Heightened fears of bioterrorism have shone the spotlight on the Army's biodefense lab—and pulled its researchers out of their isolation

On Biowarfare's Frontline

FORT DETRICK, MARYLAND—To outsiders, the research at this Army base an hour north of Washington, D.C., has always seemed slightly sinister. During World War II, scientists here embarked on a large, top-secret program to develop biological weapons that could kill thousands, even millions. Although that was ended in 1969 and scientists switched to purely defensive research, rumors about clandestine experiments in underground labs persist to this day. Even in the scientific world, the researchers have remained the odd ones out, studying exotic diseases that might cripple an army but have actually infected few people and that most other researchers cared little about.

Now, everything is different. In the post-9/11 world, the expertise built up at the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID), the main research institute at Fort Detrick, has proven invaluable—and suddenly everyone is grateful. The lab is working closely with the Federal Bureau of Investigation (FBI) to help unmask whoever sent the anthrax letters last fall; the so-called Brokaw, Daschle, and Leahy letters were sent here to be investigated; and the lab serves as the repository for anthrax strains subpoenaed from other labs. Tens of thousands popped Cipro last fall because USAMRIID's Arthur Friedlander showed it could protect monkeys from anthrax.

The institute is garnering some scientific respect, too. After two recent visits, Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases (NIAID) in Bethesda, Maryland, says he was "quite surprised" by the lab's expertise and technical capabilities. Fauci hopes to collaborate closely with the lab now that President George W. Bush has requested a whopping $1.7 billion in new bioterrorism funds for NIAID. "This has pulled us out of the intellectual backwaters and into the mainstream," says senior USAMRIID researcher Peter Jahrling, who studies smallpox and viral hemorrhagic fevers.

But at the same time that USAMRIID is helping in the bioterror investigation, the institute is under intense scrutiny as the potential source of the anthrax—and perhaps even the terrorist. The research strain called Ames, used in the letters, made its debut here after being isolated from a Texas cow, although it was subsequently sent on to more than a dozen other labs. The powder's sophistication suggests to some that the bioterrorist had connections to the earlier offensive biowarfare program, and the FBI has recently started giving employees lie detector tests. To complicate matters further, the lab has gone through several high-profile PR hiccups in recent months—including a finding of anthrax spores outside a high-containment facility that is still under investigation.

Even more threatening to the lab's future, some researchers say, is that it's missing out on the current bioterrorism bonanza. Its budget, some $50 million annually, is already far eclipsed by NIAID's spending, and no increase is in sight. Several top researchers have left over the last decade, some of them demoralized by what they see as neglect by the Department of Defense (DOD) and a stifling military leadership. Within a few years, "Rid," as it's affectionately called, might lose its edge, especially in basic science, says one of the lab's senior researchers, who asked not to be identified.

New enemies. Army researchers study a mouse that is potentially infected with a hantavirus under high-containment conditions.

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Engineering marvel

Virologist Robert Shope vividly remembers his own contribution to germ warfare at what was then still called Camp Detrick. In the mid-1950s, when human research protections were far more lenient, Shope studied whether human volunteers could be infected with an occasionally fatal rickettsial pathogen called *Coxiella burnetii*, the cause of Q fever, by means of an aerosol cloud. "You knew other people worked on other agents, but they weren't allowed to tell you which ones," says Shope, now at the University of Texas Medical Branch (UTMB) in Galveston. The project was one of the first to demonstrate the feasibility of the aerosol attack route, Shope says—and antibiotics cured the patients. "We didn't lose any subjects, fortunately," he says.

Then in 1969, President Nixon denounced chemical and biological warfare. Although a few reminders of the offensive program remain—including "Building 470," an abandoned tower used to manufacture anthrax—the lab now studies countermeasures against diseases such as smallpox, anthrax, plague, hantaviruses, West Nile virus, hemorrhagic fevers such as Ebola and Lassa, and illness from botulinum and other deadly toxins.

One of its crown jewels is a biosafety level 4 (BSL-4) facility, a series of high-containment rooms where scientists clad in pressure suits study the most dangerous pathogens on Earth—almost all of them

deadly viruses for which no vaccine nor cure exists. Only a handful of these multimillion-dollar engineering marvels exist in the United States (*Science*, 26 May 2000, p. 1320), so it draws scientists to USAMRIID. Says Jahrling: "If somebody really wants to work with the real McCoy instead of its first cousin, they have to come here!"

The lab also has the only BSL-4 mini-hospital, known as "the slammer," where people exposed to one of these viruses can be treated by doctors and nurses clad in space suits—a terrifying fate last experienced in 1985 by a researcher who pricked himself with a needle containing the Junin virus. There's even a BSL-4 morgue for high-containment autopsies. (It has never been used for humans.)

