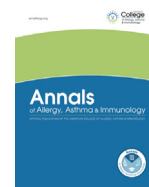




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Review

A butterfly flaps its wings

Extinction of biological experience and the origins of allergy

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Key Messages

- The once subtle effects of urbanization have escalated into a large-scale biodiversity loss, which is echoed on the microecologic scale with changes in personal and environmental microbial ecosystems. This loss is directly implicated in the epidemic of allergy and many other noncommunicable diseases.
- Modernity has also been associated with human behavioral changes, with considerably more time indoors, progressively less contact with biodiversity in natural environments, and evidence that reduced early-life experience of biodiversity primes people for immune dysregulation and a higher propensity of low-grade inflammation.
- Efforts to increase direct, personal contact with biodiversity have clear benefits for multiple aspect of physical and mental health, the skin and gut microbiome, and immune function. There are also beneficial effects on health behaviors, such as food choices, sleep, and physical activity, that favorably affect immune function.
- Increasing nature connectedness is also important for promoting environmental responsibility and value systems that are geared to restoring and preserving biodiversity.

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ABSTRACT

Objective: To explore links between biodiversity on all scales and allergic disease as a measure of immune dysregulation.

Data Sources: PubMed and Web of Science were searched using the keywords *biodiversity*, *nature relatedness*, *allergic disease*, *microbiome*, *noncommunicable diseases*, *coronavirus disease 2019*, and associated terms.

Study Selections: Studies were selected based on relevance to human health and biodiversity.

Results: Contact with natural environments enriches the human microbiome, promotes regulated immune responses, and protects against allergy and both acute and chronic inflammatory disorders. These important links to ecopsychological constructs of the extinction of experience, which indicates that loss of direct, personal contact with biodiversity (wildlife and the more visible elements of the natural world), might lead to emotional apathy and irresponsible behaviors toward the environment.

Conclusion: The immune system is a useful early barometer of environmental effects and, by means of the microbiome, is a measure of the way in which our current experiences differ from our ancestral past. Although we would benefit from further research, efforts to increase direct, personal contact with biodiversity have clear benefits for multiple aspects of physical and mental health, the skin and gut microbiome, immune function, food choices, sleep, and physical activity and promote environmental responsibility.

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Introduction

Humanity has progressively affected global environments and planetary systems to such an extent that our own well-being is now under threat.¹ In the epoch of the Anthropocene, it is abundantly clear that all the grand challenges are interrelated, including

climate change, environmental degradation, biodiversity losses, ecosystems collapse, new infectious contagions, economic instability, social unrest, and obscene inequality. For decades, human health has been under threat from a mounting pandemic of non-communicable diseases (NCDs).^{2,3} Although this crisis in slow motion has been responsible for vastly more deaths and disease than infectious disease, it has unfortunately not galvanized the same coordinated global efforts for prevention, as we are currently seeing with more imminent acute infectious threats, such as coronavirus disease 2019 (COVID-19). However, given that infectious outbreaks are also interrelated with the same disruptions in planetary health and that individuals with preexisting NCDs are far more susceptible to infections such as COVID-19, it is imperative to take a more integrated, cross-sectoral approach to health, recognizing that immune resilience is a common factor. Ultimately, this means directing resources to remediating the underlying causes of these connected challenges in ways that have cobenefits for the health of people, place, and planet in the broadest sense—as also articulated recently by the Lancet One Health Commission.⁴

Among all NCDs, the marked increase in allergic diseases during the past half century has arguably been one of the most striking measures of the effect of urbanization and adoption of a westernized lifestyle on immune health.^{5,6} The fact that asthma and allergic diseases develop so early in life provides a unique opportunity to understand how the interconnectivity between changing environments (at macro-, meso-, and microlevels) affects the human immune system from the first moments of development.

