ANTHRAX
▶AN OLD ENEMY REVISITED

A 'Sure Killer' Yields To Medicine

The clinical course of inhalational anthrax hasn't changed in centuries, but speedy diagnosis and new drugs can alter its outcome

It was Tuesday morning when a patient dubbed T.T. began complaining that his head and back ached. He left work at lunchtime. That afternoon, his doctor diagnosed the flu, giving him aspirin and codeine. It seemed to do the trick—for a day. But then something went terribly wrong. By Friday, T.T. was dead.

Now, we know the correct diagnosis: inhalational anthrax. But T.T. was not a victim of bioterrorism, and he didn't die last month. In fact, he died 44 years ago, in the fall of 1957. Three more deaths followed, in the biggest 20th century outbreak of inhalational anthrax reported in the United States. The victims all worked in a Manchester, New Hampshire, goat hair mill, where they likely inhaled anthrax spores from the hair of infected animals. These cases would have remained a historical footnote, except that history is repeating itself.

Since early October, 11 patients with inhalational anthrax have arrived at the doors of various doctors. At press time, five had died, two of whom were sent home by doctors who mistook the disease for a stomach virus or bad cold. Like the mill workers half a century ago, the recent patients had early aches that were hard to pin down. Some, too, inhaled *Bacillus anthracis* spores at work: a thin dust of bioterror coating mail.

The surge of new cases has given physicians a fresh look at an old disease in unprecedented clinical detail. Researchers familiar with anthrax say the cases look remarkably familiar, except perhaps for one aspect: Physicians have long thought that death from inhalational anthrax is almost inevitable once a patient shows advanced symptoms. Yet quick-thinking doctors armed with a trove of drugs and techniques have saved six of the 11 patients this fall—an impressive success rate. "There's nothing like seeing a patient leave the hospital with a disease that was supposed to have killed him," remarks Thomas Mayer, head of emergency medicine at Inova Fairfax Hospital in Falls Church, Virginia, where two of the survivors were treated.

But unresolved questions linger. Will the survivors face lung problems in the years to come? Did others get mild cases of anthrax that went undiagnosed? And, perhaps most pressing, could those exposed to anthrax weeks ago still fall ill? "We're learning as we go," remarks John Jernigan, an epidemiologist with the Centers for Disease Control and Prevention (CDC) and Emory University in Atlanta.

An ancient plague

Anthrax gets its name, *anthracis*, from the Greek word for coal, a reference to the legendary coal-black scabs of cutaneous, or skin, anthrax. According to the 1999 book *Anthrax: The Investigation of a Deadly Outbreak* by Boston College sociologist Jeanne Guillemin, anthrax may have been the sixth plague in the Book of Exodus, mentioned in Homer's *Iliad*, and lamented by Virgil in ancient Rome. Early microbiologists clearly knew the bacteria well. In 1876, Robert Koch first showed that *B. anthracis* causes anthrax in animals—and in the process, established Koch's postulates. Five years later, Louis Pasteur demonstrated a method of vaccinating sheep and cattle against the disease.

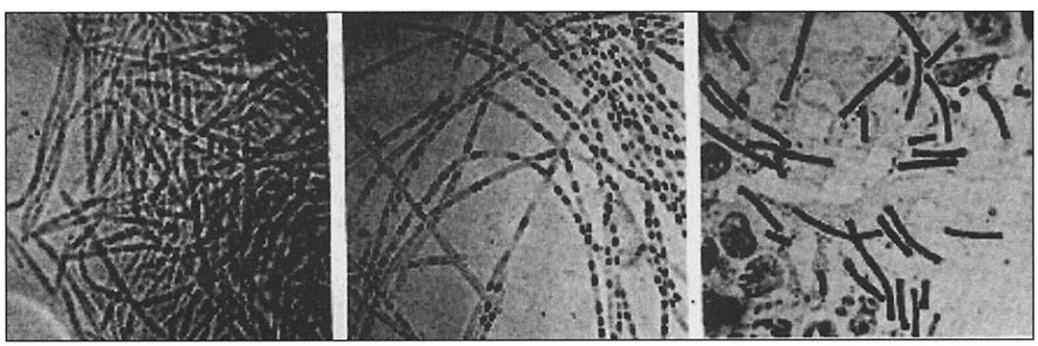
Even then, anthrax struck terror as it wiped out livestock. Grazing animals are most at risk for the disease, consuming anthrax endospores that are hidden in soil. During the 19th century, mill workers who handled infected animal hairs, wools, or hides came down with anthrax so often that the condition became known as woolsorters' or ragpickers' disease. Even in the early 1900s, about 130 people in the United States contracted some form of anthrax every year. The disease became a modern bioweapon in World Wars I and II, as countries including Germany, Japan, and the United Kingdom reportedly tested it.

