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AS I SEE IT

Biodiversity, microbes and human well-being

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ABSTRACT: The biodiversity hypothesis postulates that the rapid increase in the prevalence of allergies, asthma and other chronic inflammatory disorders in developed countries in the past few decades is caused by loss of biodiversity, which reduces human exposure to beneficial environmental microbes with essential immunoregulatory functions. The biodiversity hypothesis builds upon Graham Rook's 'old friends' concept, which highlights the long-term evolution of the human immune system with a diverse assembly of microbes. I describe a case study showing that the incidence of atopy (allergy sensitization) in adolescents decreases significantly with an increasing amount of forest and agricultural land in the surroundings of their homes. Environmental microbiota as part of broader biodiversity provides a tangible but little appreciated 'ecosystem service', which is vital for every individual.

KEY WORDS: Biodiversity · Environmental microbiota · Immune tolerance · *Proteobacteria* · *Acinetobacter*

INTRODUCTION

It is hard to convince people — politicians and ordinary citizens alike — of the importance of conserving biodiversity. Arguments about a 1000-fold increase in the rate of species extinctions compared with the background rate (Millennium Ecosystem Assessment 2005) make little impact, because these arguments make no real connection to people's own experience, hardly any more than arguments about the number of stars in the Milky Way do. It does not help biodiversity conservation that scientists may have a better estimate of the number of stars in the Milky Way than of the number of species on this planet (Mora et al. 2011). When people are told that there are at least a few million species, many will wonder whether it really matters if a few species go extinct on remote islands. Does it really matter how many thousands of species of insects inhabit decaying tree trunks in forests? People do understand the problem with fish stocks, but then again there are other issues to think about, such as how many thousands of people are already unemployed, or what the impact of fishing quotas on economic growth would be. Calculations about ecosystem services make some impression — farmers at least understand the value of pollination 'services'. But then again, what really matters is pollination, not how many species do this service. Ethical arguments about the intrinsic value of species, and of biodiversity, are appreciated by a few people, though mostly by the same individuals who understand many other arguments as well. Increasing numbers of people are willing to consider that great apes should have 'ape rights', and most people agree, publicly or privately, that they are our distant relatives. Hundreds of millions of people are feverishly attached to their pets, but there is a perplexing disparity in people's attitudes toward pet mammals versus mammals used for meat, milk, egg and fur production.

Realistically, biodiversity will continue to decline until some really tangible evidence about its significance to human well-being, including both immediate and long-term emotional, health and material

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benefits in a broad sense, emerges. This may happen at some point, though perhaps not before a massively large fraction of populations and species have gone extinct, or effectively extinct, and probably only in the context of many other environmental, social and economic disasters. In fact, huge numbers of people already suffer from biodiversity loss in developing countries, but they also suffer from so many other consequent hardships that one of the root causes, loss of biodiversity, may be hard to recognize.

I have met people who take some comfort in the thought that, whatever the human impact in the coming decades and centuries, we will not eradicate all life on Earth. There are indeed large numbers of species of animals, plants and fungi that are even more resilient than our own species, to say nothing of microbes, which occupy the full range of environments from bedrock and deep ocean bottoms to the upper atmosphere, covering environments that are already so inhospitable to life that we can hardly make them worse. Humans have supposedly eradicated smallpox, a viral disease that emerged in the human population at the time of the shift to agriculture around 10 000 yr ago, but this is an exception. Microbial life has been present on Earth for more than 3 billion yr, and microbes comprise the hard core of life — microbes run the world. If they were not here, we would not be here, whereas the reverse is not true. In the words of Stephen Jay Gould, the celebrated American evolutionary biologist, we live now in the 'Age of Bacteria' — and this planet has been in the 'Age of Bacteria' since the beginning of life.

Microbial life may appear so infinitely diverse and adaptable that one might wrongly assume it to be entirely invulnerable to human actions. One difficulty here is that censusing microbes in the environment is much harder than counting birds and butterflies. Only in the past decade have what I would call near-miraculous advances in molecular and genomic research produced the tools that are needed to conduct comprehensive microbial surveys. One area of research that is flourishing is the study of microbes in our own bodies. The massive Human Microbiome Project (Human Microbiome Project Consortium 2012a,b) aims to describe the entire community of human commensal microbes and their functions. We know that our bodies have an order of magnitude more bacterial cells than our own cells, and in terms of the number of genes, the difference is even greater — 2 orders of magnitude. And we know that the interactions between our cells and the microbial cells impact a wide range of biological processes, not just digestion in the gut. For instance, recent research has demonstrated that the gut microbiota influences brain development and adult behavior in mammals (Diaz Heijtz et al. 2011). However, the interactions among environmental microbiota, the native microbiota in our bodies and our health are less well known. To draw attention to these interactions, and their significance for both human well-being and biodiversity conservation, I have proposed, with my colleagues, 'the biodiversity hypothesis' (von Hertzen et al. 2011, Hanski et al. 2012). Below, I narrate how the biodiversity hypothesis emerged from interactions between ecologists, molecular biologists, allergy specialists and immunologists — a refreshing experience of truly bottom-up interdisciplinary research for all involved.

