PERSPECTIVE

Regulation of the immune system by biodiversity from the natural environment: An ecosystem service essential to health

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Epidemiological studies suggest that living close to the natural environment is associated with long-term health benefits including reduced death rates, reduced cardiovascular disease, and reduced psychiatric problems. This is often attributed to psychological mechanisms, boosted by exercise, social interactions, and sunlight. Compared with urban environments, exposure to green spaces does indeed trigger rapid psychological, physiological, and endocrinological effects. However, there is little evidence that these rapid transient effects cause long-term health benefits or even that they are a specific property of natural environments. Meanwhile, the illnesses that are increasing in high-income countries are associated with failing immunoregulation and poorly regulated inflammatory responses, manifested as chronically raised C-reactive protein and proinflammatory cytokines. This failure of immunoregulation is partly attributable to a lack of exposure to organisms ("Old Friends") from mankind's evolutionary past that needed to be tolerated and therefore evolved roles in driving immunoregulatory mechanisms. Some Old Friends (such as helminths and infections picked up at birth that established carrier states) are almost eliminated from the urban environment. This increases our dependence on Old Friends derived from our mothers, other people, animals, and the environment. It is suggested that the requirement for microbial input from the environment to drive immunoregulation is a major component of the beneficial effect of green space, and a neglected ecosystem service that is essential for our well-being. This insight will allow green spaces to be designed to optimize health benefits and will provide impetus from health systems for the preservation of ecosystem biodiversity.

Numerous studies demonstrate that living close to the natural rural or coastal environment, often denoted "green space or "blue space," respectively, is beneficial for human health. It reduces overall mortality, cardiovascular disease, and depressive symptoms and increases subjective feelings of well-being (1–8). The beneficial effects are particularly prominent in individuals of low socioeconomic status (1–3, 8). It is often suggested that the mechanism of this effect is psychological. Looking at green spaces or walking in parkland or forests cause rapid psychological and physiological changes that can be demonstrated not only by psychological testing (4) but also by mobile elecroencephalograms (5) and by measurements of cerebral blood flow, various cardiac parameters, blood pressure, and salivary cortisol (6, 7). Even looking at the natural environment as images or through a window is said to have beneficial effects (9). Some authors explain this from an evolutionary perspective (10). The relaxation and satisfaction derived from the natural environment might represent the equivalent of "habitat selection" in other species (11). As shown recently by analyzing carbon isotopes in tooth enamel, from as early as 3–4 Mya, hominins were evolving in wooded grassland (12) and followed rivers and coastlines or settled near lakes. Thus, humans will have evolved to obtain psychological rewards from approaching these ideal hunter-gatherer habitats (10).

This psychological explanation is often supplemented by other factors: social interactions, exercise, and sunlight. For example, the natural environment might promote social interactions and a sense of community (13) when the natural environment is an important contributor to the social capital of the individual (14). Similarly green spaces sometimes encourage physical activity (15), although city-dwellers can walk to most resources and tend to do so, whereas individuals living in leafy suburbs are often forced to use their cars to get anywhere at all, so exercise can paradoxically decrease (16, 17). Sunlight is thought to counteract seasonal affective disorder (SAD) and has been used to treat tuberculosis and heal infected wounds (18, 19).

Although all these factors may contribute to the beneficial effects, there are two major uncertainties about the psychological component. First, there is the issue of specificity. Most psychological studies fail to include appropriate controls. It is not sufficient to compare exposure to a city street with exposure to a green space. Would any suitably relaxing environment—a quiet comfortable café, or a cinema showing a feel-good film in the urban environment—have the same psychological effects as green space when tested in comparison with a busy city street? [The other suggested benefits—social interaction, exercise, and sunlight—are clearly not specific for green space. Social capital usually derives from urban social interactions, and it has not been possible, using currently available data, to determine whether exercise taken in a green space is more beneficial than similar exercise taken in a city gym (20): there are undoubtedly health effects of exercise that do not depend on green space (21)].

The second uncertainty about the psychological explanation is the absence of evidence that the measurable rapid short-term psychological and physiological changes that follow exposure to natural environments (whether specific for such environments or not) translate into long-term health benefits. In other words, are these short-term psychological effects related in any way to the suggested health benefits of living close to green space for prolonged periods (reduced mortality, cardiovascular disease, chronic inflammatory disorders, and depression) (1, 2, 22, 23), or are they a separate transient phenomenon?

Summarizing the previous paragraphs, there is suggestive evidence that living close to the natural environment (defined here as nonbuilt, including gardens and agricultural land) has long-term health benefits (1, 2, 8).

