18,32,35-38</sup>
Diet (eg, low $\omega$ -3: $\omega$ -6 fatty acid ratio, high-fructose sugars) <sup>39-41</sup>	
Diminished sleep <sup>18,42-45</sup>	
Social isolation <sup>18,46-49</sup>	
Low socioeconomic status <sup>18,50-54</sup>	
Female sex <sup>18,55</sup>	
Smoking <sup>18,56</sup>	

psychosocial stress and sickness, that are also known to strongly predict the development of MDD independently of genetic effects.<sup>6-9</sup> 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.<sup>10</sup> 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**).<sup>\*</sup> 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).<sup>18-22,25-27,31,32,35-38</sup>

#### 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- $\kappa$ B.<sup>11-17,57-59</sup> 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),<sup>60</sup> as well as circulating CD4<sup>+</sup>CD25<sup>+</sup> regulatory T (Treg) cells that are an important source of IL-10.<sup>60,61</sup> Moreover, acute stress appears to downregulate Forkhead box 3 (Foxp3), an important T cell immunoregulatory transcription factor.<sup>61</sup> Chronic traumatic life stress has also been associated with reduced numbers and percentages of circulating CD4<sup>+</sup>CD25<sup>+</sup>Foxp3<sup>+</sup> 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.<sup>62-65</sup>

In keeping with strong associations between stress and depression,<sup>66</sup> medically healthy individuals with MDD and a history of early life stress have been shown to mount larger IL-6 and nuclear factor- $\kappa$ B responses to a labora-

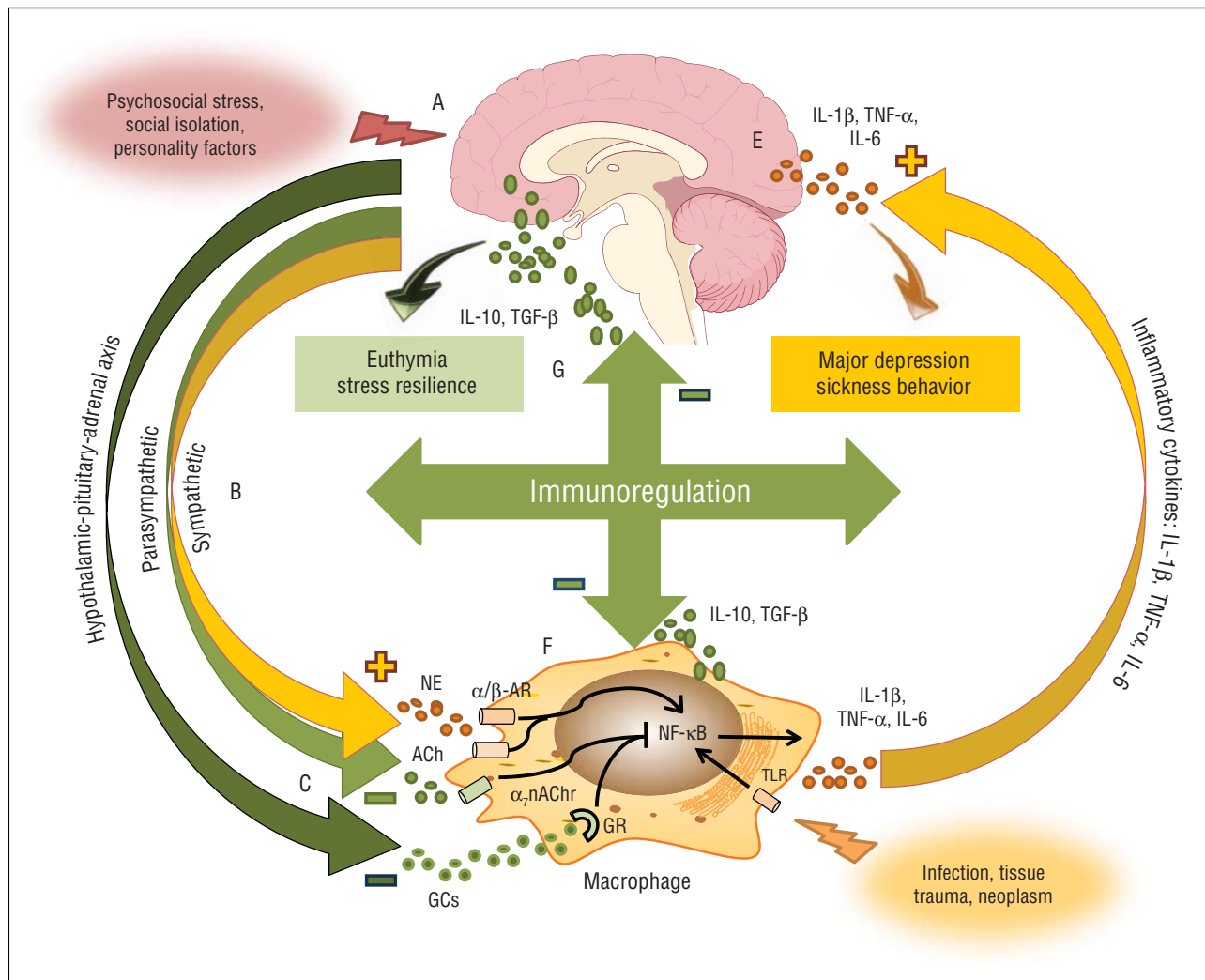
tory psychosocial stressor than do nondepressed controls.<sup>14</sup> These findings are consistent with evidence that MDD is associated with a suite of stress system changes known to promote inflammation, including glucocorticoid resistance, sympathetic overdrive, and parasympathetic withdrawal (**Figure 1**).<sup>32,67-75</sup> Recent studies suggest that these changes are also capable of suppressing the number and activity of CD4<sup>+</sup>CD25<sup>+</sup>Foxp3<sup>+</sup> Treg cells.<sup>76,77</sup>