Indeed, it has been suggested that the allergy disease epidemic is a “canary in the coalmine” that exposes the effect of modern environmental change and, in particular, the specific vulnerability of the immune system, which has wider significance for other aspects of health. The early-life experience of the immune system now appears to prime the propensity for low-grade inflammation and immune dysregulation, increasing the risk of many other later-onset NCDs. In effect, the immune system is a useful early barometer of environmental effects and, via the microbiome (microorganisms, their genetic material, and theater of activity), a measure of the way in which our current experiences in the Anthropocene differ from our ancestral past.⁷ We are also reminded that the smallest elements in our ecosystems, microorganisms, are critical to large-scale systems, including climate change biology, as highlighted in a recent warning by environmental scientists in *Nature Reviews*.⁸

Whatever label we use for the current global burden of allergic diseases and asthma—*epidemic, crisis, scourge*—we can all agree that the rates are intolerably excessive. Moreover, there is consensus that genetics cannot explain the rapid shift in the burden of disease and that environmental change has played a primary role, interacting with genetic susceptibilities over time. With good reason, the initial scientific search for causation has largely focused on environmental toxins—the increasing presence of detrimental exposures. However, it is equally important to consider that the lack of protective factors could have commensurate effects on health.

In this context, this Review focuses on the consequences of the biological extinction of experience, considering the evidence that the current burden of allergic disease may be, at least partially, driven by the absence of immune system experience with biodiversity. The “canary in the coalmine” was a useful metaphor for illuminating the once subtle concept that the increase in allergic diseases 50 years ago was a forewarning of a larger crisis of NCDs—that allergy may be an indicator species for the effects of ill-defined toxins on the risk of inflammatory disease.⁷ However, now there is nothing subtle about environmental change or the effect on human health. Indeed, the avian metaphor has become a terrible reality, with concomitant stunning real-world losses of a multitude of bird

species during the same period.⁹ It is time to understand the direct links between these phenomena, namely the links between biodiversity losses, on all scales, and the current rates of allergic diseases and immune dysregulation.

A Butterfly Flaps Its Wings

[Butterfly] disappearance indicates loss of life. When the last tiger is killed in India, it may hit the headlines, however, shrinkage of biodiversity also takes place in the micro-world close to us, but without notice. Preserving biodiverse life might have a preventive effect on allergy and other diseases of modern civilization. – Tari Haah-tela, MD, PhD¹⁰

The butterfly effect is another oft-used metaphor to explain how the most minute change in local conditions can lead to massive differences in the state of wider systems—through ripple effects across a complex interconnected web. As first postulated by Edward Lorenz as part of chaos theory, if a butterfly flaps its wings in one location, this tiny change in the atmosphere could, at least theoretically, influence weather at distant, future sites. It is rare for mathematical theories to penetrate the discourse of popular culture, but the butterfly effect has captured the imagination of the public. Perhaps because humans love both metaphors and butterflies.

Finnish physician-scientist Tari Haahtela has dedicated his career to the study of allergic diseases and allergy. He also happens to love butterflies and as a side passion has traveled the globe examining these flying flowers and their habitats (Fig 1). In 2009, *Allergy* published a Commentary from Dr Haahtela entitled “Allergy Is Rare Where Butterflies Flourish in a Biodiverse Environment”¹⁰; for many readers, it may have seemed a strange and curious outlier among critically important articles on omalizumab treatment, filaggrin mutations, gene variants, dietary carotenoids, and lipoxin A4 generation in patients with asthma and/or allergic diseases.

Research conducted by Dr Haahtela's group and others has indicated that westernized urban environments seem to lack essential elements, which otherwise provide necessary exposures for the optimal development of tolerance against foreign proteins. Notably, these observations came to light with striking differences in immune disease between Finland and neighboring Russian Karelia. Although Finland and Russian Karelia are geographically close, Dr Haahtela's group had discovered strikingly different allergy



Figure 1. Every ecosystem depends on the health of its smaller parts: “A swallowtail butterfly wondering where to go” inspired by a photograph taken by Dr Tari Haahtela in Portugal on the Atlantic coast (Tari Haahtela, MD, PhD, written communication, June 2018). Copyright 2020: Susan L. Prescott.

