Chapter 28

BIOLOGICAL WARFARE DEFENSE

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INTRODUCTION

Contrary to common beliefs, many preventive medicine measures can protect US forces on the battlefield from biological warfare agents. The importance of these measures gained visibility toward the end of the 20th century. After knowledge surfaced about the Iraqi biological warfare program before and during the Persian Gulf War, which was followed by Boris Yeltsin's 1992 announcement regarding the then-active Russian program, the United States realized the seriousness of the biological warfare threat. By the end of the 1990s, there was increasing awareness of the possibility of a terrorist attack using biological agents against civilians in the United States. The potential for military involvement in such an incident, whether as victims of an attack or as responders with the civilian medical community in a mass casualty situation, has made military preparation for and prevention of any type of biological attack a necessity.

Military medical professionals need to know the epidemiology of a biological warfare or terrorist attack and how to recognize rapidly that an attack has occurred. Timely recognition will allow the prompt institution of available medical countermeasures, which can be very effective against several of the most likely bacteria, viruses, and toxins that might be used against US forces. The public health impact of a biological weapon as well as the role public health and other assets should play in executing a program for defense against biological warfare and terrorism also need to be understood. The importance of knowledge regarding medical biological defense cannot be overemphasized. The threat is serious, and the potential for devastating casualties is high. However, with proper planning, proper surveillance techniques, and appropriate use of medical countermeasures either already developed or under development, casualties can be prevented or minimized, and the fighting strength of US forces can be conserved.

THE HISTORY OF BIOLOGICAL WARFARE

Attempted warfare with biological weapons has occurred many times, dating back to antiquity.[1] The attempts are difficult to document, as epidemiologic and microbiological data are scarce and unreliable and many programs were shrouded in secrecy, but interest in the use of biological agents as weapons has been present for centuries and continues to the present day.[2] The devastating impact that infectious diseases can have on an army has long been known and resulted in the often crude but ingenious use of disease organisms and poor sanitation to weaken the enemy. The use of corpses of humans and animals to pollute wells and other sources of water of the opposing forces was a common strategy. The fouling of water supplies was used in many European wars, in the American Civil War, and into the 20th century.[1,3]

The use of specific disease vectors, such as corpses of plague victims in the siege of Caffa (14th century) and smallpox-laden blankets and handkerchiefs in the French and Indian War (18th century), heralded a new means of disease dissemination against populations.[2] In both cases, it cannot be proven that the attempts were successful, as both diseases can occur naturally. This dilemma is still of importance today as newly emerging diseases can be confused with a biological warfare or terrorism event.

Biological warfare became more sophisticated during the 1900s; the goal was to select agents and delivery methods that could produce desired effects without harming the proliferator.[4] Allegations during World War I that Germany had been working on anti-livestock agents, such as *Bacillis anthracis* (the bacterium that causes anthrax) and *Burkholderia* (formerly *Pseudomonas*) *mallei* (the bacterium that causes glanders), led to the first attempt at an international treaty to ban biological weapons.[5]

On June 17, 1925, the Protocol for the Prohibition of the Use in War of Asphyxiating, Poisonous or Other Gases and of Bacteriological Methods of Warfare was signed. This was the first multilateral agreement that extended prohibition of chemical agents to biological agents.[1,6] A total of 108 nations, eventually including the five permanent members of the United Nations Security Council, signed the agreement, which became known as the Geneva Protocol.

World War II

Events during and after World War II were clouded by charges and countercharges of experimentation with biological warfare agents.[1,6] Probably the only use of biological agents on a large scale in the 20th century was Japan's against China.[7] In October 1940, a Japanese plane allegedly scattered contaminated rice and fleas over the city of Chuhsien in Chekiang province. Reportedly, this event was soon followed by an outbreak of bubonic

plague, a disease never previously recorded in Chuhsien. Several other mysterious flights of Japanese aircraft over at least 11 Chinese cities—with the dropping of grain (eg, wheat, rice, sorghum, corn), strange granules containing Gram-negative bacilli, and other materials suspected of being contaminated with the plague bacterium—took place through August 1942. Thousands are estimated to have been hospitalized and 700 died from artificially spread plague bacilli.[6] Despite compelling evidence, testimony, and documents, though, failure to associate directly the isolation of plague bacilli in the laboratory with actual materials dropped by the planes made prosecution difficult.

It is alleged that at least 3,000 prisoners of war were used as experimental subjects by Japan's Imperial Unit No. 731, the notorious "death factory" that conducted what was perhaps the most gruesome series of biological warfare experiments in history.[1,8] Conservatively, more than 1,000 of these prisoners are estimated to have died in experiments with agents causing anthrax, botulism, brucellosis, cholera, dysentery, gas gangrene, meningococcal infection, and plague. Subjects either died in the experiments or were "sacrificed" when they were no longer useful.[9] The Japanese experiments may also have led to the epidemics of plague that occurred in the Harbin area after World War II, possibly due to the release of thousands of infected animals during the Japanese evacuation in 1945.[9] No prisoner left Unit 731 alive.[10]

The British also experimented with biological agents during 1941 and 1942. British trials with *Bacillis anthracis* were held on Gruinard Island off the coast of Scotland. The small-bomb experiments resulted in heavy contamination, with anthrax spores contaminating parts of the island for many years.[11,12] After World War II, the United States, United Kingdom, Canada, and Soviet Union developed large biological warfare programs.[4] These are the countries that have openly admitted to having had a program; other nations have never admitted their work in biological weapons.

