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Modernization, Microbial Ecology and the Loss of Diversity

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Is variety the spice of life? It can help give us our *joie de vivre* and remarkably this may now include a discussion of microbes. Evidence supports the notion that human health and well-being is dependent upon biodiversity at every stage of life, starting as early as the perinatal period.¹ Moreover, as we argue here in this review, exposure to a variety of different microbes — not simply those in our foods, but also from our environment at large — may be an essential part of biodiversity discussions. Science hasn't yet informed us exactly what that microbial biodiversity should look like, although as we describe below, there are some tantalizing clues.

Scientists are finally starting to ask questions that perhaps should have considered when environmentalist Rachel Carson wrote her very thought provoking book *Silent Spring* over five decades ago.² Her book was the catalyst to the consideration of our human impact on the environment. She asked a fundamental question: how might our treatment of the environment affect our health, and our species? Fast-forward to 2015 and unseen aspects of biodiversity are finally getting the attention they have long deserved. Now, there is an expanded question: “is the westernized world losing crucial components of the gut microbiome irreversibly?”³ Or the microbiome of the skin, eyes, lungs, mouth and so forth?

Research on the human microbiome continues to inform us that humans live in symbiosis with a vast and diverse microbial population and raises questions, such as: what microbial exposures do we need at each stage of life and how do these exposures affect our health for the better or worse? We can ask myriad related questions. These are the questions of our time.

Will a child who is born by Caesarian section, given antibiotics within hours of their first breath and bottle fed ever catch up on the diversity of microbes that they need? What about the twenty-year-old who develops chronic viral infections but nonetheless is still

prescribed countless antibiotics and continues to live in a concrete urban environment, never going back to explore the richness of the parks, nature and microbial diversity they may have once known as a child? What about the elderly person who develops life threatening bacterial pneumonia, is given life saving antibiotics but then continues to live in the small world of their nursing home with only small exposure to the outside world for fear of their fragility? What is our measuring stick for the loss of microbes, and what exposures do they need to gain back their full richness of diversity?

To date there is very little in the research to quantify and answer these questions. International researchers raise some very interesting points with respect to an important role that nature may play in the regulation of health and disease: they state there are several important aspects of nature dose, including the quality and quantity of nature (i.e., the intensity), and the frequency and the duration of exposure. It may seem laughable to consider “doses” of nature, yet it is critically important that the human and nature interface be further studied and understood.⁴ Whether we may like it or not, when policymakers and planners make critical decisions concerning land use for communities, they need evidence to sway them.

These points emphasize the need to take a more mechanistic approach to developing measurements of exposure to nature and therefore, potentially improve our objective understanding of how it might be manipulated to deliver better health outcomes.⁵ From a more practical standpoint, being able to measure the microbiome with a gold standard agreed-upon measurement and then direct patients to what source of nature including quality, quantity, frequency and duration also makes sense.¹ What are the microbial phyla, taxa and strains — and their genetic changes — that promote health?

With the rise of non-communicable diseases (NCDs) including allergies, auto-immune disorders, asthma, obesity and depression, a connection to the environment now seems self-evident.^{6,7} But what was not considered way back when environmental groups were forming is that we as humans are also an ecosystem that can be affected by the environment just as easily as the birds and the bees. And science is now just starting to even consider this reality.

We have to ask ourselves — do we have the right mix of a microbial diversity living in, on and around us for our health and well-being? What more do we need to learn about these microbes to help us understand their place in an NCD epidemic? As health-care professionals how are we explaining to our patients that macro-

ecosystems affect our own micro-ecosystems? Are we contributing to the germ warfare mentality that may have gotten us in this mess in the first place? There are more unknowns than knowns in the use of natural antimicrobials and probiotics over the long term. What role is our single- or multi-dose probiotics playing in fixing our loss of diversity in our eco-systems? Are we even thinking about microbes, the richness of microbes in which we live, what is on our skin and in our guts and how many of our current home and working environments may not be providing what we need to sustain ourselves as a species.⁸

Human beings, it would seem, need biodiversity in their microbial world just as much as they need food, shelter and water. Consider that the planet is currently under duress due to climate change, loss of biodiversity and environmental degradation. These are critical issues to be considered in the context of the discussion of the built environment. Undoubtedly, there are multiple benefits to living in an urban environment but what are the trade-offs?

