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Missing cosmic gas found

BIOTERRORISM

This Time It Was Real: Knowledge Of Anthrax Put to the Test

Was it organized terrorism or just a madman with a grudge? Where did the attacker get the bugs? And how do you protect against anthrax anyway?

These questions were begging for answers early this week after the United States experienced what appears to have been a series of attacks with anthrax. Several contamination incidents frayed the nerves of a nation already jittery from the 11 September massacres and moved biodefense to the top of the political agenda.

As *Science* went to press, federal officials said anthrax-laden letters or packages had been mailed to the offices of American Media, a publishing company in Boca Raton, Florida; the NBC News desk in New York City; and the office of Senate majority leader Tom Daschle (D–SD) in Washington, D.C. Robert Stevens, a photo editor at American Media, had died of what appears to be inhalation anthrax, the most severe form of the disease, and a coworker was diagnosed with the disease. Two other people had the milder, cutaneous form. At least eight others had been exposed but showed no signs of infection. The reports also spawned a series of hoaxes and false alarms; by last weekend, almost any powdery substance found anywhere was being treated as a potential bioweapon.

Crime scene. FBI agents at work near the offices of American Media in Florida.

The apparent assaults posed a rare test of the country's capability to deal with a real bioterror attack—albeit a modest threat compared with the medical catastrophe that spraying a fine mist of anthrax over a big city could have wrought. But the crisis also trained a spotlight on the disease itself and the considerable investment in studying it. Thanks in part to the mounting worries about anthrax's use as a biological weapon, "there has been an explosion in knowledge," says Martin Hugh-Jones, an anthrax expert at Louisiana State University, Baton Rouge. "It's marvelous." Over the past 2 decades, researchers have puzzled together in detail how *Bacillus anthracis* makes humans sick and kills them. Even its genome of 5 million base pairs is about 95% sequenced and should be completed within a couple of months, says Timothy Read, who leads a team at The Institute for Genomic Research in Rockville, Maryland.

That molecular expertise is now being put to use on many fronts. Researchers familiar with the organism's DNA are being called on to help "fingerprint" the samples that arrived by mail in hope of identifying their origins. Others are looking at vaccines that can be administered conveniently. The old standby, the only anthrax vaccine licensed for use in the United States today, requires six shots and an annual booster. It's also in short supply, and the limited stocks are reserved primarily for military use (see p. 498). Still other researchers are developing better diagnostics to determine who is infected and who is not, as well as drugs that can block the anthrax toxin, which remains lethal even after antibiotics have killed the bacteria. All these requirements seem likely to get increased attention in the coming months.

Tough and lethal. Anthrax is a disease of livestock that occurs almost everywhere in the world. One reason it's hard to eradicate is that it forms hardy spores that can lie dormant in the soil for decades; they are found in many places in the United States. Although many researchers have worked with anthrax in animals and in the lab, precious few have ever seen anthrax in people. Even fewer have seen the pulmonary infection, caused by the same anthrax strains that cause cutaneous anthrax, provided that the spores are dispersed in minuscule particles that can descend deep into the lungs. Only 18 cases of inhalation anthrax are known to have occurred in the United States in the entire 20th century.

When the first case of the 21st century appeared this month, authorities turned to biologists for some detective work. One way to help identify the perpetrators of the attacks is to study the DNA of the spores found at the three sites and compare it to that of known strains. This could reveal whether they all came from the same source and whether they are run-of-the-mill strains available from dozens of labs or are rare varieties. Several anthrax researchers say that the FBI has enlisted the help of Paul Keim of Northern Arizona University in Flagstaff, an expert in the identification of anthrax strains. Together with Hugh-Jones, Keim has built a collection of more than 1300 strains from across the globe. Keim declines to confirm or deny his participation in the investigation, but he does point out that his lab would be better equipped than any other to do the job.

Telling anthrax strains apart is not an easy task, says Keim, because the genetic differences between strains are extremely small. One reason for their similarity may be that anthrax bacteria spend much of their time as spores, which act as evolutionary time capsules. As a result, the disease may have been around since the dawn of agriculture, but the organism has been actively evolving for only a fraction of that time, limiting its genetic variability.

Keim has developed a technique to identify different strains by focusing on a number of so-called variable-number tandem repeats, rapidly evolving spots in the microbe's genome where a small stretch of DNA is repeated multiple times. The work

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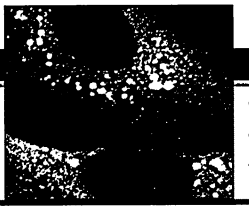
Problems with bioweapons vaccines

