

oscillations in both R and M to 60 T using pulsed magnetic fields. Their finding appears to be the first report of quantum oscillations in the resistivity (“Shubnikov-de Haas,” or SdH oscillations) in an insulator. Repeating the SdH measurements with the magnetic field tilted at an angle, Xiang *et al.* found that the angular variation of the SdH period is distinctly three-dimensional, which they argue excludes a surface origin for the SdH oscillations. The angular variation appears to describe a Fermi surface that resembles a worm hole (see the figure, bottom panel).

Theories for quantum oscillations in an insulator (5–7) may now be confronted in part by experiment. As the temperature is raised, increased scattering of the carriers by lattice vibrations leads to broadening of the Landau levels, which results in an exponential decrease in the oscillation amplitude. Typically, SdH experiments find close agreement with the Lifshitz-Kosevich (LK)

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expression, which enables the effective mass of carriers to be extracted. Likewise, Xiang *et al.* found good agreement between the damping of the SdH signal with the LK expression, which is in contradiction with some of the predictions.

Last, the quantum oscillations observed with magnetometry (“de Haas-van Alphen” oscillations) display a different behavior in the tilt-angle experiment as well as in the damping rate of the amplitude (8). Xiang *et al.* associate different origins for the two sets of oscillations. Although the new results exclude some classes of proposed theories, many aspects of the experiment pose a stiff challenge to conventional wisdom. ■

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MICROBIOLOGY

Preserving microbial diversity

Microbiota from humans of all cultures are needed to ensure the health of future generations

By Maria G. Dominguez Bello¹, Rob Knight², Jack A. Gilbert³, Martin J. Blaser⁴

Since World War II, there have been dramatic increases in metabolic, immune, and cognitive diseases, including obesity, diabetes, asthma, allergies, inflammatory bowel disease, and autism. Their incidence has risen, first in the industrialized world and more recently in developing countries (1). In addition to the health effects, there are enormous costs of these diseases: Obesity costs \$2.0 trillion and diabetes costs \$1.3 trillion per year globally (1–3). As these diseases advance in developing countries, the problem is worsening rapidly. The cost, to health and economies, is becoming unsustainable, with care of chronically ill adults competing with the proper care for the next generation. Are all these distinct diseases independent, or is there a common underlying factor? We believe that changes in the human microbiota occurring concomitantly with industrialization may be the underlying factor. The changes involve the loss of our ancestral microbial heritage to which we were exposed through millions of years of evolution.

The microbiota (and its collective genomes, the microbiome) encompasses bacteria, archaea, viruses, fungi, and other microeukaryotic colonizers that live in or on our bodies. They influence essential host processes, including nutrition, immunity, hormone activity, gut permeability, and neurochemistry. The microbiome, our “other genome,” is largely passed from generation to generation, in early life, from mothers to their children (4). The germline and somatic genomes, microbiome, and external environment are all essential features of population variation that are useful for predicting host disease and health outcomes (5, 6). Microbes acquired in early life play crucial roles in guiding the development of immune, metabolic, and neural systems in animal models (7–10) and may also be important in human development, as indicated by epidemiological

evidence. Animal studies have shown causation in the relationship between associations of microbiome perturbations in early life and later development of diseases such as obesity, juvenile diabetes, and asthma (7–10).

Industrialization is substantially correlated with reduced human microbiota diversity (11). The gut diversity of South American Amerindians is ~2-fold that of healthy people in the United States (12, 13). Comparing disparate traditional societies with industrialized peoples indicates that the loss of gut microbial diversity is associated with industrialization, not with particular diets, ethnicity, or geography. People in industrialized and developing countries from across the world can be classified into two overall groups: low and high intestinal bacterial diversity, respectively (11–13). Industrialization encompasses many influences on the microbiota, including a highly processed water supply, refined diets, and altered environmental exposure—which may affect the microbiota through effects on the immune system—and the presence of medical care, including pre-, peri-, and postnatal antibiotics; cesarean section delivery; and bottle-feeding—all of which reduce the transmitted and maintained microbial diversity, especially during the critical window of early-life development (see the figure). Loss of microbiota diversity opens up niches for opportunistic invaders, which often do not have the same coevolved constraints. Intestinal bacterial taxa of *Desulfovibrio*, *Bacteroides*, *Prevotella*, *Lactobacillus*, *Oxalobacter*, and lineages in the families Succinivibrionaceae, Paraprevotellaceae, and Spirochaetaceae (11, 12) are disappearing with industrialization. For example, *Oxalobacter formigenes* uses indigestible oxalate and its loss (12) may be hindering protection against the formation of kidney stones, which are composed of calcium oxalate. This is just the beginning of our knowledge about the impacts of living in an industrialized world—we need to better understand which strains in human populations are diminishing and what the functional and pathological implications are for these losses.

