Helsinki alert of biodiversity and health

Leena von Hertzen, Bruce Beutler, John Bienenstock, Martin Blaser, Patrice D. Cani, Johan Eriksson, Martti Farkkila, Tari Haahtela, Ilkka Hanski, Maria Jenmalm, Juha Kere, Mikael Knip, Kimmo Kontula, Markku Koskenvuo, Charlotte Ling, Thomas Mandrup-Poulsen, Erika von Mutius, Mika J. Makela, Tiina Paunio, Goran Pershagen, Harald Renz, Graham Rook, Maria Saarela, Outi Vaarala, Marc Veldhoen and Willem M. de Vos

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Helsinki Alert of Biodiversity and Health

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1. Abstract

Urban living in built, asphalt-covered environments, combined with the use of processed water and food, may not provide the microbial stimulation necessary for a balanced development of immune function. Many chronic inflammatory disorders, including allergic, autoimmune, metabolic and even some behavioral disorders, are linked to alteration in the human commensal microbiota. Sedentary lifestyle is associated with reduced exposure to a broad spectrum of environmental microorganisms and surplus energy balance, both risk factors of chronic inflammatory disorders. According to the Biodiversity Hypothesis, an environment with diverse macrobiota and microbiota modifies and enriches the human microbiota, which in turn is crucial in the development and maintenance of appropriate immune function. These issues were discussed in the symposium "*Chronic Inflammation, Lifestyle and Environment*", held in Helsinki, August 20-22, 2014, under the sponsorship of the Yrjö Jahnsson Foundation. This paper briefly outlines the recent findings in the context of the environment, lifestyle and health; discusses the forces that undermine immune tolerance in urban environments; and highlights the possibilities to restore broken immune tolerance among urban dwellers, summarizing the main messages in four statements and calling for actions to prevent major public health threats.

2. Introduction

More than half of the world's human population lives in cities. In Europe the figure is 70%, and the degree of urbanization is increasing everywhere (1). Moreover, people spend more than 90% of their lives in buildings (2), with little physical activity. Sedentary lifestyle has become a serious concern in modern societies and increases the risk of many chronic diseases. Much time spent sitting is associated with diabetes but also with other chronic diseases, including heart disease, cancer, and high blood pressure, both in adults (3) and in adolescents (4). The situation is particularly alarming among children. Parental fears ('culture of fear'), loss of natural environments in cities, increasingly busy schedules of families, and the ever-increasing time in front of the screens are some of the factors involved (5,6).

Urbanization and other forms of land conversion have caused massive loss of biodiversity -affecting populations and species and their natural habitats– which is becoming a serious threat to humankind as loss of biodiversity adversely affects vital ecosystem processes related to the supply of food, water and energy as well as climate stability (7,8). Less attention has been paid on the significance of natural environments on human health and well-being. However, the awareness of the formerly rather abstract concept of biodiversity loss is increasing with the accumulating data of its adverse health effects (9, 10,11). The epidemics of chronic inflammatory diseases (allergic and autoimmune diseases, inflammatory bowel disease and even certain cancers and depression) (9,12-14) are prime examples of such effects. Exposure to natural environments enhances physical and mental health as well as cognitive functions (8,15). Urban upbringing and dwelling affect neural systems that influence social stress processing in humans (16) and may lead to mental diseases, particularly anxiety and mood disorders (17).

The global concern about biodiversity loss, sedentary lifestyle and their adverse health effects was the impetus for the invitational symposium entitled ***“Chronic Inflammation, Lifestyle and Environment”***, which gathered more than 100 scientists from Europe, USA and Canada under the sponsorship of the Yrjö Jahnsson Foundation on August 20-22, 2014 in Helsinki. This 3-day Jahnsson 60th Anniversary Symposium featured presentations by 25 top speakers to promote exchange of knowledge and ideas for further research and to create public health programs concerning chronic inflammatory diseases, sedentary lifestyle and built environments. This paper briefly outlines the recent pivotal findings in the context of the environment, lifestyle and health, discusses the forces that undermine immune tolerance in urban

environments, and highlights the possibilities to restore broken immune tolerance among urban dwellers. The main messages of the symposium are summarized in four summary statements.