THE BIODIVERSITY HYPOTHESIS

I had known Tari Haahtela as a professional butterfly photographer who has published with his associates books on Finnish and European butterflies. But this is not his profession; he is a medical doctor specializing in allergy. In early 2010, we both attended a national meeting in Helsinki, where I talked about the rapidly declining biodiversity and Tari talked about the rapidly increasing prevalence of allergies, asthma and other chronic inflammatory disorders. After the talks, Tari came to see me and started to explain that, surely, these 2 global megatrends must be related. He had much to say about the molecular basis of allergy, which I struggled to understand. But I understood the main point, which was that we need microbes to train our immune system. And biodiversity includes microbes. Tari invited me to join the next meeting of his research group. I did, and the meeting turned out to be the beginning of a new line of research for a highly interdisciplinary group of researchers. The excitement in the room was memorable.

Tari's research group is called KARA — the Karelian Allergy Project. Karelia is the name of the region that extends across the current national border between Finland and Russia, which was until recently, and to some extent still is today, an abrupt boundary as far as people's standard of living is concerned, even though the distance is short and the natural environment is the same. What Tari and his colleagues have documented is a dramatic difference in the prevalence of allergies and asthma across the border, and a striking difference in the temporal trend: the younger the study subjects, the higher the

prevalence of such disorders, but only in Finland, not in Russia (von Hertzen et al. 2006). People in Russian Karelia have all kinds of other health problems, many of which are related to alcohol abuse, and the expected lifetime is much shorter than in Finland — but people in Russian Karelia do not suffer from allergies. The explanation in a nutshell, explained Tari, has to do with the impoverished microbial contacts of people in Finland and the reduced immunoregulatory service of microbes, especially in young children. The critical shortage could be due to the abundance and composition of microbes at home, but could it also be due to the contact with microbes in the surrounding environment outdoors? We started to talk about the biodiversity hypothesis (von Hertzen et al. 2011).

My task, as an ecologist, was to figure out what could be done in practice to characterize environmental biodiversity. We quickly realized that extending the research to Russia was not an option at this time, hence studies could only be conducted on the Finnish side. But that was not a problem, perhaps it would even be an advantage, as the results would not be dominated by the striking contrast across the border. Tari's group had studied a cohort of young school children in 2003, randomly selected across a heterogeneous region some 100 × 100 km in area, including a small town, villages of different sizes and isolated farmhouses in the rural area. Importantly for our project, the vast majority of these adolescents had not moved homes, hence each of them had been exposed to the same environment for all of their life, but different individuals to different environments. This group of study subjects would be ideal for determining whether differences in the environmental biodiversity around the home make a difference to health. We decided to act in the autumn, recruiting the same kids for another round of sampling. Blood samples would be taken to measure immunoglobulin E (IgE) antibodies, a marker of atopy (allergic sensitization). The immunologists in our group planned to measure the expression of other molecules that would reflect pro-inflammatory and anti-inflammatory immune responses. But what about biodiversity? What kind of biodiversity might matter, and even more importantly, what kind of data could be collected in practice? I came up with 3 answers. First, having the spatial coordinates of the children's homes and high-resolution remotely sensed data, we could describe the land use around each home. I decided that a radius of 3 km would delimit the right spatial scale, and that a simple classification consisting of forests, agricultural land, built-up areas, water and wetlands would do. Second, I hired a group of my students to visit the yards of every home to census all vascular plants; plant diversity around the homes would be our second measure of biodiversity. We then considered measuring microbial diversity in the environment, but decided that we did not know how to sample it in a meaningful manner with the resources available. But something we could do was to characterize the microbes in the bodies of the study subjects. Here, we decided to focus on bacteria on the skin, partly because this was easy to sample — a swab of the forearm — and partly because many contacts with the environment presumably take place via environmental microbes colonizing the skin.

