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MICROBIAL "OLD FRIENDS", IMMUNOREGULATION AND PSYCHIATRIC DISORDERS

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SUMMARY

Many diseases are increasing in prevalence in urban communities in developed countries. Immigrants are also at increased disease risk, particularly if they move from a poor to a wealthy country during infancy. Moreover, the prevalence of many of these conditions increases further in second-generation immigrants, suggesting that exposure (or lack of exposure) to critical influences during pregnancy and infancy may play an important role in conferring risk for many chronic diseases common in the modern world. The diversity of diseases involved is remarkable. They include chronic inflammatory disorders (autoimmunity, allergy and inflammatory bowel disease), many cancers, (such as prostate, colorectal and various childhood cancers) and a range of psychiatric disorders including depression, disorders precipitated by psychosocial stressors or low socioeconomic status, and disorders with a developmental component such as schizophrenia and autism. Here we explore important parallels among the increases in these diverse types of disease. We merge the immunological explanation (hygiene, or "Old Friends" hypothesis) with psychosocial explanations, and suggest that there are underlying mechanisms, many involving the gut microbiota, that are relevant to *all* these disorders and that transcend the boundaries between traditional medical disciplines.

INTRODUCTION

Many diseases are increasing in incidence in developed countries. These increases tend to be greatest in urban communities. Immigrants are also especially vulnerable to these diseases, particularly if they move from a poor to a wealthy country during infancy, suggesting that infancy provides a critical window for the influence of factors that are protective in poor countries, or detrimental in rich ones. Remarkably, the incidence of many of these conditions increases further in second-generation immigrants, suggesting that exposure (or lack of exposure) to critical influences during pregnancy may play an important role in conferring risk for many diseases common in the modern world. The most remarkable aspect of this problem is the diversity of diseases

involved. These include chronic inflammatory disorders (such as autoimmunity, allergy and inflammatory bowel disease), many cancers, (such as prostate, colorectal and various childhood cancers [Hodgkin's lymphoma, acute lymphatic leukaemia]) and, still more unexpectedly, a range of psychiatric disorders including depression and disorders with a developmental component such as schizophrenia and autism. Medicine tends to be strictly compartmentalized, so the hypotheses put forward to explain the increases in, for example, psychiatric disorders do not usually overlap with the hypotheses put forward to explain parallel increases in cancer or inflammatory diseases, despite the similar epidemiology and the very obvious tendency for all three types of disorder to occur in the same individuals. An immigrant from a developing country arriving in a modern developed city is confronted with psychosocial changes and stressors, a new diet, and a totally different microbiological environment. Psychiatrists and psychologists interpret increased incidences of psychiatric diseases in terms of the changed psychosocial environment, while immunologists naturally try to interpret the increases in the diseases that fall within their domain in terms of the changing microbial environment, and immunological inputs. The aim of this paper is to explore the parallels between the increases in these diverse types of disease in developed countries and to suggest that there are underlying mechanisms, relevant to them *all* that transcend the boundaries between traditional medical disciplines. The keys to this discussion are the profound effects that psychosocial stressors exert on the immune system and vice versa, so that the two types of influence end up operating through similar pathways, often involving the intestinal microbiota.

INFLAMMATION AND PSYCHIATRIC DISORDERS

It is increasingly apparent that inflammation is involved not only in chronic inflammatory disorders such as allergies, autoimmunity and inflammatory bowel disease (IBD) but also in many psychiatric disorders. We have pointed out elsewhere that inflammation and immunoregulation are important in depression (*Raison* et al., 2010; *Rook* and *Lowry*, 2008). A large subset of depressed individuals has persistently raised levels of pro-inflammatory cytokines and other downstream inflammatory markers (*Maes* et al., 1992; *Miller* et al., 2009a), together with a relative deficit in anti-inflammatory mediators and regulatory T cells (fully referenced in *Raison* et al., 2010). When cytokines such as interferon-alpha (IFN-α) are used therapeutically (to treat viral hepatitis or some cancers) they can cause depression-like symptoms that can be treated with standard anti-depressants, such as selective serotonin reuptake inhibitors (SSRI) (*Miller* et al., 2009a; *Musselman* et al., 2001).

It is also clear that inflammatory events during pregnancy, often triggered by infections, can lead to the central nervous system (CNS) developmental abnormalities that underlie the subsequent appearance of autism and schizophrenia (extensively reviewed and referenced in *Meyer* et al., 2011) (*Crespi* and *Thiselton*, 2011; *Schwarz* et al., 2011; *Zerbo* et al., 2012). Indeed autism is very clearly associated with a family history of other chronic inflammatory disorders

such as autoimmunity and allergies, and it is accompanied by abnormal microbiota (*Finegold* et al., 2010) (of which the immunoregulatory role is discussed more below and in other chapters in this volume) and by incontrovertible evidence of background inflammatory activity (*Becker*, 2007; *Onore* et al., 2012). This concept is powerfully supported by animal models (rodents and monkeys) showing that inflammation in the mother during pregnancy induced by injecting lipopolysaccharide (LPS) or poly I:C, or by direct injection of IL-6, will cause changes in the grey and white matter of the foetuses and behavioural changes that are reminiscent of autism and schizophrenia (*Brown* and *Derkits*, 2010; *Smith* et al., 2007; *Willette* et al., 2011). Thus immunregulatory deficits during pregnancy or adult life could play a role in these conditions.

Finally, as discussed at greater length later, inflammation is also involved in the detrimental health consequences of low socio-economic status (SES), both in humans (*Hemingway* et al., 2003; *Miller* et al., 2009b) and in captive colonies of rhesus macaques (*Tung* et al., 2012).

EPIDEMIOLOGICAL PARALLELS

The parallels between the epidemiology of chronic inflammatory disorders and the epidemiology of psychiatric disorders highlight factors that expose the individual simultaneously to a changing psychosocial environment, and to changing immunological input. In the text that follows we use as examples the psychiatric disorders outlined in the previous section, and several particularly prevalent chronic inflammatory disorders; allergies, IBD and two autoimmune disorders (multiple sclerosis [MS] and Type 1 diabetes [T1D]).

Urban versus rural

A feature shared by most of the disorders discussed here is a higher prevalence in urban communities, compared to rural ones. For example a meta-analysis of high quality studies performed in high-income countries since 1985 found that the prevalence of depression in urban areas was 39% higher than in rural areas. Similarly, the prevalence of anxiety disorders was 21% higher in urban than in rural areas (*Peen* et al., 2010), though a small minority of studies fails to find this urban-rural difference (*Kovess-Masfety* et al., 2005). Peen and colleagues also noted an increased urban prevalence of psychiatric disorders in general (38% more in urban communities) (*Peen* et al., 2010). This agrees well with another large meta-analysis which found a significantly raised prevalence of schizophrenia in urban communities (*McGrath* et al., 2004). Similarly, a study of all children born in Denmark between 1 January 1984 and 31 December 1998 found that the degree of urbanisation of place of birth was very significantly correlated to risk of autism ($p<0.0001$) (*Lauritsen* et al., 2005).

It has been suggested that mentally healthy people move away from socially deprived inner cities while vulnerable mentally ill people tend to gravitate towards these areas where deviant behaviour might be more easily tolerated (*Freeman* and *Alpert*, 1986; *Moorin* et al., 2006). However available data suggest that it is the *urban upbringing* rather than a selective migration into cities that lies behind the repeated associations of exposure to the

urban environment and an increased risk of psychiatric disturbance (*Blazer* et al., 1985; *Verheij*, 1996). This view is strongly supported by the other epidemiological parallels discussed below.