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These benefits might be an additive consequence of several effects—an evolved psychological need, plus perhaps exercise, sunlight, and social interactions—but there are no conclusive data. This issue is crucially important because urban planners need to know whether urban green space is really the best way to achieve the beneficial effects, and assuming that it is, they then need to know the mechanism so that the health advantage derived from green spaces can be optimized. We suggest here that humans do indeed have an evolutionarily predetermined need for exposure to the natural environment, but that this has two distinct components. There is an immunological component that runs in parallel with the psychological one discussed above. This discussion is needed because the field is split into two distinct trains of thought that involve different aspects of our physiology (the brain and the immune system) and different scientific and medical disciplines. We hope here to break down these interdisciplinary barriers and show that these two pathways are likely to work together in ways that can usefully benefit urban planning for human well-being.

Hygiene Hypothesis and the "Old Friends" Mechanism

The high-income countries are undergoing massive increases in chronic inflammatory disorders (24–27). The cause is at least partly a failure of immunoregulation, so that the immune system is attacking inappropriate targets, such as self, harmless airborne antigens (allergens) and gut contents. At birth the immune system is like a computer (anatomical structures) that contains programs (genetics) but almost no data in terms of knowledge of molecular structures in the environment into which the child is born. It has some knowledge of self, acquired as lymphocytes mature in the thymus, and minimal knowledge of the outside world, transferred from the mother across the placenta. After birth, it needs microbial exposures to provide teaching inputs for several crucial reasons. First, exposure to a broad biodiversity of organisms builds up memory of diverse molecular structures that accelerates subsequent rapid recognition of novel dangerous organisms (28, 29). Second, microbial components taken up systemically from the gut maintain an essential background level of activation of the innate immune system (30). Third, and most important in the current context, the system needs to develop a network of regulatory pathways and regulatory T cells (Tregs) that stop inappropriate immune attacks on (*i*) self; (*ii*) harmless allergens; and (*iii*) gut contents (Fig. 1). If immunoregulation fails to stop immune attack on any of these categories of forbidden targets, the consequences are (*i*) autoimmune diseases such as multiple sclerosis; (*ii*) allergic disorders such as hay fever and atopic asthma; and (*iii*) inflammatory bowel diseases such as ulcerative colitis and Crohn's disease (Fig. 1).

Finally, the immunoregulatory systems must also turn off inflammatory responses completely when they are not needed. A failure to do this is regularly seen in high-income countries where persistently raised levels of C-reactive protein (CRP) are common (discussed in ref. 31). Persistently raised inflammatory mediators lead to increased risk of cardiovascular disease (32) and depression (27, 33, 34). In contrast, a longitudinal study of adults in a rural low-income country where there is exposure to high microbial burdens in childhood showed that they were able to shut off the inflammatory response when there was no need for it (31). More work is needed to discover whether the same is true in other low-income settings, whether biomass or biodiversity was more important, and whether the effect was attributable to bacteria, fungi, protozoa, helminths, or other organisms. Fig. 2 illustrates some of the categories of organisms (Old Friends) implicated in driving the immunoregulatory mechanisms (reviewed and referenced in ref. 35). The crucial point is that all these organisms needed to be tolerated. Some were part of our physiology (human microbiota). Others were harmless but inevitably contaminating food and water (environmental microbiota). Similarly, there were carrier states due to organisms picked up soon after birth and helminths that persist for life. Helminthic parasites needed to be tolerated because, although not always harmless, once they were established in the host, any effort by the immune system to eliminate them was futile and merely caused tissue damage such as elephantiasis (36). Thus, helminths are powerfully immunoregulatory and act as Treg adjuvants. For example, when patients suffering from early relapsing multiple sclerosis (MS) become infected with helminths, the disease stops progressing, and circulating myelin-recognizing Tregs appear in the peripheral blood (37, 38), an exciting observation that has led to formal clinical trials (39). This view is now well supported by experimental data and molecular mechanisms. Old Friends can be shown to drive immunoregulation and to block or treat models of allergies, autoimmune disease, and inflammatory bowel disease (40–42). Some Old Friends (including members of the human gut microbiota such as *Bacteroides fragilis*) or molecules that they secrete are known to specifically expand Treg populations (42–45) or to cause dendritic cells (DCs) to switch to regulatory DCs that preferentially drive immunoregulation (46). However, it is important to remember that the gut is not the only site where immunoregulation can be induced by macro- and microorganisms. Helminths such as blood nematodes that never enter the gut are powerfully immunoregulatory (36), and recent data implicate the skin and airways also (29, 47).