The Banning of Biological Weapons

In November 1969, the World Health Organization (WHO) issued a report on chemical and biological weapons. It described the unpredictability of biological warfare weapons and the attendant risks and lack of control when such weapons are used.[13] In that same year, President Nixon declared a ban on the US offensive biological weapons program. It was soon dismantled, and all stocks of biological warfare weapons and agents were destroyed.[2]

In 1972, the Convention on the Prohibition of the Development, Production, and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on their Destruction, commonly known as the Biological Weapons Convention, was convened.[1,6] Agreement was eventually reached among the 103 signing nations (including the Soviet Union and Iraq) that

> [e]ach State party to this convention undertakes never in any circumstances to develop, produce, stockpile, or otherwise acquire or retain microbial or other biological agents or toxins, whatever their origin or method of production, of types and in quantities that have no justification for prophylactic, protective or other peaceful purposes; and weapons, equipment or means of delivery designed to use such agents or toxins for hostile purposes or in armed conflict.[6p135]

The agreement went into effect in March 1975 and reduced the concerns that some nations had about the development and use of biological agents. However, problems with verification and the interpretation of "defensive" research continued.

Recent Biological Warfare Incidents

Since the signing of the Biological Weapons Convention in 1972, the US intelligence community has identified many significant events and emerging threats in the area of offensive biological warfare. The number and identity of countries engaged in offensive biological warfare work is classified, but it can accurately be stated that the number of state-sponsored programs of this type has increased significantly. In her book entitled *Doomsday Weapons in the Hands of Many—The Arms Control Challenge of the 90's*, Kathleen C. Bailey states that Central Intelligence Agency Director William Webster said in 1988 that at least 10 nations were developing biological weapons, a number the author feels to be almost certainly too low.[14]

W. Seth Carus, in *Bioterrorism and Biocrimes: The Illicit Use of Biological Agents in the 20th Century*,[15] states there are seven confirmed countries that are state supporters of biological terrorism: Cuba, Iraq, Iran, Libya, North Korea, Sudan, and Syria. He also describes 19 confirmed uses of a biological agent in terrorist or assassination attacks during the 20th century. It can be hypothesized that the number of terrorists without state support using biological weapons is significantly higher than those with state support. Evidence of state-sponsored programs of biological agent development and use exists.

Anthrax Outbreak in Sverdlovsk

On April 3, 1979, a mysterious outbreak of anthrax at Sverdlovsk, USSR, the site of the Soviet Institute of Microbiology and Virology (VECTOR, since renamed the Russian State Research Center of Virology and Biotechnology but still known as VECTOR), raised questions about the effectiveness of any weapons control agreements.[6,16] This institute had long been suspected of being a biological warfare research facility. In spite of US accusations, the Soviets maintained for years that this outbreak was not due to an accidental release of anthrax from the military research facility but instead was due to ingestion by the local residents of contaminated animal products. Controversy raged in the lay press over the incident. Ultimately, in 1992, the President of Russia, Boris Yeltsin, admitted that there had, in fact, been an accidental airborne release of anthrax spores from the research facility, confirming the long-held belief of many in the United States.[17] In 1992, researchers from the United States interviewed survivors of the incident and confirmed at least 77 cases and 66 deaths. Human cases occurred as far as 4 km downwind of the release, with animal deaths recorded over 50 km downwind.[18] Ken Alibek, a former top-ranking Soviet biological warfare official who defected to the United States in 1992, offers an excellent detailed account of the incident.[19]

Cold War Assassinations

Toxins were used as weapons during the Cold War. In 1978, a Bulgarian exile named Georgi Markov was attacked in London with a device disguised as an umbrella. This weapon fired a tiny pellet into the subcutaneous tissue of his leg while he was waiting for a bus. He died several days later. On autopsy, the tiny pellet was found and determined to contain the toxin ricin.[20] It was later revealed that this assassination was carried out by the communist Bulgarian government with technology supplied by the Soviet Union.[21] An attempted killing with a ricin pellet occurred in Paris, France, 13 days before the Markov assassination. Similar pellet-firing weapons may have been responsible for at least six assassinations in the late 1970s and early 1980s.[22] Another alleged use of toxin is that of trichothecene mycotoxins ("yellow rain") in Laos, Kampuchea, and Afghanistan in the late 1970s and early 1980s by the Soviets.[2] Because of numerous confounding factors, this allegation is regarded by many to be suspect.[23]

Persian Gulf War

In the Persian Gulf theater during the fall and winter of 1990 to 1991, the United States and the coalition of allies faced the threat of biological and chemical warfare. Fortunately, Iraq did not use unconventional weapons, but the allies believed that Iraq retained this capability after its defeat. This belief was verified in 1995 by the UN Special Commission investigating Iraq's weapons of mass destruction.[24] In fact, Iraq had weaponized large quantities of botulinum toxin, anthrax, and aflatoxins by the time of the Persian Gulf War.[25] No concrete information on the scope of Iraq's biological warfare program was available until August 1995, when Iraq disclosed, after Husayn Kamil's defection, the existence of a biological warfare capability. Iraqi officials admitted that they had produced the biological warfare agents anthrax (8,500 L), botulinum toxin (19,000 L), and aflatoxin (2,200 L) after years of claiming that they had conducted only defensive research. Baghdad also admitted preparing biological warfare–filled munitions, including 25 Scud missile warheads (5 with anthrax, 16 with botulinum toxin, and 4 with aflatoxin), 157 aerial bombs, and aerial dispensers, during the Persian Gulf War, although they were not used. Iraq acknowledged researching the use of 155 mm artillery shells, artillery rockets, an MIG-21 drone, and aerosol generators to deliver biological warfare agents.[26]

THE BIOLOGICAL THREAT

The threat of biological and chemical weapons presents a troubling and difficult challenge to society.[27] In a statement made to the Senate Foreign Relations Committee on March 21, 2000, Director of Central Intelligence George J. Tenet stated:

> The preparation and effective use of biological weapons (BW) by both potentially hostile states and by non-state actors, including terrorists, is harder than some popular literature seems to suggest. That said, potential adversaries are pursuing such programs, and the threat that the United States and our allies face is growing in breadth and sophistication.[28]