Stockholm bound



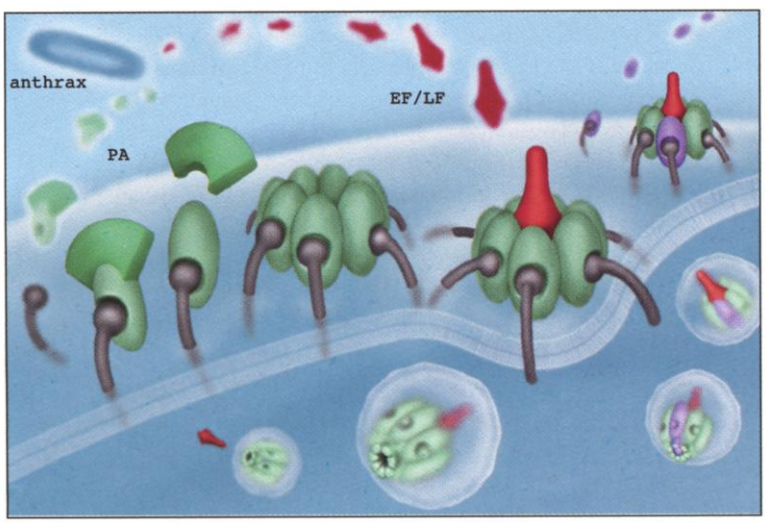
Cholesterol and Alzheimer's

has already paid off in another forensic study: Keim's team was the first to identify the strain used in a 1993 anthrax attack by the Aum Shinrikyo cult in Japan. As it turned out, the cult had sprayed a nonvirulent vaccine strain into the Tokyo air, says Keim—which explains why this attack, in contrast to the later release of nerve gas in a subway, was a flop. There's no official word yet on the origins of the strains found in the United States, however.

One of anthrax's most insidious qualities is that it produces a toxin aimed at thwarting the immune system that continues to do harm even after the source is eliminated. "You can kill the bug with no effort at all," says Hugh-Jones, "but people will still die, because they're exquisitely sensitive to the toxin." Some researchers have focused on new ways to stop this process. For instance, Harvard University's R. John Collier, who has long been fascinated by the ingenuity of anthrax's aggressive toxin, has discovered ways to disarm it.

The toxin has three components, Collier explains. One of them, called edema factor (EF), prevents cells called macrophages from gobbling up bacteria. Another, called lethal factor (LF), kills the macrophages and eventually the host, too. The third component, protective antigen or PA (so called because it can be used as a vaccine), helps shuttle the other two into macrophages. The latter process could also be the bug's Achilles' heel, says Collier. Seven PA molecules must bind to receptors on the surface of a macrophage and come together to form a doughnut-shaped complex (see figure). Then they bind EF and LF, after which the entire complex is engulfed by the cell membrane and shuttled to a so-called endosome inside the cell. Once there, the PA molecules form a special pore that pierces the endosome's membrane and lets EF and LF out to do their grisly work.

In a paper published in *Science* last spring (27 April, p. 695), Collier showed that a mutated PA molecule could form part of the doughnut like normal PA but could also disrupt the membrane pore, preventing the escape of EF and LF. Indeed, he found that rats died quickly from an injection of LF with normal PA, but survived when LF and mutant PA were injected. He hopes to create a drug based on mutant PA.



Poisoning the poison. A protein called PA delivers anthrax's deadly cargo of EF and LF into cells; adding a mutant PA (purple) can prevent release of EF/LF inside the cells.

There could be a bonus, Collier says. PA is the most important component of the licensed human anthrax vaccine. Because the mutant PA elicits antibodies just as well as the normal form does, it might do double duty: "You would have wrapped into one molecule a therapeutic and a potential vaccine." This would be valuable in a major attack, he says, when thousands of people would need immediate treatment and a vaccine to prevent infection later by lingering spores.

"It's an interesting and very important approach," says Columbia University public health expert Stephen Morse. Harvard biologist Matthew Meselson agrees that Collier's work is "marvelous," but at the same time, he cautions against relying on high-tech solutions to bioterrorism. Developing a new drug often takes years, if not decades, says Meselson. For now, he thinks simple, generic solutions are the best—from installing highly efficient air filters in many buildings to educating the public about do's and don'ts during an outbreak. **–MARTIN ENSERINK**

CREDIT: (TOP) ILLUSTRATION BY C. SLAYDEN

PROFESSIONAL TRAVEL

NIH Chafes at Limits On Attending Meetings

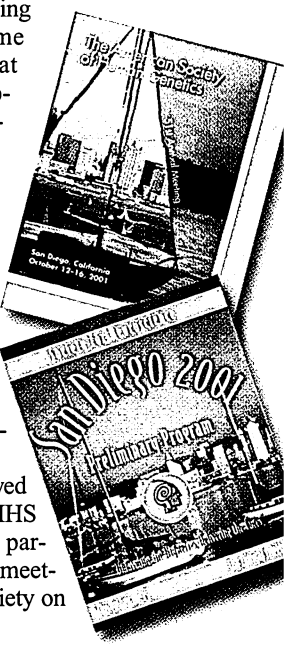
Some 200 scientists at the National Institutes of Health (NIH) may be no-shows next month at the year's biggest neuroscience meeting, thanks to a management directive by the Bush Administration to limit government travel. NIH officials hope that a personal appeal by several institute directors will persuade their bosses at the Department of Health and Human Services (HHS) that the policy could hinder progress in biomedical research.

"There's a lot of unhappiness," says a source, who requested anonymity. "We're all trying to figure out ways of explaining to the Administration how pernicious this is to the process of science."

Until recently, NIH scientists who wished to attend a scientific meeting needed clearance only from their institutes. But early this year HHS Secretary Tommy Thompson decreed that those wanting to attend meetings in foreign countries would have to get permission from his office. A few months later, the rule was extended to domestic travel. At NIH, the policy applies to groups of five or larger.

Several NIH officials—none of whom was willing to have his or her name used—told *Science* that the rationale doesn't appear to be financial. Instead, says one source, people in Thompson's office seem to "have the impression that traveling to meetings is a junket" rather than an essential part of the job. An HHS official says the policy is "just part of being a good steward of the taxpayer's dollar."

The policy first showed its bite in June, when HHS lopped the list of NIH participants in the annual meeting of the Research Society on



California dreaming? The Bush Administration wants to cut the number of NIH scientists attending these two fall meetings in San Diego.