The urban-rural phenomenon is also well established for chronic inflammatory disorders, where the aetiology is known to involve dysregulation of the immune system. This has been explored in some detail in the allergic disorders. Contact with the farming environment, whether postnatal (*Riedler* et al., 2001) or prenatal (*Ege* et al., 2008; *Schaub* et al., 2009) protects against allergic disorders, whereas the prevalence of these conditions increases with increasing urbanization (*Nicolaou* et al., 2005). The same is true for inflammatory bowel diseases (*Hou* et al., 2009), and for autoimmune diseases such as multiple sclerosis (MS) (*Antonovsky* et al., 1965; *Beebe* et al., 1967; discussed in *Lowis*, 1990). Interestingly, Type 1 diabetes (T1D, caused by autoimmune destruction of the pancreatic β cells) is more common in urban than in rural areas in some countries (Greece, southern Italy, Lithuania) (*Cherubini* et al., 1999; *Dacou-Voutetakis* et al., 1995; *Pundziute-Lycka* et al., 2003), but not in others (Finland, New Zealand or the UK) (*Miller* et al., 2011). This pattern of findings might imply that the effect is seen when the comparison is made in poorly developed countries where rural life is "traditional", with multiple exposures to animals, farm buildings, and soil.

The urban-rural comparison therefore suggests either that something beneficial is absent from the urban environment, or that something detrimental is present, and these possibilities are as relevant for chronic inflammatory disorders as they are for psychiatric conditions. However, these findings do not allow us to determine the relative importance of psychosocial factors versus immunological inputs for either group of diseases, despite the copious literature implicating the former for the psychiatric diseases, and the latter for the chronic inflammatory ones.

Immigrants

Another striking parallel between chronic inflammatory diseases and psychiatric disorders concerns the effects of immigration on these conditions. All the diseases discussed here, whether chronic inflammatory (*Ahlgren* et al., 2011; *Hou* et al., 2009; *Rottem* et al., 2005; *Söderström* et al., 2012) or psychiatric (*Breslau* et al., 2011; *Dealberto*, 2010; *Keen* et al., 2010), tend to be more common in immigrants than in the birth population from which the immigrant was derived, at least when the migration is from a developing to a developed country. Other relevant variables include the age of the individual at the time of immigration, and whether the prevalence increases in second generation immigrants, born in the adopted country. A study of these parameters provides some insight into whether the relevant influences, be they psychosocial or immunological, need to occur before birth, or in early childhood, or whether they can still exert their effects on adults.

Age at immigration, 2nd generation immigrants and psychiatric disorders

Depression is particularly interesting in this respect (*Breslau* et al., 2009; *Vega* et al., 2004). Mexicans, Cubans and African/Caribbean peoples have a 2-3-fold increase in the prevalence of depression if immigration to the USA occurred when the individual was less than 13 years old, or was born in the USA, compared to the prevalence in those who migrated after the age of 13

(*Breslau* et al., 2009). But this is not likely due to psychosocial stress related to skin colour, because white Eastern European immigrants show the same effect. In sharp contrast, the effect is not seen in immigrants from Western Europe, or from Puerto Rico, which is closely associated with the USA. (These last two populations already have a high prevalence of depression that is not increased by immigrating to, or being born in, the USA) (*Breslau* et al., 2009). These findings imply that influences important for depression occur perinatally, or in the early years of life.

The same is true for psychotic disorders (*Coid* et al., 2008). A large Danish study noted that immigration into Denmark when less than 4 years old was associated with a strikingly increased risk for psychotic disorders, whereas the increased risk gradually decreased with older age at migration and disappeared in those immigrating when more than 29 years old (*Veling* et al., 2011). Similarly a large meta-analysis confirmed that schizophrenia was increased amongst 1st generation immigrants, and further increased amongst 2nd generation immigrants, particularly when the country of origin was a developing one (*Cantor-Graae* and *Selten*, 2005). Again, early events seem crucial.

Age at immigration is irrelevant to an early onset condition such as autism, but autism is strikingly (as much as 10-fold) increased in 2nd generation Caribbean or African immigrants born in the UK, compared to children of white UK-born mothers, as discussed below (*Keen* et al., 2010).

These findings implicate crucial early events in the perinatal period or early childhood as risk factors for depression, schizophrenia and autism. Do these more specific findings, usually attributed to the psychosocial challenges of immigrant status, differentiate these psychiatric disorders from the chronic inflammatory disorders? The answer to this question is again no, as explained in the next section.

Age at immigration, 2nd generation immigrants and chronic inflammatory disorders

Migration has clear effects on the prevalence of MS, and the crucial events that confer increased risk for the disease occur very early in life, as is true for the psychiatric disorders (reviewed and referenced in *Gale* and *Martyn*, 1995; *Milo* and *Kahana*, 2010). Iranians who migrate to Sweden have twice the prevalence of MS seen in their birth country (*Ahlgren* et al., 2011). Interestingly, if the 2nd (or later) generation immigrants return to their developing country of origin, they retain their increased susceptibility to MS, which remains higher than in the local population that was not born abroad (*Cabre*, 2009). A similar phenomenon was seen when people born in the United Kingdom (UK: a high MS country) migrated to South Africa (SA: a low MS country). Migration from the UK to SA was protective when the migrant was a child, whereas adult migrants retained their high UK prevalence of MS (*Dean*, 1967). Analysis of this and other studies suggests that the environmental factors that protect from or predispose to MS act during the first two decades of life (*Gale* and *Martyn*, 1995; *Milo* and *Kahana*, 2010). The same is true for T1D. Here the crucial factor is to have been *born* in the receiving developed country, again suggesting that relevant environmental factors act very early, or even in the prenatal period (*Söderström* et al., 2012).

The role of migration in conferring risk for allergic disorders has been intensively examined. A study of chil-

dren adopted into Sweden from developing countries showed that the prevalences of asthma, hay fever and eczema were highest in those adopted when less than 2 yrs. old (*Hjern* et al., 1999). Similarly, for Mexican immigrants to the USA, the prevalence of asthma was highest for those born in the USA, while in those not born in the USA, the prevalence of asthma decreased as the age at immigration increased (*Eldeirawi* et al., 2009). This effect of age at the time of childhood immigration was also seen in immigrants to Israel from the former Soviet Union or Ethiopia who were assessed when 17 years old (*Pereg* et al., 2008). These observations suggest the importance of early environmental influences for allergy/asthma risk, a conclusion that is powerfully supported by evidence that prenatal exposure (i.e. of the pregnant mother) to the farming environment protects the infant against some allergic manifestations (*Ege* et al., 2008; *Schaub* et al., 2009). This is discussed later in another context.

Finally, a definitive study of all first- and second-generation immigrants in Sweden between January 1, 1964, and December 31, 2007 showed that some 1st generation immigrants remain partially protected from both ulcerative colitis (UC) and Crohn's disease (CD), presumably by environmental factors encountered in their countries of origin, but the diseases increased in prevalence in 2nd generation immigrants, relative to 1st generation immigrants (*Li* et al., 2011). Similarly, the prevalence of UC in South Asian immigrants to Leicester in the UK was higher in 2nd than in 1st generation immigrants (*Carr* and *Mayberry*, 1999). This again implicates perinatal factors as potentially causative of this migration effect.

Thus the influence of immigration, acting via factors that occur perinatally or very early in life, is equally consistent and highly apparent for both psychiatric and chronic inflammatory disorders.

Birth order

The study of disease prevalence in relation to birth order focuses rather specifically on perinatal factors. It was the observation that having multiple older siblings, especially male ones, provided some protection against hay fever that led to the first use of the term "Hygiene Hypothesis", highlighting the notion that grubby older brothers provided an expanded and protective microbiological environment (*Strachan*, 1989). However, subsequent studies of the effects of birth order on other inflammatory conditions have painted a less consistent picture. For example, where IBD is concerned birth order effects are sometimes significant, but the direction of the association is inconsistent (*Hampe* et al., 2003; *Van Kruiningen* et al., 2007). Results are also often contradictory in MS (*Zilber* et al., 1988). Similarly variation was seen in a meta-analysis of data from studies of childhood onset T1D, but overall, there does appear to be increased prevalence in firstborn children (*Cardwell* et al., 2011).