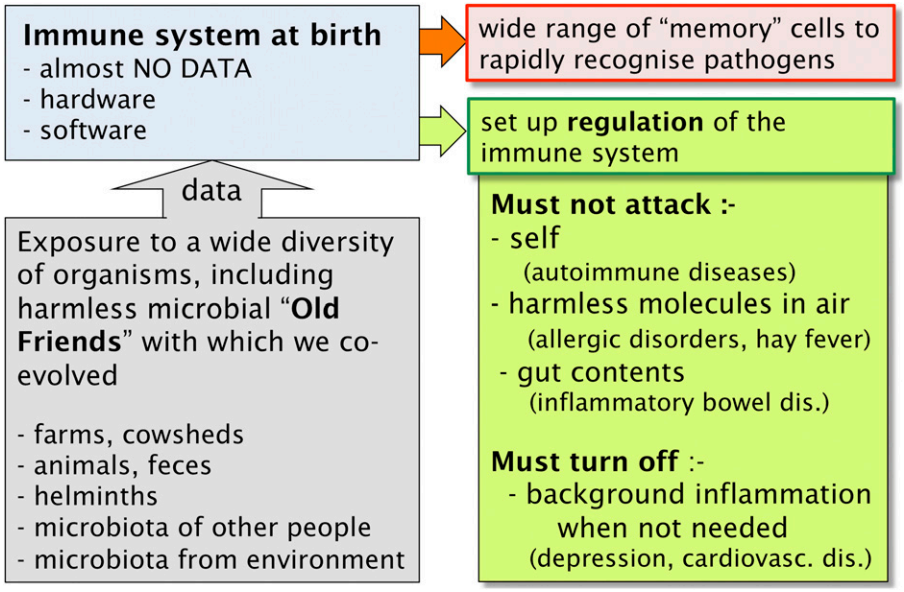

Fig. 1. The immune system does not develop normally in the absence of microbial inputs. In addition to a repertoire of potential effector cells, the system also requires regulatory circuits that inhibit damaging responses to inappropriate targets (such as self, trivial antigens in air, and gut contents) and that terminate inflammatory responses that are no longer needed. The disease groups that occur when immunoregulation fails are indicated in parentheses.

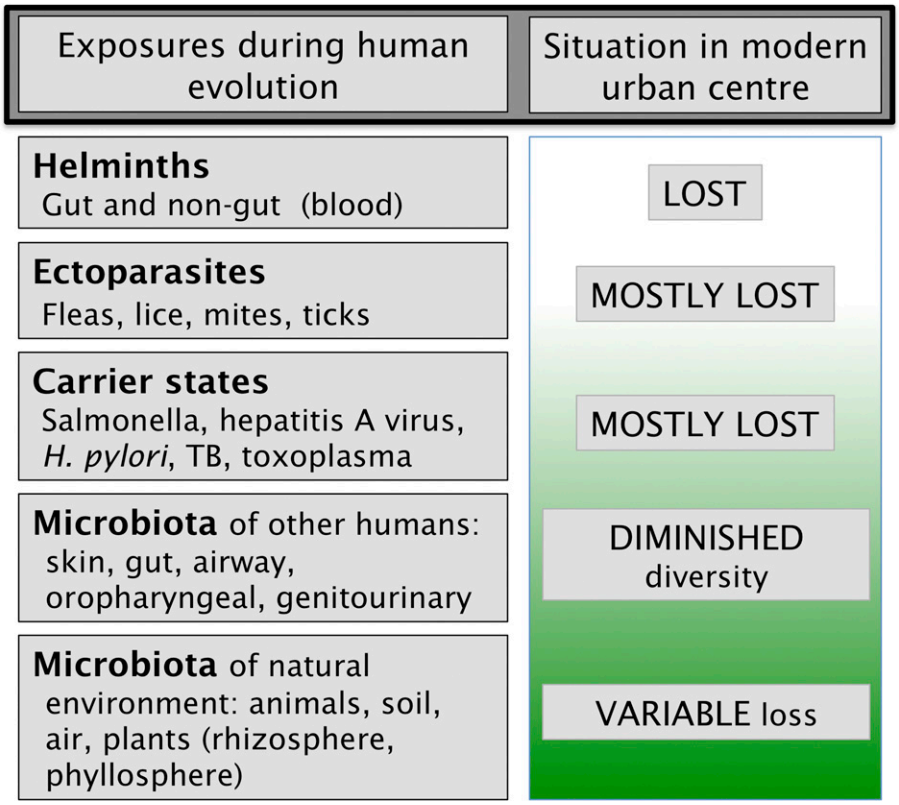

Fig. 2. A simple classification of organisms and parasites with which humans coevolved and that have been implicated by epidemiology or experimental models in the modulation of immunoregulation (although those listed as carrier states might be biomarkers of exchange of microbiota with other humans). The modern urban environment eliminates the first three categories, thus increasing our dependence on microbiota from other humans and from the natural environment.

In summary, it is now understood that the various classes of organism (Fig. 2) that had to be tolerated were entrusted by evolutionary processes with the role of setting up the immunoregulatory mechanisms and Treg populations. If this process fails, we develop susceptibility to chronic inflammatory diseases (24, 26, 37, 48), cardiovascular disease (49, 50), and some forms of inflammation-associated depression (27, 33, 51). This concept constitutes the Darwinian reformulation of the hygiene hypothesis in which the emphasis is on lifestyle changes that reduce our exposure to these immunoregulation-inducing Old Friends.