3. The current public health challenge

Urban living in built, asphalt-covered environments with little green space, together with the use of processed water and food, may not provide us with the broad microbial stimulation necessary for the development of balanced immune function. Many chronic diseases including allergic, autoimmune, metabolic and psychiatric diseases, are linked to alteration in the commensal microbial communities (18-20) and disappearance of ancient vertically and environmentally-derived species from these indigenous communities (21).

Psychiatric diseases and the gut-brain-axis have gained much attention in the past years. Consistent evidence from animal models and increasingly also from humans indicates that there is a bidirectional communication between the gut microbiota and the central nervous system (CNS) –via neural, endocrine and immune pathways- that further affects brain function and behaviour (22). For example, stress appears to influence the composition of the gut microbiota, and the microbiota in turn stress reactivity (23). Further evidence of this communication has been obtained from human studies showing that a mixture of probiotics in long-term use alleviated psychological distress and affected activity of brain regions that control emotion and sensation processing (24,25). This interesting field of research has been comprehensively reviewed elsewhere (26).

Human microbiota has become a central issue in biomedicine and is expected to hold promise for the prevention and treatment of various long-term inflammatory conditions (27). Most research so far concerns the gut microbiota, but the skin and the respiratory tract microbes have increasingly been examined (28-31).

4. The Biodiversity Hypothesis and the role of microbes in immune tolerance

Biodiversity can be broadly defined as the variety of life on Earth. It includes the genes in all living cells, populations, species and their communities, the habitats in which they occur, and the ecosystems they comprise (Convention on Biological Diversity 1992, (<http://www.biodiv.org/convention/>)). The Biodiversity Hypothesis proposes that reduced contact of people with natural diverse environments, including

environmental microbiota, adversely affects the assembly and composition of human commensal microbiotas and may thereby lead to inadequate stimulation of immunoregulatory circuits and ultimately to clinical disease (10,11) (Fig 1.)

The hypothesis is based on the concept that pathogen recognition receptor signaling and the regulatory network activation are needed for the normal development and maintenance of immune function and regulation. A decade ago a series of studies by Rakoff-Nahoum et al (32) provided evidence that in the intestine signaling of Toll-like receptors (TLRs) by microbial ligands is crucial for the development of tolerance and epithelial cell recovery after injury. Many other studies have corroborated these findings (33,34), and immunological tolerance is, rather than an event of ignoring the invader, an active process driven by the host and microbes or bioparticles (35).

Certain members of the gut microbiota have been shown to influence development of regulatory T (Treg) cells and tolerance; they are able to induce Treg cell proliferation and IL-10 production by Treg or other cells. Such bacteria include *Faecalibacterium prausnitzii*, *Bacteroides fragilis*, certain *Clostridium*, *Lactobacillus* and *Bifidobacteria* species (36-38). In the skin microbiota, *Acinetobacter lwoffii*, has been identified, among hundreds of bacteria tested (39), as a strong immunomodulator (40). The list of such immunomodulators will certainly grow in the future. The principles of TLR signaling and Treg cell functions have been reviewed comprehensively elsewhere (41-43).

5. Factors involved in poorly developed or broken immune tolerance

5.1. Early and later life microbial exposure

Compelling evidence indicates that a child's early environment, including signals transferred by the mother in prenatal life, can decisively affect the maturation of the immune system and modify the disease risk in later life (44,45). Experiments on mice have revealed that maternal TLR- signaling (exposure to commensal/environmental bacteria) has a protective effect against asthma in the progeny (46). Novel findings suggest that transfer of microbes or microbial components to the child by the mother begins already in pregnancy (47,48), indicating that adequate microbial stimulation, not only postnatally, but also prenatally, may be necessary for normal immune development (20,49).

