Some of My Best Friends Are Germs
By MICHAEL POLLAN
Published: May 15, 2013
http://www.nytimes.com/2013/05/19/magazine/say-hello-to-the-100-trillion-bacteria-that-make-up-your-microbiome.html?pagewanted=all&_r=0

I can tell you the exact date that I began to think of myself in the first-person plural — as a superorganism, that is, rather than a plain old individual human being. It happened on March 7. That's when I opened my e-mail to find a huge, processor-choking file of charts and raw data from a laboratory located at the BioFrontiers Institute at the University of Colorado, Boulder. As part of a new citizen-science initiative called the American Gut project, the lab sequenced my microbiome — that is, the genes not of "me," exactly, but of the several hundred microbial species with whom I share this body. These bacteria, which number around 100 trillion, are living (and dying) right now on the surface of my skin, on my tongue and deep in the coils of my intestines, where the largest contingent of them will be found, a pound or two of microbes together forming a vast, largely uncharted interior wilderness that scientists are just beginning to map.

I clicked open a file called Taxa Tables, and a colorful bar chart popped up on my screen. Each bar represented a sample taken (with a swab) from my skin, mouth and feces. For purposes of comparison, these were juxtaposed with bars representing the microbiomes of about 100 "average" Americans previously sequenced.
Here were the names of the hundreds of bacterial species that call me home. In sheer numbers, these microbes and their genes dwarf us. It turns out that we are only 10 percent human: for every human cell that is intrinsic to our body, there are about 10 resident microbes — including commensals (generally harmless freeloaders) and mutualists (favor traders) and, in only a tiny number of cases, pathogens. To the extent that we are bearers of genetic information, more than 99 percent of it is microbial. And it appears increasingly likely that this "second genome," as it is sometimes called, exerts an influence on our health as great and possibly even greater than the genes we inherit from our parents. But while your inherited genes are more or less fixed, it may be possible to reshape, even cultivate, your second genome.

Justin Sonnenburg, a microbiologist at Stanford, suggests that we would do well to begin regarding the human body as "an elaborate vessel optimized for the growth and spread of our microbial inhabitants." This humbling new way of thinking about the self has large implications for human and microbial health, which turn out to be inextricably linked. Disorders in our internal ecosystem — a loss of diversity, say, or a proliferation of the "wrong" kind of microbes — may predispose us to obesity and a whole range of chronic diseases, as well as some infections. "Fecal transplants," which involve installing a healthy person's microbiota into a sick person's gut, have been shown to effectively treat an antibiotic-resistant intestinal pathogen named C. difficile, which kills 14,000 Americans each year. (Researchers use the word "microbiota" to refer to all the microbes in a community and "microbiome" to refer to their collective genes.) We've known for a few years that obese mice transplanted with the intestinal community of lean mice lose weight and vice versa. (We don't know why.) A similar experiment was performed recently on humans by researchers in the Netherlands: when the contents of a lean donor's microbiota were transferred to the guts of male patients with metabolic syndrome, the researchers found striking improvements in the recipients' sensitivity to insulin, an important marker for metabolic health. Somehow, the gut microbes were influencing the patients' metabolisms.

Our resident microbes also appear to play a critical role in training and modulating our immune system, helping it to accurately distinguish between friend and foe and not go nuts on, well, nuts and all sorts of other potential allergens. Some researchers believe that the alarming increase in autoimmune diseases in the West may owe to a disruption in the ancient relationship between our bodies and their "old friends" — the microbial symbionts with whom we coevolved.
These claims sound extravagant, and in fact many microbiome researchers are careful not to make the mistake that scientists working on the human genome did a decade or so ago, when they promised they were on the trail of cures to many diseases. We're still waiting. Yet whether any cures emerge from the exploration of the second genome, the implications of what has already been learned — for our sense of self, for our definition of health and for our attitude toward bacteria in general — are difficult to overstate. Human health should now "be thought of as a collective property of the human-associated microbiota," as one group of researchers recently concluded in a landmark review article on microbial ecology — that is, as a function of the community, not the individual.

Such a paradigm shift comes not a moment too soon, because as a civilization, we've just spent the better part of a century doing our unwitting best to wreck the human-associated microbiota with a multifronted war on bacteria and a diet notably detrimental to its well-being. Researchers now speak of an impoverished "Westernized microbiome" and ask whether the time has come to embark on a project of "restoration ecology" — not in the rain forest or on the prairie but right here at home, in the human gut.

