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Bugs Inside:
What Happens When the Microbes That Keep Us Healthy Disappear?

The human body has more microbial than human cells, but this rich diversity of micro-helpers that has evolved along with us is undergoing a rapid shift--one that may have very macro health consequences

BUG OFF: Are hygienic and medical advances killing germ allies essential to our health?

Bacteria, viruses and fungi have been primarily cast as the villains in the battle for better human health. But a growing community of researchers is sounding the warning that many of these microscopic guests are really ancient allies.

Having evolved along with the human species, most of the miniscule beasties that live in and on us are actually helping to keep us healthy, just as our well-being promotes theirs. In fact, some researchers think of our bodies as superorganisms, rather than one organism teeming with hordes of subordinate invertebrates.

The human body has some 10 trillion human cells—but 10 times that number of microbial cells. So what happens when such an important part of our bodies goes missing?

With rapid changes in sanitation, medicine and lifestyle in the past century, some of these indigenous species are facing decline, displacement and possibly even extinction. In many of the world's larger ecosystems, scientists can predict what might happen when one of the central species is lost, but in the human microbial environment—which is still largely uncharacterized—most of these rapid changes are not yet understood. "This is the next frontier and has real significance for human health, public health and medicine," says Betsy Foxman, a professor of epidemiology at the University of Michigan (U.M.) School of Public Health in Ann Arbor.

Meanwhile, each new generation in developed countries comes into the world with fewer of these native populations. "They're actually missing some component of their microbiota that they've evolved to have," Foxman says.

Mice have survived largely free from microbial populations in labs. But out in the world, traditional microbes are an important line of defense against external and possibly dangerous invaders. By occupying and even protecting their historic niche, this small fauna can keep out more foreign bacteria and viruses, in turn helping to maintain their human host's health. "Someone who didn't have their microbes, they'd be naked," says Martin Blaser, a professor of microbiology and chair of the Department of Medicine at New York University Langone Medical Center in New York City.

Companies have embraced aspects of microbial research, spreading antibacterials to kill broad swaths of microbes or promoting probiotic foods to introduce other groups of bacteria into the body. These extremes, however, can make scientists in the field squirm. "There is just so much we don't know," Foxman says about manipulating these dynamics. And changes can occur quickly, even when they are unintentional.

Potent treatments

Many of the changes in the human microbiome that have surfaced in recent decades are a result of well-intentioned—and primarily salutary—developments in medical treatment and prevention. For example, overprescription of antibiotics, real lifesavers ever since the mid–20th century, has sparked the evolution of drug-resistant strains of tuberculosis and *Staphylococcus aureus*. More subtle side effects of antibiotics are just beginning to be discovered.

"When antibiotics were first introduced, they were miraculous drugs—and they still are," Blaser says. "But it really wasn't fully considered that antibiotics select for resistance." And an antibiotic will not only impact the infection it is targeted for. "It will select for resistance across the microbiome," he added.

Common side effects of antibiotic treatments, such as yeast infections, are a prime example of these silent shifts. Even as it is being taken for an infection in another part of the body altogether, an antibiotic can kill the organisms that habitually keep yeast populations in check, allowing an unintended outbreak to occur.

Whereas some of these changes are transient and possibly a worthwhile trade-off for antibiotic treatment, others are more lasting and deleterious. As Blaser notes, "the [antibiotic resistance] selection can persist for years and possibly permanently." The vanishing gastric *Helicobacter pylori* bacteria, for example, have been *facing eradication in the U.S. and other developed countries in large part from antibiotic use.* Although this bacteria's demise has been pegged to some positive outcomes, such as a decrease in the incidence of gastric cancer, shrinking its populations can also increase the risk for various reflux diseases by upsetting the regulation of hormones and pH levels.

Additionally, "H. pylori–*positive individuals have lower risks of childhood asthma, allergic rhinitis and skin allergies* than those without *H. pylori*," Blaser and Stanley Falkow, of the Department of Microbiology and Immunology at Stanford School of Medicine, wrote in an essay published in November in *Nature Reviews Microbiology*. (*Scientific American* is part of Nature Publishing Group.) They *also posited that due to the bacteria's role in mediating the hormone ghrelin, which helps regulate fat* *development and hunger*, it might also "be contributing to the current epidemics of early-life obesity, type 2 diabetes and related metabolic syndromes."

This shift in such a prominent bacterial community is detectible through various medical tests, but transitions in many other species with positive impacts on human health may still be going unnoticed. "If [*H. pylori* is] disappearing…might there be other things that are disappearing?" Blaser asks. He worries that many other, less studied species—and even certain metabolic pathways—might also be on their way out due to antibiotic use and other lifestyle changes.

Blaser doesn't call for abandoning a whole class of effective drugs, but he does advocate for a better understanding of the potential trade-offs—even if we might not yet have all the answers. "I don't think anyone was putting that trade-off on the plate," says Blaser, who notes that both doctors and patients should reserve antibiotic use to cases where they are necessary.

Precarious protection

For many illnesses, modern medicine and research has bypassed the treatment phase by developing effective prevention—ranging from vaccines to public health measures to antibacterial products. And the very successes of these measures "shows that we are changing the microbiota," Blaser notes.

