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News Release

EMBARGOED FOR RELEASE: 3 p.m. (CT) Tuesday, August 5, 1997
Media Advisory: To contact Richard Danzig, J.D., D.Phil., call 202/363-6767. To contact Pamela B. Berkowsky, M.A.L.D., call Jim Turner at 703/697-5135.

Preparations Against Biological Warfare Should be Higher Priority

Greater cooperation needed between military and agencies that protect civilian population

CHICAGO--The U.S. continues to take steps to prepare against a biological attack, but the matter requires greater emphasis, according to a commentary in the August 6 issue of *The Journal of the American Medical Association (JAMA),* a theme issue on biological warfare.

Richard Danzig, J.D., D.Phil., and Pamela B. Berkowsky, M.A.L.D., both formerly of the Office of the Undersecretary of the Navy, Department of the Navy, Washington, D.C., write on why the U.S. should be concerned about biological warfare. Richard Danzig is now a Washington, D.C. lawyer. Pamela Berkowsky is with the Office of the U.S. Secretary of Defense.

The authors write that biological warfare is possible because small groups of people with modest finances and basic training in biology and engineering can develop an effective biological weapons capability. Recipes for making biological weapons are even available on the Internet. "Most disturbingly, they can be used to threaten civilian populations and create mass panic. Used this way, biological weapons can achieve military goals by undercutting the civilian support necessary for military operations or by holding civilians hostage to prevent military operations."

The authors contend there are three reasons why biological weapons have been low on the U.S. agenda:

- Defense against a biological attack is both unfamiliar and difficult, leading to a natural tendency to put it aside in favor of problems that are more comfortable.
- There is the belief that because biological weapons have never been used they therefore never will be.
- There is a sense that a regime can be deterred from using biological weaponry if we make it clear that this would invite nuclear retaliation.

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EMBARGOED FOR RELEASE: 3 p.m. (CT) Tuesday, August 5, 1997
Media Advisory: To contact Raymond A. Zilinskas. Ph.D., call B.J. Altschul at 301/403-4696.

Iraqi Biological Warfare Still a Threat

United Nations urged to stand firm on monitoring and enforcement to limit weapons development

CHICAGO--Despite Iraq's defeat in the Persian Gulf War, the threat of biological warfare by Iraq still exists, according to an article in the August 6 issue of *The Journal of the American Medical Association (JAMA)*, a theme issue on biological warfare.

Raymond A. Zilinskas, Ph.D., of the Center for Public Issues in Biotechnology, University of Maryland Biotechnology Institute, College Park, was also a member of the United Nations Special Commission (UNSCOM) investigative team. UNSCOM and the International Atomic Energy Agency have investigated Iraq's weapons of mass destruction programs since of April of 1991.

Zilinskas warns that Iraq's biological warfare program could be quickly resurrected: "The workforce of more than 200 persons who staffed Iraq's biological warfare program is intact. Iraq's civilian biotechnological infrastructure, comprising more than 80 research, development and production facilities, is whole and well-equipped ... It is prudent to assume that the Iraqis retain hidden stores of freeze-dried organisms from its former biological warfare program."

He goes on to write: "Because Iraq maintains these human, biological and industrial resources, it could reconstitute a biological warfare program rapidly and be able to manufacture militarily significant quantities of biological warfare agents within six months."

Biological weapons are made up of four major components:

- Payload: the biological agent
- Munition: a container that keeps the payload intact and virulent during delivery
- Delivery system: a missile, artillery shell or aircraft
- Dispersal mechanism: an explosive force or spray device to disperse the agent to the target population

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Zilinskas says Iraq's biological warfare program began in earnest in 1985. By the time the Persian Gulf War ended with a cease-fire in April of 1991, Iraq's scientists had investigated the biological warfare potential of five bacterial strains (including anthrax), five viruses, four toxins (including botulinum, the most toxic chemical known to science), and one fungal strain which could be used against crops.

In 1990, Iraq produced 200 biological bombs--including 100 filled with botulinum and 50 with anthrax. The biologically armed bombs were deployed at two sites, ready for use.

Iraq's biological warfare arsenal was not used during the Gulf War. If it had been, Zilinskas says the arsenal probably would have been militarily ineffective--because it was small, the payload dispersal mechanisms were ineffective, and because the coalition forces had overwhelming air superiority and had crippled Iraq's command and communications network.

After the April 1991 cease-fire, Iraq's biological warfare program personnel were reportedly ordered to destroy all biological warfare agents. But UNSCOM has been unable to independently verify that the destruction took place. UNSCOM also cannot certify that all biological bombs have been destroyed.

Iraq today is similar to Iraq before the Gulf War, according to Zilinskas. It has the same leader, Saddam Hussein. It has a large and powerful army and air force, and it can deploy a large, well-trained civilian workforce. It has the world's third largest oil reserves. Politically, it has the same uneasy, distrustful relations with its neighbors that it had before the war.

Zilinskas suggests: "In consideration of this unsettled situation, it is wise to prepare for the possibility of Iraq's trying once again to gain a dominant position in the Middle East."

He says UNSCOM must continue to monitor Iraq's biological research, development, production and testing facilities to guarantee that they are not used once again for biological warfare applications: "As long as UNSCOM is able to continue fulfilling its monitoring responsibilities, Iraq's leadership is likely to be deterred from biological warfare acquisition."

He concludes: "Clearly, UNSCOM must remain fully operational until such time as a leadership is established in Iraq which poses no threat to its neighbors."

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(BIOLOGICAL WARFARE)

The authors say these modes of thought are "dangerously inappropriate."

They add that the Department of Defense has embarked on a challenging program to enhance its capabilities to defend against biological warfare. The program includes the development and fielding of state-of-the-art biodetectors; the creation and designation of selected military units with expertise in medical prophylaxis, hazard mitigation, and decontamination; investments in vaccine and antibiotic research, development, and stockpiling; refinement and acquisition of masks and improvements in air filtration systems and the development of doctrine regarding how to preempt and, when necessary, respond to a biological attack.

This summer, more than 100 cities in the U.S. are training their fire, police, rescue, and hospital emergency department personnel under an ambitious program conducted by the Department of Defense.

They conclude: "From another vantage point, the good news wrapped inside the particular problems posed by biological weapons is that in this arena, public health is the best form of civil defense. Our everyday domestic investments to detect and diagnose disease can and should be strengthened because of our national security trends. Biological weapons are not respectful of traditional boundaries of geography, bureaucracy, or conceptual compartmentalization. In that fact lies our challenge, our opportunity, and our call to action."

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Policy Perspectives

JAMA®

The Journal of the American Medical Association

The Cover

Between 1792 and 1815, from Valmy to Waterloo, more than five million lives were lost to war. Yet, the deaths from injuries during the more than 200 battles of the Napoleonic wars are estimated to be actually less than those from disease, especially typhus (McNeill WH. *Plagues and Peoples*. Garden City, NY: Anchor Press; 1976:229). During the campaign of 1813-1814, as much as one tenth of the population died (McNeill, 322 n 37). Even the North American continent was affected: heavy losses to yellow fever and other tropical diseases among French troops sent to Santo Domingo figured in Napoleon's decision to sell the Louisiana Territory in 1803 (McNeill, p 235). Napoleon was not unaware of the disastrous effects of disease on his campaigns: In 1805 he ordered smallpox vaccination of all troops under his command (McNeill, p 233).

But if Napoleon recognized the benefits of modern medicine to his army, he also recognized the importance of the fine arts to his public and to his reputation. Although he himself apparently had little appreciation of the fine arts, nevertheless he looted many treasures from the cities and countries he conquered and brought them to France. Even more, he recognized the propaganda value of art. Harking to the tradition of the great history painters of the 18th century, Napoleon ordered gigantic canvases celebrating himself and his commanders. One of these great history painters, David (*JAMA* cover, May 21, 1997), remarked scornfully that these new canvases, big as they were, hardly qualified as history painting; they were little more than genre, the lowest of the categories.

Favorite among Napoleon's painters was Antoine-Jean Gros (1771-1835), ironically also David's favorite pupil. They had first met in 1796 during the Italian campaign through Napoleon's bride Joséphine de Beauharnais. So pleased was Napoleon with Gros' portrayal of him that he appointed Gros to the committee selecting the Italian art works that would be removed to Paris. Gros was also commissioned to paint other Napoleonic portraits, the most notable being probably *Napoleon Visiting the Plague Sufferers at Jaffa* (*JAMA* cover, September 12, 1986). Beyond its obvious propaganda message (Napoleon appears as a near-divinity), the painting established Gros as the best colorist of his time. It also established Gros' debt to Rubens, whose Baroque style (which he had studied at the Louvre) he then imbued with his own Romantic leanings. But it is his depiction of Napoleon at Eylau, painted 3 years later, in 1807, that is his masterpiece.

Eylau was a town on the East Prussian border where, on February 7 and 8, 1807, under conditions of extreme cold, some 150 000 men, France and her allies under Napoleon on one side, Russian and Prussian armies on the other, fought a devastating battle. Except for the 50 000 who died, the outcome of the battle was inconclusive. When the Russians retreated during the night, however, France proclaimed itself the victor. Still, reports reached Paris of the appalling carnage and of the poor field medical services among the French that left the wounded to perish of the cold. A master of damage control, Napoleon seized the opportunity to institute a competition for the best painting that would tell the story of the event. Of the 26 painters who competed, Gros won easily with *Napoleon on the Battlefield of Eylau* (cover). From this competition piece he was commissioned to paint the many times larger (25 feet wide as against not quite 6 feet wide) official version for the Louvre.

As in the Jaffa painting, Napoleon is shown as the compassionate leader, concerned for the suffering soldiers. Here they are mostly Russian wounded and dead, but beneficiaries nevertheless of the best French medicine has to offer. In the background Eylau burns. To the right, across the frozen tundra, hundreds of Russian prisoners of war are guarded by French officers; to the left, nearly invisible against the buff-colored earth, are scores of bodies, dead or dying, awaiting transport. Several of Napoleon's commanders surround him, including Joachim Murat, later King of Naples, on the rearing steed. In the right foreground, wearing a red-lined cape (on the border of which Gros has signed the work), is Napoleon's chief surgeon, Dominique-Jean Larrey, the founder of modern military medicine. Here Larrey is shown caring for a terrified wounded man, preparing, perhaps, for a shoulder amputation.

Larrey had originally trained as a naval surgeon, but because he could not tolerate seasickness he transferred to the army. There he became a veteran of some 60 battles and more than 400 engagements. During the Russian campaign of 1812, he performed a record 202 amputations in one 24-hour period. He also devised a nearly bloodless method for amputation through the hip joint, which he could perform in 15 seconds. He himself was wounded three times, the last at Waterloo, where he would have been executed except for the intervention of a former student and a Prussian general whose son's life he had saved in an earlier campaign. Larrey made many other notable contributions to medicine, all of them recorded in his voluminous memoirs. They ranged from observations on the pain-dulling effect of cold to organizational matters. But his major contribution was the conception and introduction of *ambulances volantes*, or "flying ambulances." Instead of the age-old tradition of returning to the battlefield the next day to recover their dead and any wounded not already taken prisoner by the enemy, Larrey proposed a medical carriage that would "follow the advanced guard in the same manner as the flying artillery." Thus, with medical care being brought to the wounded rather than the wounded being brought to medical care, modern military medicine had its first impetus.

Larrey, now Baron, lived until 1842, dying at age 76. Gros, on the other hand, though also Baron, was not so fortunate. With the romance of war gone and public taste preferring classical religious and historical themes once again, Gros' spirits and fortunes declined. On a June day in 1835 he walked into the Seine and drowned. Spin doctor he may have been, but he nevertheless refused to disguise the true horror of war. He left its true record not in the glorious figure of Napoleon, but on the face of each individual foot soldier.

—M. Therese Southgate, MD

Antoine-Jean Gros (Baron Gros) (1771-1835), *Napoleon on the Battlefield of Eylau*, 1807, French. Oil on canvas. 104.9×145.1 cm. Courtesy of The Toledo Museum of Art, Toledo, Ohio; purchased with funds from the Florence Scott Libbey Bequest in memory of her father, Maurice A. Scott.

Biological Weapons and US Law

During the past 8 years, the US Congress has developed a comprehensive legal framework to prevent the illegitimate use of toxins and infectious agents. As part of this framework, Congress has defined as a federal crime virtually every step in the process of developing or acquiring a biological agent for use as a weapon. At the same time, Congress has vested federal law enforcement agencies with broad civil and investigative powers to enable the government to intervene before such weapons are used or even developed. Finally, Congress has directed the Centers for Disease Control and Prevention to establish a regulatory regime to monitor the location and transfer of hazardous biological agents and to insure that any use of such agents complies with appropriate biosafety requirements.

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THE PAST DECADE has witnessed a major shift in the nature and magnitude of the threat posed by biological weapons. For many years, the dangers of such weapons arose solely from the risk of their use in international conflicts. As a result, the class of potential users consisted entirely of a small number of industrialized countries that had developed (or could develop) a biological arsenal for use in warfare.

All this has now changed. In the last 10 years, the class of potential users has expanded to include not only a growing number of developing nations but also a wide range of nonstate actors such as terrorist groups, religious cults, and even individuals.[1,2] Furthermore, many of these new parties now pose a threat of an entirely different kind—the use of biological weapons as agents of terror rather than as instruments of war.[1,2]

The emergence of this threat has carried far-reaching implications for US policy. Where the US government once focused exclusively on preventing other countries from acquiring biological weapons, it now focuses increasingly on the use of such weapons by terrorists and other nonstate actors. Indeed, Congress recently passed 3 major statutes[3-5] in an effort to prevent the use of biological weapons by domestic and international terrorists as well as by nations. In addition, last year, Congress established the framework for a comprehensive regulatory regime to control the domestic use of hazardous toxins and infectious agents. Under this regime, the Centers for Disease Control and Prevention (CDC) regulate the transfer and use of more than 30 toxins, bacteria, and viruses posing significant risks to the public health and safety.

From Northwestern University School of Law, Northwestern University Medical School, and Sonnenschein Nath & Rosenthal, Chicago, Ill.

Reprints: James R. Ferguson, JD, Sonnenschein Nath & Rosenthal, 8000 Sears Tower, Chicago, IL 60606.

CURBING THE ACQUISITION OF BIOLOGICAL WEAPONS BY OTHER NATIONS: THE BIOLOGICAL WEAPONS CONTROL ACT

To understand the goals of the recent legislation dealing with biological weapons, it is first necessary to trace the history of US bioweapons policy since 1972. Until recently, US policy focused almost exclusively on preventing the acquisition and use of biological weapons by other nations. To this end, the US government relied on 3 major strategies. First, the United States entered into a series of treaties and other international agreements designed to achieve biological disarmament and to prevent the proliferation of biological arms to countries that did not yet possess them. Second, the United States imposed economic and diplomatic sanctions on governments that persisted in their efforts to develop a biological arsenal. Third, the United States created an extensive system of export controls to prevent the transfer to other countries of US goods and technologies that could be used in the development of biological weapons.

Until recently, US policy focused almost exclusively on preventing the acquisition and use of biological weapons by other nations.

These strategies originated in 1972 when the United States and more than 70 other nations entered into an agreement known as the Biological Weapons and Toxin Convention (BWC). In Article I of the BWC, the signatory nations pledged that their respective governments would refrain from developing, producing, stockpiling, or acquiring any biological or toxin weapon. In addition, in Article IV of the BWC, the nations pledged that their governments would take all necessary steps to prevent the development or retention of biological weapons by any party within their respective jurisdictions.

In the wake of the BWC, the United States initiated an aggressive arms-control policy to prevent nations from acquiring biological arms and other weapons of mass destruction. The US effort became increasingly important in the late 1980s, as several medium-sized nations (including regional aggressors such as North Korea, Libya, Syria, Iraq, and Iran)

pursued major weapons programs that included chemical and biological arms.[1,2,6,7]

In response to this development, Congress passed the Chemical and Biological Weapons Control Act of 1991.[4] In this act, Congress established an elaborate system of economic sanctions and export controls to curb the proliferation of biological arms. Most notably, Congress created a broad array of economic and diplomatic sanctions to be imposed on any country that used biological weapons in violation of international law. In addition, Congress authorized the imposition of sanctions on international companies that knowingly exported any goods or technologies used in the development of biological weapons to countries designated by the US administration as terrorist states or prohibited nations.

Finally, Congress amended the Export Administration Act of 1979[8]—to prevent US companies and individuals from exporting to certain prohibited countries any goods or technologies that would "directly and substantially assist" a government or group in developing or delivering a biological weapon. By virtue of this amendment, any domestic company or individual who knowingly exported to a prohibited country materials used for biological weapons was subject to civil and criminal penalties, including imprisonment of up to 10 years.

The Biological Weapons Control Act represented a congressional attempt to further the BWC's goal of curbing the transfer of biological weapons to other nations. But for many years after the BWC, the United States had no parallel policy governing the use of biological weapons by groups within its own borders—a parallel policy that had been required by Article IV of the BWC. In fact, until recently, the nation did not have a single law prohibiting the acquisition or use of biological weapons by domestic groups or regulating the domestic sale or transfer of pathogens and toxins.

The need for such legislation became clear in the years following the end of the cold war. During this period, the United States was confronted for the first time by a serious threat of a biological attack on its own soil—a threat that arose not so much from other nations as from subnational groups interested in using biological weapons as instruments of terror.[1,2,7,9,10] These groups included both international terrorists (such as Aun Shinrikyo) and domestic extremists (such as antigovernment groups and right-wing militias).[1,2,6,7]

To address the threat, Congress passed the Biological Weapons Act of 1989[3] and the Anti-Terrorism Act of 1996.[5] In these statutes, Congress attempted to reduce the dangers of bioterrorism in 3 ways. First, the statutes imposed severe criminal penalties on the possession, manufacture, or use of biological weapons. Second, the statutes authorized the federal government to seize any pathogens or other materials used to develop a biological weapon or its delivery system. Third, the statutes created a regulatory system for controlling the use and transfer of hazardous biological agents.

These statutes—and the strategies that underlie them—warrant closer inspection.

CURBING THE DOMESTIC THREAT OF BIOLOGICAL WEAPONS: THE BIOLOGICAL WEAPONS ACT OF 1989

The US Congress passed the Biological Weapons Act of 1989 to implement Article IV of the BWC and to protect the nation against bioterrorist acts.[11] The key provisions of the act define as a federal crime the knowing development, manufacture, transfer, or possession of any "biological agent, toxin, or delivery system" for "use as a weapon."[3] The act broadly defines "biological agent" to include any "microorganism, virus, or infectious substance" capable of (1) causing deleterious changes in the environment; (2) damaging food, water, or equipment supplies; or (3) causing diseases in humans, animals, plants, or other living organisms.[3] Furthermore, the act imposes heavy criminal penalties on those who knowingly violate its prohibitions. Indeed, unlike most other federal criminal statutes (which set forth a maximum period of imprisonment), the act expressly provides that a violator can be imprisoned for any term of years, including life. In addition to its criminal provisions, the act vests the federal government with broad civil and investigative powers to prevent the development, production, or stockpiling of biological weapons. For example, the act authorizes the government to apply for a judicial warrant to seize "any biological agent, toxin, or delivery system" that is "of a type or in a quantity" that has no "apparent justification for. . . peaceful purposes."[3] This standard enables the government to intervene almost immediately after learning of a potential violation of the criminal provisions of the act. Indeed, to effect a seizure under this standard, the government does not even have to show that the materials to be seized are intended for "use as a weapon." Rather, the government need only show that it has probable cause to believe that the materials have no apparent peaceful justification.

. . . prohibiting any party from attempting to develop or possess a pathogen, toxin, or delivery system having no apparent peaceful justification.

The Biological Weapons Act also authorizes the government to obtain a civil injunction prohibiting any party from attempting to develop or possess a pathogen, toxin, or delivery system having no apparent peaceful justification.[3] This provision enables the government to move quickly to prevent the development or production of biological arms even when the evidence is insufficient to pursue a criminal prosecution. Indeed, to obtain an injunction, the government need only show by a "preponderance of the evidence" that a party is attempting to possess a biological agent or delivery system having no apparent legitimate purpose.[3]

By enacting these provisions, Congress enabled the federal government to intervene swiftly before a potential biological weapon could be used to cause injury or environmental harm. At the same time, however, Congress recognized that these provisions, if applied too broadly, could deter scientists and physicians from pursuing legitimate research involving pathogens and toxins—for example, the use of virulent toxins to target cancer cells or the human immunodeficiency virus.[12]

As a result, in the final version of the act, Congress implemented a 2-part strategy to ensure that the criminal prohibitions would not interfere with legitimate research. First, Congress expressly provided that a criminal violation cannot occur unless an individual acquires a pathogen, toxin, or delivery system with the specific knowledge that the material is intended "for use as a weapon." Congress further provided that the phrase "for use as a weapon" does not apply to any use of a biological agent for "prophylactic, protective, or other peaceful purposes."[3]

By including this language (which applies to all nonhostile uses), Congress incorporated a suggestion repeatedly made by representatives of the biomedical community—to place the

burden of proof on the government to establish that an individual intended to use a specific biological agent to cause harm to others.[12] Accordingly, in any prosecution under the act, the government must prove beyond a reasonable doubt that the individual did not intend to use the material for a "peaceful purpose"—a burden of proof that is nearly impossible to carry whenever a scientist, physician, or researcher has a colorable claim of legitimate purpose.

CURBING THE THREAT OF BIOTERRORISM: THE ANTI-TERRORISM ACT OF 1996

In the wake of the Oklahoma City bombing, Congress passed the Anti-Terrorism Act of 1996[5] to provide the federal government with additional tools in the war against domestic terrorism. In this act, Congress conferred on law enforcement agencies a broad range of new investigative, prosecutive, and regulatory powers dealing with biological, chemical, and other weapons.

To begin with, Congress expanded the government's powers under the Biological Weapons Act by amending several key provisions of the earlier legislation. For example, Congress broadened the criminal provisions of the earlier act to reach anyone who "threatens" or "attempts" to develop or use a biological weapon.[5,13] Congress also broadened the same provisions to apply to anyone who uses recombinant technology (or any other biotechnological advance) to create new pathogens or more virulent forms of existing pathogens.[5,13]

The Anti-Terrorism Act also established a new regulatory framework for controlling the use of hazardous biological agents. In particular, Congress directed the CDC to establish a regulatory regime that would identify biological agents posing a threat to public health and regulate the transfer and use of such agents.

To achieve this goal, Congress specified that the CDC should create and maintain a list of biological agents having the "potential to pose a severe threat to public health and safety."[5] Congress further specified that the CDC should select the agents based on several factors, including the effect on human health of exposure to the agent, the contagiousness of the agent, the methods by which the agent is transmitted to humans, and the availability and effectiveness of immunizations and treatments for any resulting illness.[5]

Finally, Congress directed the CDC to establish regulations governing the use and transfer of the restricted agents. Congress specified that the regulations should establish procedures that would protect the public safety and "prevent access to such agents for use in domestic or international terrorism."[4]

In these ways, the Anti-Terrorism Act laid the groundwork for a broad regulatory system governing the acquisition, use, and transfer of biological agents posing a threat to public health and safety. It remained for the CDC to translate this broad statutory command into specific rules and regulations.

THE CDC REGULATORY FRAMEWORK

On April 15, 1997, the CDC's new regulations governing hazardous biological agents went into effect.[14] In drafting the regulations, the CDC sought to accomplish 4 major goals: (1) the identification of biological agents that are potentially hazardous to the public health; (2) the creation of procedures for monitoring the acquisition and transfer of the restricted agents; (3) the establishment of safeguards for the transportation of the restricted agents; and (4) the creation of a system for alerting authorities when an improper attempt is made to acquire a restricted agent.[14]

The Centers for Disease Control and Prevention List of Restricted Agents

- Viruses
  - Crimean-Congo hemorrhagic fever virus
  - Eastern equine encephalitis virus
  - Ebola viruses
  - Equine morbillivirus
  - Lassa fever virus
  - Marburg virus
  - Rift Valley fever virus
  - South American hemorrhagic fever viruses (Junin, Machupo, Sabia, Flexal, Guanarito)
  - Tick-borne encephalitis complex viruses
  - Variola major virus (smallpox virus)
  - Venezuelan equine encephalitis virus
  - Viruses causing hantavirus pulmonary syndrome
  - Yellow fever virus
  - Exemptions: Vaccine strains of viral agents (Junin virus strain candid #1, Rift Valley fever virus strain MP-12, Venezuelan equine encephalitis virus strain TC-83, and yellow fever virus strain 17-D).
- Bacteria
  - *Bacillus anthracis*
  - *Brucella abortus, Brucella melitensis, Brucella suis*
  - *Burkholderia (Pseudomonas) mallei*
  - *Burkholderia (Pseudomonas) pseudomallei*
  - *Clostridium botulinum*
  - *Francisella tularensis*
  - *Yersinia pestis*
  - Exemptions: vaccine strains as described in Title 9 CFR, 78.1.
- Rickettsiae
  - *Coxiella burnetii*
  - *Rickettsia prowazekii*
  - *Rickettsia rickettsii*
- Fungi
  - *Coccidioides immitis*
- Toxins
  - Abrin
  - Aflatoxins
  - Botulinum toxins
  - *Clostridium perfringens* epsilon toxin
  - Conotoxins
  - Diacetoxyscirpenol
  - Ricin
  - Saxitoxin
  - Shigatoxin
  - Staphylococcal enterotoxins
  - Tetrodotoxin
  - T-2 toxin
  - Exemptions: Toxins for medical use, inactivated for use as vaccines, or toxin preparations for biomedical research use at a median lethal dose for vertebrates of more than 100 ng/kg; national standard toxins required for biologic potency testing as described in Title 9 CFR Part 113.

To achieve these goals, the CDC regulations first identify 24 infectious agents and 12 toxins that pose a significant risk to public health[14] (Table). The current list includes 12 types of viruses and 7 bacteria as well as recombinant organisms and any genetic elements from any of the listed agents that produce or encode for a factor associated with a disease.

In addition to identifying hazardous agents, the CDC regulations set forth procedures for identifying all facilities possessing such agents and for insuring that the facilities have appropriate safeguards.[14] The regulations provide that any university, research institution, private company or individual that acquires any restricted agent (or that wants to acquire any agent) must register with the federal government. The regulations further provide that, as part of the registration process, each facility must designate a "responsible facility individual" who will certify that the facility and its laboratory operations meet the appropriate biosafety level requirements for working with the specific agent. To ensure compliance, the regulations authorize the government to inspect the facility to determine if it meets the appropriate biosafety level require-

ments. If the government approves the laboratory, the facility then receives a specific registration number that indicates the facility is authorized to work with the identified agents at the prescribed biosafety level.

The CDC regulations also establish procedures for tracking the transfer of restricted agents from 1 facility to another.[14] The regulations require that, prior to such a transfer, the shipping and receiving facilities must each complete an "official transfer form" that identifies the registration numbers of the shipping and receiving facilities, the name of the relevant restricted agent, and the proposed use and amount of the agent. A copy of the form must then be maintained in a central repository that, while not publicly accessible, is available to both federal and local law enforcement authorities.

The regulations further provide that the responsible facility official at the requesting facility must certify that the requesting researcher is officially affiliated with the facility and that the laboratory meets the appropriate biosafety level requirements.[14] Similarly, the regulations require the responsible facility official at the shipping facility to certify that the receiving facility holds a valid registration number indicating an appropriate biosafety level capability.

The regulations next identify certain clinical uses of restricted agents that are exempt from the regulatory scheme.[14] Under these exemptions, a clinical specimen containing a restricted agent is not subject to regulation if the specimen is intended for diagnostic reference, diagnostic verification, or evaluating the proficiency of diagnostic tests. Any other use, however, is subject to regulation, including any research use.

In addition, the CDC regulations exempt any attenuated strains of restricted agents that have been approved for human vaccination purposes by the Food and Drug Administration. The regulations do apply, however, to all other attenuated, avirulent, or less pathogenic strains of the restricted agents.

Finally, the CDC regulations are enforceable by criminal penalties. In particular, an individual who knowingly makes a false statement on any of the forms required for the registration of facilities or for the transfer of restricted agents is subject to a fine or imprisonment of up to 5 years. In addition, an individual who knowingly violates other provisions of the regulations is subject to a fine of $250 000 and imprisonment of up to 1 year.

CONCLUSION

The effectiveness of recent Congressional legislation enacted to address the threat of biological weapons must remain a matter of intense speculation. But at least 2 features of the recent legislation deserve recognition. First, Congress has erected new barriers to the illicit development and acquisition of biological agents by imposing stringent regulatory controls—including criminal penalties—on the transfer and use of such agents. Second, Congress has enhanced the ability of federal law enforcement agencies to intervene before a biological weapon is used or developed in the United States. In these ways, Congress has reduced the risks of bioterrorism and promoted the public safety in the transfer and use of hazardous biological agents.

James R. Ferguson, JD

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National Health and Medical Services Response to Incidents of Chemical and Biological Terrorism

In response to the growing threat of terrorism with chemical and biological weapons, the US government has developed a national concept of operations for emergency health and medical services response. This capability was developed and tested for the first time during the Atlanta Olympic Games in the summer of 1996. In the event of a chemical or biological terrorist incident that exceeded local and state-level response capabilities, federal agencies would provide specialized teams and equipment to help manage the consequences of the attack and treat, decontaminate, and evacuate casualties. The US Congress has also established a Domestic Preparedness Program that provides for enhanced training of local first-responders and the formation of metropolitan medical strike teams in major cities around the country. While these national response capabilities are promising, their implementation to date has been problematic and their ultimate effectiveness is uncertain.

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THE MARCH 1995 terrorist attack in the Tokyo subway with the chemical nerve agent sarin has provoked growing concern that terrorists could obtain and use chemical or biological agents against civilian targets in the United States and elsewhere. According to Gordon Oehler, director of the US intelligence community's Nonproliferation Center in Washington, DC, "Extremist groups worldwide are increasingly learning how to manufacture chemical and biological agents, and the potential for additional chemical and biological attacks by such groups continues to grow."[1] An incident of chemical or biological terrorism would be a low-probability, high-consequence event that could potentially generate thousands of casualties requiring prompt medical attention; it could also contaminate air, water, and food supplies, posing broader threats to public health. Planning the national response to such an incident is a complex task requiring closely integrated efforts by local, state, and federal governments. Since the consequences of chemical or biological terrorism could rapidly overwhelm local and state health and medical resources, the US federal government is seeking to improve its ability to augment and support local first-responders.[2]

During the Centennial Olympic Games held in Atlanta, Ga, from July 19 to August 4, 1996, US government officials were concerned that terrorists might be attracted to the heavily televised event. With attendance by some 2 million visitors, including more than 40 heads of state, and events at locations throughout the city, it was essential to protect athletes, visitors, and local citizens from a potential terrorist attack.[3] As coordinator of the domestic counterterrorism effort, the Federal Bureau of Investigation (FBI) worked with approximately 40 federal, state, and local agencies in Atlanta to develop an operational concept for response to an incident of chemical or biological terrorism.[4] Such preparations were further refined during the 1996 Republican and Democratic political conventions in Los Angeles, Calif, and Chicago, Ill, and the 1997 Presidential Inauguration in Washington, DC.

LOCAL AND STATE-LEVEL RESPONSES

If a terrorist incident were to result in the release of a lethal chemical agent, local first-responders—firefighters, police, paramedics—would be the first to arrive on the scene, and local hospitals and health care workers would bear the immediate burden of treating casualties. Not all fire departments are trained to deal with hazardous material incidents such as toxic chemical releases and oil spills, but the majority of municipalities have special hazardous materials (HAZMAT) teams equipped with full-body protective suits and self-contained breathing apparatus. Nevertheless, such teams are generally not trained or equipped to detect, identify, or handle chemical warfare agents, which, depending on purity, may be significantly more toxic than industrial chemicals.[5] During the sarin incident on the Tokyo subway, for example, the Tokyo Fire Department sent a total of 1364 personnel to the 16 affected subway stations and other locations. Of these first-responders, 135 (about 10%) were themselves injured by direct or indirect exposure to the poison gas.[6]

Local resources would also be central to any successful response to the terrorist use of a biological agent. An overt biological attack would require an emergency response similar to that needed in the chemical case. A more likely contingency, however, would be the covert, unnoticed release of a biological agent, which would require local hospitals and public health systems to have the capability to rapidly detect unusual disease outbreaks and begin prompt effective treatment of large numbers of exposed individuals.

If the consequences of a terrorist incident in the United States outstripped local capabilities, the state emergency management agency would be notified and commence support activities. The state governor might decide to call up the National Guard to provide medical, decontamination, transportation, and other support services unavailable from other sources. For example, National Guard and US Army Reserve component forces around the country include a total of 43 chemical defense units.[7] Nevertheless, most National Guard units require between 12 and 24 hours to mobilize to an armory and prepare to deploy to the incident site.[8] In case of a no-warning chemical terrorist attack, such units would arrive on the scene too late to be of immediate medical assistance, although they could provide se-

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curity, communications, decontamination, and other services helpful in safe and effective cleanup after the attack.

It is likely that the terrorist use of a weapon of mass destruction in a large metropolitan area that generated major health and medical consequences would overwhelm the capabilities of many local and state governments almost immediately. In this case, the state governor could request the federal government to provide emergency support including specialized expertise, equipment, and resources. Because the arrival of specialized federal response units could be delayed for several hours, however, prompt medical treatment will inevitably be the responsibility of local first-responders.

