

THE BIOLOGICAL ARMS RACE

Sept. 11, 2001, demonstrated America's vulnerability to terrorist attacks. Later, the threat was driven home when anthrax-laced letters were mailed to unsuspecting victims.

Until now, the moral repugnance of biological warfare had deterred its widespread use. But a new breed of terrorist has the financial and technological capabilities to manufacture lethal agents, such as anthrax, botulism, ricin and smallpox, with which they can attack entire cities or countries.

Dr. Robert Haley, chief of epidemiology at The University of Texas Southwestern Medical Center at Dallas, said that for the past 10 years the public-health community has tried to sound an alarm.


But by and large, the warning had fallen on deaf ears.

"Of the many things that changed after Sept. 11, we now realize that America is in a new biological arms race," said Haley, professor of internal medicine. "There is going to be a race for scientists to develop technology that will take these biological weapons off the table. This is going to be a long-term research priority. In fact, it may be indefinite."

The biological weapons revolution has created new defenders of freedom — scientists around the world and at UT Southwestern. Armed with advances in science and biotechnology, they are joining forces to develop high-tech diagnostic tools and effective treatments to stay ahead of terrorists' capabilities.

By Ione Echeverria





America's readiness will also depend on the first responders — practicing physicians in private clinics and emergency-department physicians. They will be the eyes and ears of the community. These individuals must recognize early signs and symptoms of biological exposure and apply treatments to prevent contamination, illness and death.

UT Southwestern has assembled a cadre of research scientists to prepare for any eventuality.



Dr. Robert Haley,
chief of epidemiology

History of biological warfare

Incidents of germ warfare are rare. In the mid-1300s, the Tartars used catapults to hurl plague-infected bodies over the walls of besieged cities. In the 19th century, Indians are said to have been given deadly “gifts” of smallpox-contaminated blankets by settlers.

At one time or another, the United States, Japan, Germany, Soviet Union, Britain and other countries have engaged in biological weapons experiments. In World War I, the German army used plague, cholera

and anthrax in limited attacks, mainly against horses. The British tested anthrax bombs on sheep on Guinard Island off the northern coast of Scotland in 1942. The Cold War caused further development and stockpiling of these weapons.

The United States unilaterally ended biological warfare research in 1969 and signed the Biological Warfare Convention in 1972. Now, only defensive biological warfare research is allowed.

The public-health community's attention to the potential for biological and chemical warfare was heightened in 1991 during the Persian Gulf War, said Haley.

“Although the Iraqis did not use biological weapons, their frightening capabilities served as a warning that we must prepare to defend against biological warfare agents in the future,” said Haley, holder of the U.S. Armed Forces Veterans Distinguished Chair for Medical Research, Honoring America's Gulf War Veterans. “We also became aware of the detrimental effects of chemical weapons when Gulf War veterans started to exhibit mysterious symptoms.”

With funding from the Perot Foundation, Haley and colleagues traced Gulf War veterans' chronic sleep problems, neurological problems, and muscle and joint aches to combinations of environmental exposures on toxic battlefields, though he has not yet directly linked it to the use of chemical or biological weapons.

In a groundbreaking paper in the January 1997 issue of *The Journal of the American Medical Association*, Haley identified three distinct syndromes, each related to various Gulf War chemical exposures, including pesticides, insect repellants and pyridostigmine bromide tablets soldiers took to combat the effects of nerve gas.

Haley said the attraction of biological warfare is its capability to cause large numbers of casualties with relatively minimal cost, technological expertise and logistical requirements.

“In one of the most recent studies available, the cost of producing 50 percent casualties per square kilometer was \$2,000 for conventional weapons, \$800 for nuclear devices, \$600 for chemical agents and \$1 for biological weapons,” he said. “Technology is a double-edged sword. Technology can protect us from threats, but it can also be used by terrorists to manufacture bioweapons.”

The “A” list

Bioterrorist agents can be bacteria, viruses or chemical toxins naturally produced by bacteria. The Centers for Disease Control and Prevention ranks anthrax and smallpox on its “A” list — the immediate-threat category — of biowarfare or bioterrorist agents.

In early October 2001, a tabloid photo editor from Florida was diagnosed with the first confirmed case of inhalation anthrax in the United States in more than 25 years. Subsequently, several anthrax-laced letters were mailed to different people across the United States, resulting in 22 confirmed or suspected cases of anthrax infection.

“The first confirmed case of inhalation anthrax was a rare and notable event,” Haley said. “Throughout the entire 20th century, only 18 known cases of inhalation anthrax were identified in the United States, and almost all were traced to occupational exposures, to infected animals or contaminated animal products.”

Anthrax is an acute infectious disease caused by the spore-forming *Bacillus anthracis*. The disease typically occurs in plant-eating animals, which are infected after ingesting spores from the soil.

Anthrax comes from the Greek word for burning coal, *anthrakis*, because of the black skin lesions it causes. In humans, anthrax produces three syndromes: cutaneous, inhalation and gastrointestinal. Early symptoms of inhalation anthrax include fever, malaise and cough; the late phase involves respiratory distress, shock and death.

