OUR MICROBIAL SELVES

Projects to tabulate communities of bacteria that cohabit our bodies reveal unexpected roles in health and disease

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THE OLD ADAGE that people are known by the company they keep probably doesn’t refer to the trillions of microbes living on the human body—but it might as well. Although you may be influenced by the thousands of individuals you will meet in your lifetime, at this very moment there are more bacteria hanging out just in the palms of your hands than there are humans on Earth. And the astonishing diversity of microbes that inhabit every inch of your skin as well as your gut profoundly influences your quality of life—mostly for good—from the moment you are born until the day you die.

Humans rely on our human microbiome to perform essential functions, such as protecting us from persistent pathogens, building essential vitamins, and providing us with digestive enzymes that we need to break down plant fibers for energy. Many seemingly human characteristics are also partially shaped by our bacterial shell, such as whether we are skinny or fat and how we smell. The microbes cohabitating our body outnumber human cells by a factor of 10, making us actually “superorganisms” that use our own genetic repertoire as well as those of our microbial symbionts, says Julie Segre, who works on the Human Microbiome Project at the National Human Genome Research Institute, in Bethesda, Md. We just happen to look human because our human cells are much larger than bacterial cells (C&EN, July 20, 2009, page 43).

In the past three years, several large-scale projects to map the diversity and activities of our microbial family began, in hopes of finding connections between our microbiome, health, and disease. The National Institutes of Health’s Human Microbiome Project and the European Union’s Metagenomics of the Human Intestinal Tract (MetaHIT) program are probably two of the best known. These and other projects are starting to reveal that “every part of the body has its own ecosystem,” says Rob D. Knight, a biochemist at the University of Colorado, Boulder. Our bodies provide microbes with a diversity of habitats, much like the multitude of landscapes on Earth. The damp rainforest of our armpits, the anaerobic swamp of our gut, and the dry surface of our elbows recruit unique populations of bacteria. As researchers investigate the microbes in these uncharted territories, they are learning about humanity’s rapport with our microbial cohabitants and how that relationship affects obesity, attraction, diet, drug metabolism, and ailments as diverse as Crohn’s disease and psoriasis.

With 100 times more microbial genes present on and in us than our own human DNA, the ability to tabulate the genomes of our microbial symbionts became financially possible only as sequencing became cheaper. “The cost of DNA sequencing is dropping by almost an order of magnitude every year,” Knight says. “So it is literally millions of dollars cheaper to do the kinds of experiments that we are doing now than it would have been to do them even six years ago.”

These experiments are typically either a census of the microbial species on a given body part or a deeper look at what the community is capable of doing. Researchers doing a census typically focus on sequencing a gene that is found in every microbe and acts as a taxonomical fingerprint. This turns out to be the 16S ribosomal RNA gene, which codes for a component of the ribosome, the machinery used to build all the proteins in a cell.

The 16S rRNA gene is used as a taxonomic fingerprint because it evolves much more slowly than the rest of a bacterium’s genome, says Mitchell L. Sogin, a molecular biologist at Woods Hole Oceanographic Institution who, as a graduate student in the 1970s, developed this way to categorize microorganisms. “Sequencing the 16S rRNA gene tells you about community structure and the members who are present,” he says. “However, it doesn’t tell you anything at all about the functional properties of the organisms and the community”—in effect, what the microbes can do. To find out this functional repertoire, researchers do a much more expensive and sequencing-intensive “metagenomics” survey, tabulating all the microbial genes from a particular body part.

WHEN HUMAN microbiome research projects ramped up a few years ago, the initial idea was to “round up half a dozen healthy people and half a dozen sick people and look at whatever microbes were different between sick and healthy, and that would be what contributed to the disease,” Knight says. “It’s pretty clear that this initial plan is not going to work out,” because nobody anticipated the huge diversity of bacteria present in our microbiomes, which makes the analysis much more complex than anticipated. “So we are accommodating to the new reality,” he says.

