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Why the Human Microbiome Project Should Motivate Epidemiologists to Learn Ecology

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If you are not an astronomer (amateur or otherwise), looking at the stars can be an exercise in frustration. Where are the constellations? The planets? A telescope doesn't necessarily help: you can see things more clearly, but without knowing where to look and what to look for, you can't tell what you are seeing.

A similar problem arises as we consider the microorganisms that inhabit the human body. Our microbiota (previously called microflora) have been studied by high-throughput DNA sequencing of their genomes. Each of us carries at least 100 times more genes in our microbiota than in our personal genome.¹ There is so much there that it is hard to know where to look, and so the tendency is to explore more thoroughly what we already know, just as Galileo did when he first looked through a telescope. Galileo turned a telescope towards the moon and saw mountains; he looked at the Milky Way and saw separate stars; he looked at Jupiter and saw moons. But it took another century for astronomers to identify entirely new objects in the sky not proximate to those already known. The failure was not in the technology, but in pattern recognition. William Herschel—a musician turned astronomer—discovered a new way of seeing: reading the sky like a musical score, he mapped patterns in the sky, enabling him to discern deviations from those patterns, such as the previously undetected planet of Uranus.²

The initial applications of DNA sequencing in the study of microbiota focused on individual species, particularly those that cause disease. This emphasis on disease-causing organisms followed the lead of Leeuwenhoek and Koch. In the 3 centuries since Leeuwenhoek first peered at teeth scrapings under a microscope, and the century since Koch discovered how to grow bacteria in pure culture, microbiologists have focused on the morphology, physiology, and genetics of the small subset of the microorganisms in the body that are known to cause disease.

More recently, high-throughput sequencing has been directed toward the entire human microbiota. The International Human Microbiome Consortium and the Human Microbiome Project are characterizing the genomes of microbiota found on several sites in the normal human host (<http://nihroadmap.nih.gov/hmp/>). The diversity of organisms is mind-boggling, as is the volume of data generated; literally thousands of sequence reads are generated per sample.³ While the potential for changing our understanding of health and disease is huge, at

this stage, we have merely turned the telescope inwards and are still struggling to develop ways to see patterns and interpret them.

Why should epidemiologists care? It is already apparent that the human microbiota has profound effects on health and disease. Systems of feedbacks among the various microbes within a community, and between the microbial community and its human host, go far beyond the simple one-pathogen-one-disease model that was so successful in managing infectious diseases. The presence of microbes is essential for health maintenance. Consequently, disrupting the feedback systems between microbiota and host can be harmful: periodontal disease, bacterial vaginosis, and Crohn disease are all considered diseases of disrupted microbiota.

We understand little about the complex mechanisms that disrupt microbiota and result in disease. For example, antibiotic therapy changes the microbial community of the gastrointestinal tract,⁴ and undoubtedly also the microbiota found elsewhere in the body. These changes might alter expression of cytokines, antimicrobial peptides, or other host defense mechanisms, which, in turn, can increase risk of infection or development of chronic inflammation.⁵ But we are unable to predict the circumstances when antibiotic use will cause changes that lead to disease and when it will not. Similarly unpredictable are efforts to restore the microbiota to health. Total fecal “transplants” as a treatment for recurrent *Clostridium difficile* (in which the normal microbiota is extremely disrupted) are successful about 70%–75% of the time.^{6,7} Why some are not successful though, is still a mystery.

How can we use microbial sequence data to learn how to restore the microbiota to “normal” (whatever that turns out to be)? The first step is simply to characterize how microbiota differ in healthy and disease states. However, this is a much more complex problem than looking for single pathogens as an indicator of disease, because it entails comparing entire assemblages of microbes with their various species of bacteria, phage, fungi, protists, etc. Even the seemingly-simple task of comparing the number of species in 2 samples turns out to be complicated—the number of species detected depends heavily on the sampling effort.⁸ (The definition of species is an even larger can of worms! But that is a subject for another commentary).

Fortunately, the field of ecology has developed sophisticated methodological and computational tools to compare “community structure”—the diversity, composition, and relative abundance of species of trees in a hectare of forest, or of algae in a liter of lake water, or of bacteria in a gram of soil.^{9–11} These ecological approaches have been applied to the microbiota of the mouth,¹² stomach,¹³ and skin,¹⁴ and they have been used to compare gastrointestinal microbiota among monozygotic and dizygotic twins¹⁵ and to characterize the community structure of lung bacteria among cystic fibrosis patients.¹⁶ Extending those ecological metrics of community structure to the huge volumes of genomic data from healthy and diseased microbiota will enable us to see beyond the simple presence or absence of particular species in assessing the impact of microorganisms on health.