NATIONAL LEVEL RESPONSES

The general framework for the federal government response to terrorist incidents is provided by Presidential Decision Directive 39 (PDD-39), United States Policy on Counterterrorism, signed by President Clinton on June 21, 1995. While this directive does not provide a detailed concept of operations, it defines broad responsibilities and coordination relationships among responsible federal agencies.[9] For all cases of domestic terrorism, PDD-39 assigns the FBI lead responsibility for crisis management, meaning measures to resolve a hostile situation and investigate and prepare a criminal case for prosecution under federal law. The Federal Emergency Management Agency (FEMA) is the lead agency for coordinating federal consequence management assistance to state and local governments, including emergency relief to affected individuals and businesses, decontamination of the affected area, and measures to protect public health and safety and to restore essential government services (Figure 1).[9]

Under PDD-39, other federal agencies (including the US Departments of Defense, Energy, Transportation, Agriculture, and Health and Human Services, and the Environmental Protection Agency) have been designated to provide operational support to the FBI or FEMA as required. For example, the terrorist release of a chemical or biological agent would require technical operations involving sophisticated capabilities for dealing with hazardous materials that exceed the resources of local HAZMAT teams. Such operations include measures to identify and assess the threat posed by the hazardous material, to neutralize the material, and to decontaminate exposed individuals and the environment. The lead agency for technical operations would depend on the type of hazardous material involved and the location of the incident.[9]

Forensic Sample Analysis

During the Atlanta Olympic Games, the FBI recognized the need to establish on-site a tactical capability to assess, detect, monitor, collect, and preserve evidence in the event of a chemical or biological terrorist incident, backed up by a forensic laboratory containing sophisticated analytical instruments. To this end, the Hazardous Materials Response Unit within the FBI's Scientific Analysis Section in Quantico, Va, established a forensic laboratory at the Chamblee Environmental Health campus of the Centers for Disease Control and Prevention (CDC), some 20 miles from the Olympics. Known as the Science and Technology Center, the laboratory was staffed at any one time by between 50 and 75 government chemists and biologists.[4] Arrangements were made for backup and confirmatory analyses by outside centers (Figure 2). (Special capabilities for assessing nuclear threats were also prepositioned in Atlanta.)

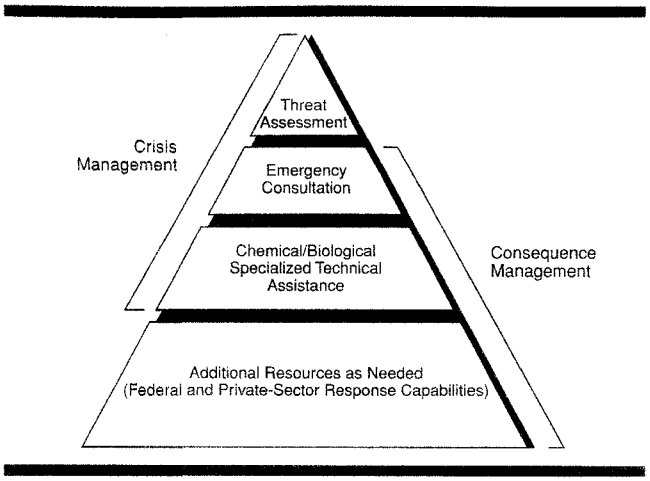

Figure 1.—Federal chemical/biological response concept.

To support the Science and Technology Center, a tactical unit known as the Chemical/Biological Response Team was stationed at Dobbins Air Force Base in Marietta, Ga. Headed by an FBI supervisory special agent, this team consisted of members of the army Technical Escort Unit and experts from the FBI Laboratory Division and the FBI Evidence Response Team. The team was on call 24 hours a day. In the event of a chemical or biological terrorist incident, team members wearing full protective gear would fly to the scene in helicopters, assess the incident, collect and preserve evidence, and ferry samples to the Science and Technology Center for analysis.[4]

When a pipe bomb went off in Centennial Olympic Park on July 27, 1996, killing 2 and wounding more than 100, the sample-collection plan was modified because of concern that the arrival of a sampling team in "moon suits" would trigger widespread panic. Since chances were low that the bomb had been tainted with chemical or biological agents, FBI agents not wearing protective gear quietly collected samples of shrapnel, soil, and clothing and transported them to the Science and Technology Center. Within 5 hours of receiving the samples, the forensic scientists stated confidently that no biological or chemical warfare agents were present.[4] During the Republican Convention in San Diego and the Democratic Convention in Chicago, these analytical capabilities were replicated on a smaller scale using mobile laboratories and field sample collection kits.

Consequence-Management Activities

After learning that an incident of chemical or biological terrorism had occurred, FEMA would use its emergency powers to notify the president and seek a presidential disaster declaration; FEMA would also inform the federal agencies and begin coordinating the delivery of federal assistance. To this end, the FEMA director would consult with the governor of the affected state to determine the scope and extent of the incident. Concurrently, the president, under the authority of the Robert T. Stafford Disaster Relief and Emergency Assistance Act (the Stafford Act), would designate a federal officer to coordinate the federal response. Then FEMA would assemble an emergency response team made up of representatives from each of the primary federal agencies and deploy it to the incident site to establish a disaster field office and begin operations.[9]

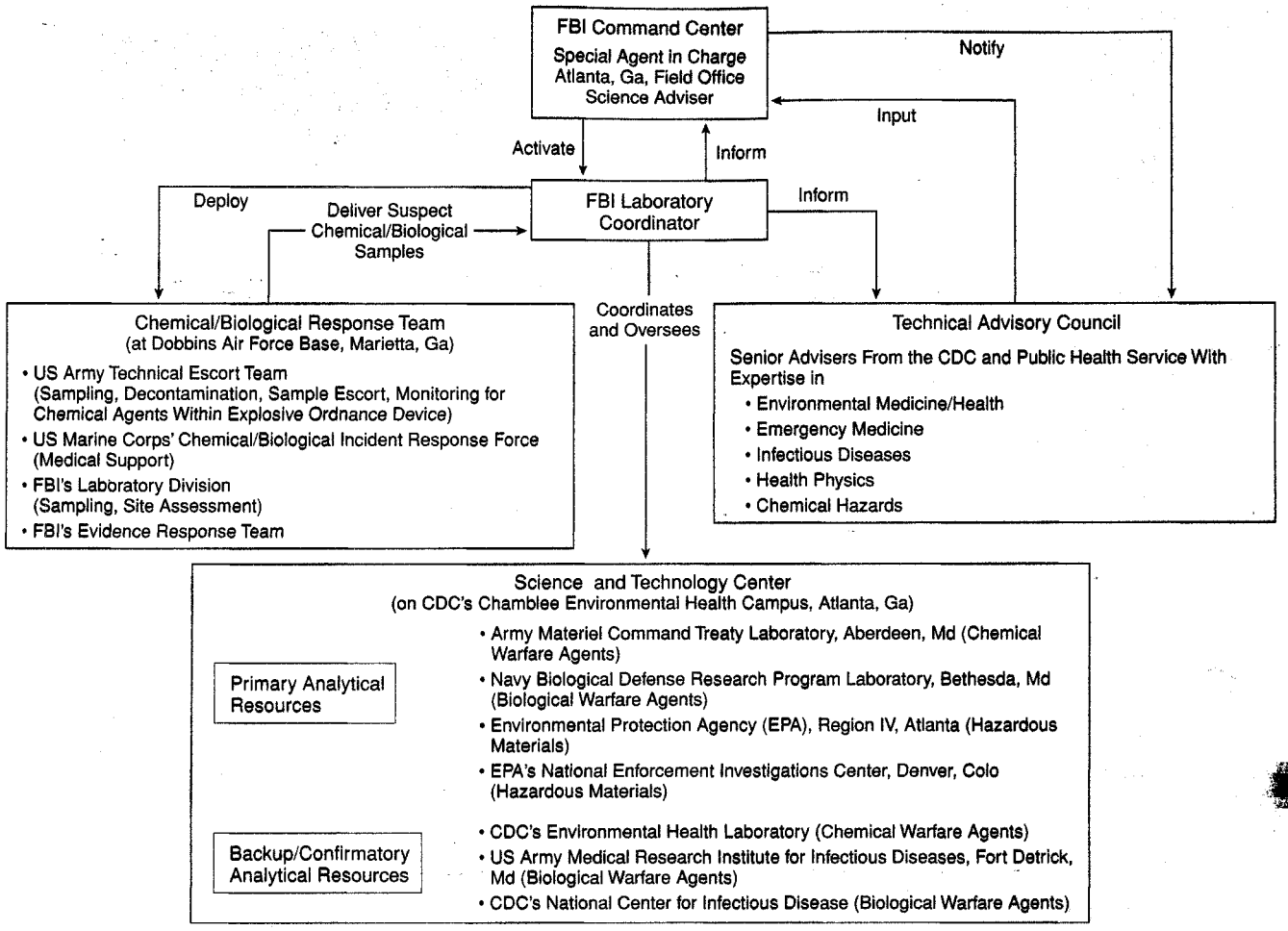

Figure 2.—Federal analytical capabilities deployed at the 1996 Summer Olympic Games in Atlanta, Ga (from Ember[4]). FBI indicates Federal Bureau of Investigation; and CDC, Centers for Disease Control and Prevention.

In coordinating federal consequence-management assistance to state and local governments, FEMA would rely largely on procedures contained in the Federal Response Plan. Published in 1992, this plan was developed by 27 federal departments and agencies and the American Red Cross for major natural or man-made disasters. The Federal Response Plan identifies 12 primary areas, or emergency support functions, where federal support may be necessary in a disaster relief operation. Each of these 12 functions is assigned to a lead federal agency, which coordinates operations within its area of expertise. For example, emergency support function 8, "health and medical services," is the responsibility of the US Public Health Service (of the Department of Health and Human Services [DHHS]).[9]

In June 1996, FEMA delivered to President Clinton an annex to the Federal Response Plan detailing the procedures for responding to incidents of nuclear, biological, or chemical terrorism in areas where state and local capabilities either do not exist or are inadequate to handle the incident.[10] This annex specifies interim emergency arrangements and coordinating structures that would be implemented rapidly before more traditional Federal Response Plan measures—involving the deployment of heavy assets and large numbers of people—could be put in place.[11] However, the extent to which these federal responses would remedy state and local shortfalls in a timely manner is unclear.

Role of the Department of Health and Human Services

The DHHS is the lead agency under the Federal Response Plan for the provision of health, medical, and health-related social services.[12] In the event of a chemical or biological terrorist incident, the Public Health Service would be primarily responsible for patient care, the delivery of medical equipment and supplies, health surveillance in the affected area, and managing the health consequences of environmental contamination (Figure 3). The Public Health Service would activate the National Disaster Medical System (NDMS), which delivers direct medical care to disaster survivors in the field. The NDMS has 3 major components: prehospital treatment, hospital evacuation, and in-hospital care. Prehospital treatment is provided by disaster medical assistance teams (DMATs), which are teams of about 37 medical personnel including physicians, nurses, paramedics, emergency medical technicians, and other medical specialists who are responsible for first aid, casualty clearing, medical staging, and field surgical intervention.[13]

A chemical or biological terrorist incident might differ from an ordinary disaster in the requirement for specialized emergency medical care, the time urgency of the response, and the

need to gather evidence to support a criminal investigation. For example, an attack with a chemical nerve agent would require immediate treatment of casualties with atropine and/or other antidotes, while a biological attack would require specialized antibiotics such as ciprofloxacin hydrochloride and doxycycline or antivirals such as ribavirin. These medications are not currently available in sufficient quantities at local or regional hospitals to treat the survivors of a large-scale terrorist incident.[12]

To address the specific demands for health and medical services entailed by an incident of chemical or biological terrorism, DHHS has prepared a Health and Medical Services Support Plan for the Federal Response to Acts of Chemical/Biological Terrorism.[12] This plan assigns the Public Health Service's Office of Emergency Preparedness the lead role within DHHS for the implementation and coordination of health and medical assistance. Various federal agencies would support DHHS in implementing the plan. For example, the Food and Drug Administration would be responsible for managing stockpiles of antidotes and pharmaceuticals.

To respond to the specific medical demands of chemical or biological terrorism, the Public Health Service has organized enhanced disaster medical assistance teams, which receive specialized training and would be activated regionally or nationally and deployed to the scene of a terrorist incident within 12 hours.[12] Casualties would be evacuated from the affected area to a network of preenrolled hospitals in major metropolitan areas. The NDMS system comprises 72 federal coordinating centers that oversee more than 118 000 private-sector beds.[11] To augment this capacity, hospitals operated by the military services, the US Department of Veterans Affairs, and DHHS would be made available as needed.[12] Disaster mortuary teams would provide victim identification and mortuary services for the dead.[11]

DHHS has also established a specialized, multiagency medical response team known as the Chemical-Biological Rapid Deployment Team (CBRDT), which is based in the Washington, DC, area and was deployed in Atlanta during the Olympics. Led by the Public Health Service, the CBRDT consists of about 25 medical and technical specialists provided by DHHS, the Department of Defense, the Environmental Protection Agency, and the Department of Energy. This team would deploy rapidly to the site of a terrorist incident and provide medical support to the on-scene manager.[12]

Role of the Department of Defense

The Department of Defense would participate in the federal response to an incident of biological or chemical terrorism by providing technical assistance, bomb disposal, decontamination, security, and other services to federal, state, and local authorities.[14] A defense coordinating officer would be appointed as the on-scene representative to coordinate military support requirements with FEMA and the other federal agencies. Because the Posse Comitatus Act (Title 18, Section 1385, of the US Code) strictly limits the use of US military forces to execute civil and criminal law, Department of Defense support to state and local authorities must be provided by military and civilian personnel who are not armed and do not engage in domestic law enforcement activities unless properly authorized by the president. The US Departments of Justice and Defense are currently developing regulations for military support during emergency operations involving weapons of mass destruction.[8]

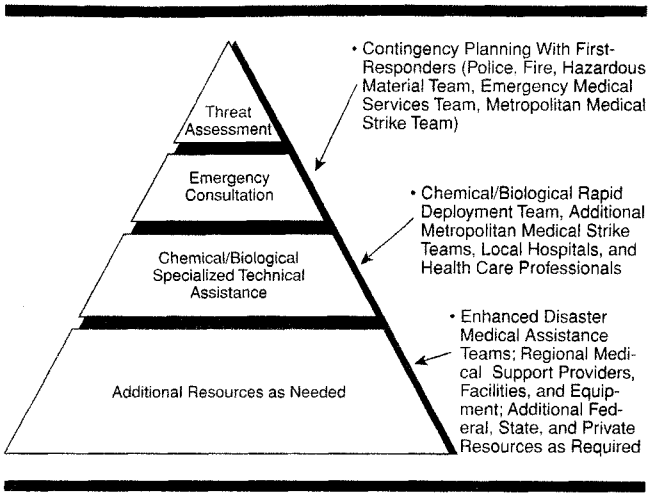

Figure 3.—US Department of Health and Human Services consequence-management actions.

In April 1996, the US Marine Corps established a new Chemical/Biological Incident Response Force (CBIRF) based at Camp Lejeune, NC. This unit consists of approximately 350 US Navy and Marine Corps personnel divided into the following 6 elements: command and control, reconnaissance, decontamination, medical, security, and service support. On notification of a chemical or biological terrorist incident, the CBIRF would deploy to the affected site by the most expeditious means possible.[15] Although its primary mission is to respond to terrorist incidents at US Navy and State Department installations worldwide, the CBIRF can also be called on in domestic incidents to provide direct support to local authorities and the Office of Emergency Preparedness. The CBIRF was activated on April 4, 1996, and was forward deployed to Atlanta a week before the Olympics began.[16] During the games, the unit served as a ready reaction force, adviser to local, state, and federal agencies, and participant in several exercises.[17]

In the event of an incident of chemical or biological terrorism, the CBIRF's medical unit of 6 medical officers and 17 marine corpsmen would enter the contaminated area and provide immediate lifesaving medical treatment to those who were injured and exposed. Since rapid evacuation of individuals from the contaminated area would be impossible in a mass-casualty situation, corpsmen would place over each exposed individual's head a socklike gas mask that has a viewport and an air filter to prevent inhalation of additional toxic material. Individuals who had stopped breathing would receive respiratory support from portable autoventilators. Once the casualties were medically stabilized, they would be decontaminated with warm water, sponged with 0.5% bleach solution, and rinsed off under showers. Decontaminated patients would then be dried, clothed in hospital garb and blankets, and evacuated in buses to local hospitals along with a sufficient supply of antidotes to ensure their continued medical stabilization. Those in critical condition would receive immediate care from the unit's shock/trauma platoon, which can provide patient stabilization for 72 hours.[18]

The medical unit of the CBIRF could also draw on outside expertise. One of the medical corpsmen who enters the contaminated incident site can carry a lightweight, miniaturized videocamera on the outside of his gas mask. Through the use of a satellite uplink, a video image of the scene can be transmitted in near real time to a remote location. This capability

allows outside experts to observe the incident scene and advise on-scene physicians on the treatment of casualties, particularly if they manifest symptoms that are not immediately identifiable.[19]

The CBIRF also has an advisory group of 9 civilian medical and scientific experts headed by biochemist Joshua Lederberg, PhD, and under the command of the US Marine Corps Security Force.[16] Members of this group carry pagers and laptop computers so they can connect to the Internet from any location. In the event of a terrorist incident, members of the advisory group would log on to the Internet and access a password-controlled homepage providing information on the incident. The group members would then conduct an interactive conference to discuss issues of containment, medical diagnosis and management, and controlling risk. Use of special software would make it possible to mark up photos of exposed individuals and lesions and maps of the incident site. According to Lederberg (written communication, June 1997), "as the CBIRF becomes better coordinated with USPHS and the CDC they will have less need for the advisers, and it is very unlikely that they would ever be deployed."

High-profile public events such as the Olympics, political conventions, a presidential inauguration, or state visits are the least demanding contingencies for consequence management, since federal emergency-response units can be prepositioned at the site to ensure maximum readiness in the event of a terrorist incident. During the Atlanta Olympics, for example, extensive preparations were made to predeploy enhanced disaster medical assistance teams and to stockpile antidotes. Plans were also made for the treatment and evacuation of those exposed to a terrorist attack.

In the event of a no-warning chemical attack in a US city, however, elite federal units such as the CBIRF would require 4 hours plus air time to deploy to the incident scene. By the time such teams arrived, the incident would be effectively over, with those exposed either dead or evacuated to hospitals. For this reason, the Marine Corps admits that "CBIRF is most effective when forward deployed in response to a credible threat to domestic or overseas installations, or to protect events of national significance from the consequences of chemical-biological incidents."[20] The only way a federal response team could get to the scene of a terrorist attack in a timely manner would be if the perpetrators provided advance warning or if reliable intelligence of an impending attack were available, but it would be imprudent to count on either of these assumptions. Elite federal response teams would also be too limited in size and capabilities to treat thousands of prompt casualties from a major chemical attack or to handle multiple, simultaneous terrorist events. For these reasons, primary responsibility for emergency health and medical services lies inevitably with local first-responders, including police, firefighters, paramedics, and hospital emergency department physicians.

Whereas the consequences of a chemical terrorist attack would be acute and immediate, those of a biological attack would be delayed for several hours or days, by which time the affected population could be widely dispersed. Thus, although prompt medical treatment would be crucial to saving those exposed during a covert biological-agent attack, early detection of a covert biological attack would be problematic. High-profile events such as a presidential inauguration can be accompanied by intensified monitoring of air and water to detect microbial or toxin agents, together with epidemiologic surveillance for unusual disease outbreaks that might be associated with a clandestine biological attack. Yet if an incident of biological terrorism were to occur without warning in a US city, no biological warfare specific monitoring or surveillance mechanisms would be in place. It would therefore be necessary to rely on existing public health systems—including the astute observations of local hospital and private-practice physicians—to detect a suspicious disease outbreak in time to initiate effective treatment. At present, capabilities for timely detection of unusual disease outbreaks vary greatly from city to city.

Current Federal Efforts

With the view that the United States currently lacks adequate planning and countermeasures to address the threat of chemical, biological, or nuclear terrorism, the US Congress enacted the Defense Against Weapons of Mass Destruction Act of 1997. Subtitle A of this act, on domestic preparedness, directs the president to enhance the capability of the federal government to prevent and respond to terrorist incidents involving weapons of mass destruction; it also directs the Department of Defense to develop and implement a domestic preparedness program to improve the ability of local, state, and federal agencies to cope with these threats and to conduct exercises and preparedness tests.[21] Congress appropriated approximately $52.6 million for activities under this section in fiscal year 1997.[8]

In response to the new legislation, the Department of Defense is establishing a multiservice Chemical/Biological Quick Response Force to rapidly assess the site of a terrorist incident and coordinate additional military support. Based at the army's Chemical and Biological Defense Command headquarters in Aberdeen, Md, the Chemical/Biological Quick Response Force may eventually include up to 500 troops. In a terrorist emergency, the force would take charge of specialists normally assigned to other units, including the Marine Corps' CBIRF and the army's Technical Escort Unit.[22]

A major focus of the Domestic Preparedness Program is on training local police, firefighters, medical personnel, and other first-responders, together with an integrated exercise program. Field exercises have demonstrated that these individuals are often poorly trained and equipped to respond to incidents of chemical or biological terrorism and that local response planning is inadequate. For example, on April 11, 1995, less than a month after the Tokyo sarin incident, New York City conducted an unrehearsed, no-warning exercise involving a simulated chemical attack on a subway station to determine the collective ability of the city's emergency services to respond. At about 7 PM, a report of an explosion and fire at a subway station at East 14th Street and 1st Avenue was broadcast over emergency radio frequencies. Fire, police, and emergency medical units arrived at the scene to find "victims" lying unconscious on the mezzanine level of the subway station. Observing no smoke and unaware that "poison gas" was present, firefighters and police officers entered the station without protective gear and, in an actual incident, would have become casualties themselves.[23] Had the incident been real and had a persistent chemical agent (such as VX or sulfur mustard) been used, ambulances, taxis, and hospital emergency departments would have rapidly become contaminated, resulting in secondary exposure of hospital workers and patients.

To help prepare first-responders to cope with the unique hazards of chemical and biological terrorism, the Department of Defense has been designated to lead interagency training

teams to major US cities. Training modules will cover the identification of chemical and biological agents, decontamination, evacuation, and emergency medical assistance.[7] The Public Health Service and other federal agencies are also cooperating with major cities to establish metropolitan medical strike teams. Each team has approximately 35 members, including physicians, basic and advanced life-support specialists, logistics support personnel, and mental health professionals, who are on call 24 hours a day.[12] In the event of a chemical or biological terrorist incident, the team would be summoned by the local, regional, or federal government to help manage the medical and public health consequences. Four of the teams will be regional teams capable of being deployed to support emergency response operations in other states.

Experience with 2 teams in Atlanta and Washington, DC, which were established to support the 1996 Summer Olympics and the 1997 Presidential Inauguration, indicates that the formation and training of each team could take between 6 and 12 months.[8] Every team will also operate within a "system," an integrated set of capabilities that ensures safe patient transportation to hospital emergency departments, provision of definitive medical and mental health treatment, and evacuation of patients to other regions should local health care resources be insufficient to meet demand.[8] Under the new legislation, the Department of Defense is funding the Public Health Service to assist local governments in the initial planning and development of teams and related systems, procurement of special antidotes and pharmaceuticals, initiation of special equipment procurements, and training of selected personnel. By the end of 1999, federal officials plan to establish teams in the nation's 120 largest cities. Yet the Department of Defense has stated that it intends to provide no funding for the program beyond fiscal year 1997, raising the question of whether the necessary resources will be available.[8]

Among other support activities, the Department of Defense is setting up an urgent hotline and a nonurgent helpline to provide expert technical advice on chemical and biological hazards to local and state officials. FEMA is also compiling a master inventory of equipment and assets owned by federal agencies that could be made available to state and local officials in a terrorist emergency.[8]

Despite these plans, however, much effort will be required to enhance the preparedness of local first-responders, even in Washington, DC. An unscheduled test of the response capabilities in the nation's capital occurred on the morning of April 14, 1997, when the mailroom at the headquarters of B'nai B'rith, a national Jewish service organization, received a padded manila envelope containing a petri dish marked with the scientific term for anthrax, along with a threatening letter. Since the petri dish was filled with a red, gelatinous substance that could have been hazardous, Washington, DC, police, FBI, and Secret Service officials sealed off the area and quarantined more than 100 employees inside the building for more than 8 hours. In addition, 14 fire and emergency personnel who had come in contact with the package were decontaminated at the site. Analysis of the suspicious material at Bethesda Naval Medical Center later revealed that it was not life threatening.[24]

Although the B'nai B'rith incident proved to be a hoax, it revealed serious weaknesses in the city's response to chemical and biological terrorism. A gelled biological agent poses no hazard except through direct contact, but it was conceivable that a toxic chemical agent was present. Thus, instead of keeping the employees quarantined inside the building for hours and possibly exposing them to a hazardous material, it would have made more sense to move them to another location and keep them under observation until the results of the sample analysis were known. A senior B'nai B'rith official said, "It is inexcusable for police and fire personnel in a city which is so vulnerable to terrorist incidents to not have the highest level of training and appropriate resources for dealing with situations as potentially deadly as this."[24]

CONCLUSIONS AND RECOMMENDATIONS

Although the terrorism annex to the Federal Response Plan and the Domestic Preparedness Program provide a solid basis for enhancing the national health and medical services response to chemical and biological terrorism, several important deficiencies remain to be addressed. The following recommendations for augmenting the national response to chemical or biological terrorism could be implemented with an additional expenditure of about $100 million per year.

- *Current ad hoc capabilities for the forensic analysis of hazardous materials associated with terrorist incidents should be further refined and institutionalized.* Since the federal agencies that participated in the Science and Technology Center at the Atlanta Olympics have other primary responsibilities and missions, the US government should establish a team of analytical chemists and biologists dedicated to the counterterrorism mission, perhaps under the auspices of the new Chemical/Biological Quick Response Force. In particular, every terrorist incident involving an explosive device should be accompanied by a routine analysis for chemical or biological contaminants.
- *Federal agency officials should elaborate more detailed coordination plans.* In particular, there is a need to develop and exercise transitional arrangements from the FBI to FEMA and from the CBIRF to other specialized federal response teams that would manage the longer-term consequences of a chemical or biological terrorist attack. Improved coordination is also required between federal response teams and state and local first-responders.
- *Public information campaigns should be prepared in advance of a terrorist incident.* To minimize the spread of chemical contamination or infectious disease, it is important to prevent people from panicking and fleeing the area. To this end, the Public Health Service should prepare public service announcements for radio and television broadcast during an incident of chemical or biological terrorism, informing citizens about the nature of the threat, the likely symptoms, and what they should do to minimize exposure or seek treatment. In the case of the B'nai B'rith incident, the lack of an effective public communications strategy led to inaccurate press reports and considerable confusion.
- *The federal government should develop and distribute appropriate detection equipment and protective gear for first-responders.* State and local first-responders should be equipped with relatively simple, inexpensive, portable, and user-friendly systems for detecting and identifying chemical and biological agents, as well as individual protective gear, ventilators for supportive care during treatment, and mass casualty decontamination systems. Military equipment may have to be modified or redesigned for civilian use and to meet the safety standards imposed by the Occupational Safety and Health Administration. Particularly lacking are portable systems for the prompt sampling and identification of biological

agents that could be released by terrorists in an urban environment. Some promising biological detection technologies, such as chip-based arrays of DNA probes and optical sensors, are currently under development.[25] Future congressional appropriations for the Domestic Preparedness Program should earmark additional support for the development of improved biological detection systems and for the procurement and distribution of detection and protection equipment to first-responders.

• *The Public Health Service and the Food and Drug Administration should establish stockpiles of necessary medical equipment, nerve agent antidotes, and broad-spectrum antibiotic and antiviral drugs in major metropolitan areas to ensure the prompt treatment of casualties in the event of an incident of chemical or biological terrorism.* Since pharmaceuticals have a finite shelf life, emergency planners will need to weigh the costs and benefits of distributed vs centralized repositories. Ultimately, such decisions will require a political assessment of acceptable risk.

• *Conflicts between the delivery of emergency medical assistance and the collection of forensic evidence must be addressed.* The site of a chemical or biological terrorist incident would be both a crime scene and a disaster area. Procedures should be developed so that urgent lifesaving operations by first-responders can proceed without destroying crucial pieces of evidence or disrupting the chain of custody of evidence needed for successful criminal prosecution. Where a conflict is unavoidable, saving human lives and ensuring the safety of investigators and emergency workers must take precedence.

• *Decentralized early warning systems to detect covert biological terrorism should be put in place around the country.* An improved epidemiologic surveillance system involving state and local public health officials, emergency department personnel, and national organizations such as the CDC would alert the FBI about suspicious outbreaks of disease that might be linked to biological terrorism. To strengthen this system, the CDC should provide grants to the states to hire additional field epidemiologists. Continuing medical education courses should be established to familiarize infectious disease specialists and general practitioners with the signs and symptoms of anthrax infection, tularemia, Q fever, brucellosis, and other biological warfare–related diseases that they would not normally encounter in their routine medical practice.

• *Training programs for first-responders should be designed to be multipurpose rather than highly specialized so that they are considered worthwhile regardless of how one assesses the threat of chemical or biological terrorism.* Enhanced infectious disease surveillance systems would also be multipurpose, serving to improve public health in the face of natural emerging infections as well as increasing vigilance against biological terrorism. Indeed, the health care savings from enhanced disease surveillance may exceed the costs by a substantial margin. By devising policies that provide social benefits independent of their value in managing the consequences of a terrorist incident, it should be easier to build political coalitions in support of these measures.

In summary, an effective national response to incidents of chemical or biological terrorism will require the improved integration of local, state, and federal capabilities. Although the current federal program provides a reasonable initial basis for action, its ultimate value will depend on how well it is implemented at the state and local levels.

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The Complementary Role of Environmental and Security Biological Control Regimes in the 21st Century

As we approach the 21st century, there is increased worldwide concern about disease, whether natural or deliberate, in humans, animals, and plants. There are 2 driving forces for multilateral biological control regimes: international/national security and environmental protection. With respect to deliberately caused disease, these seemingly disparate forces are mutually reinforcing as demonstrated by simultaneous moves to strengthen the Biological and Toxin Weapons Convention and the entry into force of the Convention on Biological Diversity. Future multilateral biological control regimes based on these developments will aid the security, prosperity, and health of the world community.

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WITH THE APPROACH of the 21st century, there is increased concern worldwide about disease, whether natural or deliberate. The director general of the World Health Organization (WHO) stated in the 1996 World Health Report[1] entitled *Fighting Disease, Fostering Development*, "we also stand on the brink of a global crisis in infectious diseases. No country is safe from them. No country can any longer afford to ignore their threat." As the world population continues to increase, new areas of land are occupied, and overcrowding is resulting in ever greater demands for both plants and animals as sources of food, providing more opportunities for new or old diseases to spread in humans, animals, or plants with damaging socioeconomic effects to the countries involved. Disease has caused more casualties in all wars than the actual weapons of war,[2] and there is increasing worldwide concern about new and emerging diseases.[3] On September 24, 1996, President Clinton said in his address[4] to the United Nations General Assembly that "we must better protect our people from those who would use disease as a weapon of war." Deliberate disease or biological warfare is of real concern; its prevention is central to the health and well-being of the global community. In the simplest sense, biological warfare is disease deliberately induced in humans, animals, or plants as a hostile act.

The past decade has also seen a greater worldwide awareness of the need to protect the environment. The United Nations Conference on Environment and Development in Rio de Janeiro in 1992 (the Earth Summit) proclaimed a set of principles and adopted Agenda 21. It also opened for signature the Convention for Biological Diversity (CBD) and the Convention on Climate Change.[5,6] The health and well-being of the global community (humans, livestock, and crops) directly affect prosperity and trade. Thus, it is in everyone's interests to ensure that disease, whether natural or deliberate, is countered. There are 2 driving forces to ensure that potentially hazardous biological materials are not misused—one stemming from national and international security considerations and the other from the recognition of the need to protect the environment. This article examines the prospects for these seemingly disparate driving forces being jointly harnessed in a system of transparent controls that builds confidence for a safer and more secure world in the 21st century.

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SECURITY CONCERNS

Arms Controls

It might be thought that with the Geneva Protocol of 1925, which prohibits the use in war of biological (bacteriological) weapons, and the Biological and Toxin Weapons Convention (BWC) of 1972 prohibiting the development, production, acquisition, and stockpiling of biological weapons, that there would be minimal security concerns about deliberate disease or biological warfare. This is not the case. Indeed, the deliberate use of disease is recognized by some analysts as the major security concern relating to weapons of mass destruction.

First, the Geneva Protocol is effectively a prohibition of first use; some signatories to the Geneva Protocol maintained their right to retaliate in kind should biological warfare be used against them. Although many nations have given up their right to retaliate, some still maintain them. It was this uncertainty about the prohibition of use that led Iran[7] at the Fourth Review Conference of the BWC to propose a formal amendment[8] to include the word "use" in the title and to amend article I to include the use of biological weapons. The final declaration[9] of the conference, however, made it clear that any use would be a violation of the BWC.

Second, the BWC has no provisions for verification of compliance. This shortcoming has been recognized by the BWC states parties. (When a treaty has been agreed, it is opened for signature. Signatory nations undertake to do nothing contrary to the aim of the treaty. The treaty enters into force when an agreed number of countries have ratified the treaty. Countries that have both signed and ratified the treaty are known as states parties. Once a treaty has entered into force, it is legally binding on all states parties but not on signatory nations. Subsequently, other countries, including signatory nations, can ratify or accede to the treaty and become states parties.) At the Second Review Conference in 1986 the states parties agreed to politically binding confidence-building measures; these were strengthened and extended at the Third Review Conference in 1991. However, after 10 years, slightly more than half of the 140 states parties have made a single annual declaration and only about 11 have made the required annual declaration—the requirement to do so is not legally binding and hence not mandatory. There has been much variation in the quality of the information declared. Also at the Third Review Conference, an Ad Hoc Group of Governmental Experts (known as VEREX [verification experts]) was mandated to examine potential verification measures from a scientific and technical viewpoint. The final report of VEREX was considered by a special conference

in 1994 that mandated another Ad Hoc Group (AHG) to consider possible measures for a legally binding instrument to strengthen the BWC. This AHG has had 6 substantive meetings; 2 in 1995, 2 in 1996, and 2 so far in 1997. Thus far, the legally binding instrument is likely to include mandatory declarations, on-site investigations, and measures addressing the transfer of materials and technology. The Fourth Review Conference encouraged the AHG to review its method of work and to move to a negotiating format; this should happen in July 1997. When the AHG completes its work, a special conference will need to be convened to consider its report, and—assuming adoption of the legally binding instrument—it will then be a matter for individual states parties to accede to this. Consequently, it will be some time before the majority of BWC states parties have acceded to the legally binding instrument.