THE HYGIENE HYPOTHESIS AND 'OLD FRIENDS'

David Strachan from the London School of Hygiene and Tropical Medicine published a very short paper entitled 'Hay fever, hygiene, and household size' in 1989 (Strachan 1989). Strachan analyzed the epidemiology of hay fever using data for 17 414 British children, and he concluded that his results could be explained 'if allergic diseases were prevented by infection in early childhood, transmitted by unhygienic contact with older siblings…' (Strachan 1989, p. 1260). Strachan's short paper has become a citation classic, which is used when researchers want to refer to the 'hygiene hypothesis', although Strachan himself did not use such a term. As a matter of fact, more recent research has shown that infectious diseases are not necessarily that beneficial, nor is hygiene critical in the sense envisioned by Strachan. On the contrary, and as we all know, many infectious diseases remain a huge health concern. Strachan's paper is nonetheless an important milestone — it pushed a new line of inquiry into motion.

Most infections that we are familiar with, including influenza, are caused by viruses. Our ancestors in the distant past did not have them, because the disease agent could not persist in sparse hunter–gatherer communities. This is the reason why vaccination works: vaccination reduces the susceptible population, which is not immune and can be infected, below a critical minimum size called the eradication threshold. The current infectious diseases began to spread in the human population following the Neolithic revolution, which gave rise to agriculture and bigger and more permanent settlements, and eventually to towns and cities. The infectious diseases that then

emerged, in one way or another, have not been around for a long time in the human population, only for some hundreds of generations, and although they may have influenced our biological evolution in some ways, any such influence is necessarily rather superficial. The situation is entirely different with those parasites, such as helminths, which do persist in low-density host populations, and with microbes that crowd the environment and our own bodies. Microbial life evolved more than 3 billion yr ago, and it is clear that our ancestors, however long back in time you want to consider, have been interacting with microbes during all our evolutionary history, and hence microbes have fundamentally shaped 'our' biology. All these microbes are not in our bodies just for our benefit, of course, but we know that many microbes interact with our cells to the extent that we could hardly survive without them. It would be unethical to do experiments on humans to show that, but researchers have done it many times with mice. The point is that our biology, for instance our immune system, has evolved in interaction with a diverse assembly of microbes. In one extreme case, the mitochondrion, the microbial companion is already part of 'us', so that it took a generation or two of researchers to find out what had happened (and arguments may still remain). The other extreme is truly commensal microbes, for which we provide temporary habitat but which do not affect us. The rest are somewhere in between. These are the ones that Graham Rook likes to call our 'old friends' (Rook 2009, Rook et al. 2014). These companions of ours are old because they have been around during all our evolutionary history; and they are friends, because they increase our well-being, in particular having a critical immunoregulatory role to play.

Graham Rook has likened our immune system to a computer that has genetically inherited mechanisms (programs) but lacks data. Our interactions with parasites and microbes, especially in infancy and early childhood, provide the database that is necessary for the immune system to react — but not to overreact! The immune system needs to develop a network of regulatory pathways and regulatory T cells that stop inappropriate immune attacks on self, harmless allergens and gut contents (Rook et al. 2014). Helminths and other parasites represent one class of organisms that provide such training to our immune system. Infections by helminths are not necessarily harmless, but once the parasite is established there is little that the immune system can do to get rid of it without causing even more damage to the host. Microbes inhabiting our gut, airway, skin and other body parts play a big role, but so do bacteria, archaea, fungi, protozoa and viruses that enter our bodies with food, water and air and via our various contacts with the environment. I like to consider the human body as a 'habitat patch' for these microbes. We have our current, more or less permanent residents, which are transmitted among parents and their offspring and among other individuals, but there are billions of hopeful newcomers from the environment, colonizing us daily, which may establish temporary or more permanent populations in the 'habitat patch' and interact with it just like the previous residents. Over the course of time, the present more permanent residents have presumably been assembled from these colonists, and this process must continue today. Here we come to the question that we wanted to address in our research: what difference does it make to the functioning of our immune system and our general well-being which kind of environment, and therefore which kinds of microbes, we happen to interact with? The biodiversity hypothesis is a version of the 'old friends' concept, with a focus on the influence of the environmental biodiversity on our immune system.