Environmental conditions may have effects that extend beyond several generations. The apparent heritability of cardiovascular and metabolic diseases may in fact stem from stressors experienced by (recent) ancestors early in life (50). Evidence from humans show that environmental conditions during pregnancy can change the birth characteristics and health in later life, not only of the children but also of

the grandchildren of a mother. Experimental data from rodents and other animal models have provided further support for such epidemiological findings (reviewed in 51).

The mechanisms involved in trans-generational effects of the environmental conditions include the inheritance of epigenetic alterations. For most cell types, the epigenetic marks (e.g. DNA methylation and histone modification) become fixed as soon as the cell differentiates or exits the cell cycle (52), whereas epigenetic alteration occurring in fully differentiated adult cells are restricted only to these particular cells (51). The epigenetic programming is the product of interactions between metabolism, microbiota as well as environmental (including perinatal stressors) and dietary factors (53). Multigenerational epigenetic studies in rodents have revealed that maternal diet-related effects on body length and weight as well as glucose tolerance are transferred to subsequent generations (54). It follows that our grandparents and our parents may have provided us repercussions of diverse, microbe-rich environments and food that have provided some protection in urban environments, but this protective effect is now becoming diluted and cannot be propagated to the next generations.

Immigration studies have provided further evidence of the significance of environmental factors in early, even perinatal, life in modulating the disease risk. This immunomodulatory effect has proven to be surprisingly consistent for both chronic inflammatory and psychiatric diseases (26). Although some adaptation occurs still in adulthood (10), many studies indicate that immigrants frequently retain the disease susceptibility level typical of their country of origin. The increase in disease risk (when moving from low to high risk area) often occurs first in the 2nd immigrant generation; important determinants in the disease risk of immigrants are thus the age at immigration and whether a person is the 1st or the 2nd generation immigrant (26).

5.2. Dietary factors

Diet affects the composition of the gut microbiota and thereby maintenance of immune tolerance, but can modulate immunity via direct effects on immune cells as well (55,56). Altered or poor microbiota, dysbiosis, contributes to compromised epithelial integrity and disrupted tolerance (57,58). Among the dietary factors, fat consumption (high-fat diets) profoundly affects gut microbiota composition (59). The deleterious effects of fat on the immune system and gut barrier may relay on the decreased expression of specific antimicrobial peptides such as regenerating islet-derived 3-gamma (Reg3g) and phospholipase A2 group-II (PLA2g2) in the intestine. Interestingly, dietary factors such as prebiotics can abolish these effects (60). Specific bacteria e.g. *Akkermansia muciniphila* may also reverse high-fat diet induced metabolic disorders and reinforce intestinal immunotolerance (61).

Comparisons of the gut microbiota of human populations living in geographically dissimilar areas have been enlightening. In addition to genetic factors, local environment and diet strongly modulate the composition of the gut microbiota (62,63), although in stationary conditions, these microbial communities remain relatively stable over time (64,65). The modulatory effect of diet on gut microbiota can also extend beyond generations. A recent study examined the influence of parental dietary fat consumption (Western diet and fatty acid profile) on offspring immunity in mice, finding that pups from parents on Western diet had worse outcomes in models of inflammatory diseases and heightened colonic inflammatory responses. The deleterious effects were related to alterations of the gut microbiota of the offspring (66). The concept of 'lard legacy' (54) was recently substantiated in a large epidemiological study with more than 13 300 elderly men and women born in Helsinki (67).

Obesity has been associated with reduced diversity of gut microbial communities. Murine models, in which gut microbiota from fat mice has been transferred to germfree or lean mice, have provided some evidence for a causal link between microbiota and obesity (reviewed in 68), though the opposite, namely that obesity affects the composition of the gut microbiota, is also plausible. Not only caloric excess but also long-term caloric restriction may lead to changes in gut communities. Experimental studies in mice have indicated that prolonged caloric restriction increased the proportion of lactobacilli and other bacterial taxa associated with health benefits and lengthened lifespan (69). In this context, immigrant studies would be valuable for elucidating long-term consequences of dietary changes upon the gut microbiota.