In March I traveled to Boulder to see the Illumina HiSeq 2000 sequencing machine that had shed its powerful light on my own microbiome and to meet the scientists and computer programmers who were making sense of my data. The lab is headed by Rob Knight, a rangy, crew-cut 36-year-old biologist who first came to the United States from his native New Zealand to study invasive species, a serious problem in his home country. Knight earned his Ph.D. in ecology and evolutionary biology from Princeton when he was 24 and then drifted from the study of visible species and communities to invisible ones. Along the way he discovered he had a knack for computational biology. Knight is regarded as a brilliant analyst of sequencing data, skilled at finding patterns in the flood of information produced by the machines that "batch

sequence” all the DNA in a sample and then tease out the unique genetic signatures of each microbe. This talent explains why so many of the scientists exploring the microbiome today send their samples to be sequenced and analyzed by his lab; it is also why you will find Knight’s name on most of the important papers in the field.

Over the course of two days in Boulder, I enjoyed several meals with Knight and his colleagues, postdocs and graduate students, though I must say I was a little taken aback by the table talk. I don’t think I’ve ever heard so much discussion of human feces at dinner, but then one thing these scientists are up to is a radical revaluation of the contents of the human colon. I learned about Knight’s 16-month-old daughter, who has had most of the diapers to which she has contributed sampled and sequenced. Knight said at dinner that he sampled himself every day; his wife, Amanda Birmingham, who joined us one night, told me that she was happy to be down to once a week. “Of course I keep a couple of swabs in my bag at all times,” she said, rolling her eyes, “because you never know.”

A result of the family’s extensive self-study has been a series of papers examining family microbial dynamics. The data helped demonstrate that the microbial communities of couples sharing a house are similar, suggesting the importance of the environment in shaping an individual’s microbiome. Knight also found that the presence of a family dog tended to blend everyone’s skin communities, probably via licking and petting. One paper, titled “Moving Pictures of the Human Microbiome,” tracked the day-to-day shifts in the microbial composition of each body site. Knight produced animations showing how each community — gut, skin and mouth — hosted a fundamentally different cast of microbial characters that varied within a fairly narrow range over time.

Knight’s daily sampling of his daughter’s diapers (along with those of a colleague’s child) also traced the remarkable process by which a baby’s gut community, which in utero is sterile and more or less a blank slate, is colonized. This process begins shortly after birth, when a distinctive infant community of microbes assembles in the gut. Then, with the introduction of solid food and then weaning, the types of microbes gradually shift until, by age 3, the baby’s gut comes to resemble an adult community much like that of its parents.

The study of babies and their specialized diet has yielded key insights into how the colonization of the gut unfolds and why it matters so much to our health. One of the earliest clues to the complexity of the microbiome came from an unexpected corner: the effort to solve a mystery about milk. For years, nutrition scientists were confounded by the presence in human breast milk of certain complex carbohydrates, called oligosaccharides, which the human infant lacks the enzymes necessary to digest. Evolutionary theory argues that every component of mother’s milk should have some value to the developing baby or natural selection would have long ago discarded it as a waste of the mother’s precious resources.

It turns out the oligosaccharides are there to nourish not the baby but one particular gut bacterium called Bifidobacterium infantis, which is uniquely well-suited to break down and make use of the specific oligosaccharides present in mother’s milk. When all goes well, the bifidobacteria proliferate and dominate, helping to keep the infant healthy by crowding out less savory microbial characters before they can become established and, perhaps most important, by nurturing the integrity of the epithelium — the lining of the intestines, which plays a critical role in protecting us from infection and inflammation.
“Mother’s milk, being the only mammalian food shaped by natural selection, is the Rosetta stone for all food,” says Bruce German, a food scientist at the University of California, Davis, who researches milk. “And what it’s telling us is that when natural selection creates a food, it is concerned not just with feeding the child but the child’s gut bugs too.”
Where do these all-important bifidobacteria come from and what does it mean if, like me, you were never breast-fed? Mother’s milk is not, as once was thought, sterile: it is both a “prebiotic” — a food for microbes — and a “probiotic,” a population of beneficial microbes introduced into the body. Some of them may find their way from the mother’s colon to her milk ducts and from there into the baby’s gut with its first feeding. Because designers of infant formula did not, at least until recently, take account of these findings, including neither prebiotic oligosaccharides or probiotic bacteria in their formula, the guts of bottle-fed babies are not optimally colonized.

Most of the microbes that make up a baby’s gut community are acquired during birth — a microbially rich and messy process that exposes the baby to a whole suite of maternal microbes. Babies born by Caesarean, however, a comparatively sterile procedure, do not acquire their mother’s vaginal and intestinal microbes at birth. Their initial gut communities more closely resemble that of their mother’s (and father’s) skin, which is less than ideal and may account for higher rates of allergy, asthma and autoimmune problems in C-section babies: not having been seeded with the optimal assortment of microbes at birth, their immune systems may fail to develop properly.

