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What Is the Microbiome and How Do We Study It?

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Since the very first report of bacteria (by Antony van Leeu-wenhoek in his September 17, 1683, letter to the Royal Society regarding his observation of bacteria living on his teeth), the colonization of humans with microbes has been a question of distinguishing friend from foe. Until relatively recently, the isolation of microbes relied on culture-dependent methods. Thanks to the advances in DNA sequencing, processing, and computational analysis, there is a new appreciation of the complexity and diversity of the microbes that inhabit the "human niche."

For those new to the discipline, the term microbiome was coined by Joshua Lederberg to describe the community of organisms that coexist with a species. Often, articles will apply the term "microbiota" to all organisms involved and reserve the term "microbiome" for the genomes of those organisms. Since 2007, when the NIH launched the "Human Microbiome Project (HMP)," there has been a global effort to sequence the microbiome and understand the vast community of microorganisms that inhabit our bodies. While in most cases these microbes exist in harmony and symbiosis with their host, disturbances in the microbiome are associated with some diseases with life-long consequences. In this issue, we focus on the role of the microbiome in reproduction.

Reproduction poses several interesting challenges that must be achieved within the communities of microbiota that exist in and on our bodies. First and foremost, male and female gametes must be able to negotiate the bacterial-infested environment and combine with fidelity to perpetuate the species. No additional genetic material is wanted and the gamete(s) must survive the perils implicit in the process of exchange of genetic material between different individuals. Second, the conceptus must be protected from interference from a hostile microbiota and deliver at term. Finally, the fetus must be inoculated with microbiota at the proper time to develop a microbiome that facilitates a sustained and healthy development. At times the process can go awry. Alterations in these complex microbial communities are associated with disease and altered development.

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To introduce the readers to the topic of the microbiome in reproduction, we have divided the topic into four sections. In Section I, the fundamentals of the microbiome will be introduced in terms of normal development. First, the issue begins with a review of whole genome sequencing (WGS) as a practical guide for clinicians, specifically comparing WGS with 16S-based metagenomics. Next, Prince et al review the microbiome from the mother's perspective. Then, Dr. Hsieh examines the current understanding of the micro-biome and probiotics in childhood.

Section II focuses on reproductive health, exclusive of pregnancy. Dr. Reid begins the section with a review of the vaginal microbiome including modulation of the vaginal microbiome with probiotics. Current understanding of the role of the microbiome in infertility and assisted reproduction is examined because the process of assisted reproduction provides a unique window into the events of the reproductive process and the vulnerability of gametes and embryos to disturbances in the microbiota. Section II concludes with a review of current understanding of the role of microbiota and pelvic infections.

Section III focuses on current understanding of the micro-biome in pregnancy. Contrary to long-standing tenets, the microbiome is actively shaped and modeled throughout pregnancy and microbial sterility is not assured, but exists in concert with the fetus.

Finally, Section IV examines how the newborn becomes colonized with the appropriate microbiome and the consequences of an unhealthy microbiome. Breast feeding is discussed by LaTuga et al. The contribution by Li et al is exceedingly important, as it illustrates the consequences of an unhealthy microbiome on immune-mediated childhood disorders.

While much has been learned in the 6 years since the HMP project was initiated, our current understanding is woefully insufficient. Many important questions remain. First, non-culture-dependent methods are currently limited in their clinical applications, as these methods have not fully penetrated to the clinical arena. Second, from the perspective of the patient and clinician, there are several conditions of the reproductive tract that have been recognized to have features of inflammation, but were "culture negative": two examples being histologic evidence of endometritis or chorioamnionitis and preterm labor. A third question that remains is to develop antibiotic regimens that do not produce protracted effects on the entire microbiome, but reestablish a milieu of reproductive health. Finally, in situations where an unhealthy microbiome foments disease, it is imperative that strategies be developed to return the microbiome to health, for the benefit of the host organism (*Homo sapiens*) and human reproduction.

In sum, over the past 350-some years, we have come to appreciate that the human microbiome is composed of distinct microbial communities at different body sites, and these different body habitats provide niches for diverse bacterial species. This microbiome is not a silent passenger—its metabolites may enhance immunity, alter the host metabolism, or prevent infections by canonical pathogens. In this upcoming era of meta-genomic medicine, reproductive health and infectious diseases must be considered in the context of the human microbiome and protective or pathogenic microbial communities. The contributions or effects of microbial communities and metagenomes may have a large impact on infection

susceptibility and disease pathogenesis, as well as the very essence of human development, adaptation, and reproductive capacity.