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DNA Pollution May Be Spawning Killer Microbes

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Rogue genetic snippets spread antibiotic resistance all over the environment.

by Jessica Snyder Sachs

On a bright winter morning high in the Colorado Rockies, a slight young woman in oversize hip boots sidles up to a gap of open water in the icy Cache la Poudre River. Heather Storteboom, a 25-year-old graduate student at nearby Colorado State University, is prospecting for clues to an invisible killer.



Image courtesy of

Jessica Snyder Sachs

Storteboom snaps on a pair of latex gloves and stretches over the frozen ledge to fill a sterile plastic jug with water. Then, setting the container aside, she swings her rubber-clad legs into the stream. “Ahh, no leaks,” she says, standing upright. She pulls out a clean trowel and attempts to collect some bottom sediment; in the rapid current, it takes a half dozen tries to fill the small vial she will take back to the DNA laboratory of her adviser, environmental engineer Amy Pruden. As Storteboom packs to leave, a curious hiker approaches. “What were you collecting?” he asks. “Antibiotic resistance genes,” she answers.

Storteboom and Pruden are at the leading edge of an international forensic investigation into a potentially colossal new health threat: DNA pollution. Specifically, the researchers are seeking out snippets of [rogue genetic material](#) that transforms annoying bacteria into unstoppable supergerms, immune to many or all modern antibiotics. Over the past 60 years, genes for antibiotic resistance have gone from rare to commonplace in the microbes that routinely infect our bodies. The newly resistant strains have been implicated in some 90,000 potentially fatal infections a year in the United States, higher than the number of automobile and homicide deaths combined.

Among the most frightening of the emerging pathogens is [invasive MRSA](#), or methicillin-resistant *Staphylococcus aureus*. Outbreaks of MRSA in public schools recently [made headlines](#), but that is just the tip of the iceberg. Researchers estimate that invasive MRSA kills more than 18,000 Americans a year, [more than AIDS](#), and the problem is growing rapidly. MRSA caused just 2 percent of staph infections in 1974; in the last few years, that figure has reached nearly 65 percent. Most reported staph infections stem from MRSA born and bred in our antibiotic-drenched hospitals and nursing homes. But about 15 percent now involve strains that arose in the general community.

It is not just MRSA that is causing concern; antibiotic resistance in general is spreading alarmingly. A 2003 study of the mouths of healthy kindergartners found that 97 percent harbored bacteria with genes for resistance to four out of six tested antibiotics. In all, resistant microbes made up around 15 percent of the children’s oral bacteria, even though none of the children had taken antibiotics in the previous three months. Such resistance genes are rare to nonexistent in specimens of

human tissue and body fluid taken 60 years ago, before the use of antibiotics became widespread.

In part, modern medicine is paying the price for its own success. “Antibiotics may be the most [powerful evolutionary force](#) seen on this planet in billions of years,” says Tufts University microbiologist Stuart Levy, author of *The Antibiotic Paradox: How the Misuse of Antibiotics Destroys Their Curative Powers*. By their nature, antibiotics [support the rise of any bug](#) that can shrug off their effects, by conveniently eliminating the susceptible competition.

But the rapid rise of bacterial genes for drug resistance stems from more than [lucky mutation](#), Levy adds. The vast majority of these genes show a complexity that could have been achieved only over millions of years. Rather than rising anew in each species, the genes spread via the microbial equivalent of sexual promiscuity. Bacteria [swap genes](#), not only among their own kind but also between widely divergent species, Levy explains. Bacteria can even scavenge the naked DNA that spills from their dead compatriots out into the environment.

The result is a microbial arms-smuggling network with a global reach. Over the past 50 years, virtually every known kind of disease-causing bacterium has acquired genes to survive some or all of the drugs that once proved effective against it. Analysis of a strain of vancomycin-resistant enterococcus, a potentially lethal bug that has invaded [many hospitals](#), reveals that more than one-quarter of its genome—including virtually all its antibiotic-thwarting genes—is made up of foreign DNA. One of the newest banes of U.S. medical centers, a supervirulent and [multidrug-resistant strain](#) of *Acinetobacter baumannii*, likewise appears to have picked up most of its resistance in gene swaps with other species.

So where in Hades did this devilishly clever DNA come from? The ultimate source may lie in the dirt beneath our feet.