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  $\beta$ .<sup>20,21,78-85</sup> Reduced total numbers and percentages of CD4<sup>+</sup>CD25<sup>+</sup> Treg cells in peripheral blood, as well as reduced expression of Foxp3, have also been observed in MDD.<sup>81</sup> 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.<sup>86-91</sup> 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-1 $\beta$  predict the later development of depressive symptoms,<sup>92,93</sup> and plasma concentrations of IL-6 immediately after a motor vehicle accident predict the development of posttraumatic stress disorder within the subsequent 6 months.<sup>63</sup>

#### 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).<sup>94-102</sup> 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.<sup>103-107</sup> These findings have been challenged more recently on methodological grounds<sup>108,109</sup>; however, recent studies with improved methods continue to suggest that rates of MDD are increasing in the United States and worldwide.<sup>110-114</sup> 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.<sup>115,116</sup>

<sup>\*</sup>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  $\alpha$ - or  $\beta$ -adrenoreceptor [ $\alpha/\beta$ -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- $\kappa$ B [NF- $\kappa$ B]) within innate immune cells (eg, macrophages and dendritic cells) leading to the production and release of inflammatory cytokines, including interleukin 1 $\beta$  (IL-1 $\beta$ ), tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ), 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  $\beta$  (TGF- $\beta$ ). 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.<sup>117</sup> But association does not establish causality,<sup>118</sup> 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<sup>23,24,119-127</sup>) 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.<sup>128-132</sup> 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.<sup>130,133-142</sup> As with MDD, the rate of increase in these disorders is too rapid to be accounted for by changes in the human genome.<sup>143</sup> 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).<sup>144</sup> 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 forebearers.<sup>105</sup>

#### 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.<sup>117</sup> 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.<sup>145</sup> Because infections typically mobilize  $T_H1$ -type inflammatory responses,<sup>146</sup> 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.<sup>143</sup>

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.<sup>128,147</sup> Moreover, allergies are most common in inner cities, where childhood infections are rife, and least common in isolated rural communities.<sup>148</sup> A Darwinian perspective also challenged the notion that sporadic childhood infections were the crucial factor in moder-

nity-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.<sup>149</sup> Similarly, nonviral childhood infections are sporadic, making it highly unlikely that they provided the constant immunoregulatory input required within a coevolutionary framework.<sup>150</sup> 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,<sup>151-153</sup> 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.<sup>154</sup> In 2002, Rook and Brunet<sup>150</sup> 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  $\beta$  (**Figure 2**).<sup>143</sup> 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,<sup>155</sup> or because, although not harmless, they are not eradicable by inflammatory processes, which therefore inflict tissue damage to no good effect.<sup>143,150</sup> 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.<sup>156(p624)</sup>

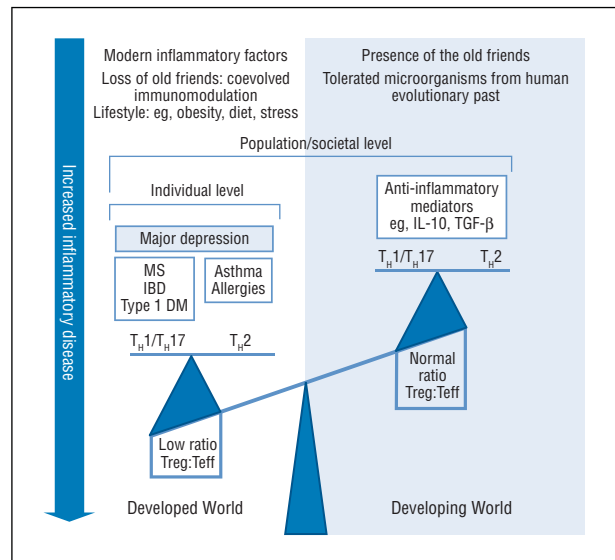
Said more simply, some factors required by the immune system to respond appropriately to the environment might have been “entrusted” over evolutionary time to microorganisms.<sup>117,143</sup>