In addition to caloric contents, also the composition of the diet is of key importance. Due to the activity of gut microbes, rural diets rich in fiber and starch will promote the generation of short chain fatty acids, including butyrate, a potent non-selective inhibitor of histone deacetylases (HDAC), a group of enzymes critical for the regulation of transcription and cell signaling. Indeed, low doses of HDAC inhibitors have proven benefit in animal models of inflammatory diseases and clinical trials of human inflammation (70). Butyrate is circulating in micromolar concentrations (Cani unpublished) ensuring sufficient coverage to inhibit HDAC activity in tissues. Thus, the environment is linked to diet, microbiota and inflammatory diseases via molecular mechanisms that we are only starting to understand. This understanding can form the basis of public health interventions.

5.3. Home and its surrounding

A number of housing and lifestyle characteristics, including the type of dwelling, affects the quantity and diversity of microbial exposure in home environments (71,72). Examination of house dust has provided valuable information of the exposure to microbes in different home environments. House dust from urban environment is poor in microbial components and has biased immunomodulatory capacity as compared with dust from farm environment (73). The link between microbial richness of farm/rural dust and health has indeed been shown in a number of studies (74,75). In addition to house dust, drinking water, milk, pets, unprocessed food as well as activities in nature are examples of everyday microbial exposures. Everything what we eat, drink, touch and breath is reflected in our commensal communities (Fig. 2).

Living in rural areas with agricultural and forested land is well known to confer protection against inflammatory diseases (reviewed in 76,77), but the protective factors at the molecular level are still only partly understood. A recent study showed that land-use around the home (within a radius of 3 km) affects the composition of the skin microbiota; classes of proteobacteria were more frequent in environments with more agricultural land and forests (39). Contrasting healthy versus atopic individuals (elevated specific IgE values to inhalant allergens), the same study showed higher generic diversity of gammaproteobacteria on the skin of healthy than atopic individuals, and that the relative abundance of one gammaproteobacterial genus, *Acinetobacter*, correlated positively with the (unstimulated) expression of anti-inflammatory IL-10 by peripheral blood mononuclear cells (PBMC) in healthy individuals (39) and conferred protection against allergic responses in mice (40). These results provide support for low biodiversity in the environment being associated with reduced commensal microbiota, which in turn increases the risk of inflammatory condition (78,79).

An illustrative study in piglets, all from the same colony, revealed that environmental exposure in early life decisively affects not only the gut microbiota in later life but also the immune transcriptome during development. Outdoor rearing was associated with the establishment of diverse microbiota and immune function, whereas indoor-housed animals showed altered gut microbiota, increased expression of pro-inflammatory genes, and reduced numbers of T reg cells (80,81).

A series of recent population-based studies has shed light on the relationship between green environments and health. One study included 267 000 randomly selected individuals in New South Wales, Australia. Percentage of green space available for recreational and physical activities within 1 km radius around the residence of each participant was measured. Comprehensive data on health, behavioral, socioeconomic and geographic aspects were collected using a questionnaire. After controlling for potential confounders, individuals living in greener surroundings have a significantly lower risk of diabetes and, particularly in women, of overweight and obesity, independently of physical activity and sitting time (82), in line with the

findings of an earlier study on green environment and health (83). In addition, greener surroundings seemed to be linked to longer/better quality of sleep, and this association remained after controlling for psychological distress, physical activity and socioeconomic factors (84). People living in greener environments also walk more and are more engaged in moderate-to-vigorous physical activity (85). Nonetheless, the health benefits of green space are not explained by exercise only as shown in these and other studies (86,87).

The availability of green space is an important but not the only determinant of the use of green areas. An individual's attitude (orientation) to nature and, in fact, the attitude towards nature may be an even stronger determinant for the use of green space among urban dwellers than the availability of green areas as such (88).