Smallpox was eradicated worldwide as a health threat in 1977. Smallpox is caused by the variola virus and is spread mainly by infected respiratory droplets. Initial symptoms include high fever, fatigue, and head and back aches. A characteristic pustular rash develops on the face, arms and legs.

“These two agents have the best mix of all features that a terrorist would look for in a biowarfare agent, but the list of possible biological weapons is much longer and expanding,” Haley said. “The challenge to researchers and physicians is to understand each agent separately because each one has a distinct diagnosis, treatment and public-health solution.”

Disarming biological weapons

For the past 10 years, Dr. Stephen Johnston, director of the Center for Biomedical Inventions at UT Southwestern, has collaborated with the Defense Advanced Research Projects Agency (DARPA) to develop technology that will disarm terrorists' biological arsenals.

DARPA is the central research and development organization for the Department of Defense. Its work has been crucial to development of, among other things, the Internet, Stealth technology and micro-

wave energy. Just last year the agency awarded \$3 million to UT Southwestern and Johnston to determine if vaccine development can be accelerated and super vaccines protecting against multiple diseases can be created. Johnston and his collaborators are initially working on vaccines against anthrax, plague and an infectious disease called tularemia.

Johnston was the first to demonstrate genetic immunization in 1992 following the development of a “gene gun,” which shoots tens of thousands of microscopic “BBs” coated with gene segments into the cells of animals. This method of delivering antigen genes provokes an immune response. The gene gun is now being tested in clinical trials.

He later pioneered a revolutionary method of vaccine development called expression library immunization (ELI), in which vaccines for any animal or human pathogen can be discovered by shooting all the genomic bits of a pathogen into an organism.

“DARPA has a good reputation of being far-thinking and being able to bring those ideas into reality,” said Johnson, holder of the Dr. Eugene Tragus Chair in Molecular Cardiology. “The three-year DARPA grant is intended to figure out if a speculative theory has legs or not. If it does, they want us to work as fast as we can to get it out commercially.”

The technologies developed with the DARPA funds, spawned MacroGenics, a biotechnology company that will continue to develop vaccines for biothreat agents.

“In many ways, we can't lose,” Johnston said. “Say we develop a better way to make vaccines, and we apply that to anthrax. That same technology could be used for conventional infectious diseases. All the technology that people are developing to counteract biological agents crosses over into standard biomedical practice. It's a win-win position.”

Johnston said two new research projects that could reduce the impact of biological warfare are the development of fast-acting vaccines and diagnostic systems that diagnose an infection soon after an exposure.

“A smaller project we are working on is to develop technology that will allow us to clinically validate vaccines and diagnostic systems for biothreat agents,” he said. “Since these pathogens are rare, it's more difficult to validate them. We are using biosignature-type approaches to see if we can create a shortcut for that challenge.”

UT Southwestern researchers have also developed a vaccine for ricin, a toxin that terrorists have used as biological “ammunition” in many parts of the world. The vaccine seems to be effective in studies with mice.



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Ricin is produced by a protein found in castor beans. A single molecule inside a cell shuts down protein synthesis, killing the cell. A group linked to the terrorist organization al-Qaeda has experimented with the poison as a weapon.

Dr. Ellen Vitetta, director of the Cancer Immunobiology Center at UT Southwestern and holder of the Scheryle Simmons Patigian Distinguished Chair in Cancer Immunobiology, reported her findings last year in the journal *Vaccine*.

Vitetta and her colleagues mutated the DNA encoding the active A chain of the toxin. They took out the site that inhibits protein synthesis, as well as the site responsible for inducing vascular leak. The new recombinant A chain induces a protective immune response in mice and protects them against very high doses of the toxin.

Haley said Vitetta’s research has found a unique solution to a potential threat.

“Ellen came up with a clever idea,” Haley said. “Her discovery could provide immunity against one of the most potent toxins known to man. This type of research will make terrorists’ biological weapons ineffective.”

Haley, Johnston and Dr. Michael Norgard, chairman of microbiology, serve as board

advisors for UT Southwestern’s Regional Center of Excellence for Bioterrorism Research. On the board’s agenda are plans to enlarge its biosafety level 3 laboratory — which incorporates special engineering features to allow researchers to handle hazardous material without endangering themselves, the community or the environment — to accommodate additional research projects.

Preparing for bioterrorism

Imagine that over the course of one week, 15 people visit an emergency department complaining of fever, physical discomfort and a cough.

Before Sept. 11, this scenario would not raise much concern. But in the post-9/11 era, nothing should be above suspicion, said Dr. Paul Pepe, chairman of emergency medicine at UT Southwestern.

“Doctors must maintain a high degree of suspicion for biological terrorism when numerous patients present with similar, unexplained symptoms,” said Pepe, who oversees the emergency medical services for Parkland Memorial Hospital. “Primary-care physicians in clinics and emergency-department personnel will be the first responders to an attack. They will experience an influx of patients and must have a viable plan to prevent illness and death.”

Since the mid-1990s, the federal government has devoted funding, resources and equipment to prepare its 120 largest metropolitan areas — Dallas is eighth — for a terrorist event.

