

GeneFilters™

Your library needs Science

SCIENCE ONLINE SCIENCE MAGAZINE HOME SCIENCE NOW NEXT WAVE SCIENCE'S STKE SCIENCE CAREERS E-MARKETPLACE

HAYS CUMMINS | Change Password | Change User Info | CiteTrack Alerts | Subscription Help | Sign Out

Science  
magazine

HELP SUBSCRIPTIONS FEEDBACK SIGN IN

SEARCH

BROWSE

▶ ORDER THIS ARTICLE

PARASITOLOGY:

## Close Encounters: Good, Bad, and Ugly

Elizabeth Pennisi

**Viewed in light of evolution, host-parasite relationships range from deadly to helpful, depending on the communication between them**

**PARIS--**Louis Pasteur was a man of many disciplines. Over the course of a career that spanned half a century, he ranged from chemistry to microbiology and virology. He even dabbled in the origins of life. His many achievements, from discovering handedness in organic molecules to showing that germs cause disease, are testimony to the power of synthesizing ideas from diverse walks of science. A similar synergy was evident last month at a meeting convened here in Pasteur's honor. As an unlikely mix of virologists, bacteriologists, parasitologists, and molecular biologists--each dealing with different microorganisms in distinct ways--discussed their work, they came to better appreciate evolutionary biologist Theodosius Dobzhansky's observation that nothing makes sense except in the light of evolution. Yet, they also lamented, evolution is often considered outside the bailiwick of microbiologists, particularly those studying infectious diseases.

Microbiologists often focus on one organism and its relationship to its host at one point in time. But stepping back to view the whole range of relationships between microbes and their hosts reveals that "there's a spectrum [of microorganisms] from the highly virulent to barely pathogenic," says Stephen Beverley, a molecular parasitologist at Washington University in St. Louis. What's more, the host-parasite relationship changes over time, often shifting from adversarial to friendly, and this relationship "is at different stages for different pathogens," adds Beverley. The best way to understand evolution's pivotal role in shaping these relationships, agrees Simon Wain-Hobson, a virologist at the Pasteur Institute in Paris, is to monitor pathogen-host interactions through time. And although some researchers, including Wain-Hobson, are now doing this, too many are not, he says.

Taking this long-term view reveals the incredible capacity of the microbial genome to change--gaining and losing nucleotide bases, entire genes, or even sets of genes. Research is also showing that much of that change is shaped by the microbe's interactions with its hosts and its environment. "At the start [of the interaction], you see genetic changes," explains Jörg Hacker, a microbiologist at the University of Würzburg in Germany. These changes might enable one bacterium to ravage a gut cell, say, or another to disarm a host's defenses. Those alterations in turn trigger changes in the host. Eventually, "you have this kind of cross talk," he explains, leading

- ▶ [Summary of this Article](#)
- ▶ [Similar articles found in: SCIENCE Online](#)
- ▶ [Search Medline for articles by: Pennisi, E.](#)
- ▶ [Alert me when: new articles cite this article](#)
- ▶ [Download to Citation Manager](#)
- ▶ [Collections under which this article appears: Microbiology](#)

to perpetual evolutionary one-upmanship or harmonious rapprochement.

## The good

Stanford University molecular biologist Sharon Long has been exploring a cooperative interaction that might once have been an adversarial one: the symbiosis between a plant and its nitrogen-fixing bacteria. "Her work gives us insights into the signaling between the bacterium and the plant," says microbiologist James Kaper of the University of Maryland, Baltimore. Over the eons, the partners have evolved a way to recognize each other's signals, thereby sidestepping the damage that typically results from many plant-bacteria interactions.