The Former Soviet Union

The Soviet Union's extensive program subsequently has been controlled largely by Russia. Rus-

sian President Boris Yeltsin stated in 1992 that he would put an end to further offensive biological research;[17] however, the degree to which the program has been scaled back is not known. It has only recently come to public attention that the Soviet government operated a massive open-air test site for studying the dissemination patterns of biological warfare–agent aerosols and methods to detect them, as well as the effective range of aerosol bomblets with biological agents of different types, on Vozrozhdeniye Island in the Aral Sea. Biological warfare agents tested at the site were developed at Ministry of Defense facilities in Kirov, Sverdlovsk (now Yekaterinberg), and Zagorsk and at the Biopreparat center in Stepnogorsk; they included the causative agents of anthrax, tularemia, brucellosis, plague, typhus, Q fever, smallpox, botulism, and Venezuelan equine encephalitis. The experiments were conducted on horses, monkeys, sheep, and donkeys, as well as on laboratory animals such as mice, guinea pigs, and hamsters. In an attempt to ascertain the extent to which the Soviet program had been scaled back, specialists from the US Department of Defense visited Vozrozhdeniye Island in August 1995 and confirmed that the experimental field laboratory had been dismantled, the site's infrastructure destroyed, and the military settlement abandoned.[29]

There is intense concern in the West about the possibility of proliferation or enhancement of offensive programs in countries hostile to the Western democracies because of the potential for these countries to hire expatriate Russian scientists.[30] Substantial numbers of scientists have departed one of the former offensive biological warfare facilities of Biopreparat—VECTOR. It now houses one of the two WHO-sanctioned repositories of smallpox virus, the other being the US Centers for Disease Control and Prevention (CDC). Where the departed scientists have gone is unknown, but Libya, Iran, Syria, Iraq, and North Korea have actively been recruiting such expertise.[31]

In the late 1990s, the United States quietly aided Russia in the opening up of former offensive Russian biological warfare facilities and their conversion to peaceful, legitimate purposes. The Clinton administration informed Congress that VECTOR had rebuffed offers from Iran to buy products, technology, and scientific expertise. As a result, Congress substantially increased the amount of money used to finance these conversions.[32] However, there remains a serious concern despite the successes being seen in the conversion of these former biological warfare facilities. Through 1999, the Russians had not opened their military biological facilities to international inspection, even though President Yeltsin promised to open those secret military installations for Western inspection in 1992. The facilities of the Ministry of Defense, most notably those at Sergiyev Posad (formerly Zagorsk), Kirov, Yekaterinburg, and Strizhi, remained to be inspected at the end of 1999. Only a few of the facilities managed by the civilian arm of the Soviet/Russian biological weapons program, Biopreparat, have been inspected but none since 1994. Until there is a full disclosure and accounting of the Russian program, doubt will remain as to its status.[33]

New Technologies, New Threats

Biological warfare agents provide a broader area of coverage per pound of payload than any other weapons system. The proliferation of technology and scientific progress in biochemistry and biotechnology have simplified production requirements in some cases and have provided the opportunity for creation of exotic agents in others.[34] Genetic engineering holds perhaps the most dangerous potential to create novel agents. Pathogenic microorganisms capable of causing a new disease could be tailor-made. If an adversary inserted a gene coding for a virulence factor lethal to humans into a virus or bacterium, that agent could then spread a disease that could overwhelm the diagnostic, therapeutic, and preventive capacity of a country's health service.[35] Genetic warfare, the targeting of specific populations or individuals with specific genotypic characteristics, could theoretically be accomplished. It has been estimated, however, that only 0.1% to 1% of the human genome can clearly be associated with pure ethnic differences. Whether this diversity is sufficient for the development of tailored agents is an open question.[36]

International proliferation of biological weapons programs broadens the range of agents that US forces may encounter. The modernization of many Third World nations, with subsequent development of industrial, medical, pharmaceutical, and agricultural facilities needed to support these advancing societies, also provides the basis for development of a biological weapons program. A biological weapons program can be easily concealed within legitimate research and development and industrial programs.[35] A report issued in 1993 by the Committee on Armed Services, US House of Representatives, on its inquiry into the chemical and biological threat noted that 11 nations possess or could

TABLE 28-1

INTERNATIONAL BIOLOGICAL WEAPONS PROGRAMS

Known	Probable	Possible
Iraq	China	Cuba
Former Soviet Union	Iran	Egypt
	North Korea	Israel
	Libya	
	Syria	
	Taiwan	

Source: Committee on Armed Services, House of Representatives, 102nd Congress. *Countering the Chemical and Biological Weapons Threat in the Post-Soviet World: Report of the Special Inquiry into the Chemical and Biological Threat*. Washington, DC: Government Printing Office: 1993.

develop an offensive biological weapons capability (Table 28-1). While many in government, intelligence, and diplomatic circles express grave concern about the proliferation of biological weapons, there has been relatively little carryover into the general public.

Incentives for the Use of Biological Warfare

An analysis of the incentives associated with a biological weapons program may offer insights into the current proliferation problem. Such a program has military, technical, and economic incentives, as well as political incentives.[37]

Military Incentives

From a military viewpoint, the ability of biological warfare to produce large numbers of casualties makes these weapons highly attractive for long-range targeting of populations. A report from the WHO[13] on the health aspects of use of these weapons details the enormous impact these weapons would have on a population. According to this report, if a biological agent such as anthrax were used on an urban population of approximately 5 million in an economically developed country such as the United States, an attack from a single plane disseminating 50 kg of the dried agent in a suitable aerosol form would affect an area far in excess of 20 km downwind. The report estimates that approximately 100,000 would die quickly and 250,000 would be incapacitated or die within several days of exposure, assuming unrecognized dissemination with no institution of prophylactic antibiotics. In the same scenario but using a different agent (eg, Q fever), it would be expected to find only several hundred deaths but the same number of people who were temporarily incapacitated.

Technical Incentives

The comparative ease with which many biological warfare agents can be produced is a strong incentive for their use. Virtually all the technology needed to support a biological weapons program is readily obtainable for a variety of legitimate purposes.[38] This technology is very different from nuclear warfare technology, which requires dedicated facilities, or chemical warfare technology, where the agent precursors have few, if any, civilian applications. In addition, both nuclear and chemical technologies require raw materials that are difficult to explain to the international community as being for innocent and legitimate use.

