Are Antibiotics Killing Us?

For every cell in your body, you support 10 bacterial cells that make vitamins, trigger hormones, and may even influence how fat you are. Guess what happens to them when you pop penicillin?.

By Jessica Snyder Sachs
Photography by Joshua Lutz
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Alan Hudson likes to tell a story about a soldier and his high school sweetheart.

The young man returns from an overseas assignment for their wedding with a clean bill of health, having dutifully cleared up an infection of sexually transmitted chlamydia.

"Three weeks later, the wife has a screaming genital infection," Hudson recounts, "and I get a call from the small-town doctor who's trying to save their marriage." The soldier, it seems, has decided his wife must have been seeing other men, which she denies.

Hudson pauses for effect, stretching back in his seat and propping his feet on an open file drawer in a crowded corner of his microbiology laboratory at Wayne State Medical School in Detroit. "The doctor is convinced she's telling the truth," he continues, folding his hands behind a sweep of white, collar-length hair. "So I tell him, 'Send me a specimen from him and a cervical swab from her.' " This is done after the couple has completed a full course of antibiotic treatment and tested free of infection.

"I PCR 'em both," Hudson says, "and he is red hot."

PCR stands for polymerase chain reaction—a technique developed about 20 years ago that allows many copies of a DNA sequence to be made. It is often used at crime scenes, where very little DNA may be available. Hudson's use of the technique allowed him to find traces of chlamydia DNA in the soldier and his wife that traditional tests miss because the amount left after antibiotic treatment is small and asymptomatic. Nonetheless, if a small number of inactive chlamydia cells passed from groom to bride, the infection could have became active in its new host.

Hudson tells the tale to illustrate how microbes that scientists once thought were easily eliminated by antibiotics can still thrive in the body. His findings and those of other researchers raise disturbing questions about the behavior of microbes in the human body and how they should be treated.

For example, Hudson has found that quiescent varieties of chlamydia may play a role in chronic ailments not traditionally thought to be related to this infectious agent. In the early 1990s, he found two types of chlamydia—Chlamydia trachomatis and Chlamydia pneumonia—in the joint tissue of patients with inflammatory arthritis. More famously, in 1996, he began fishing C. pneumonia out of the brain cells of Alzheimer's victims. Since then, other researchers have made headlines after reporting the genetic fingerprints of C. pneumonia, as well as several kinds of common mouth bacteria, in the arterial plaque of heart attack patients. Hidden infections are now thought to be the basis of still other stubbornly elusive ills like chronic fatigue syndrome, Gulf War syndrome, multiple sclerosis, lupus, Parkinson's disease, and types of cancer.

To counteract these killers, some physicians have turned to lengthy or lifelong courses of antibiotics. At the same time, other researchers are counterintuitively finding that bacteria we think are bad for us also ward off other diseases and keep us healthy. Using antibiotics to tamper with this complicated and little-understood population could irrevocably alter the microbial ecology in an individual and accelerate the spread of drug-resistant genes to the public at large.

The two-faced puzzle regarding the role of bacteria is as old as the study of microbiology itself. Even as Louis Pasteur became the first to show that bacteria can cause disease, he assumed that bacteria normally found in the body are essential to life. Yet his protégé, Élie Metchnikoff, openly scoffed at the idea. Metchnikoff blamed indigenous bacteria for senility, atherosclerosis, and an altogether shortened life span—going even so far as to predict the day when surgeons would routinely remove the human colon simply to rid us of the "chronic poisoning" from its abundant flora.

Today we know that trillions of bacteria carpet not only our intestines but also our skin and much of our respiratory and urinary tracts. The vast majority of them seem to be innocuous, if not beneficial. And bacteria are everywhere, in abundance—they outnumber other cells in the human body by 10 to one. David Relman and his team at Stanford University and the VA Medical Center in Palo Alto, California, recently found the genetic fingerprints of several hundred new bacterial species in the mouths, stomachs, and intestines of healthy volunteers.

"What I hope," Relman says, "is that by starting with specimens from healthy people, the assumption would be that these microbes have probably been with us for some time relative to our stay on this planet and may, in fact, be important to our health."

