

Founding Editor's Viewpoint

Worlds Within Worlds: The Human Microbiome

*"Humans are in fact a vastly complex, biologic 'superorganism'"*¹

It has been over a decade since I wrote an editorial celebrating the announcement from the White House that we had the ability to decode and describe—and would inevitably learn to manipulate—the human genome.² President Bill Clinton, flanked by Frances Collins and Craig Venter, explained the scope of an achievement that electrified both the scientific and the lay communities. We were giddy with hope that we had a tool of unprecedented power not only to explain what makes us ourselves, but also to prevent or treat the diseases that carry us off. Nothing, unfortunately, is ever as easy as it seems initially: the more we learn about the genome, the more we are daunted by the complexity of how genes actually work and which combinations of them make us healthy or vulnerable to illness. Indeed, understanding how our genome interacts with the environment, experience, age, and hormones challenges even the most optimistic—and gifted—teams of investigators.

Not without some amusement at how even the grandest achievements almost immediately become yesterday's news, I read that as soon as the human genome sequence was published in 2001^{3,4} at least 3 teams called for what they termed a *second human genome project* to characterize the microbial genes of the organisms that inhabit our mouth, gut, vagina, and skin.⁵⁻⁷ Thus, defining the structure and function of our own genome is proving to be only the first step in an ever-expanding series of challenges. Over and over, biologists expressed surprise that the actual number of genes in the human complement is only about 20,000—the same number as in the fruit fly! In fact, the amazing truth is that we are not only composites of our separate, individual selves, but also hosts to microorganisms that live on our surface and within us, outnumbering the number of our cells by 10 to 1! These tiny travelers are collectively termed the *human microbiota*. There are about 100 trillion of them, and they represent up to 1000 separate bacteria, the majority of which live in our gastrointestinal tracts.⁸ They, of course, have genomes of their own, which turn out to be fundamentally important to our own function and collectively contain at least 100 times as many genes as we ourselves have.⁹

These organisms are central to our phenotypes, performing metabolic tasks that we ourselves cannot manage,¹⁰ and if their balance is disturbed, havoc can ensue. Thus, gut microbiota regulate the harvest of calories from our diet, and, as Turnbaugh et al have pointed out, have an important role in regulating body size.¹¹ This same team also provided other examples of how gut microbes affect phenotype: they can make otherwise inaccessible nutrients available; synthesize vitamins; alter drug metabolism and bioavailability; promote (or retard) the health of gut epithelial cells; help develop and maintain the immune system; influence cardiac size; and, even in mice, affect locomotor activity. The microbiota play other important roles in the genesis of disease: they may modify nutrients in a way that promotes the development of colorectal cancer and play an important role in the genesis of inflammatory bowel syndromes.¹²

Gynecologists spend much of their daily practice treating vaginal infections of various types. Lamont et al pointed out that the population of vaginal flora is not constant but changes character and complexity over time in response to many factors.¹³ They showed the important role of *Lactobacillus iners* and other acid-producing bacteria in promoting an optimal vaginal pH and in combating bacterial vaginosis by the production of hydrogen peroxide. These investigators suggest that a culture-independent method of

analyzing vaginal flora utilizing molecular-based techniques may help the treatment of recurrent or persistent infections and other disorders of vaginal physiology.

Nasidze et al reviewed the diversity of the human salivary microbiome¹⁴ and suggested that in addition to helping us understand disease of the oral cavity, analysis of the human salivary microbiome can yield insights into human population structure and migrations: “when humans migrate, they take their bacteria with them.”

It is a fascinating new idea that we are not as simple as we seem but instead are walking repositories for complex colonies of trillions of organisms on which we depend for health and which, when disturbed, can cost us dearly. In fact, it is humbling to realize that we cannot live without these helpful fellow travelers. The new emphasis on the human microbiome promises that if we can decode and understand the contribution to our individual lives of this huge cache of extra genes, we will reap a whole world of new information that will help us conquer stubborn, debilitating, and even fatal illnesses.

So far, in a search of the relatively new literature on the subject, the impact of gender on the composition of the microbiome is almost never considered. Given the rich harvest of information the scientific community has generated in the past 2 decades about the differences between males and females, it is surprising that including gender as an important variable has not been incorporated into the literature on the microbiome. Indeed, one of the most comprehensive reviews of metagenomic approaches to defining the pathogenesis of inflammatory bowel diseases concluded with a list of 7 important areas for future investigation.¹⁵ The impact of sex on the composition or function, or both, of the microbiome was not one of them. An exception is the paper by Aguirre de Cárcer’s group, reporting differences in the gut microbiome in males and females.¹⁶

The Institute of Medicine is concerned enough about the general problem of difficulties in representing both sexes in clinical investigations to have planned a workshop in Washington, DC, at the end of August with, among other experts, journal editors in attendance. Perhaps one day we will not have to beg for attention to the sex-specific characteristics of data; perhaps one day it will have become second nature to investigators to wonder about the possibility of male-female differences in any and all the phenomena that interest them.

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