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The Teeming Metropolis of You

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YOU ARE MOSTLY not you. That is to say, 90 percent of the cells residing in your body are not human cells; they are microbes. Viewed from the perspective of most of its inhabitants, your body is not so much the temple and vessel of the human soul as it is a complex ambulatory feeding mechanism for a methane reactor in your small intestine.

This is the kind of information microbiologists like to share at dinner parties, and you should too, especially if you can punctuate it with a belch.

It's not that our bodies aren't enormously interesting in themselves, only that they are not the whole story—not nearly. Each of us is a colonized country, a host of multitudes, a reservoir of biodiversity. Indeed, the species of bacteria living on your left hand are different from those living on your right.

At the dawn of the twenty-first century, navel gazing is on the frontiers of biology and medicine, as proven by the Belly Button Biodiversity Project at North Carolina State University. They take swabs, sequence DNA, and post photographs of the resulting cultures. (Request a kit online!)

And our biota—all the living creatures in and on us—is not a set of merely passive passengers. The bacteria in our gut aid our digestion and, as we are increasingly discovering, help defend us from pathogens. There are a couple of ways of thinking about how they protect us, says Russell Vance, a University of California, Berkeley, professor studying the interactions of bacteria and the immune system. The first protection is by simply existing.

Think of your body as a big city apartment building. Our normal biota comprises its tenants, and they're solid folk. They keep up the maintenance, take out the trash, and pay their rent—that is to say, they promote healthy tissue growth, comprise the majority of the dry mass in our feces, and, by fermenting carbohydrates, provide us with roughly a quarter of our calories. Just by maintaining building occupancy, they keep bad elements from moving in as squatters, beating up the superintendent, ripping out the copper pipes, and turning the whole place into a crack den—that is, they compete for nutrients, occupy the mucous lining, and sites in the intestine where pathogens might attach and attack.

Another way our tenants protect the place is by actively policing the hallways—a healthy biota makes the pH of our guts inhospitable and even toxic to many pathogens.

What's more, the bacteria in our guts act as a scrimmage team for our immune system. Over our lifetimes, our bacteria and our immune systems compete with each other, but for reasons scientists are still figuring out, never too aggressively. They take the field against each other, but they don't play tackle football.

To some extent, this makes sense; after all, if harmless bacteria were playing for keeps, they wouldn't be harmless—they would be attacking our intestinal cells and colonizing the rest of our body. Similarly, if our immune systems were fighting at full strength, we would be sick all the time, since most of the experience of being ill—fevers, aches, coughing, runny noses, and so on—is the result of our body trying to make itself inhospitable to microorganisms.

Compelling evidence for our biota's role in our immune system comes from the laboratory's quick-breeding little helpers: mice. It's possible, Vance says, to breed sterile—as in germ-free—mice, ones with absolutely no gut biota. These mice live in sterile cages, eat special food, and breathe filtered air. If they are taken out of their cages, their immune systems collapse when exposed to the meekest pathogens, and the mice die.

Unfortunately, there are cases when the body's biota and its immune system stop their friendly scrimmage and start playing like the 1970s Oakland Raiders. This is thought to cause or play a role in autoimmune illnesses, including environmental allergies, Crohn's disease, and inflammatory bowel disease.

Vance's lab at Cal uses mice to study how our body's innate immune system distinguishes between pathogens and our normal

gut bacteria. So far, it seems that our body is guarded not so much by watchdogs as by burglar alarms: they can't differentiate friend from foe. All they can do is make themselves known if something gets in.

Vance is looking at one particular burglar alarm, a protein in the cell that under certain circumstances will signal the immune system to attack all bacteria, including healthy gut bacteria. It's not clear exactly when those circumstances might occur, but the fact that this protein doesn't distinguish between good and bad bacteria could help us understand what triggers autoimmune diseases.

Life, however, is struggle, and our immune system and friendly gut bacteria are not the only players in the game. Sometimes a pathogen causes our immune systems and our biota to turn against each other. Research by Andreas J. Bäumler at the University of California, Davis, shows that *Salmonella typhimurium*, a bacterium that causes gastroenteritis, actually benefits from our immediate immune response. This reaction is a flood of antimicrobial agents and an overall change in your intestinal environment that is very noticeable to you and the person in the bathroom stall next to you. This changed environment is hostile to all bacteria, including your own. In fact, it is more harmful to your biota than it is to salmonella. Because your immune system is better at thrashing your biota than it is at thrashing salmonella, the salmonella suddenly has more nutrients to eat and more space to grow.

We are just beginning to understand the role our biota plays in human health and disease, says Rob Knight, a biophysics researcher at the University of Colorado, Boulder. Knight works on the Human Microbiome Project, sequencing and analyzing the genetic makeup of our biota, work that has only recently begun to take off as gene sequencing has become much cheaper and faster.

Right now, he says, we're still not sure how many species we play host to. In our gut alone there may be anywhere from one hundred to a thousand species. (The answer depends not only on how many we can discover but on how finely one defines "species.") And the particular makeup of the community living in one's gut varies wildly from individual to individual.

It seems we acquire our first colonists literally at the moment of birth. You get most of it from your mother, but even identical twins don't end up with identical biota, and a sibling born by cesarean section will have a very different set than his vaginally

birthed brother—the C-section child is exposed to the biota on his mother's skin, while the child passing through his mother's vagina meets biota more like those in mom's guts. The differences between unrelated strangers are even more pronounced, Knight says. Two unrelated North Americans will share only 10 percent of their intestinal bacteria, and a North American and a South American will share only 5 percent.

And the differences in our biota have a wide-ranging effect on our health. For one, it could even be that our biota is making us fat.

Knight points to a series of experiments in which the gut biota is transplanted out of obese mice and into healthy ones, whereupon the healthy mice either become obese or develop colitis. This is why Knight is interested in the potential of healthy bacteria called probiotics to treat human obesity and other conditions. "We're probably where, I don't know, radium was in 1910, where people thought making everything radioactive would just be great," Knight says. "And while that wasn't true, it doesn't proscribe the important uses of radiation in, say, cancer therapy."

So far probiotics are more popular as a marketing term for nutritional supplements and bacteria-enriched yogurt than as recognized medical treatments. In the coming years, Knight says, probiotics will likely become an increasingly legitimate medical tool. But not quite yet. There have been some very promising studies where mice were successfully treated with probiotics for inflammatory bowel disease. "We're really good at curing diseases in mice and somewhat less good at curing them in humans."

Scientists are only now beginning to figure out just how important our biota can be. For instance, Knight says, one study has shown that these harmless bacteria can change our metabolism in a way that affects our behavior, and not only behavior related to eating.

Again, mice are involved. Take some lab-grown sterile mice. Take some normal bacteria-infested mice. Run them both through a maze that includes a high beam without rails. It turns out that the sterile mice are much bolder and will spend more time on the beam than their normal cousins.

Even more interesting, if you introduce normal bacteria into adult sterile mice, their behavior doesn't change. If, however, you take mice that are still growing and colonize them with the same

bacteria, they will develop more typical fear responses. This suggests that our biota can influence brain development. It makes a certain amount of sense, Knight says, considering that our guts produce many of our neurotransmitters, including 90 percent of our serotonin, a linkage that, in a term of complete scientific awesomeness, is called the "gut-brain axis."

In other words, it's looking increasingly likely that it's not so much that you are mostly not you as that you are also the slime sloshing around your innards. If the medical advances of the twentieth century taught us to stop thinking of our minds and bodies as separate entities, the twenty-first may teach us to include our symbiotic biota: Our Bacteria, Ourselves.