At dinner, Knight told me that he was sufficiently concerned about such an eventuality that, when his daughter was born by emergency C-section, he and his wife took matters into their own hands: using a sterile cotton swab, they inoculated the newborn infant’s skin with the mother’s vaginal secretions to insure a proper colonization. A formal trial of such a procedure is under way in Puerto Rico.

While I was in Boulder, I sat down with Catherine A. Lozupone, a microbiologist who had just left Knight’s lab to set up her own at the University of Colorado, Denver, and who spent some time looking at my microbiome and comparing it with others, including her own. Lozupone was the lead author on an important 2012 paper in Nature, “Diversity, Stability and Resilience of the Human Gut Microbiota,” which sought to approach the gut community as an ecologist might, trying to determine the “normal” state of the ecosystem and then examining the various factors that disturb it over time. How does diet affect it?

Antibiotics? Pathogens? What about cultural traditions? So far, the best way to begin answering such questions may be by comparing the gut communities of various far-flung populations, and researchers have been busy collecting samples around the world and shipping them to sequencing centers for analysis. The American Gut project, which hopes to eventually sequence the communities of tens of thousands of Americans, represents the most ambitious such effort to date; it will help researchers uncover patterns of correlation between people's lifestyle, diet, health status and the makeup of their microbial community.

It is still early days in this research, as Lozupone (and everyone else I interviewed) underscored; scientists can't even yet say with confidence exactly what a "healthy" microbiome should look like. But some broad, intriguing patterns are emerging. More diversity is probably better than less, because a diverse ecosystem is generally more resilient — and diversity in the Western gut is significantly lower than in other, less-industrialized populations. The gut microbiota of people in the West looks very different from that of a variety of other geographically dispersed peoples. So, for example, the gut community of rural people in West Africa more closely resembles that of Amerindians in Venezuela than it does an American's or a European's. These rural populations not only harbor a greater diversity of microbes but also a different cast of lead characters. American and European guts contain relatively high levels of bacteroides and firmicutes and low levels of the prevotella that dominate the guts of rural Africans and Amerindians. (It is not clear whether high or low levels of any of these is good or bad.) Why are the microbes different? It could be the diet, which in both rural populations features a considerable amount of whole grains (which prevotella appear to like), plant fiber and very little meat. (Many firmicutes like amino acids, so they proliferate when the diet contains lots of protein; bacteroides metabolize carbohydrates.) As for the lower biodiversity in the West, this could be a result of our profligate use of antibiotics (in health care as well as the food system), our diet of processed food (which has generally been cleansed of all bacteria, the good and the bad), environmental toxins and generally less "microbial pressure" — i.e., exposure to bacteria — in everyday life. All of this may help explain why, though these rural populations tend to have greater exposures to infectious diseases and lower life expectancies than those in the West, they also have lower rates of chronic disorders like allergies, asthma, Type 2 diabetes and cardiovascular disease.
"Rural people spend a lot more time outside and have much more contact with plants and with soil," Lozupone says. Another researcher, who has gathered samples in Malawi, told me, "In some of these cultures, children are raised communally, passed from one set of hands to another, so they're routinely exposed to a greater diversity of microbes." The nuclear family may not be conducive to the health of the microbiome.

As it happens, Lozupone and I had something in common, microbially speaking: we share unusually high levels of prevotella for Americans. Our gut communities look more like those of rural Africans or Amerindians than like those of our neighbors. Lozupone suspects that the reasons for this might have to do with a plant-based diet; we each eat lots of whole grains and vegetables and relatively little meat. (Though neither of us is a vegetarian.) Like me, she was proud of her prevotella, regarding it as a sign of a healthy non-Western diet, at least until she began doing research on the microbiota of H.I.V. patients. It seems that they, too, have lots of prevotella. Further confusing the story, a recent study linking certain gut microbes common in meat eaters to high levels of a blood marker for heart disease suggested that prevotella was one such microbe. Early days, indeed.

