Caution: Killing Germs May Be Hazardous to Your Health

Our war on microbes has toughened them. Now, new science tells us we should embrace bacteria.

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Behold yourself, for a moment, as an organism. A trillion cells stuck together, arrayed into tissues and organs and harnessed by your DNA to the elemental goals of survival and propagation. But is that all? An electron microscope would reveal that you are teeming with other life-forms. Any part of your body that comes into contact with the outside world—your skin, mouth, nose and (especially) digestive tract—is home to bacteria, fungi and protozoa that outnumber the cells you call your own by 10, or perhaps a hundred, to one.

Their ancestors began colonizing you the moment you came into the world, inches from the least sanitary part of your mother's body, and their descendants will have their final feast on your corpse, and join you in death. There are thousands of different species, found in combinations "as unique as our DNA or our fingerprints," says Stanford biologist David Relman, who is investigating the complex web of interactions microbes maintain with our digestive, immune and nervous systems. Where do you leave off, and they begin? Microbes, Relman holds, are "a part of who we are."

Relman is a leader in rethinking our relationship to bacteria, which for most of the last century was dominated by the paradigm of Total Warfare. "It's awful the way we treat our microbes," he says, not intending a joke; "people still think the only good microbe is a dead one." We try to kill them off with antibiotics and hand sanitizers. But bacteria never surrender; if there were one salmonella left in the world, doubling every 30 minutes, it would take less than a week to give everyone alive diarrhea. In the early years of antibiotics, doctors dreamed of eliminating infectious disease. Instead, a new paper in The Journal of the American Medical Association reports on the prevalence of Methicillin-resistant Staphylococcus aureus (MRSA), which was responsible for almost 19,000 deaths in the United States in 2005—about twice as many as previously thought, and more than AIDS. Elizabeth Bancroft, a leading epidemiologist, called this finding "astounding."

As antibiotics lose their effectiveness, researchers are returning to an idea that dates back to Pasteur, that the body's natural microbial flora aren't just an incidental fact of our biology, but crucial components of our health, intimate companions on an evolutionary journey that began millions of years ago. The science writer Jessica Snyder Sachs summarizes this view in four words in the title of her ground-breaking new book: "Good Germs, Bad Germs." Our microbes do us the favor of synthesizing vitamins right in our guts; they regulate our immune systems and even our serotonin levels: germs, it seems, can make us happy. They influence how we digest our food, how much we eat and even what we crave. The genetic factors in weight control might reside partly in their genes, not ours. Regrettably, it turns out that bacteria exhibit a strong preference for making us fat.

Our well-meaning war on microbes has, by the relentless process of selection, toughened them instead. When penicillin began to lose its effectiveness against staph, doctors turned to methicillin, but then MRSA appeared—first as an opportunistic infection among people already hospitalized, now increasingly a wide-ranging threat that can strike almost anyone. The strain most commonly contracted outside hospitals, dubbed USA300, comes armed with the alarming ability to attack immune-system cells. Football players seem to be especially vulnerable: they get scraped and bruised and share equipment while engaging in prolonged exercise, which
some researchers believe temporarily lowers immunity. In the last five years outbreaks have plagued the Cleveland Browns, the University of Texas and the University of Southern California, where trainers now disinfect equipment almost hourly. The JAMA article was a boon to makers of antimicrobial products, of which about 200 have been introduced in the United States so far this year. Press releases began deluging newsrooms, touting the benefits of antibacterial miracle compounds ranging from silver to honey. Charles Gerba, a professor of environmental microbiology at the University of Arizona, issued an ominous warning that teenagers were catching MRSA by sharing cell phones. Gerba is a consultant to the makers of Purell hand sanitizer, Clorox bleach and the Oreck antibacterial vacuum cleaner, which uses Microban to kill germs on your rug.