. . . biological weapons are sometimes referred to as the poor man's atomic bomb . . .

Finally, when other weapons of mass destruction (nuclear and chemical weapons) are considered, the shortcomings of the BWC are thrown into sharp relief. Comparisons of the effects of biological, chemical, and nuclear weapons have long been made.[10-13] These analyses demonstrate that the effects from a biological warfare attack are much greater than those from a chemical warfare attack and can also be as great as if not greater than those resulting from a nuclear attack. It is for that reason that biological weapons are sometimes referred to as the poor man's atomic bomb; the costs associated with a biological weapons program are much less—and are being reduced further by the advances in microbiology and biotechnology—than those for a nuclear weapons program. With the indefinite extension of the Nuclear Non-Proliferation Treaty in 1995, the opening for signature of the Comprehensive Test Ban Treaty in 1996, and the entry into force on April 29, 1997, of the Chemical Weapons Convention with its intrusive verification regime, it is evident that there is an urgent need to strengthen the regime for the third class of weapons of mass destruction, the BWC.

Concern about the proliferation and potential acquisition of biological weapons in the changing world of the 1990s is justified. At the Fourth Review Conference of the BWC, John Holum concluded, "Overall, the United States believes that twice as many countries now have or are actively pursuing offensive biological weapons capabilities as when the Convention went into force."[14] This concern has been underlined by the admission by Russia that the former Soviet Union had continued an offensive biological weapons program up to 1992. The former Soviet Union, along with the United Kingdom and the United States, was a codepository (ie, maintains the record of which nations have signed, ratified, or acceded to a treaty and may also be responsible for dealing with proposals for amendment of the treaty) of the BWC. Investigations to determine that this program has indeed terminated continue.[15] Further concern arises from the extent of the Iraqi biological weapons program, which has been disclosed through the efforts of the United Nations Special Commission (UNSCOM).[16]

Although there is a perception that for verification to be worthwhile, it needs to guarantee that a prohibited program would be detected, this is inaccurate. The UNSCOM experience has demonstrated that even in a situation in which Iraq was clearly seeking to retain a capability, compliance concerns could be readily identified through inconsistencies in the information available to UNSCOM. The work of the AHG to strengthen the BWC through a regime of mandatory declarations, on-site investigations, and transfer measures recognizes that such a regime would contribute to deterrence of would-be proliferators, and it would be effective without unreasonable demands on the legitimate medical and biotechnology communities. After all, these communities in the developed world are increasingly being regulated and monitored to allay public concerns about the hazards associated with the materials being studied. Enhanced transparency of the activities of such communities contributes both to public confidence and to international security.

A further dimension also has to be addressed. The possibility that biological materials may become attractive to nonstate actors, splinter groups, or terrorists cannot be discounted. The incidents in the Tokyo subway in March 1995 in which the Aum Shinrikyo sect used nerve gas has heightened international awareness of such dangers.[17,18] Subsequent reports made it clear that the Aum Shinrikyo sect had started by working on developing biological weapons, that these had been their weapon of choice, and that they were close to completing work in March 1995.[17,18] The Aum Shinrikyo sect also sent a team to Zaire in 1992 to assist in the treatment of individuals infected by Ebola, and it is claimed that its aim was to obtain a sample of Ebola virus to take back to Japan for culturing purposes. The Tokyo incident shows all too clearly the potential impact of such attacks.

The dangers of terrorist use of biological weapons was underlined by the G7/8 heads of state meeting in Lyon, France, on June 27, 1996, when they stated that "special attention should be paid to the threat of utilization of nuclear, biological and chemical materials, as well as toxic substances, for terrorist purposes."[19]

An example of a counter to such terrorist use is the US Antiterrorism and Effective Death Penalty Act of 1996, which requires both the regulatory control of biological agents and the regulation of transfers of listed biological agents.[20] Insofar as the regulatory control of biological agents is concerned, the secretary to the US Department of Health and Human Services is required to "establish and maintain a list of each biological agent that has the potential to pose a severe threat to public health and safety" and on transfers, to enact regulations for "(1) the establishment and enforcement of safety procedures for the transfer of biological agents listed . . . including measures to ensure (*a*) proper training and appropriate skills to handle such agents; and (*b*) proper laboratory facilities to contain and dispose of such agents; (2) safeguards to prevent access to such agents for use in domestic or international terrorism or for any other criminal purpose; (3) the establishment of procedures to protect the public safety in the event of a transfer or potential transfer of a biological agent in violation of the safety procedures established under paragraph 1 or the safeguards established under paragraph 2; and (4) appropriate availability of biological agents for research, education and other legitimate purposes." The proposed rules published in the *Federal Register* are comprehensive.[21]

The final declaration of the Fourth Review Conference recognized "the need to ensure, through the review and/or adoption of national measures, the effective fulfillment of their obligations under the Convention in order, inter alia, to exclude use of biological and toxin weapons in terrorist or criminal activity." The declaration stated that states parties "should also consider ways and means to ensure that individuals and subnational groups are effectively prevented from acquiring, through transfers, biological agents and toxins for other than peaceful purposes."

Export Controls

Article III in the BWC requires that "each State Party to this Convention undertakes not to transfer to any recipient whatsoever, directly or indirectly, and not in any way to assist, encourage, or induce any State, group of States or international organizations to manufacture or otherwise acquire any of the agents, toxins, weapons, equipment or means of delivery specified in Article I of the Convention." While this is a national responsibility, there are international arrangements that seek to harmonize and coordinate such controls. The principal international arrangement relating to transfers of biological materials (such as anthrax) and dual-purpose equipment (such as fermenters and spray driers) is the Australia Group. This group was founded in 1985 to constrain the trade in the technologies and materials of chemical warfare. The Australia Group was created in response to the rapid proliferation of chemical weapons during that period, their use in the Iran-Iraq war, and the long process of negotiating the Chemical Weapons Convention. In 1990, its scope was extended to include biological weapons, and in 1991, 1992, and 1993, the group finalized a set of lists of controlled technologies and materials relevant to biological weapons. Since then, the work of the Australia Group has focused on implementation and enforcement. There are now some 30 participating nations.[22]

Such export monitoring and controls are frequently alleged to inhibit trade despite the absence of evidence to support this assertion.[23] On the contrary, the United States in its statement to the Fourth Review Conference noted[14] that in 1995 while they had "approved well over $250 million dollars in export license applications relevant to the Convention, we denied applications worth a grand total of $2443." The evidence is that export monitoring and controls are indeed trade enablers.[24] There is no evidence that such monitoring and controls have had any harmful effect on international biomedical research.

Although the regime relating to Iraq arising from the 1991 United Nations (UN) Security Council Resolution 687 is a special one, it is relevant in considering what biological regimes might be appropriate for the future.[25] Security Council Resolution 687 requires among other things that a plan be developed for future ongoing monitoring and verification to ensure that Iraq does not develop, construct, or acquire any of the items specified in the proscribed weapons of mass destruction programs. These plans were prepared and approved by the UN Security Council in October 1991.[26] They were complemented in March 1996 by another resolution, which approved an export/import monitoring mechanism to ensure that Iraq does not reconstitute its programs for weapons of mass destruction. This mechanism requires prior notification by all nations as well as by Iraq of any items identified in the plans for ongoing monitoring and verification.[26-28] Should an item be found in Iraq that should have been notified, this would constitute a case of noncompliance.The strong presumption would be that the item had been procured for prohibited purposes and so would be subject for disposal by UNSCOM and the International Atomic Energy Agency.

Thus, all states have agreed to implement a system in which notifications are made to a monitoring unit at the UN headquarters of any planned imports to Iraq of any items identified in comprehensive lists of biological weapons materials and dual-purpose equipment. The system has been designed so that it "will not impede Iraq's legitimate right to import or export for non-proscribed purposes, items and technology necessary for the promotion of its economic and social development."[28] This export-import mechanism provides a model for a multilaterally agreed system based on prior notifications and backed by on-site monitoring and verification, thus providing confidence that imported materials are indeed being used for permitted purposes.

Environmental Controls

The past decade has seen an increasing awareness of the importance of protecting health and the environment. This was highlighted by the holding of the UN Conference on Environment and Development (the Earth Summit) in Rio de Janeiro in June 1992, which saw the adoption of a set of principles, Agenda 21, and the opening for signature of the Convention on Biological Diversity (CBD).[6] The principles are amplified in a series of chapters and program areas that include chapter 16, "Environmentally Sound Management of Biotechnology," which has a section on "enhancing safety and developing international mechanisms for cooperation."[29] This section also states that "there is a need for further development of internationally agreed principles of risk assessment and management of all aspects of biotechnology, which should build upon those developed at the national level. Only when adequate and transparent safety and border-control procedures are in place will the community at large be able to derive maximum benefit from, and be in a much better position to accept the potential benefits and risks of, biotechnology." The desirability of transborder controls was echoed in the legally binding CBD, which entered into force in December 1993. Paragraph 3 of article 19 on "Handling of Biotechnology and Distribution of its Benefits" states that "the Parties shall consider the need for and modalities of a protocol setting out appropriate procedures, including in particular advance informed agreement in the field of the safe transfer, handling, and use of any living modified organism resulting from biotechnology that may have an adverse effect on the conservation and sustainable use of biological diversity."[6]

In November 1995 an open-ended Ad Hoc Working Group was set up to negotiate in "the field of the safe transfer, handling and use of living modified organisms, a protocol on biosafety, specifically focusing on transboundary movement, of any living modified organism resulting from modern biotechnology that may have adverse effect on the conservation and sustainable use of biological diversity, setting out for consideration, in particular, appropriate procedure for advance informed agreement."[30] The working group's first meeting was held in July 1996 when an advance informed agreement procedure was identified as a key component of the protocol.[24] The Third Conference of Parties to the Convention on Biological Diversity held in Buenos Aires, Argentina, on November 4-15, 1996, urged the Ad Hoc Working Group on Biosafety to complete its work on developing a protocol in 1998 as a matter of urgency; 2 further meetings of the Ad Hoc Working Group are to be held in 1997.

It is thus apparent that the negotiations are proceeding apace to develop a protocol to ensure that living modified organisms are handled safely and are used and transferred without danger to human health and to the environment. These negotiations parallel similar moves being taken to negotiate a legally binding Prior Informed Consent Convention to control trade in banned or severely restricted chemicals so as to ensure that such potentially hazardous chemicals are not misused. A prior informed consent procedure is already being operated voluntarily by national authorities in 148 countries.[31] These negotiations are now well advanced and are likely to be completed at a meeting to be held in Rotterdam, the Netherlands, before the end of 1997.

FUTURE BIOLOGICAL CONTROL REGIMES

In considering biological control regimes for the future, it is instructive to look back over the developments in both security and environmental controls. While security controls have developed gradually during the past 70 years, with increased attention being given to both biological arms and export controls during the past 5 years since the Persian Gulf War of 1990-1991, environmental controls, although starting later than security controls, have received greater attention and made faster progress since 1992. Security and environmental considerations are both important. They share a common aim of ensuring transparency in the use and transfer of biological materials, thereby building confidence that such materials are not being misused.

The AHG is considering existing and enhanced transparency and confidence-building measures, compliance measures, and measures to ensure effective and full implementation of peaceful uses of microbiology. The objective is to devise an integrated protocol incorporating a balance of measures that will be efficient and effective in strengthening the BWC. It is already clear that attention will be given to measures to strengthen the undertaking in the BWC "not to transfer to any recipient whatsoever, directly or indirectly, and not in any way to assist, encourage, or induce any state, group of states, or international organizations to produce or acquire biological weapons" while not impeding the undertaking to promote the peaceful uses of microbiology and biotechnology.

At the Fourth Review Conference there appeared to be a readiness to accept that states parties are required to implement a system of monitoring and controls of transfers of materials and equipment relevant to the BWC. The nonaligned states called for a system multilaterally agreed between the states parties of the BWC. When the requirements arising from Agenda 21 for adequate and transparent safety and transborder procedures, the agreed export-import mechanism for notification of exports to Iraq, and the measures for the legally binding instrument for the BWC are considered, it would appear that the basic ingredients for a system are already available. Those working on the BWC protocol need to work with those developing on the advance informed agreement protocol to produce a transparent system using these existing ingredients to meet the requirements of the BWC and to protect the environment and public health. Such a system will be to the mutual advantage of all nations; cooperative action to minimize the risks from deliberate and natural disease will aid the security and prosperity of the world community.

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Pentagon-Funded Research Takes Aim at Agents of Biological Warfare

LAST spring, mail-room workers at the Washington, DC, headquarters of the B'nai B'rith Jewish service organization discovered a leaking package. The contents: a broken petri dish, its label indicating that it harbored deadly anthrax bacteria.

In the wake of this discovery, more than 100 employees were quarantined in their offices for about 9 hours. Several city blocks were sealed off, while authorities and emergency personnel evaluated the situation. Some workers exposed to the unknown agent underwent an emergency decontamination process that involved stripping to their underwear in public to be sprayed with a bleach-and-water solution.

Some hours later, however, tests revealed that the incident was a hoax: The petri dish contained only common bacteria that posed no threat. But the affair and other recent events have underscored a growing sense of vulnerability to attacks by terrorists or rogue nations wielding biological weapons rather than bombs.

Department of Defense

Researchers are investigating more innovative ways to safeguard against biological weapons than unwieldy protective suits and face masks.

An Increasing Threat

After the 1991 Persian Gulf conflict, revelations about the extent of Iraq's biological weapons program made clear to military officials just how unprepared the United States and its allies were to deal with bioweapons. Such agents have also piqued the interest of terrorist and fringe groups because they are relatively inexpensive to make and require materials that are fairly easy to acquire. Aum Shinrikyo, the apocalyptic cult responsible for the March 1995 sarin gas attack on the Tokyo subway system that killed a dozen people and injured about 5000 others, also had a large biological weapons program involving such agents as anthrax and botulinum toxin.

In these instances, the military, police, or emergency personnel would have been unable to quickly detect potentially devastating biological agents and block their effects in exposed individuals. And although the Department of Defense (DoD) is working with officials in the 120 largest US cities to develop and train metropolitan medical strike teams to provide the emergency medical response after a terrorist attack, it became clear to the military that more innovative approaches were needed to detect biological agents and prevent soldiers and civilians exposed to them from becoming ill.

Not quite 2 years ago, such concerns sparked interest at the Defense Advanced Research Projects Agency (DARPA), a DoD agency that has been funding defense-related engineering and electronics projects for 3 decades. With a $2 billion budget, the agency—described as "the venture capitalists of government-funded research" by a scientist who is happily engrossed in antipathogen research funded by the agency—has both the desire and the financial clout to back "revolutionary" ideas for military defense.

The move into biological research is a new one for DARPA, which funded seminal research leading to such advances as the development of a computer network that was a forerunner to the Internet, stealth technology, and a field called microelectromechanical systems, or MEMS, that applies the same processes used to make silicon chips to build tiny mechanical structures like the sensors used in automobile airbags.

DARPA officials are applying the same approach to foster the development of innovative technology for detecting and neutralizing biological weapons—providing seed money, a lot of it, for ideas that "are revolutionary rather than evolutionary," said CDR Shaun B. Jones, MC, USN, project manager for the agency's new unconventional pathogens countermeasures program.

"In general, DARPA attacks problems that are *really* hard," said Jane Alexander, PhD, deputy director of the agency's defense sciences office. Coming up with new ways to detect and defend against biological agents presents a formidable challenge, she added.

President Clinton's proposed budget for FY 1998 earmarks $61.6 million for DARPA's biological weapons defense research, which includes work aimed at developing computer software tools to help in managing the consequences of a bioweapons attack; sensors to detect the presence of pathogens and biological toxins in the environment; diagnostics technology to quickly identify the cause of illness in a stricken individual; and the development of novel ways to prevent infection or shore up the body's ability to block the effects of pathogens and toxins.

"And we expect the budget will continue to grow," said Alexander.

Although DARPA focuses only on projects that target defense against biological warfare and terrorism, any success from such work has important implications for the problem of emerging microbial infections arising from "natural" causes. The need to quickly identify the cause of a disease outbreak, prevent its spread, and treat those stricken is the same whatever the source of the infection.

"The concerns raised by biological and chemical agents are real and significant," said Steve Kornguth, PhD, of the University of Wisconsin, Madison, who is leading an effort to investigate ways to short-circuit viral infections. "But while we're funded to do military research, the spin-off of this work obviously also has enormous applications for emerging infections."

In fact, because DARPA provides seed money rather than conducting research itself, the agency fully expects that useful discoveries will be carried forward by others—researchers in academia, government, and industry—who recognize their value for nonmilitary purposes. The agency won't fund clinical trials for a promising therapeutic agent, for example.

"If there's value there, we expect that industry will take it up," said Jones. Instead, he noted, the agency sees itself as an incubator of daring ideas—ambitious, high-risk projects that may fail because they break unknown ground but, if they pay off, open up vast new possibilities.

"We're seeking those ideas that can make a significant advance in pathogen defense," said Jones, advances with the impact of, say, the advent of antibiotics, the polymerase chain reaction, or mass spectrometry.

Canary on a Chip

DARPA is focusing some of its resources on encouraging the development of environmental sensors—unmanned, remote-controlled mobile laboratories with an array of detectors to identify a large number of agents. Ideally, such devices should be able not only to distinguish hazardous live pathogens from their dead counterparts but also to detect the presence of potentially deadly bioengineered organisms created by outlaw nations or terrorist groups.

One project, a 21st-century version of the caged canaries used by miners to signal the presence of hazardous gases, uses nerve cells grown on silicone chips that monitor the cells' responses to neurotoxins in the environment. Another effort involves linking specific antibodies to a range of pathogens and toxins to chemicals that will fluoresce different colors, providing rapid information about whether such agents are present on the battlefield or elsewhere.

The agency also recently sent out a call for research proposals for a new program in advanced diagnostics, aimed at developing techniques that will allow clinicians to rapidly identify exposure or infection with significant pathogens.

"Most of the early symptoms caused by organisms used in biological warfare look just like a case of flu," said Stephen S. Morse, PhD, who will direct efforts in this program. Identifying as quickly as possible whether patients with such symptoms as fever, headache, or chills have a life-threatening infection or something more benign is essential to offering optimal treatment and protecting others.

Infection Protection

Although vaccination is the best current defense against pathogens that medical science has to offer military troops in the field, existing vaccines offer protection against only a few of the potential hazards. Adding to the concern is the possibility that hostile forces could engineer and deploy new genetically engineered organisms.

To tackle this problem, a DARPA program called "unconventional pathogens countermeasures" is plowing millions of dollars into projects aimed at improving defenses against multiple agents by gaining a better understanding of how pathogens attack the body. Last year the agency's 2 calls for proposals for research contracts totaling $50 million drew more than 250 responses. Awards went to researchers at universities and foundations, as well as biotechnology and pharmaceutical companies.

Rather than trying to find defenses against specific organisms, "we're trying to find disease processes that are fundamental to virulence, to try to turn them off," said Alexander.

For example, microbiologist Stanley Falkow, PhD, of Stanford University School of Medicine, Stanford, Calif, and other investigators have found that bacteria, particularly gram-negative enteric organisms such as cholera and salmonella, use similar mechanisms to transport virulence factors that enable such bugs to overwhelm normal host defenses. With DARPA's backing, he and his colleagues are investigating whether drugs that interfere with this mechanism can offer broad-spectrum protection against multiple pathogens.

Other researchers are seeking new ways to fight biological agents by enhancing the body's own immune system to fight such devastating pathogens as arenaviruses, alphaviruses, and filoviruses. David Scadden, MD, and colleagues at Harvard Medical School, Boston, Mass, are attempting to develop a multipronged approach, from identifying substances made by cytotoxic T lymphocytes that might be able to incite broad antiviral defenses immediately after exposure to a pathogenic virus, to genetically engineering hematopoietic stem cells as prophylaxis for troops entering areas where bioweapons may be used.

Yet another project is aimed at developing some remarkable tools for gathering fundamental knowledge about how pathogens attack cells—technology that conventional funding agencies judged too speculative to back but that may allow researchers to peer inside a single cell to study how pathogens affect normal cell function.

A research team led by physical chemist Raoul Kopelman, PhD, of the University of Michigan, Ann Arbor, is developing minute optical sensors that can be implanted into a single cell to report how the cell's biochemistry changes in response to various stimuli. The goal is to enable scientists to monitor such changes, as they occur, in response to events such as the invasion of a cell by a virus.

One of the most appealing aspects of DARPA's willingness to generously fund audacious proposals, Kopelman said, is that scientists applying for limited biomedical research funds are reluctant to propose projects they fear will be judged too speculative to merit support.

"Some of the work that reviewers [of grant proposals] thought was too speculative has already been published [in the technical literature]," he said.

Blood Scrubbing

One project that has stirred considerable interest is a strategy to use red blood cells to sweep up pathogens in the bloodstream and ferry them to the liver to be phagocytosed and destroyed. This approach, which is being developed by physical chemist Ronald Taylor, PhD, and colleagues at the University of Virginia, Charlottesville, involves using a bispecific polymer with a monoclonal antibody on each end: One antibody targets a particular protein on the surface of red blood cells called complement receptor, or CR1, while the other nabs the pathogen of choice.

Taylor and his colleagues have demonstrated in monkeys that the technique successfully removed huge quantities of a model virus from the blood to the liver within 90 minutes, without apparent adverse effects to blood or liver. Having demonstrated "proof of principle" in model systems, the group is currently turning its attention to a number of pathogens that could be used in biological warfare.

The group's ultimate goal is to determine whether the technique will offer a means of passive immunization or serve as a therapy for acute infections associated with pathogens in the circulation. "We hope to initiate human studies in less than 2 years," Taylor said.

Kornguth and colleagues at the University of Wisconsin are looking for ways to derail viral infection during the window between exposure and local replication of virus in the mucosa and the subsequent spread to such secondary target sites as the nervous system, liver, or kidney. Their strategy involves identifying and synthesizing compounds that temporarily and selectively block the virus from entering cells, inhibit the transport of substances needed by the virus to mature and replicate, and interfere with chaperone proteins that play a role in folding and packaging the viral components into mature viruses, explained Kornguth.

Skin Creams and Milk Shakes

Other investigators are working on strategies that would serve as barriers between exposure to pathogens and infection. In one such endeavor, a team of researchers led by James R. Baker, Jr, MD, chief of the Division of Allergy at the University of Michigan Medical

School , Ann Arbor, is studying 2 novel materials to be applied to the skin and mucous membranes or swallowed in a "milk shake" to prevent pathogens and toxins from attacking the body.

One of the materials is a group of lipid vesicles that disrupts the surfaces of viruses, bacteria, and bacterial spores through a detergentlike action, said Baker. The second material uses tiny polymer-based molecules called "dendrimers" coated with substances that enable them to attach selectively to bacteria, viruses, and toxins and block their entry into cells.

So far, toxicity testing in animals indicates that the substances are remarkably "biofriendly" to mammalian cells, while in vitro studies show a million-fold decrease in infectious organisms for up to 96 hours, with no regrowth.

"We're very hopeful about these materials—at the very least, they could be used as decontaminants," said Baker, who envisions such possibilities as cleansing an area contaminated with Ebola virus or sanitizing hospitals harboring antibiotic-resistant bacteria.

DARPA officials and researchers agree that working on projects funded by the agency is far different from conducting biomedical research funded by traditional sources, such as foundations or the National Institutes of Health.

"We tend to spend more money on a project than NIH or the Howard Hughes [Medical Institute]," said Jones, with grants ranging from $200 000 to $2 million to $3 million per year. "But our expectations are higher, too."

Grant recipients agree, noting that DARPA project managers are frequently in touch, offering suggestions and asking about the latest data.

"They call me about every week, but I think that's probably a good thing," said Baker, whose project is receiving $10.8 million from the agency over a 4-year period. "They expect a return on their investment."

—by Joan Stephenson, PhD

Physician Group Declares War on Land Mine Injuries

PHYSICIANS Against Land Mines (PALM)—a not-for-profit organization of health care professionals and other self-defined "people of conscience"—is establishing a center for the prevention and treatment of land-mine injuries.

Land mines are deployed in more than 60 countries around the world, according to a PALM spokesperson. Each year at least 1 million additional land mines are sown, and each year another 25 000 men, women, and children are killed or maimed by these devices.

"We urgently need an immediate and comprehensive ban on these weapons and expanded access to treatment," said William Kennedy Smith, MD, president of the Chicago–based organization and a staff physician at the Veterans Administration Chicago Health Care System—Lakeside Division, in a recent interview. "The United States should be the first country to respond [to the problem]."

To advance the medical care of land mine survivors, PALM will work with international experts in cooperation with 2 other Chicago-based institutions, the Rehabilitation Institute of Chicago and Northwestern University Prosthetics/Orthotics Education Center and Research Laboratory, to create improved protocols for postoperative care and rehabilitation. The center will directly assist land-mine survivors and help educate and train health care workers from the United States and abroad to work with them. In countries where mines have been planted, there is dire need for appropriate, low-cost artificial limbs and community-based rehabilitation programs, Smith said.

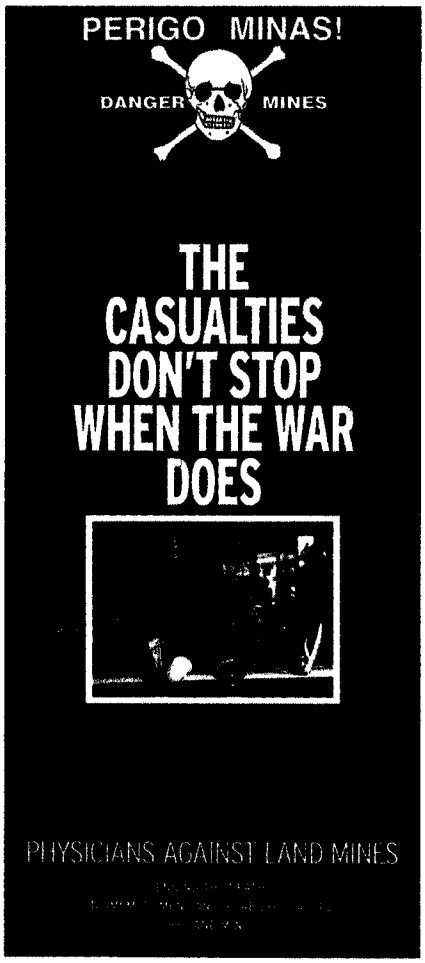
PALM is also working to persuade the United States to join the more than 150 nations that support the elimination of what the International Campaign to Ban Landmines calls "weapons of mass destruction in slow motion."

On June 21, PALM held a press conference in conjunction with a special 2-hour educational seminar during the American Medical Association's (AMA) annual House of Delegates meeting in Chicago. At the press conference, Smith and other seminar speakers called on President Bill Clinton to join representatives from more than 100 countries at a conference to be held in Ottawa, Ontario, in December. The purpose of the meeting is to draw up a treaty banning the manufacture, stockpiling, transfer, and use of antipersonnel land mines.

Prevention, Treatment Update

The seminar held in June, entitled "Land Mines: Epidemiology and Response," brought together several medical groups and international medical experts for an update on the prevention and treatment of injuries caused by the devices. It was sponsored by PALM in cooperation with the AMA, Physicians for Human Rights, American Public Health Association, Physicians for Social Responsibility, and International Physicians for the Prevention of Nuclear War.

Seminar speakers included Robin M. Coupland, MD, coordinator of surgical services for the Medical Division of the International Committee of the Red Cross; Scott R. Lillibridge, MD, associate director for emergency, refugee, and international health at the Centers for Disease Control and Prevention, Atlanta, Ga; Smith, who specializes in rehabilitation medicine, prosthetics, and the care of amputees; and Ken Rutherford, a land-mine survivor who is cofounder of the Landmine Survivors Network. Rutherford lost both legs after being severely injured by a land mine while working on an international relief mission in Somalia in 1993.



Philippe Dutoit/Sipa Press

Information brochure distributed by PALM.

A Large Community Outbreak of Salmonellosis Caused by Intentional Contamination of Restaurant Salad Bars

Thomas J. Török, MD; Robert V. Tauxe, MD, MPH; Robert P. Wise, MD, MPH; John R. Livengood, MD; Robert Sokolow; Steven Mauvais; Kristin A. Birkness; Michael R. Skeels, PhD, MPH; John M. Horan, MD, MPH; Laurence R. Foster, MD, MPH†

Context.—This large outbreak of foodborne disease highlights the challenge of investigating outbreaks caused by intentional contamination and demonstrates the vulnerability of self-service foods to intentional contamination.

Objective.—To investigate a large community outbreak of *Salmonella* Typhimurium infections.

Design.—Epidemiologic investigation of patients with *Salmonella* gastroenteritis and possible exposures in The Dalles, Oregon. Cohort and case-control investigations were conducted among groups of restaurant patrons and employees to identify exposures associated with illness.

Setting.—A community in Oregon. Outbreak period was September and October 1984.

Patients.—A total of 751 persons with *Salmonella* gastroenteritis associated with eating or working at area restaurants. Most patients were identified through passive surveillance; active surveillance was conducted for selected groups. A case was defined either by clinical criteria or by a stool culture yielding *S* Typhimurium.

Results.—The outbreak occurred in 2 waves, September 9 through 18 and September 19 through October 10. Most cases were associated with 10 restaurants, and epidemiologic studies of customers at 4 restaurants and of employees at all 10 restaurants implicated eating from salad bars as the major risk factor for infection. Eight (80%) of 10 affected restaurants compared with only 3 (11%) of the 28 other restaurants in The Dalles operated salad bars (relative risk, 7.5; 95% confidence interval, 2.4-22.7; $P<.001$). The implicated food items on the salad bars differed from one restaurant to another. The investigation did not identify any water supply, food item, supplier, or distributor common to all affected restaurants, nor were employees exposed to any single common source. In some instances, infected employees may have contributed to the spread of illness by inadvertently contaminating foods. However, no evidence was found linking ill employees to initiation of the outbreak. Errors in food rotation and inadequate refrigeration on ice-chilled salad bars may have facilitated growth of the *S* Typhimurium but could not have caused the outbreak. A subsequent criminal investigation revealed that members of a religious commune had deliberately contaminated the salad bars. An *S* Typhimurium strain found in a laboratory at the commune was indistinguishable from the outbreak strain.

Conclusions.—This outbreak of salmonellosis was caused by intentional contamination of restaurant salad bars by members of a religious commune.

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OUTBREAKS of foodborne infection are caused by foods that are intrinsically contaminated or that become contaminated during harvest, processing, or preparation. It is generally assumed that such contamination events occur inadvertently; intentional contamination with a biologic agent is rarely suspected or reported.[1,2]

On September 17, 1984, the Wasco-Sherman Public Health Department in Oregon began to receive reports of persons ill with gastroenteritis who had eaten at either of 2 restaurants in The Dalles, Ore, several days before symptom onset. Local and state public health officials confirmed an outbreak of *Salmonella* Typhimurium associated with the 2 restaurants and then noted an abrupt increase in reports of gastroenteritis the following week among persons who had eaten or worked at other restaurants in The Dalles. Because many patients reported eating food from salad bars, the local health department closed all salad bars in the town on September 25, 1984, and the Oregon Health Division requested assistance from the Centers for Disease Control (CDC) for further evaluation and control of the outbreak.

The epidemiologic investigation identified the vehicles of transmission as foods on multiple self-service salad bars and probable times when contamination occurred. Common mechanisms by which salad bars could have become contaminated were excluded. A subsequent criminal investigation found that members of a nearby religious commune had intentionally contaminated the salad bars on multiple occasions.

BACKGROUND

The Dalles, population 10 500 (1980 census), is the county seat of Wasco County, population 21 000, a region of orchards and wheat ranches. Located near the Columbia River on Interstate 84, The Dalles is a frequent stop for travel-

From the National Center for Infectious Diseases and Epidemiology Program Office, Centers for Disease Control and Prevention, Atlanta, Ga (Drs Török, Tauxe, Wise, Livengood, and Horan and Ms Birkness); and the Oregon Health Division, Portland (Messrs Sokolow and Mauvais and Drs Skeels and Foster). Dr Wise is now with the US Food and Drug Administration.

†Deceased.

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Trade names are used for identification only and does not imply endorsement by the US Department of Health and Human Services or the US Public Health Service.

Reprints: Thomas J. Török, MD, Centers for Disease Control and Prevention, Mailstop G-17, 1600 Clifton Rd NE, Atlanta, GA 30333.

ers. Two independent water systems serve The Dalles: a smaller system supplied by a well and a larger system that serves most restaurants and uses surface water augmented by well water during the summer. From 1980 through 1983, only 16 isolates of salmonellae were reported by the local health department; 8 isolates were *S* Typhimurium. No case of salmonellosis was reported in the first 8 months of 1984.

In 1981, followers of Bhagwan Shree Rajneesh purchased a large ranch in Wasco County to build a new international headquarters for the Indian guru.[3-5] Construction of the commune was controversial from its inception; cultural values and land-use issues were the major areas of conflict. Part of the ranch was incorporated as the city of Rajneeshpuram, but the charter was challenged in the courts, effectively limiting new construction. Commune members believed that the outcome of the November 6, 1984, elections for Wasco County commissioners would have an important impact on further land-use decisions.[3-5]

METHODS

Case Definition

A case was defined as an illness with diarrhea and at least 3 of the following symptoms: fever, chills, headache, nausea, vomiting, abdominal pain, or bloody stools, or by a stool culture yielding *S* Typhimurium. A patient was considered to have had an outbreak-associated case if onset of symptoms or collection of an *S* Typhimurium–positive stool specimen occurred between September 9 and October 10, 1984, and the patient resided in or had visited The Dalles during that interval. A case in a person who ate at a restaurant in The Dalles within 7 days before the onset of illness or who worked at a restaurant in The Dalles was considered to be a restaurant-associated case. A single restaurant exposure (SRE) denotes that only 1 restaurant exposure occurred during the 7 days before onset of symptoms. A case was considered to be secondary if it occurred in an individual who had not eaten or worked at a restaurant in The Dalles in the 7 days before onset of symptoms, but was exposed to a case patient during that interval.

