The hygiene hypothesis and psychiatric disorders

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The hygiene hypothesis proposes that several chronic inflammatory disorders (allergies, autoimmunity, inflammatory bowel disease) are increasing in prevalence in developed countries because a changing microbial environment has perturbed immunoregulatory circuits which normally terminate inflammatory responses. Some stress-related psychiatric disorders, particularly depression and anxiety, are associated with markers of ongoing inflammation, even without any accompanying inflammatory disorder. Moreover, pro-inflammatory cytokines can induce depression, which is commonly seen in patients treated with interleukin-2. Therefore, some psychiatric disorders in developed countries might be attributable to failure of immunoregulatory circuits to terminate ongoing inflammatory responses. This is discussed in relation to the effects of the immune system on a specific group of brain serotonergic neurons involved in the pathophysiology of mood disorders.

The hygiene hypothesis

The incidences of several chronic inflammatory disorders have been increasing strikingly in the developed countries. These include allergic disorders (asthma, hay fever), some autoimmune diseases (for example, type 1 diabetes and multiple sclerosis) [1] and inflammatory bowel diseases (IBD; ulcerative colitis and Crohn’s disease) [2]. The ‘hygiene,’ or ‘old friends’ hypothesis attributes some of these increases to a failure of immunoregulation [3]. We know that a failure of immunoregulatory mechanisms can lead to simultaneous increases in all these diverse types of pathology, because genetic defects of Foxp3, a transcription factor that plays a crucial role in the development and function of regulatory T cells (Treg), lead to a syndrome known as X-linked autoimmunity–allergic dysregulation syndrome (XLAAD) that includes aspects of all of them [4].

In support of this view, there is evidence that allergic disorders [5] and some autoimmune diseases [6,7] are accompanied by a failure of the regulatory mechanisms that should terminate inflammatory responses. The situation is less clear in IBD but defective regulatory pathways are the key etiological factor in animal models of IBD [8], and tolerance to gut contents is broken in human IBD [9].

The old friends hypothesis suggests that the lack of appropriate levels of immunoregulatory pathways in developed countries is a consequence of diminished exposure to two categories of organism. First, harmless organisms associated with soil, untreated water and fermenting vegetable matter, and second, helminth infections (parasitic worms) that are still common in developing countries but almost completely absent from developed ones [3]. The former need to be tolerated because they are harmless and were present in food and water throughout human evolution. The helminth parasites need to be tolerated because, although not always harmless, once they are established in the host any effort by the immune system to eliminate them is likely to cause tissue damage. For instance, a futile effort to destroy Brugia malayi microfilariae results in lymphatic blockage and elephantiasis [10].

The mechanism by which these organisms prime immunoregulation and mediate protection from allergies, autoimmunity and IBD is explained in Figure 1. Rather than provoking aggressive immune responses, these organisms cause a pattern of maturation of dendritic cells (DC) that drives Treg rather than T helper cell 1 (Th1) or Th2 effector cells [11,12]. This in turn leads to two mechanisms that help to control inappropriate inflammation. First, the constitutive presence of the ‘old friends’ causes continuous background activation of the regulatory DC (DCreg) and of Treg specific for the old friends themselves, resulting in constant background bystander suppression of inflammatory responses. Thus, strikingly raised levels of IL-10 and TGF-β can be seen in individuals with parasite infections [13,14], and suppression of allergic manifestations in these individuals is attributed to the IL-10 [13]. Second, these DCreg inevitably sample self, gut contents and allergens, and so induce Treg specific for the illicit target antigens of the three groups of chronic inflammatory disorder. These inhibitory mechanisms are aborted when there are legitimate ‘danger’ signals [15].

The validity of this hypothetical model is supported by clinical trials and experimental models in which exposure to microorganisms that were ubiquitous during mammalian evolutionary history, but are currently ‘missing’ from the environment in rich countries, will treat allergy [16–18], autoimmunity [19] or intestinal inflammation [20].