5.4. Sedentary lifestyle

Disconnection of man and nature has had consequences that are unexpected and multi-faceted. Our generation's children have been claimed to suffer from 'nature-deficit-disorder' (5), a disorder that results from inactivity and staying indoors and includes various behavioral and health problems. Urbanization and economic welfare have led to sedentary lifestyle - inactivity has become a normal state of living from the early childhood. Our lives have become increasingly dominated by technological advancements nudging us towards physical inactivity. The new innovations, while labor- and time-saving reduce the daily energy expenditure (89). A recent report from the US reveals that young people at the age of 8 to 18 years spend on average roughly 7.5 hours per day consuming some forms of electronic media (90). Sitting has become the cardinal feature in western lifestyle, and particularly work-associated sitting is a serious public health concern as it is difficult to target.

Exercise is beneficial for human health, but the scientific basis for the epidemiology of physical activity was laid only 60 years ago. Morris and coworkers showed in 1953 that bus drivers were at a substantially increased risk of cardiac events than were their physically active conductor peers (91). Physical inactivity is indeed a risk factor of the same magnitude as tobacco for poor health (92). Physical inactivity may account for 6-10% of all deaths from the major chronic diseases (coronary heart disease, type 2 diabetes, breast and colon cancer), which means 5.3 million of the 57 million premature deaths worldwide (93). At the molecular level, physical activity directly decreases the levels of inflammatory markers, CRP, TNF and in most studies also IL-6, increases Treg cell numbers and enhances the production of IL-10 and TGF β (94, 95), indicating clear anti-inflammatory properties. In asthmatic school children, physical training for 3 months

decreased both total and allergen (mite)-specific IgE levels (96). However, physical activity still remains a largely neglected aspect of prevention and intervention of non-communicable diseases (92).

5.5. Antibiotics

Recent evidence from humans indicates that the use of the most common antibiotics, β -lactams and macrolides, not only disturbs the composition of the gut microbiota (by decreasing its diversity and reducing the number of core taxa (97), but can also affect many metabolic functions, including sugar metabolism and synthesis and degradation of intestinal/colonic epithelium components (98). Resilience of the gut microbiota often takes months after the cessation of the antibiotic use, although there are great variations between different antibiotics; their effect on the gut microbiota is dependent on the properties of the antimicrobial agent, and the structure, function and resistance genes of the microbial community (99). Long-term effects of these metabolic changes in the gut community still remain largely unknown.

Helicobacter pylori, an ancient member of the human gut microbiota, is an example of indigenous organisms in the human gut that were earlier common, but are now progressively disappearing. This disappearance, due to changes in the environment, lifestyle and behaviour, has been associated with the rising trends of chronic inflammatory diseases, such as asthma and allergies (21). In general, our indigenous microbiota has gradually changed and evidently we are losing many ancient, vertically and environmentally-derived species that likely have had an important role in fine-tuning the immune responses.

6. Restoring broken tolerance

The adverse health effects of the disconnection of man from natural environments (100) are increasingly acknowledged. Identifying the specific factors involved is a prerequisite to strategies to restore the current situation. Sedentary lifestyle is associated with reduced exposure to environmental microbiota, together with reduced exposure to sunlight (and vitamin D), and often with surplus energy balance, all factors involved in immunity and inflammation (101). An environment with diverse macrobiota and microbiota modifies and enriches the microbiota on human skin and mucosae, which may have far-reaching consequences in conferring protection against chronic inflammation, together with dietary and other lifestyle factors. Readopting traditional dietary and lifestyle patterns, at least partly, could improve our health (101), but is difficult to attain in modern urban setting. Increasing the amounts of locally produced

fresh fruits, berries and vegetable in our diet is beneficial, not only due to their nutritional values but also due to the high amounts of environmental friendly bacteria they carry on their surfaces (102).

As exposure to environmental microbes clearly affects the composition of the indigenous microbiota and the development of the immune system, *how can a healthy balanced microbiota be obtained and maintained in urban environments?* Manipulation of microbiotas, evidently very early in life, even prenatally (20), may at best provide an opportunity to change the courses of chronic inflammatory diseases (103). Alterations in commensal communities may also give clues of early stages of these diseases (104-107).

7. Connecting people with nature

In most studies, microbiota associated with health are more diverse than those associated with various diseases (107-109). The diversity of the indigenous microbiota is linked to diversity of microbiota and macrobiota in the living environment (39), according to the biodiversity hypothesis (10,11).