In many ways, the loss of our microbial diversity resembles climate change: Industrialization has led to substantial unintended pressures on global ecology. Currently, over 50% of the world’s population lives in urban environments, and cities are likely to ab-

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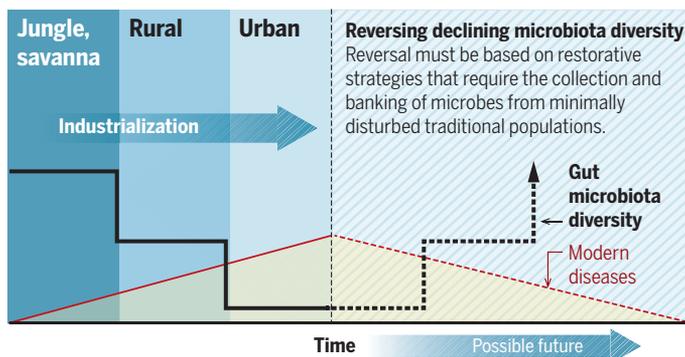
sorb future population growth. We suspect that the microbes disappearing in urban societies are those that are needed to maintain health and prevent many metabolic, immune, and cognitive diseases. If microbial disruption due to urbanization increases the diseases of industrial societies, then the current global pandemics will worsen, with economic impact jeopardizing health care systems.

However, much can be accomplished through better stewardship: curtailing the overuse of antibiotics, limiting cesarean sections to those that are necessary and not for convenience, promoting breastfeeding, removing antibacterial compounds from everyday activities, and changing diets to emphasize the nutrients and foods that promote microbial diversity and metabolism that benefits our health (14). But, these efforts will likely only diminish the rate of decline. We must examine ways to accelerate microbial restoration to recover functional activities, those reduced through microbiota depletion or those that, like weeds, overgrew in an affected microbiota, suppressing normal activities and health. We can replace specific microbial gut functions through the targeted provision of microbial metabolites (for example, intestinal butyrate to signal to and nourish colonocytes, or vaginal lactate to select for acid-tolerant microbes) to replace the fermentative activities of endogenous microbiota. Further scientific exploration will enable the development of dietary additives to help replace our lost chemistry. But nature is hard to micromanage because individual organisms have complex functions, with (often overlooked) context-dependent characteristics. This might explain the utility of fecal microbiota transplantation (FMT), a restorative technique for returning ecological balance to the colon, including eliminating life-threatening *Clostridium difficile* infections (15), and is being tested for other conditions associated with altered microbiotas. Identifying the activities of specific microbial species and strains is essential for more targeted and effective interventions, such as the provision of specific bacteria or probiotics.

Controlled restoration of the missing microbiota must be balanced against the importance of not introducing harmful microbes. Additionally, there needs to be greater knowledge of the specificity of microbe-host interactions; for example, does

Declining human intestinal microbial diversity with industrialization

There has been a progressive decline in human gut microbiota diversity with industrialization. The compounded effects of chlorinated water, antibiotics, antiseptics, cesarean section birthing, and formula feeding may all contribute. This decline has been linked to the rise of modern diseases: obesity, asthma, food allergies, diabetes, inflammatory bowel disease, and cognitive disorders.



a proposed intervention yield the same outcome in Dublin and Dhaka? Identifying nutrients that specifically enhance the colonization of the selected microbes to be restored, yet maintaining the desired diversity, will be challenging. Moreover, restoration may be dependent on host age, gender, and/or genotype, meaning that finding universal treatments that are broadly effective may be difficult. Fiber (14) and other nutrients present in the diet of peoples with more traditional lifestyles may represent some of the key compounds to sustain the microbes that are needed for restoration. The antigenic and metabolic properties of microbes may have been selected based on specific host phenotypes or environments. If a person's ancestors were milk-drinking cattle farmers, then their microbial exposures, immune responses, and endogenous microbe-immune interactions might differ radically from people whose ancestors were fishermen. Reducing microbial extinctions due to industrialization is important but unlikely to be sufficient to arrest the current disease trend without restoration. Purposeful microbial restoration emphasizes prevention rather than treatment and is possibly the only way that microbial losses can be reversed.

Most urgently, we need to preserve the diversity of ancestral microbes from globally diverse human populations and especially include those who have had the least exposure to urbanization. Using current technology, and under the precautionary principle (to avoid the introduction of products and processes the ultimate effects of which are unknown), it is paramount that we expand the efforts to capture and preserve the human microbiota while it still exists. This is a needed step toward restoration and could help mitigate the potential risk to hu-

man health that urbanization encompasses.

Biobanking initiatives are arising in universities and companies, but most are focused on preserving specimens and strains from individuals in industrialized societies. These collections are prepared for custom microbiome analysis and for clinical uses, such as FMT. Research collections that contain microbes from geographically diverse individuals have begun, but few have collected high-diversity microbiotas from traditional peoples in developing countries, which hold promise for disease-prevention restoration strategies. Such biobanking has challenges, including accessing remote peoples, relying on local teams

of scientists who hold the required permits, and training local microbiologists to foster collections, as well as our limited capacity to culture a wide diversity of microbiota species and to classify it. Biobanking efforts need to be supported and expanded into developing countries (that hold the richest human microbial biodiversity) (11–13). This will involve sharing and transferring the required technologies from industrialized countries (that hold depleted human microbiotas) to the ancestral microbe-rich developing countries. A global repository of human-associated microbes should back up existing research collections, similar in principle to the inspiring example of the Seed Vault established in the permafrost of Svalbard Island in Norway to preserve the natural biodiversity of plants. We owe future generations the microbes that colonized our ancestors for at least 200,000 years of human evolution. We must begin before it is too late. ■

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