Progressive Loss of Microbial Inputs

Fig. 2 points out that in modern high-income societies, we have lost many of these categories of immunoregulatory Old Friends, so we are now much more dependent on the immunoregulation-inducing effects of the microbiota of other humans and on organisms from the natural environment. These sources of biodiversity are all that remain. However, increasing trends toward agricultural monoculture are likely to decrease rural microbial biodiversity because each crop is associated with strikingly different populations of bacteria, archaea, fungi, protozoa, nematodes, etc. (52). Similarly, the chronic inflammatory disorders that have risen strikingly in prevalence in developed high-income countries are usually found to be still more common in urban environments from which the immunoregulatory Old Friends are essentially absent (Fig. 2). This urban increase is true for allergies (53, 54), inflammatory bowel disease (55), and for autoimmune diseases such as MS (56–58). These urban-rural differences are equally obvious in psychiatric disorders (59). 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 (60), although a small minority of studies fails to find this urban-rural difference (61). Peen and colleagues also noted an increased urban prevalence of psychiatric disorders in general (38% more in urban communities) (60), and this is strikingly true for schizophrenia (62) and autism (63)—both of which involve an inflammatory component (64). It is usually suggested that these results are explained by greater stressfulness of urban life, or poor urban social networks, but data to establish these explanations are not provided (59). Meanwhile, an increasingly strong case can be made for the involvement of inflammation, secondary to failing immunoregulation in urban environments (27).

It should, however, be noted that not all studies find higher disease prevalences in urban rather than in rural environments. A study performed in the United States found no link between city-level greenness and heart disease and found greater overall mortality in greener cities, possibly attributable to greater car use (17). However, this city-level study did not provide data at the level of the proximity of the individual to green space. Moreover, it combined data from cities in cool wet environments with data from deserts, and apart from heart disease, did not document the chronic inflammatory disorders that are influenced by the immunological mechanisms discussed here.

Another situation that leads to a loss of exposure to microbial biodiversity is immigration from a developing country to a high-income urban center. This migration leads to rapid loss of the first three categories of organism shown in Fig. 2. In such immigrant populations, there are large increases in autoimmunity (27, 65–69), inflammatory bowel disease (55, 70, 71), depression (27, 72, 73), and allergic disorders (74–77). For allergic disorders, this has been rigorously documented for children adopted into Sweden from low/middle-income countries (75), for Mexican immigrants to the United States (76), and for immigrants to Israel from the former Soviet Union or Ethiopia (77).

Natural Environment and Immunoregulation

Some aspects of the Old Friends mechanism (such as immunoregulatory effects of helminths) are clearly not directly relevant to the green space phenomenon in high-income countries. Their absence merely increases our dependence on immunoregulation-inducing exposures from elsewhere, and the focus of this paper is the natural environment. Observations linking exposure to green environments and agriculture to protection from illness were made as early as the 19th century by Blackley who noticed that hay fever was rare among farmers (78). This observation has now been confirmed in many countries using rigorous epidemiological methods (54, 79). Moreover exposure to farms also protects from juvenile forms of inflammatory bowel disease (80). In agreement with the theme of this paper, recent studies indicate that the mechanism of this protection from allergic disorders involves exposure to microbial biodiversity (81).

Mattress dust was screened for bacterial DNA (48) and in a separate study samples of settled dust from children's rooms were gathered with electrostatic dust samplers and evaluated for bacterial and fungal taxa using culture techniques. In both studies, the diversity of microorganisms found was inversely related to the risk of asthma (48). Some of the microorganisms found in dust collected from protective farms have been shown to exert potent antiallergic effects in animal models (82–84) and constitute environmental Old Friends. Recently Hanski and colleagues recorded the skin microbiota as well as allergic sensitization to common allergens in an ecologically mixed area of Finland. Subjects living close to agricultural land rather than urban agglomerations had higher generic diversity of proteobacteria in their skin microbiota and less atopic sensitization (47). Similarly, a genetically homogeneous population living in Karelia is partitioned between Finland and Russia. In Finnish Karelia, the prevalence of type 1 diabetes is sixfold higher and childhood atopy is fourfold higher than in Russian Karelia. These differences are associated with strikingly different microbial populations in the home, with much greater diversity and many more animal-associated strains in Russian homes and more plant-associated species in the Finnish homes (85, 86). We cannot at this stage know whether the crucial factor is biodiversity, total microbial biomass, animal-derived organisms, or organisms from other environmental sources.

