The Diverse Microbiome of the Hunter-Gatherer

The Hadza of Tanzania offer a snapshot of the co-adaptive capacity of the gut ecosystem

By Stephanie L. Schnorr

We tend to forget that modern humanity is largely sheltered from the last vestiges of wild untamed Earth and that our way of life bears little resemblance to how our ancestors lived during 90 percent of human history. We have lost nearly all trace of these former selves—and, worse, have marginalized the few remaining humans who retain their hunter-gatherer identity. In Tanzania, tribes of

wandering foragers called the Hadza, who have lived for thousands of years in the East African Rift Valley ecosystem, tell us an immense and precious story about how humans, together with their microbial evolutionary partners, are adapted to live and thrive in a complex natural environment.

Ongoing research with the Hadza to characterize the hunter-gatherer-microbiome relationship has yielded not only insight into the co-adaptive capacity of this microbial ecosystem but also a profound

appreciation for how versatile human life can be. The microbiome is central to our biology. It mediates the interaction and exchange of information across host-environment thresholds such as the mouth, skin and gut.

The strength and importance of this mediation are borne out in the Hadza gut microbiota. Their microbiome harbors incredibly high taxonomic diversity, indicating great ecosystem stability and flexibility. It is capable of withstanding the perpetual presence of parasites and pathogens and can respond to fluctuations in diet caused by an unpredictable and seasonally dependent food supply. Interestingly, bacterial taxonomic abundance is different in Hadza men and women. Because of the sexual division of labor in Hadza society, men and women tend to consume more of their respective foraged food resources. The women primarily collect and eat tubers and other plant foods. As a result, it appears that women carry more bacteria to help process the plant fiber in their diets. This difference has direct implications for how the gut microbiota may enable Hadza

germ-free mice with bacteria taken from the intestines of another mouse strain, the recipient animals would take on aspects of the donor's personality. Naturally timid mice would become more exploratory, whereas more daring mice would become apprehensive and shy. These tendencies suggested that microbial interactions with the brain could induce anxiety and mood disorders.

Bercik and Collins segued into gut-brain research from their initial focus on how the microbiome influences intestinal illnesses. People who suffer from these conditions often have co-occurring psychiatric problems such as anxiety and depression that cannot be fully explained as an emotional reaction to being sick. By colonizing germ-free mice with the bowel contents of people with irritable bowel syndrome, which induces constipation, diarrhea, pain and low-grade inflammation but has no known cause, the McMaster's team reproduced many of the same gastrointestinal symptoms. The animals developed leaky intestines, their immune systems activated, and they produced a barrage of pro-inflammatory metabolites, many with known nervous system effects. Moreover, the mice also displayed anxious behavior, as indicated in a test of their willingness to step down from a short raised platform.

AUTISM CONNECTION?

SCIENTISTS HAVE ALSO BEGUN to explore the microbiome's potential role in autism. In 2007 the late Paul Patterson, a neuroscientist and developmental biologist at the California Institute of Technology, was

intrigued by epidemiological data showing that women who suffer from a high, prolonged fever during pregnancy are up to seven times more likely to have a child with autism. These data suggested an alternative cause for autism besides genetics. To investigate, Patterson induced flu-like symptoms in pregnant mice with a viral mimic: an immunostimulant called polyinosinic:polycytidylic acid, or poly(I:C). He called this the maternal immune activation (MIA) model.

The offspring of Patterson's MIA mice displayed all three of the core features of human autism: limited social interactions, a tendency toward repetitive behavior and reduced communication, which he assessed by using a special microphone to measure the length and duration of their ultrasonic vocalizations. In addition, the mice had leaky intestines, which was important because anywhere from 40 to 90 percent of all children with autism suffer from gastrointestinal symptoms.

Then Caltech microbiologist Sarkis Mazmanian and his doctoral student Elaine Hsiao discovered that MIA mice also have abnormal microbiomes. Specifically, two bacterial classes—Clostridia and Bacteroidia—were far more abundant in the MIA offspring than in normal mice. Mazmanian acknowledges that these imbalances may not be the same as those in humans with autism. But the finding was compelling, he says, because it suggested that the behavioral state of the MIA mice—and perhaps by extension autistic behavior in humans—might be rooted in the gut rather than the brain. “That raised a provocative question,” Mazmanian says. “If we treated gastrointestinal

women to obtain adequate nutrition for fertility and reproductive success, despite a resource-limited environment. Through our work with the Hadza, we have been able to contribute to mounting evidence that human microbiota exerts a powerful influence on host health and survival, especially in natural fertility- and subsistence-based populations.

