

work that can't be done elsewhere. The Navy and Army, for instance, run some similar applied science programs, and academia and industry have traditionally argued that they could take on much of the work now done by government employees. But supporters hope the Pentagon will develop special criteria for evaluating its R&D operations that create a level playing field for Kirtland and other research-heavy bases. "You can't weigh the value of an [applied] technical center the way you would a strategic air wing or a basic research laboratory," says Michael Hogan, president of MassDevelopment, Massachusetts's economic development authority. He is active in efforts to protect Hanscom Air Force Base in Bedford, another Air Force facility with technical know-how.

The lack of suitable yardsticks helped doom previous consolidation efforts. During the 1995 BRAC, for instance, Pentagon leaders concluded that there was about 35% "excess capacity" in defense labs after examining workloads and trends in total work hours at various labs. But that "methodology was flawed ... it unrealistically treated scientists and engineers as interchangeable, conveyable, replicable items—such as hospital beds and hangar space," concluded Don DeYoung, a research fellow at the Pentagon's National Defense University, in a recent paper.* The experience, DeYoung says, suggests that "the only viable metric for evaluating a laboratory is its track record" of results.

Kirtland advocates believe that they have delivered the goods, citing work through the years on synthetic aperture radar and devices for detecting and disarming explosives. "Kirtland has created a lot of technology for both military and [civilian] uses," says Charles Thomas, a Sandia manager and leader of the Kirtland Partnership, a pro-base advocacy group.

Kirtland and Hanscom also see themselves as potential beneficiaries of Rumsfeld's insistence that the three services unify similar R&D efforts. Hogan, for instance, suggests that Hanscom could easily accommodate similar research and technology purchasing programs from other services. "We've got the red carpet out," he says.

A trump card for Kirtland and Hanscom may be their skilled workforces and links to surrounding labs. "If they decided tomorrow to move Hanscom to Ohio, most of the physicists and scientists working at [Massachusetts Institute of Technology and nearby companies] probably wouldn't go," says Hogan. And any move could compound current Pentagon difficulties in recruiting new technical talent. "It's easier to move a [fight-

er jet] wing than R&D," agrees Hirsch.

It's not clear how such arguments will play with Pentagon brass and the independent commission that will make final closure recommendations in 2005. But a memo leaked last October has already stirred up some defense R&D advocates. In it, DOD Deputy Undersecretary Michael Wynne concluded that the major defense "labs are out of favor and ... their overall utility is in question." To solve the problem, he recommended appointing an internal commission that would identify "those laboratories that are imperative for defense to retain," close or privatize the rest, and then combine "the remnants" into a DOD-wide research facility—a long-controversial concept. The

memo has helped "spark discussion" and "renewed attention to the labs," Wynne reported wryly at a Senate hearing last month.

The episode suggests that the Pentagon's political leaders are aiming to "manage the BRAC process with an iron hand" and not allow the turf-conscious services to shelter favorite facilities, says Steve Karalekas, a Washington, D.C.-based consultant working on the Hanscom campaign. "There isn't going to be anywhere [for the labs] to hide."

That prospect doesn't bother Kirtland advocates, who are inviting BRAC planners to take a close, hard look. They hope to emerge stronger from a process that may prune sister facilities that fail to show that Uncle Sam needs them, too.

—DAVID MALAKOFF

Infectious Diseases

Taming Pathogens: An Elegant Idea, But Does It Work?

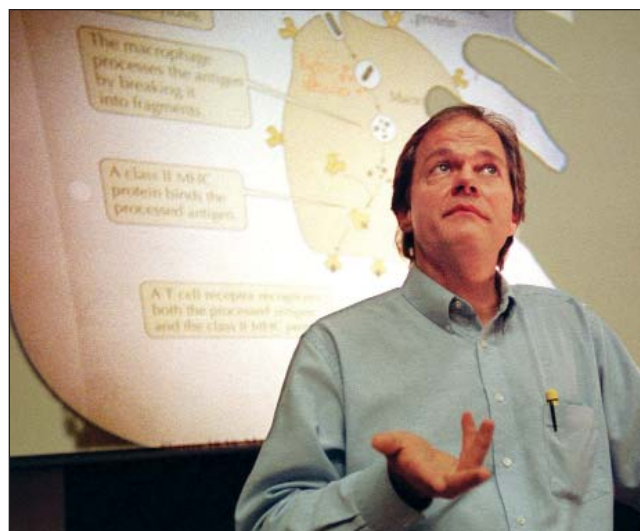
Skeptics are challenging the popular idea that an evolutionary tradeoff faced by pathogens may be the secret to making diseases less harmful

In 1859 a rancher decided to introduce European rabbits into Australia so that he could have something to hunt. Before long the rabbits had exploded across the continent, eating so much vegetation that they began to cause serious soil erosion. In the 1950s scientists deployed a biological counteroffensive, myxoma virus, a pathogen from South America. It didn't eliminate the rabbits, but it did provide grist for an ongoing debate about virulence.