Meanwhile, the behavior of even well-known bacterial inhabitants is challenging the old, straightforward view of infectious disease. In the 19th century, Robert Koch laid the foundation for medical microbiology, postulating: Any microorganism that causes a disease should be found in every case of the disease and always cause the disease when introduced into a new host. That view prevailed until the middle of this past century. Now we are more confused than ever. Take Helicobacter pylori. In the 1980s infection by the bacterium, not stress, was found to be the cause of most ulcers. Overnight, antibiotics became the standard treatment. Yet in the undeveloped world ulcers are rare, and H. pylori is pervasive.

"This stuff drives the old-time microbiologists mad," says Hudson, "because Koch's postulates simply don't apply." With new technologies like PCR, researchers are turning up stealth infections everywhere, yet they cause problems only in some people sometimes, often many years after the infection.

These mysteries have nonetheless not stopped a free flow of prescriptions. Many rheumatologists, for example, now prescribe long-term—even lifelong—courses of antibiotics for inflammatory arthritis, even though it isn't known if the antibiotics actually clear away bacteria or reduce inflammatory arthritis in some other unknown manner.

Even more far-reaching is the use of antibiotics to treat heart disease, a trend that began in the early 1990s after studies associated C. pneumonia with the accumulation of plaque in arteries. In April two large-scale studies reported that use of antibiotics does not reduce the incidence of heart attacks or eliminate C. pneumonia. But researchers left antibiotic-dosing cardiologists a strange option by admitting they do not know if stronger, longer courses of antibiotics or combined therapies would succeed.

Meanwhile, many researchers are alarmed. Infectious-diseases specialist Curtis Donskey, of Case Western Reserve University in Cleveland, says: "Unfortunately, far too many physicians are still thinking of antibiotics as benign. We're just now beginning to understand how our normal microflora does such a good job of preventing our colonization by disease-causing microbes. And from an ecological point of view, we're just starting to understand the medical consequences of disturbing that with antibiotics."

Donskey has seen the problem firsthand at the Cleveland VA Medical Center, where he heads infection control. "Hospital patients get the broadest spectrum, most powerful antibiotics," he says, but they are also "in an environment where they get exposed to some of the nastiest, most drug-resistant pathogens." Powerful antibiotics can be dangerous in such a setting because they kill off harmless bacteria that create competition for drug-resistant colonizers, which can then proliferate. The result: Hospital-acquired infections have become a leading cause of death in critical-care units.
"We also see serious problems in the outside community," Donskey says, because of inappropriate antibiotic use.

The consequences of disrupting the body's bacterial ecosystem can be minor, such as a yeast infection, or they can be major, such as the overgrowth of a relatively common gut bacterium called Clostridium difficile. A particularly nasty strain of C. difficile

has killed hundreds of hospital patients in Canada over the past two years. Some had checked in for simple, routine procedures. The same strain is moving into hospitals in the United States and the United Kingdom.

Jeffrey Gordon, a gastroenterologist turned full-time microbiologist, heads the spanking new Center for Genomic Studies at Washington University in Saint Louis. The expansive, sun-streaked laboratory sits above the university's renowned gene-sequencing center, which proved a major player in powering the Human Genome Project. "Now it's time to take a broader view of the human genome," says Gordon, "one that recognizes that the human body probably contains 100 times more microbial genes than human ones."

Gordon supervises a lab of some 20 graduate students and postdocs with expertise in disciplines ranging from ecology to crystallography. Their collaborations revolve around studies of unusually successful colonies of genetically engineered germ-free mice and zebra fish.

Gordon's veteran mouse wranglers, Marie Karlsson and her husband David O'Donnell, manage the rearing of germ-free animals for comparison with genetically identical animals that are colonized with one or two select strains of normal flora. In a cavernous facility packed with rows of crib-size bubble chambers, Karlsson and O'Donnell handle their germ-free charges via bulbous black gloves that serve as airtight portals into the pressurized isolettes. They generously supplement sterilized mouse chow with vitamins and extra calories to replace or complement what is normally supplied by intestinal bacteria. "Except for their being on the skinny side, we've got them to the point where they live near-normal lives," says O'Donnell. Yet the animals' intestines remain thin and underdeveloped in places, bizarrely bloated in others. They also prove vulnerable to any stray pathogen that slips into their food, water, or air.