What about the psychiatric disorders? Again the picture is rather variable. For depression an association with birth order is sometimes reported, but the relationship is inconsistent (*Bergeron* et al., 2007; *Schmidt* and *Tolle*, 1977; *Wells* et al., 1985). The effect may be more pronounced for autism and schizophrenia. A comprehensive Finnish study of families with at least two children, one of whom was schizophrenic, found that being the first-born was a significant risk factor for schizophrenia, but the protective effect of older siblings was complex and depended on how much older they

were (*Haukka* et al., 2004). The relevance of birth order to autism has been reviewed in detail elsewhere (*Becker*, 2007). Briefly, the risk of autism has been shown to fall as the number of older siblings rises in studies in the United States, Western Australia and England, though not every study shows this (*Becker*, 2007). In view of the significant epidemiological association with familial allergic disorder, where the birth order effect is clear, as mentioned earlier, this is of great interest (discussed in *Meyer* et al., 2011; *Onore* et al., 2012).

THE OLD FRIENDS HYPOTHESIS AND IMMUNOREGULATION

These epidemiological findings, when applied to the chronic inflammatory disorders, are usually explained by the Hygiene Hypothesis or by the variant of that hypothesis that we prefer, the "Old Friends" hypothesis (plus a few additional recent factors discussed later). The Old Friends hypothesis states that mammals co-evolved with an array of organisms and conditions that, because they needed to be tolerated, took on a role as inducers of immunoregulatory circuits (*Rook*, 2010; *von Hertzen* et al., 2011a). Such organisms and conditions include various microbiotas and commensals (gut, skin, lung etc.), chronic infections picked up at birth, helminths that persist for life, and environmental organisms from animals, mud and untreated water with which we were in daily contact. For example, helminthic 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 futile, and merely causes tissue damage (*Babu* et al., 2006). Contact with the "Old Friends" rapidly diminishes when industrialization occurs, and we start to inhabit a plastic and concrete environment, to consume washed food and chlorine-treated water, and to minimize our contact with mud, animals and faeces. This withdrawal of the organisms that drive immunoregulatory circuits results in defective immunoregulation that, depending on the genetic background of any given individual, can manifest as a variety of chronic inflammatory disorders, including allergies, IBD and autoimmunity. In contradistinction to early articulations of the hygiene hypothesis that focused more exclusively on allergic conditions, we now know that a failure of immunoregulatory mechanisms really can lead to simultaneous increases in diverse types of pathology. For example, genetic defects of the gene encoding the transcription factor Foxp3 lead to the X-linked autoimmunity–allergic dysregulation syndrome (XLAAD) that includes aspects of allergy, autoimmunity and enteropathy (*Wildin* et al., 2002).

The crucial underlying points are these. First, the chronic inflammatory disorders all show evidence of failed immunoregulation (*Rook*, 2009). Secondly, "Old Friends" (such as helminths, non-pathogenic environmental bacteria [pseudo-commensals] or certain gut commensals, probiotics) can be shown to drive immunoregulation, and to block or treat models of *all* of these chronic inflammatory conditions (*Karimi* et al., 2009; *Osada* and *Kanazawa*, 2010; *Round* and *Mazmanian*, 2009). Thirdly, some Old Friends, or molecules that they secrete, can be shown to specifically expand Treg populations (*Atarashi* et al., 2011; *Grainger* et al., 2010; *Karimi* et al.,

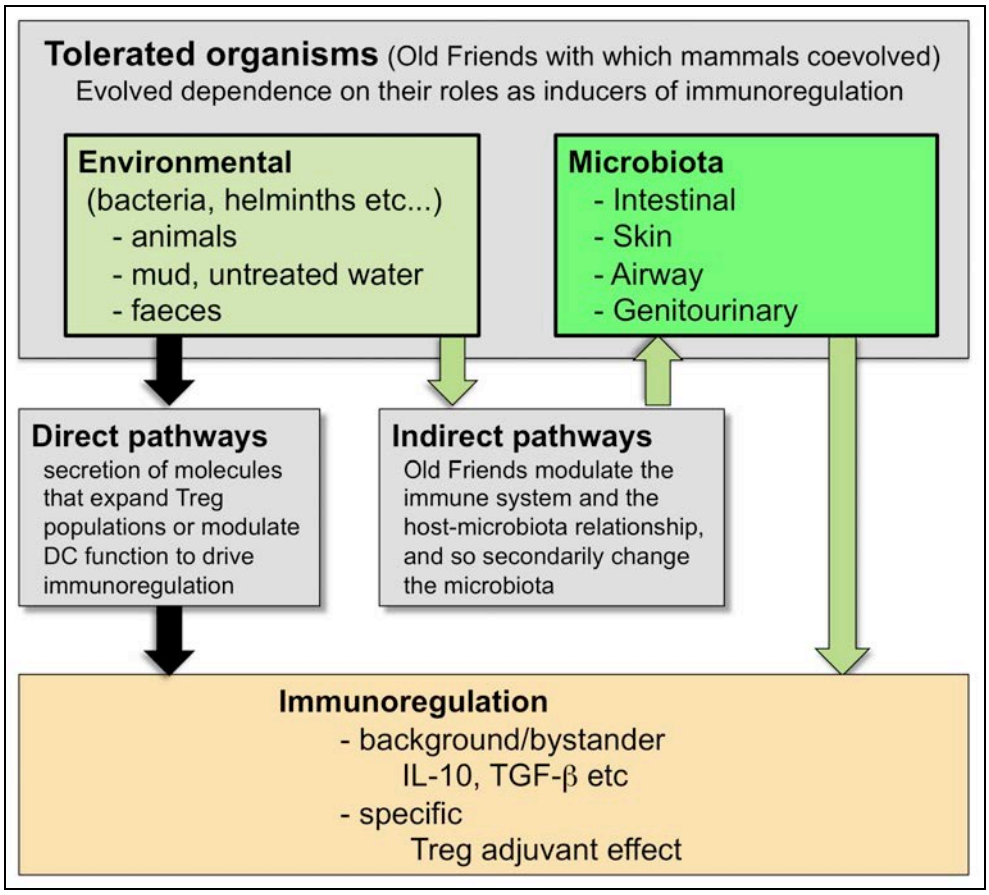

Figure 1: Microorganisms with which mammals co-evolved ("Old Friends"), and that had to be tolerated, have been entrusted with roles in the induction of immunoregulation. These include direct effects on the immune system (for example, driving expansion of Treg, and of regulatory DC), and indirect effects secondary to changes in the host-microbiota relationship. The latter causes changes in the composition of the microbiota that then secondarily modify immune function.

2009; *Round* et al., 2011), or to cause dendritic cells (DC) to switch to regulatory DC that preferentially drive immunoregulation (*Smits* et al., 2005). Finally, when MS patients become infected with helminths, the disease stops progressing, and circulating myelin-recognising regulatory T cells (Treg) appear in the peripheral blood (*Correale* and *Farez*, 2007; *Correale* and *Farez*, 2011), indicating that the helminths act as Treg adjuvants. This is an exciting observation that has led to formal clinical trials (*Fleming* et al., 2011).

Old Friends Hypothesis and the gut Microbiota

We emphasise that many "Old Friends" are (or were, until changed or depleted) gut microbiota, or gut parasites (*Atarashi* et al., 2011; *Grainger* et al., 2010; *Round* et al., 2011). Others were environmental saprophytes in mud and untreated water that inevitably passed though the gut in large numbers every day (*Le Bert* et al., 2011). Moreover new data show that other microbiota such as those of the skin or oral mucosa can also be relevant to immunoregulation (*Friberg* et al., 2010;

Hanski et al., 2012; *Singhal* et al., 2011). But one of the most important discoveries in recent years is the fact that manipulations of the immune system may act *indirectly* via changes in the gut microbiota. For example, Wen and colleagues showed that specific pathogen free (SPF) non-obese diabetic (NOD) mice that spontaneously develop a condition resembling T1D, are protected from the disease following knockout of the gene encoding MyD88 (an adaptor for multiple Toll-like receptors) (*Wen* et al., 2008). However this did not mean that MyD88 was directly involved in the autoimmune response to β cells in the pancreas. Rather it emerged that the modification of the immune system resulting from knocking out MyD88 caused profound changes in the interactions between the immune system and the microbiota, leading to changes in the composition of the latter. It was these changes in the composition of the microbiota that were responsible for the immunoregulatory effect that blocked the autoimmune process. Thus changes in the microbiota, which is profoundly different in Europeans than in people living in a traditional rural African village (*De Filippo* et al., 2010), must be regarded as part of the Old Friends hypothesis, whether these changes are attributable to diet (*Cani* and *Delzenne*, 2011) or to diminished exposures. In either case altered exposure to "Old Friends" will simultaneously exert direct effects on the immune system, and indirect effects via secondarily induced changes in the microbiota (Figure 1).