Although myxoma was almost 100%

deadly at first, its virulence soon dropped significantly. This fit with a widely held view at the time that all parasites evolve into milder forms as they adapt to the environment. Evolution favors mildness, the argument went, because it allows host and pathogen to enjoy a peaceful coexistence. "If you found a virulent association, you assumed it was recent," says evolutionary biologist Bruce Levin of Emory University in Atlanta, Georgia. "It was even used as a way of dating parasite-host associations."

In hindsight, this conventional wisdom seems naïve. Myxoma became milder, but its decline stopped after a few years and it still remains lethal to many of its rabbit hosts. When evolutionary biologists took a hard look in the 1980s, they realized that a pathogen can evolve to become harmless, more deadly, or anything in between, depending on the forces guiding natural selection. Such forces can also pull the pathogen in opposite directions at the same time, creating an evolutionary tradeoff.



Pathogen tamer. Paul Ewald argues that virulence can be reduced by shaping the environment to favor milder organisms.

* "The Silence of the Labs," *Defense Horizons*, National Defense University, January 2003 (www.ndu.edu/inss/DefHor/DH21/DH21.pdf).

Experts began to model the competing forces, and some confidently suggested that the models could serve public health, through “virulence management.” For example, by making it more difficult for a cholera-causing bacterium to be transmitted from one individual to the next, they argued, health programs could take advantage of an evolutionary balance to favor benign strains. Deadly organisms, whose toxic machinery is somewhat burdensome, might compete poorly and yield to milder strains. The notion that virulence could be managed in this way has grown increasingly popular; last year Cambridge University Press published an entire book on the topic.

Now, two prominent evolutionary biologists—James Bull of the University of Texas, Austin, and Dieter Ebert of the University of Fribourg, Switzerland—have raised a provocative dissent. They directly challenge the assumptions that underlie virulence management, arguing that the models used to forecast pathogens’ behavior collapse in the face of the true complexity of diseases, and that the quest to manage the virulence of widespread infestations is doomed to failure. Yet even the skeptics agree that the idea might be useful in planning vaccination campaigns (see sidebar).

Born to be mild

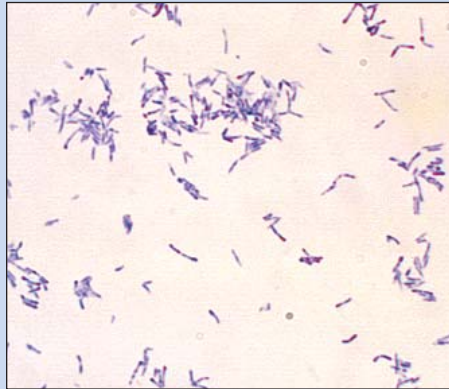
The concept of virulence management emerged from a particular tradeoff in evolution: the one between how fast a pathogen breeds and how easily it can infect new hosts. Evolution favors parasites that can produce lots of offspring, the argument goes, but producing offspring takes a toll on the host. The more the pathogen feeds on its host, spews out toxins, or otherwise causes damage, the more likely it is to kill. If it kills its host before its offspring can get to a new host, all its efforts are for naught. Some biologists predicted that a parasite’s virulence would evolve out of the balance between its competing needs to breed and spread. Changing the balance might change a disease’s deadliness. As it becomes easier for a parasite to infect new hosts, pathogens can afford to evolve into deadlier forms. As transmission gets rarer, gentler strains should take over.

Many evolutionary biologists were charmed by the elegance of the tradeoff model. Bull himself found support for it in experiments with a virus that infects bacteria. “I confess that when I first heard the ideas I bought them hook, line, and sinker,” says Bull. “A lot of people in the field did. The appeal of the original proposal was that you could take this simple concept of a tradeoff and you could apply it to any infectious disease.”

