Microbiome and Health in Past and Present Human Populations

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The human body contains approximately 100 trillion cells, of which more than 90 percent are microbial. These underexplored and mostly nameless microorganisms, collectively known as the *human microbiome*, weigh about as much as the human brain and harbor an immense diversity of genes that far exceed the functional capacity of our own genome, playing critical roles in digestion, vitamin production, drug metabolism, and immunity. This intimate relationship between humans and their microbes is being increasingly described by evolutionary biologists as that of a *holobiont*, a large interdependent and symbiotic community that evolves as a unit and cannot be understood by examining independent members alone (Zilber-Rosenberg and Rosenberg 2008). In part to address this reconceptualization of what it means to be human, the National Institutes of Health Common Fund launched the Human Microbiome Project (HMP) in 2007, an initiative whose goal was to better understand the human holobiont by sequencing all symbiotic microorganisms in and on the human body (Peterson et al. 2009).

Over the past decade, high-throughput DNA and protein sequencing has opened up dramatic new opportunities to study the human microbiome; we now possess the tools necessary to comprehend and characterize the evolutionary ecology of the human microbiome and its role in health and disease. Numerous studies have revealed the complex and surprisingly central role the human microbiome plays in aspects of health as diverse as allergies and asthma risk (Gronlund et al. 2007; McLoughlin and Mills 2011), chemotherapy effectiveness (Karin et al. 2014), heart disease (Kholy et al. 2015), weight gain and loss (Angelakis et al. 2012), preterm labor risk (Witkin 2015), periodontal disease (Wang et al. 2013), and susceptibility to insect-borne infection (Verhulst et al. 2010). Moreover, microbiome therapies have been shown to alleviate the symptoms of disorders and diseases such as antibiotic-associated colitis (Kassam et al. 2012) and rheumatoid arthritis (Ortiz et al. 2009).

It is becoming increasingly clear that no study of human health or evolution is complete without consideration of our microbial self. Yet, while we have made great strides in revealing the diversity, variation, and evolution of the human genome, we know surprisingly little about the origins and diversity of the microbial portion of ourselves. Until very recently, nearly all studies of human evolution focused on the 10 percent of our cells and 0.7 percent of our genes that we conventionally call human. How has the other 90 percent of our cells and 99.3 percent of our hologenome evolved through time? Moreover, with few exceptions, even studies of the human microbiome have focused almost exclusively on Western industrialized societies, presenting a severe sampling bias that favors affluent metropolitan groups, potentially fostering downstream health disparities for under-represented peoples (Lewis et al. 2012). Anthropology can help remedy this.

Much like traditional anthropological genetics, anthropological microbiome research will improve our understanding of human evolution and diversity. How did the primate gut evolve and adapt to climate and habitat changes? Were certain microbes passed down, mother to child, forming a unique aspect of heritability? What role did microbes and their diverse genetic functions play as hominins expanded into new continents and as humans transitioned from low-density bands of hunter-gatherers to dense urban-dwelling populations reliant on industrial agriculture and globalized supply chains? Addressing these questions not only expands our understanding of what it means to be human, but it also provides a much-needed foundation for improving the human condition.

With the advent of industrialization, globalization, and modern sanitation, it is intuitive that we have changed our relationship with our own native microbiota, but we have little information about the ancestral state of our microbiome, and we therefore lack a foundation for characterizing this change and its impact on our health today. It has been persuasively argued that many of today's so-called "diseases of civilization," such as allergies, may be

exacerbated, if not caused, by recent changes in family size, living conditions, sanitation, diet, and antibiotics in industrialized nations, a concept known as the "hygiene hypothesis" (Strachan 1989). This hypothesis, which has been expanded to include the microbiome (Bendiks and Kopp 2013), posits that reduced microbial exposure and microbiome diversity early in life disrupts normal immune system development, leading to heightened predisposition to allergic diseases and autoimmune disorders. However, understanding how our industrialized lifestyle has affected our microbial health requires more precise knowledge of our preindustrial selves and the ancestral structure and function of our microbiome.

An anthropological approach to the study of the human microbiome differs conceptually in important ways from research being conducted in the fields of medicine and microbiology, which primarily focus on clinical frameworks of disease risk and experimental manipulation of model microbial communities, respectively. Guided by biological anthropology's traditional branches of primatology (nonhuman primates), paleoanthropology (extinct hominins), bioarchaeology (historic and prehistoric peoples), and human biology (diverse peoples today) and made possible by extraordinary technological advancements in molecular biology, investigations of the ancestral human microbiome are poised to make considerable contributions to evolutionary medicine and human health. The impact is already becoming apparent.

The ancestral human microbiome appears to be characterized by a richer and more diverse array of microbes than those found in modern industrialized peoples. Primate studies have found evidence of rapid gut microbiome evolution in the human lineage (Moeller et al. 2014), where individual wild apes harbored a more diverse assortment of microbes than observed in humans today. Similarly, investigations of traditional hunter-gatherer societies have revealed major reductions in gut microbial diversity associated with the adoption of industrialized diets (Obregon-Tito et al. 2015; Schnorr et al. 2014). We found that among the microbes that have been lost is a multispecies clade of bacteria belonging to the genus *Treponema* (Obregon-Tito et al. 2015). These treponemes, which are found in nonhuman primates and which are common and relatively abundant in the gut microbiota of traditional peoples, irrespective of geography or diet, are puzzlingly absent in the guts of industrial peoples. Although the exact roles and functions of these treponemes remain to be elucidated, partial genome reconstructions from metagenomic data and comparison to related taxa in animals suggest that they metabolize complex carbohydrates and produce short-chain fatty acids as waste products, a trait that in other microbial species is associated with anti-inflammatory properties (Fukuda et al. 2011; Hijova and Chmelarova 2007). It is thus tempting to hypothesize that the loss of these and other similar microbial species may be contributing factors in the rise of chronic inflammatory diseases, especially those originating in the gut.

Much like the study of human genes, the study of microbiomes is not limited to extant traditional peoples and primates. Ancient samples, such as archaeological feces (coprolites), can provide valuable information about the ancient human gut microbiome (Tito et al. 2008), and indeed we have found that prehistoric feces contain treponemes and more closely resemble the gut microbiota of present-day traditional peoples than those in industrialized societies (Tito et al. 2012), again reinforcing the conclusion that the human-gut microbiome has undergone rapid and recent changes. Turning to the oral cavity, calcified dental plaque (calculus) provides direct access to ancestral oral microbiomes (Warinner et al. 2015b), and our discovery that it is the richest known source of ancient DNA in the archaeological record opens many doors for sophisticated analyses (Warinner et al. 2015a). Moreover, unlike coprolites, dental calculus is nearly ubiquitous and frequently abundant in skeletal assemblages, making detailed diachronic studies of ancestral oral microbiomes possible. Already, genetic and proteomic investigations of archaeological dental calculus have documented the presence of numerous periodontal and opportunistic pathogens in the oral cavities of historic and prehistoric populations (Warinner et al. 2014b), and they have even revealed dietary components that otherwise leave few traces (Warinner et al. 2014a; Warinner et al. 2014b). As such, coprolite and dental calculus studies are paving new paths to understanding the ancestral state of human biology and diet.

The microbiome is a core component of our humanity. Anthropology has great potential to illuminate the long and intimate relationship between humans and their microbes and to lead to a deeper understanding of human health in the modern world.