Anthrax comes in three forms, of varying lethality. Skin anthrax—caused when *B. anthracis* spores seep into a cut—is the most common and treatable form of the disease. During the current outbreak, at least seven people have gotten skin anthrax. In the 1957 episode, four people did; all recovered. Less common but more dangerous is gastrointestinal anthrax, from eating tainted meat. Finally, there is inhalational anthrax, the most feared variety. A 1994 paper in *Clinical Infectious Diseases* sums up the traditional thinking: "Inhalation anthrax is virtually always fatal."

At the outset, however, the disease seems deceptively benign: Patients may feel achy, feverish, nauseated, or fatigued. This first phase typically lasts several days, during which time macrophage cells are gobbling up anthrax spores and carrying them to the lymph nodes near the lungs. There, the spores germinate into full-fledged bacteria, break free from the phages, and multiply.

Then the real trouble starts. During the second stage of infection, anthrax bacteria flood the bloodstream, releasing toxins that make many tissues swell and bleed. Within hours, a patient's blood pressure can plummet, oxygen levels dip, and organs fail. "This is not a diagnosis you want to sit around and ponder," remarks H. Clifford Lane, clinical director of the National Institute of Allergy and Infectious Diseases in Bethesda, Maryland. "The key is to act quickly."

The problem is, rare outbreaks of inhalational anthrax catch doctors off guard. "The cases in 1957 came as a real surprise," recalls infectious disease specialist Philip Brachman of Emory University, who was testing a vaccine on mill workers at the time. "We'd only seen sporadic cases of anthrax in the U.S., and these workers just came in with flulike symptoms. By the time doctors realized they were dealing with anthrax, it was usually too late." Today, anthrax still falls under the radar of most physicians. "I've never seen a case of anthrax, and I've never seen anybody

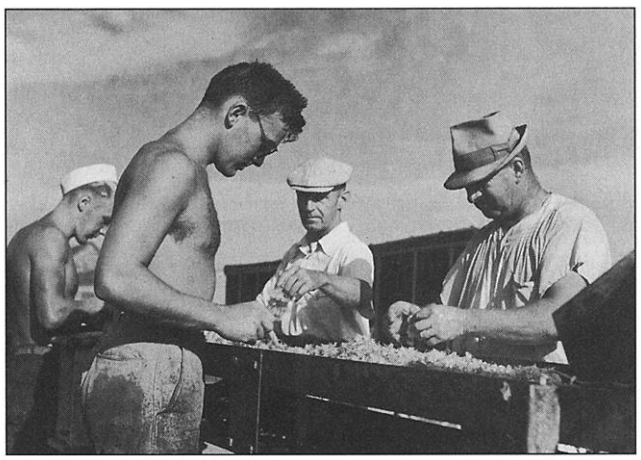


An old enemy. Robert Koch first showed that *Bacillus anthracis* causes anthrax in animals in 1876, establishing Koch's postulates in the process. Shown are his original micrographs.

who's seen a case of anthrax," comments Bill Roper, dean of the school of public health at the University of North Carolina, Chapel Hill.

Researchers did have one recent glimpse of anthrax bioterror in action. In the spring of 1979, at least 66 people in the industrial city of Sverdlovsk (now Yekaterinburg), Russia, died. At first, authorities blamed tainted meat. But death certificates cited influenza, sepsis, and pneumonia, among other conditions. Finally, in 1992, a team of Russian and U.S. scientists concluded that a local military facility had accidentally released a cloud of anthrax bacteria, killing scores of people and animals who inhaled it.

The outbreak might have provided a wealth of anthrax data, but the KGB confiscated most relevant medical records, leaving only autopsy notes and tissue samples behind. "What we glimpsed was the clinical endpoint: the end of life with anthrax," says David Walker, a pathologist at the University of Texas Medical Branch in Galveston who studied the Sverdlovsk cases.



Woolsorters' disease. By handling wool or hides from infected animals, mill workers like these, shown in New Hampshire during the 1950s, once commonly came down with anthrax.

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Dusty data

One puzzling question is who succumbs to the bacteria and why. The Sverdlovsk and New Hampshire cases provide some clues.