Two other features of my microbiome attracted the attention of the researchers who examined it. First, the overall biodiversity of my gut community was significantly higher than that of the typical Westerner, which I decided to take as a compliment, though the extravagantly diverse community of microbes on my skin raised some eyebrows. "Where have your hands been, man?" Jeff Leach of the American Gut project asked after looking over my results. My skin harbors bacteria associated with plants, soil and a somewhat alarming variety of animal guts. I put this down to gardening, composting (I keep worms too) and also the fact that I was fermenting kimchi and making raw-milk cheese, "live-culture" foods teeming with microbes. Compared to a rain forest or a prairie, the interior ecosystem is not well understood, but the core principles of ecology — which along with powerful new sequencing machines have opened this invisible frontier to science — are beginning to yield some preliminary answers and a great many more intriguing hypotheses. Your microbial community seems to stabilize by age 3, by which time most of the various niches in the gut ecosystem are occupied. That doesn't mean it can't change after that; it can, but not as readily. A change of diet or a course of antibiotics, for example, may bring shifts in the relative population of the various resident species, helping some kinds of bacteria to thrive and others to languish. Can new species be introduced? Yes, but probably only when a niche is opened after a significant disturbance, like an antibiotic storm. Just like any other mature ecosystem, the one in our gut tends to resist invasion by newcomers.
You acquire most of the initial microbes in your gut community from your parents, but others are picked up from the environment. "The world is covered in a fine patina of feces," as the Stanford microbiologist Stanley Falkow tells students. The new sequencing tools have confirmed his hunch: Did you know that house dust can contain significant amounts of fecal particles? Or that, whenever a toilet is flushed, some of its contents are aerosolized? Knight's lab has sequenced the bacteria on toothbrushes. This news came during breakfast, so I didn't ask for details, but got them anyway: "You want to keep your toothbrush a minimum of six feet away from a toilet," one of Knight's colleagues told me.

Some scientists in the field borrow the term "ecosystem services" from ecology to catalog all the things that the microbial community does for us as its host or habitat, and the services rendered are remarkably varied and impressive. "Invasion resistance" is one. Our resident microbes work to keep pathogens from gaining a toehold by occupying potential niches or otherwise rendering the environment inhospitable to foreigners. The robustness of an individual's gut community might explain why some people fall victim to food poisoning while others can blithely eat the same meal with no ill effects.

Our gut bacteria also play a role in the manufacture of substances like neurotransmitters (including serotonin); enzymes and vitamins (notably Bs and K) and other essential nutrients (including important amino acid and short-chain fatty acids); and a suite of other signaling molecules that talk to, and influence, the immune and the metabolic systems. Some of these compounds may play a role in regulating our stress levels and even temperament: when gut microbes from easygoing, adventurous mice are transplanted into the guts of anxious and timid mice, they become more adventurous. The expression "thinking with your gut" may contain a larger kernel of truth than we thought.

The gut microbes are looking after their own interests, chief among them getting enough to eat and regulating the passage of food through their environment. The bacteria themselves appear to help manage these functions by producing signaling chemicals that regulate our appetite, satiety and digestion. Much of what we're learning about the microbiome's role in human metabolism has come from studying "gnotobiotic mice" — mice raised in labs like Jeffrey I. Gordon's at Washington University, in St. Louis, to be microbially sterile, or germ-free. Recently, Gordon's lab transplanted the gut microbes of Malawian children with kwashiorkor — an acute form of malnutrition — into germ-free mice. The lab found those mice with kwashiorkor who were fed the children's typical diet could not readily metabolize nutrients, indicating that it may take more than calories to remedy malnutrition. Repairing a patient's disordered metabolism may require reshaping the community of species in his or her gut.

Keeping the immune system productively engaged with microbes — exposed to lots of them in our bodies, our diet and our environment — is another important ecosystem service and one that might turn out to be critical to our health. "We used to think the immune system had this fairly straightforward job," Michael Fischbach, a biochemist at the University of California, San Francisco, says. "All bacteria were clearly 'nonself' so simply had to be recognized and dealt with. But the job of the immune system now appears to be far more nuanced and complex. It has to learn to consider our mutualists" — e.g., resident bacteria — "as self too. In the future we won't even call it the immune system, but the microbial interaction system." The absence of constructive engagement between microbes and immune system (particularly during certain windows of development) could be behind the increase in autoimmune conditions in the West.

So why haven't we evolved our own systems to perform these most critical functions of life? Why have we outsourced all this work to a bunch of microbes? One theory is that, because microbes evolve so much faster than we do (in some cases a new generation every 20 minutes), they can respond to changes in the environment — to threats as well as opportunities — with much greater speed and agility than "we" can. Exquisitely reactive and adaptive, bacteria can swap genes and pieces of DNA among themselves. This versatility is especially handy when a new toxin or food source appears in the environment. The microbiota can swiftly come up with precisely the right gene needed to fight it — or eat it. In one recent study, researchers found that a common gut microbe in Japanese people has acquired a gene from a marine bacterium that allows the Japanese to digest seaweed, something the rest of us can't do as well.

This plasticity serves to extend our comparatively rigid genome, giving us access to a tremendous bag of biochemical tricks we did not need to evolve ourselves. "The bacteria in your gut are continually reading the environment and responding," says Joel Kimmons, a nutrition scientist and epidemiologist at the Centers for Disease Control and Prevention in Atlanta. "They're a microbial mirror of the changing world. And because they can evolve so quickly, they help our bodies respond to changes in our environment."