Microbial Diversity and the Air

What are the microbial exposures that result from proximity to the natural environment or farms or that fall onto settle plates in a child's bedroom? First, the air itself contains large numbers of microorganisms, some of which may actively metabolize and replicate in the air (87). Particulate matter in the air such as pollen carries a load of bacteria (88). Many airborne particles are more than 5 μm and will therefore be deposited in the upper airways, so that after being carried up the trachea by the action of cilia, they will be swallowed. Therefore, airborne microorganisms end up on the skin, in the airways, and in the gut where they modulate the immune system.

When total numbers of organisms in air were counted (i.e., not only the cultivable ones) levels of $10^5/m^3$ or more were regularly encountered over a grassy field on clear sunny days, and estimates approaching $10^6/m^3$ have been reported above shrubs and some grasslands (reviewed in ref. 89). The air in facilities housing agricultural animals can contain still higher numbers, reaching 10^7–10^8 archaea and bacteria/m^3 (90). Aerosols collected in Texas contained at least 1,800 different bacterial types, representing diversity comparable to that seen in some soils (91). Indeed bacteria commonly found in soil and water are abundant in outdoor air (92, 93). Recent samples from the upper troposphere contained variable proportions of bacteria thought to originate from soil, feces, fresh water, or the sea (94). Thus, blue space is another source of microbial biodiversity. Living by the coast does yield health benefits (8), and marine spray is a rich source of usually harmless microorganisms (95, 96). Interestingly, an organism that is not harmless provides proof of physiologically significant levels of intake of marine aerosols and their contained life forms. There is rapid (<1 h) onset of symptoms of brevetoxin poisoning while walking on beaches during algal blooms (97) and parallel increases in pulmonary problems at some distance inland from such beaches (98).

The microbial diversity that we encounter in the natural environment comes mostly from the soil and from plants and from any animals that are present (89, 92, 93). The microbiota of the soil has huge complexity, and is only now beginning to be explored in a global effort (www.earthmicrobiome.org/) (99). Our ignorance of what is out there remains profound, and these gaps in our understanding have been referred to as microbial "dark matter" (100). Tens of thousands of microbial species are associated with the rhizosphere (the below ground microbial habitat constituted by plant root systems) and the phyllosphere (above ground microbial habitats provided by plants). The crucial point is that plants are able to shape the microbiota of their rhizospheres (101). Thus, the nature of the vegetation in a green space will directly modulate the microbiota present in the soil, rhizosphere, and phyllosphere (102) and indirectly modulate the microbiota available from coexisting animal life. The nature, quantity, and diversity of microorganisms present is strikingly affected by agricultural practices (52), and it is likely that the modern trend toward vast areas of monoculture will reduce that diversity and further decrease exposure to immunoregulation-inducing organisms in wealthy countries.

Microbiota from Animals and Other People

The issue of microbiota derived from animals deserves further comment. The microbiota in dust from households with dogs is significantly richer and more diverse than that found in homes without pets (93, 103). This observation is interesting because exposure to pets, particularly dogs, in early life, protects against allergic sensitization and allergic disorders (104, 105). Moreover dogs were domesticated between 33,000 and 11,000 y ago, so humans have coevolved with dog microbiota for many millennia (106). Considered together with the protective effects of early exposure to cowsheds (79), other animal-derived strains (85), or animal feces (31), this might suggest that animals are a particularly important component of the natural environment. However, other humans are also relevant in this context. Some consider that social interactions are an important consequence of access to the natural environment, and it may be true that such interactions promote well-being by boosting social capital (13, 14), but they will also increase the diversity of organisms to which the individual is exposed. Teammates playing a contact sport tended to share a microbiota, but this converged with that of the opposing team after a match (107). Similarly cohabiting individuals tend to share microbiota (108). Interestingly people tend to share even more microbiota with their dogs (108), increasing exposure to the dog-associated microbial diversity mentioned above (93, 103). In sharp contrast, elderly people shut up in care homes with little variety in human contact (and little exposure to the natural environment) have diminished gut microbiota diversity that correlates with poor health outcomes and increased levels of biomarkers of inflammation such as IL-6 (109).

Microbiota of the Built Environment

The airborne microbiota of buildings is still poorly defined but can be different from that of the natural environment. The phylogenetic diversity of the airborne bacteria in mechanically ventilated rooms was lower than that seen in rooms ventilated via open windows or in the outdoor air itself (92, 93). Similarly the organisms derived from soil and water were abundant in samples of outdoor air but rare or absent from the indoor samples, which were dominated by organisms related to human pathogens and commensals (92). Air in cities tends to contain more particulate matter, such as diesel particulates and metallic fragments from subway wheels. *Micrococcus* species often dominate in urban air, perhaps associated with such particles (87, 110). The crucial point in the current context is that people living close to agricultural land have more biodiverse microbial populations on their skin than those living close to urban centers (47), and this correlates with immunoregulatory differences and reduced atopy. These organisms are also encountered via the airways and gut. By contrast, the use of biocides in the home may decrease microbial biodiversity (111).