In effect, there isn’t any species of bacteria that every human shares. “There are microbes [species and lineages] that are common in many people, but not all people,” Knight says. So for example, in the human gut, most people have some microbes in common, but everyone has a unique combination of microbes. This lack of one or more hallmark human microbiome species has made it difficult to establish a baseline signature for all healthy people, which researchers could then compare with diseased individuals.
Furthermore, the microbial species living in the cleft of your nostril are entirely different from those between your toes. Even nearby areas can have statistically different microbial populations: For example, the microbiomes on separate fingers of the same person are significantly different—both in the microbial species present and their relative abundance, Knight says (Proc. Natl. Acad. Sci. USA, DOI: 10.1073/pnas.1001621107). Because even our fingers have their own unique microbiomes, forensic investigations might one day sequence genomes from individual fingerprints left at a crime scene, Knight says. Although you can’t pick out a single species of bacteria found in a specific body site on all humans, trends are beginning to emerge: Consider the surface of Earth instead of the contours of a body. You could expect to find coniferous trees in the forests of a northern cool climate, but the exact species of coniferous trees in Siberia will be different from the species of coniferous trees in Vermont or those in Sweden. But even if the exact species are different, these cool ecosystems all feature a high population of trees with spiky needles that remain year-round. But you don’t expect to find many—if any—coniferous trees in Indonesia’s equatorial rainforest. It’s the same with the bacteria on our bodies, where certain habitats will be more appealing to some lineages of bacteria over others. “The microbiome on my left elbow is more similar to the microbiome on your left elbow than the microbiome on my left elbow is to the microbiome on my own forehead,” Segre says.

This is why microbiome-related diseases often appear in similar areas on different people. Eczema, for instance, is typically found on the inside of people’s arms. On the outside of people’s elbows, where the skin conditions and the microbial community are different, you will typically find psoriasis, another microbiome-related disease.

Both of these skin diseases are suspected to be at least in part caused by an overreaction of the immune system to otherwise benign microbes living on skin, causing inflammation and skin lesions. Opportunistic bacteria can then infect the lesions. In one study of this type of process, Segre’s group is trying to figure out how increases in the population of *Staphylococcus aureus* associated with the onset of eczema relate to the disease. “During eczema flare-ups, staph bacteria outcompete all the rest of the microbial diversity that is normally present,” Segre says.

**RESEARCHERS ALSO** believe that other autoimmune diseases such as irritable bowel syndrome and Crohn’s disease are a consequence of an overreaction of our own immune system to the trillions of bacteria living in the gut, which normally help extract energy from food, Segre says.

In fact, in a milestone paper for the microbiome field, Jeffrey J. Gordon and his colleagues at Washington University in Saint Louis reported in 2006 that a person’s gut microbiome affects whether they are obese. They found that obese people and mice had a consistently higher proportion of several bacterial phyla than do leaner folks (Nature, DOI: 10.1038/444102a). The microbial phyla that are present in a greater fraction in obese people’s guts are more efficient at extracting energy from food because they have more genes coding for more carbohydrate-extracting enzymes than the microbes in thin people.

In March of this year, researchers led by Emory University’s Andrew T. Gewirtz found that the gut microbiome of mice could also influence appetite and eating behavior (Science, DOI: 10.1126/science.1179721). Mice that had a mutation in a gene coding for an immune protein that
recognizes bacteria with flagella at 10% more than normal mice and also responded more severely to high-fat diets, showing symptoms seen in individuals at high risk for obesity-related diabetes and heart disease. When the unhealthy gut microbiome was transferred to healthy mice, they too started eating more, showing that the microbial community actually makes mice want to eat more, which in turn makes them obese, says Knight, who was also involved in the work.

But before you blame your gut bacteria for an undesired influence on your waistline, keep in mind that they also protect you from pathogens such as *Clostridium difficile*. Michael J. Sadowsky, a medical researcher at the University of Minnesota, Minneapolis, sampled the gut microbiome of a patient who had *C. difficile*-associated disease (CDAD), which causes diarrhea and colitis, and for whom antibiotic treatments had been unsuccessful. The team took fecal matter from a healthy donor and transplanted it into the patient. “Transplantation had a dramatic impact on the composition of the patient’s gut microbiota,” elevating members of the Firmicutes and Bacteroidetes bacterial phyla, note the researchers in a recent paper (J. Clin. Gastroenterol., DOI: 10.1097/MCG.0b013e3181c87e02). Fourteen days later, “the change in bacterial composition was accompanied by resolution of the patient’s symptoms,” they wrote.