To be sure, MRSA is a scary infection, fast-moving and tricky to diagnose. Hunter Spence, a 12-year-old cheerleader from Victoria, Texas, woke up one Sunday in May with pain in her left leg. "I think I pulled a calf muscle," she told her mother, Peyton. By the next day, the pain was much worse and she was running a low-grade fever, but there was no other sign of infection. A doctor thought she might have the flu. By Wednesday her fever was 103 and the leg pain was unbearable. But doctors at two different community hospitals couldn't figure out what was wrong until Friday, when a blood culture came up positive for MRSA. By the time she arrived at Driscoll Children's Hospital in Corpus Christi—by helicopter—her temperature was 107 and her pulse 220. Doctors put her chance of survival at 20 percent.

Hunter needed eight operations over the next week to drain her infections, and an intravenous drip of two powerful new antibiotics, Zyvox and Cubicin. She did survive, and is home now, but her lung capacity is at 35 percent of normal. "We are seeing more infections, and more severe infections" with the USA300 strain, says Dr. Jaime Fergie, who treated her at Driscoll. In many cases, there's no clue as to how the infection was contracted, but a study Fergie did in 2005 of 350 children who were seen at Driscoll for unrelated conditions found that 21 percent of them were carrying MRSA, mostly in their noses. Then all it may take is a cut ... and an unwashed hand.

And there are plenty of unwashed hands out there; Gerba claims that only one in five of us does the job properly, getting in all the spaces between the fingers and under the nails and rubbing for at least 20 seconds. Americans have been obsessed with eradicating germs ever since their role in disease was discovered in the 19th century, but they've been partial to technological fixes like antibiotics or sanitizers rather than the dirty work of cleanliness. Nancy Tomes, author of "The Gospel of Germs," believes the obsession waxes and wanes in response to social anxiety—about diseases such as anthrax, SARS or avian flu, naturally, but also about issues like terrorism or immigration that bear a metaphoric relationship to infection. "I can't protect myself from bin Laden, but I can rid myself of germs," she says. "Guarding against microbes is something Americans turn to when they're stressed." The plastic squeeze bottle of alcohol gel, which was introduced by Purell in 1997, is a powerful talisman of security. Sharon Morrison, a Dallas real-estate broker with three young daughters, estimates she has as many as 10 going at any time, in her house, her car, her purse, her office and her kids' backpacks. She swabs her grocery cart with sanitizing wipes and, when her children were younger, she would bring her own baby-seat cover from home and her own place mats to restaurants. Sales of Purell last year were $90 million, so she's clearly not alone. There's no question it kills germs, although it's not a substitute for washing; the Centers for Disease Control Web site notes that alcohol can't reach germs through a layer of dirt. Alcohol gels, which kill germs by drying them out, don't cause the kind of resistance that gives rise to superbugs like MRSA. But they're part of the culture of cleanliness that's led to a different set of problems.

In terms of infectious disease, the environment of the American suburb is unquestionably a far healthier place than most of the rest of the world. But we've made a Faustian bargain with our antibiotics, because most researchers now believe that our supersanitized world exacts a unique price in allergies, asthma and autoimmune diseases, most of which were unknown to our ancestors. Sachs warns that many people drew precisely the wrong conclusion from this, that contracting a lot of diseases in childhood is somehow beneficial. What we need is more exposure to the good microbes, and the job of medicine in the years to come will be sorting out the good microbes from the bad.

That's the goal of the Human Microbiome Project, a five-year multinational study that its advocates say could tell us almost as much about life as the recently completed work of sequencing the human genome. One puzzling result of the Human Genome Project was the paltry number of genes it found—about 20,000, which is only as many as it takes to make a fruit fly. Now some researchers think some of the "missing" genes may be found in the
teeming populations of microbes we host.