Comparative analysis of the gut microbiota of hunter-gatherers with that of Westernized industrial populations is also beginning to yield important insights. The microbial diversity in industrial groups is far below that of the Hadza, as well as those of other rural farming communities in Burkina Faso, Malawi and South Africa. Whereas a reduction in diversity may not seem ideal, it is the predictable response of an ecosystem facing a narrow range of selective pressures and is therefore no less adaptive. Some technological interventions, such as hypersanitation, consumption of refined foods and habitual use of antibiotics, have had a dramatic impact over time on the functional role of the microbiome in industrial populations. These

aspects of a Westernized way of life have to a large extent displaced much of the original mutualistic functions of the microbiome in stabilizing our bodies against foreign microorganisms, allowing us to digest unprocessed foods and helping train our immune system to effectively fight disease.

We are just beginning to understand how the microbiome evolves over our lifetimes as a dynamic and mutualistic ecosystem that helps to facilitate human health. Thanks to the Hadza, we know that ancient human hunter-gatherers must have maintained a direct and persistent interface with the natural environment. As a result, the ancestral human microbiome was almost certainly a taxonomically diverse community, providing the functional flexibility that accompanied global colonization and is our adaptive legacy.

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Each horizontal bar represents an individual in the study group
Each color represents a different microbe phylum (■ = Firmicutes)

TAXONOMIC TREASURE TROVE:

A survey of fecal microbiota of 43 subjects revealed a more varied mix of gut bacteria phyla among Hadza hunter-gatherers compared with urban Italians.

symptoms in the mice, would we see changes in their behavior?"

Mazmanian and Hsiao investigated by dosing the animals with a microbe known for its anti-inflammatory properties, *Bacteroides fragilis*, which also protects mice from experimentally induced colitis. Results showed that the treatment fixed intestinal leaks and restored a more normal microbiota. It also mitigated the tendency toward repetitive behavior and reduced communication. Mazmanian subsequently found that *B. fragilis* reverses MIA deficits even in adult mice. "So, at least in this mouse model, it suggests features of autism aren't hardwired—they're reversible—and that's a huge advance," he says.

LIMITS OF RESEARCH

THE HUMAN GUT MICROBIOME evolved to help us in myriad ways: Gut microbes make vitamins, break dietary fiber into digestible short-chain fatty acids and govern normal functions in the immune system. Probiotic treatments such as yogurt supplemented with beneficial strains of bacteria are already being used to help treat some gastrointestinal disorders, such as antibiotic-induced diarrhea. But there are little data about probiotic effects on the human brain.

In a proof-of-concept study Mayer and his colleagues at U.C.L.A. uncovered the first evidence that probiotics ingested in food can alter human brain function. The researchers gave healthy women yogurt twice a day for a month. Then brain scans using functional magnetic resonance imaging were taken as the women were shown pictures of

actors with frightened or angry facial expressions. Normally, such images trigger increased activity in emotion-processing areas of the brain that leap into action when someone is in a state of heightened alert. Anxious people may be uniquely sensitive to these visceral reactions. But the women on the yogurt diet exhibited a less "reflexive" response, "which shows that bacteria in our intestines really do affect how we interpret the world," says gastroenterologist Kirsten Tillisch, the study's principal investigator. Mayer cautions that the results are rudimentary. "We simply don't know yet if probiotics will help with human anxiety," he says. "But our research is moving in that direction."

Strains of *Bifidobacterium*, which is common in the gut flora of many mammals, including humans, have generated the best results so far. Cryan recently published a study in which two varieties of *Bifidobacterium* produced by his lab were more effective than escitalopram (Lexapro) at treating anxious and depressive behavior in a lab mouse strain known for pathological anxiety. Although Cryan is optimistic that such findings may point the way to the development of psychobiotics, he is wary of hype. "We still need a lot more research into the mechanisms by which gut bacteria interact with the brain," he says.

Charles Schmidt is a recipient of the National Association of Science Writers' Science in Society Journalism Award. His work has appeared in *Science*, *Nature Biotechnology*, *Nature Medicine* and *the Washington Post*.