Detrimental Microbiota in Unhealthy Buildings

This point leads on to a further problem with the environment in modern buildings. Humans evolved in a natural environment and

in contact with animals. Until recently even our homes were constructed with timber, mud, animal hair, animal dung, thatch, and other natural products and were ventilated by outside air. By contrast, modern buildings are constructed with synthetic materials, plastics, and concrete, and the timber and cardboard are treated with adhesives and biocides, and the buildings are ventilated by air conditioning systems. When these modern structures degrade, become damp, or accumulate condensation in cavity walls, they do not become colonized with the bacterial strains with which we coevolved. They become habitats for unusual strains that we did not encounter during our evolutionary history, some of which synthesize toxic molecules that we are unable to inactivate (112, 113). Some examples of "sick building syndrome" have been tentatively attributed to prolonged exposure to these inappropriate airborne microbiota (112, 113).

Environment and the Human Microbiota

To what extent does exposure to these various environmental sources of microbial diversity directly modulate the human microbiota? Do organisms from green space become members of the human microbiota, or are these organisms "pseudocommensals" that impinge on the skin, airways, and gut and have independent immunoregulatory properties? Both mechanisms probably occur, although there are rather limited data on these issues. The environment does play an important role in the formation and maintenance of our microbiota. Fig. 3 illustrates several potential mechanisms.

From birth, our microbiota are constituted by colonization with organisms from our mothers, from other social contacts (107, 108), and from the environment, and then further modified by factors such as diet and antibiotics (114, 115). Thus, the lifestyle of the individual has major effects on that individual's microbiota. The gut microbiota of children from traditional villages in Burkina Faso is totally different from that of Europeans (114). An interesting animal experiment compared piglets that were housed in a natural outdoor environment with genetically similar piglets that had been reared in a very clean indoor facility. Firmicutes, in particular *Lactobacillus* strains, were dominant in the gut microbiotas of the outdoor piglets, whereas the hygienic indoor piglets had reduced *Lactobacillus* and more potentially pathogenic phylotypes (116). The indoor piglets also had dramatically different patterns of gene expression in the ileum, discussed in the next section (116). Were these effects due to direct colonization by immunoregulation-inducing organisms from the outdoor environment (pathway A in Fig. 3), or did these organisms fail to colonize but exerted indirect effects on the immune system? The answer is unclear, but indirect effects certainly can occur in several ways. Some organisms compete with or antagonize established organisms (pathway B) and therefore alter the microbiota (117). Others alter the immune system directly (pathway D) or modulate the immune system in ways that lead secondarily to a change in the host–microbiota relationship, which in turn leads to changes in the microbiota (pathway C in Fig. 3). The last mechanism is well established in experimental models. Genetic manipulations of the innate immune system that have profound effects on immune function (such as gene knockout) often operate indirectly by altering the gut microbiota. The phenotypic effects can then be transferred to WT mice that have not been genetically modified, by transferring the altered microbiota (118, 119). It is the altered microbiota that is the proximate cause of the altered immunoregulation (118, 119). At least one environmental saprophyte that will not colonize (and is dead when used in experimental models and in human clinical trials), can be shown to evoke immunoregulatory effects that suppress allergic responses whether injected s.c. (120) or given orally (121) and also exerts antidepressant-like effects on the CNS (122). Probiotic strains such as some lactobacilli can at least temporarily colonize the gut and induce changes in the microbiota via a variety of mechanisms discussed elsewhere (117).

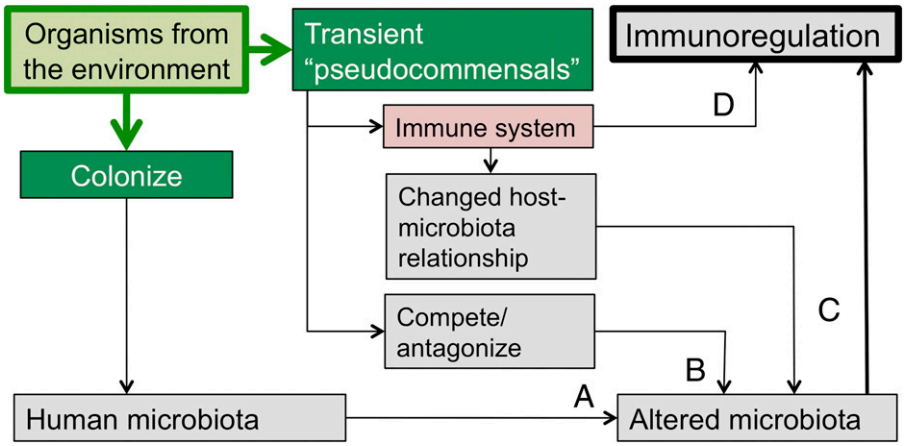

Fig. 3. Multiple ways in which the microbiota of the natural environment can modulate the immune system. This modulation may or may not involve colonization. There can be direct interaction with the immune system (pathway D) or indirect effects secondary to changes in the microbiota (pathways A, B, and C, fully explained in text).