The Old Friends hypothesis and genetics

In parts of the world where there was a heavy load of organisms causing immunoregulation (such as helminths), there has been selection for single nucleotide polymorphisms (SNP) or other variants to partially compensate for this immunoregulation, or to combat new infections such as malaria that spread from gorilla to man about 10,000 years ago (*Liu* et al., 2010; *Sotgiu* et al., 2008). This is seen for several pro-inflammatory cytokines (*Fumagalli* et al., 2009), IgE (*Barnes* et al., 2005) and STAT6, a transcription factor involved in Th2 responses (*Moller* et al., 2007). There is also an increased frequency of a truncated form of the serotonin transporter promoter that also has a marked pro-inflammatory effect (*Fredericks* et al., 2010). The problem here is clear (Figure 2). As soon as the immunoregulation-inducing organisms are withdrawn by the modern lifestyle, these genetic variants lead to excessive inflammation, and become risk factors for chronic inflammatory disorders (*Barnes* et al., 2005; *Fredericks* et al., 2010; *Fumagalli* et al., 2009; *Moller* et al., 2007). This constitutes a second layer of evolved dependence on the continuing presence of the "Old Friends" (Figure 2).

This is important because work that identifies proximate "causes" for diseases that were rare or non-existent before the Second Epidemiological Transition may merely be unravelling a problem that would be irrelevant if the microbial status of the modern world could be returned to that seen in the paleolithic. For instance, the recent claim to have discovered that the "cause" of Crohn's disease is a genetically determined defect in the homing of neutrophils (*Smith* et al., 2009) is difficult to reconcile with the fact that 100 years ago the disease barely existed. But recent environmental changes could conceivably have caused this phenotype to become a risk factor (Figure 2).

It is clear how the Old Friends hypothesis can provide an explanation for

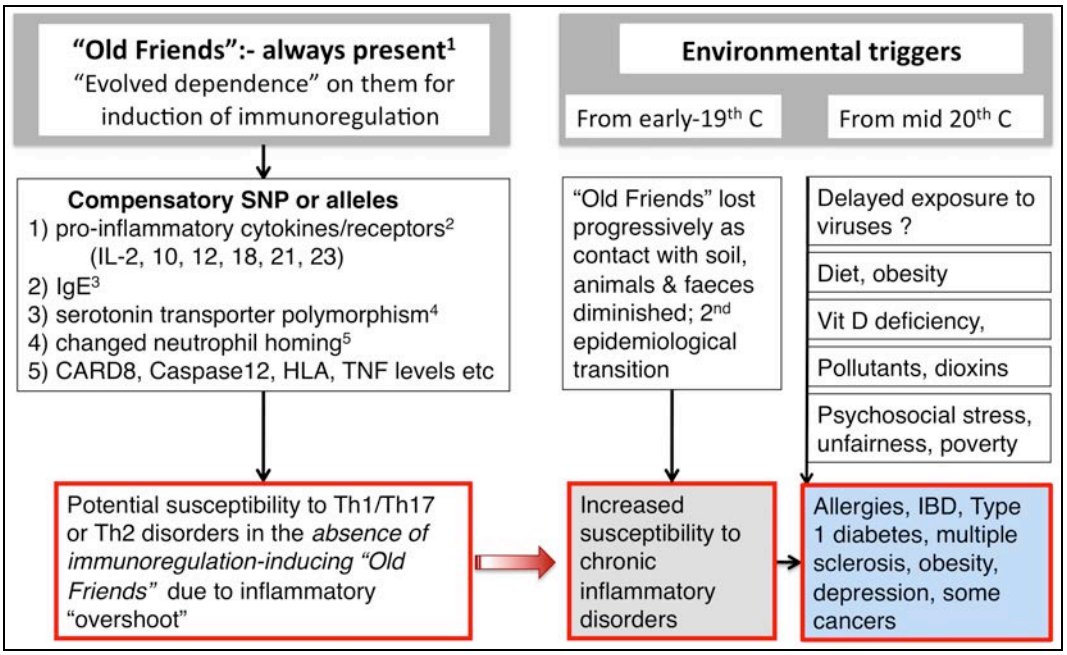

Figure 2: Interaction of genetics and loss of the "Old Friends". The Old Friends had to be tolerated and so co-evolved roles as triggers of immunoregulatory pathways. In areas with very high loads of these and other organisms, particularly helminths, compensatory genetic variants accumulated, to partially restore inflammatory responses. In the absence of the Old Friends, not only is immunoregulation inadequately primed, but also these genetic variants cause excessive inflammation and become risk factors for chronic inflammatory disorders. Genetic variants that were advantageous, and did not cause disease in the past, start to do so when the Old Friends are lost after the 2nd epidemiological transition (referenced in main text). More recently several aspects of modern life are exacerbating the effects of the lack of "Old Friends" at the level of immunoregulation. Obesity is associated with altered gut microbiota and excessive release of pro-inflammatory cytokines. Stress also alters gut microbiota, and drives corticotropin-releasing hormone (CRH) that increases permeability of the gut mucosa. Increased absorption of lipopolysaccharide (LPS) and other microbial components drives further release of pro-inflammatory cytokines. Lack of vitamin D exacerbates immunodysregulation, as does the triggering of Th17 cells by dioxins. Meanwhile the changes in the gut are also likely to impact on Th17 development. Viruses that used to be encountered harmlessly in early infancy (under cover perhaps of maternal antibody) can trigger autoimmunity if encountered for the first time later in life. Psychosocial stressors exacerbate these problems, as outlined in the main text.

rural-urban differences in the prevalence of chronic inflammatory diseases, and for the consequences of immigration from poor to rich countries. The rural environment and above all the farming environment, provide a microbiological input that is closer to that with which we evolved, so more likely to prime appropriate immunoregulation. Similarly, the developing country lifestyle exposes us to more diverse and numerous Old Friends than does the rich Western lifestyle.