For the past decade, Gerry Wright has been [trying to understand](#) the rise of drug resistance by combing through the world’s richest natural source of resistance-enabling DNA: a clod of dirt. As the head of McMaster University’s antibiotic research center in Hamilton, Ontario, Wright has the most tricked-out laboratory a drug designer could want, complete with a \$15 million high-speed screening facility for simultaneously testing potential drugs against hundreds of bacterial targets. Yet he says his technology pales in comparison with the elegant antibiotic-making abilities he finds encoded in soil bacteria. The vast majority of the antibiotics stocking our pharmacy shelves—from old standards like tetracycline to antibiotics of last resort like vancomycin and, most recently, daptomycin—are derived from soil organisms.

Biologists assume that soil organisms make antibiotics to beat back the microbial competition and to establish their territory, Wright says, although the chemicals may also serve other, less-understood functions. Whatever the case, Wright and his students began combing through the DNA of soil microbes like streptomycetes to better understand their impressive antibiotic-making powers. In doing so the researchers stumbled upon [three resistance genes](#) embedded in the DNA that *Streptomyces toyocaensis* uses to produce the antibiotic teicoplanin. While Wright was not surprised that the bug would carry such genes as antidotes to its own weaponry, he was startled to see that the antidote genes were nearly identical to the resistance genes in vancomycin-resistant enterococcus (VRE), the scourge of American and European hospitals.

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“Yet here they were in a soil organism, in the exact same orientation as you find in the genome of VRE,” Wright says. “That sure gave us a head-slap moment. If only we had done this experiment 15 years ago, when vancomycin came into widespread use, we might have understood exactly what kind of resistance mechanisms would follow the drug into our clinics and hospitals.” If nothing else, that foreknowledge might have prepared doctors for the inevitable resistance they would encounter soon after vancomycin was broadly prescribed.



Image courtesy of the

USDA

Wright wondered what else he might find in a shovelful of dirt. So he handed out plastic bags to students departing on break, telling them to bring back soil samples. Over two years his lab amassed a collection that spanned the continent. It even included a thawed slice of tundra mailed by Wright's brother, a provincial policeman stationed on the northern Ontario-Manitoba border.

By 2005 Wright's team had combed through the genes of nearly 500 streptomyces strains and species, many never before identified. [Every one proved resistant](#) to multiple antibiotics, not just their own signature chemicals. On average, each could neutralize seven or eight drugs, and many could shrug off 14 or 15. In all, the researchers found resistance to every one of the 21 antibiotics they tested, including Ketek and Zyvox, two synthetic new drugs.

"These genes clearly didn't jump directly from streptomyces into disease-causing bacteria," Wright says. He had noted subtle variations between the resistance genes he pulled out of soil organisms and their doppelgängers in disease-causing bacteria. As in a game of telephone, each time a gene gets passed from one microbe to another, slight differences develop that reflect the DNA dialect of its new host. The resistance genes bedeviling doctors had evidently passed through many intermediaries on their way from soil to critically ill patients.

Wright suspects that the antibiotic-drenched environment of commercial livestock operations is [prime ground for such transfer](#). "You've got the genes encoding for resistance in the soil beneath these operations," he says, "and we know that the majority of the antibiotics animals consume get excreted intact." In other words, the antibiotics fuel the rise of resistant bacteria both in the animals' guts and in the dirt beneath their hooves, with ample opportunity for cross-contamination.

Nobody knows how long free-floating DNA might persist in the water.

A 2001 study by University of Illinois microbiologist Roderick Mackie [documented this flow](#). When he looked for tetracycline resistance genes in groundwater downstream from pig farms, he also found the genes in local soil organisms like Microbacterium and Pseudomonas, which normally do not contain them. Since then, Mackie has found that soil bacteria around conventional pig farms, which use antibiotics, carry 100 to 1,000 times more resistance genes than do the same bacteria around organic farms.

"These animal operations are real hot spots," he says. "They're glowing red in the concentrations and intensity of these genes." More worrisome, perhaps, is that Mackie pulled more resistance genes from his deepest test wells, suggesting that the genes percolated down toward the drinking water supplies used by surrounding communities.

An even more direct conduit into the environment may be the common practice of irrigating fields with wastewater from livestock lagoons. About three years ago, David Graham, a University of Kansas environmental engineer, was puzzled in the fall by a [dramatic spike in resistance genes](#) in a pond on a Kansas feedlot he was studying. "We didn't know what was going on until I talked with a large-animal researcher," he recalls. At the end of the summer, feedlots receive newly weaned calves

from outlying ranches. To prevent the young animals from importing infections, the feedlot operators were giving them five-day “shock doses” of antibiotics. “Their attitude had been, cows are big animals, they’re pretty tough, so you give them 10 times what they need,” Graham says.