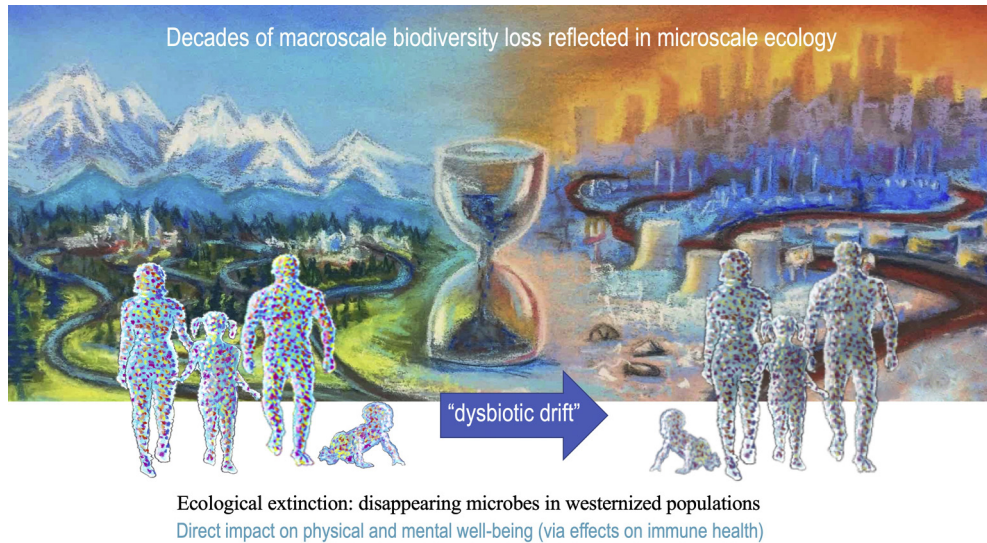


Figure 2. Time is of the essence in addressing dysbiotic drift. Decades of macroscale biodiversity loss reflected in microscale ecology with a direct effect on physical and mental well-being (many mediated via effects on immune health). The longer we delay addressing this, the more we risk irreversible loss of ecosystems. Copyright 2020: Susan L. Prescott.

prevalence in the borderlands of these areas. The higher microbial quantity and diversity in the drinking water and house dust were among the implicated factors associated with a reduced risk of allergic disease in Russian Karelia.^{11,12}

From his broader vantage, Dr Haahtela also noted that allergic diseases appeared to be rarer in regions where butterfly populations enjoy rich diversity. It was a generalized observation, and although it lacked detailed investigation on butterfly populations per se, the plausibility matched evolving knowledge derived from the hygiene hypothesis: the overarching idea of the original hypothesis¹³ and its related variants¹⁴ that the global increase in allergic disease could be related to diminished opportunity for early-life exposure to microbial diversity via antibiotic overuse, smaller family sizes, excessive use of personal and household cleaning products (including detergents), and lower exposure to nonpathogenic bacteria in foods (eg, lowered consumption of fermented foods). According to the hypothesis, the mediator between these environmental changes and immune system training was proposed to be an abnormally stable microflora.¹⁴ A new-normal microbiome may characterize the lived experience in urbanized, western industrial nations, reflecting a more generalized decrease in biodiversity. In essence, a manifestation of wider dysbiotic drift¹⁵ (Fig 2).