A handful of microbiologists have begun sounding the alarm about our civilization's unwitting destruction of the human microbiome and its consequences. Important microbial species may have already gone extinct, before we have had a chance to learn who they are or what they do. What we think of as an interior wilderness may in fact be nothing of the kind, having long ago been reshaped by unconscious human actions. Taking the ecological metaphor further, the "Westernized microbiome" most of us now carry around is in fact an artifact of civilization, no more a wilderness today than, say, the New Jersey Meadowlands.

To obtain a clearer sense of what has been lost, María Gloria Dominguez-Bello, a Venezuelan-born microbiologist at New York University, has been traveling to remote corners of the Amazon to collect samples from hunter-gatherers who have had little previous contact with Westerners or Western medicine. "We want to see how the human microbiota looks before antibiotics, before processed food, before modern birth," she told me. "These samples are really gold."

Preliminary results indicate that a pristine microbiome — of people who have had little or no contact with Westerners — features much greater biodiversity, including a number of species never before sequenced, and, as mentioned, much higher levels of prevotella than is typically found in the Western gut. Dominguez-Bello says these vibrant, diverse and antibiotic-naïve microbiomes may play a role in Amerindians' markedly lower rates of allergies, asthma, atopic disease and chronic conditions like Type 2 diabetes and cardiovascular disease.

One bacterium commonly found in the non-Western microbiome but nearly extinct in ours is a corkscrew-shaped inhabitant of the stomach by the name of Helicobacter pylori. Dominguez-Bello's husband, Martin Blaser, a physician and microbiologist at N.Y.U., has been studying H. pylori since the mid-1980s and is convinced that it is an endangered species, the extinction of which we may someday rue. According to the "missing microbiota hypothesis," we depend on microbes like H. pylori to regulate various metabolic and immune functions, and their disappearance is disordering those systems. The loss is

cumulative: “Each generation is passing on fewer of these microbes,” Blaser told me, with the result that the Western microbiome is being progressively impoverished.

He calls H. pylori the “poster child” for the missing microbes and says medicine has actually been trying to exterminate it since 1983, when Australian scientists proposed that the microbe was responsible for peptic ulcers; it has since been implicated in stomach cancer as well. But H. pylori is a most complicated character, the entire spectrum of microbial good and evil rolled into one bug. Scientists learned that H. pylori also plays a role in regulating acid in the stomach. Presumably it does this to render its preferred habitat inhospitable to competitors, but the effect on its host can be salutary. People without H. pylori may not get peptic ulcers, but they frequently do suffer from acid reflux. Untreated, this can lead to Barrett’s esophagus and, eventually, a certain type of esophageal cancer, rates of which have soared in the West as H. pylori has gone missing.

When after a recent bout of acid reflux, my doctor ordered an endoscopy, I discovered that, like most Americans today, my stomach has no H. pylori. My gastroenterologist was pleased, but after talking to Blaser, the news seemed more equivocal, because H. pylori also does us a lot of good. The microbe engages with the immune system, quieting the inflammatory response in ways that serve its own interests — to be left in peace — as well as our own. This calming effect on the immune system may explain why populations that still harbor H. pylori are less prone to allergy and asthma. Blaser’s lab has also found evidence that H. pylori plays an important role in human metabolism by regulating levels of the appetite hormone ghrelin. “When the stomach is empty, it produces a lot of ghrelin, the chemical signal to the brain to eat,” Blaser says. “Then, when it has had enough, the stomach shuts down ghrelin production, and the host feels satiated.” He says the disappearance of H. pylori may be contributing to obesity by muting these signals.

But what about the diseases H. pylori is blamed for? Blaser says these tend to occur only late in life, and he makes the rather breathtaking suggestion that this microbe’s evolutionary role might be to help shuffle us off life’s stage once our childbearing years have passed. So important does Blaser regard this strange, paradoxical symbiont that he has proposed not one but two unconventional therapeutic interventions: inoculate children with H. pylori to give them the benefit of its services early in life, and then exterminate it with antibiotics at age 40, when it is liable to begin causing trouble.

These days Blaser is most concerned about the damage that antibiotics, even in tiny doses, are doing to the microbiome — and particularly to our immune system and weight. “Farmers have been performing a great experiment for more than 60 years,” Blaser says, “by giving subtherapeutic doses of antibiotics to their animals to make them gain weight.” Scientists aren’t sure exactly why this practice works, but the drugs may favor bacteria that are more efficient at harvesting energy from the diet. “Are we doing the same thing to our kids?” he asks. Children in the West receive, on average, between 10 and 20 courses of antibiotics before they turn 18. And those prescribed drugs aren’t the only antimicrobials finding their way to the microbiota; scientists have found antibiotic residues in meat, milk and surface water as well. Blaser is also concerned about the use of antimicrobial compounds in our diet and everyday lives — everything from chlorine washes for lettuce to hand sanitizers. “We’re using these chemicals precisely because they’re antimicrobial,” Blaser says. “And of course they do us some good. But we need to ask, what are they doing to our microbiota?” No one is questioning the value of antibiotics to civilization — they have helped us to conquer a great many infectious diseases and increased our life expectancy. But, as in any war, the war on bacteria appears to have had some unintended consequences.