We do not understand all of the ways in which DCreg and Treg block or terminate inflammatory responses. However, the release of the anti-inflammatory cytokines IL-10 and TGF-β is often involved [16,17]. In the next sections, we summarize the evidence that chronic inflammation is able...
to trigger or exacerbate certain psychiatric disorders, and that these anti-inflammatory mediators can oppose these effects.

Cytokines and inflammation in psychiatric disorders
The data showing that depression is associated with increased circulating levels of pro-inflammatory cytokines come from a range of direct and indirect sources, many of which are reviewed elsewhere [21–23], so we give only brief examples.

First, patients presenting with major depression but no other obvious disorder often have raised levels of these cytokines [24]. Similarly, in a community-based study of 3024 well-functioning older persons 70–79 years of age, depression was found to correlate with higher circulating levels of IL-6 and tumor necrosis factor (TNF) [25]. Second, the occurrence of depression in chronic illnesses, such as cancer or heart failure, is related to serum levels of IL-1, IL-6 or TNF rather than to physical symptoms [26–28]. Interestingly, obese people are two to three times more likely to be depressed [29]. Adipose tissue is a potent source of pro-inflammatory cytokines (IL-1, IL-6, TNF) and chemokines such as IL-8, macrophage inflammatory protein (MIP-1α), eotaxin, CCL2 (also known as MCP-1) and of the hormone leptin, which is also pro-inflammatory [30].

Because the pro-inflammatory cytokines, particularly IL-6, drive the acute phase response, there should be evidence of this and of associated hematological changes in psychiatric disorders. This has been demonstrated repeatedly [25,31,32].

There is little direct information on levels of the Th2 cytokines IL-4, IL-5 and IL-13 in psychiatric disorders. However, the inflammation in human allergic disorders is mixed, with a Th1 component and relatively high levels of TNF [33]. Large multisite epidemiological studies in the USA, France and Puerto Rico indicate that childhood asthma is associated with both depression and anxiety disorder [34]. Interestingly, despite considerable comorbidity of depression with anxiety, a history of asthma is more often associated with the latter [34]. This is in sharp contrast to the known association between other chronic illnesses and depression [28], and poses an interesting dilemma. Is the anxiety a direct consequence of the psychological effects of the asthma, or is anxiety exacerbated by the Th2 cytokines or, finally, are both asthma and anxiety the result of a third, possibly genetic factor? Evidence for a shared genetic component has emerged from twin studies [35].

Significance of small changes in cytokine levels
It is possible then that chronic exposure to either the Th1-dominant pro-inflammatory cytokine pattern, or to the Th2 or mixed pro-inflammatory pattern seen in allergic disorders, is able to influence psychiatric symptoms. However, the changes in cytokine levels seen are usually very modest, typically representing a doubling of control background levels [36]. Are such small increases biologically relevant? In fact, there is good evidence that very modest changes in levels of pro-inflammatory cytokines have biological effects. For instance, small diurnal variations in
levels of TNF and IL-1 in blood and cerebrospinal fluid (CSF) play a role in the regulation of the spontaneous sleep–wake cycle [37]. Direct experimental studies also support this view. When very low doses of endotoxin (LPS; 0.2 ng/kg) were administered to healthy volunteers, there was a doubling of circulating levels of cytokines and soluble cytokine receptors, and significantly increased deep NREM (slow-wave) sleep, despite the fact that this dose of LPS was too low to alter rectal temperature, heart rate or cortisol levels [38]. Similarly, negative changes in mood following injection of a vaccine (Salmonella typhi) that caused no subjective symptoms in normal volunteers correlated significantly with a doubling in serum IL-6 [39].

The causality dilemma

The next major issue is whether the elevated cytokines increase the vulnerability to depression (or anxiety), or vice versa. It is well established that exposure to psychological stress can lead to increased production of pro-inflammatory cytokines [40]. Moreover, it has been reported that this ability of stress to drive inflammatory responses is exaggerated in depressed individuals [41]. Insofar as depression is thought to be a form of psychological stress, or at least associated with enhanced stress reactivity, these points seem to suggest that the depression might drive the cytokine release [42]. However, many other observations outlined below lead to the reverse conclusion.