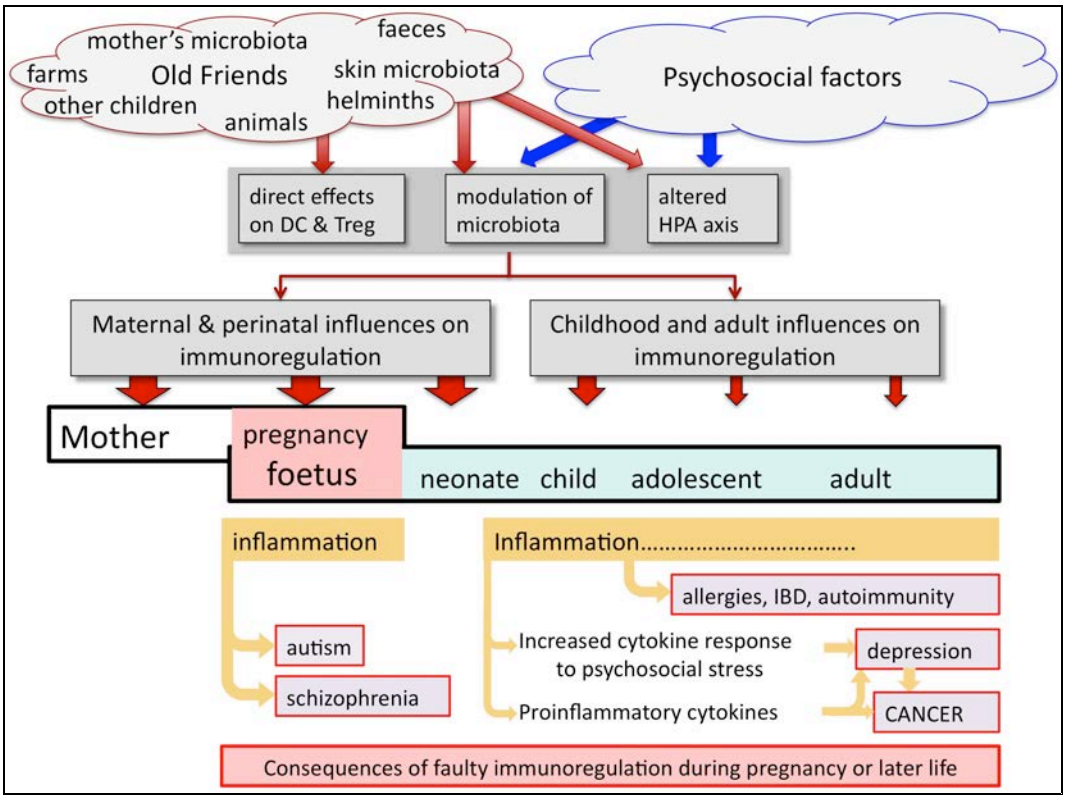

Figure 3: Immunoregulatory influences throughout life, and the consequences of their failure. The immunoregulatory Old Friends and psychosocial factors influence immunoregulation, and converge strikingly on the microbiota and HPA axis in the perinatal period. Withdrawal of Old Friends, and/or perinatal psychosocial stressors predispose to inflammatory disorders. During pregnancy this can predispose to neurodevelopmental problems such as autism and schizophrenia. In adolescence or adult life poor immunoregulation can predispose to chronic inflammatory disorders or to depression or to both together. A late consequence, exacerbated by depression, is inflammation-associated oncogenesis, and promotion of cancer growth and spread.

OLD FRIENDS AND PSYCHOSOCIAL STRESSORS IN THE PERINATAL PERIOD

The previous sections have used three psychiatric disorders to point out that aspects of their epidemiology that are usually interpreted as indicating a crucial role for exposure to psychosocial stressors, are not significantly different from the findings that emerge from the epidemiology of chronic inflammatory disorders such as allergies, IBD and autoimmunity. In the context of the latter disorders these findings are usually explained by the "Old Friends" hypothesis. Does this mean that we should we be changing our view of the role of the psychosocial stressors in psychiatric disease, or should be blaming psychosocial stressors for these chronic inflammatory disorders? The answer, we suggest, is both. Psychosocial stressors and inflammation are closely linked, as discussed below.

Perinatal psychosocial stress and immunoregulation

Although immigrants certainly meet a changed microbial environment, it is equally certain that they face a barrage of psychosocial stressors. Indeed we know that prenatal psychosocial stress (i.e. experienced by the pregnant mother) or early postnatal stress can cause long-term changes in neurogenesis (reviewed in *Korosi* et al., 2012), in cognition, memory (*Entringer* et al., 2009a) and in hypothalamic-pituitary-adrenal (HPA) axis function (*Entringer* et al., 2009b). These dilemmas are partly resolved when one considers the close links between psychosocial stressors and the immune system. We suggest below that psychosocial stressors will exacerbate the immunoregulatory dysfunction caused by the lack of "Old Friends", while the lack of "Old Friends" will exacerbate the inflammatory effects of psychosocial stressors (Figure 3). There are clear synergistic pathways to the simultaneous development of a mixture of psychiatric and chronic inflammatory problems. The crucial point is that perinatal stress also has long-term modulatory effects on immune system function. This issue is the topic of the following sections.

Perinatal stress and long-term changes to immune function

Many studies in animals and humans have shown that a variety of stressors, including psychosocial ones, during pregnancy activate inflammation (*Haroon* et al., 2012; *Howerton* and *Bale*, 2012). For example, prenatal maternal stress during otherwise normal human pregnancies was associated with raised circulating levels of the pro-inflammatory cytokines IL-6 and tumour necrosis factor-alpha (TNF-α), raised C-reactive protein (CRP) and low levels of the anti-inflammatory cytokine IL-10 (*Coussons-Read* et al., 2005). Similarly overall stress levels during pregnancy correlated with increased release of IL-1β and IL-6 by lymphocytes stimulated *in vitro* during the 3rd trimester (*Coussons-Read* et al., 2007).

However, the important point here is that perinatal stress results in adults who themselves show exaggerated inflammatory responses to stress (*Carpenter* et al., 2010; *Danese* et al., 2007, 2008). For example, peripheral blood mononuclear cells from healthy young women whose mothers had experienced major negative life events during pregnancy showed altered responses to phytohaemagglutinin compared to cells from a control group. There was a bias towards production of T-helper 2 (Th2) cytokines and both IL-6 and IL-10 were also significantly elevated (*Entringer* et al., 2008). Similarly maltreated children develop higher levels of IL-6 in response to a standardized social stressor (the Trier Social Stress Test; TSST) when tested as adults in comparison to a non-maltreated control group (*Carpenter* et al., 2010; *Pace* et al., 2006), and maltreated children tend to have higher levels of CRP 20 years later (*Danese* et al., 2007). Low early life social class (socio-economic status; SES) is similarly associated in adult life (aged 25-40) with increased production of IL-6 in cultures of peripheral blood leukocytes stimulated with ligands for toll-like receptor 3 (TLR3) or TLR5 (*Miller* et al., 2009b). These findings all imply that perinatal stress itself leads to long-lasting problems with immunoregulation (*Carpenter* et al., 2010; *Danese* et al., 2007, 2008). Interestingly, negative life events during the first years of life, whether they affect the child directly, or indirectly via traumatic experiences of the mother, predispose to the autoimmune disease T1D (reviewed in *Peng* and *Hagopian*, 2006; *Sepa* et al.,

2005; *Vlajinac* et al., 2006). It is likely that this reflects an influence of perinatal negative life events on subsequent immunoregulation.

Many mechanisms are involved in the relationship between perinatal stress and immune activation (*Haroon* et al., 2012; *Howerton* and *Bale*, 2012). We consider two particularly relevant and important mechanisms below; the HPA axis and the microbiota.

Perinatal stress and long-term changes to the HPA axis

In monkeys, exposure to high levels of maternal stress hormones (whether induced by stressing the mother, or by injecting dexamethasone or adrenocorticotropic hormone [ACTH] during pregnancy) causes prolonged changes in the reactivity of the infant's lymphocytes *in vitro* (*Coe* et al., 1996, 1999). Numerous animal models have demonstrated associations between prenatal stress and long-term alterations in HPA axis function (*Kapoor* et al., 2006; *Weinstock*, 2005).

Healthy young human adults who had been exposed to "prenatal stress", because their mothers had experienced severe negative life events such as the death of someone close during pregnancy, responded differently to a standardized social stressor (TSST) when compared to an age-matched comparison group of healthy young women who had not been exposed to prenatal stress. The prenatal stress group had lower cortisol levels ($p=0.007$) before the TSST, and a larger increase in response to the TSST ($p=0.03$) (*Entringer* et al., 2009b). Similar changes have been associated with severe stress in early childhood (*Heim* et al., 2000). Moreover adults with PTSD symptoms who were abused as children show increased NFκB and decreased glucocorticoid sensitivity and these two findings are highly correlated (*Pace* et al., 2012). This is consistent with the idea that HPA axis changes as a result of early abuse or neglect contribute to increased inflammatory drive.

Interestingly, a transcriptional profiling of adults whose childhood background had been of low or high socioeconomic status (SES) revealed that those from a low childhood SES background had up-regulation of genes bearing response elements for the cAMP response element binding (CREB)/activating transcription factors (ATF) family of transcription factors involved in signalling to leukocytes, heightened expression of transcripts bearing response elements for nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), and down-regulation of genes with response elements for the glucocorticoid receptor (GR) involved in anti-inflammatory function (*Miller* et al., 2009b). A similar pro-inflammatory bias in gene expression emerged from a comparison of asthmatic children from low or high SES backgrounds (*Chen* et al., 2009). In conclusion, perinatal and early neonatal stressors are likely to induce long-term changes in HPA axis function (Figure 3), with obvious consequences for immune function.