The 38 restaurants in The Dalles were divided into 3 groups based on the number of culture-confirmed case customers with an SRE. Group 1 restaurants were definitely affected and had at least 3 culture-confirmed case customers with an SRE. Group 2 restaurants were possibly affected and had at least 1 case customer with an SRE, but fewer than 3 culture-confirmed case customers with an SRE. Group 3 restaurants were not affected and had no case customers with an SRE.

Outbreak Investigation

Cases were identified through passive surveillance. Press releases encouraged reporting by case patients and health care professionals. We interviewed possible case patients about symptoms and risk factors and obtained comprehensive food histories for restaurant meals eaten during the 3-day period before onset of symptoms. Case customers with an SRE were asked to identify all other persons with whom they had eaten at the restaurant. Histories were obtained from persons so identified, and those who were not ill and reported no other restaurant exposure served as controls for food-specific case-control analyses. Potentially exposed cohorts, such as banquet participants and take-out food patrons, were identified from restaurant records, and attempts were made to interview these persons.

Employees of group 1 restaurants were interviewed twice. During the outbreak, investigators interviewed employees when restaurant involvement was first suspected. In October 1984, immediately following the outbreak, all employees were asked to complete a self-administered questionnaire. Work schedules were obtained from review of time cards, interviews with restaurant managers, and review of insurance claims for workers' compensation.

Laboratory Methods

Stool specimens were submitted to local and regional laboratories to be cultured for enteric pathogens. Employees from group 1 restaurants were required to submit a stool sample to be cultured or be excluded from work. Ill employees with a single negative stool specimen were required to submit a second stool specimen for confirmation before returning to work. The Oregon Public Health Laboratory and the Washington Public Health Laboratory serotyped human *Salmonella* isolates and performed antibiotic-susceptibility testing on a sample of isolates. A representative sample of outbreak isolates, based on epidemiologic criteria, was submitted to CDC for further biochemical characterization and plasmid profile analysis with restriction endonuclease digestion, using *Hin*dIII.[6,7] The Oregon Public Health Laboratory also submitted *S* Typhimurium isolates from other outbreaks and sporadically occurring cases, collected during 1984 and thought to be unrelated to the outbreak, to CDC for comparison with the outbreak strain by plasmid analysis. The Oregon Department of Agriculture and the Oregon Public Health Laboratory cultured suspected foods.

The Dalles outbreak strain was compared with human isolates included in 2 national surveys of salmonellae in 1979 and 1980 and in 1984 and 1985.[8,9] To identify a possible animal reservoir, CDC characterized all available veterinary isolates of *S* Typhimurium identified between October 1, 1984, and September 30, 1985, by the US Department of Agriculture National Veterinary Services Laboratory in Ames, Iowa.

Environmental Studies

Local health department sanitarians and US Food and Drug Administration representatives investigated the distributors and original suppliers of foods used in group 1 restaurants. All group 1 restaurants were inspected by sanitarians. Records of the city water system were reviewed for the month of September 1984. Tap water samples were collected during the outbreak from restaurants for analysis. Temperatures maintained by ice-chilled salad bars were evaluated.

Statistical Analysis

Food exposure data were analyzed separately by restaurant and by date of onset of illness at the 2 restaurants that had recurrent outbreaks. Univariate analyses were performed and odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using the Epi Info computer program Version 6.03.[10] Foods found to be associated with illness in univariate analyses were analyzed using a stepwise logistic regression model. Univariate analyses of employee survey data were performed, and relative risks (RRs) with 95% CIs were calculated using Epi Info.

Criminal Investigations

Managers of affected restaurants were interviewed about unusual incidents or disgruntled employees. Suspicious events were referred to the Oregon State Police and the Wasco County sheriff for investigation. The Federal Bureau of Investigation (FBI) reviewed local investigation efforts. Following the completion of the epidemiologic investigation and after the collapse of the Rajneeshee commune, the FBI, with technical assistance from the Oregon Public Health Laboratory, investigated clinic and laboratory facilities in Rajneeshpuram. A sample of *S* Typhimurium seized from the Rajneesh Medical Center on October 2, 1985, was compared with the outbreak strain.

RESULTS

We identified 751 patients who met the case definition; 441 patients (59%)

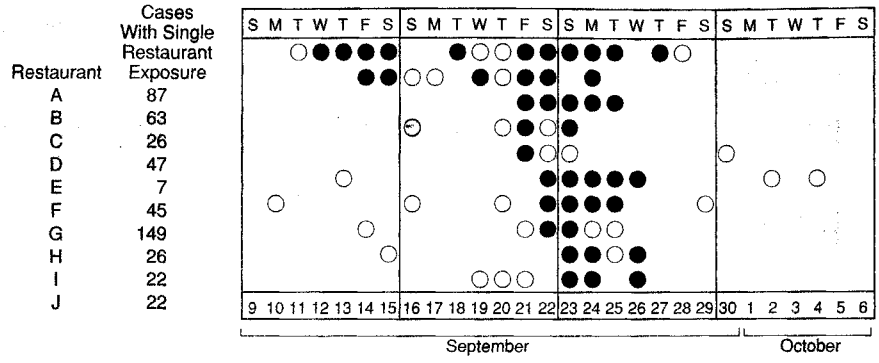

Figure 2.—Dates of exposure at group 1 restaurants reported by 494 case customers with single restaurant exposures. Circles indicate days reported by case customers; filled circles indicate days when 1 customer or more had culture-confirmed *Salmonella* Typhimurium infection.

Two of the group 1 restaurants (restaurants A and B) had banquet facilities. No cases were identified among attendees of 20 banquets during the outbreak period, after customers with other restaurant exposures were excluded. Banquet salad bar items were made up in the same kitchen as the public salad bar items, but the banquet salad bars had a more restricted choice of foods and were in operation for only 1 to 1½ hours per day. The sources of foods placed on the public salad bars were the same as those for banquets.

Investigation of Illness Among Restaurant Employees

During September 1984, 254 employees worked at group 1 restaurants; 242 (95%) were interviewed. Of these, 56 (23%) met the clinical case definition, 41 (17%) had at least 1 symptom but did not meet the case definition, and 145 (60%) were asymptomatic. At least 1 stool specimen was submitted by 231 employees (91%). Specimens from 74 (32%) were culture-positive, including those from 39 employees whose symptoms met the case definition, 16 employees with at least 1 symptom but who would not have met the case definition except for their positive culture, and 19 asymptomatic employees. Of the 19 asymptomatic culture-positive employees, only 3 had possible exposures to another group 1 restaurant or to ill friends or family members.

Onset of symptoms in employees did not, in general, precede exposure among restaurant customers. Five case employees (2 culture-confirmed) at 4 group 1 restaurants (restaurants C, D, F, and G) reported onset of illness before September 19, during the first wave of the outbreak. They had not worked at either restaurant (restaurants A and B) involved in that early wave, nor had they eaten at those restaurants on a date when any case customer was exposed in the early wave. There was no known social contact between the 5 case employees and any employee of restaurants A or B.

Detailed information on work schedules was available for employees of 8 of the 10 group 1 restaurants (all but restaurants I and F), including data on 66 symptomatic case employees. Assuming an average symptom duration of 3 days, then 40 case employees (61%) worked while symptomatic. When the work schedules of 3 case employees with early-onset illness were compared with dates reported for case customer exposure to their restaurant, 1 case employee's work schedule closely coincided with customer exposure. This employee had onset of symptoms on September 10, worked at restaurant G, and had primary responsibility for preparing the salads that were consumed by customers, including the potato salad that was most strongly associated with illness at this restaurant. This employee ate regularly from the salad bar at work, but had not eaten at either of the 2 restaurants with early involvement in the outbreak and reported having no social contacts with other ill employees of any other restaurant.

A total of 307 persons completed the second employee survey, including 227 (89%) of 254 employees of group 1 restaurants. The attack rate (54%) for those employees who ate at their own salad bars was significantly greater than the attack rate (30%) for those who did not (RR, 1.8; 95% CI, 1.2-2.7; $P<.01$). This was true for case employees who were ill in the first wave and for those who were ill in the second wave, compared separately with control employees. Excluding employees who became ill in the first wave, the attack rate (53%) for those employees who ate at another group 1 restaurant salad bar also was greater than the attack rate (28%) for those who did not (RR, 1.9; 95% CI, 1.2-2.9; $P=.01$). There was no association between illness and female sex (after controlling for eating from the salad bar), type or frequency of work performed, number of restaurant meals per week, amount of water consumed at work, raw egg consumption, raw milk consumption, antacid use, or travel.

Laboratory Investigations

Salmonella Typhimurium was isolated from stool specimens of 388 patients (52%). The outbreak strain did not ferment dulcitol, which is an unusual biochemical characteristic found in only about 2% of nontyphoidal salmonellae.[11] The outbreak strain was sensitive to ampicillin, cephalothin sodium, chloramphenicol, gentamicin sulfate, kanamycin sulfate, nalidixic acid, sulfisoxazole, and trimethoprim-sulfamethoxazole. Intermediate sensitivity was noted to tetracycline and streptomycin sulfate. Plasmid profiles were determined[6,7] for 52 outbreak-associated isolates, including an isolate from at least 1 case employee and 1 case customer from each group 1 restaurant. All outbreak isolates had the same plasmid profile, with a single plasmid of approximately 60 Md.

Salmonella Typhimurium was isolated from blue cheese salad dressing collected from restaurant B during the second wave of the outbreak, but was not isolated from dry mix used to prepare the dressing. *Salmonella* Typhimurium was not isolated from cultures of lettuce from restaurants D and G, which came from the same lettuce shipments used during the outbreak.

None of 6 *S* Typhimurium isolates collected in Oregon from sporadically occurring cases between July and December 1984 resembled the outbreak strain from The Dalles. Two isolates of *S* Typhimurium from 2 other outbreaks that occurred in Oregon during that time did resemble the outbreak strain by dulcitol metabolism, antibiogram, plasmid profile, and restriction endonuclease digests of plasmid DNA.

The 2 outbreaks included an outbreak in August 1984 affecting 26 persons who became ill after eating at a hospital cafeteria in the central Willamette Valley of Oregon. Illness was associated with eating ranch dressing at the salad bar. The other outbreak of *S* Typhimurium occurred after a banquet at a hotel in Portland, Ore, in December 1984, affecting at least 36 persons; illness was associated with eating rare roast beef. Previously, in November 1984, another outbreak of *S* Typhimurium occurred after a banquet at the same Portland hotel and affected at least 73 persons; illness was also associated with eating rare roast

beef. That outbreak strain had a single plasmid similar to The Dalles strain, but no further laboratory comparisons were made. No links were identified between these outbreaks and the outbreak in The Dalles.

The 1979 to 1980 national survey included 233 strains of *S* Typhimurium (excluding variant copenhagen); none had antibiograms similar to The Dalles outbreak strain.[8] The 1984 through 1985 national survey included 175 strains of *S* Typhimurium (excluding variant copenhagen); 35 strains had antibiograms similar to the strain from The Dalles, and 6 of these did not ferment dulcitol.[9] One of the 6 strains was epidemiologically linked to The Dalles outbreak, but the other 5 isolates had no known link with the The Dalles outbreak.

Among 34 animal *S* Typhimurium isolates from the National Veterinary Services Laboratory collected from June 1984 through November 1984, 1 isolate that did not ferment dulcitol, collected from a turkey in June 1984, matched the outbreak strain by plasmid restriction endonuclease analysis.

Environmental Studies

Review of records at the municipal water department showed no evidence of water treatment failure in September 1984. Tap water samples from 10 restaurants were negative for bacteria and had acceptable turbidity readings, and 9 had chlorine residuals of at least 1.0 mg/L.

Detailed information on distributors and suppliers was collected for 8 of the group 1 restaurants. Of 40 food items served at 4 or more of the 8 restaurants, no supplier or distributor provided a single food for more than 4 restaurants. There was no common supplier or distributor for any of the foods served by the 2 restaurants involved in the first wave of illness. Many of the distributors served large areas in Oregon and Washington.

Sanitary inspections revealed minor violations of hygienic food-handling practices in some restaurants. Employees commonly put out fresh, full containers of a food item on the salad bar, but then placed the remainder from the old container on top of the fresh items. All salad bars were ice chilled. An evaluation of temperatures maintained on a typical ice-chilled salad bar showed that the surface of a bowl of potato salad was likely to reach 13°C to 16°C (55°F-60°F), which exceeds the maximal temperature of 7°C (45°F) recommended by the Food and Drug Administration. In 1 restaurant, there was no soap dispenser or towel in the employee rest room.

Criminal Investigation

During the criminal investigation, testimony by commune members indicated that the outbreak in The Dalles was the result of deliberate *S* Typhimurium contamination of salad bars in multiple restaurants by residents of Rajneeshpuram.[13] Clandestine laboratories in Rajneeshpuram were used to prepare cultures of *S* Typhimurium that were poured on food items on salad bars and, in some restaurants, into coffee creamers. Commune members said they were testing a plan to incapacitate voters in preparation for an upcoming election. They intended to make citizens of The Dalles sick on election day to prevent them from voting and thus influence the outcome of the election. The information obtained from informant testimony was incomplete or insufficiently precise to allow direct comparison of dates of contamination with dates of exposure for case customers and case employees on a restaurant-by-restaurant basis. It is likely that some salad bars were contaminated more than once. Informant testimony did indicate that other restaurants, in addition to the 10 identified as group 1 restaurants, might have been targets and that other foods were deliberately contaminated. In addition, produce in at least 1 supermarket was contaminated with *S* Typhimurium and plans were made to contaminate city water.[13]

Oregon State and FBI investigators confiscated an open vial containing a standard strain of *S* Typhimurium (American Type Culture Collection 14028, Rockville, Md) from the clinic laboratory in Rajneeshpuram. Clinic records indicated that the laboratory had obtained this vial from a commercial supplier of biologic products before the outbreak. The *S* Typhimurium strain was indistinguishable from the outbreak strain by antibiogram, biochemical markers, plasmid profiles, and restriction endonuclease digestion of plasmid DNA.

On March 19, 1986, 2 commune members were indicted for conspiring to tamper with consumer products by poisoning food in violation of the federal antitampering act.[12,13] In April 1986, the defendants pleaded guilty to the charges, and in July 1986 they were sentenced to 4½ years in prison, to serve concurrently with other sentences.[14]

COMMENT

This outbreak of salmonellosis, affecting at least 751 persons, was caused by intentional contamination of restaurant salad bars by members of a religious commune. It was the largest outbreak of foodborne disease reported to CDC in the United States in 1984. Despite extensive investigation, the source of *S* Typhimurium initially went unrecognized. It was not until more than a year after the outbreak that sufficient evidence had accumulated to link the religious commune with the outbreak. Essential evidence was collected during the course of criminal investigations independent from the epidemiologic field investigation.

There was no evidence to suggest that the *S* Typhimurium was waterborne. Employee illness was not associated with water consumption, and affected restaurants were served by 2 different water systems. Unaffected restaurants shared the same water supply with affected restaurants. Water testing detected no evidence of contamination during the epidemic period.

The outbreak was clearly associated with food consumption at restaurants. Almost all case patients either worked at a restaurant in The Dalles or reported eating at 1 or more restaurants located in the town during the week before onset of illness. Many culture-confirmed cases occurred in nonresidents who had a single restaurant meal as their sole exposure. Self-service salad bars were implicated in transmission of *S* Typhimurium. Affected restaurants in The Dalles were much more likely to have a self-service salad bar than were unaffected restaurants, and eating food from self-service salad bars was highly associated with disease. Culture of salad dressing in 1 restaurant yielded the outbreak strain. The incidence of cases declined abruptly after all salad bars were closed, and this intervention may have terminated the outbreak. However, these findings were difficult to reconcile with the observations that sanitary practices in implicated restaurants were not grossly deficient, private banquets with salad bars were not affected, and no food sources were common to the majority of affected restaurants. Therefore, other possible modes of transmission were considered.

Transmission of nontyphoidal salmonellae from infected food handlers has been documented uncommonly in epidemiologic investigations.[15-19] In The Dalles outbreak, infected food handlers may have contributed to the spread of infection by inadvertent contamination of foods at restaurants where they worked. Some ill employees continued to work until they were excluded by the health department. Direct contamination of foods by ill employees may have occurred at 1 restaurant without a salad bar because of the lack of soap and hand towels in the employee lavatory. In 1 affected restaurant with a salad bar, a case employee was identified who prepared the salad bar food items, including the implicated potato salad, and whose work schedule coin-

cided with the dates of exposure reported by case customers. Nonetheless, other findings suggested that contamination by employees was not the most important factor in transmission. Eating at restaurant salad bars was a risk factor for employees, not just customers. Exclusion of symptomatic and asymptomatic case employees occurred several days after the abrupt decline in new cases had begun, suggesting that exclusion of infected employees did not play a large role in terminating the outbreak.

Laboratory analyses were conducted that compared the outbreak strain with available human and animal isolates from national surveys. The characteristic antibiotic-sensitivity pattern, biochemical testing results, and plasmid analysis conclusively demonstrated a single outbreak strain and excluded the remote possibility of independent, simultaneous outbreaks. The outbreak strain was not common before the outbreak. None of the human isolates from the 2 national surveys, excluding several isolates obtained after the outbreak, matched The Dalles strain. The 1 animal isolate that matched the outbreak strain had no identifiable epidemiologic link to The Dalles outbreak. Isolates from 3 other 1984 Oregon outbreaks matched the outbreak strain, including a salad bar–associated outbreak which preceded The Dalles outbreak. However, no connection between these outbreaks and The Dalles outbreak was ever established.

The source of the outbreak strain of *S* Typhimurium was finally identified in October 1985. During a search by law enforcement agents, an Oregon Public Health Laboratory official found an open vial of commercial stock culture disks containing *S* Typhimurium in a clinical laboratory operated by the religious commune. Records showed that it was purchased before the outbreak,[13] and laboratory testing during the following months demonstrated that the isolate matched the outbreak strain. Informant testimony provided additional information about the motives for the conspiracy and details of its implementation.[5,12-14] Testimony indicated that several attacks were directed at some restaurants. In some restaurants, liquid coffee creamer was also contaminated, produce was contaminated in a grocery store, and plans were made to contaminate municipal water supplies.[5,12-14] The epidemiologic investigation did not identify these other exposures as risk factors. The source of infection for employees who became ill before customer exposure was documented remains unknown. These illnesses may have been the result of an abortive early attempt at contamination. The informants indicated that the saboteurs were frustrated when their initial attempts did not cause widespread illness and they may have used higher inoculums in later attacks.[13]

In retrospect, intentional contamination is consistent with the epidemiologic findings. When *S* Typhimurium was introduced into food on the ice-chilled salad bars, the holding temperatures may have permitted propagation; reuse of foods and addition of old products on top of new ones allowed *S* Typhimurium to persist for several days, and other foods on the salad bar may have been cross-contaminated. Intentional contamination explains why different foods were contaminated in different restaurants and the nearly simultaneous involvement of many restaurants despite the lack of common food sources. It also explains why persons attending private banquets at 2 affected restaurants did not become ill even though salad bars were set up for these events. Most importantly, intentional contamination explains the observations without relying on multiple complex modes of transmission.

The possibility that intentional contamination caused the outbreak was specifically considered early in the investigation, but this hypothesis was initially rejected for several reasons. (1) No motive was apparent. Despite concern in The Dalles about the potential for election fraud, the outbreak of illness in September and October was not obviously related with elections occurring in November. We had not considered that this incident had merely been a trial run for further attacks at the time of the election. (2) No one claimed responsibility for the incident, and no demands or ultimata were issued. We assumed that if the motive was either extortion or terrorism, a public statement would have been issued to intimidate or create widespread fear. In fact, the incident was planned as a covert tactical strike. (3) Law enforcement officers investigated the few questionable activities reported among restaurant patrons and did not establish a recognizable pattern of unusual behavior. (4) No disgruntled employee was identified who might seek revenge on their employer. The criminal investigation confirmed that restaurant employees did not participate in the contamination efforts. (5) The epidemic exposure curves indicated that salad bars were contaminated multiple times during a several-week period, suggesting that a sustained source of *S* Typhimurium was necessary. It seemed more likely to us that a saboteur would have acted on 1 occasion, rather than risk repeated attacks and exposure. (6) A few employees had onset of illness before the recognized patron exposures in their restaurants. (7) To our knowledge, such an event had never happened. We were aware of only 2 reports of foodborne illness caused by intentional contamination with biologic agents, and neither incident appeared to be politically motivated.[1,2] (8) On the basis of our experience in other investigations, we believed that other hypotheses, although more complicated, appeared more likely, because individually each of the components had been well documented in other outbreaks. (9) Finally, even in thoroughly investigated outbreaks, the source sometimes remains occult, and, of all the reasons considered for failing to identify a source, this would be the most common.

There was a risk that publicity about this outbreak may have had the unfortunate side effect of inciting other events, similar to the copycat poisonings following the Tylenol-cyanide poisonings in 1982. When the cause of the outbreak was identified, it was reported by the regional news media; however, we know of no additional outbreaks motivated by these reports. A report of the findings of the CDC investigation was distributed to state and territorial public health officials, but not submitted for publication. The recent discovery of the stockpiling and use of biological agents by the Japanese cult Aum Shinrikyo serves to remind us of a continuing threat that biological weapons might be used by other terrorist groups in the future.[20] It is hoped that wider dissemination today of the epidemiologic findings from The Dalles outbreak will lead to greater awareness of the possibility of other incidents and earlier recognition, when or if a similar incident occurs. This potential benefit should outweigh the risk of a copycat incident. It may be that with a higher index of suspicion in The Dalles, the source of *S* Typhimurium would have been identified sooner. However, the epidemiologic method is inherently limited; it determines risk and association and can indicate how contamination probably occurred. It cannot establish motive.

Can another outbreak like the one that occurred in The Dalles be prevented? It seems unlikely that any regulation of commercially available pathogens could have prevented this outbreak. It would not be necessary to purchase them because this type of culture could be easily obtained from clinical isolates or from raw foods of animal origin available in grocery stores. Production of large quantities of bacteria is inexpensive and involves simple equipment and skills. Standard practices for maintaining salad bars may be inadequate to prevent similar outbreaks in the future with salmonellae or other pathogens. As in many areas of our open society, current practices are inad-

equate to prevent deliberate contamination of food items by customers.

With this in mind, the public is best protected when health care professionals and laboratories cooperate with local and state health departments to report notifiable diseases and unusual disease clusters. Routine reporting is essential in disease surveillance at both the local and national level, and efforts to improve surveillance will assist in the detection of future outbreaks in general. The epidemiologic approach to an outbreak need not be changed. The methods of determining the pathogen, vehicle, and route of contamination and relating them to time, place, and person remain the same. On the basis of our experiences in The Dalles, we also suggest that if investigation of a large and cryptic outbreak implicates a mechanism of contamination that does not resemble established patterns, then the possibility of intentional contamination should be considered and law enforcement agencies should be asked to consider undertaking an independent investigation.

This article is dedicated to the memory of Laurence R. Foster, MD, MPH, in honor of his investigation of this outbreak and his inspirational leadership as Oregon State Epidemiologist.

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An Outbreak of *Shigella dysenteriae* Type 2 Among Laboratory Workers Due to Intentional Food Contamination

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Context.—*Shigella dysenteriae* type 2 is rare in the United States, and outbreaks associated with this pathogen are uncommon.

Objective.—To determine the magnitude and source of an outbreak of *S dysenteriae* type 2.

Design.—Retrospective cohort.

Setting.—Laboratory of a large medical center.

Patients.—Case patients were identified as laboratory workers who had diarrhea on or after October 28 and a positive stool culture or temperature greater than 37.8°C. Laboratory workers with diarrhea only were probable case patients.

Main Outcome Measures.—We interviewed laboratory staff and performed identification, serotyping, and pulsed-field gel electrophoresis on isolates from case patients, implicated food, and laboratory stock culture.

Results.—From October 29 through November 1, a total of 12 (27%) of 45 laboratory staff developed severe, acute diarrheal illness; 8 had *S dysenteriae* isolated from stool and 4 were hospitalized. All case patients reported having eaten muffins or doughnuts placed in the staff break room on October 29. Pulsed-field gel electrophoresis showed stool isolates from 9 case patients were indistinguishable from *S dysenteriae* type 2 recovered from an uneaten muffin and from the laboratory's stock strain, a portion of which was missing.

Conclusions.—The source of the outbreak was most likely the laboratory's stock culture, which was used to contaminate the pastries. Results of this investigation underscore the need for adequate precautions to prevent inadvertent or intentional contamination from highly pathogenic laboratory specimens.

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SHIGELLA dysenteriae type 2, also known as Schmitz bacillus, is a relatively rare organism that causes bacillary dysentery.[1] Although little historical information about this serotype is found in the medical literature, it was apparently first described by Schmitz in 1917 after observing a winter epidemic of diarrhea in an eastern European prison camp during World War I.[2] Although outbreaks from this serotype were not common in the general population, outbreaks among patients in psychiatric hospitals in Wales were reported in 1938.[3]

Sporadic cases and outbreaks of *S dysenteriae* type 2 infection are now uncommon in developed countries.[4] During the late 1980s a small outbreak occurred among family members in Sicily, where *S dysenteriae* type 2 had not been reported since 1953.[5] Surveillance data from 1985 through 1995 from the US Centers for Disease Control and Prevention indicate that an average of about 20 individual cases of *S dysenteriae* type 2 are reported annually in the United States. The last reported outbreak in the United States occurred in 1983 among cafeteria workers in a Maryland medical center.[6]

Illness caused by *S dysenteriae* type 2 is not well described. Although it may cause significant morbidity, *S dysenteriae* type 2 appears to cause a milder illness compared with *S dysenteriae* type 1.[1] Unlike *S dysenteriae* type 1, which is associated with hemolytic uremic syndrome and toxic megacolon, *S dysenteriae* type 2 does not produce Shiga toxin.[7,8]

BACKGROUND

From October 29 through November 1, 1996, 12 laboratory workers at a large medical center in Texas experienced a severe gastrointestinal illness after eating muffins and doughnuts anonymously left in their break room between the night and morning shifts of October 29. After stool cultures from these persons revealed *S dysenteriae*, all local emergency departments and infectious disease physicians were alerted and urged to report any additional cases. This article describes the findings of our investigation to characterize the magnitude and source of this outbreak.

METHODS

We defined a case patient as a laboratory worker with a diarrheal illness beginning on or after October 29, 1996, with a positive stool culture for *S dysenteriae* or an oral temperature greater than 37.8°C. A laboratory worker with diarrhea alone, with an oral temperature 38°C or less, or a negative stool culture was a probable case patient. We interviewed laboratory personnel who worked during the morning and night shifts and assessed demographics, food histories, social activities, and signs and symptoms of illness.

Stool was cultured on eosin methylene blue and xylose lysine desoxycholate agar media, then sent with a food specimen to the Bureau of Laboratories of the Texas Department of Health for further analysis and serotyping. The medical center's stock culture was also sent to the Texas Department of Health. Food was analyzed using established

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procedures from the *Bacteriological Analytical Manual* from the Food and Drug Administration.[9]

In addition, pulsed-field gel electrophoresis was performed on the food and stool *S dysenteriae* type 2 isolates and the hospital stock culture on *Xba* I and *Not* I (New England BioLabs, Beverly, Mass) chromosomal DNA digests. The fragments were separated using a CHEF-Mapper [clamped homogenous electric field] (BIO-RAD, Hercules, Calif), and the isolates were visually compared. All epidemiologic data were collected onto standardized forms, entered into a computer, and analyzed using Epi Info Version 6 software.[10]

RESULTS

We interviewed 45 laboratory employees who worked during the first or third shifts. Six laboratory workers were unavailable for interview, and 1 refused to participate; however, according to coworkers, 6 of these persons were not ill and did not eat pastries. One unavailable worker was reportedly ill, but attempts to confirm this were unsuccessful.

Laboratory employees recalled that during the night and morning shift change on October 29, an unsigned e-mail from a supervisor's computer appeared on laboratory computer screens with an invitation to eat pastries in the laboratory break room. The supervisor was temporarily away from the office at the time the message was sent. The break room is separate from the laboratory and cannot be accessed without entering a numerical security code. Two boxes of commercially prepared pastries containing blueberry muffins and assorted doughnuts were available.

Twelve workers who ate muffins or doughnuts reported diarrhea with fever, headache, or vomiting. Eleven met the definition for case patients, and 1 was a probable case patient. The mean age of the ill workers was 41 years (range, 33-52 years) and 9 (75%) were women. Ill persons reported having eaten a pastry on October 29 between 7:15 AM and 1:30 PM. Additionally, 1 worker did not eat a muffin at work, but took it home and shared it with a family member around 7 PM. The onset of diarrhea among the laboratory workers occurred between 9 PM on October 29 and 4 AM on November 1 (Figure 1). The mean incubation period until onset of diarrhea was 25 hours (median, 18 hours; range, 11-66 hours) and was preceded by nausea, abdominal discomfort, and bloating. Eleven patients were examined by a physician, while 1 consulted a physician by telephone. Five workers were treated in emergency departments and released, and 4 other patients were hospitalized (mean, 4 days; range, 2-10 days). Eight patients received intravenous fluids. Stool cultures were obtained from 11 ill workers; 8 cultures yielded *S dysenteriae* type 2, and 3 were negative. The *S dysenteriae* isolates were sensitive to all antibiotics tested for antimicrobial susceptibility. Eleven patients were treated with ciprofloxacin, and 1 received a homeopathic medication. No deaths occurred among the ill workers.

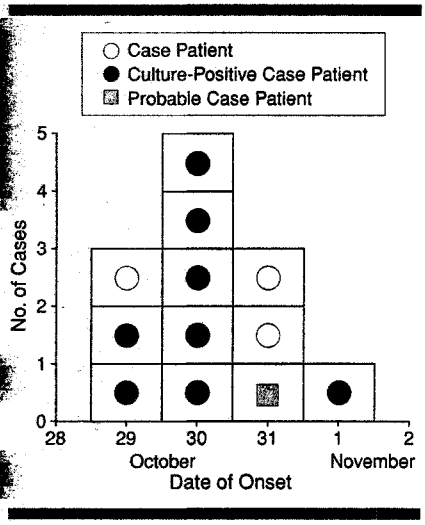

Figure 1.—Cases of shigellosis by onset of diarrhea among laboratory workers in a Texas medical center, 1996.

The attack rate was 100%. All 12 persons who ate pastries became ill, vs none of 33 persons who did not eat pastries, resulting in an undefined relative risk for shigellosis among those who ate pastries ($P<.001$). There was no increased risk from eating food from the break room refrigerator or drinking any beverage, including coffee, tap water, or other drinks. Similarly, eating in the hospital cafeteria or attending social gatherings during the week of October 25 through 31 was not associated with a higher risk for disease.

Although no secondary transmission of the illness was observed, a family member of 1 worker became ill after eating a muffin that was brought home from the laboratory's break room. The worker reported ingesting some crumbs and also became ill. Stool cultures from the worker and family member yielded *S dysenteriae* type 2.

Our investigation of the storage freezer in the laboratory suggested that the reference culture of *S dysenteriae* type 2 had been disturbed. The laboratory stores various reference cultures, including *S dysenteriae* type 2 in Microbank vials, a low-temperature storage system for microorganisms. Each vial contains 25 porous, doughnut-shaped beads that can be impregnated with microorganisms. The *S dysenteriae* type 2 culture, which had been stored by the laboratory for several years, had been transferred to Microbank vials during the 1980s. During the outbreak investigation, the *S dysenteriae* type 2 vial was discovered to have only 19 beads, although it had reportedly never been used.

Shigella dysenteriae type 2 was isolated in virtually pure culture from *Shigella* broth enrichment cultures of the muffin specimen. *Shigella dysenteriae* type 2 was also isolated from stools of 8 patients. Additionally, *S dysenteriae*

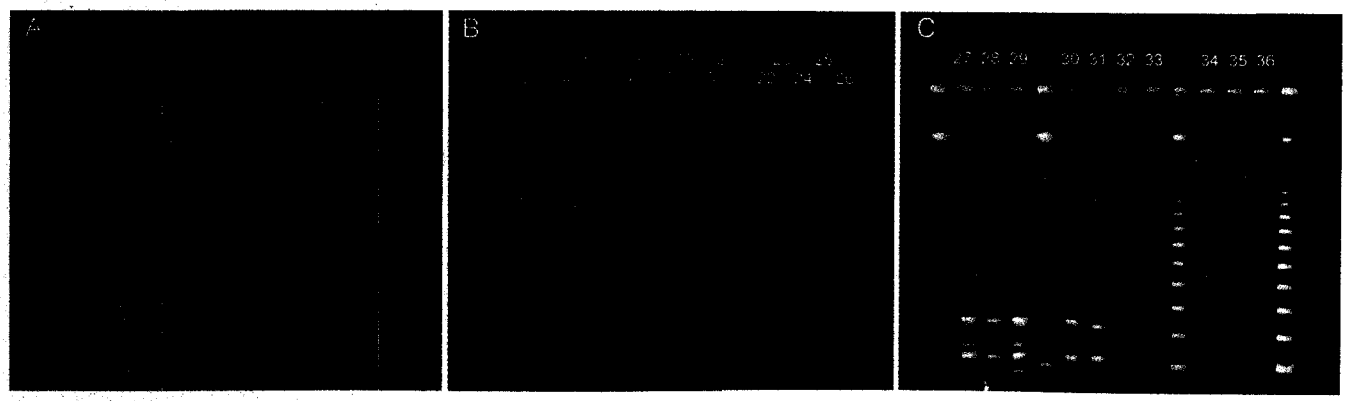

Figure 2.—Pulsed-field gel electrophoresis patterns from *Shigella dysenteriae* isolates. *Xba* I restriction digests—*S dysenteriae* type 3 isolates: 1-5 (panel A); *S dysenteriae* type 2 isolates: case isolates, 6, 8-15 (panels A, B); hospital stock culture, 7 (panel A); muffin isolates, 17,18 (panel B); and nonoutbreak isolates, 16 (panel B). *Not* I restriction digests—*S dysenteriae* type 3 isolates: 27-31 (panel C); *S dysenteriae* type 2 isolates: hospital stock culture, 19-23, 32, 34-36 (panels B,C); muffin isolates, 25-26 (panel B); and nonoutbreak isolates, 24 (panel B).

type 2 was confirmed in the medical center's reference culture. Pulsed-field gel electrophoresis revealed that the reference culture isolates were indistinguishable from those of the muffin and the stool cultures, but differed from 2 nonoutbreak isolates of *S dysenteriae* type 2 from other Texas counties in 1995 and 1996 (Figure 2). The outbreak strains differed from the nonoutbreak strains by more than 5 bands. Useful information was not obtained on the dose of *S dysenteriae* type 2 in the food sample.