Microbiota Diversity and Regulation of Inflammation

The piglets discussed in the previous section, which had been reared in clean interiors without exposure to the natural environment, had different patterns of gene expression in the ileum, much of it related to the immune system. For example, they had increased type 1 IFN activity, increased MHC class 1, and up-regulation of many chemokines (116), implying a more inflammatory state in the guts of animals whose microbiota had not been modified and diversified by exposure to the natural environment. This correlation between reduced gut microbial biodiversity and poor control of inflammation is a common finding. Mice exhibit at least two enterotypes (bacterial ecosystems in the gut microbiota), one of which has low biodiversity and correlates with biomarkers of inflammation (123). Gut microbiota of limited diversity is also characteristic of human inflammation-associated conditions such as obesity and inflammatory bowel disease (124, 125). Similarly, diminished microbiota biodiversity in institutionalized elderly people correlates with diminished health and raised levels of peripheral inflammatory markers such as IL-6 (109). Adequate microbial inputs are required to maintain diversity of the gut microbiota, and such diversity plays a role in the regulation of inflammation.

Microbial Biodiversity as an Ecosystem Service

Interestingly, provision of microbial biodiversity is not conventionally listed as an "ecosystem service." Ecosystem services are ecologically mediated functions essential to sustaining healthy human societies. Major reviews of these services do not contain the words inflammation or immunity (126, 127), despite the fact that the immunoregulatory roles of microorganisms have been known for decades. It is hoped that this perspective article will help to bridge the chasm between ecology and medicine/immunology, so that when ecologists consider how to maximize the services obtained from

ecosystems, the contained microbial biodiversity is taken into consideration.

Psychology vs. Immunology

The major conclusion of this review is that the beneficial effects of exposure to natural environments are likely to have two separate but interacting components. First, there are well-established rapid psychological effects that might be explained by an evolved psychological reward from contemplating the ideal hunter-gatherer habitat. However, the specificity of the effect for green space has not been proven by comparison with other relaxing environments, and the relevance of such rapid transient changes for long-term health benefits is unknown.

However, there is good evidence that the long-term benefit of exposure to the natural environment is one component of a broad range of effects that fall under the umbrella terms hygiene hypothesis or Old Friends mechanism or biodiversity hypothesis. These terms refer to the evolved need for the immune system to receive inputs provided by microbial biodiversity, and in particular, by organisms that need to be tolerated, and therefore have coevolved roles as inducers of the immunoregulatory pathways (26, 27). These immunoregulatory mechanisms help to stop chronic inflammation and its associated chronic inflammatory diseases, cardiovascular problems, and depression (27). Unlike the rapid psychological effects, this requires prolonged exposures, particularly important during childhood when much of the education of the immune system occurs. It might not be sufficient to encounter only the biased microbiota of the modern synthetic indoor environment that lacks the Old Friends and probably bears little resemblance to the microbiota we encountered throughout our evolutionary history. As illustrated in Fig. 2, modern life deprives us of many of the inputs that our immune systems evolved to anticipate, so we are now more dependent on the microbiota of other people and the microbiota of the natural environment and green spaces. Fig. 4 provides a list of probable components of the beneficial effects of the natural environment, with the parallel psychological and immunological explanations. It seems likely that both types of explanation are important. The underlying principle of the immunological explanation is that for many reasons, exposure to green spaces will lead to increased immunoregulation, resulting in lower background inflammation, manifested as lower resting CRP. Improved control of inflammation results in lower prevalence of inflammatory disorders, cardiovascular disease, and depression and increased stress resilience (27). It is interesting that sunlight and exercise both contribute to this effect.