Although perhaps beyond the scope of this discussion document, it is worth noting briefly that the persistence into adult life of HPA axis effects triggered in the perinatal period might be explained by epigenetic changes, such as altered DNA methylation patterns (*Guo* et al., 2011; *Miller* et al., 2008; *Weaver* et al., 2004), or by shortened telomere length, and reduced telomerase activity (*Choi* et al., 2008; *Entringer* et al., 2011; *Jacobs* et al., 2011; *Ornish* et al., 2008). Reduced telomere length is associated with inflammation and autoimmunity as well as with premature immunosenescence (*Carrero* et al., 2008; *Fitzpatrick* et al., 2007; *Hohen-*

sinner et al., 2011), though whether as cause or consequence is not certain.

Perinatal stress and long-term changes to the intestinal microbiota

It has been known for some time that stress alters the microbiota of experimental animals (*Kiliaan* et al., 1998), and the same is true of the microbiota of severely stressed critically ill humans, where the changes are rapid and prolonged (*Hayakawa* et al., 2011). Crucially important in the current context is the observation that the stress of maternal separation for 3 hours per day from post-natal days 2-12 has long-term effects on the subsequent 16S rRNA diversity of the microbiota that is still apparent when the pups become adult rats, compared to control adults that had not been exposed to maternal separation as pups (*O'Mahony* et al., 2009). Similarly, *prenatal* stressors have been shown to alter the microbiome in rhesus monkeys by reducing the overall numbers of bifidobacteria and lactobacilli during adulthood (*Bailey* et al., 2004).

This might be an important mechanism because the nature of the microbiota during the first weeks of life has a profound effect on development of the CNS and the HPA axis. For example, germ-free mice have increased motor activity, reduced anxiety, altered gene expression in several brain areas, and increased turnover of noradrenaline, dopamine and 5-HT in the striatum (*Heijtz* et al., 2011). These abnormalities persist into adulthood, and cannot be corrected by reconstitution of the microbiota of adult animals (*Heijtz* et al., 2011). Moreover, the nature of the microbiota is crucial. In another study it was noted that germ-free mice had abnormal responses to restraint stress, specifically increased ACTH and corticosterone responses, together with reduced expression of brain-derived neurotrophic factor (BDNF) in cortex and hippocampus, reduced glucocorticoid receptors (GR) in the cortex, and raised corticotrophin-releasing hormone (CRH) in the hypothalamus (*Sudo* et al., 2004). Oral reconstitution with a normal microbiota normalised the HPA axis function if done at 6 weeks, but not if done later. Early mono-association with *Bifidobacterium infantis* also normalized HPA axis function, but mono-association with enteropathogenic *E. coli* made the abnormalities more severe. Thus not only is the microbiota modified by stress, but it is also involved in development of the CNS, so given these observations it is possible that perinatal stress might exert physiological effects on the brain in adulthood at least in part via its impact on the microbiota

Consequences of changes to the intestinal microbiota

The nature of the microbiota is likely to modulate both the subsequent response to psychosocial stressors and the functions of the immune system. When mice are stressed by being housed with an aggressive dominant male, they develop altered microbiota, and raised circulating levels of IL-6, TNF and IFN-γ. However, if the microbiota is depleted by an antibiotic cocktail, the same social stressor fails to cause increased pro-inflammatory cytokine levels (*Bailey* et al., 2011). It seems that increased permeability in the gut caused by stress, results in increased intake of LPS and other pro-inflammatory molecules, which exert a positive feedback on the stress-induced inflammatory response. Stress-induced increases in gut permeability might be partly due to release of CRH by T cells, and by cells within the submucosa and muscle layers of the gut, myenteric neurons, serotonin-containing enterochromaffin cells, and lamina propria

cells of the mucosa in stomach and colon (*Stengel* and *Tache*, 2009). CRH is not only a regulator of intestinal permeability (*Gareau* et al., 2008; *Teitelbaum* et al., 2008), but also a potent pro-inflammatory cytokine in its own right in the periphery of the body (*Calcagni* and *Elenkov*, 2006). These changes may help explain the finding that depressed patients have raised levels of antibody to a range of intestinal bacteria (*Maes* et al., 2008).

Alterations in the microbiota will also impact immunoregulation (Figure 3). The fundamental role of the microbiota in immunoregulation has been reviewed extensively elsewhere (*Round* and *Mazmanian*, 2009). The organisms that comprise the microbiota can be thought of as one component of the "Old Friends". Recent observations suggested that, as in animals, in humans fluctuations in the microbiota early after surgery (bone marrow transplantation) may lead to an increased risk of immunoregulatory failure, manifested in this study as graft-versus-host disease (*Jenq* et al., 2012).

SYNERGY BETWEEN THE OLD FRIENDS MECHANISM AND STRESS

The previous section makes clear that perinatal stress can cause long-term dysregulation of the immune response, both via changes to the HPA axis and changes to the microbiota. (No doubt there are other changes too, e.g., changes to the sympathetic and parasympathetic systems, but these are beyond the scope of this paper). However we have also pointed out that in the modern urban environment a second mechanism is also reducing the efficiency of immunoregulatory mechanisms: depletion of immunoregulation-inducing "Old Friends". In this section we explore the hypothesis that these two mechanisms interact to modulate those psychiatric disorders where inflammation is known to play a role. As outlined in the section immediately after the introduction, inflammation is implicated in depression (*Raison* et al., 2010), and in driving the developmental abnormalities that underlie many cases of schizophrenia and autism (*Meyer* et al., 2011) and in the health consequences of low socio-economic status (*Hemingway* et al., 2003; *Miller* et al., 2009b; *Tung* et al., 2012). There are several ways in which the psychosocial and microbial pathways might work together via immunoregulation to alter patterns of psychiatric disease.

Urban versus rural upbringing, and response to an experimental stressor

A recent functional magnetic resonance imaging (fMRI) study compared the effects of an experimental social stressor on individuals brought up in urban or rural environments. Urban versus rural upbringing correlated with significant differences in activation of the perigenual anterior cingulate cortex, a region involved in regulation of negative affect and the physiological stress response (*Lederbogen* et al., 2011). The authors attributed their findings to putatively different levels of social stressors in individuals with an urban versus rural upbringing. But would social stressors in children differ significantly in the two environments in a wealthy European country (Germany)? It is equally likely that the findings were due to the "Old Friends" mechanism, leading to diminished regulation of pro-inflammatory mediators in those subjects who had an urban upbringing. Indeed the protective effects of the German farming environment against allergies and early onset in-