The operators cut back on the drugs when Graham showed them that they were coating the next season’s alfalfa crop with highly drug-resistant bacteria. “Essentially, they were feeding resistance genes back to their animals,” Graham says. “Once they realized that, they started being much more conscious. They still used antibiotics, but more discriminately.”

While livestock operations are an obvious source of antibiotic resistance, humans also take a lot of antibiotics—and their waste is another contamination stream. Bacteria make up about one-third of the solid matter in human stool, and Scott Weber, of the State University of New York at Buffalo, studies what happens to the antibiotic resistance genes our nation flushes down its toilets.

Conventional sewage treatment skims off solids for landfill disposal, then feeds the liquid waste to sewage-degrading bacteria. The end result is around 5 billion pounds of bacteria-rich slurry, or waste sludge, each year. Around 35 percent of this is incinerated or put in a landfill. Close to 65 percent is recycled as fertilizer, much of it ending up on croplands.

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Weber is now investigating how fertilizer derived from human sewage may contribute to the spread of antibiotic-resistant genes. “We’ve done a good job designing our treatment plants to reduce conventional contaminants,” he says. “Unfortunately, no one has been thinking of DNA as a contaminant.” In fact, sewage treatment methods used at the country’s 18,000-odd wastewater plants could actually affect the resistance genes that enter their systems.

Every tested strain in a dirt sample proved resistant to multiple antibiotics.

Most treatment plants, Weber explains, gorge a relatively small number of sludge bacteria with all the liquid waste they can eat. The result, he found, is a spike in antibiotic-resistant organisms. “We don’t know exactly why,” he says, “but [our findings](#) have raised an even more important question.” Is the jump in resistance genes coming from a population explosion in the resistant enteric, or intestinal, bacteria coming into the sewage plant? Or is it coming from sewage-digesting sludge bacteria that are taking up the genes from incoming bacteria? The answer is important because sludge bacteria are much more likely to thrive and spread their resistance genes once the sludge is discharged into rivers (in treated wastewater) and onto crop fields (as slurried fertilizer).

Weber predicts that follow-up studies will show the resistance genes have indeed made the jump to sludge bacteria. On a hopeful note, he has shown that [an alternative method](#) of sewage processing seems to decrease the prevalence of bacterial drug resistance. In this process, the sludge remains inside the treatment plant longer, allowing dramatically higher concentrations of bacteria to develop. For reasons that are not yet clear, this method slows the increase of drug-resistant bacteria. It also produces less sludge for disposal. Unfortunately, the process is expensive.

Drying sewage sludge into pellets—which kills the sludge bacteria—is another way to contain resistance genes, though it may still leave DNA intact. But few municipal sewage plants want the extra expense of drying the sludge, and so it is instead exported “live” in tanker trucks that spray the wet slurry onto crop fields, along roadsides, and into forests.

Trolling the waters and sediments of the Cache la Poudre, Stortebom and Pruden are collecting solid evidence to support suspicions that both livestock operations and human sewage are major players in the dramatic rise of resistance genes in our environment and our bodies. Specifically, they have found unnaturally high levels of antibiotic resistance genes in sediments where the river comes into contact with treated municipal wastewater effluent and farm irrigation runoff as it flows 126 miles from Rocky Mountain National Park through Fort Collins and across Colorado’s eastern plain, home to some of the country’s most densely packed livestock operations.

“Over the course of the river, we saw the concentration of resistance genes increase by several orders of magnitude,” Pruden says, “far more than could ever be accounted for by chance alone.” Pruden’s team likewise found dangerous genes in the water headed from local treatment plants toward household taps.

Presumably, most of these genes reside inside live bacteria, but a microbe doesn’t have to be alive to share its dangerous DNA. As microbiologists have pointed out, bacteria are known to scavenge genes from the spilled DNA of their dead.

"There's a lot of interest in whether there's naked DNA in there," Pruden says of the Poudre's waters. "Current treatment of drinking water is aimed at killing bacteria, not eliminating their DNA." Nobody even knows exactly how long such free-floating DNA might persist.

All this makes resistance genes a uniquely troubling sort of pollution. "At least when you pollute a site with something like atrazine," a pesticide, "you can be assured that it will eventually decay," says Graham, the Kansas environmental engineer, who began his research career tracking chemical pollutants like toxic herbicides. "When you contaminate a site with resistance genes, those genes can be transferred into environmental organisms and actually increase the concentration of contamination."