Economic Incentives

The start-up costs of biological weapons programs are not prohibitive, especially when compared with the cost of embarking on a nuclear weapons program.[35] The cost of a biological program is much less than either a nuclear or chemical program: estimates range from $2 billion to $10 billion for a nuclear program, tens of millions for a chemical program, and less than $10 million for a biological program.[39] From an economic standpoint, biological weapons are, according to a famous saying, a poor man's nuclear bomb.[40] Even the weapons used to deliver these agents are relatively cost-effective. A group of chemical and biological experts appearing before a UN panel in 1969 estimated that

> for a large-scale operation against a civilian population, casualties might cost about $2,000 per square kilometer with conventional weapons, $800 with nuclear weapons, $600 with nerve-gas weapons, and $1 with biological weapons.[41(p16)]

Political Incentives

Two distinct political incentives might persuade a country to pursue a biological weapons program: (1) domestic and international status and (2) a favorable risk-benefit ratio. First, a country's ability

to threaten its enemies with a weapon capable of inflicting mass casualties offers some tangible advantages.[37] W. Seth Carus, then Director of Defense Strategy on the Policy Planning Staff in the Office of the Secretary of Defense, summarized this political incentive:

> The perceived need for deterrence or compellence [*sic*] capabilities, a desire to influence the political-military calculations of potential adversaries, the search for national status, and even bureaucratic and personal factors can play a role in the initiation of such programs.[38(p22)]

Second, detecting a clandestine biological warfare program is difficult. The risk is relatively low that biological weapons research and development will be uncovered and confirmed—unlike a nuclear or chemical weapons program. Because virtually all of the equipment associated with biological weapons can be used for legitimate purposes, there is no incriminating, unambiguous evidence.[38] A country can undertake many illicit biological warfare activities toward developing a sophisticated offensive biological warfare program, short of actual use, without provoking inquiries from the international community.[37]

Nations With Biological Warfare Capability

The most likely route for the United States or its allies to become involved in a biological conflict would be in regional conflicts, whether as members of a UN peacekeeping force or through an act of terrorism.[37] Of the nations currently believed to have an offensive biological warfare program, only a few are potential candidates for engaging in a direct armed conflict with the United States. Iraq is one and continues to defy UN resolutions mandating inspection and dismantling of its weapons of mass destruction program. Weapons inspectors and intelligence officials also have reason to fear that Iraq is working on more-sophisticated programs to develop viral agents for use as biological weapons.[42]

North Korea possesses the capability to produce significant quantities and varieties of biological warfare agents. It also possesses the ability to employ such weapons both on the Korean peninsula and, to a lesser degree, worldwide, using unconventional methods of delivery. North Korean biological warfare research is believed to have begun sometime during the early 1960s and to have focused primarily on 10 to 13 different strains of bacteria, including the causative agents of anthrax, cholera, and typhoid fever. There are also reports that they have worked on smallpox and maintain this agent in their inventory. Not surprisingly, substantive details concerning the North Korean program are lacking but are worrisome nonetheless and need to be taken seriously.[43]

A statement issued in February 1993 by Russia's Foreign Intelligence Service, the successor to the Soviet Union's KGB, stated:

> North Korea is performing applied military-biological research in a whole number of universities, medical institutes and specialized research institutes. Work is being performed in these research centers with inducers of malignant anthrax, cholera, bubonic plague and smallpox. Biological weapons are being tested on the island territories belonging to the DPRK (Democratic Peoples Republic of Korea).[44pA10]

Biological Terrorism

Although biological warfare is most often discussed in terms of weapons of mass destruction and usually in the context of war, foreign and domestic use of biological agents by terrorists or other subversive forces cannot be ignored. Biological warfare agents are, for the most part, inexpensive and relatively readily obtainable, although effective large-scale distribution may be more difficult to achieve. To lethally infect large numbers of people, the terrorist would have to create an agent that remains viable in a respirable cloud and is retained in the airways. Advanced expertise, methods, and equipment are required to achieve this level of sophistication. Even without advanced technology, though, the terrorist can still effectively accomplish the mission. The goals of terrorists include creating fear in the populace. Just the threat of using a biological agent, let alone the creation of even small numbers of actual cases of disease, can have a significant impact and achieve the terrorist's goals.

In November 1995, hearings conducted by the US Senate Permanent Subcommittee on Investigations revealed that the Japanese Aum Shinrikyo cult had worked to produce both botulinum toxin and anthrax, ostensibly for use as terrorist weapons. Since then, the number of hoaxes involving biological warfare agents has increased dramatically in the United States, but actual incidents remain quite rare.[45] There have been only a few instances where subversive groups tried to inflict mass casualties, and only one where they were successful—the 1984 use of *Salmonella* bacteria to contaminate salad bars

by the Rajneeshee cult in The Dalles, Oregon. This attack, which was motivated by a desire to test the ability to incapacitate voters and so influence an upcoming election, resulted in 751 cases of food poisoning.[46] The threat that a subversive organization could carry out a successful biological attack is one reason that the US Congress dramatically increased funding for preventive measures against biological terrorism at the end of the 20th century. At the request of President Clinton and with bipartisan support from Congress, $133 million was appropriated in fiscal year 1999 for countering biological and chemical threats, $51 million of which was for an emergency stockpile of antibiotics and vaccines. Most of the funds were allocated to the CDC, primarily for strengthening the infectious disease surveillance network and increasing the capacity of federal and state laboratories.[31]

It seems clear that resolution of this problem should be given the highest priority. If enough cause for concern, though, the recent progress in the biomedical sciences threatens the development of an entirely new class of weapons of mass destruction: genetically engineered pathogens. As George Orwell put it, "Life is a race between education and catastrophe."[27(p75)] Matthew Meselson, a well-known Harvard biochemist who described so well the 1979 Sverdlovsk anthrax outbreak, made the statement:

> Every major technology—metallurgy, explosives, internal combustion, aviation, electronics, nuclear energy—has been intensively exploited, not only for peaceful purposes but also for hostile ones…. Must this also happen with biotechnology, certain to be the dominant technology of the coming century?[47(pA14)]

USE OF BIOLOGICAL WEAPONS

Biological warfare agents would in most cases be primarily delivered as small-particle aerosols, and they are silent, odorless, and invisible in such aerosols. Once the particles are of optimal size and condition (the difficult part), they can be delivered by relatively easily available, technologically unsophisticated devices from long distances away. Many cannot be sensed by currently fielded detection devices. The attackers may escape days before the attack is even noticed because of the incubation period necessary for the clinical effects on humans to occur. Use may cause fear and even mass panic in the population attacked. A biological warfare agent need not be highly lethal to be effective, though, because incapacitation and confusion may be all the disruption necessary to cause the intended effects. Biological weapons may also be used in combination with other types of weapons or to add to the disruption produced by conventional weaponry.

Technical Considerations

Initial symptoms resulting from a biological warfare agent may often be similar to those produced by infections endemic to an area, such as influenza. When one member of a unit falls ill, others may still be incubating disease. Service members deployed to foreign lands are known to be at greater risk for exotic endemic disease agents since they may lack natural immunity. Therefore, a biological warfare attack may not be suspected even after the first patients have presented to medical personnel.

Biological agents may enter the human body via several routes:

- entering the lungs as an aerosol (the inhalational route),
- being ingested in food or water (the oral route),
- being injected through the skin (the percutaneous route), and
- being absorbed through the skin or placed on the skin to do damage to the integument (the dermal route).

The inhalational or aerosol route of entry into the body is by far the most important to consider when planning defenses against biological warfare attacks. An ideal biological warfare agent would be of a particle size that would allow it to be carried for long distances by prevailing winds and inhaled deeply into the lungs of unsuspecting victims. Particles that meet both of these conditions are 1 to 20 μm in diameter. Smaller particles would be inhaled and exhaled without deposition in the lungs. Larger particles would either settle onto the ground or be filtered out in the upper respiratory tract of those who inhale them. Particles in the 1-to-20-μm size range also are invisible to the human eye, so a cloud of such particles would not usually be detected by those attacked.

In addition to having the proper particle size, an ideal biological warfare agent might also be dried, which would make it easier to disseminate widely and over long distances. Dry powders composed of

very small particles tend to have better dissemination characteristics and have advantages in storage and handling. Dried agents require an increased level of technological sophistication to produce, but the technology to do so has been available in industry for a number of years.

Logistical difficulties mitigate against using toxins of low lethality as open-air weapons, but they could be used on a smaller scale (eg, in an enclosed space such as a building or as an assassination or terrorist weapon). Such uses may become more likely in light of the kinds of limited conflicts and terrorist scenarios facing US forces in the post–Cold War world.

Line Source. Biological warfare agents might be released by an aggressor by means of sprays, explosive devices, and contamination of food and water. Most of these delivery methods use aerosolized agent. The agent can be dispersed by attaching a spray device to a moving conveyance; an industrial insecticide sprayer designed to be mounted on an aircraft is an example. A line of release would then occur while the sprayer is operating. This is known as a *line source*, and the agent is sprayed perpendicular to the direction of the wind upwind of the intended target area. Anyone downwind of such a line source, within a certain range, is theoretically at risk. The range of the infectious or toxic agent depends on a number of factors (eg, wind speed and direction, atmospheric stability, presence of inversion conditions), and on characteristics of the agent itself (eg, stability to desiccation or ultraviolet light).

Point Source. A second type of aerosol source, *point source*, is a stationary device for aerosolization of the agent, such as a stationary sprayer. A modified point source would be a group of spray devices, such as specially designed bomblets dispersed in a pattern on the ground by a missile or artillery shell. Bomblets may be designed to disseminate on impact or at a predetermined altitude above the ground. They may be released from missiles or aircraft and may have special designs to improve their aerodynamics or pattern in the target area. Other types of delivery systems for biological agents have been designed by various countries. These include bombs or bomblets that release the agent by exploding (generally very inefficient delivery systems), land and sea mines, and pipe bombs.[48]

Clandestine Sources. Clandestine means of delivering biological warfare agents are potentially available to terrorists or special forces units; these include devices that penetrate and carry the agent into the body via the percutaneous route, (eg, pellets, flechettes) or means to contaminate food or water supplies so that the agent is ingested.

Physiological Effects

Biological warfare agents are likely to be selected for their ability to either incapacitate or kill the human targets of the attack. An agent such as staphylococcal enterotoxin B (SEB) has the potential to render entire military units ineffective by incapacitating a high percentage of unit personnel. If one of an adversary's aims is to overload field medical care systems, an incapacitating agent such as SEB might be chosen rather than a lethal biological agent, as SEB casualties may require hospitalization for 1 to 2 weeks. If lethality is the goal, agents such as *Bacillus anthracis* (anthrax); the causative agents of Ebola, Marburg, and Crimean-Congo viral hemorrhagic fevers; or *Yersinia pestis* (plague), might be used. Inhalational anthrax, pneumonic plague, and certain viral hemorrhagic fevers have high case-fatality rates once infection is established in nonimmune hosts.

Psychological Effects

An attack using biological weapons may be more sinister than an attack using conventional, chemical, or nuclear weapons, where the effects are immediate and obvious. By the time the first casualty is recognized, the agent may have already been ingested, inhaled, or absorbed by many others, and more casualties may be inevitable despite medical countermeasures. The psychological and demoralizing impact of the use of a lethal infection or toxin should not be underestimated. Use of these agents against command and control infrastructure in the US could result in far-reaching consequences. The ease and low cost of producing an agent; the difficulty in detecting its presence, protecting its intended victims, and treating those who fall ill; and the potential to selectively target humans, animals, or plants conspire to make defense against this class of weapon particularly difficult.[49] An enemy may also be able to deny the use of such a weapon after casualties occur, claiming that a natural outbreak of an endemic disease with similar symptoms is to blame for the occurrence of disease in opposing forces.