COMMENT

The source of the organism was most likely the medical center's own stock culture of *S dysenteriae* type 2. There is a strong epidemiologic link between the ill persons, the uneaten food, and the laboratory's stock culture of this rare pathogen. All persons who developed shigellosis reported the same exposure (eating pastries). The stock culture and isolates from the stool and food sample were indistinguishable by pulsed-field gel electrophoresis, which has been shown to be highly discriminatory in subtyping strains of *Shigella sonnei* and many other enteric organisms.[11-13] *Shigella dysenteriae* type 2 isolates are uncommon in the United States and only 2 nonoutbreak strains existed in the Texas Department of Health's laboratory collection. These nonoutbreak type 2 strains and 5 type 3 strains also were analyzed and differed from the outbreak strain by more than 5 bands each.

The medical center's stock culture of *S dysenteriae* type 2 had been stored by the laboratory for years, and details of its origin are unclear. However, it was not a commercially prepared culture. The culture may have been obtained from a patient and previously used for medical technician training. No cases of *S dysenteriae* type 2 had been diagnosed in the hospital laboratory during the past 5 years, and no research was being conducted with this pathogen. Therefore, a gross laboratory error seems an unlikely cause of this outbreak.

Contamination of the pastries during commercial handling also seems unlikely. No additional cases were reported, despite prompt contact with all area emergency departments and infectious disease physicians. In addition, no concurrent outbreaks of *S dysenteriae* type 2 were reported in Texas or any other state in the United States. A recall of the pastry products was not requested.

Although the motive and method of contamination are still unknown, the most likely hypothesis is that it was done by someone who had access to the freezer, had the laboratory skills to culture the organism from the beads and inoculate the pastries, and had access to the locked break room. Although we were unable to determine the dose of *S dysenteriae* type 2 added to the food sample, only 10 to 100 organisms are necessary to cause shigellosis infections in humans.[7] As of this writing, a criminal investigation is ongoing.

The medical center has implemented security measures to safeguard against future incidents of this type. The laboratory freezer is now secured and must be unlocked by a supervisor to gain entry. Stock culture labels no longer identify microorganisms by name and have been replaced by a numerical identification system.

To our knowledge, this is the first reported intentional contamination of food items with *S dysenteriae* type 2. Bioterrorism through food contamination with microorganisms rarely is reported in the scientific literature and reports appear about once each decade. During the mid 1960s, several outbreaks of typhoid fever and dysentery in Japanese hospitals were traced to food contaminated by a research bacteriologist who later infected family members and neighbors.[14] In 1970, 4 Canadian university students became ill with pulmonary infiltrates, asthma, and eosinophilia after eating food maliciously contaminated with embryonated *Ascaris suum* ova, a large ringworm infecting pigs.[15] Later, in 1984, multiple *Salmonella* outbreaks in Oregon were suspected to be caused by intentional contamination of restaurant salad bars.[16,17] Details of this outbreak are reported by Török et al[18] elsewhere in this issue.

The results of this investigation underscore the biological threat that accompanies malicious use of pathogenic microbiologic agents. Although no system can provide absolute security, measures to reduce the risk of such occurrences might include controls similar to those implemented by the medical center described in this article. These include controlled access to laboratory areas where these materials are stored, locked freezers that can be opened only by designated personnel, and maintenance of a written record of persons entering these areas and handling these materials. Guidelines should be established for secure storage and close surveillance of laboratory stock cultures.

The authors wish to express their sincere gratitude to all of those at the medical center, Dallas County Health and Human Services, Texas Department of Health, and Centers for Disease Control and Prevention who contributed to this investigation.

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Clinical Recognition and Management of Patients Exposed to Biological Warfare Agents

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Concern regarding the use of biological agents—bacteria, viruses, or toxins—as tools of warfare or terrorism has led to measures to deter their use or, failing that, to deal with the consequences. Unlike chemical agents, which typically lead to violent disease syndromes within minutes at the site of exposure, diseases resulting from biological agents have incubation periods of days. Therefore, rather than a paramedic, it will likely be a physician who is first faced with evidence of the results of a biological attack. We provide here a primer on 10 classic biological warfare agents to increase the likelihood of their being considered in a differential diagnosis. Although the resultant diseases are rarely seen in many countries today, accepted diagnostic and epidemiologic principles apply; if the cause is identified quickly, appropriate therapy can be initiated and the impact of a terrorist attack greatly reduced.

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THE BREAKUP of the Soviet Union, the perceived dominance of the United States as a conventional military world power, and the rise of radical groups focused on destroying what they believe to be evil have raised concern regarding the use of biological warfare (BW) against military forces in combat and even as a new tool of terrorists against civilians.

The potential impact of biological weapons is well illustrated by a 1970 World Health Organization (WHO) publication.[1] It is estimated that 50 kg of aerosolized *Bacillus anthracis* spores, for example, dispensed by an airplane 2 km upwind of a population center of 500 000 unprotected people in ideal meteorological conditions would travel more than 20 km and kill or incapacitate up to 220 000 people, nearly half of those in the path of the biological cloud. If *Francisella tularensis* were dispensed, the number of dead or incapacitated would be about 155 000. Thus, if properly used as offensive weapons under ideal meteorological conditions, certain biological agents could cause mass casualties.

In addition to their detrimental health effects on the targeted population, the hostile use of BW agents would be likely to cause significant impacts on the health care system. Patients would present in unprecedented numbers, and demands for intensive care might overwhelm medical resources. Special medications or vaccines not generally available in standard pharmaceutical stocks potentially would be required. Health care professionals and laboratory personnel might need added physical protection, and autopsy and interment of remains could present unusual hazards.

The medical response to the threat or use of biological weapons differs depending on whether medical measures are used before exposure or after exposure and whether symptoms are present. If provided before exposure, active immunization or prophylaxis with antibiotics may prevent illness. Active immunization is probably the best modality for future protection of military forces against a wide variety of biological threats. For civilian populations, preexposure medical contermeasures would likely not be used. After exposure, but before symptoms arise, active or passive immunization, as well as pretreatment with therapeutic antibiotics or antiviral drugs, may ameliorate disease symptoms. After onset of illness, only diagnosis of the disease and general supportive care plus specific medical treatment are left to health care providers. Effective vaccines and antitoxins exist for several of the most likely BW agents. Additional vaccines and new therapies are under development.

Information on diagnostics, medical management, and vaccines is available by contacting Commander, USAMRIID, at 301-619-2833 . . .

Bacteria, viruses, or toxins (of microbial, plant, or animal origin) may be used as BW agents. Examples of microbial agents and toxins that could be used as BW agents include *B anthracis* (anthrax), botulinum toxin, *Yersinia pestis* (plague), staphylococcal enterotoxin B (SEB), and Venezuelan equine encephalitis (VEE) virus. Despite the very different characteristics of these organisms and toxins, these agents used as weapons share some common characteristics. They can be dispersed in aerosols of particle size approximately 1 to 10 µm, which may remain suspended (in certain weather conditions) for hours and, if inhaled, can penetrate into distal bronchioles and terminal alveoli of the exposed. The aerosols may be delivered by simple technology, including industrial sprayers with nozzle and energy source modi-

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The views, opinions, and findings contained herein are those of the authors and should not be construed as an official US Department of the Army position, policy, or decision unless so designated by other documentation.

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Summary of Biological Warfare Agents*

Agent	Infective Dose (Aerosol)	Incubation Period	Diagnostic Samples (BSL)[96]	Diagnostic Assay	Patient Isolation Precautions	Chemotherapy (Rx)
Anthrax	8000 to 50 000 spores	1-5 d	Blood (BSL-2)	Gram stain Ag-ELISA, Serology: ELISA	Standard precautions	Ciprofloxacin 400 mg IV q 8-12 h Doxycycline 200 mg IV, then 100 mg IV q 8-12 h Penicillin 2 million units IV q 2 h plus streptomycin 30 mg/kg IM qd (or gentamicin)
Brucellosis	10-100 organisms	5-60 d (occasionally months)	Blood, bone marrow, acute and convalescent sera (BSL-3)	Serology: agglutination Culture	Standard precautions Contact isolation if draining lesions present	Doxycycline 200 mg/d PO plus rifampin 600-900 mg/d PO×6 wk
Plague	100-500 organisms	2-3 d	Blood, sputum, lymph node aspirate (BSL-2/3)	Gram or Wright-Giemsa Stain Ag-ELISA, Culture, Serology: ELISA, IFA	Pneumonic: droplet precautions until patient treated for 3 d	Streptomycin 30 mg/kg IM qd in 2 divided doses ×10 d (or gentamicin) Doxycycline 200 mg IV then 100 mg IV q 12 h×10-14 d Chloramphenicol 1 g IV q 6 h×10-14 d
Q fever	1-10 organisms	10-40 d	Serum (BSL-2/3)	Serology: ELISA, IFA	Standard precautions	Tetracycline 500 mg PO q 6 h×5-7 d Doxycycline 100 mg PO q 12 h×5-7 d
Tularemia	10-50 organisms	2-10 d	Blood, sputum, serum EM of tissue (BSL-2/3)	Culture Serology: agglutination	Standard precautions	Streptomycin 30 mg/kg IM qd ×10-14 d Gentamicin 3-5 mg/kg/d ×10-14 d
Smallpox	Assumed low (10-100 organisms)	7-17 d	Pharyngeal swab, scab material (BSL-4)	ELISA, PCR, virus isolation	Airborne precautions	Cidofovir (effective in vitro)
Viral encephalitides	10-100 organisms	VEE, 2-6 d EEE/WEE, 7-14 d	Serum VEE (BSL-3) EEE (BSL-2) WEE (BSL-2)	Viral isolation Serology: ELISA or hemogglutination inhibition	Standard precautions (mosquito control)	Supportive therapy analgesics anticonvulsants as needed
Viral hemorrhagic fevers	1-10 organisms	4-21 d	Serum, blood Most viral hemorrhagic fevers (BSL-4) RVF, KHF, and YF (BSL-3)	Viral isolation Ag-ELISA RT-PCR Serology: Ab-ELISA	Contact precautions Consider additional precautions if massive hemorrhage	Supportive therapy Ribavirin (CCHF/arenaviruses) 30 mg/kg IV initial dose 15 mg/kg IV q 6 h×4 d 7.5 mg/kg IV q 8 h×6 d Antibody passive for AHF, BHF, Lassa fever, and CCHF
Botulinum	0.001 µg/kg (type A)	1-5 d	Nasal swab (possibly) (BSL-2)	Ag-ELISA, Mouse neutral	Standard precautions	DOD heptavalent antitoxin for (Serotypes A-G) (IND): equine despeciated 1 vial (10 mL) IV CDC Trivalent equine antitoxin for Serotypes A, B, E (licensed)
Staphylococcal enterotoxin B	30 ng/person (incapacitating); 1.7 µg/person (lethal)	1-6 h	Nasal swab, serum, urine (BSL-2)	Ag-ELISA Serology: Ab-ELISA	Standard precautions	Ventilatory support and supportive care

*Information on diagnostics, medical management, and vaccines is available by contacting Commander, USAMRIID, at 301-619-2833 (phone) or 301-619-4625 (fax). Readers are advised to consult product literature before administering drugs or vaccines. BSL indicates biosafety level; Rx, chemotherapy; Px, chemoprophylaxis; Ag, antigen; ELISA, enzyme-linked immunosorbent assay; IV, intravenously; q, every; IM, intramuscular; qd, each day; bid, twice a day; PO, by mouth; IFA, immunoflourescent assay; IND, Investigational New Drug; SC, subcutaneous; EM, electron microscopy; PCR, polymerase chain reaction; VIG, vaccinia immune globulin; DOD, Department of Defense; VEE, Venezuelan equine encephalitis; EEE, eastern equine encephalitis; WEE, western equine encephalitis; NA, not available; RVF, Rift Valley fever; KHF, Korean hemorrhagic fever; YF, yellow fever; RT-PCR, reverse transcriptase polymerase chain reaction; Ab, antibody; CCHF, Congo-Crimean hemorrhagic fever; AHF, Argentine hemorrhagic fever; BHF, Bolivian hemorrhagic fever; CDC, Centers for Disease Control and Prevention.

fied to generate the smaller particle size. The aerosol could be delivered from a line source, such as an airplane or boat, traveling upwind of the intended target or from a point source, such as a stationary sprayer or missile bomblets, containing agent in an area upwind of the target. The meteorological conditions in the target area are very important in the use of BW agents as aerosols because higher wind speeds and turbulence tend to break up the aerosol cloud. Other possible routes of exposure for BW agents include oral, by intentional contamination of food and water, and percutaneous. In general, these other routes of exposure are considered less important than the respiratory route in the context of strategic use of BW agents. However, terrorists may not be constrained by either the agent characteristics or the route of exposure required on the biological battlefield.

Diseases produced by the offensive use of biological agents against military forces or civilians could be disabling or lethal. Because biological agents, inca-

Chemoprophylaxis (Px)	Vaccine Availability	Comments
Ciprofloxacin 500 mg PO bid×4 wk if unvaccinated, begin initial doses of vaccine Doxycycline 100 mg PO bid×4 wk plus vaccination	Michigan Biological Products Institute vaccine (licensed): 0.5 mL SC at 0, 2, 4 wk and 6, 12, 18 mo, then annual boosters	Vaccine: boost at-risk annually Alternates for Rx: gentamicin, erythromycin, and chloramphenicol
Doxycycline and rifampin for 3 wk in inadvertently inoculated persons	No vaccine available for human use	Trimethoprim-sulfamethoxazole may be substituted for rifampin; however, relapse rate with this drug may be up to 30%
Tetracycline 500 mg PO qid×7 d Doxycycline 100 mg PO q 12 h×7 d	Greer inactivated vaccine (licensed): 1.0 mL, then 0.2 mL boost at 1-3 and 3-6 mo	Boost at-risk 12, 18 mo & yearly. Plague vaccine not protective against aerosol in animal studies Alternate Rx: chloramphenicol or trimethoprim-sulfamethoxazole Rx: chloramphenicol for plague meningitis
Tetracycline start 8-12 d postexposure ×5 d Doxycycline start 8-12 d postexposure ×5 d	IND 610-inactivated whole cell vaccine given as single 0.5 mL SC	Recommend skin test before vaccination
Doxycycline 100 mg PO q 12 h×14 d Tetracycline 2 g/d PO×14 d	Live attenuated vaccine (IND): scarification	Culture difficult and potentially dangerous
Vaccinia immune globulin 0.6 mL/kg IM (within 3 d of exposure; best within 24 h	Wyeth calf lymph vaccinia vaccine (licensed) DOD cell-culture derived vaccinia vaccine (IND): scarification	Preexposure and postexposure vaccination recommended if >3 y since last vaccination
NA	VEE DOD TC-83 live attenuated vaccine (IND): 0.5 mL SC×1 dose VEE DOD C-84 (formalin inactivated TC-83)(IND): 0.5 mL SC for up to 3 doses EEE inactivated (IND): 0.5 mL SC at 0 & 28 d WEE inactivated (IND): 0.5 mL SC at 0, 7, and 28 d	TC-83 reactogenic in 20% No seroconversion in 20% Only effective against subtypes 1A, 1B, and 1C Vaccine used for nonresponders to TC-83 EEE and WEE inactivated vaccines are poorly immunogenic, and multiple immunizations are required
NA	AHF Candid #1 vaccine (x-protection for BHF)(IND) RVF inactivated vaccine (IND)	Aggressive management of secondary infections and hypotension is important
NA	DOD pentavalent Toxoid for serotypes A-E (IND): SC at 0, 2, & 12 wk, then yearly boosters	Skin testing for hypersensitivity before equine antitoxin administration Ventilatory assistance
NA	No vaccine available	Vomiting and diarrhea may occur if toxin is swallowed

pacitating or lethal, produce a more prolonged period of illness than chemical agents, the impact on the health care infrastructure could be enormous. Person-to-person spread could be important for some agents, and local disease cycles might occur if a competent vector for a bacterium or virus is present in the environment. The following is an overview of several BW threat agents, the disease syndromes resulting from exposure to them, and medical countermeasures available to clinicians (see Table).

ANTHRAX

History and Significance

Anthrax is caused by *B anthracis*, a gram-positive, sporulating bacillus. The reservoir of *B anthracis* is the soil; the organism is distributed worldwide.[2,3] The organism exists in the infected host as the vegetative bacillus and in the environment as a spore. Spores do not form in the infected host unless the body tissues are exposed to air. Anthrax spores can survive adverse environmental conditions and can remain viable for decades. The spore is the stage of the bacterial life cycle that is the usual infective form. Animals contract spores while grazing. Susceptible animals include cattle, sheep, goats, and horses, but other animals may develop infection. Humans contract anthrax via inoculation of minor skin lesions with spores from contact with infected animals, their hides, wool, or other products, from ingesting contaminated meat, from inhaling spores during the processing of wool for textiles, or possibly from biting flies.[3]

Anthrax spores were weaponized by the United States in the 1950s and 1960s before the US offensive program was terminated. Iraq admitted to a United Nations inspection team in August 1991 that it had conducted research on the offensive use of *B anthracis* before the Persian Gulf War and, in 1995, admitted to "weaponizing" anthrax. Other countries have also been suspected of weaponizing anthrax spores. The deaths of at least 66 people after an accidental release of anthrax spores in the former Soviet Union underscores the weapons potential of this agent.[4]

Clinical Features

Anthrax has 3 clinical presentations in humans: cutaneous, gastrointestinal, and inhalational.[3,5,6] A biological attack with anthrax spores would most likely occur by aerosol delivery and would result in inhalational anthrax. This illness, known as woolsorter's disease, occurs in the textile and tanning industries among workers handling contaminated wool, hair, and hides.[7] After being inhaled and deposited in the lower respiratory tract, spores are phagocytized by tissue macrophages and transported to hilar and mediastinal lymph nodes. The spores germinate into vegetative bacilli, producing a necrotizing hemorrhagic mediastinitis.[5-8]

Inhalation anthrax begins with a prodrome featuring fever, malaise, and fatigue. A nonproductive cough and vague chest discomfort may be present. This prodrome may be followed by symptomatic improvement for 2 to 3 days or may progress directly to the abrupt onset of severe respiratory distress with dyspnea, stridor, diaphoresis, and cyanosis. Bacteremia, septic shock, metastatic infection (meningitis in approximately half of cases), and death usually follow within 24 to 36 hours.[6,7] Once symptoms of inhalational anthrax appear, treat-

ment is almost invariably ineffective, although there are anecdotal reports of patients surviving after early, aggressive therapy.[6,7]

Diagnosis and Management

Physical findings are usually nonspecific. The chest x-ray film is typically without infiltrates but may reveal a widened mediastinum with pleural effusions, which may be hemorrhagic. Meningitis, often hemorrhagic, has been reported in up to 50% of cases.[6,8] *Bacillus anthracis* can be visualized by Wright or Gram stain of peripheral blood and isolated by blood cultures but often not until late in the disease course. Vegetative bacilli are present during infection and sporulation does not occur in vivo. Animal studies of inhalational anthrax demonstrate that bacilli and toxin appear in the blood late on day 2 or early on day 3 after aerosol challenge. Toxin levels parallel the development of bacteremia. An enzyme-linked immunosorbent assay (ELISA) to detect circulating toxin is available for rapid diagnosis.

Historically, penicillin has been the treatment of choice for inhalational anthrax, with 2 million units given intravenously every 2 hours. Some animal studies suggest that addition of streptomycin may have additional benefit. All naturally occurring strains tested to date have been sensitive to erythromycin, chloramphenicol, gentamicin, and ciprofloxacin. In the absence of antibiotic sensitivity data, treatment should be instituted at the earliest signs of disease with intravenous ciprofloxacin (400 mg every 8-12 hours). Supportive therapy for shock, fluid volume deficit, and adequacy of airway may be indicated.

A licensed vaccine, an aluminum hydroxide–adsorbed preparation, is derived from culture fluid supernatant taken from an attenuated strain.[3] The vaccination series consists of 6 subcutaneous doses at 0, 2, and 4 weeks, then at 6, 12, and 18 months, followed by annual boosters. There are insufficient data regarding efficacy against inhalational anthrax in humans, although studies in rhesus monkeys indicate it is protective. If there is information indicating that a BW attack is imminent or may have occurred, prophylaxis of unimmunized individuals with ciprofloxacin (500 mg by mouth twice a day), or doxycycline (100 mg by mouth twice a day) is recommended.[9] The vaccination series should be initiated for unimmunized individuals. Should an anthrax attack be confirmed, chemoprophylaxis should be continued for at least 4 weeks and until at least 3 doses of vaccine have been received by all those exposed.

BRUCELLOSIS

History and Significance

Brucellae are small, slow-growing, pleomorphic, gram-negative aerobic nontoxigenic, non–spore-forming coccobacilli. Although the 6 species of *Brucella* are closely related,[10] they each characteristically infect different animal hosts, in which they usually cause infertility or abortion. Of the 4 species pathogenic for humans, *Brucella melitensis* usually infects goats, *Brucella suis* infects swine, *Brucella abortus* infects cattle, and *Brucella canis* infects dogs. A pattern of disease severity in humans is as follows: *B melitensis* > B suis > *B abortus* > *B canis*. Most human infections occur by contact with infected animal tissues or ingestion of contaminated raw meat or dairy products. Person-to-person transmission typically does not occur. The bacteria are highly infectious by aerosol and commonly cause infections in laboratory workers.[11] Brucellae are susceptible to commonly used disinfectants and heat but may survive for 6 weeks in dust and 10 weeks in soil or water.

The United States weaponized *B suis* in the 1940s and 1950s but stopped offensive work on the agent in the 1960s. Other countries have or are suspected to have weaponized brucellae.[12] The organism could be delivered as a slurry in bomblets or, theoretically, as a dry aerosol.

Clinical Features

Brucellae are facultative intracellular macrophage parasites, and localize in organs (especially the lung, spleen, liver, central nervous system, bone marrow, and synovium) with large numbers of macrophages.[13] Disease manifestations reflect this distribution. Symptoms and signs are similar in patients with presumed oral, aerosol, or percutaneous infection. Patients usually have fever, chills, and malaise.[14,15] Respiratory symptoms (cough, pleuritic chest pain) may occur in 20% of patients but do not usually denote pneumonia. Sacroiliitis, large joint infections, and vertebral osteomyelitis are the most common osteoarticular manifestations.[16-18] Genitourinary infections and hepatitis may also occur.[19] Endocarditis and central nervous system infections are rare, but account for nearly all fatalities, which occur in less than 5% of untreated patients.[20] Systemic symptoms may last for weeks or months. Even without antibiotics, most patients recover within a year, but relapses are common.[21] Hematological abnormalities, including anemia, neutropenia, and thrombocytopenia, may be present.[22]

Diagnosis and Management

Symptoms and signs of brucellosis are nonspecific. A serum tube agglutination test is the usual diagnostic method.[23] Cultures of blood, bone marrow, and focal sites of infection may be positive.[24] The organism grows slowly, but adequately, in conventional blood culture bottles. Cultures must be kept for at least 6 weeks with periodic blind subculturing onto enriched agar plates. A special biphasic culture technique (Castaneda bottle), if available, may facilitate *Brucella* isolation.[25]

Patients should be treated with combinations of antibiotics, as treatment with single agents leads to poor response or relapse. A combination of 200 mg/d of doxycycline orally and 600 to 900 mg/d of rifampin orally for 6 weeks is usually the treatment of choice.[26,27] Trimethoprim-sulfamethoxazole may be substituted for rifampin. For bone and joint infections, endocarditis, and central nervous system disease, streptomycin or another aminoglycoside should be included, and therapy should be prolonged. Treatment of endocarditis may require valve replacement.[28] There is no approved Brucella vaccine for humans.

PLAGUE

History and Significance

Yersinia pestis, the etiologic agent of plague, is a gram-negative bacillus of the family Enterobacteriaceae that is maintained in numerous and diverse rodent reservoirs.[29,30] Plague is transmitted via flea vectors from rodents to humans and by respiratory droplets from animals to humans or humans to humans.[29-32]

During World War II, Japan investigated the use of plague as a biological weapon. The United States studied *Y pestis* as a potential BW agent in the 1950s before the offensive BW program was terminated, and other countries have been suspected of weaponizing plague.

Clinical Features

The clinical presentations of plague are bubonic, primary septicemic, and pneumonic disease.[29-31] The most likely clinical presentation after a BW attack would be primary pneumonic plague.[29,30] After an incubation period of 2 to 3 days, patients present with pneumonia featuring the acute and often fulminant onset of malaise, high fever, chills, headache, myalgia, cough with production of a bloody sputum, and clinical sepsis. The chest x-ray film reveals a patchy or consolidated bronchopneumonia. Pneumonic plague progresses rapidly, resulting in dyspnea, stridor, and cyanosis. The terminal course may feature respiratory failure, shock, and ecchymoses.

Diagnosis and Management

A presumptive diagnosis can be made by identifying a gram-negative coccobacillus and safety-pin bipolar staining organisms in gram-stained or Wright-Giemsa–stained smears from peripheral blood, lymph node needle aspirate, sputum, or other clinical specimens. Immunofluorescent staining for the capsule is diagnostic. The diagnosis can be confirmed by culturing the organism from blood, sputum, and bubo aspirates. The organism grows slowly at standard incubation temperatures and may be misidentified by automated systems because of delayed biochemical reactions. Most strains of *Y pestis* produce F1 capsule antigen in vivo, which can be detected in serum samples by immunoassay. A 4-fold rise in antibody titer is also diagnostic.

Streptomycin sulfate, tetracycline, chloramphenicol, and gentamicin sulfate are effective therapies for bubonic plague, especially if begun within 24 hours of the onset of symptoms.[30] Plague pneumonia is almost always fatal if treatment is not initiated within 24 hours of the onset of symptoms. Streptomycin is given intramuscularly in a dose of 30 mg/kg per day in 2 divided doses for 10 days. Gentamicin may be substituted for streptomycin. Chloramphenicol given intravenously is indicated for treating plague meningitis and in cases of circulatory compromise. Intravenous doxycycline (200 mg initially, followed by 100 mg every 12 hours) for 10 to 14 days is also effective. Results obtained from an animal model suggest that quinolones may be effective for treating plague, but they have not been evaluated in humans.[32] Supportive therapy includes intravenous crystalloids and hemodynamic monitoring.

A licensed, killed whole-cell vaccine is available for use in those considered to be at risk of exposure.[33] While epidemiologic evidence supports the efficacy of the current vaccine against bubonic plague, its efficacy against aerosolized *Y pestis* is believed to be poor.[34]

Q FEVER

History and Significance

Q fever, a febrile, zoonotic disease with a worldwide distribution, typically results from exposure to domestic livestock animals (mainly sheep, cattle, and goats). The infection is caused by *Coxiella burnetii,* an obligate intracellular rickettsialike organism of low virulence but remarkable infectivity.[35]

Coxiella burnetii produces a sporelike form that may cause infection after indirect exposure to infected animals or animal products, such as can occur in individuals who live or work in the vicinity of infected animals.[36-38] In addition, the ability of this sporelike form to withstand heat and drying and to survive on inanimate surfaces allows the organism to persist in the environment for weeks or months after an infected animal has vacated an area and for dissemination by wind with induction of infection at sites miles distant from a source.[38]

Individuals are at risk for acquisition of Q fever, both in the United States and abroad.[39,40] Q fever is currently recognized as a potential BW agent, with a degree of infectivity and casualty production rivalling that of anthrax.[1] *Coxiella burnetii* was studied as a BW agent before the US BW program ended.[41]

Clinical Features

There is no single syndrome characteristic for acute Q fever, and the infection may be manifested by asymptomatic seroconversion in up to 50% of infections.[36-44] The onset of Q fever may be abrupt or insidious, with fever, chills, and headache being the most common symptoms. Diaphoresis, malaise, fatigue, anorexia, and weight loss are also common. Myalgia is a frequent complaint, while arthralgia is less common. Cough tends to appear somewhat late in the illness and may not be a prominent complaint. Chest pain occurs in a minority of patients and may be pleuritic or a vague substernal discomfort. Although nonspecific evanescent skin eruptions have been reported, there is no characteristic rash. Temperature tends to fluctuate, with peaks of 39.4°C to 40.6°C, and approximately 25% of the cases are biphasic. In two thirds of patients with acute disease, the febrile period lasts 13 days or fewer.[43] Neurological symptoms are not uncommon and have been observed in up to 23% of acute cases.[44]

Rales are the most common physical finding; evidence of pleural effusion (including friction rub) and consolidation may also be noted. Although hepatomegaly, splenomegaly, and jaundice have all been reported, they are relatively unusual in acute infection. Reports of abnormalities on chest radiograph vary with locale, but can be identified in 50% to 60% of symptomatic patients and may persist for several months.[38] An abnormal chest radiograph may be seen in the absence of pulmonary symptoms, while a normal chest radiograph may be observed in a patient with pulmonary symptoms.[38]

Laboratory abnormalities associated with acute Q fever usually involve liver function tests, and patients may present with a clinical and laboratory picture consistent with acute hepatitis. Twofold and 3-fold elevations of aspartate aminotransferase and/or alanine aminotransferase are observed in 50% to 75% of patients, while elevations of the alkaline phosphatase and/or total bilirubin are observed in only 10% to 15%.[38] The white blood cell count is usually normal; mild anemia or thrombocytopenia may also be observed.

The case-fatality rate of acute Q fever is low, even without treatment, and chronic disease, usually manifested by endocarditis, probably develops in less than 1% of acute infections.[38,45] Malaise and easy fatiguability lasting for months after acute infection have been reported in up to 32% of patients.[38]

Diagnosis and Management

Diagnosis of Q fever is usually accomplished by serological testing; the most common methods are antibody detection by indirect fluorescent antibody (IFA) or ELISA. Significant antibody titers are not consistently identifiable until 2 to 3 weeks into the illness. Convalescent antibody titers, 2 to 3 months after onset of illness, typically demonstrate a 4-fold increase.[46,47] After acute infection, significantly elevated antibody titers may persist for years.[48] Chronic infection almost always induces significant antibody titers.[45]

Treatment of acute Q fever shortens the course of the disease and prevents disease when administered during the incubation period.[48] Tetracyclines remain the mainstay of therapy for acute disease. Macrolide antibiotics, such as erythromycin and azithromycin, are also effective. Quinolones, chloramphenicol, and trimethoprim-sulfamethoxazole have also been used to treat Q fever, but clinical experience with these antibiotics is limited.

Although an effective vaccine (Q-Vax) is licensed in Australia, all Q fever vaccines used in the United States are investigational.[49,50] Individuals already immune to Q fever frequently develop severe local reactions at the site of vaccine injection.[51,52] These reactions can be avoided by prior screening with an intradermal skin test to detect presensitized or immune individuals.[53]

TULAREMIA

History and Significance

Francisella tularensis, the etiologic agent of tularemia, is a small, nonmotile, aerobic, facultative intracellular gram-negative coccobacillus. Tularemia (also known as rabbit fever and deer fly fever) is a zoonotic disease, and humans acquire the disease under natural conditions through inoculation of skin or mucous membranes with blood or tissue fluids of infected animals or bites of infected deerflies, mosquitoes, or ticks. Although less common, inhaling contaminated dusts or ingesting contaminated foods or water may also produce clinical dis-

ease.[54,55] Respiratory exposure by aerosol would cause typhoidal tularemia, which often has a pneumonic component. The organism can remain viable for weeks in water, soil, carcasses, and hides, and for years in frozen rabbit meat.[55]

Francisella tularensis was weaponized by the United States in the 1950s and 1960s before the US offensive BW program was terminated, and other countries may have weaponized this agent for delivery by aerosol.