They show just how mercurial inhalational anthrax is: sickening some but not others; causing illness within days—or weeks—after exposure; prompting heavy sweating or just fatigue. In Sverdlovsk, for instance, people fell ill anywhere from 2 to 43 days after inhaling bacterial spores. Some who died were farther from the point of exposure than were 11 reported survivors. Of 77 known patients, 55 were men, with a mean age of 42. For some reason, no children were reported ill. Although the demographics are sketchy, researchers say these numbers raise questions about differences in individual susceptibility to anthrax.

The same questions are being asked today. Why did these 11 patients get sick with inhalational anthrax—and others not? Was their exposure level higher, or did something else make them particularly vulnerable? One possibility, speculates Jernigan, is that some additional people did contract the disease, but in a mild form that went undetected.

Other lessons are hidden in the dusty data. Some doctors have made much of the "nonclassic" symptoms seen in recent anthrax victims, such as drenching sweat and nausea, asserting that these clinical signs are new. In Sverdlovsk, however, many patients felt sick to their stomach; researchers documented gastrointestinal lesions in 39 of the dead. Similarly, in the hours before patient T.T. died in the New Hampshire outbreak, he sweated so much his bed sheets were changed five times. "If you really want to understand anthrax, go to the literature," advises Lane.

Animal studies lend some sobering perspective as well. Although the medical spotlight shines on just 11 patients, many more may still be at risk of anthrax, says Colonel Arthur Friedlander, senior science adviser at the U.S. Army Medical Research Institute of Infectious Diseases at Fort Detrick, Maryland. He notes that anthrax spores germinate at different rates inside the body. During experiments with monkeys, for instance, fatal anthrax occurred as long as 98 days after exposure.

And those people now taking preventive antibiotics—typically a regimen of drugs twice a day, for 60 days—could be in trouble if they fail to complete the full course. In one primate study done before the Gulf War, experimental animals exposed to anthrax and given prophylactic antibiotics still came down with the disease when the drugs were stopped after 30—and in one case, 58—days. According to CDC scientist Julie Gerberding, the agency is working with health departments and other groups to urge people to finish their medicine, although she notes that compliance with such a long regimen rarely reaches 100%.

New lessons

What distinguishes this outbreak from earlier episodes is the sheer power of modern medicine. Over the weekend of 19 October, when physicians referred two postal workers to Inova Fairfax Hospital, the emergency room staff immediately ordered chest x-rays—and then chest computerized tomography scans. The CDC had not yet cautioned postal workers about anthrax risk, but at least one of the patients was concerned.

And that concern was merited: In both patients, chest scans showed massive lymph nodes, as well as swelling between the lungs, in a space called the mediastinum—telltale signs of advancing anthrax. Doctors gave the patients triple antibiotics to kill the bacteria: ciprofloxacin, rifampin, and clindamycin. They also drained bloody fluid around the patients' lungs. "We decided to treat the fluid buildup aggressively, and I think that made a big difference," says Naaz Fatteh, an Inova Fairfax doctor and co-author of a report on the cases in the 28 November *Journal of the American Medical Association*.

From the new cases, a more coherent clinical picture of inhalational anthrax is emerging. As their disease progressed, the first 10 patients showed striking similarity. All had some abnormality on the chest x-ray. Eight had pleural effusions, or fluid around the lungs—another common finding in Sverdlovsk. Seven of the patients had a widened mediastinum. And seven showed cobweblike fibers, called infiltrates, in their lungs.

By the time the patients arrived at the emergency room, many already had alarming amounts of anthrax bacteria in their bodies. One challenge, says Jernigan, lead author of a paper analyzing the 10 cases in the November-December issue of *Emerging Infectious Diseases*, is to better recognize this brief window, before the toxic second stage kicks in. "Once toxin production reaches some critical level, treatment is much less likely to succeed," he notes.

Doctors aren't quite ready to declare the current outbreak over. Just last week, they announced this fall's 11th case of inhalational anthrax: a 94-year-old woman in Oxford, Connecticut, whose route of exposure to the bacteria remains a mystery. "While it's extremely gratifying to see these first survivors," Inova's Mayer says, "we have to realize that there could be more cases, either now or in the future. The genie is out of the bottle."

And the inhalational anthrax survivors face an uncertain prognosis. "Will they develop scarring in the middle of their chest or lymph nodes?" asks Fatteh. "And will that decrease lung function?" There's no way to know, because so few people have ever survived inhalational anthrax. These patients, Fatteh says, will need regular lung tests for years to come. Along the way, doctors hope to learn more about anthrax—and prepare for whatever form of bioterror arrives at the emergency room next.

–KATHRYN BROWN