RESULTS

So does the environment around us influence the kinds of microbes we have in our bodies? There is clear evidence showing that the type of food we consume affects the composition of gut microbiota (Wu et al. 2011), which is not surprising, as the microbes in the gut obtain their nourishment from what we swallow, and different microbes are specialized, to some extent at least, to use different resources. In our project, we sampled the skin microbiota. Comparing adolescents with more or less forest and agricultural land within a 3 km radius from the home, we observed a clear pattern, which is shown in Fig. 1: the more forest and agricultural land around the home, the more *Proteobacteria* on the skin. *Proteobacteria* comprise nearly half of all prokaryotic genera and include the majority of Gram-negative bacteria of medical, veterinary, industrial and agricultural importance. Most *Proteobacteria* are free-living and they are very common in soils. One study (Eilers et al. 2009) found that the relative abundance of *Beta-/Gammaproteobacteria* (both classes of *Proteobacteria*) ranged between 2 and 20% in different soil types, making it reasonable that they would show much variation along the environmental gradient in our study (Fig. 1).

Many *Proteobacteria* are pathogenic, which may cast doubt on their beneficial immunoregulatory

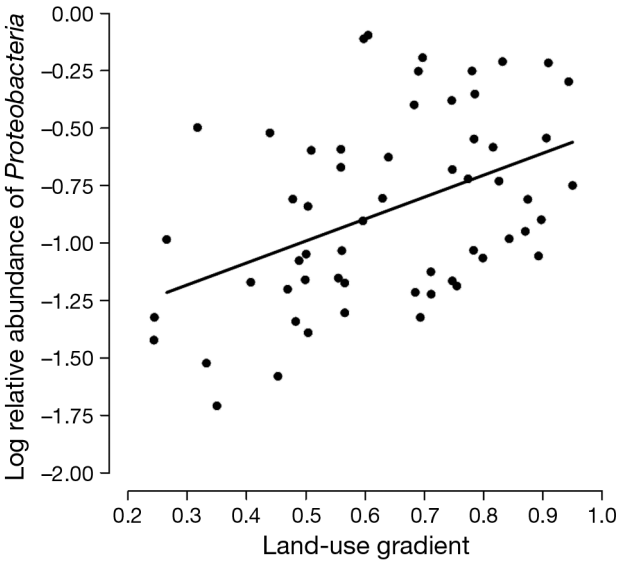

Fig. 1. Relative abundance of *Proteobacteria* on the skin of healthy individuals is associated with a land-use gradient ($p = 0.0005$, $R^2 = 0.19$), which describes the relative amount of forest and agricultural land within 3 km of the home of the study subject (L. Ruokolainen et al. unpubl.)

role, but this does not need to be so; rather this may imply that they have the capacity to prime our immune system — as well as become harmful under some conditions. A puzzling feature in our results was that the relative abundance of *Proteobacteria* was related to the amount of forest and agricultural land around the home in healthy individuals only, whereas in atopic individuals, namely those with elevated IgE antibody levels in their blood, there was no such relationship. This may indicate that the cause and the effect is not one way only; perhaps being atopic somehow influences the skin microbiota. Another interesting finding was that healthy individuals had a significantly higher diversity of *Gammaproteobacteria*, on their skin than atopic individuals (Hanski et al. 2012). Other studies have shown that reduced diversity of intestinal microbiota is associated with increased risk of allergic diseases (Bisgaard et al. 2011) and that exposure to more diverse environmental microbiota has a protective effect for asthma and atopy (Heederik & von Mutius 2012). Paralleling the result on *Gammaproteobacteria* on the skin, we found that healthy individuals were living in homes with more species of native flowering plants in the yard than around the homes of atopic individuals. The mechanism remains unknown, but may be related to microbes on plant surfaces (Hanski et al. 2012).

The biggest surprise was yet to come. The immunologist Nanna Fyhrquist measured a range of molecules excreted by cells in the blood samples we had obtained from the study subjects. I correlated these results with the relative abundance of different bacterial genera on the skin of the same individuals, and found a striking relationship. If the subject had a lot of bacteria belonging to the genus *Acinetobacter* on his or her skin, the measurements showed that some cells excreted a lot of a molecule called interleukin-10 (IL-10), which is a key anti-inflammatory molecule in our immune system (Fig. 2). In other words, the more *Acinetobacter* you have on your skin, the more your immune system produces a molecule that increases your immune tolerance. *Acinetobacter* belongs to *Gammaproteobacteria* connecting the immunological result in Fig. 2 to the environment-related pattern shown in Fig. 1.