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.<sup>117</sup> Among organisms that colonized the body and provided essential services for their hosts are commensal and

probiotic members of the gut microbiota.<sup>157</sup> It is likely that numerous intestinal species contribute to immunoregulatory activities<sup>158</sup>; 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.<sup>117</sup>

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.<sup>117,159</sup> 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.<sup>156,160</sup> 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.<sup>161-165</sup> 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.<sup>161</sup> Prebiotics shown to increase *Bifidobacterium* species in the rodent gut markedly reduced plasma concentrations of IL-1 $\beta$ , TNF- $\alpha$ , IL-6, and monocyte chemoattractant protein 1,<sup>162</sup> 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.<sup>162</sup> 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.<sup>166-168</sup>

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.<sup>156,169</sup> However, despite different proximal mechanisms (eg, production of polysaccharide A in *Bacteroides fragilis*, schistosoma-specific phosphatidylserine in *Schistosoma mansoni*, and lipoteichoic acid in *Lactobacillus plantarum*<sup>156,170,171</sup>), 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.<sup>156,170,172-175</sup> 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<sub>H</sub>1) and/or T<sub>H</sub>17 activity. In other individuals, T<sub>H</sub>2 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<sub>H</sub>1 or T<sub>H</sub>2 inflammatory responses is susceptible to central nervous system effects of cytokines, including major depressive disorder. However, conditions associated with T<sub>H</sub>1/T<sub>H</sub>17 and T<sub>H</sub>2 dysregulation are highly comorbid with major depressive disorder. IL-10 indicates interleukin 10; TGF- $\beta$ , transforming growth factor  $\beta$ .

tuberculosis showed that the pseudocommensal microorganism *M vaccae* markedly reduced serum and unstimulated peripheral blood mononuclear cell supernatant TNF- $\alpha$  concentrations over a 3-month period when compared with placebo (while also improving radiological findings).<sup>176</sup> Given multiple studies showing increased serum/plasma concentrations of TNF- $\alpha$  in MDD,<sup>22,78,84,177-179</sup> as well as evidence that antidepressants reduce TNF- $\alpha$  concentrations,<sup>22,31</sup> 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

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

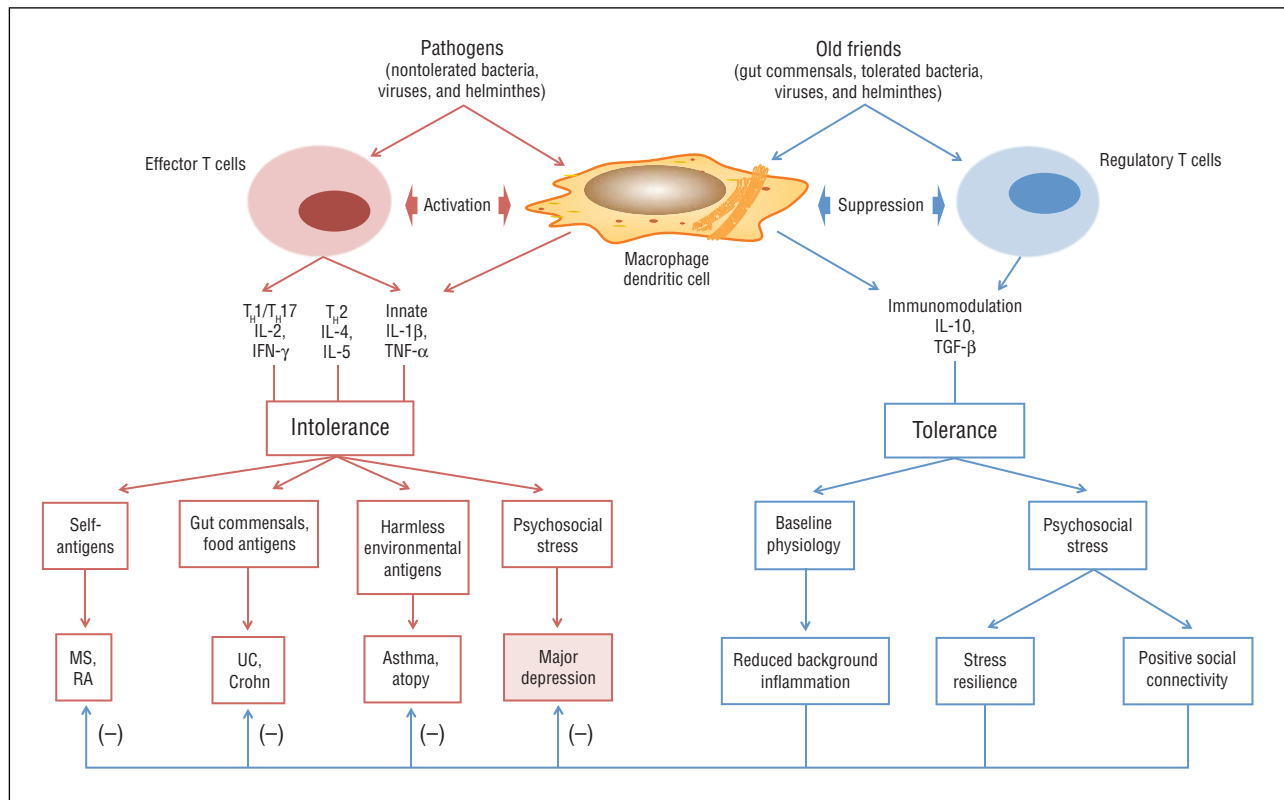
an inescapable consequence of the 20th century increase in hygiene and decrease in rates of parasitic infection. Although much interest in this regard has focused on potential diet- and medicinally induced (ie, antibiotic) changes in the gut microbiota,<sup>180</sup> helminthes and several species of 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.<sup>181-184</sup> In some cases, these microbes also act as Treg adjuvants, resulting in Treg that specifically recognize allergens or autoantigens.<sup>185</sup> 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 co-evolutionary 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 loss of a host of autoimmune diseases).<sup>154</sup> We suggest that any 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,<sup>184</sup> 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.<sup>66</sup> 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).