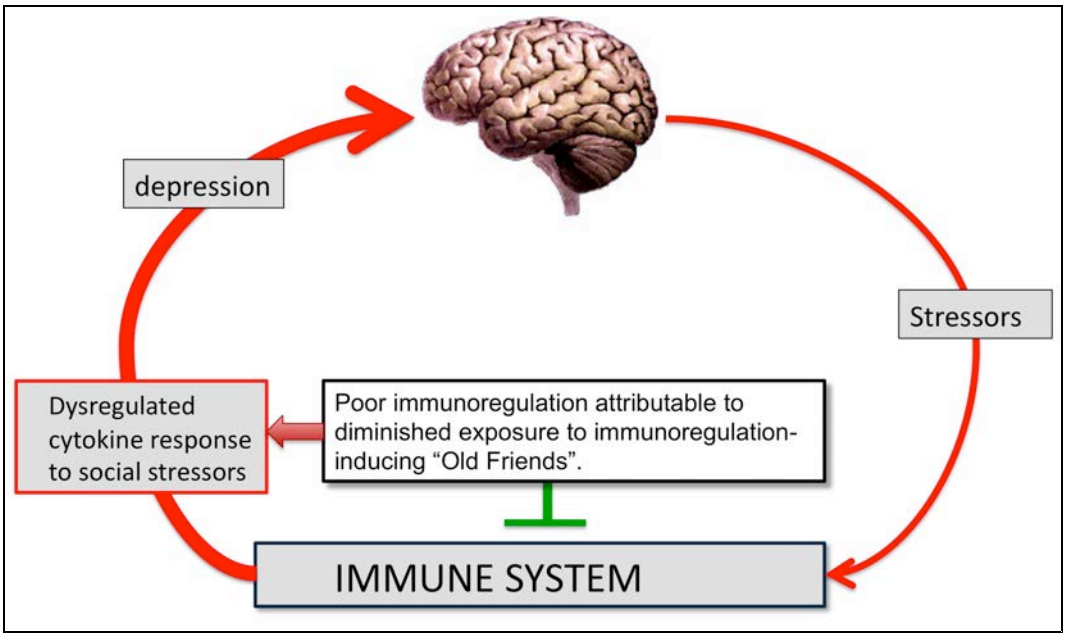

Figure 4: Exaggerated cytokine release in response to a psychosocial stressor leading to depression. Populations that have undergone the 2nd epidemiological transition have minimal exposure to immunoregulation-inducing "Old Friends" such as helminths. The consequent diminished efficiency of immunoregulation is manifested as rising prevalences of chronic inflammatory disorders such as allergies, autoimmunity and inflammatory bowel disease (IBD). Poor immunoregulation will also leave the individual susceptible to excessive and prolonged cytokine release in response to psychosocial stressors, which may result in inappropriate triggering of depressive episodes.

flammatory bowel disease are well documented and require that a child be exposed to the farming environment during the first 2.5 years of life…a rural upbringing (*Radon* et al., 2007; *Riedler* et al., 2001). The authors of the fMRI study did not measure the stress-induced levels of circulating pro-inflammatory cytokines in the two populations. The "Old Friends" view of the data would postulate higher levels in the subjects who had urban upbringings.

Depression

Exposure to psychosocial stressors in later life would be expected to cause greater increases in circulating pro-inflammatory cytokines in individuals with poor immunoregulation as a consequence of lack of exposure to Old Friends. Thus people living in rich developed countries should have a greater likelihood of becoming depressed when confronted with a given level of psychosocial stress, compared to the citizens of a developing country environment rich in immunoregulation-inducing "Old Friends" (Figure 4). We know that depressed individuals with histories of early life trauma or neglect release more IL-6 in response to the TSST (*Pace* et al., 2006). To put it another way, it might be that depression is increasing in the USA (*Compton* et al., 2006) not because our lives are becoming more stressful, but rather because in developed countries our immune systems release more depression-inducing pro-inflammatory cytokines in response to any given level of psychosocial stressor. This would imply

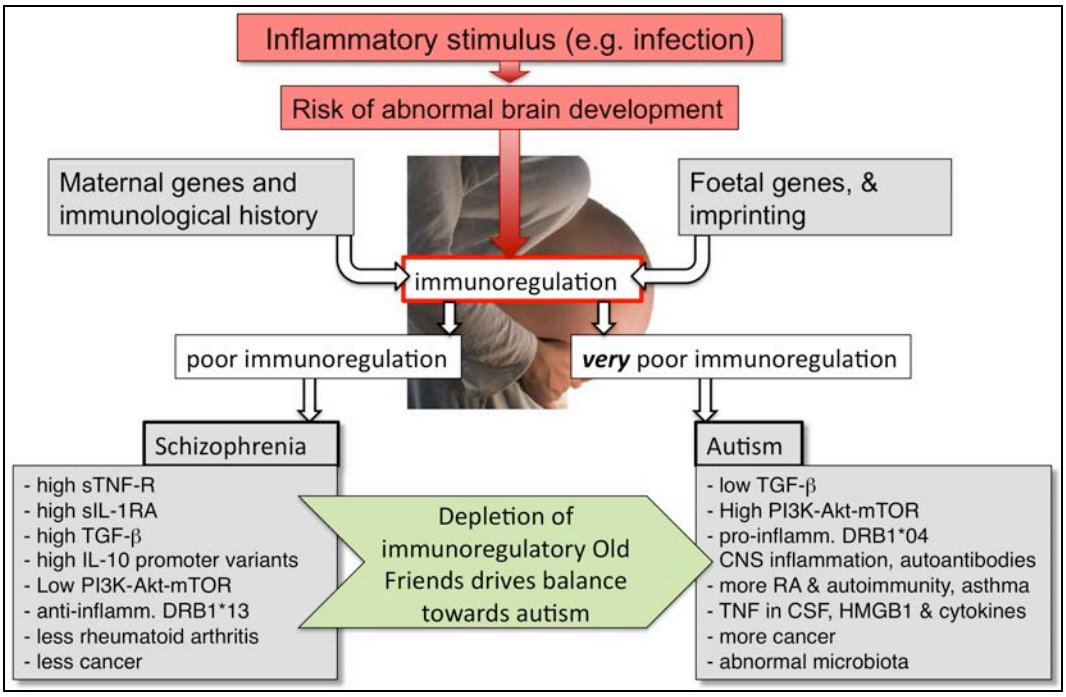

Figure 5: Reduced efficiency of immunoregulation during pregnancy, due to loss of the immunoregulation-inducing Old Friends could explain the reduction in schizophrenia and the increase in autism that are suggested in the recent literature (see main text). Both disorders are associated with inflammatory episodes during pregnancy that lead to neurodevelopmental abnormalities. But the severity of the failure of immunoregulation is much greater in autism, and persists into adulthood. The immunological points listed in the boxes at lower left and right are taken from, and fully explained within, the references discussed in the main text.

that the prevalence of depression should be greater in developed countries than in developing ones. Comparative studies are difficult to do but this is indeed what is indicated by data gathered by the World Health Organization (*Ustun* et al., 2004).

Schizophrenia and autism

In developed countries pregnant women will themselves have poor immunoregulation as a result of reduced contact with immunoregulation-inducing Old Friends. This will mean that they have reduced ability to shut off or modulate inflammatory episodes during pregnancy (Figure 5), such as those involved in driving the developmental abnormalities that lead to many cases of autism or schizophrenia (*Meyer* et al., 2011), (see Figure 3). Because the inflammatory component of autism is much greater than that seen in schizophrenia, one likely consequence of failing immunoregulation would be a reduction in the prevalence of schizophrenia, and an increase in autism. There is evidence that autism is becoming more common (*Williams* et al., 2006) while schizophrenia may be showing the opposite trend (*Der* et al., 1990; *Woogh*, 2001). It is of particular interest to note that genetic studies have revealed that some maternal genes, such as HLA DR4, are involved in modulating the risk of these disorders even when not inherited by the foetus (*Johnson* et al., 2009). It will be

