MICROBIOLOGY

Quick-Change Pathogens Gain an Evolutionary Edge

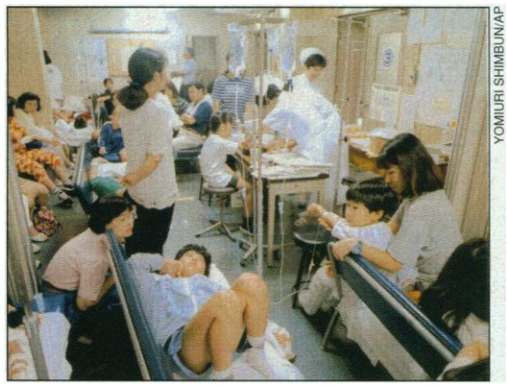
Over the past few months, a particularly nasty bug called *Escherichia coli* 0157:H7 has shaken up health authorities on two continents. Earlier this year, it sickened thousands of people in Japan who ate uncooked radish sprouts, and during the past month, it felled more than 60 Americans who consumed fruit drinks containing unpasteurized apple juice, killing one child. The same bacterium had struck before: It killed three children in the United States in 1993 and caused serious illness in 600 other people who ate contaminated hamburger meat.

Such outbreaks, caused by a strain that was not even known before 1982, are humbling reminders of the prodigious abilities of bacteria to reinvent themselves, speedily adapting to new hosts, new conditions, and new antibiotic countermeasures. Now, a group of researchers at the Food and Drug Administration (FDA) has uncovered what may be one of the secrets of that versatility, at least in *E. coli* and another pathogen, *Salmonella enterica*.

By studying strains from different outbreaks, the researchers, led by Thomas Cebula, found an exceptionally high percentage of "mutators"—microbes with a genetic flaw that makes them a prolific source of new variants. As the group reports on page 1208, these mutators can't repair errors in their own DNA, and they readily take up DNA from other bacteria. It's a "double whammy" speeding up their evolution, Cebula says. And because the findings may apply to other pathogenic bacteria as well, says Philip Hanawalt, an expert on DNA repair at Stanford University, "this work has very far-reaching implications and is even a bit ominous."

Researchers already knew that bacteria have a seemingly limitless capacity to alter their genes by trading bits of DNA between strains. But to Cebula, who studies foodborne pathogens, those mechanisms by themselves didn't seem enough to account for the swift pace of change and the high variability of microorganisms like *E. coli* and *S. enterica*. In just the past few years, for instance, strains of *E. coli* have emerged that can thrive in salted foods like sausage or acidic foods such as apple juice, and certain strains of *Salmonella* have developed the ability to resist food-processing temperatures that kill other organisms. Moreover, antibiotic resistance has become commonplace.

Cebula wondered if this swift evolution is being driven by a subset of microbes capable of much faster than normal variation. To test the hypothesis, he turned to a rogues' gallery of organisms: "We [had] a collection of all the outbreak strains we've collected over the years," he says. "We thought, there's probably nothing here, but let's screen some of these strains and see if we find a mutator." He and his colleagues cultured the strains and then used antibiotics to screen for "hypermutable" strains that quickly developed drug resistance. "We were surprised at how often we found mutators," Cebula says.



YOMIURI SHIMBUN/AP

Microbes win a round. *E. coli* sickened Japanese children who ate uncooked radish sprouts.

Researchers had expected that, because most mutations are deleterious, mutators would tend to die out, limiting them to no more than 0.01% of a bacterial population. But Cebula and his colleagues found that the frequency of mutators in the *E. coli* and *S. enterica* isolates was far higher than that: more than 1%, and exceeding 5% and 6% in some strains.

What's more, says Cebula, studies of the mutators showed that they were defective in genes needed for methyl-directed mismatch repair—the ability to correct mismatches between a newly synthesized DNA strand and the template it was copied from. Because of this flaw, such bacteria would not only alter their own genes faster than normal; they should also take in DNA from other bacteria more readily. As Miroslav Radman of the Institut Jacques Monod in Paris suggested in 1989, defects in mismatch repair open the genetic door between bacterial species: They allow recombinations that the system would normally abort when the foreign DNA creates mismatches.

Because the genes for antibiotic resistance often travel between bacteria on foreign DNA, says Hanawalt, the FDA group's findings could account for the rapid spread of resistance among *Salmonella* and *E. coli* strains. "This can actually explain why resistance-transfer factors can get an edge in these cells," he says. The same goes for genes that can make a bacterium more virulent, for example by helping it penetrate epithelial cells, says Paul Sniegowski, who worked on mutators at Michigan State University and is moving to the University of Pennsylvania: "There are chunks of DNA called pathogenicity islands that are quite similar to one another between otherwise different bacterial strains, and Cebula offers a route whereby those chunks could be more easily passed between the species."

These effects could explain why mutators are so common among the pathogenic strains of *E. coli* and *Salmonella*, Cebula and his colleagues say. Radman agrees. "Mutators win races much of the time, both in the lab and in vivo," he says. "The mutator phenotype allows a much faster, 100- to 1000-fold faster, evolution in terms of adapting to the host." To Radman, "The interesting question, then, is why are not all bacteria mutators?"

Radman suggests that despite their advantages, mutators are ultimately less fit than organisms with more stable genomes. The isolates from disease outbreaks that Cebula studied, for instance, were most likely in the process of adapting to new niches and under pressure to escape immune surveillance and pharmaceutical assaults. Without that pressure, he says, the mutator frequency would drop. Cebula speculates that there may even be subpopulations of mutators that can actually regulate their mutation rates in response to their living conditions, keeping their mutational abilities in reserve for times of stress.

The findings sound a warning note about food processing, says Douglas Archer, a food scientist at the University of Florida, Gainesville: "We have to think about different approaches, about assuring lethality, or building in multiple barriers that can't be overcome by microbes." Indeed, in response to the latest *E. coli* outbreak in the United States, the government is now considering a requirement that fruit juices be pasteurized.

But to Radman, the work also raises a hopeful possibility. "One could think seriously about devising a bactericidal drug or treatment that would be particularly effective in eliminating mutator bacteria," he says. "But I would never promise people that even if we do find a trick to kill the mutators, the bacteria won't find another trick to avoid it. And then we'll have to find another. And so on. That's life."

–Denise Grady

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