And the microbe project—which as a first step requires sampling every crevice and orifice of 100 people of varying ages from a variety of climates and cultures—is "infinitely more complex and problematic than the genome," laments (or boasts) one of its lead researchers, Martin Blaser of NYU Medical School. Each part of the body is a separate ecosystem, and even two teeth in the same mouth can be colonized by different bacteria. In general, researchers know what they'll find—Escherichia (including the ubiquitous microbial Everyman, E. coli) in the bowel, lactobacilli and staphylococcus on the skin. But the mix of particular species and strains will probably turn out to be unique to each individual, a product of chance, gender (men and women have different microbes on their skin but are similar in their intestines) and socioeconomic status and culture. (Race seems not to matter much.) Once the microbes establish themselves they stay for life and fight off newcomers; a broad-spectrum antibiotic may kill most of them but the same kinds usually come back after a few weeks. The most intriguing question is how microbes interact with each other and with our own cells. "There is a three-way conversation going on throughout our bodies," says Jane Peterson of the National Human Genome Research Institute. "We want to listen in because we think it will fill in a lot of blanks about human health—and human disease."

The vast majority of human microbes live in the digestive tract; they get there by way of the mouth in the first few months of life, before stomach acid builds to levels that are intended to kill most invaders. The roiling, fetid and apparently useless contents of the large intestine were a moral affront to doctors in the early years of modern medicine, who sought to cleanse them from the body with high-powered enemas. But to microbiologists, the intestinal bacteria are a marvel, a virtual organ of the body which just happens to have its own DNA. Researchers at Duke University claim it explains the persistence of the human appendix. It serves, they say, as a reservoir of beneficial microbes which can recolonize the gut after it's emptied by diseases such as cholera or dysentery.

Microbes play an important role in digestion, especially of polysaccharides, starch molecules found in foods such as potatoes or rice that may be hundreds or thousands of atoms long. The stomach and intestines secrete 99 different enzymes for breaking these down into usable 6-carbon sugars, but the humble gut-dwelling Bacteroides theta produces almost 250, substantially increasing the energy we can extract from a given meal.

Of course, "energy" is another way of saying "calories." Jeffrey Gordon of Washington University raised a colony of mice in sterile conditions, with no gut microbes at all, and although they ate 30 percent more food than normal mice they had less than half the body fat. When they were later inoculated with normal bacteria, they quickly gained back up to normal weight. "We are finding that the nutritional value of food is pretty individualized," Gordon says. "And a big part of what determines it is our microbial composition."

We can't raise humans in sterile labs, of course, but there's evidence that variations between people in their intestinal microbes correspond to differences in body composition. And other factors appear to be at work besides the ability to extract calories from starch. Bacteria seem able to adjust levels of the hormones ghrelin and leptin, which regulate appetite and metabolism. Certain microbes even seem to be associated with a desire for chocolate, according to research by the Nestlé Research Center. And a tiny study suggests that severe emotional stress in some people triggers an explosion in the population of B. theta, the starch-digesting bacteria associated with weight gain. That corresponds to folk wisdom about "stress eating," but it is also a profoundly disturbing and counterintuitive observation that something as intimate as our choice between a carrot and a candy bar is somehow mediated by creatures that are not us.

But these are the closest of aliens, so familiar that the immune system, which ordinarily attacks any outside organism, tolerates them by the trillions—a seeming paradox with profound implications for health. The microbes we have all our lives are the ones that colonize us in the first weeks and months after birth, while our immune system is still undeveloped; in effect, they become part of the landscape. "Dendritic" (treelike) immune cells send branches into the respiratory and digestive tracts, where they sample all the microbes we inhale or swallow. When they see the same ones over and over, they secrete an anti-inflammatory substance called interferulin-10, which signals the microbe-killing T-cells: stand down.