Genetics

Links between polymorphisms of genes encoding inflammatory cytokines (IL-1 and TNF) and depression imply direct involvement rather than a bystander role [43,44]. For example, a single-nucleotide polymorphism of the gene encoding TNF (the TNF2 allele) that leads to higher production of TNF was previously linked to autoimmune and inflammatory diseases [45], but it is also significantly associated with major depression in a Korean population [43].

**Induction of depression by clinically administered cytokines**

The behavioral changes caused by direct or indirect effects of pro-inflammatory mediators in the brain are collectively known as ‘sickness behavior’ and overlap with the symptoms of depression [46]. Direct proof that cytokines can modulate the emotional state is provided by the occurrence of anxiety and depressive symptoms in patients treated with interleukin-2 (IL-2) or interferon-α (IFN-α), cytokines that are used to treat some forms of hepatitis and cancer [23]. Anorexia, fatigue, altered sleep and pain developed within 2 weeks of IFN-α therapy in a large proportion of patients. Later during the treatment with IFN-α there was depressed mood, anxiety and cognitive dysfunction in the patients who developed major depression. There were also differences in the timing and nature of symptoms that depended on whether IL-2 or IFN-α or both were used [47]. Cytokine-treated patients also show secondary rises in other cytokines such as IL-6 and the anti-inflammatory cytokines IL-10 and IL-1 receptor antagonist (IL-1Ra) [48]. This implies that different patterns of poorly regulated cytokine release (for instance, Th1- or Th2-dominated) might lead to different effects on the emotional state (Figure 2).

Cytokine-induced depression can be treated by paroxetine, a serotonin reuptake inhibitor antidepressant (SSRI), suggesting that by this criterion at least it resembles spontaneously occurring depression [49]. The same is true in animals with respect to depressive-like behavioral responses evoked by LPS or cytokine administration [50,51].

One important observation is that patients who had raised background levels of inflammatory cytokines before the cytokine treatment was initiated were more likely to develop depression during treatment with IFN-α or IL-2 [52]. This implies that unexplained background inflammation was a predisposing factor, rather than a consequence of depression.

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**Figure 2.** In populations adequately exposed to old friends, the levels of priming of regulatory cells (T_{reg}) are sufficient to suppress inappropriate inflammation (right side of large balance). When the priming of T_{reg} is too low, the population is at risk of a variety of syndromes attributable to inadequate termination of inappropriate inflammatory responses. Some individuals have a genetic background and immunological history that make their Th1 mechanisms more likely to become pathologically uncontrolled, and these people are at risk of Th1-mediated conditions (type 1 diabetes, multiple sclerosis, Crohn’s disease). In other individuals it is the Th2 response that is most liable to lack of control, resulting in allergic disorders. A further category of individuals suffering from failure to terminate inflammation does not develop any gross pathology, but is susceptible to CNS effects of chronic cytokine exposure. The symptoms tend toward anxiety when these are Th2, and toward depression when these are Th1, IL-1 and TNF. It is relatively common, however, for the patients to have both the inflammatory disorder and the psychiatric disturbance.
Treating depression with anti-inflammatory drugs

If chronic release of cytokines plays a role in driving the depression that accompanies chronic inflammation, then neutralizing these cytokines in vivo should relieve the depression. At least two examples of this are known. First, administration of neutralizing anti-TNF antibody to patients with Crohn’s disease alleviated depressive symptoms in a way that could not be secondary to improvements in comfort and lifestyle [53]. Treatment with anti-TNF was also said to relieve symptoms of depression in patients with psoriasis [54]. Similarly, the cyclooxygenase-2 (COX2) inhibitor celecoxib has therapeutic effects in major depression [55]. Anti-inflammatory drugs of this class can both inhibit inflammation-induced increases in pro-inflammatory cytokines and oppose their effects in the central nervous system (CNS) (reviewed in Ref. [55]).