Darwinian Vaccines

Dieter Ebert of the University of Fribourg, Switzerland, and Paul Ewald of the University of Louisville, Kentucky, are for the most part on opposite sides of the current debate over taming pathogens. But there is one point on which they agree: Vaccines may offer a good opportunity for “virulence management.” Ebert calls them “a promising example,” and Ewald says that “you should be able to engineer these vaccinations so that you can drive paths towards mildness.”

The most cited example of this evolutionary effect is diphtheria. The bacteria that cause it come in two forms. A harmless form usually found in the throat takes up whatever nutrients happen to float by, whereas a deadly form produces a toxin that rips open surrounding cells to feast on their contents. Making toxin lets the bacteria reproduce faster; it also triggers coughs that may help it spread. But the toxic strategy is risky because it can be fatal to the host.



Jekyll and Hyde. Diphtheria has two forms, and studies show that vaccination helps cut down the virulent type, even among unvaccinated people.

The diphtheria vaccine targets the toxin produced by the bacteria. It has proven very successful since its introduction in the 1920s; in countries with good vaccination programs, death rates from diphtheria have dropped dramatically. According to Benoit Soubeyrand of Aventis Pasteur in Lyon, France, disease records suggest that the vaccine has steered the evolution of the bacteria as well. The harmless bacteria have become more common while the toxin-producing ones have become rare. Yet in places where vaccination programs have been allowed to slip—such as Russia—virulent forms have made a comeback.

Soubeyrand and others have suggested that vaccines drive the evolution of milder forms because they target the toxin and not the organism, selectively increasing the cost of virulence. As a result, the deadly bacteria end up at an evolutionary disadvantage. This may explain why vaccination benefits everyone in a diphtheria-vaccinated area—even the unvaccinated.

Some researchers believe that diphtheria can point the way to the design of other evolution-altering vaccines. But Andrew Read of the University of Edinburgh, U.K., questions some parts of this hypothesis. “I think the data on that is pretty poor,” he says. Read believes that vaccines can have evolutionary effects, but the mathematical models he and his colleagues have constructed hint that those effects could end up being harmful. “If you vaccinate a population, you’re protecting the hosts from dying, but you’re also protecting the nasty parasites” from the consequences of being nasty, Read explains. The penalty for toxicity isn’t high enough. According to Read, unless a vaccine program is 100% effective, newly virulent pathogens will eventually find some unprotected hosts to attack. “In unvaccinated individuals, they’ll be nastier than they were before,” Read warns. It may be possible in the future to tailor vaccines to alter the evolution of other pathogens, he thinks, but scientists will have to be careful.

—C.Z.

As the tradeoff model gained strength, some evolutionary biologists thought it could become the basis for fighting human diseases. Paul Ewald, a biologist now at the University of Louisville, Kentucky, argued that altering the transmission of diseases could make them less dangerous. Putting up mosquito nets over beds and windows, for example, would make it harder for mosquitoes to carry malaria parasites from an infected person to a new host. The virulent form of malaria, which makes its hosts bedridden and often kills them, would be put at a disadvantage. “You should be able to

have the milder strains favored strongly by natural selection,” Ewald predicts.

But some biologists—Bull among them—started to have misgivings. Bull and his colleagues ran new experiments in which bacteria-dwelling viruses evolved under more realistic conditions. They found that faster transmission made the viruses more harmful, as the tradeoff model had predicted, but the difference was so slight that Bull “became much less impressed with the results,” he now says. “I began to think, hmm, this doesn’t work too well.”

Bull last year discovered a kindred spirit

in Ebert, who has independently carried out some of the most important experiments on the evolution of virulence. “They’re two giants of the field,” says Michael Hochberg of the University of Montpellier, France. Although Ebert’s results seemed to support the tradeoff model, he had grown disenchanted as well. “We had similar frustrations,” says Ebert. The two decided to attack the tradeoff model in the January issue of *Trends in Microbiology*. “We’re not pioneers here,” says Bull. “We know lots of other people who feel the same way.”

They claim that most of the support for the model comes from extreme, unnatural conditions. Myxoma, a veritable poster child for virulence, was not in any sort of equilibrium with its host; an imported pathogen, it was matched against a vulnerable population that had never been exposed to it before. As for experiments, the more natural their conditions, the fuzzier their results became. “You always need additional explanations to keep the tradeoff model working,” says Ebert.