By virtue of their invisibility and undetectability, biological agents may be more psychologically disruptive than conventional weapons to an unprepared military unit. Most military organizations

have little experience in dealing with casualties of biological warfare, and facing an unknown threat can give rise to considerable anxiety and fear. Even the prospect of facing such a threat can create a great deal of concern. Worry about biocontamination may affect or even halt operations at key bases or facilities. Medical personnel may be even more susceptible to concerns over biological warfare, as they are more likely to understand the challenging circumstances that would follow enemy use of such weapons.

Use Against Civilians

Many characteristics of biological weapons make them particularly attractive for use by subversive forces against civilian populations. Biological weapons may, in fact, be much more effective if used against unsuspecting, unprotected, and nonimmune civilian populations than against a fast-moving, immunized military force. The objectives of a terrorist group may not be typical military objectives, so biological weapons may be better suited to their purposes.[50] Biological weapons can be employed effectively as a means of terrorism or sabotage, especially in rear-echelon areas, port or staging sites, and industrial and storage areas. The stealth with which these weapons can be employed is a factor, especially if the terrorist wishes to escape detection. Terrorist use of a biological agent could create panic and cause hundreds or even thousands of people to demand medical care. The potential impact on health care facilities in the area of an attack or a threatened attack is tremendous. Emergency departments may be overrun with patients, unfilled hospital beds scarce, intensive care units filled, and antibiotic stocks depleted. The extent of panic may make traditional approaches to triage, which are based on accident scenarios, very difficult to execute. Public health and medical personnel must be prepared to prevent, detect, and treat biological casualties so as to decrease the panic and the morbidity and mortality rates. Beyond the impact on the health care system, panic associated with a biological terrorist attack could lead to large-scale flight and civil unrest.

BIOLOGICAL THREAT AGENTS AND MEDICAL COUNTERMEASURES

There are three basic types of biological agents: bacteria, viruses, and toxins. Other types of advanced biochemical agents, such as bioregulators, are causing increased concern and attention in the Department of Defense. Unfortunately, at the time of publication there are no available, approved medical countermeasures for these new types of agents, and they will not be discussed further. For the traditional biological agents, their characteristics (Table 28-2) and their available vaccines, chemoprophylaxis, and chemotherapy (Table 28-3) are summarized here. More detailed information on anthrax, brucellosis, cholera, tularemia, plague, Q fever, the viral encephalitidies, and the viral hemorrhagic fevers is presented elsewhere in this textbook and will not be duplicated here. Information on smallpox and the most likely toxin agents are included in this chapter.

Smallpox

The last natural case of smallpox occurred in Somalia in 1977; in 1980, the WHO declared the worldwide eradication of the disease.[51,52] Two WHO-approved repositories exist for the agent of smallpox, variola virus, at the CDC in Atlanta and at VECTOR in Russia. However, the extent of clandestine stockpiles of the virus is unknown.[53]

The United States stopped commercial distribution of vaccine to civilians in May 1983 and phased out vaccination of the military at the end of that decade.[4] Most of the population is now susceptible to infection with variola major. It is stable, infectious by aerosol, transmissible from person to person, has a mortality rate of up to 30%, and is a potentially potent biological weapon when combined with an immunologically naïve population. The potential of genetic recombination to produce a modified poxvirus with enhanced virulence increases the threat of smallpox as a weapon.[53]

After an incubation period of from 7 to 17 days, clinical symptoms begin abruptly with malaise, fever, rigors, vomiting, headache, and backache. Fifteen percent of patients develop delirium. Two to three days later, a rash appears on the face, hands, and forearms. Mucous membrane lesions shed infectious secretions from the oropharynx after the first few days of the rash.[54] Eruptions then appear on the lower extremities and spread to the trunk. The lesions start as macules and quickly progress to papules and pustular vesicles. In contrast to varicella, smallpox lesions are more abundant on the extremities and face and remain generally synchronous in their stage of development. After 8 to 14 days, the pustules form scabs, which may leave scars. Although virus in the throat, conjunctiva, and

TABLE 28-2

CHARACTERISTICS OF BIOLOGICAL WARFARE AGENTS

Disease	Transmissible Person to Person	Infective Dose	Incubation Period	Duration of Illness	Lethality	Persistence (aerosol exposure)	Vaccine Efficacy
Inhalation Anthrax	No	8,000–50,000 spores	1–6 d, possibly longer	3–5 d (usually fatal if untreated)	High	Very stable, spores remain viable for years in soil	2-dose efficacy against 200–500 LD_{50}s in monkeys
Brucellosis	No	10–100 organisms	5–60 d	Weeks to months	< 5% untreated	Very stable	No vaccine
Cholera	Rare	10–500 organisms	4 h to 5 d	≥ 1 wk	Low with treatment, high without	Unstable in aerosols and fresh water; stable in salt water	No data on aerosol
Glanders	Low	Assumed low	10–14 d via aerosol	Death in 7–10 d in septicemic form	> 50%	Very stable	No vaccine
Pneumonic Plague	High	100–500 organisms	2–3 d	1–6 d (usually fatal)	High unless treated within 12–24 h	For up to 1 y in soil; 270 d in live tissues	3 doses not protective against 118 LD_{50}s in monkeys
Tularemia	No	1–50 organisms	2–10 d (avg 3–5 d)	≥ 2 wk	Moderate if untreated	For months in moist soil or other media	80% protection against 1–10 LD_{50}s
Q Fever	Rare	1–10 organisms	10–40 d	2–14 d	Very low	For months on wood and sand	94% protection against 3,500 LD_{50}s in guinea pigs
Smallpox	High	Assumed low (10–100 organisms)	7–17 d (avg 12 d)	4 wk	High to moderate	Very stable	Vaccine protects against large doses in primates
Venezuelan Equine Encephalitis	Low	10–100 organisms	2–6 d	Days to weeks	Low	Relatively unstable	TC 83 protects against 30–500 LD_{50}s in hamsters
Viral Hemorrhagic Fevers	Moderate	1–10 organisms	4–21 d	Death between 7–16 d	High for Zaire strain of Ebola, lower for others	Relatively unstable	No vaccine
Botulism	No	0.001 μg/kg is LD_{50} for type A	Variable (hours to days)	Death in 24–72 h; lasts months if not lethal	High without respiratory support	For weeks in non-moving water and food	3 doses give efficacy of 100% against 25–250 LD_{50}s in primates
Staphylococcal Enterotoxin B	No	0.03 μg/person incapacitation	3–12 h	Hours	< 1%	Resistant to freezing	No vaccine
Ricin	No	3–5 μg/kg is LD_{50} in mice	18–24 h	Days; death within 10–12 d for ingestion	High	Stable	No vaccine
T-2 Mycotoxins	No	Moderate	2–4 h	Days to months	Moderate	For years at room temperature	No vaccine