Taken together, these findings drive home the urgency of efforts to reduce [flagrant antibiotic overuse](#) that fuels the spread of resistance, whether on the farm, in the home, or in the hospital.

For years the livestock pharmaceutical industry has played down its role in the rise of antibiotic resistance. "We approached this problem many years ago and have seen all kinds of studies, and there isn't anything definitive to say that antibiotics in livestock cause harm to people," says Richard Carnevale, vice president of regulatory and scientific affairs at the Animal Health Institute, which represents the manufacturers of animal drugs, including those for livestock. "Antimicrobial resistance has all kinds of sources, people to animals as well as animals to people."

The institute's own data testify to the magnitude of antibiotic use in livestock operations, however. Its members sell an estimated 20 million to 25 million pounds of antibiotics for use in animals each year, much of it to promote growth. (For little-understood reasons, antibiotics speed the growth of young animals, making it cheaper to bring them to slaughter.) The Union of Concerned Scientists and other groups have long urged the United States to follow the European Union, which in 2006 completed its [ban on the use of antibiotics](#) for promoting livestock growth. Such a ban remains far more contentious in North America, where the profitability of factory-farm operations depends on getting animals to market in the shortest possible time.

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On the other hand, the success of the E.U.'s ban is less than clear-cut. "The studies show that the E.U.'s curtailing of these compounds in feed has resulted in more sick animals needing higher therapeutic doses," Carnevale says.

"There are cases of that," admits Scott McEwen, a University of Guelph veterinary epidemiologist who advises the Canadian government on the public-health implications of livestock antibiotics. At certain stressful times in a young animal's life, as when it is weaned from its mother, it becomes particularly susceptible to disease. "The lesson," he says, "may be that we would do well by being more selective than a complete ban."

McEwen and many of his colleagues see no harm in using growth-promoting livestock antibiotics known as ionophores. "They have no known use in people, and we see no evidence that they select for resistance to important medical antibiotics," he says. "So why not use them? But if anyone tries to say that we should use such critically important drugs as [cephalosporins](#) or [fluoroquinolones](#) as growth promoters, that's a no-brainer. Resistance develops quickly, and we've seen the deleterious effects in human health."

A thornier issue is the use of antibiotics to treat sick livestock and prevent the spread of infections through crowded herds and flocks. "Few people would say we should deny antibiotics to sick animals," McEwen says, "and often the only practical way to administer an antibiotic is to give it to the whole group." Some critics have called for restricting certain classes of critically important antibiotics from livestock use, even for treating sick animals. For instance, the FDA is considering approval of cefquinome for respiratory infections in cattle. Cefquinome belongs to a powerful class of antibiotic known as fourth-generation cephalosporins, introduced in the 1990s to combat hospital infections that had grown resistant to older drugs. In the fall of 2006, the FDA's veterinary advisory committee voted against approving cefquinome, citing concerns that resistance to this vital class of drug could spread from bacteria in beef to hospital superbugs that respond to little else. But the agency's recently adopted guidelines make it difficult to deny approval to a new veterinary drug unless it clearly threatens the treatment of a specific foodborne infection in humans. As of press time, the FDA had yet to reach a decision.