Ebert and Bull also point out that many real-world diseases fail to support the model. The Spanish flu epidemic of 1918 broke out in the cramped, foul conditions of World War I in which transmission was easy, killing millions, Ebert and Bull acknowledge. But they wonder why foul, cramped

that’s why I don’t work in the field anymore.”

The mobility factor

The original architects of the tradeoff model are not impressed by Ebert and Bull’s arguments, however. “Nothing very new in this,” says Roy Anderson of Imperial College in London. Ewald calls it “very sad and dangerous.”

Ewald complains that the critics are trying to demolish a straw man. He says that they leave out a crucial component of his work, for example, the mode by which a disease infects new hosts. If hosts become so sick they can’t move, a parasite can only infect other people who come close, unless a vector such as a mosquito can transport it. This factor is crucial in Ewald’s explanation of Spanish flu. He doesn’t ascribe the deadliness of the epidemic simply to cramped conditions. “That wasn’t my argument,” says Ewald. “My argument was that at the Western Front you had conditions in which people who were completely immobilized could contact hundreds or thousands of people.” Sick soldiers were moved on stretchers to triage areas, then to makeshift hospitals, then onto crowded trains. In these conditions, a flu virus could devastate its host but still infect vast numbers of people. “My argument was that we *wouldn’t* see a 1918 pandemic arise unless we duplicated this situation which occurred on the Western Front,” says Ewald.

Nor does Ewald think critics have addressed his evidence on cholera. *Vibrio cholerae* makes people sick by releasing a toxin that triggers diarrhea. As a result, competing organisms get flushed out of the bowels while *V. cholerae* clings to the intestinal lining. It can then release its offspring into the diarrhea to infect new hosts. The bacteria reach those new hosts by two routes. Untreated sewage or runoff from laundered sheets can contaminate drinking water. Alternatively, an infected person can transmit the bacteria while handling food, shaking hands, or engaging in other social interactions—which generally require a host healthy enough to get out of bed.

Ewald argues that in places with poor sanitation, cholera can make hosts deathly ill but still find new hosts. As a result, it will evolve to high virulence. On the other hand, in places with protected water supplies, that route is cut off. The bacteria’s only option



Disillusioned. An expert on the evolution of pathogens, Dieter Ebert doubts that virulence management can work.

for survival is to let the host move around, which translates into reduced virulence.

Ewald’s observations of the cholera outbreak that struck South America in the 1990s support the hypothesis. In countries with poor sanitation, such as Ecuador, the outbreak was far deadlier than in countries with clean water, such as Chile. Ewald also measured the toxins produced by strains of cholera from different countries. He found that toxin production in Chile dwindled through the 1990s. “In Ecuador, it’s the mirror image of Chile,” says Ewald. “Over a 6-year period, you have only the virulent strains winning out.”

Other experts agree that the critics have not yet made their case. Andrew Read of the University of Edinburgh, U.K., says of Bull and Ebert, “I think they’re reacting to a quite old view. ... There was a lot of optimism flung around in the late 1980s and early 1990s. I think the last 10 years have given everybody a feel for the complexity involved and the lack of data, so that nobody that I know of is making wildly optimistic statements. So they’re tilting at a caricature.”

Read nevertheless concedes that evolutionary biologists are a long way from becoming virulence managers: “We don’t know enough about any one disease to be enacting anything now.” Even Ewald grants that it will be a tough hike. Just demonstrating that a change in the transmission of a pathogen can make it less harmful to humans would take a colossal study of thousands of people. In some cases the scale would require “billion-dollar experiments.” For now, Ewald suggests, we may have no choice but to continue studying “natural experiments” to see whether virulent pathogens behave as the theorists have predicted.

—CARL ZIMMER

Carl Zimmer is the author of *Evolution: The Triumph of an Idea*.

Image not available for online use.

Virulence in action. The virus that caused the 1918 flu pandemic may have caused millions of deaths because it was able to propagate easily in WWI battlefields.

conditions have never triggered another flu epidemic since then. And even when the tradeoff model is relevant, its practical value may be remote. “If I told you I can do something about malaria, but it will take me 10,000 years, you’d tell me to forget about it,” says Ebert.

Ebert and Bull’s challenge has been seconded by other researchers. “It’s long overdue,” says Levin. Marc Lipsitch of Harvard University adds, “They’re quite correct, and