Microbiota: Concrete Environments Vs. Natural Environments

In 1851, 13% of Canadians lived in urban environments versus 87% living in rural environments. In 2011, over 80% of our population lived in urban environments.⁹ When we consider this on a global scale, the rate of urbanization is so significant it is projected that 9-billion people could be disconnected from nature. Recently, many of the theories around why nature is good and why this disconnect is concerning have been focused on the psychosocial aspects of nature. But our green space is not just about the perfect view and how this makes us feel; it is much more complex.¹ It is about entire external ecosystems, including the microbes we breathe, touch and consume – and how this in turn affects our own ecosystem. On top of this, and beyond the scope of our discussion, consider climate change, industrial farming and the associated loss of species. How are these factors affecting the microbes of modernity? This significant change to the way we live our lives is also highlighted by the amount of time we spend indoors. Canadians are spending an increasing amount of time within man-made structures, with new research indicating that close to 90% of our activity patterns occur indoors.¹⁰

Our built environment with our bricks and mortar, HVAC systems, air filters, synthetic chemicals is divergent from the ecosystems we lived in during the past. What are we missing out on in our built environments? This switch to an urbanized society has vast consequences, one of the most significant being a massive loss of microbial biodiversity. Our loss of microbial diversity also can be due to a host of factors, including: changes in our water systems, air, methods of agriculture, ingestion of processed foods along with a loss of rural land and forests. This change in our outdoor environment has impacted our overall microbiome leading to changes in our lifestyle and health through a loss of immune tolerance, inflammatory changes, stress regulatory responses and mental health, to name a few.¹¹ In the review article, *The Helsinki Alert of Biodiversity and Health*, it is stated that “urban living in

built environments, combined with the use of processed water and food, may not provide the microbial stimulation necessary for a balanced development of immune function”.¹²

What we have learned from an ever growing list of studies involving isolated communities and those living those very traditional lifestyles, is that we as westerners have a much smaller diversity of microbes than these “hunter-gatherer” type communities.¹³⁻¹⁷ The day-to-day existence of our relatives living these traditional lifestyles is vastly different from our own in terms of their regular exposures to microbial content. As clinicians, we have to be asking ourselves, are these microbial exposures necessary to decrease our risk of NCDs? Furthermore, with what measuring stick are we examining the microbial diversity of our patient’s microbial environment? It would be easy to argue, as our colleague Dr. Alan C. Logan has done,⁸ that all North Americans are relatively dysbiotic to one degree or another.

‘Old Friends’ Hypothesis

Much has been discussed around the idea of the hygiene hypothesis; generally, that we don’t have enough early-life microbial exposure to prime the immune system. Dr. DP Strachan introduced his idea of the hygiene hypothesis in 1989, suggesting that a lower rate of infection in young children could explain the rise of allergy related diseases.¹⁸ Dr. Graham A.W. Rook, a noted expert in microbiology, extended this original hygiene hypothesis to a more ancestral viewpoint. He states that our co-evolution with microbes is as old as the history of humans. The disturbed relationship between human and microbes, as a result of modernization, may be far more complex than simply the number and type of early childhood infections. In his extension of the hygiene hypothesis, Rook argues that as humans, we have co-evolved with exposure to a wide variety of organisms, including these harmless microbial “Old Friends”, through farms, animals, feces, helminths and the basic microbiota from our environment and those around us.^{19,20} He postulates this interaction with organisms in our environment provides us with microbial exposure from birth, beginning the population explosion in our gut leading to a training of the immune and inflammatory system.

The microbial contact helps provide a basic level of activation of the innate immune system and develops a regulatory system that stops inappropriate immune attacks on the self (autoimmunity), harmless allergens and our gut contents. In addition, his theory addresses the high level of chronic inflammation being seen in modern urban centres. For example, it has been found that in the Philippines and lowland Ecuador, where children have been exposed to a high microbial diversity right from infancy, those children even into adolescence have the lowest levels of the inflammatory marker C-reactive protein.²¹

Studies have shown that the Western microbiome is associated, most commonly, with changes in richness and evenness, otherwise known as our overall diversity of the microbiome. Our loss of rural/forest environment has led to a distinct loss of microbial diversity.³³

What has changed is we are no longer walking through the jungle, woodlands, old growth forests as we used to; we are very different from our ancestors. For many people, these types of exposures to a wide diversity of microbes might happen on their summer holiday once a year, or maybe not at all.