Glucocorticoid resistance

Depression is commonly associated with hypercortisolemia and glucocorticoid resistance [56]. This might imply that the raised levels of inflammatory cytokines seen in depression are secondary to a failure of glucocorticoid-mediated feedback leading to elevated cortisol, subsequent glucocorticoid resistance and a decrease in glucocorticoid-mediated immunosuppression. However, recent analysis revealed that the raised cytokines cause the glucocorticoid resistance by impairing the function of glucocorticoid receptors [56]. Thus, glucocorticoid resistance might constitute further evidence that failure of immunoregulation is a primary factor.

Effects of drugs used to treat depression

More tenuous evidence that the increased serum cytokines might be contributing to vulnerability to depression, rather than merely a consequence of depression, comes from the observation that antidepressant drugs modulate cytokine production in vitro (Box 1). It has been suggested that all antidepressants reduce the IFN-γ:IL-10 ratio, and so exert an overall anti-inflammatory effect [57]. Therefore, there might be relevant peripheral as well as CNS targets of these drugs, and some that could be relevant in this context (serotonin transporter [SERT] and indoleamine-2,3-dioxygenase [TDO]) are discussed in Box S1 online.

Regulatory cytokines (IL-10, TGF-β)

If we are to apply the hygiene hypothesis to depression and anxiety, we need to show that circulating levels of regulatory cytokines, such as IL-10 and TGF-β, are associated with alleviation of symptoms.

Levels of IL-10 are frequently raised in patients with depression [58]. However, this can be seen as secondary to the increases in pro-inflammatory cytokines such as IFN-γ, IL-1, IL-6 and TNF. Hence, the crucial factor might be the ratio of IL-10 to the pro-inflammatory mediators. In patients with chronic heart failure, those who were depressed had higher levels of TNF but lower levels of IL-10 than those who were not depressed [59]. Moreover, the TNF:IL-10 ratio correlated significantly with the severity of depressive symptoms [59]. As outlined earlier (Box 1), antidepressants reduce secretion of IFN-γ but increase secretion of IL-10 [57], and we also know that IL-10 opposes several of the CNS effects of inflammatory agents (see Box S2 online).

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There is then considerable evidence that levels of pro-inflammatory cytokines tend to be high in patients with depression and anxiety disorders, and there is some evidence that absolute or relative levels of anti-inflammatory cytokines tend to be low. Moreover, the latter can block sickness behavior or depression-like behavior. This suggests that the hygiene hypothesis might be relevant to certain types of anxiety disorder and depression. The global distribution of depression and anxiety is consistent with this view. Although fraught with problems in interpretation, estimates of the incidence of depression in rich industrialized nations are consistently higher than in poor rural nations. Indeed, in young adults (15–29 year olds), the incidence of depression in men in the United States and Canada is estimated to be twice, while that in women is estimated to be three times, that seen in Africa [63], and within Europe depression tends to be more prevalent in urban than in rural communities [64]. Recent studies of a saprophytic environmental mycobacterium,
**Mycobacterium vaccae**, have provided direct experimental links between the hygiene hypothesis and events in the CNS. *M. vaccae* induces T<sub>reg</sub> that downregulate chronic inflammatory states [16]. It has undergone clinical trials for allergic disorders, psoriatic arthritis and some cancers. In several studies, patients who had received intradermal injections of a heat-killed preparation of this organism showed unexpected improvements in quality-of-life scores [65–67]. This led to investigation of the properties of *M. vaccae* in a mouse model, and to the discovery that intracerebral or subcutaneous administration of heat-killed *M. vaccae* activated a specific subset of serotonergic neurons in the interfascicular part of the dorsal raphe nucleus (DRI) of mice [68]. *M. vaccae*-induced activation of DRI serotonergic neurons was associated with increases in serotonin (5-hydroxytryptamine; 5-HT) levels and metabolism within the medial prefrontal cortex (mPFC), a known target of neurons within the DRI [69]. These effects were temporally associated with reductions in immobility in the forced swim test, which is a standard test for antidepressant activity [68].