DISCUSSION AND CONCLUSION

The conclusion we drew from our results was that the environment in which children grow up makes a difference because this affects the composition of the microbiota on their skin, which was related to their diagnosis as healthy versus atopic, presumably because their immune system responded to microbial stimulation, for which we found some evidence. We

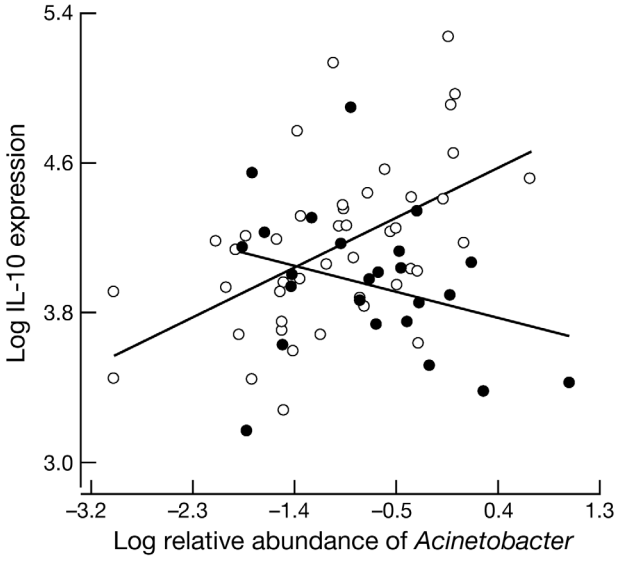

Fig. 2. Cytokine interleukin-10 (IL-10) expression against the relative abundance of *Acinetobacter* on the skin of healthy (white circles) and atopic individuals (black circles). The interaction term is highly significant ($p = 0.0009$, $R^2 = 0.23$; Hanski et al. 2012)

found, as others have found in their studies, that not all bacteria are equal — some are likely to have a more potent effect than others. Our results point to *Proteobacteria*, and especially to *Gammaproteobacteria*, in particular the gammaproteobacterial genus *Acinetobacter*. Our results and others results (Conrad et al. 2009, Zhang et al. 2010) suggest that *Acinetobacter* is especially beneficial in inducing immunoregulation. Other bacteria are key species in other parts of the body. For instance, immunological studies have shown that *Bacteroides fragilis* causes certain T cells to secrete IL-10 in the gut (Round & Mazmanian 2010), and a mixture of *Clostridium* strains promotes intestinal regulatory T cell activity (Atarashi et al. 2013).

Many scientifically challenging and societally crucial questions remain to be answered. Is early childhood exposure to environmental microbes all that matters, or does our exposure as adults further enhance the immunoregulatory circuits? The latter is supported by observations that individuals moving from developing countries with a low prevalence of chronic disorders to countries with a high prevalence tend to converge to the disorder profile of the recipient country within 10 yr (Newbold 2005). We found that forests and agricultural land had similar beneficial effects, but most likely the kind of forest and agricultural land the home is surrounded by makes a difference. Would city parks do, and which kinds of parks? This is a hugely significant question for city planning. Which particular components of biodiversity in the 'macrobiota' (fungi, plants and animals) are important? Notably, *Gammaproteobacteria* are common on plant surfaces (Junker et al. 2011). And what about wild animals? We share common agents of infection with them, surely we also share loads of beneficial commensals. Studies have shown that children growing up on traditional farms (von Mutius & Vercelli 2010) or in homes with a dog when the child is young (Ownby et al. 2002) have reduced incidence of allergies and asthma in late childhood.

At this point, many readers may ask whether it would be possible to culture the good bacteria and apply them on our skin. I take probiotics, including several species of *Lactobacillus*, *Bifidobacterium* and others, and I believe that they contribute to my healthy gut flora and well-being. Perhaps the same could apply to other microbes and other parts of the body. Perhaps, but perhaps not. The microbiota inhabiting our bodies is hugely diverse and complex, and its interactions with the even more diverse environmental microbiota can hardly fail to be even more complex. A technological fix with a few bacteria might work, but it might not. This question is reminiscent of the question whether 'novel ecosystems', consisting of largely non-native species in largely human-dominated landscapes, will provide the ecosystem services that we would expect from natural ecosystems (Hobbs et al. 2006). There is unlikely to be a black-and-white answer; the answer most likely depends on the particular species and the particular ecosystems. There are also the well-known risks associated with invading species (Mack et al. 2000), and we should ask whether we really want to reduce, and is it wise to reduce, biodiversity to just ecosystem services, and biodiversity conservation to conservation of a small number of currently appreciated ecosystem services. In the case of bacterial communities in our bodies, some of these concerns may appear less relevant, but perhaps they are not. There is no other biodiversity with which we are equally connected than the biodiversity on our skin and in our gut, but this biodiversity may be less independent of environmental biodiversity than we think. We are the innermost doll in a Russian matryoshka, protected by 2 layers of biodiversity.

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