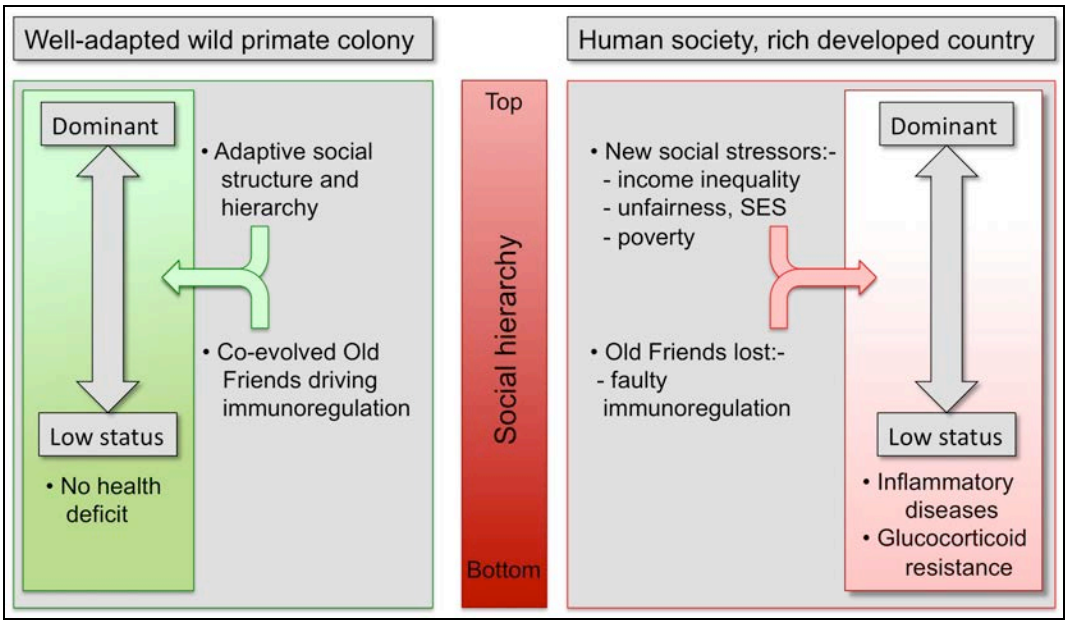

Figure 6: The consequences for long-term health of socioeconomic status and dominance hierarchies. It is often assumed that low position in a dominance hierarchy automatically leads to health deficits, particularly chronic inflammatory problems and cardiovascular disease. This seems maladaptive in a Darwinian sense because low status individuals may later become leaders and breeders. Some recent studies have revealed that in monkeys and primates low status can be compatible with health (i.e. no evidence of stress or raised glucocorticoids). This is likely to be the evolutionarily adaptive state, prevalent in the wild, when habitat is undisturbed and unrestricted, and human observers are absent. We suggest that the health penalty of low socioeconomic status (SES) in modern human communities is attributable to failing immunoregulation (loss of Old Friends) superimposed on the social stress of poverty and perceived "unfairness" (income inequality etc.).

interesting to ask whether many of these genes, like HLA DR4 (*Johnson* et al., 2009), have a role in the control of inflammation.

Health deficits of low socioeconomic status

In the Whitehall study of UK civil servants, circulating levels of CRP and IL-6 were inversely correlated with employment grade, implying an inverse relationship between socioeconomic status (SES) and background inflammation (*Hemingway* et al., 2003). This and other studies show that this gradient is associated with a health deficit that is measurable at every rank below the top of the gradient, despite the fact that at these upper levels diet and nutrition and healthcare access are not significantly different (*Marmot*, 2006; *Sapolsky*, 2004). A similar phenomenon has been seen in rhesus macaques. In this species there is a linear dominance hierarchy. It has emerged that the lower the position of a given animal within this hierarchy in a captive colony, the higher the expression in the peripheral blood of genes involved in inflammatory responses (*Tung* et al., 2012). There are also links with chronic inflammatory disorders (*Chen* et al., 2009), and low SES in early life leads to decreased glucocorticoid sensitivity and increased pro-inflammatory signalling in adulthood when cells are

stimulated with various ligands *in vitro* (*Miller* et al., 2009b).

While these findings are often thought to indicate that psychosocial stress increases as one's position in a hierarchy decreases, it may well be that disruptions in our relationship with Old Friend organisms may contribute to the association between status and health and inflammation. This possibility is highlighted by the fact that the Old Friends mechanism also impacts serum CRP levels (*McDade* et al., 2010). CRP is lower in adults who experienced greater microbial exposures in childhood (*McDade* et al., 2010). Moreover when CRP levels were followed in the same individuals over several months it emerged that in a developing country the baseline CRP is very low (i.e. fully shut off), with intermittent peaks when inflammation is needed to cope with infection. Thus the prevalence of ''high risk'' CRP (>3 mg/l) is greater in a remote Amazonian population with high rates of infectious disease than in the USA (*Gurven* et al., 2008), but these are *transient peaks* triggered by infection (*McDade* et al., 2012). In contrast, in the USA CRP is often not fully turned off despite lack of a valid requirement for inflammation (*McDade* et al., 2012). There is chronic persistent low-level inflammation indicating poor immunoregulation (*McDade* et al., 2012), and it is this uncontrolled chronic inflammation that can predispose to chronic inflammatory disorders, including the psychiatric effects outlined above.

A simple hypothesis therefore would be that the health deficit driven by low SES is exaggerated in individuals deprived of immunoregulation-inducing Old Friends (Figure 6). If we could compare the health gradients of SES hierarchies in developing and rich countries, an Old Friends perspective would predict that we would find less health deficit at the bottom end of the social gradient in developing countries (assuming that we could eliminate confounders such as unequal access to health care, etc.) than in a developed ones.

But there is also the possibility of a much stronger version of this hypothesis. Perhaps the health deficit of low SES does not occur at all unless immunoregulation is compromised. The notion that any position below the top of a dominance or SES hierarchy is associated with long-term inflammation-mediated damage to health is anti-intuitive and incompatible with Darwinian medicine. Subordinate individuals may later become dominant and play crucial roles as the main leaders and breeders (reviewed in *Sapolsky*, 2004). It is maladaptive for such future breeding stock to receive permanent damage (for instance to the cardiovascular system) earlier in life. Most observations of stress and/or inflammation in subdominant animals have been made in populations that were captive (so partly depleted of Old Friends), and/or undergoing social disruption as a result of human observers and interventions and perimeter fencing. For example in many troops of macaques or baboons subordinate animals have high basal glucocorticoid levels, but in other troops of the same species this effect is not seen (reviewed in *Sapolsky*, 2004). The latter, more difficult to observe and record, is likely to be the adaptive situation, and the norm in thriving undisturbed communities. We tentatively suggest that in human communities, when confounders such as access to nutrition and health care have been eliminated, it will be found that the SES-linked health deficit is a Western artefact of modern social stressors (poverty, unfairness, income disparity) driving inflammation in the context of a dysregulated immune system (Figure 6).

FINAL REMARKS

The purpose of this paper is to explore the relationship between the Hygiene or "Old Friends" hypothesis and the psychosocial stressor hypothesis. The "bottom line" is found in Figures 4, 5 and 6 where we illustrate diagrammatically the ways in which we suggest that these two mechanisms, both equally valid and proven, interact and contribute to the changing patterns of disease in the modern world. These consequences are relevant both to psychiatric disorders and to chronic inflammatory disorders.

This paper is not intended to be a comprehensive review. We did not include the role of immunoregulation and inflammation in cancer apart from a brief comment in the introduction, because this topic was extensively reviewed elsewhere (*Rook* and *Dalgleish*, 2011; *von Hertzen* et al., 2011b). Similarly, we do not include discussion of all the factors known to be relevant to associations between environmental conditions, immune function and physical and mental health (though some of these are listed in Figure 2). For example diet is a major factor that has been omitted. Diet has profound effects on the microbiota, and therefore indirectly on immunoregulation (*Maslowski* and *Mackay*, 2011). Another important factor is delayed exposure to viruses caused by hygienic modern living conditions. Many viruses are harmless when met by neonates, perhaps because of the presence of maternal antibodies, but when encountered later such viruses may trigger inflammatory disorders such as allergies and autoimmunity (*Filippi* and *von Herrath*, 2008; *Harrison* et al., 2008; *Serreze* et al., 2000). Lack of vitamin D is also a feature of modern western lifestyles that has a major impact on immunoregulation and has been implicated in schizophrenia (*McGrath* et al., 2010) as well as in several chronic inflammatory disorders (*Hewison*, 2010; *Poon* et al., 2004; *VanAmerongen* et al., 2004), and exposure to modern pollutants such as dioxins might drive pro-inflammatory Th17 cells via the aryl hydrocarbon receptor (*Veldhoen* et al., 2008).

Similarly, had space permitted there are other psychiatric conditions that could have been included in the discussion because of evidence for inflammatory components (attention deficit hyperactivity disorder [ADHD], and post-traumatic stress disorder [PTSD]) (*Oades*, 2011; *Sommershof* et al., 2009).

In conclusion, we suggest here that the pathways controlling brain development, stress responses and mood are so closely related to those controlling immunoregulation that they all need to be considered together. Breaking down the interdisciplinary barriers might focus more attention on the relevance of psychosocial stressors in inflammatory disorders, and more attention on the potential for anti-inflammatory and immunomodulatory treatments for psychiatric ones.

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