Dr Haahtela's Commentary served to underscore the potential relevancy of biodiversity at all scales to the work of practitioners and scientists working in the field of allergy and immunology. More than 10 years on, the global collapse of insect species is far more devastating than even imagined. In 2019, Australian researchers reported shocking decreases in flying insect populations and projections that indicated extinction of as many as 40% of the world's insect species during the next few decades.¹⁶ Butterflies are among the species experiencing devastating decreases.^{17,18} Although some insect species are resilient, urbanization is detrimental to both abundance and species richness.¹⁹ If these decreases continue, the implications are catastrophic; insects are integral in freshwater ecosystems and the entire food web; they are food for countless larger species and perform vital roles, such as pollination, pest control, and nutrient recycling.²⁰

Perhaps the more relevant question for humanity now pertains to what might happen in a system if a butterfly does not flap its

wings. In the realm of asthma and allergic diseases, Dr Haahtela was provoking our profession to consider the answer to that question. It was not his contention that butterflies have unique antiallergic properties but rather that this colorful, flamboyant species might be informing us about the relationship between biodiversity in general and allergic diseases in particular.

Dr Haahtela's original Commentary in *Allergy* has since spawned a larger biodiversity hypothesis, which states that contact with natural environments enriches the human microbiome, promotes immune balance, and protects against allergy and inflammatory disorders. It argues that there are nested layers of biodiversity: an outer mantle that includes soil, water, plant, and animal-associated microbiota and an inner layer that includes the microbiota of the skin, lungs, and alimentary canal. The outer layer plays a large role in the colonization of the inner layer and, by extension, the operations of the immune system^{21,22}; given the recent discoveries on the immune-nervous system interface, the natural environment and its outer mantle of biodiversity can potentially extend its reach to the brain through microbe-mediated nonsensory pathways.^{15,23}

Extinction of Experience

“What is the extinction of the Condor to a child who has never seen a wren?” – Robert Pyle, PhD²⁴

As experts in the field of allergy explored lifestyle factors that might contribute to the increase in allergic diseases (coincident with global urbanization), our colleagues in ecology and psychology expressed concern about the transgenerational loss of cognitive-emotional experience with the natural environment. Dr Robert Pyle, an ecologist who specialized in the study of butterflies, coined the term *extinction of experience*.²⁴ He and others worried that loss of direct, personal contact with biodiversity—wildlife and the more visible elements of the natural world—might lead to emotional apathy and irresponsible behaviors toward the environment.²⁵

Although more research is needed on the topic of emotional disconnection from nature, several studies support the idea that adults and children in westernized, industrial, and technologically mature nations are spending more time indoors^{26–28} and less time

in natural environments, untethered to screen-based devices.^{29,30} There are also indications that losses in local biodiversity and environmental degradation are associated with greater time spent indoors³¹; in Japan, researchers have found an age-related, cross-generational decrease in childhood experiences with indicators of biodiversity.³²

Psychologists have developed scales to assess individual levels of awareness of, and fascination with, the natural world; for example, the Nature Relatedness Scale (or separate Nature Connectivity or Nature Connectedness scales) capture the degree to which participants in research studies have an interest in making contact with nature. Higher scores on nature relatedness have been linked with general health and mental well-being^{33,34} and with higher concern for the sustainability of the natural environment.^{35,36} Intervention research that involves children exposed to biodiversity-rich environments indicates that psychological well-being and nature relatedness can improve in tandem.³⁷ Recently, psychologists have argued that available evidence supports that the humans have a basic psychological need for nature relatedness.³⁸

For the most part, the work of professionals in allergic diseases has yet to intersect with the burgeoning nature relatedness and psychological extinction of experience research. But perhaps it is time for the twain to meet. The microbiome revolution may yet deliver on its many therapeutic promises,^{39,40} but in the meantime, it has already transformed how we view the human self and helped erase the imaginary dividing line between the biological and psychological.^{41,42}

Also sitting at the periphery of mainstream immunology and the study of allergic diseases is an increasing body of in vivo research typically housed within environmental psychology or physiological anthropology. The study of shinrin-yoku (now generally referred to in Japanese studies as simply forest medicine or forest therapy) exemplifies an intriguing line of preliminary evidence that may be of interest to our field. Loosely translated, shinrin-yoku means forest-air bathing or absorbing the forest air and places an emphasis on the entire forest experience.⁴³ Several small, short-term intervention studies (under the shinrin-yoku rubric) have found that spending time in a forest environment vs an urban built environment can influence stress physiology, cytokines, and other

markers of inflammation, immune parameters (eg, natural killer cells), blood pressure, and heart rate variability⁴⁴ (Fig 3).