Like many plants, the legumes pea clover and alfalfa make compounds that sometimes serve as pigments or as deterrents to either insects or microbial pests. But to the *Rhizobium* bacterium, those compounds--in this case, substances called flavonoids--are perfume that help identify its future partner. As Long and others have shown, the relationship has evolved so that one flavonoid plays an ever more intimate role. Once inside the bacterium, this flavonoid turns on a set of microbial genes called *nod*. In response, the microbe generates a small carbohydrate, tailoring its exact chemical makeup so it will be recognized by the plant producing that flavonoid. Without these chemical modifications, the carbohydrate might trigger the plant to let loose its defenses, as this same basic carbohydrate is also produced by pathogenic fungi. But the tailored version "is specifically recognized by the host plant," says Long. The plant then prompts root hairs to grow and entangle the nearby *Rhizobium* bacteria, forming the characteristic root nodules that enable legumes to "fix" nitrogen.

As the plant becomes an ally in promoting this infection, it builds a tunnel of extracellular material around the dividing bacteria and allows them entry into some of its cells. Studies suggest that decisions about which plant cells are invaded--and, later, when and how diversification of some bacteria into nitrogen-fixing units proceeds--are under joint control of the two partners. Each step, "recognition [by] and escape of the host's defenses, will be played out many times over" to maintain the plant-microbe alliance, Long adds.

## The bad

The alliance between the gut bacterium *Escherichia coli* and its human host isn't as mutually beneficial as that between *Rhizobium* and plants, but it's usually amicable enough. With some strains of *E. coli*, however, the relationship can get downright nasty. Harmless *E. coli* can acquire new genes, evolving into virulent organisms that cause a variety of symptoms. Kaper, who studies pathogenic *E. coli*, has preliminary evidence that these strains may also co-opt the communication between harmless gut *E. coli* and their human hosts. "My work, along with that of others, has shown how an organism that is typically considered nonpathogenic can acquire virulence traits to become not just one kind of pathogen but several," Kaper explains. Take the pathogenic *E. coli* strain O157:H7. This strain has mastered the insidious trick of acquiring genes from other microbes, including a toxin from *Shigella*, that enable it to invade and destroy the cells in the human gut. Such genetic acquisitions can have devastating effects; in some circumstances, *E. coli* O157:H7 can kill.

Pathogenic *E. coli* can also exert their gut-wrenching effects by taking cues from other *E. coli* strains. Both normal and pathogenic *E. coli* often aggregate, homing in on ever stronger concentrations of a chemical called A1-2, which they secrete to guide them to their fellow bacteria, at which time they, too, start producing A1-2. In test tube experiments over the past several years, Kaper has determined that pathogenic *E. coli* require a strong A1-2 signal--usually indicative of large numbers of the microbes in one place--to activate their attack genes. Last year, Kaper showed that the pathogenic *E. coli* can add the A1-2 signals produced by the gut's normal *E. coli* to their own so they can do their dirty work even when their actual numbers are small.

Moreover, preliminary evidence indicates that the gut itself may provide a boost to its attacker. Kaper and his colleagues engineered pathogenic *E. coli* that lacked the gene needed for making A1-2. Then they put the mutants in a culture dish with human epithelial cells derived from tumors. To their surprise, the microbes began

their attack, even though there were no *E. coli* present to supply the AI-2 quorum signal. And that, says Kaper, suggests that the human cells secrete an AI-2-like signal. "Just like bacteria frequently seize upon [and use] host signals, the host may be able to seize upon bacterial signals and manipulate them," says Beverley. He suspects that the human gut may somehow regulate harmless *E. coli* by secreting AI-2 and, as an unfortunate consequence, the gut may now play a role in stimulating the pathogen's attack. "There's so much that's important in terms of communication [among bacteria], and then we add another layer [of communication] with host cells," he adds, intrigued by how complex the interactions are turning out to be. "More attention needs to be paid" to these connections.

## The ugly

The nasty interaction of *E. coli* O157:H7 with the human gut and the constructive partnership between plants and *Rhizobium* represent two extremes. Many evolutionary biologists see the host-microbe relationship as a continuum; even the most destructive pathogens often shift to less virulent forms over time. From an evolutionary perspective, the pathogen's goal is to pass on its genes, explains Wain-Hobson. And sometimes those genes are passed on most efficiently when the host lives longer or is less sick--when the relationship may be a bit ugly but, ultimately, not disastrous for the host.