As mentioned, studies comparing rural populations versus urban populations, isolated communities and those living what amounts to a hunter-gatherer lifestyle have shown vast differences in microbial variety and diversity compared to more Westernized urban dwellers. Adaptation to the post-industrialized Western lifestyle is coincident with a reduction in human-associated microbial diversity, and as a result, a decline in gut microbial stability. Diversity and stability are factors with major health implications, particularly now that the human gastrointestinal tract is increasingly recognized as the gateway to pathogenic, metabolic and immunologic diseases.^{6,7} Co-speciation between host and microbiota over millions of years has shaped both sets of organisms into a mutualistic superorganism.²² Dissolving that contact through our limited environmental exposure has had a drastic effect on health and immune function of modern Westernized human groups.

Noncommunicable Diseases

We now know that “biologically diverse environments modify and enrich our indigenous microbiota, which are fundamental for the development and maintenance of a balanced/well-functioning immune system”.¹² The hygiene and its extended hypotheses brought into consideration the idea that evolutionary recent germ warfare against infection could be associated with increased levels of conditions like asthma, allergies and eczema, especially in countries with high economic status. But as our modern societies progress we are seeing our health concerns changing from an infectious disease focus to noncommunicable diseases (NCDs) — conditions that have an underlying level of inflammation.^{6,7}

Whereas these conditions, including atopy, are partially explained in the hygiene hypothesis, we have also seen a substantial increase in autoimmune disease, cardiovascular disease, metabolic conditions and neurodegenerative disease. In the past, our focus has been on a genetic component to these conditions with the addition of environmental risk factors such as poor diet and smoking. Now, we can consider this concept of the “Old Friends” Hypothesis as an additional explanation of many of these changes, relating to altered microbiota patterns — most commonly this loss of diversity and dysbiosis.²³

We tend to think of inflammation as a protective response — allowing our body to deal with infection or trauma. Symptoms of redness, pain, heat, loss of function and/or swelling allowed the body to remove the damaging initiator and begin the healing process. This however, doesn't explain inflammation in chronic disease and our body's traditional feedback mechanisms, meant to prevent inappropriate immune responses, do not necessarily downregulate

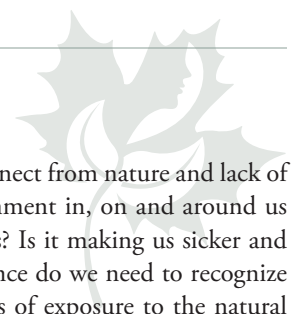
as normal.²³ Based on our previous understanding of inflammation, it would be expected that due to the high prevalence of infection in low-income countries, especially in early life, there should be high levels of overall inflammation into adulthood. Yet, the opposite is seen.

What research has shown is the continued exposure to immune-regulating “Old Friends”, the immune response is strong during infection, but it is relatively quiescent when it is no longer needed — resulting in a ‘resting’ CRP close to zero. In contrast, high economic status countries have shown a chronic low-grade inflammation, seen as an elevated CRP or IL-6, in the absence of any apparent inflammatory stimulus such as infection or trauma.²³ This inability to effectively turn off an acute inflammatory response leads to a relatively high baseline of inflammatory mediators that contribute to the development of chronic disease.

Do Where You Are Born and Where You Live Matter?

Exposure to these ‘Old Friends’ seems to be a strong predictor of lowering risk to inflammatory and psychiatric-associated disease. This can be demonstrated, especially in immigrant populations where the birth country was a low/middle-income region and the adopted country was high-income. Children from low-income countries adopted into Swedish families showed a prevalence of asthma, allergies and eczema that was highest in those who were adopted when they were less than 2 years old. This was also seen in children who immigrated from Mexico, as compared to those who were born in the USA and it was found the prevalence of asthma decreased as the age at immigration increased.^{1,21} Overall, the longer a person lived in a low- to middle-income country — with higher exposure to a diversity of microbes — prior to moving to a country of a higher economic status, the lower the prevalence of asthma, allergy and eczema.

Autoimmunity has shown a similar pattern as we have seen with migration studies on individuals leaving Iran for Sweden. The risk of multiple sclerosis (MS) is doubled for Iranians immigrating to Sweden versus if they stayed in their country of origin. Yet, second generation or beyond ethnic Iranians born in Sweden, who return to their parents' country of origin (Iran) retain the susceptibility to MS found in those born in Sweden. Conversely, individuals born in the United Kingdom who migrate to South Africa maintain an increased risk for MS, rather than the lower risk found in those born in South Africa. Genetics and environmental factors such as diet and smoking do not explain these immigration patterns. The pattern is also seen in psychiatric disorders. For Mexicans, Cubans and African-Caribbean, who were born in the USA or immigrated before the age of thirteen, they had a 2-3 fold increase in the likelihood of depression, as compared to those who immigrated after the age of thirteen. This was found in immigrants from Eastern Europe, as well, but not from individuals coming from Western Europe.^{1,21}