These shinrin-yoku studies are limited by small sample sizes and short duration; moreover, given that potential allergens are among the components emitted from trees and flowering plants, they cannot be used to make arbitrary decisions about public policy (eg, planting certain trees or flowers) that might otherwise influence millions of people with allergy. Immense planting of new growth cedar (sugi) trees in postwar Japan is still considered to be a factor in sugi-pollinosis, considered now to be a national affliction.⁴⁵

However, the emerging research on psychological extinction of experience and nature relatedness is of importance to the biodiversity hypothesis; in particular, inclusion of validated nature relatedness scores (identifying personal connection to nature or lack thereof) might provide further insight into existing epidemiologic work. For example, early-life familial pet ownership has been linked to reduction in allergic disease,^{46,47} yet we know little about the psychological underpinnings that might drive pet ownership (such as nature relatedness) in the first place. These psychological constructs might be associated with several differing lifestyle variables, differences that might explain the conflicting findings on pet ownership and allergic diseases.^{48–50}

Consider also the several large-scale studies using satellite technology and land use data to link geographic greenness (as a surrogate of trees, shrubs, and plant-based biodiversity) with lower rates of wheezing, asthma, respiratory disorders, and allergic diseases.^{51,52} Similar to pet ownership, the results are conflicting, with some research indicating that living near coniferous forests (and unspecified green space) is associated with worse outcomes in asthma and allergic diseases.^{53,54} Several studies have found relationships between residential proximity to farms and arable lands, exposure to farm-associated microbiota, and protection against allergic diseases and asthma.^{55,56} However, all farms cannot be painted with the same brush, and efforts to bring protective soil and farm-associated microbiota to practitioners and patients awaits lengthy translation.⁵⁷ In the meantime, it may be helpful to know more about the psychological antecedents (beyond the oft-discussed term *stress*) that might influence risk, and the cognitive-emotional drivers of the behavior that might place one in contact with biodiversity.

Loss of contact with biodiversity can also be imagined in the form of wholesale changes to dietary patterns; it has been argued that for children in westernized nations the loss of whole plant foods (relatively unprocessed and high in fiber and phytochemicals) from the diet, coincident with the massive encroachment of the “invasive species” known as ultraprocessed foods^{58,59} (which now dominate the nutritional landscape, such as weeds, displacing nutrient-dense foods), is also an extinction of experience.⁶⁰ Displacement of relatively unprocessed foods with ultraprocessed foods is another contemporary disconnection from nature and the products of biodiversity with direct implications for the gut microbiome.⁶¹ Ironically, it appears that animal studies exploring environmental determinants of immune resilience may more accurately resemble human immune responses if they are reared in more natural environments.⁶²

Ongoing research is currently evaluating strategies to promote nature relatedness in preschool children and how this may improve dietary habits and exercise among parents and children in the same household,⁶³ as well as affect microbiome and immune function. Green prescriptions, also known as nature-based solutions, may have considerable cobenefits for individuals, community, and the wider environment⁶⁴ (Fig 3). Similarly, microbiome-inspired green infrastructure provides ecologic solutions that promote personal biodiversity through healthier, more biodiverse cities and urban environments.⁶⁵ These place-based environmental strategies will



Figure 3. Multidimensional health benefits of nature-based solutions (green prescriptions). Decades of research show health benefits across all domains, including improved mental health (improved mood and sleep, reduce depression, anxiety, and posttraumatic stress disorder), improved performance (improved concentration and cognitive performance), reduced inflammation, reduced cortisol and stress responses, reduced asthma and allergies, lower blood pressure, lower heart rate, lower oxidative stress, and reduction and buffering of noncommunicable disease. There is also evidence that increasing urban greenspaces can reduce health inequalities because of social disadvantage. Copyright 2020: Susan L. Prescott.

also provide opportunities to study the effect on immune function, especially in children.