Take *Leishmania*, a protozoan parasite that now infects some 12 million people worldwide, often causing disfiguring disease and sometimes death. At the meeting, Beverley described how one of the organism's genes seems to be designed to hold virulence in check, at least in mice; this is one of the first well-documented examples of a gene that moderates virulence, he adds. This gene converts a key nutrient needed by the parasite into a biologically active form. But it also seems to keep the number of infective forms of the parasite down, thereby limiting its damage.

Beverley and his colleagues first stumbled upon this gene in 1984 when they were looking for drug targets. In hope of eventually disabling *Leishmania*, they were studying how the parasite takes up and makes use of two essential vitamin-like substances, folic acid and bipterin. One drug candidate was a protein called pteridine reductase (*PTR1*), which converts bipterin into a biologically active form. Recently, they knocked out the gene, expecting to cripple the parasite and limit infection in the mice they tested. Instead, "we got 50-fold more parasites," says Beverley. It turns out that *Leishmania* with intact *PTR1* genes produce fewer infective forms than those without the gene. "*PTR1* is a candidate gene that limits parasite virulence and pathology," Beverley concludes.

Many bacteria on the run from antibiotics or immune systems prove to be not only moderately virulent but also highly mutable, says François Taddei, an evolutionary biologist at the University of René Descartes--Paris V. Populations of pathogens often include a few fast-evolving individuals, so-called mutators. These are organisms with DNA repair enzymes or genome quality-control mechanisms that don't work all that well, so they mutate up to 1000 times faster than normal individuals do.

These mutator strains have long fascinated Taddei: Theoretically, they should accumulate so many genetic defects that they die off quickly, but they persist. Furthermore, his computer simulations suggest that when populations of bacteria--in this case, *E. coli*--are challenged by environmental stresses such as exposure to antibiotics or a new host, the proportion of mutators increases. This, in turn, speeds the evolution of organisms adapted to that change, such as drug-resistant strains. This model also suggests that pathogenic organisms--which are continually under siege by the host or by antibiotics--have a higher proportion of mutators than their nonpathogenic cousins.

Experimental results are bearing out this assumption. A network of eight labs coordinated by Taddei looked for mutator strains of different bacteria in some 900 samples taken from a wide range of environments: water, soil,

healthy or sick people, and wild animals. The percentage of mutators among commensal organisms, which don't cause disease, was 3%. But among pathogens, mutators were much more in evidence. Fully 12% of the bacteria involved in certain infections had these high mutation rates; another research group found that 20% of the bacteria in the lungs of cystic fibrosis patients were mutator strains.

In mouse studies, infections caused by bacteria with a high proportion of mutators tend to be less deadly than those in which the number of mutators is low, notes Taddei. But mutator-rich strains are nonetheless harder to treat. Working with mice, Taddei was unable to cure an infection caused by a mutator-rich strain with one antibiotic; even trying a second antibiotic proved ineffective. Instead, it took an all-out assault with several drugs simultaneously. Together, these data suggest that evolutionary principles could help design effective therapeutic strategies, especially against chronic infections that seem to resist current treatment. "If you have a mutator strain, you better use a very potent cocktail of antibiotics," Taddei suggests.

This advice runs counter to the way physicians tend to prescribe antibiotics but makes sense in light of evolution, says Wain-Hobson. He'd like to see more of his colleagues share Taddei's appreciation of how organisms change through time. "One hundred and forty years of microbiology without evolution is more than enough," he notes. Pasteur, too, would probably agree.

▼ [Summary of this Article](#)

▼ Similar articles found in:  
[SCIENCE Online](#)

▼ Search Medline for  
articles by:  
[Pennisi, E.](#)

▼ Alert me when:  
[new articles cite this  
article](#)

▼ [Download to Citation  
Manager](#)

▼ Collections under which  
this article appears:  
[Microbiology](#)

Volume 290, Number 5496, Issue of 24 Nov 2000, pp. 1491-1493.  
Copyright © 2000 by The American Association for the Advancement of Science.

---

▲ [PAGE TOP](#)