**The DRI, mPFC and depression**

Do other compounds with similar antidepressant-like behavioral effects enhance serotonergic activity in these areas? In fact, there is much evidence that antidepressant drugs with diverse pharmacological properties increase serotonergic neurotransmission in the mPFC; importantly, antidepressant drugs do not increase 5-HT release indiscriminately in the cortex (see Box S3 online for further details). Why then do SSRIs, other antidepressants and *M. vaccae* increase 5-HT release in some brain regions but not others? One possibility is that these compounds increase the neuronal activity of subpopulations of serotonergic neurons including DRI serotonergic neurons. Serotonergic neurons with unique electrophysiological properties and behavioral correlates have been identified in the DRI, and have been referred to as type II serotonergic neurons [70] (Box 2).

The DRI gives rise to a majority of the median raphe forebrain bundle tract, traveling within the ventromedial part of the medial forebrain bundle to the dorsomedial prefrontal cortex, dorsolateral prefrontal cortex, anterior cingulate cortex, orbitofrontal cortex, mediodorsal thalamus and hippocampus, suggesting that activation of DRI serotonergic neurons is likely to modulate circuits well beyond the mPFC [69,71]. We concentrate on the mPFC because this is the area where the acute effects of antidepressant drugs have been most thoroughly documented (see Box S3 online). However, it is important to note that these additional circuits have been implicated in the pathophysiology of depression [69,72–74], and the median raphe forebrain bundle tract has been proposed previously to play an important role in adaptation, tolerance or coping with stressful events [75].

**Consequences of activation of the raphe-mPFC circuit**

Given the evidence for activation of the raphe-mPFC circuit by multiple agents with antidepressant-like behavioral effects, it is instructive to consider the potential consequences. Although the effects of 5-HT in the mPFC are complex, at the cellular level, 5-HT within the mPFC increases the gain for excitation of layer V pyramidal output neurons [76]. This effect was mimicked to some extent by noradrenalin and therefore could be relevant to the antidepressant-like properties of SSRIs, NRIs (noradrenalin reuptake inhibitors) and SNRIs (serotonin/noradrenalin reuptake inhibitors). Several important consequences of activation of these layer V pyramidal neurons (see Box S4 online for further details), consistent with adaptation, tolerance or coping with stressful events, have been identified (brown arrows in Figure 3).

Figure 3 also illustrates the point that there might be at least two different stress- or anxiety-related serotonergic systems: (i) a raphe-amygdala circuit that facilitates anxiety- and fear-related responses (yellow in Figure 3) and (ii) a raphe-mPFC circuit that suppresses them (green in Figure 3).

**Serotonergic circuits and the hygiene hypothesis**

**Pro-inflammatory cytokines and stress activate the raphe-mPFC circuit**

Injection of mice with endotoxin selectively increases immediate-early gene expression within DRI serotonergic neurons [77]. Similarly, treatment of rodents with endotoxin or pro-inflammatory cytokines such as IL-1 induces prolonged increases in extracellular 5-HT concentrations in the mPFC and hippocampus [78–80]. If activation of DRI serotonergic neurons and 5-HT release in the mPFC is a biomarker of compounds with antidepressant-like behavioral effects, then we would predict that endotoxin would have antidepressant-like behavioral effects. Indeed, endotoxin has been shown to have antidepressant-like behavioral effects when tested at a time that corresponds to the activation of DRI serotonergic neurons [77,81], although the opposite effect can be seen at other time points.

As discussed above, stress (whether physical or psychological) also increases plasma concentrations of pro-inflammatory cytokines, and many studies have shown that stress activates the raphe-mPFC circuit [82,83]. The evidence highlighted above suggests that this might be part of a mechanism designed to promote adaptation, tolerance or coping with stressors (see also Figure 3).

### Box 2. Type II serotonergic neurons

The firing rates of classic or type I serotonergic neurons are tightly correlated with behavioral state (high neuronal firing rates during active waking and decreasing neuronal firing rates during quiet waking and sleep states).