Although such details, along with the lab's scientific history, easily stir the public's imagination, there's nothing secret about what goes on at USAMRIID, and the research gets published in regular scientific journals, Colonel Edward Eitzen, the institute's commander, told *Science* during a recent interview. A giant *National Geographic* map of the world is affixed under a glass plate on a table in Eitzen's office; atop it sit two glass bowls heaped with M&M's candy. Eitzen, a pediatrician and Desert Storm veteran whose 2-year tenure will end on 19 June, patiently explained how the lab has come under fire in the media recently—often unjustly so, he says.

In January, for instance, papers released as part of an age-discrimination lawsuit filed by three former employees showed that one of them, Ayaad Assaad, had been the subject of intense and cruel harassment in the early 1990s. Colleagues circulated a sexually explicit poem ridiculing Assaad and started the Camel Club—a reference to his native Egypt—which periodically honored the least productive researcher in their group with an obscene rubber camel.

Around the same time, newspapers reported that USAMRIID had lost samples of anthrax, Ebola, and other pathogens encased in electron microscopy slides in the early 1990s. One of the three researchers suing the Army, Richard Crosland, says such mishaps were typical of the lax security and chaotic management at USAMRIID. "7-Eleven keeps a better inventory," sneers Crosland, who now works at the National Institutes of Health (NIH) in Bethesda.

Eitzen counters that the Camel Club was an isolated incident that could have happened in any organization. He says it was a gross violation of the Army's "seven values" and that the perpetrators have been punished accordingly. The missing slides were a non-starter, he says. Their loss was recorded in a 10-year-old report recently obtained by *The Hartford Courant*. In the meantime, 26 of the 27 missing sets have been found, says Eitzen, but more important, all of the samples had been "killed twice," using an aldehyde fixative and a high dose of radiation —which would render them completely innocuous.

Pushing the envelope. Assisting the FBI in its investigation of last fall's anthrax attacks, a USAMRIID researcher opens the Leahy letter.

CREDITS: FBI

But another recent incident is being taken much more seriously. Last month, USAMRIID revealed that live anthrax spores had been found outside the high-containment facility where they are studied. The discovery was made after one of Friedlander's fellow anthrax researchers was found secretly testing environmental samples outside the high-containment area, which is not routinely done and was seen as suspicious. Three of his samples, taken in a locker room, an office, and a hallway, turned out to be positive. Eitzen says the FBI is currently investigating the incident, and Paul Keim's lab at Northern Arizona University in Flagstaff is determining the genetic fingerprint of the spores to find out where they came from. It's unclear whether there's a connection to the bioterrorism investigation, most of which is going on in another part of the lab, says Eitzen; the scientist might simply have been concerned about possible contamination.

Eitzen says he immediately took elaborate measures, securing the area, taking samples from more than 1000 sites throughout the building, and testing personnel for exposure and reeducating them about biosafety. "In a perverse way," he insists, "the incident is a good news story," because only two of the new samples came back positive, both of them from the areas that had tested positive before by the researcher. "We've shown that we don't have a widespread contamination problem."

Ticket-punching

In any case, says Eitzen, such mishaps should not detract from USAMRIID's accomplishments—and many outside the lab agree. "They have hung on to diseases that often weren't the most popular things to work on," says Franklin Top, executive vice president at MedImmune and a former commander of USAMRIID's sister institute, the Walter Reed Army Institute of Research. Friedlander's decades of research, for instance, paved the way for the current Cipro regimen, and he also developed what is widely regarded as the next-generation anthrax vaccine, based on a recombinant protein called Protective Antigen.

Jahrling and his colleagues have pioneered a groundbreaking, although controversial, series of experiments with the variola virus, which causes smallpox (*Science*, 15 March, p. 2001). Because an international treaty bans moving smallpox outside the only two labs where it's officially stored, the work was carried out at the Centers for Disease Control and Prevention (CDC) in Atlanta. It has resulted in the first—albeit crude—animal model of variola. In addition, the group has identified an antiviral compound, cidofovir, that might be used to treat smallpox. Another example of "first-class work," says Top, are the studies by USAMRIID's Connie Schmaljohn, a world expert in the field of hantaviruses.

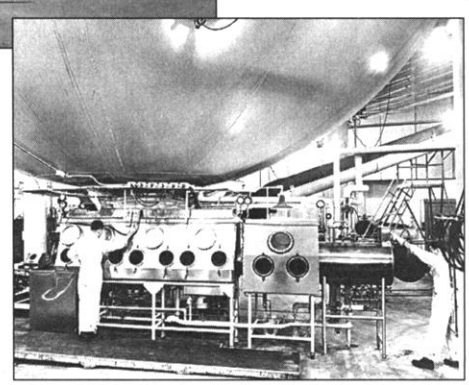
Working on a relative shoestring, USAMRIID has also led the way in developing new diagnostic tests for a range of pathogens, including ricin and botulinum toxins, plague, and poxviruses. Although it was never set up as a reference lab, its six-member diagnostics development team

swelled to a regiment of 82 that worked around the clock and ran some 200,000 tests—many more than any other lab—during the anthrax scare. Eitzen also likes to point out that many former employees have moved on to top positions elsewhere: C. J. Peters, head of UTMB's Center for Biodefense; James LeDuc, who now leads CDC's Division of Viral and Rickettsial Diseases; Thomas Monath, chief scientific officer at Acambis, the company producing smallpox vaccine for the U.S. government; and David Huxsoll, who heads the Plum Island Animal Disease Center, an Alcatraz for veterinary pathogens off the Long Island coast.