One of the more striking results from the sequencing of my microbiome was the impact of a single course of antibiotics on my gut community. My dentist had put me on a course of Amoxicillin as a precaution before oral surgery. (Without prophylactic antibiotics, of course, surgery would be considerably more dangerous.) Within a week, my impressively non-Western “alpha diversity” — a measure of the microbial diversity in my gut — had plummeted and come to look very much like the American average. My (possibly) healthy levels of prevotella had also disappeared, to be replaced by a spike in bacteroides (much more common in the West) and an alarming bloom of proteobacteria, a phylum that includes a great many weedy and pathogenic characters, including E. coli and salmonella. What had appeared to be a pretty healthy, diversified gut was now raising expressions of concern among the microbiologists who looked at my data.

“Your E. coli bloom is creepy,” Ruth Ley, a Cornell University microbiologist who studies the microbiome’s role in obesity, told me. “If we put that sample in germ-free mice, I bet they’d get inflamed.” Great. Just when I was beginning to think of myself as a promising donor for a fecal transplant, now I had a gut that would make mice sick. I was relieved to learn that my gut community would eventually bounce back to something resembling its former state. Yet one recent study found that when subjects were given a second course of antibiotics, the recovery of their interior ecosystem was less complete than after the first.

Few of the scientists I interviewed had much doubt that the Western diet was altering our gut microbiome in troubling ways. Some, like Blaser, are concerned about the antimicrobials we’re ingesting with our meals; others with the sterility of processed food. Most agreed that the lack of fiber in the Western diet was deleterious to the microbiome, and still others voiced concerns about the additives in processed foods, few of which have ever been studied for their specific effects on the microbiota. According to a recent article in Nature by the Stanford microbiologist Justin Sonnenburg, “Consumption of hyperhygienic, mass-produced, highly processed and calorie-dense foods is testing how rapidly the microbiota of individuals in industrialized countries can adapt.” As our microbiome evolves to cope with the Western diet, Sonnenburg says he worries

that various genes are becoming harder to find as the microbiome's inherent biodiversity declines along with our everyday exposure to bacteria.

Catherine Lozupone in Boulder and Andrew Gewirtz, an immunologist at Georgia State University, directed my attention to the emulsifiers commonly used in many processed foods — ingredients with names like lecithin, Datem, CMC and polysorbate 80. Gewirtz's lab has done studies in mice indicating that some of these detergentlike compounds may damage the mucosa — the protective lining of the gut wall — potentially leading to leakage and inflammation.
A growing number of medical researchers are coming around to the idea that the common denominator of many, if not most, of the chronic diseases from which we suffer today may be inflammation — a heightened and persistent immune response by the body to a real or perceived threat. Various markers for inflammation are common in people with metabolic syndrome, the complex of abnormalities that predisposes people to illnesses like cardiovascular disease, obesity, Type 2 diabetes and perhaps cancer. While health organizations differ on the exact definition of metabolic syndrome, a 2009 report from the Centers for Disease Control and Prevention found that 34 percent of American adults are afflicted with the condition. But is inflammation yet another symptom of metabolic syndrome, or is it perhaps the cause of it? And if it is the cause, what is its origin?

One theory is that the problem begins in the gut, with a disorder of the microbiota, specifically of the all-important epithelium that lines our digestive tract. This internal skin — the surface area of which is large enough to cover a tennis court — mediates our relationship to the world outside our bodies; more than 50 tons of food pass through it in a lifetime. The microbiota play a critical role in maintaining the health of the epithelium: some bacteria, like the bifidobacteria and Lactobacillus plantarum (common in fermented vegetables), seem to directly enhance its function. These and other gut bacteria also contribute to its welfare by feeding it. Unlike most tissues, which take their nourishment from the bloodstream, epithelial cells in the colon obtain much of theirs from the short-chain fatty acids that gut bacteria produce as a byproduct of their fermentation of plant fiber in the large intestine.