Static snapshots of microbiota communities hold promise, but such description is just the first step. A key characteristic of ecological systems—whether tropical forests or human microbiota—is that they are highly variable over time and space. (The notion of a “balance of nature,” a finely-tuned equilibrium that is static in the absence of anthropogenic disturbance, has long since been discarded in modern ecology.¹⁷) It is already clear that microbiota in apparently healthy humans are quite variable; even identical twins differ considerably in gastrointestinal microbiota.¹⁵ How the microbiota of a single individual changes over time is less well known, although the structure of the microbial community of

human skin for a given person is quite variable when tested 4–6 months later,¹⁸ as is the vaginal microbiota when sampled weekly over the course of the menstrual cycle.¹⁹ Quantifying the magnitude of temporal and spatial variability in the microbiota of healthy individuals is essential to understanding the wider role of the microbiome in health and disease. Especially important would be the discovery of changes in the microbiota community structure associated with later disease risk. It would be useful, for example, to be able to look at oral microbiota and identify children at high risk of developing caries, or to look at the gut microbiota and be able to predict for whom a course of antibiotics is most likely to cause chronic diarrhea.

Finally, and perhaps most importantly, data from the Human Microbiome Project and associated research can help to identify the mechanisms driving variations in the microbiome, and how this variation is associated with health and disease. A thorough understanding of such mechanisms will ultimately enable us to design appropriate prevention and treatment strategies for conditions that involve changes in the microbiota. Understanding the underlying disease mechanisms clearly requires knowledge of immunology, cell physiology, and molecular biology. These cellular and molecular mechanisms are, however, enabled by the structure of the microbial community present and community changes over time and space. Understanding community structure and dynamics is an ecological question, and so answering mechanistic questions also requires knowledge of ecology.

Ecologists have developed extensive theories to understand and interpret spatial-temporal variations in highly dynamic systems such as those in microbiota based on mechanisms, including dispersal, interactions among organisms, and direct physiological responses to environmental conditions. Epidemiologists are well aware of the critical importance of transmission of disease (“dispersal,” in ecological lingo), and already are collaborating with ecologists to develop models of transmission of single pathogens at the population level.^{20,21} The role of transmission in community dynamics of the microbiome is even more complex; however, ecologists have developed meta-community theory that could be applied to these systems. Interactions among microbes also can affect community dynamics, for example, through competition for nutrients, through mutualism and facilitation in biofilms, and through predation by phages. Ecological theory incorporating these mechanisms has been well-tested in relatively small systems; however, its application in highly-diverse systems is still extremely difficult. For example, resource competition theory has been successfully applied to systems of 2 competing species of algae or bacteria,^{22,23} but models falter in predictive capacity with even 3 or 4 interacting species.^{24,25} While modeling data on the dynamics of diverse communities is an active area of research, directly modeling human microbiome data using such mechanistic models is not likely to be useful in the short term.

An alternative is to use these models more heuristically in combination with patterns identified in human microbiome project data to generate hypotheses about mechanisms involving subsets of organisms. These hypotheses can then be tested experimentally. For example, Crohn disease is characterized by disrupted microbiota. Is this disruption due to transient microbes that invade the resident microbiota and subsequently change the community, which in turn modifies physiological function? Or do environmental factors (eg, diet) modify a resident community, which then leads to altered function, including perhaps greater susceptibility to invasion of transients? Appropriate interventions will differ depending on the answer. The design, conduct, and analysis of studies to differentiate among these alternatives will need both ecological and epidemiological expertise.

In order for epidemiologists to take full advantage of the new genomic data characterizing human microbiota, we believe that epidemiologists need to learn ecology. Like Herschel reading the stars, community ecology enables epidemiologists to interpret the patterns in microbiota data by providing strategies to link mechanisms to the complexity found in microbial communities. This, in turn, offers great potential to identify new diagnostic and prognostic indicators, mediators of disease processes, and clinical and population-level interventions.

Such studies will require huge data sets and complex study designs, given the extreme levels of variation in microbiota. Designing and conducting these studies is an epidemiological problem, but characterizing the microbial community structure and dynamics is an ecological problem. The analysis of such studies will need to go beyond the usual statistical approaches to incorporate dynamic mechanistic models with feedback systems that are common in ecology, and understanding the underlying mechanism(s) will require expertise in immunology and other disciplines.

In short, understanding the relationship of the microbiome to human health and disease will require a major interdisciplinary effort. Fortunately, putting together interdisciplinary teams is something epidemiologists also do well.

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