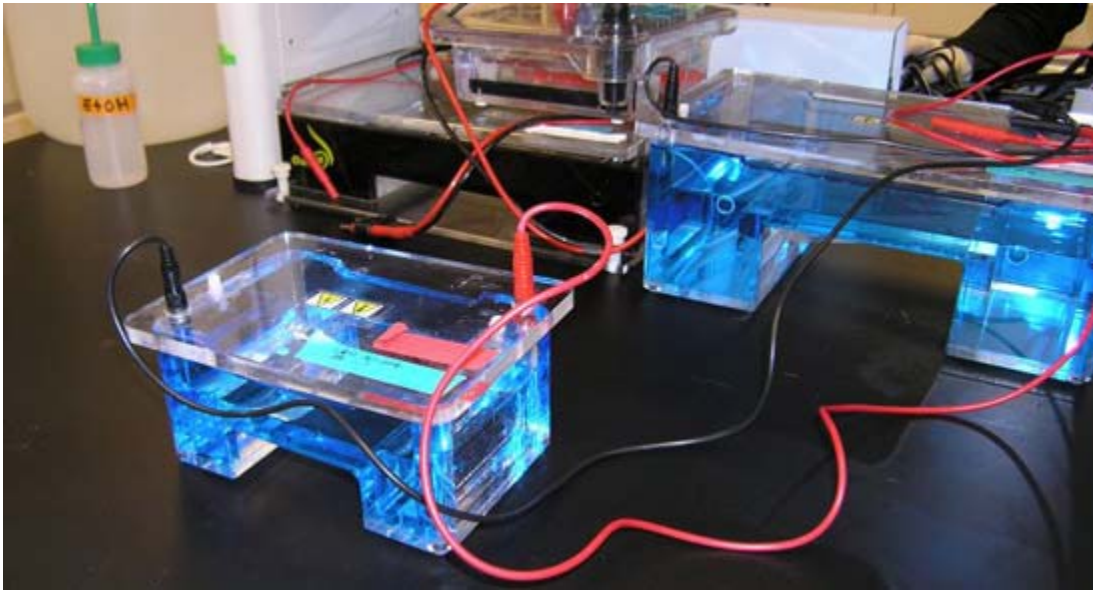


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Jessica Snyder Sacs

Consumers may contribute to the problem of DNA pollution whenever they use antibacterial soaps and cleaning products. These products contain the antibiotic-like chemicals triclosan and triclocarban and send some 2 million to 20 million pounds of the compounds into the sewage stream each year. Triclosan and triclocarban have been shown in the lab to promote resistance to medically important antibiotics. Worse, the compounds do not break down as readily as do traditional antibiotics. Rolf Halden, cofounder of the Center for Water and Health at Johns Hopkins University, has [shown that triclosan and triclocarban](#) show up in many waterways that receive treated wastewater—more than half of the nation’s rivers and streams. He has found even greater levels of these two chemicals in sewage sludge destined for reuse as crop fertilizer. According to his figures, a typical sewage treatment plant sends more than a ton of triclocarban and a slightly lesser amount of triclosan back into the environment each year.

For consumer antibacterial soaps the solution is simple, Halden says: “Eliminate them. There’s no reason to have these chemicals in consumer products.” Studies show that household products containing such antibacterials don’t prevent the spread of sickness any better than ordinary soap and water. “If there’s no benefit, then all we’re left with is the risk,” Halden says. He notes that many European retailers have already pulled these products from their shelves. “I think it’s only a matter of time before they are removed from U.S. shelves as well.”

Consumers may contribute to the problem of DNA pollution whenever they use soaps and cleaning products containing antibiotic-like compounds.

Finally, there is the complicated matter of the vast quantity of antibiotics that U.S. doctors prescribe each year: some 3 million pounds, according to the Union of Concerned Scientists. No doctor wants to ignore an opportunity to save a patient from infectious disease, yet much of what is prescribed is probably unnecessary—and all of it feeds the spread of resistance genes in hospitals and apparently throughout the environment.

“Patients come in asking for a particular antibiotic because it made them feel better in the past or they saw it promoted on TV,” says Jim King, president of the American Academy of Family Physicians. The right thing to do is to educate the patient, he says, “but that takes time, and sometimes it’s easier, though not appropriate, to write the prescription the patient wants.”

Curtis Donskey, chief of infection control at Louis Stokes Cleveland VA Medical Center, adds that “a lot of antibiotic overuse comes from the mistaken idea that more is better. Infections are often treated longer than necessary, and multiple antibiotics are given when one would work as well.” In truth, his studies show, the longer hospital patients remain on antibiotics, the more likely they are to pick up a multidrug-resistant superbug. The problem appears to lie in the drugs’ disruption of a person’s protective microflora—the resident bacteria that normally help keep invader microbes at bay. “I think the message is slowly getting through,” Donskey says. “I’m seeing the change in attitude.”

Meanwhile, Pruden’s students at Colorado State keep amassing evidence that will make it difficult for any player—medical, consumer, or agricultural—to shirk accountability for DNA pollution.

Late in the afternoon, Storteboom drives past dairy farms and feedlots, meatpacking plants, and fallow fields, 50 miles downstream from her first DNA sampling site of the day. Leaving her Jeep at the side of the road, she strides past cow patties and fast-food wrappers and scrambles down an eroded embankment of the Cache la Poudre River. She cringes at the sight of two small animal carcasses on the opposite bank, then wades in, steering clear of an eddy of gray scum. "Just gross," she mutters, grateful for her watertight hip boots.

Of course, the invisible genetic pollution is of greater concern. It lends an ironic twist to the river's name. According to local legend, the appellation comes from the hidden stashes (cache) of gunpowder (poudre) that French fur trappers once buried along the banks. Nearly two centuries later, the river's hidden DNA may pose the real threat.