But if the epithelial barrier isn't properly nourished, it can become more permeable, allowing it to be breached. Bacteria, endotoxins — which are the toxic byproducts of certain bacteria — and proteins can slip into the blood stream, thereby causing the body's immune system to mount a response. This resulting low-grade inflammation, which affects the entire body, may lead over time to metabolic syndrome and a number of the chronic diseases that have been linked to it.
Evidence in support of this theory is beginning to accumulate, some of the most intriguing coming from the lab of Patrice Cani at the Université Catholique de Louvain in Brussels. When Cani fed a high-fat, "junk food" diet to mice, the community of microbes in their guts changed much as it does in humans on a fast-food diet. But Cani also found the junk-food diet made the animals' gut barriers notably more permeable, allowing endotoxins to leak into the bloodstream. This produced a low-grade inflammation that eventually led to metabolic syndrome. Cani concludes that, at least in mice, "gut bacteria can initiate the inflammatory processes associated with obesity and insulin resistance" by increasing gut permeability.

These and other experiments suggest that inflammation in the gut may be the cause of metabolic syndrome, not its result, and that changes in the microbial community and lining of the gut wall may produce this inflammation. If Cani is correct — and there is now some evidence indicating that the same mechanism is at work in humans — then medical science may be on the trail of a Grand Unified Theory of Chronic Disease, at the very heart of which we will find the gut microbiome.
My first reaction to learning all this was to want to do something about it immediately, something to nurture the health of my microbiome. But most of the scientists I interviewed were reluctant to make practical recommendations; it's too soon, they told me, we don't know enough yet. Some of this hesitance reflects an understandable abundance of caution. The microbiome researchers don't want to make the mistake of overpromising, as the genome researchers did. They are also concerned about feeding a gigantic bloom of prebiotic and probiotic quackery and rightly so: probiotics are already being hyped as the new panacea, even though it isn't at all clear what these supposedly beneficial bacteria do for us or how they do what they do. There is some research suggesting that some probiotics may be effective in a number of ways: modulating the immune system; reducing allergic response; shortening the length and severity of colds in children; relieving diarrhea and irritable bowel symptoms; and improving the function of the epithelium. The problem is that, because the probiotic marketplace is largely unregulated, it's impossible to know what, if anything, you're getting when you buy a "probiotic" product. One study tested 14 commercial probiotics and found that only one contained the exact species stated on the label.

But some of the scientists' reluctance to make recommendations surely flows from the institutional bias of science and medicine: that the future of microbiome management should remain firmly in the hands of science and medicine. Down this path — which holds real promise — lie improved probiotics and prebiotics, fecal transplants (with better names) and related therapies. Jeffrey Gordon, one of those scientists who peers far over the horizon, looks forward to a time when disorders of the microbiome will be treated with "synbiotics" — suites of targeted, next-generation probiotic microbes administered along with the appropriate prebiotic nutrients to nourish them. The fecal transplant will give way to something far more targeted: a purified and cultured assemblage of a dozen or so microbial species that, along with new therapeutic foods, will be introduced to the gut community to repair "lesions" — important missing species or functions. Yet, assuming it all works as advertised, such an approach will also allow Big Pharma and Big Food to stake out and colonize the human microbiome for profit.

When I asked Gordon about do-it-yourself microbiome management, he said he looked forward to a day “when people can cultivate this wonderful garden that is so influential in our health and well-being” — but that day awaits a lot more science. So he declined to offer any gardening tips or dietary advice. “We have to manage expectations,” he said.

Alas, I am impatient. So I gave up asking scientists for recommendations and began asking them instead how, in light of what they’ve learned about the microbiome, they have changed their own diets and lifestyles. Most of them have made changes. They were slower to take, or give their children, antibiotics. (I should emphasize that in no way is this an argument for the rejection of antibiotics when they are medically called for.) Some spoke of relaxing the sanitary regime in their homes, encouraging their children to play outside in the dirt and with animals — deliberately increasing their exposure to the great patina. Many researchers told me they had eliminated or cut back on processed foods, either because of its lack of fiber or out of concern about additives. In general they seemed to place less faith in probiotics (which few of them used) than in prebiotics — foods likely to encourage the growth of “good bacteria” already present. Several, including Justin Sonnenburg, said they had added fermented foods to their diet: yogurt, kimchi, sauerkraut. These foods can contain large numbers of probiotic bacteria, like L. plantarum and bifidobacteria, and while most probiotic bacteria don’t appear to take up permanent residence in the gut, there is evidence that they might leave their mark on the community, sometimes by changing the gene expression of the permanent residents — in effect turning on or off metabolic pathways within the cell — and sometimes by stimulating or calming the immune response.

