





THE TRANSCENDENT MICROBIOME

How do the trillions of bacteria that live in our stomach, skin, teeth, and genitals influence our health? NYU Langone researchers are finding out.

BY JOSIE GLAUSIUSZ

Illustration by JEFFREY DECOSTER

A JUNGLE OF MICROBES IS HARDLY WHAT MOST people imagine when they examine their arms. Several years ago, however, Martin J. Blaser, M.D. ('73), the Frederick H. King Professor of Internal Medicine and professor of microbiology, discovered just such a motley zoo when he sequenced the DNA of bacteria taken from the forearms of three men (including himself) and three women. All told, 182 different species were found cohabiting with one another on the subjects' skin.

To identify the bacteria, Dr. Blaser, who also chairs the Department of Medicine, and his colleagues used a complicated and labor-intensive method in which fragments of DNA from the bacteria were cloned and amplified in a bacterial vector, then sequenced and compared to parallel strands from previously identified bacteria. The entire study, based on a total of 2,000 sequences, took three years to complete.

Today such a study would take mere weeks to conduct and analyze—thanks to the development of state-of-the-art, high-throughput genome sequencers that decode up to 1.25 million DNA sequences at one time. These machines can sequence tens of millions of DNA samples by reading them in fragments of up to 600 to 800 base pairs in length, and still faster machines, the so-called next generation, can read microbial genomes as even shorter lengths of DNA (each up to 450 base pairs), which can then be reassembled.

This new technology has transformed genomic research, allowing Dr. Blaser and other researchers to sequence and study the largely unexplored world of microbes that reside on our skin and inside the nose, mouth, esophagus, stomach, intestine, and vagina. These microbial cells, collectively known as the human microbiome, outnumber the cells of our own bodies by 10 to 1; they communicate with our own cells and with our immune systems, carry out essential metabolic tasks, crowd out pathogens, degrade toxins, and help digest our food.

“Most germs are pretty wonderful,” says Dr. Blaser. “The microbes that are living in us have been with us forever. And the reason they have been with us forever is that they do good things for us. They have been selected because they are part of human physiology.”

MAPPING THE MICROBIOME



HIS NEW ABILITY

to analyze the genetic makeup of these microbial denizens has garnered intense interest from the NIH. In 2007 the NIH launched the Human Microbiome Project, which will award \$115 million in research grants over the next five years for the sequencing of up to 600 microbial genomes and for selected demonstration projects that will examine the relationship between the microbiome in a specific niche of the body with a particular disease. The goal is to figure out whether individuals share a core human microbiome, and to examine how changes in microbial populations correlate with changes in human health.

Ultimately, understanding these bugs

could lead to new therapies for human diseases. For example, if the microbiome is altered by certain skin diseases or, say, obesity, doctors could replace the missing microbes with probiotic bacteria—beneficial microbes that would help restore a healthy balance by crowding out destructive bacteria.

“The microbiome is a very sexy topic at the moment,” says Jane Carlton, Ph.D., associate professor in the Department of Medical Parasitology, who studies the microbes that live in the vagina. “The NIH is providing lots of funding for this.”

“It’s a great time to do microbiome research,” Dr. Blaser agrees. “The tools are fantastic, and they keep getting better.” In fact, his lab has already begun using NIH funds to sequence about 20 species of skin bacteria and to examine

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how the microbiome of psoriatic lesions on the skin differs from normal skin. Dr. Blaser’s group and that of his colleague Dr. Zhiheng Pei are 2 out of only 10 teams selected in the United States to help jump-start the project. “This is a big deal for us, since NYU received 20 percent of the country’s grants,” says Dr. Blaser, whose work is also supported by a grant from NYU Life Trustee Diane Belfer.

Dr. Blaser was at the forefront of microbiome research long before it was sexy: for more than two decades, he has studied the bacterium *Helicobacter pylori*, a once-ubiquitous inhabitant of the human stomach that causes peptic ulcers and stomach cancer. Thanks to improved hygiene and antibiotics, *H. pylori* has been slowly disappearing from developed countries over the past century—with unexpected consequences. In 1998, Dr. Blaser reported that people lacking *H. pylori* in their gut are more likely than others to develop gastroesophageal reflux disease (GERD), perhaps because their stomachs secrete more acid. In research published last year in *The Journal of Infectious Diseases*, Dr. Blaser and Yu Chen, Ph.D., M.P.H., assistant professor in the Departments of Medicine and Environmental Medicine, reported that

children between the ages of 3 and 13 are nearly 60 percent less likely to have asthma if they carry *H. pylori*.

Fritz Francois, M.D., a gastroenterologist and assistant professor of medicine, has found that *H. pylori* also influences gastric and serum levels of leptin, an appetite-suppressing hormone, and ghrelin, an appetite-stimulating hormone. In ongoing studies, Dr. Francois measured acid and serum hormone levels in people before and after they ate a meal, and found that among those who lacked *H. pylori*, appetite-stimulating ghrelin levels were high before they ate and decreased afterward—as would be expected. In the *H. pylori* carriers, ghrelin levels also decreased as expected after they had eaten. However, six months after antibiotics had eliminated the bacteria from these patients, their premeal levels of ghrelin shot up and remained elevated after a meal.

Dr. Francois hypothesizes that *H. pylori* acts to suppress ghrelin production and stimulate production of leptin—thereby quashing appetite—in order to prevent feelings of hunger, which trigger the stomach

to boost acid levels in preparation for a meal. *H. pylori* carriers must work hard to produce ghrelin, like a cyclist pedaling uphill. When the bacterium is banished, they suddenly produce a lot more ghrelin, like a cyclist barreling downhill without brakes. Although *H. pylori* bacteria can tolerate acid, they prefer to live in the lining of the stomach where the pH is closer to neutral. “If you eat less and make less acid, that favors the bacteria’s survival,” Dr. Francois explains. Indeed, after *H. pylori* elimination, the former carriers’ average body mass index (BMI)—weight in kilograms divided by height in meters, squared—increased significantly.