By contrast, type II serotonergic neurons:

- fire at relatively constant rates regardless of behavioral state;
- respond differently to phasic auditory and visual stimuli compared to type I serotonergic neurons;
- have only been identified within the DRI.

Using visualized whole-cell recordings in living rat brain slices, the intrinsic properties of DRI serotonergic neurons are indistinguishable from those of other serotonergic neurons (C.A.L.; unpublished observations), supporting the contention that the unique properties of type II serotonergic neurons in vivo are a result of unique afferent control mechanisms.
Chronic overstimulation of the raphe-mPFC circuit, and dysregulated midbrain serotonergic systems

An important question then is, what happens when this system is chronically overstimulated, as will occur during clinically apparent chronic inflammatory disorders, or in individuals with chronic unexplained inflammatory responses discussed earlier? Chronic overproduction of pro-inflammatory cytokines, although adaptive at first, might lead to downregulation or desensitization of the raphe-mPFC circuit, rendering the individual incapable of mounting appropriate coping responses to stress or continued immune activation. This would be expected to lead to altered postsynaptic 5-HT signaling mechanisms in the prefrontal cortex and disruption of coping mechanisms (Figure 3). Interestingly, there is strong evidence for dysregulated midbrain serotonergic systems in depression (Box 3) [84–94].

**M. vaccae**

The studies with heat-killed *M. vaccae* cast further light on this area. A single injection of this material into pre-immunized animals will cause delayed cytokine release via the Th1 response, and therefore activate the DRI serotonergic neurons and the raphe-mPFC circuit in the same way as LPS, although after a longer delay (6–12 h required for the Th1 response to develop), concurrent with reduced immobility in the forced swim test in the animal model [68]. However, at later time points and after repeated injections, there will be a buildup of Treg cells that tend to terminate ongoing inflammatory responses [16,18]. We suggest that it is this long-term effect that accounts for the unexpected improvements in quality-of-life scores seen in patients with cancer or chronic inflammatory disorders who were treated with monthly injections of this material [65–67]. Reducing chronically raised levels of pro-inflammatory cytokines will allow recovery of the physiological role of the raphe-mPFC circuit in facilitating coping functions (brown arrows in Figure 3).

**Conclusions: inflammatory responses as a vulnerability factor for psychiatric disorders**

Three primary factors have been implicated in determining vulnerability to depression. These include genetic
influences, adverse early life experiences and major stressful life events [95,96]. Interactions among these vulnerability factors appear to be particularly important [97]. In the hypothesis outlined here, we do not propose that chronic inflammatory conditions play a singular causative role in the etiology of anxiety and affective disorders, but accumulating evidence suggests that they should be considered as an additional vulnerability factor. In addition, we provide a hypothetical framework through which a failure of immunoregulatory mechanisms to terminate inflammatory responses might increase vulnerability to stress-related psychiatric disorders, and we specifically implicate cytokine-mediated effects on the DRI-mPFC axis, although this in no way rules out involvement of other neurotransmitter systems including noradrenergic or even dopaminergic pathways [98]. We suggest that in developed countries, the immunoregulatory failure that leads to persistently high pro-inflammatory cytokine levels might be the deficit in T_{reg} activity that has already been implicated in the increased incidences of chronic inflammatory disorders such as allergies and autoimmunity (hygiene hypothesis). Treatments that induce regulatory immune responses, such as M. vaccae, could have therapeutic value in patients with anxiety or depression associated with chronic pro-inflammatory states, whether accompanied by a clinically apparent inflammatory disorder (allergic disease, autoimmunity, IBD) or not. Indeed, as others have suggested, an anti-inflammatory effect might be an integral part of the activity of several currently used antidepressants [57,99–101].

Note added in proof
Since our review was written, Amaral et al. (Proc. Natl. Acad. Sci. U. S. A. [2008] 105, 2193–2197) have shown that the balance of pro-inflammatory cytokines to IL-10 also affects nociception.

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Supplementary data
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AGORA initiative provides free agriculture journals to developing countries

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