**YOUR GUT MICROBIOME** is not just changing the way you fight pathogens or digest food. It also plays a role in how you metabolize the pills you take. For example, Jeremy K. Nicholson of Imperial College London has shown that your microbiome affects the way you metabolize acetaminophen (Proc. Nat. Acad. Sci., DOI: 10.1073/pnas.0904489106). “We can expect to find many other instances where modern drugs interact with the gut microbiome in unexpected ways,” Ian D. Wilson, a clinical pharmacist at AstraZeneca, wrote of the acetaminophen work (Proc. Natl. Acad. Sci., DOI: 10.1073/pnas.0907721106).

Recent research also shows that gut bacteria accommodate specialized diets. This year, researchers led by Gurvan Michel of the University of Pierre & Marie Curie, in Paris, reported that people in Japan—but not in North America—possess a bacteria, *Bacteroides plebeius*, that has the ability to break down special carbohydrates found in seaweed, a common component of the Japanese diet (Nature, DOI: 10.1038/nature09377).

Besides breaking down our favorite foods, our microbiome can also spark a little romance—for fruit flies, at least. Eugene Rosenberg of Tel Aviv University and his colleagues found that fruit flies that have a microbiome with certain *Lactobacil-*
lus species preferred to mate with flies possessing similar bacteria. This predilection disappeared when the flies were fed antibiotics that destroyed their Lactobacillus population (Proc. Natl. Acad. Sci. USA, DOI: 10.1073/pnas.1009906107).

Although researchers are just getting a handle on how to perform large-scale genome sequencing of our microbial family (and that of model organisms such as rodents and fruit flies), some researchers are taking delicate steps toward studying our microbiome’s proteome. “The genome is the shopping list of all possible genes, the entire inventory of the things the microbiome could bring to bear,” says Robert L. Hettich, a chemist at Oak Ridge National Laboratory. “But the proteins are where the rubber hits the road.” A bacterial species could, for example, have a variety of genes in its genome that are never expressed and thus do not reflect actual molecular activity in the microbiome. Hettich and his colleagues have been developing techniques to work on proteomics of the gut microbiome. However, “working with raw fecal material adds some complications,“ he says. It’s a “pretty formidable task” to do mass spectrometry on these samples, for instance. Because the gut microbiome varies in response to diet, health, and even time of day, it’s also a challenge to know when to take a sample and how many samples are needed to get an accurate picture of what’s going on.

BUT MOST RESEARCHERS agree that the biggest challenge to any human microbiome study is the bioinformatics and data analysis it entails. The software used to analyze and align gene sequences wasn’t initially developed to compare a half-million genomes at a given time, Knight says.

“With dropping costs of sequencing, there’s no ceiling to the number of genomes researchers will want to align,” says Eric Nawrocki, a bioinformatician at Janelia Farm Research Campus, in Loudoun County, Va. “In a year, researchers may want to align 10 million sequences.” Nawrocki is developing software that can arrange 16S rRNA sequences not only on the basis of its code but also the structure of the molecule. Other researchers, such as Christopher Quince at the University of Glasgow, are trying to develop filters that can clean up inherent errors in gene sequencing. For example, when researchers detect a rare sequence in a microbiome sample, they want to know whether it’s evidence of a new functionality, a new microbiome member, or just an error, Quince explains.

As researchers learn more about how our extended microbial family affects our behavior, appearance, and health, people may start thinking more about how food and drugs affect their microbiome—say, by boosting certain microbes with probiotics or devastating their good bacteria with antibiotics. Some researchers, such as New York University’s Martin J. Blaser, propose that changes to our human microbiome from widespread antibiotic use, increased Caesarean births, and sterile food are leading to increased human obesity and asthma. Others, such as Nicholson, suggest that the medicine cabinets of the future will be stocked with drugs targeting our microbiome. But no matter how you look at it, it’s high time we acknowledge that part of being human is being microbial. ■