Clinical Features

Tularemia may appear in 2 forms in humans depending on the route of inoculation: ulceroglandular or typhoidal. In humans, as few as 10 to 50 organisms will cause disease if inhaled or injected intradermally. The most common ulceroglandular form is usually acquired through inoculation of the skin or mucous membranes with blood or tissue fluids of infected animals. The typhoidal form, which occurs mainly after inhalation of infectious aerosols, accounts for 15% to 25% of naturally occurring cases. Typhoidal or septicemic tularemia manifests as fever, prostration, and weight loss, but without adenopathy.[55-57] Respiratory symptoms of substernal discomfort and a nonproductive cough may also be present. Radiological evidence of pneumonia, with associated pleural effusion in some cases, may be present in all forms of tularemia, but is most common with typhoidal disease. The case-fatality rate with all forms of untreated typhoidal disease is approximately 35%.[54,55]

Diagnosis and Management

Diagnosis can be established by isolating the organism from blood, sputum, skin, or mucosal membrane lesions, but it is difficult due to unusual growth requirements and/or overgrowth of commensal bacteria. Diagnosis of primary typhoidal tularemia is also difficult because signs and symptoms are nonspecific and frequently there is no suggestive exposure history. The diagnosis can best be established retrospectively by serologic testing.[51,52]

Streptomycin (30 mg/kg per day intramuscularly in 2 divided doses for 10-14 days) is the treatment of choice.[58] Gentamicin (3-5 mg/kg per day parenterally for 10-14 days) also is effective .[57,59] Tetracycline and chloramphenicol are effective as well but are associated with significant relapse rates.[59] Although laboratory-related infections with this organism are common, human-to-human spread is unusual and respiratory isolation is not required. A live attenuated tularemia vaccine is available as an Investigational New Drug (IND).[60]

SMALLPOX

History and Significance

After the last natural case of variola in Somalia in 1977,[61,62] smallpox was declared eradicated in 1980 by the WHO. Natural smallpox outbreaks were contained by rapid vaccination of contacts of the index cases, facilitated by the ease of vaccinia administration. There is no animal reservoir for variola; however, monkeys are susceptible to infection.[63] Although a laboratory accident[64] prompted the consolidation of variola virus stocks into 2 WHO-approved repositories at the Centers for Disease Control and Prevention (CDC) in Atlanta and at NPO (Scientific and Production Association) in the Novosibirsk region of Russia, the extent of clandestine stockpiles remains a matter of contention and concern.

The aerosol infectivity, high mortality, and stability of variola make it (and potentially monkeypox virus) a potential threat in BW and terrorism scenarios.[1(pp69-70),65] Although some have argued that smallpox would have limited potential as a biological weapon,[62(p1841)] the discontinuation of routine vaccination has rendered civilian and military populations more susceptible to a disease that is infectious by aerosol and infamous for its devastating morbidity and mortality. In 1970, the WHO expressed concerns that smallpox "can easily be produced in large quantities in the laboratory and freeze-dried and its virulence thus preserved for months or years."[1(pp69-70)] The theoretical potential that genetic recombination could produce a modified animal poxvirus with enhanced virulence for humans has raised the specter that other poxviruses besides smallpox might constitute serious BW or reemergent public health problems. Mass vaccination of civilian populations is now complicated by the increasing number of immunocompromised patients (eg, those with human immunodeficiency virus infection, organ transplant, and chemotherapy).

Clinical Features

After aerosol exposure, variola travels from the upper or lower respiratory tract to regional lymph nodes where it replicates and gives rise to viremia followed soon thereafter by rash. During the prodrome before onset of pox lesions, variola virus can be recovered from the blood. The abrupt onset of clinical manifestations is marked by systemic toxicity with prominent malaise, fever, rigors, vomiting, headache, and backache; 15% of patients develop delirium. Approximately 10% of light-skinned patients exhibit an erythematous rash during this phase. Two to 3 days later, an enanthem appears concomitantly with a discrete rash about the face, hands, and forearms. The mucous membrane lesions shed infectious oropharyngeal secretions in the first few days of the eruptive illness.[66] These respiratory secretions are the most important but not the sole means of virus transmission to contacts. After eruptions on the lower extremities, the rash spreads centrally to the trunk over the next week. Lesions quickly progress from macules to papules and eventually to pustular vesicles. Lesions are more abundant on the extremities and face, and this centrifugal distribution is an important diagnostic feature. In distinct contrast to varicella, lesions on various segments of the body remain generally synchronous in their stage of development. In the second week after onset, the pustules form scabs that leave depressed depigmented scars on healing. Although variola titers in the throat, conjunctiva, and urine diminish with time,[67] virus can readily be recovered from scabs throughout convalescence.[68] Therefore, patients should be isolated and considered infectious until all scabs separate.

In distinct contrast to varicella, lesions on various segments of the body remain synchronous in their stage of development.

During this past century, the prototypical disease variola major caused mortality of 3% and 30% in the vaccinated and unvaccinated, respectively.[62(p591)] Other clinical forms associated with variola major, flat-type and hemorrhagic-type smallpox, were notable for severe mortality. A naturally occurring relative of variola, monkeypox, occurs in Africa and is clinically indistinguishable from smallpox exception for a notable enlargement of cervical and inguinal lymph nodes. Secondary bacterial pneumonia is associated with greater than 50% mortality.[69] Concern has been raised whether monkeypox could be weaponized like variola. Although previous evidence suggested that monkeypox had limited potential for person-to-person transmission,[70] recent reports indicate greater potential for sustained interhuman transmission,[71] perhaps owing to declining vaccinia immunity of the populace.

Diagnosis and Management

Given the eradication of endemic smallpox, it requires an astute clinician to distinguish the forme fruste of this disease from other vesicular exanthems, such as chickenpox, erythema multiforme with bullae, or allergic contact dermatitis. Many exposed persons may shed virus

Biological Warfare

A Historical Perspective

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The deliberate use of microorganisms and toxins as weapons has been attempted throughout history. Biological warfare has evolved from the crude use of cadavers to contaminate water supplies to the development of specialized munitions for battlefield and covert use. The modern development of biological agents as weapons has paralleled advances in basic and applied microbiology. These include the identification of virulent pathogens suitable for aerosol delivery and industrial-scale fermentation processes to produce large quantities of pathogens and toxins. The history of biological warfare is difficult to assess because of a number of confounding factors. These include difficulties in verification of alleged or attempted biological attacks, the use of allegations of biological attacks for propaganda purposes, the paucity of pertinent microbiological or epidemiologic data, and the incidence of naturally occurring endemic or epidemic diseases during hostilities. Biological warfare has been renounced by 140 nations, primarily for strategic and other pragmatic reasons. International diplomatic efforts, including the 1972 Biological Weapons Convention, have not been entirely effective in preventing the enhancement and proliferation of offensive biological warfare programs. The threats posed by biological weapons are likely to continue into the future.

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HUMANS, regrettably, have used available technologies for destructive as well as for beneficial purposes throughout history. Modern attempts to "weaponize" biological toxins such as botulinum and ricin were anticipated by the use of curare and amphibian-derived toxins as arrow poisons by aboriginal South Americans using neolithic technology. Fomites (ie, objects that harbor and can transmit disease agents) have been used to deliberately transmit infectious diseases since antiquity. The study of the history of biological warfare is confounded by several factors. These include difficulties confirming allegations of biological attack, the lack of reliable microbiological and epidemiologic data regarding alleged or attempted attacks, the use of allegations of biological attack for propaganda, and the secrecy surrounding biological weapons programs. However, a review of historical sources demonstrates that interest in developing biological weapons has persisted throughout history and is likely to continue into the future.

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The opinions expressed in this article are those of the authors and do not reflect the positions or policies of the US Department of the Air Force, the US Department of the Army, the US Department of Defense, or the US government.

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EARLY ATTEMPTS

Recognition of the potential impact of infectious diseases on armies resulted in the crude use of filth, cadavers, animal carcasses, and contagion as weapons. These have been used to contaminate wells, reservoirs, and other water sources of armies and civilian populations under attack since antiquity, through the Napoleonic era, and into the 20th century.[1] The use of fomites directly against humans has continued, as evidenced by the smearing of pungi sticks with excrement by the Viet Cong in the early 1960s.[2]

One of the earliest recorded attempts of using fomites against a population illustrates the complex epidemiologic issues raised by biological warfare. During the 14th-century siege of Kaffa (now Feodossia, Ukraine), the attacking Tatar force experienced an epidemic of plague. The Tatars attempted to convert their misfortune into an opportunity by catapulting the cadavers of their deceased into the city to initiate a plague epidemic. An outbreak of plague was followed by the retreat of defending forces and the conquest of Kaffa. Ships carrying plague-infected refugees (and possibly rats) sailed to Constantinople, Genoa, Venice, and other Mediterranean ports and are thought to have contributed to the second plague pandemic.[3] However, given the complex ecology and epidemiology of plague, it may be an oversimplification to implicate the biological attack as the sole cause of the plague epidemic in Kaffa. Plague may have been imported into Kaffa by a natural cycle involving sylvatic and urban rodents and their fleas,[4,5] and the population under siege may have been at increased risk of epidemics because of deteriorating sanitation and hygiene. Since plague-transmitting fleas leave cadavers to parasitize living hosts, we would suggest that the corpses catapulted over the walls of Kaffa may not have been carrying competent plague vectors.

. . . it may be an oversimpification to implicate the biological attack as the sole cause of the plague epidemic in Kaffa.

Smallpox was used as a biological weapon against Native Americans in the 18th century. During the French and Indian War (1754-1767), Sir Jeffrey Amherst, commander of British forces in North America, suggested the deliberate use of smallpox to "reduce" Native American tribes hostile to the British.[6] An outbreak of smallpox at Fort Pitt resulted in the generation of fomites and an opportunity to execute Amherst's plan. On June 24, 1763, Captain Ecuyer, one of Amherst's subordinates, gave blankets and a handkerchief from the smallpox hospital to the Native Americans and recorded in his journal, "I hope it will have the desired effect."[7] While this adaptation of the Trojan horse ruse was followed by epidemic smallpox among Native American tribes in the Ohio River valley,[8] other contacts between colonists and Native Americans may have contributed to these epidemics.[9] Smallpox epidemics among immunologically naive tribes of Native Americans following initial contacts with Europeans had been occurring for more than 200 years. In addition, the transmission of smallpox by fomites was inefficient compared with respiratory droplet transmission.[9]

Both of these early attempts at biological warfare illustrate the difficulty of differentiating naturally occurring epidemics from alleged or attempted biological attack. This problem has had continued relevance because naturally occurring endemic diseases have been ascribed to alleged biological attacks for propaganda purposes.

THE ERA OF MODERN MICROBIOLOGY AND THE USE OF BIOLOGICAL WEAPONS DURING THE WORLD WARS

The formulation of Koch's postulates and the development of modern microbiology during the 19th century afforded the capability to isolate and produce stocks of specific pathogens. Substantial evidence suggests that Germany developed an ambitious biological warfare program during World War I, featuring covert operations in neutral trading partners of the Allies to infect livestock and contaminate animal feed to be exported to Allied forces.[10] *Bacillus anthracis* and *Burkholderia (Pseudomonas) mallei*, the etiologic agents of anthrax and glanders, were to be used to infect Romanian sheep for export to Russia. Cultures confiscated from the German Legation in Romania in 1916 were identified as *B anthracis* and *B mallei* at the Bucharest Institute of Bacteriology and Pathology.[4,5] *Burkholderia mallei* was allegedly used by German saboteurs operating in Mesopotamia to inoculate 4500 mules and in France to infect horses of the French cavalry.[4] Argentinian livestock intended for export to Allied forces were infected with *B anthracis* and *B mallei*, resulting in the deaths of more than 200 mules from 1917 to 1918.[4] Operations in the United States included attempts to contaminate animal feed and to infect horses intended for export during World War I.[11]

In response to the horror of chemical warfare during World War I, international diplomatic efforts were directed toward limiting the proliferation and use of weapons of mass destruction. The first diplomatic attempt at limiting biological warfare was the 1925 Geneva Protocol for the Prohibition of the Use in War of Asphyxiating, Poisonous or Other Gases, and of Bacteriological Methods of Warfare.[12] This treaty prohibited the use of biological weapons. However, the treaty did not proscribe basic research, production, or possession of biological weapons, and many countries ratified the protocol while stipulating a right of retaliation.[12] There were no provisions for inspection. Parties to the Geneva Protocol that began basic research programs to develop biological weapons after World War I included Belgium, Canada, France, Great Britain, Italy, the Netherlands, Poland, and the Soviet Union.[13] The United States did not ratify the Geneva Protocol until 1975.

Japan conducted biological weapons research in occupied Manchuria from 1932 until the end of World War II under the direction of Shiro Ishii (1932-1942) and Kitano Misaji (1942-1945). Unit 731, a biological warfare research facility located near the town of Pingfan, was the center of the Japanese biological weapons development program and contained 150 buildings, 5 satellite camps, and a staff of more than 3000 scientists and technicians. Additional units were located at Mukden, Changchun, and Nanking. Prisoners were infected with pathogens including *B anthracis*, *Neisseria meningitidis*, *Shigella* spp, *Vibrio cholerae*, and *Yersinia pestis*.[13,14] At least 10 000 prisoners died as a result of experimental infection or execution following experimentation during the Japanese program between 1932 and 1945.[14]

As many as 15 million fleas were released per attack to initiate epidemics of plague.

Participants in the Japanese program who had been captured by the Soviet Union during World War II admitted to 12 large-scale field trials of biological weapons in testimony obtained during war crimes prosecution.[15,16] At least 11 Chinese cities were attacked with biological agents. Attacks featured contaminating water supplies and food items with pure cultures of *B anthracis*, *V cholerae*, *Shigella* spp, *Salmonella* spp, and *Y pestis*. Cultures were also tossed directly into homes and sprayed from aircraft.[13-16] Plague was allegedly developed as a biological weapon by allowing laboratory-bred fleas to feed on plague-infected rats. These potentially infected fleas were then harvested and released from aircraft over Chinese cities. As many as 15 million fleas were released per attack to initiate epidemics of plague. Dr P. Z. King, director general of the Chinese National Health Administration, attributed epidemic plague to these attacks; however, rigorous epidemiologic and bacteriologic data are not available.[17] In addition, the Japanese had not adequately prepared, trained, or equipped their own troops for the hazards of biological weapons. An attack on Changteh in 1941 reportedly led to approximately 10 000 biological casualties and 1700 deaths among Japanese troops, with most cases due to cholera.[16] Field trials were terminated by Misaji in 1942, although basic research continued until the end of the war.[14]

Hitler reportedly issued orders prohibiting biological weapons development in Germany. However, with the support of high-ranking Nazi party officials, German scientists began biological weapons research, although their results lagged far behind those of other countries. A German offensive biological weapons threat never materialized.[18] Prisoners in Nazi concentration camps were forcibly infected with *Rickettsia prowazekii*, *Rickettsia mooseri*, hepatitis A virus, and *Plasmodia* spp and treated with investigational vaccines and drugs. These inhumane experiments were done to study pathogenesis, to develop vaccines against rickettsiae, and to develop sulfonamides rather than to develop biological weapons.[18] The only known German tactical use of biological warfare was the pollution of a large reservoir in northwestern Bohemia with sewage in May 1945.[1] Ironically, the combination of a vaccine and a serologic test was used as a biological defense against the Nazis. The German army avoided areas with epidemic typhus by using the Weil-Felix reaction for diagnosis. Consequently, physicians used formalin-killed *Proteus* OX-19 as a vaccine to induce biological false-positive tests for typhus in an area of occupied Poland, and residents were protected from deportation to concentration camps.[19]

The Allies developed biological weapons for potential retaliatory use in response to German biological attack. Bomb experiments of weaponized spores of *B anthracis* were conducted on Gruinard Island near the coast of Scotland and resulted in heavy contamination. Viable anthrax spores persisted until the island was decontaminated with formaldehyde and seawater during 1986.[20]

THE US PROGRAM

In the United States, an offensive biological program was begun in 1942 under the direction of a civilian agency, the War Reserve Service. The program included a research and development facility at Camp Detrick, Md (renamed Fort Detrick in 1956), testing sites in Mississippi and Utah, and a production facility in Terre Haute, Ind. Experiments were conducted using pathogens, including *B anthracis* and *Brucella suis*. However, the production facility lacked adequate engineering safety measures. For example, tests of the fermentation and storage processes using nonpathogenic *Bacillus subtilis* var *globigii* as a *Banthracis* simulant disclosed contamination of the plant and environs. These findings precluded large-scale production of biological weapons during World War II, although 5000 bombs filled with *B anthracis* spores were produced at a pilot plant at Camp Detrick.[21] After the war, the production facility was leased and converted to commercial pharmaceutical production.[21] Basic research and develop-

ment activities were continued at Camp Detrick. Ishii, Misaji, and other Japanese scientists in American custody who had participated in the Unit 731 program were granted immunity from war crimes prosecution on the condition that they would disclose information obtained during their program. Secret debriefings were conducted during the postwar era.[13,16]

The US program was expanded during the Korean War (1950-1953). A new production facility incorporating adequate biosafety measures was constructed at Pine Bluff, Ark. Technical advances allowed large-scale fermentation, concentration, storage, and weaponization of microorganisms; production was begun in 1954. In addition, a program to develop countermeasures, including vaccines, antisera, and therapeutic agents to protect troops from possible biological attack, was begun in 1953.

Cities were surreptitiously used as laboratories to test aerosolization and dispersal methods . . .

Animal studies were performed at Fort Detrick, at remote desert sites, and on barges in the Pacific Ocean. Human experimentation using military and civilian volunteers was initiated in 1955. Biological munitions were detonated inside a 1-million-liter, hollow, metallic, spherical aerosolization chamber at Fort Detrick known as the "eight ball." Volunteers inside the chamber were exposed to *Francisella tularensis* and *Coxiella burnetii*. These and other challenge studies were done to determine vulnerability to aerosolized pathogens and the efficacy of vaccines, prophylaxis, and therapies under development. Additional studies were done using simulants. *Aspergillus fumigatus*, *B subtilis* var *globigii*, and *Serratia marcescens* were selected for use as simulants; these organisms were thought to be nonpathogenic and were used to study production and storage techniques as well as aerosolization methods, the behavior of aerosols over large geographic areas, and the effects of solar irradiation and climatic conditions on the viability of aerosolized organisms. Cities were surreptitiously used as laboratories to test aerosolization and dispersal methods when simulants were released during covert experiments in New York City, San Francisco, and other sites between 1949 and 1968.[21,22,23]

Concerns regarding potential public health hazards of simulant studies were raised after an outbreak of urinary tract infections caused by nosocomial *S marcescens* (formerly *Chromobacterium prodigiosum*) occurred at Stanford University Hospital between September 1950 and February 1951.[24] The outbreak followed covert experiments using *S marcescens* as a simulant in San Francisco.[23] The outbreak involved 11 cases, resulting in 1 transient bacteremia and 1 death from endocarditis. All patients had undergone urinary tract catheterization, and 5 had undergone cystoscopy for urologic indications. Exposure to multiple antibiotics was cited as a contributing factor to the outbreak.[24] No similar outbreaks were reported by other hospitals in the San Francisco area. This outbreak is thought to represent an early example of nosocomial epidemics caused by opportunists of low virulence, related to antibiotic use, new medical devices, and surgical procedures.[25]

In view of the temporal relationship of the outbreak with the simulant studies, the army convened an investigative panel in 1952, including members from the Communicable Disease Center, the National Institutes of Health, the City of New York Health Department, and Ohio State University. The panel did not comment directly on the possible association of the nosocomial outbreak and the simulant studies. The panel recommended continued use of *S marcescens* in view of its low virulence, but added that a search for better simulants to replace *S marcescens* should be pursued.[23] However, simulant studies using *S marcescens* continued until 1968. Public interest in these covert experiments was aroused in 1976 when the *Washington Post* reported them[26] and implied that the endocarditis death was a direct result of the simulant testing. It was further implied that sudden increases in the incidence of pneumonia in Calhoun County, Alabama, and Key West, Fla, were related to simulant studies at those locales. As a result of the ensuing public outcry, Senate hearings were held in 1977, and the army was severely criticized for the continued use of *S marcescens* following awareness of the Stanford outbreak.[22]

Nonetheless, several facts cast doubt on an etiologic relationship between military use of *S marcescens* and outbreaks of human disease. The Centers for Disease Control reported that in 100 outbreaks of *S marcescens* infection, none was caused by the 8UK strain used by the army (biotype A6, serotype O8:H3, phage type 678).[27] Numerous reports during the 1970s postulated a link between the army experiments and cases of *S marcescens* endocarditis, septic arthritis, and osteomyelitis in California heroin addicts; where strains were available for testing, they were likewise shown to differ antigenically from the army test strain.[27] A review of the role of *S marcescens* in the army biological program was published in 1979.[25]

Table 1.—Biological Agents Weaponized and Stockpiled by the US Military (Destroyed 1971-1973)

Lethal agents*
Bacillus anthracis
Botulinum toxin
Francisella tularensis
Incapacitating agents*
Brucella suis
Coxiella burnetii
Staphylococcal enterotoxin B
Venezuelan equine encephalitis virus
Anticrop agents†
Rice blast
Rye stem rust
Wheat stem rust

*Weaponized.
†Stockpiled, but not weaponized.

There were 456 cases of occupational infections acquired at Fort Detrick during the offensive biological program (1943-1969), at a rate of less than 10 infections per 1 million hours worked. The rate of occupational infection was well within the contemporary standards of the National Safety Council and below the rates reported from other laboratories. There were 3 fatalities due to occupationally acquired infections—2 cases of anthrax in 1951 and 1958 and a case of viral encephalitis in 1964. The mortality rate was lower than those of other contemporary surveys of laboratory-acquired infections. There were 48 occupational infections and no fatalities reported from production and testing sites. The safety program included the development and use of new vaccines as well as engineering safety measures.[23]

By the late 1960s, the US military had developed a biological arsenal that included numerous bacterial pathogens, toxins, and fungal plant pathogens that could be directed against crops to induce crop failure and famine (Table 1).[23] In addition, weapons for covert use using cobra venom, saxitoxin, and other toxins were developed for use by the Central Intelligence Agency; all records regarding their development and use were destroyed during 1972.[28]

KOREAN WAR AND COLD WAR ALLEGATIONS

The Soviet Union, China, and North Korea accused the United States of using biological warfare against North Korea and China during the Korean War. These accusations were supported by a series of investigations conducted by the International Scientific Commission, a group of scientists, and other organizations not part of the commission. Although these investigations were described as impartial, they were carefully controlled by the North Korean and Chinese governments.[29] The United States admitted to having biological warfare capabilities, but denied using biological weapons. The United States requested impartial investigations. The Interna-

tional Committee of the Red Cross suggested the formation of a special commission to investigate, and the World Health Organization offered to intervene. Neither China nor North Korea responded to the International Committee of the Red Cross, and the World Health Organization's offer was rebuffed as a disguised attempt at espionage. Consequently, the United States and 15 other nations submitted a resolution to the United Nations (UN) requesting the formation of a neutral commission to investigate the allegations; however, implementation of the resolution was prevented by the Soviet Union. The credibility of the United States was undermined by its failure to ratify the 1925 Geneva Protocol, by knowledge of its offensive biological warfare program, and the suspected covert collaboration with the Unit 731 scientists.[29] Although unsubstantiated, the accusations of US use of biological weapons attracted wide attention and resulted in a loss of international goodwill toward the United States. This episode demonstrated the propaganda value of biological warfare allegations, regardless of veracity.[29,30]

Numerous unsubstantiated allegations were made during the cold war era. These included Soviet accusations of US biological weapons testing against Canadian Eskimos resulting in a plague epidemic[31] and of a US and Columbian biological attack on Columbian and Bolivian peasants.[32] The United States also was accused of planning to initiate an epidemic of cholera in southeastern China[33] and of the covert release of dengue in Cuba.[34]

Similarly, the US allegations that Soviet armed forces and their proxies had used aerosolized trichothecene mycotoxins ("yellow rain"), potent inhibitors of DNA and protein synthesis derived from fungi of the genus *Fusarium*, in Laos (1975-1981), Kampuchea (1979-1981), and Afghanistan (1979-1981) are widely regarded as erroneous. The remote locations of the alleged attacks made intelligence investigations extremely difficult. Attacks were never witnessed by Western intelligence operatives, and samples of the aerosols were not recovered. Confounding factors included the following: contradictory testimonies from survivors of the alleged attack, discrepancies in reported symptoms, low disease rates in the allegedly exposed populations, the recovery of mycotoxin in less than 10% of the clinical and environmental samples submitted, the presence of *Fusarium* organisms as environmental commensals, the possible decay of toxin under prevailing environmental conditions, conflicting results of toxin assays from different laboratories, the similarity of alleged yellow rain deposits recovered from environmental surfaces to bee feces in ultrastructural appearance and pollen and mold content, and the natural occurrence of showers of bee feces from swarms of honey bees in the rain forests of southeast Asia.[35]

DISARMAMENT EFFORTS

During the late 1960s, there was increasing international concern regarding the indiscriminate nature, unpredictability, epidemiologic risks, and lack of epidemiologic control measures for biological weapons, as well as the ineffectiveness of the 1925 Geneva Protocol for preventing biological weapons proliferation. In July 1969, Great Britain submitted a proposal to the Committee on Disarmament of the UN prohibiting the development, production, and stockpiling of biological weapons and providing for inspections in response to alleged violations. During the following September, the Warsaw Pact nations submitted a biological disarmament proposal similar to the British proposal, but without provisions for inspections. Two months later, the World Health Organization issued a report regarding the potential consequences of biological warfare.[36] Estimates of the casualty figures that could result from biological attacks were staggering (Table 2).[36]

Table 2.—Estimates of Casualties Produced by Hypothetical Biological Attack*

Agent	Downwind Reach, km	No. Dead	No. Incapacitated
Rift Valley fever	1	400	35 000
Tick-borne encephalitis	1	9500	35 000
Typhus	5	19 000	85 000
Brucellosis	10	500	125 000
Q fever	>20	150	125 000
Tularemia	>20	30 000	125 000
Anthrax	>20	95 000	125 000

*Release of 50 kg of agent by aircraft along a 2-km line upwind of a population center of 500 000.[36]

Subsequently, the 1972 Convention on the Prohibition of the Development, Production, and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on Their Destruction (BWC) was developed.[37] The treaty prohibits the development, possession, and stockpiling of pathogens or toxins in "quantities that have no justification for prophylactic, protective or other peaceful purposes." The BWC also prohibits the development of delivery systems intended to disperse biological agents and requires parties to destroy stocks of biological agents, delivery systems, and equipment within 9 months of ratifying the treaty. Transferring biological warfare technology or expertise to other countries is also prohibited. Signatories that have not yet ratified the BWC are obliged to refrain from activities that would defeat the purpose of the treaty until they explicitly communicate their intention not to ratify. However, there are unresolved controversies regarding the quantities of pathogens required for benevolent research and the definition of "defensive" research. Allegations of infractions may be lodged with the UN Security Council, which may in turn initiate inspections of accused parties; however, this provision is undermined by the right of Security Council members to veto proposed inspections.

The treaty was ratified in April 1972 and went into effect in March 1975. There were more than 100 signatory nations, including Iraq and the members of the Security Council (which included the United States and the Soviet Union). Review conferences were held in 1981, 1986, 1991, and 1996. Annual reports regarding biological research facilities, scientific conferences held at specified facilities, scientific exchanges, and epidemics are submitted to the UN as an additional confidence-building measure.[37]

President Nixon terminated the US offensive biological weapons program by executive order in 1969 and 1970. The United States adopted a policy never to use biological weapons, including toxins, under any circumstances whatsoever. National Security Decisions 35 and 44, issued during November 1969 (microorganisms) and February 1970 (toxins), mandated the cessation of offensive biological research and production and the destruction of the biological arsenal. Research efforts were directed exclusively to the development of defensive measures such as diagnostic tests, vaccines, and therapies for potential biological weapons threats. Stocks of pathogens and the entire biological arsenal were destroyed between May 1971 and February 1973 under the auspices of the US Department of Agriculture, the US Department of Health, Education, and Welfare, and the Departments of Natural Resources of Arkansas, Colorado, and Maryland. Small quantities of pathogens were retained at Fort Detrick to test the efficacy of investigational preventive measures and therapies. The Central Intelligence Agency was admonished during a 1975 congressional hearing for illegally retaining samples of toxins after presidential orders mandating their destruction.[28]

While many welcomed the termination of the US offensive program for moral and ethical reasons, the decision to terminate the offensive biological program was motivated by pragmatic considerations. Given the available conventional, chemical, and nuclear weapons, biological weapons were not considered essential for national security. The potential effects of biological weapons on military and civilian populations were still conjectural, and for obvious ethical and public health reasons could not be empirically studied. Biological weapons were considered untried,

unpredictable, and potentially hazardous for the users as well as for those under attack. Field commanders and troops were unfamiliar with their use. In addition, the United States and allied countries had a strategic interest in outlawing biological weapons programs to prevent the proliferation of relatively low-cost weapons of mass destruction. By outlawing biological weapons, the arms race for weapons of mass destruction would be prohibitively expensive, given the expense of nuclear programs.[38]

After the termination of the offensive biological program, the US Army Medical Research Institute of Infectious Diseases (USAMRIID) was established to continue the development of medical defenses for the US military against potential biological attack. The mission of USAMRIID is to conduct research to develop strategies, products, information, and training programs for medical defense against potential biological weapons. Endemic or epidemic infectious diseases due to highly virulent pathogens requiring high-level containment for laboratory safety are also studied. The USAMRIID is an open research institution; no research is classified. The in-house programs are complemented by contract programs with universities and other research institutions.

FOLLOWING THE 1972 BWC

Several signatory nations of the 1972 BWC, including Iraq and the former Soviet Union, have participated in activities outlawed by the convention. These events demonstrate the ineffectiveness of the convention as the sole means for eradicating biological weapons and preventing further proliferation.

Biological weapons were used for covert assassination during the 1970s. Ricin, a lethal toxin derived from castor beans, was weaponized by the secret service of the Soviet Union and deployed by the Bulgarian secret service. Metallic pellets that were 1.7 mm in diameter were cross drilled, filled with ricin, and sealed with wax intended to melt at body temperature. The pellets were discharged from spring-powered weapons disguised as umbrellas. These weapons were used to assassinate Georgi Markov, a Bulgarian defector living in London, and during an unsuccessful assassination attempt against another defector, Vladamir Kostov, in 1978. Similar weapons may have been used for at least 6 other assassinations.[39]

An epidemic of anthrax occurred during April 1979 among people who lived or worked within a distance of 4 km in a narrow zone downwind of a Soviet military microbiology facility in Sverdlovsk (now Ekaterinburg, Russia). In addition, livestock died of anthrax along the extended axis of the epidemic zone out to a distance of 50 km.[40] The facility was suspected by Western intelligence of being a biological warfare research facility, and the epidemic was attributed by Western analysts to the accidental airborne release of anthrax spores.

The Soviets maintained that the epidemic was caused by ingestion of contaminated meat purchased on the black market. In 1992, Boris Yeltsin, the president of Russia, admitted that the facility had been part of an offensive biological weapons program and that the epidemic had been caused by a nonintentional release of anthrax spores.[41] It was determined that air filters had not been activated early on the morning of April 3.[42] Inhalation anthrax was identified at autopsy as the cause of death in victims.[43] At least 77 cases and 66 deaths occurred, constituting the largest documented epidemic of inhalation anthrax in history.[42] The Soviets continued an offensive biological warfare program after the BWC of 1972 under the aegis of Biopreparat, an organization under the Ministry of Defense.[44] During the 1970s and 1980s, Biopreparat operated at least 6 research laboratories and 5 production facilities and employed up to 55 000 scientists and technicians.[45] The extensive program of the former Soviet Union is now controlled largely by Russia. Yeltsin stated in 1992 that he would end further offensive biological research and production[41]; however, the degree to which the program has been reduced is not known. A 1995 report estimated that the Russian program continues to employ 25 000 to 30 000 people.[45]

Before the Persian Gulf War, intelligence reports suggested that the Iraqi regime had sponsored an ambitious biological warfare program. Coalition forces prepared for potential biological warfare by training in protective masks and equipment, reviewing decontamination procedures, and immunizing troops against potential biological warfare threats. Approximately 150 000 US troops received a Food and Drug Administration–licensed toxoid vaccine against anthrax, and 8000 received a botulinum toxoid vaccine approved by the Food and Drug Administration as an Investigational New Drug. In addition, 30 million 500-mg oral doses of ciprofloxacin were stockpiled in the theater of operations to provide a 1-month course of chemoprophylaxis for the 500 000 US troops in the event that anthrax spores were used as a biological weapon.

Information regarding the Iraqi offensive biological program was obtained after the Persian Gulf War during UN weapons inspections. Iraqi officials admitted to having had an offensive biological weapons program that included basic research on *B anthracis*, rotavirus, camel pox virus, aflatoxin, botulinum toxins, mycotoxins, and an anticrop agent (wheat cover rust).[46,47] Fortunately, biological weapons were not used during the Persian Gulf War. The Iraqi government claims to have destroyed its biological arsenal after the war. Research and production facilities that had escaped destruction during the war were demolished by the UN Special Commission on Iraq (UNSCOM) in 1996. The Persian Gulf War and postwar findings have lead to a recent decision by the US military to develop a plan to immunize troops against anthrax.[48]

The biological threat posed by nonstate-sponsored terrorists was demonstrated by the intentional contamination of salad bars in Oregon restaurants with *Salmonella* Typhimurium by the Rajneeshee cult during late September 1984. This incident resulted in 751 cases of enteritis and 45 hospitalizations. Although the Rajneeshees were suspected, and despite rigorous epidemiologic analyses by the Wasco-Sherman Public Health Department, the Oregon State Health Division, and the Centers for Disease Control,[49,50] the origin of the epidemic as a deliberate biological attack was not confirmed until a cult member admitted to the attack in 1985.[51,52]

The threat of biological terrorism resurfaced following the Aum Shinrikyo sarin attack of the Tokyo subway system in March 1995. Police raids and investigations of the cult's facilities disclosed evidence of a rudimentary biological weapons program. The cult was allegedly conducting research of *B anthracis*, *Clostridium botulinum*, and *C burnetii*. The cult's arsenal seized by police allegedly contained botulinum toxin and drone aircraft equipped with spray tanks.[53] The cult had allegedly launched 3 unsuccessful biological attacks in Japan using *B anthracis* and botulinum toxin and had sent members to the former Zaire during 1992 to obtain Ebola virus for weapons development.[54]

CONCLUSIONS

Allegations of biological attacks have been made since World War I. However, most of these have not been confirmed in the absence of compelling microbiological or epidemiologic data supporting a biological attack. Furthermore, the Rajneeshee incident in Oregon demonstrated that biological attacks may be easy to conceal despite state-of-the-art microbiological and epidemiologic analysis. These incidents underscore the difficulty of differentiating biological attacks from naturally occurring epidemics or endemic disease and emphasize the increased risk of epidemics during hostilities because of deteriorating hygiene, sanitation, and public health infrastructure. The practice of ascribing

naturally occurring epidemic or endemic diseases to alleged biological attacks for propaganda purposes demonstrates the perception of psychological vulnerability to the threat of biological warfare.