The Role of Helminths

Although it may be unsettling to the general public and health care providers alike, humans have co-evolved and were colonized with helminths.²⁴ Paleoparasitological samples dating back 10,000 years show that infections with multiple types of nematodes (roundworms), cestodes (flatworms including tapeworms) and trematodes (flukes) were common.¹ Less than one hundred years ago, almost all humans were colonized with helminths, but modern sewage treatment, changes in agriculture and the food industry and urban city design in high-income cities has eliminated lifecycle pathways required to maintain their presence. In less-developed countries, human infections with helminths remains more common – with just *Ascaris lumbricoides* (giant roundworm) and *Trichuris trichiura* (human whipworm) alone infecting 1.2 billion and 795 million respectively worldwide.^{25,26}

Whereas our desire to eliminate pathogenic infections is understandable given our modern take on hygiene, epidemiological studies are beginning to demonstrate the benefit of our colonization by helminths, namely, protection against some immune-related disease. In numerous studies, exposure to helminth colonization showed signs of lowered symptoms of asthma and allergy. Less wheezing was found in *A. lumbricoides* infections compared to those without,²⁷ Gabonese children infected with *Schistosoma hematobium* had decreased skin-test positivity to dust mites versus those without colonization and children treated for *T. trichiura* and *A. lumbricoides* had increased dust-mite skin responses versus those untreated.^{28,29}

Support for the epidemiological evidence for the immune benefits from co-evolution with helminths is found in animal studies. Exposure to helminths may prevent or reverse colitis in animal models of inflammatory bowel disease (IBD). And preliminary studies in humans have shown high remission rates in IBD patients treated with *T. suis*.

Colonization with helminths can induce specific immune regulatory circuits in the gastrointestinal tract that decrease an over response of gut inflammation. Interestingly, the conditions studied have seemingly disparate immune responses — conditions such as IBD, MS and type 1 diabetes are thought to result from a dysregulation of Th1 responses, unlike asthma which is considered to be an overacting Th2 response. As helminths can induce Th2 response, it could be predicted to make asthma worse, yet helminths can also upregulate IL-10 and TGF- β , along with T cells, preventing airway inflammation in response to allergens.^{1,30}

Our co-evolution with helminths, epidemiological studies, human trials and experimental animal models, are all showing a picture that our evolutionarily recent loss of exposure to helminths may be increasing our susceptibility to some non-communicable diseases. Whereas certain helminths may be too virulent, others may be part of returning us to the immune-modulating benefits of some of our 'Old Friends' that were historically abundant and shaped the human immune system.³¹

Conclusion

Is our lack of microbial diversity, disconnect from nature and lack of understanding of the microbial environment in, on and around us compromising the health of our species? Is it making us sicker and increasing mortality? How much evidence do we need to recognize that our 'Old Friends' matter? The loss of exposure to the natural environments and all of its organisms — seen and unseen — is almost assuredly contributing to the overall increased risk of NCDs including allergies, asthma, auto-immunity, depression and other mental health risks.³²

The evidence is mounting; a collection of experimental and epidemiological research demonstrates that our loss of interaction with the natural environment is changing our health. Some of this can be described in a straightforward way, through visual and auditory senses that change stress reactions. The benefits of natural environments can also be explained by their ability to encourage physical activity and build social capital. Then we have microbes; our interactions with the hundreds of trillions of microbial inhabitants that otherwise guide, train and shape our health.

Epidemiological studies, animal models, human trials, paleofecal samples are demonstrating that our co-evolution with microbes has recently changed and it is rapidly changing our health. These studies suggest that loss of contact with microbial biodiversity could be increasing our susceptibility to many of our diseases of affluence. One could further argue this loss of contact may permanently alter our evolutionary trajectory.^{3,11,33}

It is with this in mind that we conclude with a firm statement: as naturopathic doctors, are we doing all we can, individually and collectively, to consider our 'Old Friends' in clinical recommendations and as a unified profession? Do we have the tools and knowledge necessary to guide our patients? The advanced research on the human microbial environment may be in its infancy; however, there is enough available research for naturopathic doctors to become thought leaders and start making the connections for our communities on the need for biodiversity both in, on, and around us. The interrelatedness of external and internal ecosystems is yet another reason to explore the medicinal aspects of natural environments. Microbes provide more evidence concerning how and why we should be 'prescribing' nature to our patients. 🌿

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