Adopting old-fashioned lifestyles and diets is hardly a realistic alternative in industrialized and urbanized work-oriented populations. Reconnection to nature should be built in early life to get the greatest benefits, e.g. we need more outdoor kindergartens and family/school nature clubs. We need changes in attitudes; physical activity should be a part of our daily routines. The benefits of nature in stress coping should be more acknowledged. Locally produced, unprocessed food should be preferred. The significance of what we eat, touch and breathe must be underscored. Politicians in urban planning should take into account people's need of natural environments and possibilities for physical activity in the near surroundings.

One effective tool to increase people's nature orientation and awareness of the health effects of nature contacts could be a national or local programme aiming at reconnecting people to nature and reducing their daily sitting time. For example, in Finland, both the National Asthma Programme 1994-2004 and the ongoing National Allergy Programme 2008-2018 (110, Haahtela, unpublished) have been successful. The National Health & Nature Programme, with clearly defined goals, tools and outcome measures, targeted to both health professionals and the whole population, could be carried out in the wave of these earlier programs, based on the large experience from their implementation. New measures to reverse the increasing trends in prevalence of chronic inflammatory diseases are necessary as the old ones have been mostly ineffective.

An interesting example of practical, grassroots action plans is the Australian initiative launched in August 2014. This 'Green Army' programme is targeted to young people, aged 17-24 years, to generate real benefits for the country, e.g. restoring and protecting habitat, weeding, planting and cleaning local environments as well as conserving cultural places. Participants, working in teams of 10 persons for 6 months, are school leavers, gap year students, graduates, unemployed job seekers and so forth, and they are paid a wage, similar to that of traineeship, by the state. The programme, in addition to improving local environments, provides young people training, skills, experience and physical activity in nature (111).

8. Concluding statements

Biologically diverse environments modify and enrich our indigenous microbiota, which are fundamental for the development and maintenance of a balanced/well-functioning immune system. Changes in microbiota on skin and mucosal surfaces are linked to dysfunction in the regulatory network and broken tolerance. Dysbiosis in the gut microbiota has been associated, not only with immune-mediated intestinal diseases, but also to many extra-intestinal inflammatory conditions (18).

Chronic inflammatory diseases in the context of increasing loss of biodiversity and increasing prevalence of sedentary lifestyle were the topics of the 60th Anniversary Yrjö Jahnsson Symposium. The following summary statements emerged:

1. The epidemics of chronic inflammatory disease are largely the result of reduced exposure to natural environments, sedentary lifestyle and changed diet. Naturally biodiverse environments include ancient micro-organisms important for human health.
2. Environmental biodiversity is reflected in the diversity of human skin and mucosal microbiota. Diversity is a central element of healthy microbiota in reducing the risk of chronic inflammatory diseases.
3. A National Health & Nature Programme (action plan) is needed to increase awareness of nature's health effects, and to affect attitudes and orientation. Especially important is to target children and adolescents; both the environment and the youngsters would benefit.

4. Politicians and stakeholders in urban planning must become more aware about the effects of natural environments on human health. People are not moving in masses back to the countryside, but elements of country life should be moved to cities, including measures that increase the diversity of microbiota.

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Legends for figures

Figure 1.

Biodiversity loss, together with sedentary lifestyle and unhealthy diet, may lead to immune dysregulation, poor tolerance and ultimately to clinical disease. Modified from (112).

Figure 2.

‘We are what we host, and we host what we eat, touch and breathe’. Outdoor activities in biodiverse environments together with unprocessed food can provide us microbial exposure necessary for the development and maintenance of healthy balanced microbiota and immunoregulatory circuits.

Biodiversity and health

Acquisition/maintenance of healthy indigenous microbiotas

- Diet, drinking water, milk
- Pets in household, farm animal contacts
- Land-use type in the surroundings
- Dwelling type, housing characteristics
- Lifestyle, daily sitting time
- Outdoor activities, nature contacts
- Vertical transmission