Changes in the local microbiota could affect other parts of the digestive tract too. Zhiheng Pei, M.D., Ph.D., assistant professor of pathology and medicine, and Dr. Francois have now shown that the inflammation of the esophagus that accompanies GERD is linked to a change in the bacteria that colonize this muscular tube. Until Drs. Pei, Francois, and Blaser examined the esophagus several years ago, it was believed to be devoid of bacteria. To their surprise, they discovered that nearly 200 different species of bacteria inhabit the human esophagus. The bacteria live

together harmoniously most of the time. The researchers speculate that when esophageal tissue becomes inflamed by acid, immune cells gear up to fight the bacteria, releasing signaling molecules called cytokines that in turn activate host cells in the lining of the esophagus. Over decades, they suspect these charged-up cells may turn cancerous, leading to adenocarcinoma of the esophagus, which has increased six-fold since the 1970s—the fastest-increasing cancer in the Western world.

In a study to be published in *Gastroenterology*, Dr. Pei and his colleagues collected and sequenced bacteria from the esophagus in both healthy people and those suffering from GERD in an elderly male population. They found that in the normal esophagus, bacteria of the genus *Streptococcus* dominate the mix, while in the diseased esophagus, Gram-negative anaerobic bacteria were more abundant. These findings have opened a new approach to understanding the pathogenesis of reflux-related disorders, says Dr. Pei, who is expanding his studies to the general population and to patients with esophageal cancer. Because this new field of research is just beginning, Dr. Pei still doesn't know whether the changes in bacterial populations are triggering GERD and related tissue inflammation or are simply a response to it. But if changes in the bacterial population do indeed cause reflux, it may be possible to design new therapies with antibiotics, probiotic bacteria, or prebiotics (undigestible foods, such as dietary fiber, that stimulate the growth of beneficial bacteria in the intestine).

BACTERIAL BAD GUYS

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URTHER UP THE

body, in the mouth, yet another mélange of bacteria prevails. Microbiologist Page W. Caufield, D.D.S., Ph.D., professor of microbiology at the NYU College of Dentistry, and professor of medicine at the School of Medicine, has studied these bacteria for 24 years, particularly *Streptococcus mutans*, the microbe that causes dental caries. Until the advent of sugar in the human diet—which *S. mutans* metabolizes into tooth-boring lactic acid—the bacterium was beneficial: with its fellow bacteria, it forms a biofilm that crowds out harmful bacteria, and it also secretes an antibiotic that kills, among other microbes, *Streptococcus pyogenes*, a malevolent bug that causes strep throat.

As Dr. Caufield explains, *S. mutans* gets the blame for a situation that is really of our own making. “Many millions of people on the planet have limited access to sugar and are caries free,” he notes. “Our ancestors had no access to refined sugar—only very small amounts coming from honey and maybe beets, but nowhere near what modern, postagriculture humans experience.” In the absence of sugar, he adds, bacteria in the mouth like *S. mutans* “are guardians against the portal of entry” protecting us from infectious diseases, most of which come in through the mouth.

In a study published last year, Dr.

Caufield showed that the type of *S. mutans* we inherit from our mothers can determine whether or not we develop cavities: children suffering severe caries carry an especially destructive strain of the bacteria, bearing 10 to 12 genes coding for virulence factors (some snatched from “foreign” bacteria) not seen in people with healthy mouths. Avoiding sugar, however, can still prevent caries even in these carriers.

As these scientists' research reveals, most microbes that inhabit our bodies don't harm us, and often are essential to our existence. Others, however, wreak havoc. Some of these bacterial villains have survived through human history because they attack us later in life. For example, the same streptococci that defend us against strep throat when we are young can cause a condition called subacute bacterial endocarditis (SBE) in older people if the bacteria infect the bloodstream and land on calcified, deteriorated heart valves. Before antibiotics, this condition was invariably fatal.

Other destructive bacteria survive because, while they make humans sick, they usually aren't fatal. One such specimen is *Trichomonas vaginalis*, a protozoan parasite that infects the vagina in 170 million women worldwide—the most-common nonviral, sexually transmitted disease. This is Dr. Carlton's area of expertise. In 2007, she led a group that published a map of the microbe's massive genome, all 60,000 genes. *T. vaginalis* is especially insidious because it increases the risk of HIV infection by attracting the immune cells that the virus invades; it also eats good bacteria, such as *Lactobacillus*, that live in the vagina, keep it acidic, and form a biofilm that is a barrier to STDs. By devouring *Lactobacillus*, *T. vaginalis* makes the vagina more alkaline and attractive to sexually transmitted bacteria such as *Chlamydia*.

Dr. Carlton is collecting samples of vaginal flora from women attending STD clinics across New York City. She plans to sequence the flora to better understand how these microbes interact with one another, how the balance affects women's fertility, and how changing this balance with beneficial probiotic bacteria can perhaps prevent STDs.

Understanding the microbial world within us, adds Dr. Francois, is essential to understanding human physiology: “To not be interested would be like walking through a park with your eyes closed to avoid noticing the flowers and the trees, and pretending that the only thing that exists is you.” ●



The bacterium *Enterococcus faecium* (in red) on the surface of human skin and on the shaft of a hair follicle, shown in a composite from a scanning electron microscope.