What about increasing our exposure to bacteria? “There’s a case for dirtying up your diet,” Sonnenburg told me. Yet advising people not to thoroughly wash their produce is probably unwise in a world of pesticide residues. “I view it as a cost-benefit analysis,” Sonnenburg wrote in an e-mail. “Increased exposure to environmental microbes likely decreases chance of many Western diseases, but increases pathogen exposure. Certainly the costs go up as scary antibiotic-resistant bacteria become more prevalent.” So wash your hands in situations when pathogens or toxic chemicals are likely present, but maybe not after petting your dog. “In terms of food, I think eating fermented foods is the answer — as opposed to not washing food, unless it is from your garden,” he said.

With his wife, Erica, also a microbiologist, Sonnenburg tends a colony of gnotobiotic mice at Stanford, examining (among other things) the effects of the Western diet on their microbiota. (Removing fiber drives down diversity, but the effect is reversible.) He’s an amateur baker, and when I visited his lab, we talked about the benefits of baking with whole grains. “Fiber is not a single nutrient,” Sonnenburg said, which is why fiber supplements are no magic bullet. “There are hundreds of different polysaccharides” — complex carbohydrates, including fiber — “in plants, and different microbes like to chomp on different ones.” To boost fiber, the food industry added lots of a polysaccharide called inulin to hundreds of products, but that’s just one kind (often derived from the chicory-plant root) and so may only favor a limited number of microbes. I was hearing instead an argument for a variety of whole grains and a diverse diet of plants and vegetables as well as fruits. “The safest way to increase your microbial biodiversity is to eat a variety of polysaccharides,” he said.

His comment chimed with something a gastroenterologist at the University of Pittsburgh told me. “The big problem with the Western diet,” Stephen O’Keefe said, “is that it doesn’t feed the gut, only the upper G I. All the food has been processed to be readily absorbed, leaving nothing for the lower G I. But it turns out that one of the keys to health is fermentation in the large intestine.” And the key to feeding the fermentation in the large intestine is giving it lots of plants with their various types of fiber, including resistant starch (found in bananas, oats, beans); soluble fiber (in onions and other root vegetables, nuts); and insoluble fiber (in whole grains, especially bran, and avocados).

With our diet of swiftly absorbed sugars and fats, we’re eating for one and depriving the trillion of the food they like best: complex carbohydrates and fermentable plant fibers. The byproduct of fermentation is the short-chain fatty acids that nourish the gut barrier and help prevent inflammation. And there are studies suggesting that simply adding plants to a fast-food diet will mitigate its inflammatory effect.

The outlines of a diet for the new superorganism were coming clear, and it didn’t require the ministrations of the food scientists at Nestlé or General Mills to design it. Big Food and Big Pharma probably do have a role to play, as will Jeffrey Gordon’s next-generation synbiotics, in repairing the microbiota of people who can’t or don’t care to simply change their diets. This is going to be big business. Yet the components of a microbiota-friendly diet are already on the supermarket shelves and in farmers’ markets.

Viewed from this perspective, the foods in the markets appear in a new light, and I began to see how you might begin to shop and cook with the microbiome in mind, the better to feed the fermentation in our guts. The less a food is processed, the more of it that gets safely through the gastrointestinal tract and into the eager clutches of the microbiota. Al dente pasta, for example, feeds the bugs better than soft pasta does; steel-cut oats better than rolled; raw or lightly cooked vegetables offer the bugs more to chomp on than overcooked, etc. This is at once a very old and a very new way of thinking about food: it suggests that all calories are not created equal and that the structure of a food and how it is prepared may matter as much as its nutrient composition.

It is a striking idea that one of the keys to good health may turn out to involve managing our internal fermentation. Having recently learned to manage several external fermentations — of bread and kimchi and beer — I know a little about the vagaries of that process. You depend on the microbes, and you do your best to align their interests with yours, mainly by

feeding them the kinds of things they like to eat — good “substrate.” But absolute control of the process is too much to hope for. It’s a lot more like gardening than governing.

The successful gardener has always known you don’t need to master the science of the soil, which is yet another hotbed of microbial fermentation, in order to nourish and nurture it. You just need to know what it likes to eat — basically, organic matter — and how, in a general way, to align your interests with the interests of the microbes and the plants. The gardener also discovers that, when pathogens or pests appear, chemical interventions “work,” that is, solve the immediate problem, but at a cost to the long-term health of the soil and the whole garden. The drive for absolute control leads to unanticipated forms of disorder.

This, it seems to me, is pretty much where we stand today with respect to our microbiomes — our teeming, quasi-wilderness. We don’t know a lot, but we probably know enough to begin taking better care of it. We have a pretty good idea of what it likes to eat, and what strong chemicals do to it. We know all we need to know, in other words, to begin, with modesty, to tend the unruly garden within.

Michael Pollan is the Knight professor of journalism at the University of California, Berkeley, and the author, most recently, of “Cooked: A Natural History of Transformation.”
Editor: Ilena Silverman