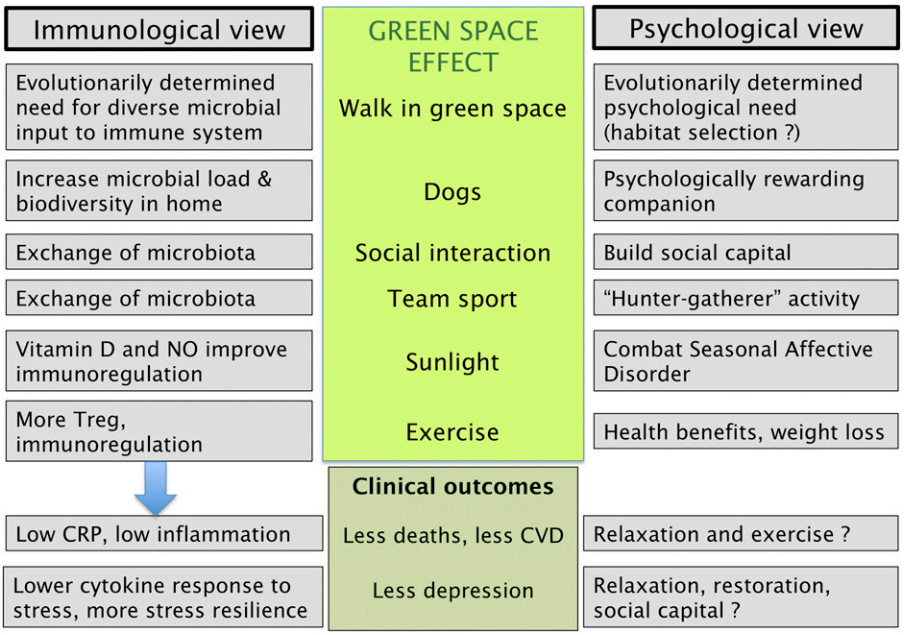

Fig. 4. Immunological and psychological explanations for the health benefits derived from contact with the natural environment. (NO, nitric oxide). There are many studies of exposures during the perinatal period that point to the immunological mechanisms, whereas most studies in adult life have been orientated toward psychological explanations, and have not included investigation of the immunoregulatory aspects.

Sunlight enhances production of vitamin D (128) and nitric oxide (129), both of which play critical roles in immunoregulation. Similarly exercise increases the activity of Tregs (21, 130). Therefore, multiple physiological consequences of exposure to the natural environment will supplement the immunoregulatory effects of microbial biodiversity.

Urgent Questions and Research Issues

Much research will be needed to consolidate this immuno-microbiological view of the health benefits of exposure to the natural environment. We need new epidemiological studies that concentrate on inflammatory disorders attributable to defective immunoregulation. More studies that use high sensitivity CRP levels as a surrogate biomarker for background inflammation will be valuable. We need more information about the organisms people encounter in their own homes and how this is affected by the proximity to natural environments and by the nature of that environment. Humans evolved as a grassland species, so we can guess, for example, that deserts and some types of monoculture might be less beneficial than grassland and its associated animals. The exposures of individuals can be monitored by sampling skin and gut microbiota and perhaps by studying antibodies. We have worryingly little knowledge about the relationship between environmental strains and those that colonize humans, because current methods of studying microbiota usually give only a broad taxonomic grouping.

If it turns out that the immuno-microbiological view is correct, we will also need to know when the educational and immunoregulatory inputs to our immune systems need to occur. At least some of the immunoregulatory effects of Old Friends are exerted very early in life. For example, factors that delay (caesarian births) or distort (perinatal antibiotic use) the establishment of the gut microbiota of the infant increase the frequency of allergic disorders (131, 132). Similarly, the reduced prevalence of allergic disorders after exposure to the farm environment only occurs if the exposure is during pregnancy or the neonatal period (79, 133). Does this mean that all these immunoregulatory effects occur during the perinatal period? Might it be sufficient to design preschool daycare centers so that infants are exposed to relevant microbiota? This view is unlikely because later childhood might also be important. For example, environmental factors, probably microbial, that influence the risk of developing MS in later life seem to operate during childhood up to the age of 10–15 y (65, 68, 69, 134). Therefore, could the problem be solved by ensuring the presence of appropriate organisms in homes and schools until after adolescence? This possibility also seems unlikely because we know that helminth infections, even when they did not enter the gut, were powerfully immunoregulatory even in adults (36–38), and there is mounting evidence that dysbiosis or diminished biodiversity of the gut microbiota is associated with a variety of inflammatory

conditions (109, 124, 125). There is a worrying lack of data on this point, but overall, it seems probable that most education of the immune system occurs in the perinatal period but that there is also an ongoing requirement for microbial inputs throughout life.

Conclusions

It is interesting that the beneficial effects of proximity to the natural environment are particularly prominent in individuals of low socioeconomic status (1–3, 8). Perhaps wealthier individuals are better able to supplement such exposures with holiday travel and rural second homes. This disturbing health gradient emphasizes the need for more research that will enable us to design urban green spaces that provide not only the psychological input to our brains but also an optimized microbial input to our immune systems. The research outlined above will help us to know what is needed and when. If a significant part of the role of the natural environment is to provide an appropriate airborne microbiota, then multiple, small, widely distributed urban green spaces of high microbial quality might suffice as supplements to a core of large recreational parks. There is already huge interest in the construction of roof gardens, vertical gardens and urban green spaces motivated by aesthetics and by organizations wishing to promote urban habitats for birds and insects and by urban planners wishing to delay the entry of rain downpours in sewer systems. However, we suggest that combating the epidemic of inflammation-associated illnesses in high-income urban environments provides another compelling motive for creating green spaces, and we hope that this paper will enhance collaboration between the medical profession, ecologists, and urban planners.

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