All Gordon's protégés share an interest in following the molecular cross talk among resident microbes and their host when they add back a component of an animal's normal microbiota. One of the most interesting players is Bacteroides thetaiotaomicron, or B. theta, the predominant bacterium of the human colon and a particularly bossy symbiont.

The bacterium is known for its role in breaking down otherwise indigestible plant matter, providing up to 15 percent of its host's calories. But Gordon's team has identified a suite of other, more surprising skills. Three years ago, they sequenced B. theta's entire genome, which enabled them to work with a gene chip that detects what proteins are being made at any given time. By tracking changes in the activity of these genes, the team has shown that B. theta helps guide the normal development and functioning of the intestines—including the growth of blood vessels, the proper turnover of epithelial cells, and the marshaling of components of the immune system needed to keep less well behaved bacteria at bay. B. theta also exerts hormonelike, long-range effects that may help the host weather times when food is scarce and ensure the bacterium's own survival.

Fredrik Bäckhed, a young postdoc who came to Gordon's laboratory from the Karolinska Institute in Stockholm, has caught B. theta sending biochemical messages to host cells in the abdomen, directing them to store fat. When he gave germ-free mice an infusion of gut bacteria from a conventionally raised mouse, they immediately put on an average of 50 percent more fat although they were consuming 30 percent less food than when they were germ-free. "It's as if B. theta is telling its host, 'save this—we may need it later,' " Gordon says.

Justin Sonnenburg, another postdoctoral fellow, has documented that B. theta turns to the host's body for food when the animal stops eating. He has found that when a lab mouse misses its daily ration, B. theta consumes the globs of sugary mucus made every day by some cells in the intestinal lining. The bacteria graze on these platforms, which the laboratory has dubbed Whovilles (after the dust-speck metropolis of Dr. Seuss's Horton Hears a Who!). When the host resumes eating, B. theta returns to feeding on the incoming material.

Gordon's team is also looking at the ecological dynamics that take place when combinations of normal intestinal bacteria are introduced into germ-free animals. And he plans to study the dynamics in people by analyzing bacteria in fecal samples.

Among the questions driving him: Can we begin to use our microbiota as a marker of health and disease? Does this "bacterial nation" shift in makeup when we become obese, try to lose weight, experience prolonged stress, or simply age? Do people in Asia or Siberia harbor the same organisms in the same proportions as those in North America or the Andes?

"We know that our environment affects our health to an enormous degree," Gordon says. "And our microbiota are our most intimate environment by far."

A couple hundred miles northeast of Gordon's laboratory, microbiologist Abigail Salyers at the University of Illinois at Urbana-Champaign has been exploring a more sinister feature of our bacteria and their role in antibiotic resistance. At the center of her research stands a room-size, walk-in artificial "gut" with the thermostat set at the human intestinal temperature of 100.2 degrees Fahrenheit. Racks of bacteria-laced test tubes line three walls, the sealed vials purged of oxygen to simulate the anaerobic conditions inside a colon. Her study results are alarming.

Salyers says her research shows that decades of antibiotic use have bred a frightening

degree of drug resistance into our intestinal flora. The resistance is harmless as long as the bacteria remain confined to their normal habitat. But it can prove deadly when those bacteria contaminate an open wound or cause an infection after surgery.

"Having a highly antibiotic-resistant bacterial population makes a person a ticking time bomb," says Salyers, who studies the genus Bacteroides, a group that includes not only B. theta but also about a quarter of the bacteria in the human gut. She has tracked dramatic increases in the prevalence of several genes and suites of genes coding for drug resistance. She's particularly interested in tetQ, a DNA sequence that conveys resistance to tetracycline drugs.

When her team tested fecal samples taken in the 1970s, they found that less than 25 percent of human-based Bacteroides carried tetQ. By the 1990s, that rate had passed the 85 percent mark, even among strains isolated from healthy people who hadn't used antibiotics in years. The dramatic uptick quashed hopes of reducing widespread antibiotic resistance by simply withdrawing or reducing the use of a given drug. Salyers's team also documented the spread of several Bacteroides genes conveying resistance to other antibiotics such as macrolides, which are widely used to treat skin, respiratory, genital, and blood infections.