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,<sup>66,186</sup> 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.<sup>187</sup> 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.<sup>188,189</sup> Interestingly, these changes are mediated in part by reduced vagal parasympathetic signaling and by the induction of glucocorticoid insensitivity,<sup>190,191</sup> both of which are classic neuroendocrine hallmarks of MDD.<sup>67</sup> Consistent with these observations, psychological stress in humans has been associated with reduced fecal *Lactobacilli* levels,<sup>192</sup> and a recent study found increased translocation of gram-negative gut bacteria with concomitant increases in plasma lipopolysaccharide in patients with MDD.<sup>193</sup> 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-galactooligosaccharide (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.<sup>194</sup> 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.<sup>195</sup> 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.<sup>196</sup>

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.<sup>197</sup> 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.<sup>198</sup> 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 1 $\beta$  (IL-1 $\beta$ ) and tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ). 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<sub>H</sub>1) and/or T<sub>H</sub>17 responses from the cellular immune system, characterized by production of cytokines such as IL-2 and interferon  $\gamma$  (IFN- $\gamma$ ). T<sub>H</sub>2 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<sub>H</sub>1 and/or T<sub>H</sub>17 responses are hyperactive and asthma and atopic conditions when T<sub>H</sub>2 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  $\beta$  (TGF- $\beta$ ). These cytokines suppress T<sub>H</sub>1/T<sub>H</sub>17, T<sub>H</sub>2, 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.<sup>199</sup> 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.<sup>165,200,201</sup>

#### TESTING AND APPLYING AN OLD FRIENDS HYPOTHESIS OF DEPRESSION

The hypothesis that disruptions in tolerogenic, co-evolved 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-1 $\beta$ , TNF- $\alpha$ , 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.<sup>202-207</sup> 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,<sup>208</sup> 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.<sup>209-214</sup> 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.<sup>8,215</sup> 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.<sup>216</sup> 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.<sup>217</sup> 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.<sup>218,219</sup> 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.<sup>87,220-222</sup> 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,<sup>223,224</sup> a brain area critical for the detection and correction of errors.<sup>225</sup> 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.<sup>223</sup> 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,<sup>226</sup> neuroticism,<sup>227</sup> and obsessive-compulsive disorder,<sup>228</sup> 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.<sup>229,230</sup>

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.<sup>231</sup> Most currently available data suggest that antidepressants reduce proinflammatory and augment anti-inflammatory signaling in humans<sup>19</sup> and reduce many metrics of emotional intolerance, including neuroticism, hostility, interpersonal and stress sensitivity, and perfectionism independently of effects on depressive symptoms.<sup>232-240</sup> 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- $\alpha$  when compared with sedentary individuals.<sup>241</sup>

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,<sup>182-184</sup> 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.

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