And that's an essential step in the development of a healthy immune system. The immune reaction relies on a network of positive and negative feedback loops, poised on a knife edge between the dangers of ignoring a deadly invader and over-reacting to a harmless stimulus.
But to develop properly it must be exposed to a wide range of harmless microbes early in life. This was the normal condition of most human infants until a few generations ago. Cover the dirt on the floor of the hut, banish the farm animals to a distant feedlot, treat an ear infection with penicillin, and the inflammation-calming interleukin-10 reaction may fail to develop properly. "Modern sanitation is a good thing, and pavement is a good thing," says Sachs, "but they keep kids at a distance from microbes." The effect is to tip the immune system in the direction of overreaction, either to outside stimuli or even to the body's own cells. If the former, the result is allergies or asthma. Sachs writes that "children who receive antibiotics in the first year of life have more than double the rate of allergies and asthma in later childhood." But if the immune system turns on the body itself, you see irritable bowel syndrome, lupus or multiple sclerosis, among the many autoimmune diseases that were virtually unknown to our ancestors but are increasingly common in the developed world.

That is the modern understanding of the "Hygiene Hypothesis," first formulated by David Strachan in 1989. In Strachan's original version, which has unfortunately lodged in the minds of many parents, actual childhood illness was believed to exert a protective effect. There was a brief vogue for intentionally exposing youngsters to disease. But researchers now believe the key is exposure to a wide range of harmless germs, such as might be found in a playground or a park.

The task is complicated, in part because some bacteria seem to be both good and bad. The best-known is Helicobacter pylori, a microbe that has evolved to live in the acid environment of the stomach. It survives by burrowing into the stomach's mucus lining and secreting enzymes that reduce acidity. Nobel laureates Barry Marshall and Robin Warren showed it could cause gastric ulcers and stomach cancer. But then further studies discovered that infection with H. pylori was protective against esophageal reflux and cancer of the esophagus, and may also reduce the incidence of asthma. H. pylori, which is spread in drinking water and direct contact among family members, was virtually universal a few generations ago but is now on the verge of extinction in the developed world. The result is fewer ulcers and stomach cancer, but more cancer of the esophagus—which is increasing faster than any other form of cancer in America—more asthma, and ... what else? We don't know. "H. pylori has colonized our guts since before humans migrated out of Africa," says Blaser. "You can't get rid of it and not expect consequences."

Blaser questions whether eliminating H. pylori is a good idea. Someday, conceivably, we might intentionally inoculate children with a bioengineered version of H. pylori that keeps its benefits without running the risk of stomach cancer. There is already a burgeoning market for "probiotics," bacteria with supposed health benefits, either in pill form or as food. Consumers last year slurped down more than $100 million worth of Dannon's Activia, a yogurt containing what the Web site impressively calls "billions" of beneficial microbes in every container. The microbes are a strain of Bifidobacterium animalis, which helps improve what advertisers delicately call "regularity," a fact Dannon has underscored by rechristening the species with its trademarked name "Bifidus regularis." Other products contain Lactobacillus casei, which is supposed to stimulate production of infection-fighting lymphocytes. Many others on the market are untested and of dubious value. Labels that claim ANTIBIOTIC RESISTANT ought to be considered a warning, not a boast. Bacteria swap genetic material among themselves, and the last thing you want to do is introduce a resistant strain, even of a beneficial microbe, into your body.

And there's one more thing that microbes can do, perhaps the most remarkable of all. Mycobacterium vaccae, a soil microbe found in East Africa that has powerful effects on the immune system, was tested at the University of Bristol as a cancer therapy. The results were equivocal, but researchers made the startling observation that patients receiving it felt better regardless of whether their cancer was actually improving. Neuroscientist Chris Lowry injected mice with it, and found, to his amazement, that it activated the serotonin receptors in the prefrontal cortex—in other words, it worked like an antidepressant, only without the side effects of insomnia and anxiety. Researchers believe M. vaccae works through the interleukin-10 pathway, although the precise mechanism is uncertain. But there is at least the tantalizing, if disconcerting, suggestion that microbes may be able to manipulate our happiness. Could the hygiene hypothesis help explain the rise in, of all things, depression? We're a long way from being able to say that, much less use that insight to treat people. But at least we are asking the right questions: not how to kill bacteria, but how to live with them.