Despite those successes, some researchers say the lab still faces problems—most of which are related to its military leadership and its position within the Pentagon. Army officers—many of them trained as doctors or scientists—make up about a third of the lab's 650 employees, and they tend to occupy most of the management positions, whereas civilian scientists do the bulk of the benchwork. Officers are often rotated to new positions elsewhere in the country or overseas, resulting in frequent changes in leadership and perpetual confusion about scientific priorities, says Crosland. (One former employee, Robert Wellner, says he had five different department chiefs during his 7-year stint at the lab.) What's more, officers at USAMRIID have become increasingly obsessed with what UTMB's Peters calls "ticket-punching": attending all sorts of meetings and classes that have little to do with science but are essential to get promoted. "That has had a really negative effect on the atmosphere," he says, as they have little time to lead the research.

But USAMRIID researchers such as Jahrling and Friedlander—both of whom started out in the Army but later became civilians—counter that the transfers are less frequent than most people think: Eitzen, for instance, spent 9 years at the institute before taking the helm. And many of the alleged ticket-punching activities actually help soldiers become better managers, says Jahrling.

Some say the trend of rewarding military rather than scientific experience is also visible in the lab's management. Although some past leaders at USAMRIID were well-respected scientists with a nose for what's important and the guts to take scientific risks, such as Huxsoll and Philip Russell, nowadays going to the right military school seems to have become more important, some gripe. "Have you seen Eitzen's résumé?" one prominent scientist asks. "I rest my case." But others disagree. "How many CEOs of biotech companies could say they're a well-respected scientist in their own right?" asks Jonathan Smith, who left as head of USAMRIID's virology division in 1999 and is now senior vice president at a biotech company called AlphaVax in Research Triangle Park, North Carolina. "You need a different skill set today to run an organization."



Bad old days. Remnants of Fort Detrick's offensive biowarfare program: "Building 470," where anthrax was produced, and the "Eight Ball," a chamber in which humans and animals were exposed to aerosolized pathogens.

In principle, says Donald Burke, another prominent former Army scientist, the military command structure is an excellent way to keep the quest for vaccines and drugs tightly focused—something that is almost impossible in academe, he finds. But Burke, a longtime Walter Reed researcher who in 1997 left for Johns Hopkins University in Baltimore, Maryland, says the research has suffered from neglect higher up in the Pentagon. The lab had to lay off about a third of its employees in several budget cuts in the 1990s, undermining morale among Army scientists, he says: "There's a lot of dissatisfaction because the work has not been seen as important by the command chain."

Some researchers have also become frustrated, says Burke, with the fact that many promising vaccines—USAMRIID has candidates for anthrax, smallpox, plague, staphylococcal enterotoxin, and botulinum toxin—still haven't made it to human tests or the Food and Drug Administration. The responsibility for that rests with a government office called the Joint Vaccine Acquisition Program, which for a variety of reasons has failed to deliver and is widely considered a failure (*Science*, 19 October 2001, p. 498). What's needed to get the drugs and vaccines that the military needs is much more money, says Burke: "Industry would recognize that in a second."

Testing facility

The funding problem is aggravated by the fact that in Army circles, it's deemed inappropriate to beat one's own drum too loudly or to let politically savvy directors lobby in Congress. "We have no senators, no Fauci," says a prominent USAMRIID researcher. "We're an orphan lab." Nor does USAMRIID have the well-oiled PR machines used by universities and NIH to tout their scientific accomplishments and offset bad news.

So while NIAID's coffers are bulging, "I'm looking at a flat budget," says Erik Henchal, who currently heads the diagnostic systems division at USAMRIID but is slated to take over from Eitzen later this month. Both Eitzen and Henchal put on a brave face when asked about this discrepancy. "The answer to that is: We support the DOD and the president's budget," says Eitzen. Indeed, Henchal says there's room enough for everybody, and he looks forward to collaborating with NIAID-sponsored researchers during his tenure.

But privately, some fret that the hundreds of new researchers now flocking to the field might eclipse USAMRIID's contributions and might fundamentally change the mission of the lab. Looming on the horizon, researchers see a tremendous need for animal tests of new drugs and vaccines, and NIH has already indicated that it would like to enlist USAMRIID to do them—after all, it boasts decades of experience as well as specialized safety cabinets in which animals can be exposed to aerosols. But USAMRIID scientists worry that this will reduce their institute to a testing facility and that basic research will fall by the wayside.

Still, Jahrling says he's at least satisfied that the rest of the research world has seen the light. "We believe passionately in what we're doing," he says. "I'm glad we no longer have to defend it to people who don't believe there's a threat."

–MARTIN ENSERINK

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