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Playing by the Rules

How and Why Organisms Turn Nasty

By MARJORIE CENTOFANTI

We left Vashe Noire at 6.... I was so weak that I was unable to sit on the little seat. . . . I suffered that night, but a 20 km jaunt in a camion to another evacuation hospital was so much worse that there was no comparison.... We were then taken by ambulance to Crepy, where they loaded us into a hospital train and we were off . . . to Toulouse. The hospital train was a string of boxcars fitted with four tiers of three stretchers each....At Toulouse we were taken... to a ward with 20 doughboys from the 1st and 2nd divisions. . . .

Guy E. Bowerman Jr., *Diary of an Ambulance Driver During the Great War*

Evacuated from the front in 1918 with a case of dysentery, Bowerman found time to jot down this tale of misery. Though he didn't realize it, the conditions he described may have brought about the deaths of more people than World War I itself.

The war killed 10 million people. But the influenza pandemic of 1918 took the lives of another 20 million, according to population biologist Paul W. Ewald of Amherst (Mass.) College. Last year, he included the excerpt from Bowerman's diary in his book *Evolution of Infectious Disease* (Oxford University Press).

Ewald theorizes that carrying sick soldiers through miles of trenches and field hospitals—and past hundreds of healthy people—created ideal conditions for the spread of the influenza virus. Moreover, this easy access to people enabled a milder strain of flu to evolve into a more virulent one.

In the last 10 years, scientists have begun to combine ideas from evolutionary biology and population biology to understand how virulence evolves. Some, like Ewald, try to determine what situations favor, say, a nastier flu. Others, like Allen E. Herre, a population biologist at the Smithsonian Tropical Research Institute in Panama, take a more ecological view. Herre studies how small changes in the damage done by tiny nematode worms to the wasps they prey on—another example of virulence—can tip the balance among worms, wasps, the figs that the wasps pollinate, and the fruit bats that eat the figs.

Scientists first began thinking about the evolution of virulence in the 1930s. At that time, Ewald writes, they brought forth the idea of benign-over-time evolution. The theory holds that virulence flares when parasites, including disease-causing microbes, and their hosts first get together. In time, though, the parasite becomes milder, so as not to destroy the host it depends on.

"This idea is very appealing," Herre told SCIENCE NEWS, "because people see signs of it all the time. If you take Englishmen and put them in Africa or take cattle from Northern Europe and put them someplace else, they can get very sick."

Recently, however, scientists have begun to believe that virulence may obey a more complex set of rules. Knowing those rules, Ewald says, could suggest ways to nudge disease organisms back to a gentler state or to make people or crops less vulnerable to them.

Herre says he and others began to doubt that parasites always evolved to mildness after a spate of mathematical models appeared in the 1980s. Robert May and Roy Anderson, now at the University of Oxford in England, modeled the effects of parasite populations on the course of infectious diseases. Their equations gave no indication that the infecting organisms would always end up kinder and gentler.

More doubts arose from experiments in which other researchers examined hosts that were slightly different genetically. In 1993, for example, Dieter Ebert, a zoologist at the University of Basel in Switzerland, collected samples of the water flea *Daphnia* from ponds scattered across Europe. A protozoan parasite, *Pleistophora intestinalis,* causes diarrhea in the water flea. The diarrhea carries the parasite's spores into ponds, thus spreading disease.

To each *Daphnia* sample, Ebert added the same variety of *P. intestinalis* from English ponds. "I wanted to see if I'd get a continuum of being able to cope and not being able to cope," he says.

He did. However, the *Daphnia* that suffered most came from the same English ponds as the parasites. Those from a pond in Moscow tolerated the English parasites with few ill effects, he reported in the Aug. 19, 1994 SCIENCE.

The "worst" parasites, Ebert reported, are sometimes the local, presumably well-adapted ones. "Not at all a benign evolution," he says.

Such results prompted scientists to ask what Herre calls the broader question: "Is there any rationale, any sort of sense in what pushes diseases to be more or less nasty?"

Ewald's analysis of the 1918 flu pandemic highlights a possible requirement for increased virulence: The disease organism must have an improved chance of transmission.

"In 1918, we had a special situation at the Western Front," Ewald says. "People who were completely immobilized with a bad case of influenza could still infect many who were well. Normally, if a person can't get around, the disease organism within can't reach new hosts. The organism dies out. But in this case, thanks to stretchers and trains, even the severely ill—those with a more harmful virus—could infect hundreds of new hosts."

This unusual ease of transmission, he explains, favored the rapid spread of more aggressive viruses over more moderate ones. The flu started out less virulent in the rest of the world and peaked at the front, shoring up this theory, Ewald says.

In a corollary to the ease of transmission rule, Ewald suggests that some disease organisms can get away with being more harmful because they can survive longer outside a host. "If you look at all the respiratory tract diseases of humans," he says, "you find a good correlation between how much harm the disease organism causes, measured by the [host's] death rate, and how durable it is."

Smallpox, tuberculosis, and diphtheria head a "harmful diseases" list Ewald compiled. They also rank high in durability:

Smallpox can live without a warm body for nearly a decade. At the bottom of the list are mumps and the common cold. "These viruses last [outside a host] only hours," he says. "They're so mild most people have no risk of death."

Intriguing as these historical studies are, Ewald and many other researchers say, there's no substitute for direct observation of how virulence works in nature. That's what Herre does in his field studies on Barro Colorado Island.

At least 11 species of figs grow on the island. Each type of fig comes with its own wasp species. Each wasp species, moreover, is preyed on by a specific nematode worm.