LD_{50}: a dose that is lethal for 50% of the subjects
Source: *Medical Management of Biological Casualties Handbook.* Fort Detrick, Md: US Army Medical Research Institute of Infectious Diseases; 1998.

urine gradually decreases,[55] variola can be recovered from scabs throughout convalescence, and patients should be isolated and considered infectious until all scabs separate.[56]

The disease caused by variola major had a case fatality rate of 3% in the vaccinated and 30% in the unvaccinated.[52] Other forms of variola major infection, such as flat-type and hemorrhagic-type smallpox, had higher mortality rates. Monkeypox, caused by a naturally occurring viral relative from Africa, is associated with greater than 50% mortality if a secondary bacterial pneumonia develops.[57] It can cause disease in humans but has limited potential for person-to-person transmission.[58] Recent reports suggest that declining smallpox immunization may result in sustained person-to-person transmission,[59] raising the concern that smallpox could be weaponized.

Since few practicing clinicians in the US have seen cases of smallpox, distinguishing this disease from other vesicular exanthems, especially initially, may be difficult. It is also possible that close contacts to cases may shed virus from the oropharynx without manifesting signs of disease.[60] Therefore, rapid and accurate diagnosis is urgently needed so that effective quarantine and other countermeasures can be put in place to decrease panic and the spread of disease.

The standard diagnostic method is detection of characteristic virions with electron microscopy or of Guarnieri bodies under light microscopy.[61] Discrimination between variola, vaccinia, monkeypox, and cowpox is not possible with these techniques. In the past, virus isolation on chorioallantoic membrane was performed, but today polymerase chain reaction techniques promise more accurate and rapid methods to distinguish between the poxviruses.[62]

The occurrence of smallpox is an international public health emergency. Any suspected or confirmed case should be isolated and droplet and airborne precautions implemented. Public health authorities must be notified immediately. If confirmed, all persons in direct contact with the patient should be isolated for 17 days, especially unvaccinated personnel. All those exposed to either weaponized variola virus or a clinical case of smallpox should be vaccinated immediately. Nosocomial transmission is thought to require close person-to-person contact, but in two hospital outbreaks, its potential to spread in low-humidity environments was alarming.[63]

Treatment of smallpox is supportive. Some antivirals have demonstrated good in vivo and in vitro activity against *Poxviridae* and may eventually prove useful as treatments.[53]

Stocks of smallpox vaccine (vaccinia virus) were allowed to drop to very low levels following the eradication of naturally occurring disease. In recent years, increasing this stockpile has received significant attention. Smallpox vaccine must be given by scarification. During the WHO eradication program, a clinical "take" (vesicle with scar formation) following vaccination within the past 3 years correlated with protective immunity. Side effects include low-grade fever and axillary lymphadenopathy. More-severe reactions, such as secondary inoculation to other sites or other persons and generalized vaccinia, can also occur but much less frequently. Vaccination is contraindicated in immunocompromised individuals, during pregnancy, and in those with eczema. However, with the exception of significant impairment of systemic immunity, there are no absolute contraindications to vaccination of a person with a confirmed exposure to variola. Since the antibody response after primary vaccination usually occurs 4 to 8 days earlier than after naturally acquired infection, vaccination within a few days after exposure to variola may be effective in preventing disease or decreasing morbidity and mortality.[64]

Biological Toxins

While biological toxins are not usually regarded as the most effective biological weapons agents, they have been used or their use has been threatened by more terrorist groups and individuals than the more traditional replicating agents.[4] Toxins are defined as any toxic substance produced by a living organism—animals, plants, or microbes. They are different from bacteria and viruses in that they do not replicate in the body. Unlike chemical agents, they are not man-made, not dermally active (except for the trichothecene mycotoxins), and are not volatile. Therefore, they require some sort of weapon system to bring them into contact with the human respiratory tract. Because of this trait, they would not be a persistent battlefield threat or produce secondary or person-to-person exposures. Some of the toxins are quite stable, but their utility as a military weapon can be limited by low toxicity or difficulty in producing large enough quantities for battlefield use. Out of the hundreds of biological toxins that occur naturally, only a very small number have the right characteristics to be an effective weapon. Mechanisms of action, clinical syndromes, treatment, and prophylaxis of the three highest threat toxins will be described here.