In summary, the psychological constructs of extinction of experience and nature relatedness are highly relevant to the work of professionals in our field of allergic diseases; it can be argued that up to now, work within the biodiversity hypothesis rubric has involved searching for clues in the immunologic extinction of experience (eg, missing microbes) and that such work will be bolstered by looking more deeply at the upstream drivers of behaviors that otherwise put us in contact with biodiversity.

An Exposome Perspective

[The physician] must master a new science focused on the effects that the total environment exerts on the human condition...knowledge of environmental biology must therefore become one of the essential bases of medical science and practice. — Rene Dubos⁶⁶

The complexity of the biodiversity hypothesis underscores the need to evaluate intertwined temporal exposures, including those that at first glance may seem unrelated to the microbiome-immune system interface. For this reason, many in our field are adopting an exposome perspective. The exposome refers to the study of accumulated exposures (ie, physical, sensory, and positive or negative emotional experiences) and their interaction with genes over time. The exposome vantage takes the position that genes alone cannot explain disparities in allergic diseases and asthma and underscores that individual exposures we have been measuring during the previous decades (eg, airborne particulate matter, farm-associated microbes, and pollen allergenicity) do not occur independently of the total environment.⁶⁷

The dysbiotic effects of gray space in urban environments are multidimensional, from the displacement of greenspace and biodiversity on all scales to the aggregate effects of inequalities in income, education, and social cohesion, which differentially affect choices and behaviors that contribute to NCDs.⁶⁸ Living in westernized urban environments has been clearly associated with lower biodiversity in the human gut microbiome.^{69,70} Moreover, migration to more urbanized regions, such as the United States, is associated with immediate loss of microbiome diversity and function, with displacement of native strains (such as *Prevotella* strains) with US-associated strains (such as *Bacteroides* strains).⁷¹ These effects increase over time and across generations and are compounded by obesity.

Again, there are direct implications for immune resilience and the predisposition for inflammation—not only for the chronic inflammation of NCDs but also acutely as seen with adverse outcomes with inflammatory responses to the severe acute respiratory system coronavirus 2 (SARS-CoV-2), causing COVID-19.⁷² Approximately 79% of people requiring intensive care for COVID-19 in the United States and 86% of deaths in New York State, as elsewhere around the world, have occurred in those with comorbid NCDs.⁷³ There is also speculation that perturbations in the gut microbiome, which are well characterized in many NCDs, may be implicated in the susceptibility to COVID-19.⁷⁴ Indeed, even in healthy individuals, there is preliminary evidence that difference in the gut microbiome may be associated with proteomic biomarkers and inflammatory cytokines that predict the progression to severe COVID-19.⁷⁵ There are now calls to consider the role of lifestyle, diet, and the microbiome and the wider exposome in susceptibility and resilience to COVID-19,⁷⁶ notably because expression of angiotensin-converting enzyme 2, the receptor for entry of the SARS-CoV-2 spike protein, is modulated by environmental and lifestyle factors.⁷⁷ This finding underscores the importance of ecologic approaches to environmental and lifestyle health that

promote resilience to inflammation across the life course, particularly when the foundations of health are laid.⁷⁸ Indeed, for decades the field of allergic disease has been at the forefront of efforts to underscore the importance of early-life ecology for life-long immune health.