Herre thinks the different species of wasps and nematodes evolved from common wasp and nematode ancestors; the fossil record and genetic similarities bear this out. But the originally benign relationship of the organisms has changed, he says. Herre described in the March 5, 1993 SCIENCE how he assessed the virulence of nematodes by counting the offspring of wasps. The effects "range from almost nondetectable, where no one could tell nematodes are there, to so harmful the wasps may produce 20 percent fewer offspring."

Could this virulence result from crowding?

Some figs are invaded by a single female wasp. In such cases, Herre found, the nematodes associated with the species are generally benign. But where several female wasps invade each fig, the nematodes are more harmful.

On the surface, the situation looks straightforward. Where nematodes have many a young wasp to prey upon, they can afford to be callous. But when fewer offspring roam the fig, the nematodes have to be gentler.

That's not the real story, though, Herre says. When several wasps invade a fig, each carries a slightly different nematode strain. The various strains infect the young wasps. A grand battle then ensues; the most virulent young nematode strain in each wasp "wins."

Several years ago, James J. Bull, an evolutionary biologist at the University of Texas at Austin, wanted to study the emergence of virulence in a laboratory system. To see changes within a reasonable time, he and his colleagues picked the *Escherichia coli* bacterium and the virus that attacks it. The virus typically latches onto an *E. coli* cell and inserts its DNA into the host.

The researchers created two distinct scenarios for the virus. In one, the virus had easy access to many new *E. coli* cells for several days. In the other, the original bacteria were not replenished. At the end of the study, the scientists found a marked difference between the two viruses. The virus that could reach many new hosts became more virulent. The one that had to stick with the original host reined in its own reproduction so the host could survive, the team reports in the August 1991 EVOLUTION.

A recent variation of Bull's study was reported at a meeting of several evolutionary biology societies in Montreal last summer by Sharon Messenger, also at Austin. She showed how flexible virulence can be. When she kept viruses with the same bacteria for different periods of time, she found that they adjusted their harmfulness. "It was like a thermostat on a furnace," she says. The longer the contact, the less harm was done.

In the August PARASITOLOGY, Ebert describes a similar result after testing the interaction of *Daphnia* and a second type of parasite.

The idea that human disease organisms can become more harmful if they have easier access to a smorgasbord of humankind is tempting but controversial.

Ewald speculates, for example, that relative ease of transmission might explain why HIV-1, the most common AIDS virus, is less virulent than the less infective HIV-2, found in western Africa.

The differences in the two viruses may "reflect different social patterns" in western Africa and in central and eastern Africa, Ewald writes in the April 1993 SCIENTIFIC AMERICAN. In the east, for example, economic crises a few decades ago caused migrations of men into the cities. That resulted in "an increased market for sexual commerce." No such movement took place in western Africa.

Many researchers are wary of extrapolating too far from laboratory or field models. "Are we going to say that the same principles that apply to a wasp that pollinates figs apply to people? To HIV?" Herre asks. "Maybe yes, but you have to be quite careful that you understand exactly what's at work in this system and what elements could be applied somewhere else."

As a relatively new field, virulence is still hazy with questions.

For one thing, most studies have focused on the parasites, even though researchers know that virulence is a two-sided affair. Parasites, with their quicker rates of reproduction, generally change more rapidly, so their evolution is easier to explain. "It's a simplification to help us see how things are at the moment," Ebert says, "but in the long run, we're going to have to start looking at hosts."

Most scientists, as Bull notes in the October 1994 EVOLUTION, see virulence as an adaptation to increase a parasite's success, just as thick coats or stout bodies help arctic animals.

But not everything fits that mold, says Bruce R. Levin of Emory University in Atlanta. Levin has concluded that some virulence may be a mistake. In the March 1994 TRENDS IN MICROBIOLOGY, he and Bull describe "short-sighted evolution," a process in which organisms may wreak great havoc in a host with no apparent benefit to themselves. The polio virus, says Levin, usually inhabits the intestine. "But sometimes—we're not sure whether by accident or for some local advantage—it changes and gets out into the nervous system. People then get polio. The virus, apparently, gets nowhere."

Despite the unanswered questions that swirl around them, studies of virulence suggest fresh approaches to the problem of disease. The typical broad-range vaccine sparks an immune response to most forms of an organism. "But we could change that," Ewald says. "Don't wipe out the milder variants with the very harmful. Instead, identify the part of a disease organism responsible for virulence. Develop a vaccine to target that. What happens? You tip the balance in favor of the milder organisms."

"It's probably the mechanism we've used to control a past terror: diphtheria," he adds. Unlike most vaccines, the diphtheria vaccine targets a toxin that the bacterium cranks out. The toxin promotes the survival and increases the virulence of diphtheria bacteria. Once the toxin is neutralized, the virulent diphtheria loses its advantage.

"We're not eradicating the diphtheria bacteria. We're replacing one variant of [it] with another," notes Ewald. "Now, those mild forms are working for us. They're still generating immune responses that cross-react with the severe strains. So the mild forms act as a free live vaccine."

In the long term, Bull says, research will yield more rules of virulent behavior.

M. Centofanti

Two species of tropical figs make ideal models for studying virulence. The flowering fig (right) was invaded by a tiny wasp (arrow) ready to lay its eggs. In the ripe fig (left), some seeds bulge with unhatched wasps. Microscopic nematodes wait for the wasps to hatch.

"Direct observations of virulence evolution are scant in human disease," he says. But, adds Herre, "Basic research in odd corners of the intellectual landscape are producing useful results. We may have something to contribute to agriculture or medicine other than a collection of just-so stories." □