As drug-resistant genes become common in bacteria in the gut, they are more likely to pass on their information to truly dangerous bugs that only move periodically through our bodies, says Salyers. Even distantly related bacteria can swap genes with one another using a variety of techniques, from direct cell-to-cell transfer, called conjugation, to transformation, in which a bacterium releases snippets of DNA that other bacteria pick up and use.

"Viewed in this way, the human colon is the bacterial equivalent of eBay," says Salyers. "Instead of creating a new gene the hard way—through mutation and natural selection—you can just stop by and obtain a resistance gene that has been created by some other bacterium."

neither bug colonizes the intestine, they are routinely inhaled and swallowed, providing a window of 24 to 48 hours in which they can commingle with intestinal flora before exiting. "That's more than long enough to pick up something interesting in the swinging singles bar of the human colon," she quips.

Most disturbing is Salyers's discovery that antibiotics like tetracycline actually stimulate Bacteroides to begin swapping its resistance genes. "If you think of the conjugative transfer of resistance genes as bacterial sex, you have to think of tetracycline as the aphrodisiac," she says. When Salyers exposes Bacteroides to other bacteria such as Escherichia coli under the disinhibiting influence of antibiotics, she has witnessed the step-by-step process by which the bacteria excise and transfer the tetQ gene from one species to another.

YOUR BODY'S ABUNDANT BACTERIA

More than 100 trillion bacteria inhabit your body. And they aren't just silent partners. They digest your food, make vitamins, and protect you from pathogens. A recent study has found they may even play a role in regulating appetite and weight. *—Jocelyn Selim*

Nor is Bacteroides the only intestinal resident with such talents. "In June 2002, we passed a particularly frightening milestone," Salyers says. That summer, epidemiologists discovered hospital-bred strains of the gut bacterium enterococcus harboring a gene that made them impervious to vancomycin. The bacterium may have since passed the gene to the far more dangerous Staphylococcus aureus, the most common cause of fatal surgical and wound infections.

"I am completely mystified by the lack of public concern about this problem," she says.

With no simple solution in sight, Salyers continues to advise government agencies such as the Food and Drug Administration and the Department of Agriculture to reduce the use of antibiotics in livestock feed, a practice banned throughout the European Union. She supports the prescient efforts of Tufts University microbiologist Stuart Levy, founder of the Alliance for the Prudent Use of Antibiotics, which has been hectoring doctors to use antibiotics more judiciously.

Yet just when the message appears to be getting through—judging by a small but real reduction in antibiotic prescriptions—others are calling for an unprecedented increase in antibiotic use to clear the body of infections we never knew we had. Among them is William Mitchell, a Vanderbilt University chlamydia specialist. If antibiotics ever do prove effective for treating coronary artery disease, he says, the results would be "staggering. We're talking about the majority of the population being on long-term antibiotics, possibly multiple antibiotics."

Hudson cautions that before we set out to eradicate our bacterial fellow travelers, "we'd damn well better understand what they're doing in there." His interest centers on chlamydia, with its maddening ability to exist in inactive infections that flare into problems only for an unlucky few. Does the inactive form cause damage by secreting toxins or killing cells? Or is the real problem a disturbed immune response to them?

Lately Hudson has resorted to a device he once shunned in favor of DNA probes: a microscope, albeit an exotic $250,000 model. This instrument, which can magnify organisms an unprecedented 15,000 times, sits in the laboratory of Hudson's spouse, Judith Whittum-Hudson, a Wayne State immunologist who is working on a chlamydia vaccine. On a recent afternoon, Hudson marveled as a shimmering chlamydia cell was beginning to morph from its infectious stage into its mysterious and bizarre-looking persistent form. "One minute you have this perfectly normal, spherical bacterium and the next you have this big, goofy-looking doofus of a microbe," he says. He leans closer, focusing on a roiling spot of activity. "It's doing something. It's making something. It's saying something to its host."