Although the desire for such an approach has been advocated by experts in allergic diseases for decades,⁷⁹ the new era of omics technologies (the ability to simultaneously measure large numbers of biomolecules that represent genes, genes expressions, proteins, and metabolites) provides optimism that researchers can identify biological markers of relevance to the total lived experience of individuals (including experiences of parents and grandparents) and entire populations.^{80–82} Such technologies, leveraged by the microbiome revolution, can help us pick apart the influences of dietary choices, stress, sleep, exercise, and psychological drivers of biological outcomes over time. It may finally be possible to reconcile various aspects of total lifestyle, vis à vis disease risk, and place them into the context of larger mediators of Anthropocene-associated disease.⁸³ This understanding cannot be achieved without also addressing the value systems that drive the attitudes and actions of individuals and whole societies.^{84,85}

There is little doubt that in the Anthropocene, conversations about medicine, science, and health (at all scales) are political discussions. There is ample evidence that authoritarianism is detrimental to health at all scales. Hence, experts in planetary health have advocated for a broad introduction of political science into medical and health-related graduate programs. These conversations are described in detail elsewhere, but a part of this must be in understanding the corporate and commercial determinants of health.^{86–88}

In addition to numerous important, well-established top-down public health and environmental initiatives, solutions will increasingly depend on grassroots strategies that improve the health of people and places. These strategies empower communities, engender optimism, and encourage collaboration among different sectors of government, industry, science, and the public⁸⁹ and increase opportunities for people to engage in change—personally and collectively.

Research indicates that most people have clear preference for a more caring and responsible society in which progress does not erode warmth and social cohesion, with opportunities to participate and make a difference.^{90,91} Optimism promotes engagement, and change is more likely and more meaningful when there are tangible pathways for people to engage and when we believe that our actions can make a meaningful difference.⁸⁹ At the community level, researchers have found that the mere greening of vacant lots can improve mental health⁹²; when the topic of environmental factors and a healthy diet is approached from a food justice and power inequity issue, young adults are more engaged and motivated for nutritional change.⁹³ Thus, finding solutions to complex, interconnected problems will require research-based collaboration between academia and the communities they serve.

Recent events with COVID-19 have shown how a subcellular molecular event on one side of the planet can have rapid and far-reaching cascading effects across the entire globe. This finding has heightened the awareness of the connections between personal and planetary health and has demonstrated the capacity for a galvanizing coordinated response to an acute threat, with rapid changes to personal and collective behavior for mutual benefit. The same level of effort is now needed to address the NCD pandemic in the post-COVID-19 world, from the first moments of life, when many of these conditions have their origins.⁷⁸ Although the NCD pandemic has occurred on a much slower time frame and is seemingly more insidious, the devastating large-scale personal, economic, and societal effect of these chronic diseases is arguably far more significant and long-lasting—and no less important.



Figure 4. Small changes can have large effects. Recent events reveal how small changes in one part of the planet can have global ripple effects as a result of human behavior. We can apply the same principles to affect positive change. Copyright 2020: Susan L. Prescott.

Without the same coordinated, large-scale efforts to address these conditions, the burden on our societies and our health care systems is unsustainable. This burden is also ultimately rooted in the way we live—our behaviors, our attitudes, and our relationship with the environment that sustains us.

Conclusion

Experts working in the field of allergy should be proud of a progressive legacy of scientific research into the effects of the total environment on human health. Many of our early findings on environmental toxins and microbes have influenced virtually every branch of science and medicine; for example, research in the early days of microflora and the immune system and allergy set the table for the burgeoning gut-brain-microbiome field.⁹⁴

However, the interrelated challenges of the Anthropocene, including those directly and indirectly associated with allergic disease, demand interdisciplinary work; to truly explore the merits of the biodiversity hypothesis, the closed silo system is untenable; our colleagues in psychology, ecology, and other fields can help us with a more fine-grained understanding of how the disappearance of the Monarch butterfly might be connected not only to allergic disease but also to the myriad of noncommunicable and communicable threats that we face today. As we reflect on the butterfly effect we are again reminded that small changes can have large effects (Fig 4) and that we should not underestimate the importance of our contribution as individuals to much-needed global change for greater good.

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