The vaccine for pneumococcal disease has been, by most accounts, a success story, reducing the number of pneumonia cases and infections. *But* Streptococcus pneumoniae *is, in fact, a frequent occupant of healthy individuals, and keeping this element out of the human body has opened space for different and potentially more harmful pathogens.* "The pneumococcal vaccine, which is extremely well intended, may be having some untoward consequences," Blaser says. Staphylococcus aureus*, which causes staph infections (a growing number of which are community-associated methicillin-resistant* Staphylococcus aureus*, or MRSA) and the traditional* S. pneumoniae *are "competitors, and that loss of the former is leading to the expansion of the latter,"* Blaser and Falkow wrote in their *Nature Reviews Microbiology* paper. Like antibiotics, however, vaccines are still important, Blaser says, but some of these long-term consequences should be examined in the future.

Like modern medical developments, improved sanitation and the proliferation of cleansers have saved countless lives and made the rest of us seemingly healthier, but *microbiologists are also rooting out the dark side to clean living.*

Those who subscribe to the "hygiene hypothesis" assert that overall cleanliness has resulted in the recent increase of ailments such as allergies and other immune system abnormalities. Such a line of thinking asserts that "if you're a good parent you should have your children eat dirt," Blaser says. Indeed, a study published online December 7 in *The Journal of Experimental Medicine* found that even while in the womb, mice whose mothers were exposed to a common barnyard microbe (*Acinetobacter lwoffii* F78) were less likely to suffer from allergies and asthma.

An overexuberance for the hygiene hypothesis, however, may be leading people astray, Blaser notes. "It's my hypothesis that the microbes that are present in dirt are irrelevant to humans," he says. "What are relevant are the microbes that we've had for hundreds of thousands of years—[and] are disappearing."

Extreme hygiene, on the level of using antibacterial products, is an asset in health care settings, such as hospitals, where risk of infection is high, Blaser notes. But such measures are not likely working to our long-term advantage elsewhere, where the "benefit is minimal if any," he says. "We have to begin to realize that we may be doing some harm—we may be losing some of the good guys and thus become more susceptible to the bad guys."

On the other end of the spectrum, popular probiotic products, which promise to introduce beneficial bacteria by way of fortified food, such as yogurt, are just one of the ways the primitive understanding of human microbiota has begun to permeate popular culture. But many researchers think confidence in such an approach is premature. "There's clearly something there," Foxman says, "but if you want to push a system to be a healthy system, you have to know what a healthy system is."

And that's something researchers are frantically trying to figure out. Blaser says: "If we understood what we're losing, then we could replace it." He imagines a future where vaccinations are not just for viruses but for microbial populations, as well. Infants may one day be screened for native microbiota and given immunizations to fill in important missing niches.

Mapping the microscopic

Even though it is such an apparently integral and ancient aspect of human health, scientists are still grasping for better ways to study human microbiota—before it changes beyond historical recognition. Borrowing models from outside of medicine has helped many in the field gain a better understanding of this living world within us. "The important concept is about extinctions," Blaser says. "It's ecology."

Deborah Goldberg, a plant ecologist by trade and professor in the Department of Ecology and Evolutionary Biology at U.M., happened upon the field by chance, but she has found her ecological perspective to be quite "relevant in talking about pathogens," she says. Microbiologists had already begun to apply rudimentary ecological thinking about niches and disturbance to microbial work, she says. But newer developments in the field of ecology—from invasion biology to spatial dynamics and dispersal—have brought new insights, notes Goldberg, who co-authored a 2007 paper with Foxman in *Interdisciplinary Perspectives on Infectious Diseases* about human microbiota.

For many current research purposes, however, the ecological model can be daunting. "As an overall approach, ecology is hard," Goldberg says. "It's complex systems and highly dimensional."

These challenges have led many to think of human microbiota more as biologists conceptualize organ systems, looking for inputs and outputs and putting aside—for now—what happens in the so-called black box. "It's conceptually easy to think of it as an organ system," Foxman says. "But there are lots of reasons to go into the black box…. Ultimately, we really do need to understand the system."

The first step in understanding these systems is simply taking stock of what archaea, bacteria, fungi, protozoa and viruses are present in healthy individuals. This massive micro undertaking has been ongoing since 2007 through the National Institutes of Health's (NIH) Human Microbiome Project. So far it has turned up some surprisingly rich data, including genetic sequencing for some 205 of the different genera that live on healthy human skin.

Despite the flood of new data, Foxman laughs when asked if there is any hope for a final report from the Human Microbiome Project any time soon. "This is the very, very beginning," she says, comparing this project with the NIH's Human Genome Project, which jump-started a barrage of new genetic research. "There are basic, basic questions that we don't know the answers to," she says, such as how different microbiota are between random individuals or family members; how much microbiota change over time; or how related the microbiota are to each other on or inside a person's body.

Rapid advances in sequencing technology, however, have allowed researchers to accelerate their work by leaps and bounds. "I can do today what I couldn't do six months ago," Foxman says. "It's going to be a wild ride [with] lots of surprises," she adds. "We will be getting in that black box pretty quickly, but we may not like what we find."