Confirmed incidents involving biological weapons since World War II include the Sverdlovsk accident, the ricin assassination attempts, the Rajneeshee incident, and the discovery of the Aum Shinrikyo biological weapons effort. The most immediate threat of biological warfare to date was posed by Iraq during the Persian Gulf War. The reasons behind Saddam Hussein's decision not to use his biological arsenal are unknown. The most frequently proposed hypothesis forwarded by Western military analysts and intelligence sources has been possible Iraqi concern regarding the risk of provoking massive retaliation. Alternatively, other considerations may have included the possible ineffectiveness of Hussein's biological weapons and hazards to his own forces because of deficiencies in Iraqi training and equipment.[55]

International agreements to limit biological weapons proliferation have not been completely effective, as evidenced by events in the former Soviet Union and Iraq, both of which demonstrated activities prohibited by the BWC of 1972. Efforts to formulate legally binding measures to verify compliance with the BWC have been undertaken but, as of the Fourth Review Conference in December 1996 in Geneva, Switzerland, such efforts have not been successful. Disagreements continue regarding the utility of routine inspections at biological research facilities and the political, economic, commercial, and security consequences of such inspections. The Ad Hoc Group of Government Experts on Verification will continue to negotiate measures to verify compliance and is charged to complete its work "as soon as possible," and no later than 2001. A Fifth Review Conference is to be held in 2001.[56,57]

Concern continues regarding the possibility of proliferation or enhancement of state-sponsored, offensive biological weapons programs and the possible use of biological weapons by terrorist organizations. Following the termination of the US offensive program from 1969-1970, biological defense in the US military has focused on the development of countermeasures including detection capabilities, personal protective equipment, vaccines, diagnostics, and therapies to protect our military members.

This article is dedicated to the late Jay P. Sanford, MD, in appreciation for his invaluable contributions to the fields of infectious diseases, military medicine, and medical education.

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Iraq's Biological Weapons

The Past as Future?

Raymond A. Zilinskas, PhD

Between 1985 and April 1991, Iraq developed anthrax, botulinum toxin, and aflatoxin for biological warfare; 200 bombs and 25 ballistic missiles laden with biological agents were deployed by the time Operation Desert Storm occurred. Although cause for concern, if used during the Persian Gulf War, Iraq's biological warfare arsenal probably would have been militarily ineffective for 3 reasons: (1) it was small; (2) payload dispersal mechanisms were inefficient; and (3) coalition forces dominated the theater of war (ie, they had overwhelming air superiority and had crippled Iraq's command and control capability). Despite the Gulf War defeat, the Iraqi biological warfare threat has not been extinguished. Saddam Hussein remains in power, and his desire to acquire weapons of mass destruction continues unabated. In this context, the international community must be firm in its enforcement of United Nations resolutions designed to deter Iraq from reacquiring biological warfare capability and must take steps to develop a multidisciplinary approach to limiting future development of weapons of mass destruction.

JAMA. 1997;278:418-424

THE United Nations Special Commission (UNSCOM) and the International Atomic Energy Agency (IAEA) have investigated Iraq's weapons of mass destruction programs since April 1991. During 1995 and 1996, UNSCOM analysts were able to clarify most aspects of Iraq's biological warfare program. This article draws on information available in open sources[1-5] and my experience as a member of the UNSCOM investigation.

A biological weapon is more than just a pathogenic microorganism or toxin.[6,7] It is a system composed of 4 major components—payload (the biological agent), munition (a container that keeps the payload intact and virulent during delivery), delivery system (missile, artillery shell, aircraft, etc), and dispersal mechanism (an explosive force or spray device to dispense the agent to the target population). This report includes analysis of each component individually and their functioning in unison as a system.

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All of the opinions and analyses expressed in this article are the author's own and do not necessarily reflect or agree with those of the agencies or organizations with which he has been associated.

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IRAQ'S BIOLOGICAL WARFARE PROGRAM

After initial explorations in the late 1970s, Iraq's biological warfare program commenced in earnest in 1985. By the time Operation Desert Storm ended with a cease-fire in April 1991, Iraqi scientists had investigated the biological warfare potential of 5 bacterial strains, 1 fungal strain, 5 viruses, and 4 toxins. In addition, 2 bacterial species, *Bacillus subtilis* and *Bacillus thuringiensis*, were developed for use as simulants (ie, nonpathogens used for testing purposes).

Two pathogenic bacteria were studied—*Bacillus anthracis* (the cause of anthrax) and *Clostridium perfringens* (the cause of gas gangrene). Research on anthrax was initiated in 1985 at Muthanna State Establishment, the principal Iraqi chemical weapons facility, but was trans-

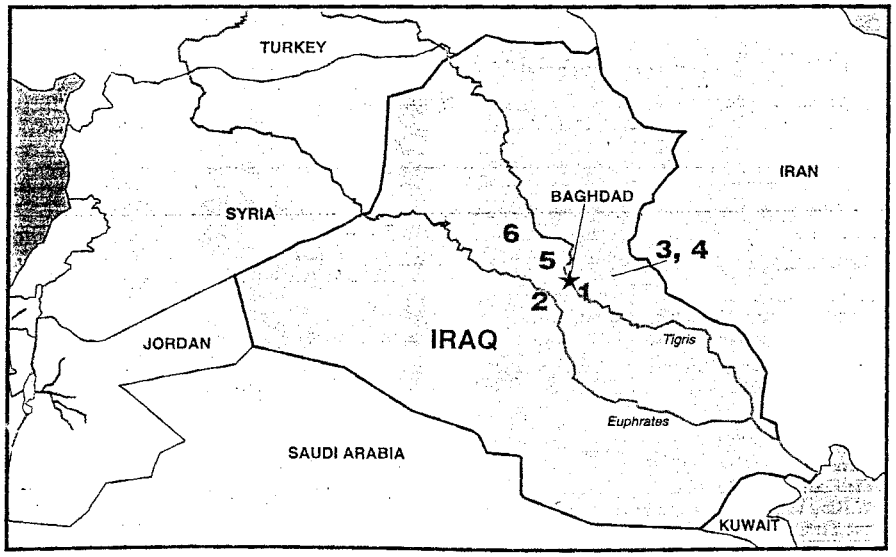

Figure 1.—Six major declared facilities involved in Iraq's biological weapons program: (1) Salman Pak; (2) Al Hakam Single-cell Protein Production Plant; (3) Daura Foot and Mouth Disease Vaccine Facility; (4) the Agricultural and Water Resources Research Center, Fudaliyah; (5) Taji Single-cell Protein Plant; and (6) Muthana State Establishment.

ferred in 1987 to Salman Pak just south of Baghdad, which became the center for biological warfare research and development (Figure 1). Some anthrax strains were imported from culture collections in France and the United States; others were local isolates. At Salman Pak, 4 strains were characterized, their media and storage requirements were established, and their pathogenicity was evaluated in animal models. Research findings were applied at the Al Hakam Single Cell Protein Production Plant, Iraq's major production facility for biological warfare agents, to begin mass production of anthrax in 1989. Eventually, approximately 8000 L of solution with an anthrax spore and cell count of 10^9/mL was produced. Of this, 6000 L was used to fill weapons; the remainder was stored at Al Hakam (Figure 2).

A reference strain of *C perfringens* was imported from the United States in 1985. Experimental work using mice commenced in 1988 to determine the infectivity of *Clostridium* spores, the ability of spores to initiate disease, and their degree of virulence. During 1990, 340 L of solution containing *Clostridium* was produced at Al Hakam. The Iraqis claim, however, that no attempt was made to develop *Clostridium* for weapons use.

One fungal strain with crop-destroying potential, wheat cover smut, was evaluated for use as a weapon. Research carried out at Salman Pak in 1985 demonstrated that wheat cover smut spores sprayed over immature wheat plants would be lethal to the crop. In 1988, young wheat plants growing in large fields near the town of Mosul were infected with this agent; the infected wheat subsequently was harvested and moved to Fudaliyah for storage. The Iraqis claim that no attempt was made to recover fungus from the harvest and that the infected crop was destroyed in 1990. The investigation of wheat smut implies that Iraqi leaders knew that biological weapons were more than antipersonnel weapons; they could also be used against crops as part of economic warfare.

Beginning in early 1990, scientists at the Foot and Mouth Disease Center at Al Manal investigated 5 viruses for their potential utility as biological weapons. Two agents, Congo-Crimean hemorrhagic virus and yellow fever virus, were found to be unsuitable since they required vectors for dispersal. The remainder, enterovirus 17, human rotavirus, and camelpox virus, were researched further, and a large egg incubator was obtained to mass produce the viruses. Reportedly, only certain growth characteristics of the viruses were elucidated before the program was terminated in 1990. Enterovirus 17 and human rotavirus may have been investigated for use as incapacitating biological warfare agents (both cause gastrointestinal disorders), while camel pox might have been considered an "ethnic" weapon (ie, persons reared where no camels exist might prove especially susceptible to this zoonotic disease).

Figure 2.—Main facility for the production of biological warfare agents at Al Hakam Single-Cell Protein Plant (destroyed in June 1996). (Photo courtesy of UNSCOM.)

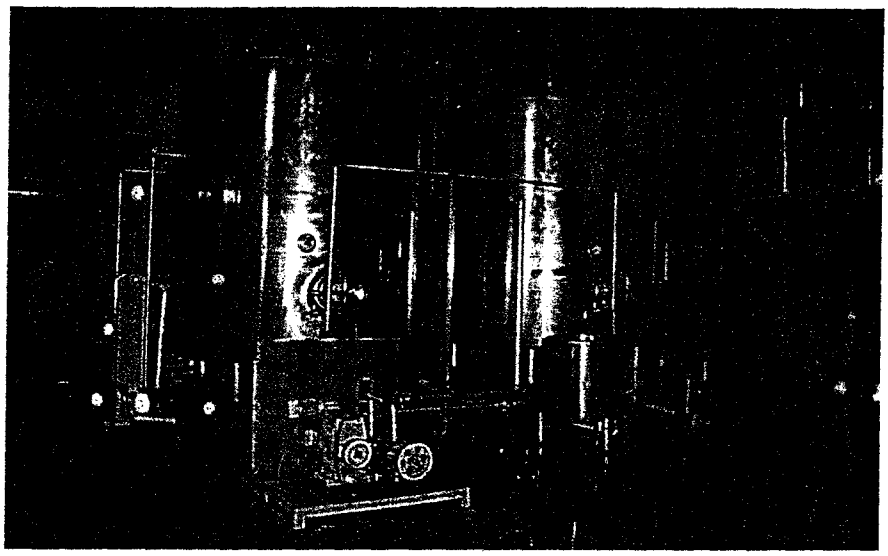

Figure 3.—Two 1450-L fermenters at the Al Hakam Single-Cell Protein Plant used to produce botulinum toxin for biological warfare. (Photo courtesy of UNSCOM.)

Substantial attention was given to weaponizing aflatoxin, botulinum toxin, ricin, and tricothecenes. (Many types of aflatoxin, botulinum, and tricothecene toxins are known to exist; however, since the Iraqis manufactured crude solutions containing undefined mixtures of toxin types, these toxins are referred to in the singular in this article.) Iraqi research of organisms that produce aflatoxin, including *Aspergillus flavus* and *Aspergillus parasiticus*, led to the development of methods for growing aflatoxin-producing organisms on wet rice. Individual types of aflatoxin were identified, and some aflatoxin-containing solutions were tested in animal models. Production of aflatoxin began in 1989 at Salman Pak, where approximately 2200 L of solution was eventually manufactured. An unknown quantity of this cache was used to fill weapons; the remainder was stored.

Using a *Clostridium botulinum* strain imported from the United States, the Iraqis produced 20 000 L of solution containing botulinum toxin of unknown strength and type at Al Hakam and Al Manal during 1989 and 1990 (Figure 3). Of this, 12 000 L was used in field testing or to fill warheads; unused toxin was stored at Al Hakam.

The castor bean plant (*Ricinus communis*), grown widely in Iraq, naturally produces ricin. During 1989, approximately 10 L of concentrated ricin solution was manufactured at Salman Pak.

While some was tested in animal models and some used as payload in artillery shells, the fate of most is unknown. Ricin might have been researched because it is plentiful and known to be effective for assassination.[8]

In 1990, the ability of *Fusarium oxysporium* and *Fusarium granarium* to produce tricothecene mycotoxins was investigated by Iraqi scientists. The fungi were grown on damp, supplemented rice; toxins were extracted by organic solvents and dried in a rotary evaporator. The Iraqis claim to have produced 20 mL of tricothecene-containing solution, some of which was tested in animal models. The fate of the remainder is unknown. Tricothecenes may have been investigated because some can penetrate skin or because of their alleged history as components of "yellow rain." (During the late 1970s, the US State Department alleged that the Vietnamese, abetted by the Soviet Union, had used toxin weapons against the H'mong and other native peoples of the Indochina peninsula.[9] Supposedly, the main constituents of the dispersed agent, named yellow rain because of its appearance, were tricothecenes.)

The microbial and toxin agents produced at Al Hakam, Al Manal, and Salman Pak usually were transported to the Muthanna State Establishment, where they were used as payloads in various types of munitions.

Iraq's chemical arsenal included 250-lb (LD-250) and 400-lb (R-400) bombs. Based on successful chemical warfare, some of these bombs were adapted to hold 60 L and 85 L of biological solution, respectively. When deemed necessary, the walls of the chambers containing the payload were coated with an inert epoxy paint to protect the biological agents from the toxic effects of contact with metal. Testing determined that the R-400 was the more suitable munition for biological warfare. In 1990, 200 R-400 biological bombs were produced; of these, 100 were filled with botulinum toxin, 50 with anthrax, and 7 with aflatoxin. These biologically armed bombs were deployed at 2 sites, ready for immediate use.

A few 155-mm caliber artillery shells were filled with ricin for field testing. Reportedly, tests did not go well and no further attempts were made to develop artillery shells for biological warfare.

Iraq had procured more than 800 SCUD missiles from Soviet bloc countries before 1991 and had manufactured about 80 itself (most of which proved faulty). The SCUD had a range of 300 km and could carry high-explosive payloads of up to 1 metric ton. Some SCUDs, renamed Al Husseins, were enhanced to double their range—although the trade-off was diminished payload capacity. In 1990, the Muthanna State Establishment received a special shipment of 100 Al Husseins. Of these, 25 were fitted with biological warheads: 13 with botulinum toxin, 10 with aflatoxin, and 2 with anthrax. All reportedly were deployed: 10 in a deep railway tunnel and 15 in holes dug along the Tigris River.[10]

The warheads of an unknown number of SAKR-18 122-mm rockets were filled with botulinum toxin, aflatoxin, or the simulant *B subtilis*, and field tested. As far as is known, no biological rockets were actually deployed.

All Iraqi munitions that depended on explosion for agent dispersal were of similar design—a tube filled with an explosive charge (burster) was placed in the center of a chamber containing the biological agent. At the moment of impact, the burster would explode, rupturing the outer wall of the munition and dispersing the payload.

The Iraqis possessed several hundred modern Italian-made pesticide dispersal systems that were fitted with sprayer nozzles capable of generating aerosols of the 1-μm to 5-μm size optimal for biological warfare. Some sprayers and appropriate holding tanks were installed on aircraft and land vehicles. Most important, in 1990, the Iraqis modified a MIG-21 fighter plane to be a remotely piloted vehicle and equipped it with a 2200-L belly tank (taken from a Mirage-F1 fighter plane) and a spray mechanism. In a field test carried out in January 1991, the remotely piloted vehicle sprayed a solution laden with a biological simulant over a practice target range. The results of this test are not known.

Soon after Iraq had accepted a cease-fire under United Nations Security Council Resolution 687 in April 1991,[11] biological warfare program personnel reportedly were ordered to destroy all biological warfare agents. A 2-step process was used for this purpose: first, stores of biological warfare agents were treated with formaldehyde and potassium permanganate; second, the residuum was poured onto bare ground near Al Hakam's perimeter. Five years later, UNSCOM was unable to recover either residuum or its breakdown products from the claimed dump sites. What this means is not clear. Natural forces might have completely degraded the residuum over time, Iraqi authorities may be mistaken as to the location of dumps, or they may be lying about the purported destruction. Since UNSCOM cannot ascertain what took place, it is unable to independently verify the destruction of biological warfare agent stores.

Biological warfare munitions supposedly were destroyed at the same time as the agents. Bombs and warheads were opened and formaldehyde and potassium permanganate were added to the solution they contained. Later, munitions were crushed by bulldozers and burned in pits. Finally, the remains were concealed by detonating general purpose bombs among them. Many test munitions were simply thrown into the Tigris River. While some whole and many fragmented R-400s have been recovered by UNSCOM, it cannot certify that all biological bombs have been destroyed, nor does it have solid evidence on the fate of missile warheads.

Soon after Iraq had accepted a cease-fire . . . in April 1991, biological warfare program personnel reportedly were ordered to destroy all biological warfare agents.

United Nations Security Council Resolution 687 specifies that facilities and equipment used in support of any of Iraq's weapons of mass destruction programs are to be destroyed by UNSCOM or the IAEA. Actually, a few days before the first UNSCOM biological inspection team arrived at Salman Pak on August 2, 1991, the Iraqis themselves blew up part of the facility and covered it with a thick layer of dirt. In addition, some implicative equipment, such as aerosol test chambers, were removed and crushed. However, other biological warfare facilities remained operational and the Iraqis tried to conceal their real purpose. Nevertheless, their true function was eventually discerned.[12] Accordingly, in May and June 1996, Iraqi workers, overseen by UNSCOM inspectors, obliterated the Al Hakam plant and the equipment at Al Manal that had produced biological warfare agents.

ASSESSING IRAQ'S BIOLOGICAL WEAPONS CAPABILITY

Anthrax

In the past, anthrax has been weaponized by Japan,[13,14] the United Kingdom,[15,16] the United States,[17,18] and the Soviet Union,[19,20] so anthrax's attributes as a biological warfare agent are well known.[21,22] Anthrax spores are extremely hardy, and they retain virulence during storage. Anthrax cells and spores dispersed in aerosol can inflict heavy casualties on unprotected populations, and if treatment with appropriate antibiotics is not begun soon after exposure, a morbidity rate of 65% to 80% will result.[23,24]

Anthrax slated for weapons may be produced as slurry (an insoluble liquid mixture) or dry powder. Anthrax slurry, while easier to manufacture than powder, is less efficient for biological warfare purposes; agents in slurry lose virulence relatively quickly and, more importantly, slurry is troublesome to disperse as an aerosol with particles of optimal size.[23,25] Yet, although Iraq possessed dryers and grinders that could have been used to produce dry anthrax, all of its deployed biological warfare munitions were filled with wet anthrax. The Iraqis may have been unable to overcome either the technical difficulties or the safety problems inherent in dry anthrax production.

Botulinum Toxin

Since botulinum toxin is the most toxic chemical known to science,[26,27] biological warfare programs in other nations have investigated its military utility.[22] While most cases of botulinum intoxication are caused by ingested contaminated food, aerosolized toxin is deadly.[28] For example, 8 kg of the concentrated botulinum toxin dispersed over an area of 100 km^2 would deliver a median lethal dose (LD_{50}) dose to the entire unprotected population located therein, assuming optimal meteorological conditions.[27] These properties may have proven attractive to the Iraqis who, as noted above, had produced large quantities of botulinum toxin-containing solution of unknown concentration. Given the extreme lethality of the agent, it is reasonable to assume that this solution would be deadly in small doses if delivered effectively to unprotected persons.[29]

Aflatoxin

It is difficult to understand why the Iraqis developed aflatoxin for weapons use. Although well known to medical science as a powerful nephrotoxin and hepatotoxin,[28,30] aflatoxin has no known property useful for biological warfare. Possible explanations for Iraq's interest in aflatoxin include (1) Iraqi scientists may have discovered that aflatoxin possessed a previously unknown property useful for biological warfare applications; (2) Iraqi planners may have intended to use aflatoxin's long-term carcinogenic properties as a means of terrorizing targeted civilian populations; or (3) since aflatoxin is easier to manufacture than most other toxins, the Iraqi biological warfare program's staff might have chosen to produce it to meet production goals set by higher authorities, rather than for its perceived biological warfare value. Whatever the case, Iraq's aflatoxin-based weapons had little military utility.

The Tactical Threat

Though in possession of several hundred biological weapons, Iraq's tactical biological warfare capability during the Persian Gulf War actually was quite limited. As noted, Iraqi biological warfare munitions depended on impact detonation for primary dispersal of agents. This method is exceedingly inefficient because (1) an explosion inevitably renders harmless much of the payload; (2) impact detonation drives a substantial part of the payload into the ground; (3) the small part of the payload aerosolized by explosion generally is not propelled beyond a few tens of meters; and (4) the size of aerosolized particles varies widely, from large clumps to particles of smaller than 1 μm. (Large particles would settle quickly to the ground, while fine dust would be quickly dispersed by wind.) For these reasons, had Iraq's biological warfare munitions actually been used, their effect would have been limited to contaminating a relatively small area of ground surrounding the point of impact and exposing nearby individuals to aerosolized pathogens or toxins. In addition, Al Husseins lacked an inertial guidance system, which made them inaccurate.[31] Therefore, biological-laden Al Husseins launched in support of tactical military missions probably would have missed the target.

Biological agents delivered by aerosol would have presented a more credible threat to coalition forces, but such a system most probably was not in use during Operation Desert Storm.

The defensive capabilities of coalition forces also must be taken into account. First, coalition forces had overwhelming air superiority and unsurpassed ability to detect and destroy airborne aircraft. In addition, Iraq's meteorological stations and communications network had been destroyed by coalition bombings.[31] Without accurate forecasts, airborne biological agents might have been blown onto friendly forces or been dispersed over empty desert. Second, coalition forces had been trained to expect chemical attacks by Iraq, and were well equipped to defend themselves. The standard antichemical defense methods and equipment would also have provided adequate protection against all known Iraqi biological weapons.

However, protection comes at a cost. The military effectiveness of troops garbed in protective suits is decreased because the ability of soldiers to perform complex manual tasks is limited, their observational powers reduced, and they tire quickly, especially in hot weather.[32] Therefore, just by making its opponents believe that a biological attack was imminent, the Iraqis would have forced them to garb themselves, which would have impaired the coalition forces' combat effectiveness and mobility.

Investigations of US forces taking part in the Persian Gulf War found several deficiencies with biological warfare defense preparedness, including shortfalls in defensive equipment, inadequate training, and shortages in medical support.[33,34] However, the primary weakness of the coalition forces in regard to biological warfare was that they did not have "stand-off" or "point detection" capabilities (ie, they could not reliably detect agent-laden aerosol clouds or plumes created by explosion at a distance or on-site). Therefore, had the Iraqis against all odds been able to mount a surprise attack using aerosol laden with anthrax or botulinum toxin and had wind conditions been such that the aerosol was carried into positions held by coalition forces, the attack probably would not have been detected. Thus, no warning would have been sounded for troops to protect themselves by garbing or seeking shelter. Because only approximately 150 000 troops received the first vaccination against anthrax and a smaller proportion of that 150 000 received a second vaccination[35] (6 vaccinations in 1 year are necessary for full protection), the first indication of the attack would have appeared 3 to 6 days later when soldiers began to present symptoms of pneumonic anthrax. Although anthrax is treatable by commonly available antibiotics, it is questionable whether sufficient supplies would have been on hand to adequately treat a large number of exposed individuals.

Had the Iraqis been able to attack the coalition forces' rear positions, such as airfields, ports, and troop assembly areas, with anthrax or botulinum toxin aerosol, a similar situation would have ensued. Heavy casualties among troops and civilian workers, compounded by panic, would have caused serious disruptions. The coalition forces' ability to operate would have been severely compromised as the flow of vital supplies decreased to a trickle, communications were hindered, and medical facilities overwhelmed.

The Threat Posed to Civilian Populations

During the Iraq-Iran war of 1980 to 1986, 1 episode (called the War of the Cities) demonstrated that the Iraqi leadership is capable of ordering attacks on purely civilian targets. It began when the Iraqis launched missiles against helpless Iranian cities of no obvious military value. The Iranians retaliated in kind.[36] After an exchange of several hun-

dred missiles, the episode ended with, apparently, neither side having gained militarily from the exchange. The cost to both, however, was immense—many thousand dead and wounded civilians, as well as incalculable misery for hundreds of thousands of city dwellers.

Cities were also targeted during the Persian Gulf War but on a much smaller scale. The Iraqis launched 39 SCUD missiles against Israeli cities,[37] but the Israelis chose not to retaliate. Although all missiles launched against Israel carried high explosive warheads, Iraq was capable of having launched Al Husseins with biological warheads. If this had occurred, what would the consequences have been?

Since cities occupy large areas, it is likely some of the Al Husseins would have reached their targets. (Also, solitary bombers equipped with R-400 bombs might have evaded detection by hugging the ground.) While the number of casualties caused directly by biological weapons probably would have been low, the targeted population's terrified reaction to these bombs or missiles may have caused more harm than the weapons themselves. (For example, of the 1060 Israeli casualties [including 11 deaths] caused by Iraqi missiles, only 234 injuries [2 deaths] resulted from explosion.[37]) The combination of direct casualties brought about by disease in combination with casualties caused by the resultant panic likely would have caused more injuries and death than were produced by high explosives.[38-41] The outrage felt by the Israeli population most likely would have compelled Israel to retaliate and, perhaps, enter the Persian Gulf War.

A RESURGENT IRAQI WEAPONS OF MASS DESTRUCTION PROGRAM

Had Operation Desert Storm not intervened, it is likely that Iraq would have possessed a formidable suite of weapons of mass destruction by 1997.[10,42,43] It could have deployed ballistic missiles with a range of about 2000 km capable of delivering up to a 1-ton payload. Further, Iraqi commanders would have been able to select the type of warhead required for a particular mission. Thus, a nuclear or biological warhead might have been used to achieve a strategic objective; for example, to destroy the capital of a neighbor or to threaten more distant nations that might wish to intervene on the side of Iraq's opponent in any conflict. If, on the other hand, a tactical strike was to be undertaken, for example, the destruction of a smaller target such as a troop formation, a short-range missile fitted with a chemical warhead might have been appropriate. Thus, the ballistic missile component was the heart of Iraq's weapons of mass destruction program; each missile could have been fitted with a warhead appropriate for achieving the tactical or strategic objective set for it before launching.

A resurgent overt program by Iraq to develop weapons of mass destruction is, for now, deterred by UNSCOM's and the IAEA's ongoing monitoring and verification program and the imposition of import and export controls.[44,45] If these agencies were removed from Iraq, either by the United Nations Security Council deciding to terminate their missions or by the Iraqi government expelling them, Iraq might restart such a program. If so, it probably would be reconstructed along lines familiar to Iraqi planners, beginning with the acquisition of a powerful ballistic missile capability.

It appears that Iraq may already be on its way to realizing such a capability. The main missile research station, Sa'ad 16 located at Al Kindi, which was demolished by bombs during the Persian Gulf War, has been completely rebuilt.[46] Iraq possesses hundreds of ballistic missiles with a range of 150 km or less allowed by the terms of the 1991 cease-fire. It may also possess HY-2, SS-N-2, and C-601 cruise missiles,[10] although UNSCOM has seen no firm evidence of this. The United Nations Special Commission has dismantled or otherwise accounted for the destruction of most of the SCUD missiles that survived the Persian Gulf War, but commission members still believe some operational SCUD missiles remain undetected. Iraqi rocket scientists are believed to be honing their skills while working for Libya's leader, Mu'ammar Qaddaffi.[47] For these reasons, and despite limitations imposed by UN Security Council Resolution 647, Iraq might already possesses potent ballistic and, perhaps, cruise missile capabilities and the trained personnel to deploy and operate them.

The question then is this: What kind of warheads could be fitted to these missiles to meet Iraq's desire for weapons of mass destruction? Nuclear warheads cannot be acquired for at least 5 years because the IAEA has destroyed most if not all Iraqi nuclear weapons–related facilities.[41,48-52] Similarly, UNSCOM has supervised the destruction of most, perhaps all, of Iraq's chemical warfare agents, as well as equipment and facilities used by the chemical warfare program.[1,2,3,5] Thus, no chemicals would be available immediately to arm ballistic missiles (unless hidden stores of agents remain).

The situation differs markedly in regard to biological warfare. The workforce of more than 200 persons who staffed Iraq's biological warfare program is intact. Iraq's civilian biotechnological infrastructure, comprising more than 80 research, development, and production facilities, is whole and well equipped.[53] Since most biotechnological equipment is dual use, some of the currently operative facilities could be rapidly converted to biological warfare work. It is prudent to assume that the Iraqis retain hidden stores of freeze-dried organisms from its former biological warfare program. Because Iraq maintains these human, biological, and industrial resources, it could reconstitute a biological warfare program rapidly and be able to manufacture militarily significant quantities of biological warfare agents within 6 months. Further, the armorers who adapted chemical munitions to hold biological agents before the Persian Gulf War are still available. With their assistance, stockpiled conventional munitions could be modified within the 6-month time frame and loaded with biological warfare agents.

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Weapons produced immediately by a resurgent Iraqi biological warfare program, even if unimproved over the weapons developed before 1991, could be deployed in support of aggressive moves. Except for the coalition partner countries and Israel, the armed forces of the region's nations probably are inadequately prepared to defeat a biological attack. (All have chemical warfare training and doctrines, but are desultory about implementation.) Further, all of the region's civilian populations are unprotected. Thus, if Iraq were able to maintain secrecy and deploy biological weapons to tactical sites, opponents would face a very difficult situation because most soldiers and all civilians would be vulnerable both to diseases brought about by biological warfare agents and to panic that these weapons would induce among threatened or attacked populations. Clearly, by once again possessing these weapons, Iraq would be in a position to intimidate neighboring countries.

If the Iraqi leadership were patient, its biological weapons could be significantly improved in a short time. Thus, within a year of commencing a resurgent program, it is probable that Iraqi scientists could perfect techniques for drying biological warfare agents and engineers could install improved aerosol-forming

and disseminating equipment on suitable aircraft. Thereafter, remotely piloted vehicles, long-range fighter-bombers, or cruise missiles equipped with tanks and sprayers and programmed to avoid detection by flying low and following ground contours could reach populations located within 1000 km of Iraq's borders and disperse agents under conditions favorable for carrying out a successful biological attack. With these added capabilities, Iraq would be able to mount a militarily significant biological threat to even the most powerful opponent in the region.

CONCLUSIONS

The Iraq of today is similar to Iraq before the Persian Gulf War—it has the same leader and form of governance, it possesses a large and powerful army and air force, and it is able to deploy a large, well-trained civilian workforce. Its oil reserves are the world's third largest, and the infrastructure for oil exploitation has been rebuilt and is gearing up for full production. As to its geopolitical standing, the same uneasy, distrustful relations exist between Iraq and its neighbors as before; in fact, Iraq's leader may perceive himself as even more beleaguered and as having additional scores to settle. In consideration of this unsettled situation, it is wise to prepare for the possibility of Iraq's trying once again to gain a dominant position in the Middle East.

It is reasonable to assume that, as before, Iraq will attempt to overcome the numerical superiority of regional opponents by resorting to the use of weapons of mass destruction. Iraq's former ballistic and cruise missiles and biological warfare components would be the easiest and quickest to reassemble. How can such disquieting developments be prevented?

The key barrier to Iraq reacquiring weapons of mass destruction undoubtedly is the collective international will that sustains the several United Nations Security Council resolutions designed to ensure a subdued Iraq. A further reflection of that will is the support the council gives UNSCOM, especially with regard to biological warfare. Before the Persian Gulf War, Iraq placed high priority on developing a strong biotechnological capability. This effort will probably be continued and expanded once the United Nations lifts economic sanctions. The Iraqi government may attempt to apply biotechnology for various legitimate enterprises, including enhancing the ability of crop plants to withstand abiotic and biotic stress, manufacturing biological fertilizers and pesticides, producing single-cell protein, and developing diagnostic methods for animal and human diseases. Due to the dual-use character of biotechnology, however, much of the expertise, equipment, supplies, and facilities devoted to civilian biotechnological pursuits could be redirected to biological warfare applications. The UN Commission's actions to closely and continuously monitor Iraq's biological research, development, production, and testing facilities is the best guarantee that these facilities are unable to take up such work. Further, UNSCOM's awareness of the locations of Iraq's bioscientists and chemical engineers who staffed the former biological warfare program makes it less likely that they could be used by secret facilities to perform illicit research and development. As long as UNSCOM is able to continue fulfilling its monitoring responsibilities, Iraq's leadership is likely to be deterred from biological warfare acquisition. Clearly, UNSCOM must remain fully operational until such time as a leadership is established in Iraq which poses no threat to its neighbors.

The Iraq of today is similar to Iraq before the Persian Gulf War . . .

Possibly the most important lesson for international arms control that can be drawn from UNSCOM's experiences relates to the need to apply broad, multidisciplinary expertise to arms control. The Iraqis took a "holistic" approach toward acquiring weapons of mass destruction (ie, rather than seeking to acquire only 1 type of weapon, it sought to acquire a comprehensive arsenal with ballistic missile, biological, chemical, and nuclear components). The agencies charged with destroying Iraq's former weapons of mass destruction program and making certain that it is not resurrected, UNSCOM and IAEA, were able to address this multifaceted problem by fielding inspection teams that included biological, chemical, and ballistic missile experts. No international treaty compliance regime is so flexible.