The Dallas Metropolitan Medical Response Team was developed to teach police, fire, and emergency and medical personnel how to minimize the impact of a terrorist attack, limit morbidity and, hopefully, prevent mortality.

Government agencies have recognized Parkland, the primary teaching hospital for UT Southwestern faculty physicians, as a model system.

According to the American Hospital Association, approximately 25 percent of hospitals are currently at some state of readiness for a chemical or biological incident. As the Dallas County hospital, Parkland’s emergency-room personnel and physicians have been planning since 1998 for what most people used to believe was unthinkable.

The response team developed a disaster plan by running mock scenarios and functional chemical exercises. These drills are intended to identify both strengths and weakness in response-system planning.

“One of the UT Southwestern/Parkland initiatives is to train first responders to administer smallpox vaccinations under expert supervision,” said Pepe, holder of the Riggs Family Chair in Emergency Medicine and medical director of the response team. “Currently there are fewer than 100 people who are designated to administer smallpox vaccinations. Training other personnel, such as paramedics, on

this technique will expedite the vaccination of large populations of people in case of a disaster.”

Many terrorist agents — anthrax, pneumonic plague and tularemia among them — mimic symptoms of other naturally occurring diseases, said Dr. Kathy Rinnert, assistant professor of surgery at UT Southwestern and on-scene medical team leader of the response team.

“It’s vital for doctors and medical personnel to differentiate between symptoms of a garden-variety flu and those associated with a biological exposure,” she said. “Diseases of the past are coming back, and rare diagnoses could become mainstream. Physicians must be taught that weapons of destruction are a reality and their practice could end up in the war zone.”

To fulfill this educational need, the department is developing a national “all hazards” disaster-medicine training course to instruct first responders on the most likely weapon — explosive, chemical or biological — that a foreign or domestic terrorist may deploy.

Biological agents are the weapons of choice for terrorists because they disrupt civil order and infrastructure, overwhelm emergency response systems, and create panic, confusion and fear.

The Dallas County Biotel system links Parkland with other area trauma center hospitals and emergency medical services so they can share day-to-day information on patient loads and types of cases being admitted. In case of an attack, the system can help to disperse patients to appropriate hospitals.

“In case of an emergency, the Biotel system can be used to triage patients to surrounding hospitals so that one particular hospital is not overwhelmed and to detect trends in suspicious patient loads, county-wide, long before any individual facility can,” Pepe said.

Delving into a terrorist’s mind

The attacks on the World Trade Center and the Pentagon left the nation in a state of shock. People struggled to comprehend terrorists’ actions and their disregard for human life.

Dr. Jaye Crowder, associate professor of psychiatry at UT Southwestern, has insight into criminal thinking and behavior from his work as a forensic and threat-assessment consultant and profiler.

“Terrorists come to identify with a particular ideology and wish to see that agenda enacted in the world,” said Crowder, head of forensic psychology at UT Southwestern.

Crowder said terrorism is facilitated by the injunction of a transcendent authority — like the self-proclaimed religious leader Osama bin Laden,

head of the fundamentalist terrorist group al-Qaeda and mastermind behind the Sept. 11 attacks — to remove the internal human imperative that one person not harm another.

“It’s really their own aggressive impulses that they project onto God,” Crowder said. “They say, ‘God wants me to kill you,’ to avoid the responsibility of abrogating the natural law that we all follow. This rationalization allows terrorists to act out their aggressive impulses and not feel guilty.”

Fundamentalist terrorists perceive a threat to their group identity. The Muslim religion is facing a rapidly changing world that is encroaching on the traditional values of Islam.

“A small subset react to this infringement by striking out,” Crowder said. “The subtext is, ‘I feel impotent to preserve my sense of self in the midst of this cultural confusion, but I will feel powerful if I can do something dramatic and destructive to the more prosperous and influential United States. I feel out of control in my life, but I can regain mastery if I can hurt the great Satan which threatens our lives, lifestyle, religion and morality.’”

Aside from the physical damage, biological warfare can also inflict psychological damage. Americans are adapting to a new way of life that includes national security alerts from the Department of Homeland Security. For some people, the threat of terrorism consumes their lives.

“Concerns about loved ones who travel, especially overseas, are normal and appropriate,” Crowder said. “However, some people project the problems and fears in their lives onto the threat of terrorism. They displace the fear and pain of the troublesome issues they deal with on a daily basis onto a dread terrorism will devastate who and what they cherish the most. Rumination about the terrorist threat substitutes for other problems, which seem paradoxically more difficult to solve.

“So instead of worrying about your son who is in prison, or that your daughter is marrying the wrong man, or losing your job, you direct your repressed anxieties towards the threat of terrorism.”

While it is impossible to avoid much of the danger because of the random nature of attacks, people shouldn’t let terrorism disrupt their lives.

“Statistically speaking, we all face more serious dangers on a daily basis,” he said. “You can lose your physical life to a terrorist, but too many people lose their psychological lives by worrying about terrorism and restricting their activities.” ❀

Dr. Paul Pepe, chairman of emergency medicine



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