As matters now stand, international arms control treaties are disciplinary (ie, each treaty addresses 1 type of weapon system, be it nuclear, chemical, or biological). Further, each treaty that specifies the establishment of a compliance regime, such as the Chemical Weapons Convention, also contains provisions that limit that regime's detection and monitoring functions to the discipline under the treaty's purview. Since no international arms control treaty has an interdisciplinary reach, no compliance regime has the capability to operate in a multidisciplinary weapons of mass destruction environment. For example, a Chemical Weapons Convention inspection team probably would not be able to detect activities that contravene treaties bearing on biological or nuclear weapons, and if such activity was detected, the team would be reporting to a treaty secretariat that could not act on this information.

The international arms control community must reassess its disciplinary approach. An improved response would be to negotiate multidisciplinary arms control treaties that encompass several types of weapons of mass destruction. The primary drawback to this approach is that negotiations to achieve multidisciplinary arms control treaties would be even more complex and drawn out than the difficult and extended negotiations undertaken to achieve single discipline treaties. For example, it took almost 20 years to accomplish the Chemical Weapons Convention. Yet, even while recognizing the problems inherent in developing multidisciplinary arms control treaties, it seems worthwhile to consider such a response. Nations that belong to all major disarmament treaties, including the Biological Weapons and Toxins Convention, Chemical Weapons Convention, and the Nuclear Nonproliferation Treaty, would be in a good position to initiate this effort.

A response that could be accomplished more easily and quickly would be to establish 1 facility where all the compliance regimes would be headquartered. The tendency now is to headquarter each compliance regime in a city that offers the best package of inducements to the respective treaty organization. For example, the Chemical Weapons Convention compliance regime is located in The Hague and the Nonproliferation Treaty compliance regime is in Vienna. Substantial benefits could be derived from taking this unifying step: (1) it would make it easier to create an environment where experts from all disciplines could consult with one another; (2) the international arms control community could set up a comprehensive, unified computerized database containing information from all disciplines; and (3) costs would be reduced by eliminating the need for separate facilities for each compliance regime. Most important, by gathering the various treaty compliance regimes under one roof and taking steps to ensure that they communicate continuously with one another, the international arms control community would ensure that a major lesson from the experience in Iraq has been learned, namely, the need to take an interdisciplinary approach towards limiting the development and use of weapons of mass destruction.

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Biological Terrorism

Preparing to Meet the Threat

Jeffrey D. Simon, PhD

The threat of terrorists using biological warfare agents has received increased attention in recent years. Despite the hope that, with the right mix of policies, security measures, and intelligence gathering, a major biological warfare terrorist attack can be prevented, the history of conventional terrorism indicates otherwise. The greatest payoff in combating biological terrorism lies in focusing on how best to respond to a terrorist attack. The medical and emergency service communities will play the most important role in that process. Ensuring that they are trained to recognize the symptoms of diseases caused by biological warfare agents and have Critical Incident Stress Debriefing teams available to help them cope with the emotional aspects of treating exposed survivors should be part of contingency planning. By improving our readiness to respond to biological terrorism, many lives can be saved and terrorists denied their goal of creating panic and crisis throughout the country.

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THE THREAT of terrorists using biological warfare (BW) agents has received increased attention in recent years. Congressional hearings,[1] research studies,[2-5] government warnings,[6] and commentaries[7,8] have all pointed to a potentially more ominous terrorism future. Many factors account for this concern—revelations that Iraq, a state sponsor of terrorism, stockpiled anthrax, botulinum toxin, and other BW agents during the Persian Gulf War; the discovery that Aum Shinrikyo, the Japanese religious cult that released the chemical agent sarin in the Tokyo subway system in 1995, had a research and development program for BW agents; the low cost and minimum scientific knowledge required for producing BW agents; and the tendency for terrorists to move into new areas of violence when current ones no longer achieve the intended effect—publicity, reaction, chaos.[9]

Despite this growing concern, however, we still know very little about the nature of BW terrorism. There has never been a major BW terrorist attack. Therefore, there is no track record of incidents, groups, tactics, motives, and targets for analysis to determine the best strategies for combatting this global threat. In this regard, we are today with respect to BW terrorism where we were nearly 30 years ago with respect to "conventional" terrorism. A new international threat was emerging then, but it was unclear as to the direction it would take.

It took several years after the first major international hijacking in 1968 for the diverse nature of conventional terrorism (hijackings, bombings, hostage situations) to become clear and for governments to take action against the threat. Biological warfare terrorism, however, will not allow governments, publics, and the international community the luxury of time to watch this threat unfold and then determine the proper responses. Since BW terrorist attacks could have catastrophic effects in terms of lives lost and create a medical, political, and social crisis unparalleled in our history, it is important to prepare now for this new age of terrorism.

. . . we are today with respect to BW terrorism where we were nearly 30 years ago with respect to "conventional" terrorism.

The first step is to accept the reality that we will not be able to prevent every act of BW terrorism. Governments have learned that painful lesson with respect to conventional terrorism. While preventive measures must continue to be pursued, the greatest payoff in fighting BW terrorism lies in improving our response to an incident. There will be more opportunity for saving lives in the emergency medical response to a BW terrorist attack than in the response to a conventional terrorist attack. Whereas most of the fatalities in a conventional terrorist bombing occur immediately or shortly after the explosion,[10] in BW terrorism the incubation period for the virus, bacterium, or toxin could be several days. Accurate diagnosis and speedy treatment could save many lives.

The medical and health communities will therefore play the most significant role in combatting BW terrorism, and they will have to carry out their duties at a time of unprecedented crisis and fear throughout the country. To the extent that we can reduce the uncertainty about how BW terrorist incidents are likely to

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unfold, the better the medical and health professions will be prepared to deal with the aftermath of this most dangerous form of global terrorism.

BIOLOGICAL TERRORISM: LIKELY TACTICS AND TARGETS

The most distinguishing feature separating BW terrorism from conventional terrorism is the extraordinarily larger number of casualties that could follow a major terrorist attack involving biological agents. Whereas bombings of airplanes or buildings with conventional explosives have occasionally resulted in a few hundred deaths, each act of BW terrorism could result in hundreds of thousands or even millions of casualties.[2] Adding to the death toll would be the fact that civilian populations are not immunized against most BW agents and do not have protective equipment, such as filtered respirators and gas masks, readily available.[1]

Some biological agents have been used in the past for selective attacks. For example, Bulgarian agents assassinated Georgi Markov, a Bulgarian emigré and writer for the British Broadcasting Company, by stabbing him in London with an umbrella-type weapon that contained ricin,[11] which is a potent protein toxin derived from the bean of the castor plant (*Ricinus communis*).[12] (Another Bulgarian émigré, Vladimir Kostove, was attacked in a similar fashion in Paris in 1978, but lived when physicians removed the pellet containing ricin from his body.) However, a terrorist group that uses BW agents will likely be attracted to the mass killing potential of these weapons. It makes little sense for terrorists to experiment with dangerous biological agents—they could be killed handling and using them—if their goal is a limited attack that could have been achieved by using safer and more familiar conventional weapons.

Biological warfare terrorism will also encompass a narrower range of tactics than conventional terrorism. Although BW agents could be used during a hijacking or hostage situation, there would be little incentive for terrorists to do so. The projected death toll would be no higher than if conventional weapons were used. And while BW agents could be delivered against a target by means of a bomb or missile, the likelihood that the organisms will be destroyed in the explosion makes this an unattractive delivery method.[2]

Rather, the most likely BW terrorist tactic will be to release BW agents—anthrax spores, botulinum toxin, ricin, or other deadly agents—into the air as a biological aerosol, a stable cloud of suspended microscopic droplets of bacterial or virus particles.[3] Since BW agents are invisible, odorless, and tasteless, no one would know that a terrorist attack is under way. The aerosol release of BW agents could be accomplished in several ways, including using low-flying airplanes, crop dusters, or trucks equipped with spray tanks and releasing the BW agent upwind of populated areas; leaving aerosol canisters filled with the BW agent and timing devices in subways, airports, air-conditioning/heating systems in buildings, or other crowded places; or directly contaminating bulk food supplies in restaurants, supermarkets, or other places with a BW agent. However, large US water supplies such as a city water supply would not be an attractive target for contamination due to the large amount of BW agent required and water purification procedures used by most cities in the United States.

Since there are no reliable detection systems for BW agents, terrorists will be able to strike any target they desire. Whereas terrorists with conventional weapons have to be concerned about metal detectors, x-ray machines, and other physical security measures, terrorists with BW agents do not face those means of detection. With maximum casualties the likely goal, metropolitan areas are the most at risk. At the present time and for the foreseeable future, major cities in the United States and around the world remain indefensible to a BW terrorist attack.

RESPONDING TO BW TERRORISM: UNCHARTERED WATERS

The heightened concern regarding biological terrorism has led to studies of how well prepared the United States is to respond to a major incident. The findings are not encouraging. During hearings held in 1995 and 1996, the US Senate Permanent Subcommittee on Investigations, for example, found that the United States did not have a plan that coordinated federal, state, and local agencies in managing the consequences of a terrorist attack with a weapon of mass destruction.[1] The subcommittee also found that principal field officers with police, fire, and emergency service departments in major cities are inadequately trained and do not have basic equipment to deal with biological, chemical, or nuclear terrorism, including protective gear, breathing apparatus, decontaminants, and antidotes.[1,13]

The lack of preparedness is attributable to several factors. One is that since the casualties from a biological terrorist incident are so disturbing even to think about, many public officials cling to the hope that with the right mix of police, security measures, and intelligence gathering, BW terrorism can be prevented. Funding for emergency responses to BW terrorism therefore has not been given the high priority it deserves until very recently. The second factor is the difficult task of planning for an event that has never occurred before. Emergency response teams are therefore left only with alternative scenarios to guide them in their plans.

An amendment to the 1997 Defense Authorization Act addresses some of these issues by calling for better training, equipment, and coordination among emergency response personnel in the United States to deal with a terrorist incident involving a weapon of mass destruction.[14] There is also a need for hospitals to have adequate supplies—or ways to quickly obtain these supplies—of antibiotics and antitoxins that could be used to treat those exposed to BW agents. Medical personnel also should be trained to recognize the different symptoms of various BW agents so that those exposed can be treated quickly. Most physicians do not see cases of anthrax in their daily practices.[1]

Since BW agents are invisible, odorless, and tasteless, no one would know that a terrorist attack is under way.

An important part of the response to BW terrorism will be dealing with the psychological reactions among survivors, emergency workers, and the public. Terrorism is a form of psychological warfare with terrorists often perpetrating their violence to cause fear among the public. In BW terrorism, that fear will understandably be great as people watch their fellow citizens fall ill and possibly die in large numbers due to anthrax, botulism, or other diseases. Contingency plans for dealing with public hysteria and disruption of health care delivery systems—including the possibility of health care professionals' becoming ill from the BW attack, or fleeing the affected area if they are not confident that they have adequate equipment to protect themselves—should be established in every large city.

The mental health of emergency workers and medical personnel will have to be monitored during a BW terrorism crisis. Research indicates that the most traumatic events for emergency nurses are the death of a child and the death of a coworker.[15] A major BW incident will likely have many of these types of victims. Dealing with dead bodies can also cause emotional and psychological problems for disaster rescue and recovery workers.[6] During a BW terrorist incident, rescue workers will face the unique situation of dealing with large numbers of deaths in a setting that otherwise seems very normal. There will not be any collapsed or bombed-out buildings, fires, plane crashes, and so forth. The psychological impact of that situation on first-

responders needs to be addressed in contingency plans.

The Critical Incident Stress Debriefing (CISD) process could help in dealing with the psychological aspects of a BW terrorist attack. This process is part of a broad crisis intervention program known as Critical Incident Stress Management (CISM), which is designed to prevent or mitigate the development of adverse psychological reactions among emergency service and public safety personnel, nurses, physicians, and disaster workers. The program has been used during earthquakes, plane crashes, terrorist bombings, and other tragic events. Through various psychological intervention techniques, a CISD team led by mental health professionals and including peer support personnel from the emergency services can help emergency workers and medical personnel recover as quickly as possible from the stress associated with the crisis.[17]

A potential problem, however, is that some CISD and CISM teams could become a hindrance to first-responders. They might interfere with the duties of emergency service personnel, or inadvertently aggravate the emotional trauma being experienced by making incorrect assessments of mental health needs. It is therefore crucial that CISD and CISM teams be properly trained for crisis intervention services.

The military will also play an important role in the aftermath of a BW terrorist attack. They will be called on to assist federal and local authorities, just as they have helped local communities following domestic disasters such as hurricanes, floods, and earthquakes.[15] But since their BW training has focused on defending against BW perpetrated by enemy troops in a battlefield setting, there will be a need to retrain them for responding to a BW terrorist attack in a civilian setting.

CONCLUSION

Terrorists with BW agents pose a threat to this nation's—and all nations'—vital interests. In the 1960s, the physicist Herman Kahn wrote a book on fighting a nuclear war entitled *Thinking About the Unthinkable.*[18] Fortunately, we never had to experience that event, and the end of the cold war hopefully means we never will. But we face a new threat at the dawn of the 21st century, and it is one that we must think about and for which we must prepare. By improving our readiness to respond to a BW terrorist attack, many lives can be saved and the terrorists denied their goal of creating panic and crisis in this country.

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Why Should We Be Concerned About Biological Warfare?

There is a widespread tendency to think about defense against biological warfare as unnecessary, as someone else's responsibility, or as simply too difficult. Unfortunately, however, the dangers posed by biological weapons did not disappear when the United States began to unilaterally dismantle its own offensive program in 1969. The dangers did not vanish with the signing of the Biological and Toxin Weapons Convention of 1972, and they did not dissipate with the end of the Cold War or the threat of nuclear retaliation against Iraq during the Persian Gulf conflict. Only by planning and investing in the right training and defensive measures can we diminish the likelihood that biological weapons will be used and reduce the risks, disruption, and casualties in the event that such weapons are used.[1] Fortunately, significant improvements can be made in our defensive posture at relatively modest levels of investment, and both the Department of Defense and the medical community can play a substantial role in this regard.

Biological weapons are unfortunately characterized by low visibility, high potency, substantial accessibility, and relatively easy delivery. The basic facts are well known: a millionth of a gram of anthrax constitutes a lethal inhalation dose. A kilogram, depending on meteorological conditions and means of delivery, has the potential to kill hundreds of thousands of people in a metropolitan area. These small quantities make the concealment, transportation, and dissemination of biological agents relatively easy. Many of these agents—bacteria, viruses, and toxins—occur naturally in the environment. Moreover, many are used for wholly legitimate medical purposes (such as the development of antibiotics and vaccines), and much of the technology required to produce and "weaponize" them is available for civilian or military use. Unlike nuclear weapons, missiles or other advanced systems are not required for the delivery of biological weapons. Since aerosolization is the predominant method of dissemination, extraordinarily low-technology methods, including agricultural crop dusters, backpack sprayers, and even purse-size perfume atomizers will suffice. Small groups of people with modest finances and basic training in biology and engineering can develop an effective biological weapons capability. Recipes for making biological weapons are even available on the Internet.

These unique characteristics make both military and civilian society vulnerable to biological weapons. It is true that their delayed effects and vulnerability to weather make these weapons ill-suited to military purposes such as seizing territory. But biological weapons can effectively impede the mobilization and massing of troops that would be required to sustain our role in a conventional conflict. Most disturbingly, they can be used to threaten civilian populations and create mass panic. Used this way, biological weapons can achieve military goals by undercutting the civilian support necessary for military operations or by holding civilians hostage to prevent military operations.

Why Have Biological Weapons Been Low on Our Agenda?

If biological weapons are so potent and so cheap, if the technology is readily available, and if so many of our adversaries have biological warfare capabilities, then why has this issue been so low on our national security agenda?

There are 3 principal reasons. First, because defense against a biological attack is both unfamiliar and difficult, there is a natural tendency to put it aside in favor of problems that are more comfortable. This is abetted by a second factor: the belief that because biological weapons have never been used they therefore never will be. And this is in turn buttressed by a sense that a regime can be deterred from using biological weaponry if we make it clear that this would invite nuclear retaliation.

These modes of thought are dangerously inappropriate. If we address deterrence first, many argue that Saddam Hussein's unwillingness to unleash Iraq's biological arsenal, in the face of not-so subtle threats of nuclear retaliation, validates the primacy of our deterrent. However, nations are not the only potential users of biological weapons. If one of the most likely scenarios entails their use by nonstate actors, small groups, or even individuals, a nuclear deterrent may be ineffective. Of course, terrorists can often be associated with state sponsors, but the quantum of proof we would require before responding to such a perceived linkage with a nuclear attack would be awfully high. Consider, for example, the forensic difficulty in assigning responsibility for the tragic attack against Pan Am Flight 103 that exploded over Lockerbie, Scotland, in 1988. In the event of a biological contingency, it is especially easy to mask the nature and source of an attack and even to obscure whether it is a natural occurrence. In such circumstances, can we credibly rely on a threat of assured nuclear retaliation? Depending on the agent used, if those exposed just got sick but did not die, what would constitute a proportional response?

The assumption that biological weapons will not be used in the future because they have not been used in the past is based on an error of fact. History is replete with examples in which biological weapons have been used, including the following[2]: in the Middle Ages infected cadavers were catapulted over the walls of European cities and castles under siege; in

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the French and Indian Wars, the British supplied Indians with smallpox-infected blankets; during World War II, Japanese Unit 731 experimented with biological weapons on prisoners of war in Manchuria, resulting in more than 1000 deaths.

There are also abundant examples that bring the threat much closer to home. In 1995, 2 members of a Minnesota militia group were convicted of possession of ricin, which they had produced themselves for use in retaliation against local government officials.[3,4] In 1996, an Ohio man with connections to an extremist group was able to obtain bubonic plague cultures through the postal service.[3] It has even come to light that Aum Shinrikyo, the Japanese cult organization responsible for the sarin attacks on the Tokyo subway system, was working on anthrax and botulism as weapons.[5] The group's biological capability, its production and testing and laboratory infrastructure, and its experimental delivery systems existed for years while escaping detection by Western intelligence.

While it is often said that familiarity breeds contempt, no national security establishment can let unfamiliarity breed neglect. Biology is unfamiliar terrain. As Alan Beyerchen, PhD, has pointed out, the history of the absorption of technology into the war fighting capabilities of the Department of Defense suggests a reason for this blind spot.[6] World War I brought chemists and war fighters together; World War II brought physicists into the fold; and the cold war represented an era of the primacy of the computing, telecommunications, and electronics communities in the defense arena. What little connection the US government maintained with the biological community dissipated when, in 1969, we foreswore any offensive biological and toxin weapon capability. But our forbearance does not imply that of others. The United Nations' inspections of Iraq after the Persian Gulf conflict should be a wake-up call in this regard.[7] Along with the information of a high-level defector who had responsibility for Iraq's unconventional weapons program, these inspections revealed a large-scale biological production and "weaponization" effort that had gone substantially undetected by the West.

What Should We Do About the Threat of Biological Warfare?

The Department of Defense has embarked on a challenging program to enhance its capabilities to defend against biological warfare. The program includes, among other things, the development and fielding of state-of-the-art biodetectors; the creation and designation of selected military units with expertise in medical prophylaxis, hazard mitigation, and decontamination; investments in vaccine and antibiotic research, development, and stockpiling; refinement and acquisition of masks and improvements in air filtration systems to preclude infection via inhalation; improved intelligence collection and analysis; enhanced training; and the development of doctrine regarding how to preempt and, when necessary, respond to a biological attack.

An additional critical element of this program, however, is the need for an enhanced relationship between the military and those agencies charged with protecting the civilian population of the United States. In that regard, biological weapons necessarily alter our strategic thinking about national security and the nature of warfare. Wars may not always be fought on set-piece traditional battlefields, and it is time to throw away the anachronistic notion that the military's only role is to defend the United States against threats on foreign soil.

In the event of a domestic incident of biological weapons use, no matter who the perpetrator, it is unlikely that the response would be left to local law enforcement and health officials or even to the Federal Bureau of Investigation, the Federal Emergency Management Agency, or the US Public Health Service. The military would undoubtedly be called on because of its resources, capabilities, and expertise. At the same time, if a biological incident were to occur in a military context, the Department of Defense would look to and need the help of such civilian agencies as the Centers for Disease Control and Prevention (CDC).

Although achieving it is one of our greatest challenges, an enhanced cooperation between military and civilian institutions is also likely to pay big dividends. In some respects the Atlanta Olympics were a good case in point, and the multiagency partnerships that spanned federal, state, and local jurisdictions will serve as a model for future response.[8] Not only were the Olympics a model of cooperation, but they also marked a milestone for our response capabilities. In the immediate aftermath of the Centennial Park pipe-bomb explosion, bomb fragments were analyzed by Department of Defense assets—set up at a temporary laboratory at the CDC headquarters—to detect the presence of chemical or biological agents; none was found. This marked the first time that a domestic explosive had been routinely screened for those agents.

To facilitate and enhance this civil-military cooperation, Congress recently enacted the Defense Against Weapons of Mass Destruction Act of 1996, which seeks to enhance our domestic preparedness in several fundamental ways, including the following: by strengthening the federal government's ability to prevent and respond to terrorist incidents involving weapons of mass destruction; by enabling the Department of Defense and other federal supports to state and local prevention and response efforts; and by improving the capabilities of state and local emergency responders themselves. More than 100 cities in the United States have already been designated under the provisions of this legislation; their fire, police, rescue, and hospital emergency department personnel will receive training and equipment in an ambitious program conducted by the Department of Defense that began this summer.[9]

From another vantage point, the good news wrapped inside the particular problems posed by biological weapons is that in this arena, public health is the best form of civil defense. Our everyday domestic investments to detect and diagnose disease can and should be strengthened because of our national security trends. Biological weapons are not respectful of traditional boundaries of geography, bureaucracy, or conceptual compartmentalization. In that fact lies our challenge, our opportunity, and our call to action.

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Botulism Surveillance and Emergency Response

A Public Health Strategy for a Global Challenge

Botulism is a neuroparalytic disease caused by a neurotoxin produced from an anaerobic spore-forming bacterium known as *Clostridium botulinum*.[1] The lethal potency of this toxin has mandated intensive surveillance and control measures in the United States. Recent outbreaks of botulism have raised questions regarding the international supply and therapeutic use of botulism antitoxin, and reports that national governments[2] and terrorist groups[3] have stockpiled botulism toxin have increased levels of concern regarding global preparedness for an intentional episode of botulism poisoning. It is estimated that as little as 1 g of aerosolized botulism toxin has the potential to kill at least 1.5 million people, and modern techniques of aerosolization via tactical ballistic missiles or aeronautical spraying may be capable of disseminating up to 60% of this dosage to a target population.[4]

A description of the clinical features of aerosolized botulism toxin poisoning appears elsewhere in this issue.[5] Herein, we describe the US Botulism Surveillance System. The implementation of a similar system on a global scale would (1) establish a more efficient system for detection and diagnosis of the disease, (2) ensure a coordinated and effective public health response to future outbreaks of foodborne botulism, (3) provide a mechanism for distribution of antitoxin in the event of an intentional poisoning, and (4) provide data regarding the epidemiology of botulism that could prevent future cases.

Botulism Surveillance

The Centers for Disease Control and Prevention (CDC) maintain intensive surveillance for cases of botulism in the United States. To identify possible outbreaks of botulism as rapidly as possible, CDC provides epidemiologic consultation and laboratory diagnostic services to state and local health departments in suspected noninfant botulism cases. Physicians are encouraged to contact their state epidemiologists as soon as they suspect a patient may have botulism. State epidemiology offices maintain emergency contact numbers and have been provided with detailed CDC guidelines on diagnosis, management, and prevention of botulism. Epidemiologists from the Foodborne and Diarrheal Diseases Branch are available 24 hours a day to answer calls from state and local health departments or physicians treating potential cases of botulism (emergency number: [404] 639-2888). In concert with state epidemiology offices, CDC epidemiologists recommend appropriate laboratory testing (performed either at CDC or in state laboratories) and ancillary studies to either confirm or rule out the diagnosis. Local public health authorities and national food safety authorities are involved from the beginning, to investigate possible sources and determine the need for further investigation and preventive measures.

Physicians are encouraged to contact their state epidemiologists as soon as they suspect a patient may have botulism.

When foodborne, wound, or adult infectious botulism is suspected, antitoxin is released from CDC quarantine stations located in airports in New York, Chicago, Atlanta, Miami, Los Angeles, San Francisco, Seattle, and Honolulu. The states of California and Alaska control the release of botulism antitoxin independently of CDC, because of the relatively large number of botulism cases in those states and the need for local storage of antitoxin in isolated areas of Alaska. In most cases in the United States, antitoxin is administered to the patient within 12 hours of the decision to release the product (CDC, unpublished data). All data regarding antitoxin releases and laboratory confirmation of cases (including Alaska and California) are recorded annually by CDC. Because CDC is the only source of botulism antitoxin administered in the United States, nearly all diagnosed cases of botulism are reported. The rapid investigation of cases by local health officials and CDC prevents additional cases of botulism from implicated foods.

International Provision of Antitoxin

The CDC has an agreement with the Pan American Health Organization (PAHO) to supply botulism antitoxin to other countries in the Western Hemisphere, with the exception of Canada, which maintains its own supply. Antitoxin is released by CDC for cases of suspected botulism in other nations in the Western Hemisphere, after consultation with regional physicians and in collaboration with PAHO. The cost of this program is absorbed by PAHO from funds provided by each country. This system ensures a coordinated release program for

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the entire hemisphere and allows CDC to maintain some surveillance of botulism outbreaks throughout the Americas. In 1995, CDC released 14 vials of antitoxin in collaboration with PAHO for use in Mexico and Argentina.

Sources of Antitoxin

The US surveillance and antitoxin release program depends on the maintenance of a sufficient supply of antitoxin. This is ensured through a contract with Connaught Laboratories Ltd, Willowdale, Ontario, which is one of the few suppliers of trivalent equine antitoxin worldwide. The CDC contracts for a guaranteed supply of antitoxin each year, and the amount ordered varies minimally from year to year. In addition, CDC has an agreement with the US Army to release antitoxin kept by the army for use in emergency situations such as a terrorist attack with botulism toxin.

In contrast to the Western Hemisphere, there is no reliable source of antitoxin elsewhere in the world. Botulism antitoxin production takes approximately 2 years because of the complicated process of immunizing and then collecting serum from horses, although excess product can be freeze-dried and stored indefinitely for future use. Other than Connaught Laboratories Ltd, we know of only 3 suppliers of botulism antitoxin (although no information is available regarding production in the countries of the former Soviet Union or in China). Of the 3 known suppliers, 1 company does not supply antitoxin outside of Japan and the 2 European suppliers maintain limited quantities and have recently suffered from shortages because of unanticipated demand. Because there is no consistent purchase of antitoxin by governments other than the United States, Canada, and Japan, international suppliers need to estimate demand for their product on a year-to-year basis. This unpredictable demand, coupled with a complex production process, has driven several suppliers out of the market in recent years.

Responding to the Threat of Biological Warfare

As many as 17 countries are suspected of either including or developing biological agents in their offensive weapons programs[3]; botulism toxin is frequently one of these agents because it is relatively easy to produce and highly lethal in small quantities. To date, there have been no reported intentional botulism toxin poisonings in the world. However, in August 1995, Iraq revealed that during the Persian Gulf War 11 200 L of botulism toxin preparation were loaded into specially designed SCUD missile warheads.[3] These warheads were specifically designed for the delivery of biological agents. The Aum Shinrikyo cult in Japan also produced botulism toxin before its 1995 terrorist attack on the Tokyo subway system, although it used the nerve agent sarin in the attack.[6] Instructions for the production of botulism toxin have been broadcast on the Internet as well. In the event of large-scale biological warfare using botulism toxin, a likely route of poisoning would be through an atmospheric explosion or aircraft spraying that releases aerosolized particles of toxin (most likely type A), which are approximately 0.1 to 0.3 μm.[4] Although foodborne or waterborne routes are also possible, these are less effective vehicles for large-scale terrorism or warfare. If an attack is suspected, the exposure can be either avoided or averted through cooking, because cooking destroys the toxin. Botulism toxin is naturally inactivated in fresh water in 3 to 6 days; chlorinated water supplies inactivate toxin within 20 minutes.[7,8] However, because foodborne and waterborne poisonings avoid the need for technically sophisticated explosive devices or aerial spraying, these enteric routes of transmission remain a significant threat for terrorist attacks on a smaller scale.

In contrast to the Western Hemisphere, there is no reliable source of antitoxin elsewhere in the world.

Supportive care through the rapid mobilization of mechanical ventilators would be the primary means of caring for patients exposed to either an aerosolized or large-scale enteric botulism toxin exposure. The rapid administration of botulism antitoxin is the only pharmacologic treatment available; antitoxin administration is effective in preventing progression of illness and in shortening the duration of ventilatory failure in severe cases of botulism if given early in the course of neurologic dysfunction.[9] In US Army experiments, equine F(ab')2 botulism antitoxin given therapeutically to rhesus monkeys as late as 24 hours after an aerosol challenge with a lethal dose of type A toxin provided high levels of survival.[4] However, without mechanical ventilation, the toxin was uniformly lethal if antitoxin administration was delayed until clinical signs had occurred, which was between 29 and 46 hours from exposure in these experiments.[4] Prophylactic immunization with a vaccine against botulism toxin also would be protective against an exposure to botulism toxin.[10] However, the botulism toxoid vaccine is an unlicensed vaccine, and the immunization process would need to begin months in advance of an exposure. It does not provide lifelong immunity, and administration is impractical outside of a select high-risk group (eg, laboratory workers who work with botulism specimens or military personnel with risk of exposure in battlefield conditions).

Creating a Network

Countries outside of the Western Hemisphere may be unprepared for either a foodborne outbreak or a botulism terrorism attack since there is no coordinated system for antitoxin release. Recent foodborne botulism outbreaks in Egypt,[11] Italy,[12] Austria, and Turkey (CDC, unpublished records, 1996) have demonstrated the need for a coordinated antitoxin release system and have exposed shortages in the available European supply. The United States only releases antitoxin internationally through its contract with PAHO, since this contract ensures an efficient, coordinated release process and a relatively predictable demand. Because of long flight times, it is unrealistic to supply other parts of the world on an emergency basis from stocks in the Western Hemisphere.

A program similar to the US Botulism Surveillance System could be adopted elsewhere in the world, with antitoxin release stations in several geographic regions. An ideal system would have multinational funding and be coordinated through an international organization or a participating group of nations. In such a program, 3 to 5 botulism antitoxin release sites would be designated throughout the world, creating a network that would also provide laboratory and technical support for each region. All nations would know where to call regionally for emergency assistance and that a source of antitoxin was always available for cases that met diagnostic criteria.

Resident Forum

Resident Physicians Section

Chemical and Biological Warfare: A Personal Point of View

One hopes that few nonmilitary physicians will ever need a detailed knowledge of chemical and biological weapons. My immersion in the topic occurred in early August 1990, when I was the general medical officer for the USS *Trenton*. The *Trenton*, an amphibious ship that delivers marines to the beach via landing craft and helicopters, carried more than 1100 marines and sailors, and I was responsible for their health and welfare. The ship had just returned from Panama where it had been deployed to support Operation Just Cause. I was making plans to take a short vacation with my wife when I was suddenly called back to duty.

Iraq had invaded Kuwait, and all officers and senior enlisted personnel were recalled to the ship for an emergency meeting. A military general medical officer is expected to be an instant expert in a variety of areas, some more directly related to medicine than others. One of my assigned areas of expertise included nuclear, biological, and chemical warfare.

Despite treaties to the contrary, the threat of chemical and biological warfare during any armed conflict is a real one. Chemical and biological warfare are not topics typically covered in a traditional medical school curriculum. The most closely related education I'd had was memorizing the common organophosphate insecticides and their antidotes during a second-year pharmacology course.

During our 3 days of predeployment, my senior corpsman and I prepared the ship's medical department to meet the needs of the crew. I soon became more familiar than I ever could have imagined with the effects of nerve agents such as sarin and VX. The caustic vesicant blistering agents such as lewisite and nitrogen mustard posed a different but every bit as important threat to personnel because they could cause severe burns and incapacitate troops. The equipment used for protecting and decontaminating personnel and casualties also posed the challenge of treating trauma patients while wearing one of these cumbersome outfits. We had to reconsider the triage system for handling multiple trauma patients, because triage becomes more complicated when some of the casualties are contaminated, or even affected, by chemical agents.

Troops began to embark for deployment of an uncertain duration under potentially hostile conditions. My chief corpsman and I pooled our experiences and resources to devise a training program for the crew and troops. We orchestrated drills and developed casualty care plans, so that after the 2-week transit to the Persian Gulf all personnel would be adequately prepared to handle a nuclear, biological, or chemical warfare scenario.

Because of the limited number of clinicians present on the ship, each crew member had to be trained to provide initial first aid to injured personnel. The training consisted of didactic sessions, practical simulations, and daily mass-casualty drills. The key to any successful coordinated response during a disaster is for nonmedical personnel to have their roles down so well that their actions are predictable and efficient, even in the heat of battle.

We trained personnel in the use of atropine and pralidoxime chloride autoinjectors for self-aid and buddy aid and emphasized the personal protection devices, especially a tight-fitting mask with a micropore filter. The crew and troops were vaccinated against known potential pathogens. Unfortunately, casualties in this scenario can appear hours to days after exposure, and there was no way to ensure absolute protection against all possible biological warfare agents.

In the end, I am pleased to say, all of the preparation and training was underutilized. Deterrence is one of the greatest tools the military has to prevent the use of chemical and biological weapons. Unfortunately, as long as there are unstable countries and individuals in the world who are willing to use chemical and biological weapons, health professionals will need to be familiar with the effects of these agents and the treatment of associated casualties.

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The opinions expressed herein are solely Dr Caruso's and do not represent official policy of the US Department of the Navy, the US Department of Defense, or the US government.

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