TABLE 28-3

VACCINES, CHEMOPROPHYLAXIS AND CHEMOTHERAPEUTICS FOR BIOLOGICAL WARFARE AGENTS

Disease	Vaccine	Chemotherapy
Anthrax	Bioport vaccine (licensed) 0.5 mL SC @ 0, 2, 4 wk, 6, 12, 18 mo, then annual boosters	Ciprofloxacin 400 mg IV q 8–12 h Doxycycline 200 mg IV, then 100 mg IV q 8–12 Penicillin 2 million units IV q 2 h
Cholera	Wyeth-Ayerst Vaccine 2 doses 0.5 mL IM or SC @ 0, 7–30 d, then boosters q 6 months	Oral rehydration therapy during period of high fluid loss Tetracycline 500 mg q 6 h x 3 d Doxycycline 300 mg once, or 100 mg q 12 h x 3 d Ciprofloxacin 500 mg q 12 h x 3 d Norfloxacin 400 mg q 12 h x 3 d
Q Fever	IND 610-inactivated whole cell vaccine given as single 0.5 mL SC injection	Tetracycline 500 mg PO q 6 h x 5–7 d Doxycycline
Glanders	No vaccine available	Sulfadiazine 100 mg/kg in divided doses x 3 wk may be effective, TMP-SMX may be effective
Plague	Greer inactivated vaccine (FDA licensed): 1.0 mL IM; 0.2 mL IM 1-3 mo later; 0.2 mL 5-6 mo after dose 2; 0.2 mL boosters @ 6, 12, 18 mo after dose 3 then q 1-2 y	Streptomycin 30 mg/kg/d IM in 2 divided doses x 10 d (or gentamicin) Doxycycline 200 mg IV then 100 mg IV bid x 10–14 d Chloramphenicol 1 gm IV QID x 10–14 d
Tularemia	IND: Live attenuated vaccine, one dose by scarification	Streptomycin 30 mg/kg IM divided BID x 10–14 d Gentamicin 3-5 mg/kg/d IV x 10–14 d
Brucellosis	No human vaccine available	Doxycycline 200 mg/d PO plus rifampin 600–900 mg/d PO x 6 wk Oflaxacin 400 mg/rifampin 600 mg/d PO x 6 wk
Viral Encephalitidies	VEE DoD C-83 live attenuated vaccine (IND): 0.5 mL SC x 1 dose VEE DoD C-84 (formalin inactivated TC-83 (IND): 0.5 mL SC for up to 3 doses q 2 wks EEE inactivated (IND): 0.5 mL SC at 0 and 28 d WEE inactivated (IND): 0.5 mL SC at 0, 7, 28 d	Supportive therapy, analgesics, and anticonvulsants prn
Viral Hemorrhagic Fevers	AHF Candid #1 vaccine (x-protection for BHF) (IND) RVF inactivated vaccine (IND)	Ribavirin (CCHF/arenaviruses), 30 mg/kg IV initial dose, 15 mg/kg IV q 6 h x 4 d, 7.5 mg/kg IV q 8 h x 6 d Passive antibody for AHF, BHF, Lassa fever, and CCHF
Smallpox	Wyeth calf lymph vaccinia vaccine (licensed): 1 dose by scarification	Cidofovir (effective in vitro)
Botulism	DoD pentavalent toxoid (A-E) (IND) 0.5 mL SC at 0, 2, 12 wk, then yearly boosters	DoD heptavalent equine despeciated antitoxin (A-G) (IND): 1 vial (10 mL) IV CDC trivalent equine antitoxin (A,B, &E) (licensed)
Staphylococcus Enterotoxin B	No vaccine available	Ventilatory support for inhalation exposure
Ricin	No vaccine available	Inhalation: supportive therapy; GI: gastric lavage, superactivated charcoal, cathartics
T-2 Mycotoxins	No vaccine available	

BID: twice a day, CDC: Centers for Disease Control and Prevention, DoD: Department of Defense, EEE: eastern equine encephalitis, GI: gastrointestinal, IM: intramuscularly, IND: investigational new drug, IV: intravenously, q: every, QID: four times a day, SC: subcutaneously, VEE: Venezuelan equine encephalitis, WEE: western equine encephalitis

Source: *Medical Management of Biological Casualties Handbook.* Fort Detrick, Md: US Army Medical Research Institute of Infectious Diseases; 1998.

Chemoprophylaxis	Comments
Ciprofloxacin 500 mg PO bid x 4 wk; if unvaccinated, begin initial doses of vaccine Doxycycline 100 mg PO bid x 4 wk plus vaccination	Potential alternates for Rx: gentamicin, erythromycin, and chloramphenicol Penicillin for sensitive organisms only Vaccine not recommended for routine protection in endemic areas (50% efficacy, short term) Alternatives for Rx: erythomycin, trimethoprim and sulfamethoxazole, and furazolidone Quinolones for tetracycline-/doxycycline-resistant strains
Tetracycline start 8–12 d postexposure x 5 d Doxycycline start 8–12 d postexposure x 5 d	Currently testing vaccine to determine the necessity of skin testing before use.
Postexposure prophylaxis may be tried with TMP-SMX	No large therapeutic human trials have been conducted owing to the rarity of disease
Ciprofloxacin 500 mg PO bid x 7 d Doxycycline 100 mg PO bid x 7 d, Tetracycline 500 mg PO qid x 7 d Doxycycline 100 mg PO bid x 14 d, Tetracycline 500 mg PO qid x 14 d	Plague vaccine not protective against aerosol challenge in animal studies Alternate Rx: TMP-SMX Chloramphenicol for plague/meningitis
Doxycycline and rifampin x 3 wk	TMP-SMX may be substituted for rifampin, but relapse rate may reach 30%
Not applicable	TC-83 reactogenic in 20%, no seroconversions in 20%, only effective against subtypes 1A, 1B, and 1C C-84 vaccine used for nonresponders to TC-83 EEE and WEE inactivated vaccines are poorly immunogenic, multiple immunizations required
Not applicable	Aggressive supportive care and management of hypotension very important
Vaccinia immune globulin 0.6 mL/kg IM (within 3 d of exposure, best within 24 h)	Preexposure and postexposure vaccination recommended if > 3 y since last vaccine Need to skin test before use of antitoxin
Decontamination of clothing and skin	

TABLE 28-4

COMPARATIVE LETHALITY OF SELECTED TOXINS AND CHEMICAL AGENTS IN LABORATORY MICE

Agent	LD_{50} (μg/kg)	Molecular Weight	Source
Botulinum toxin	0.001	150,000	Bacterium
Shiga toxin	0.002	55,000	Bacterium
Tetanus toxin	0.002	150,000	Bacterium
Abrin	0.04	65,000	Plant (Rosary Pea)
Diphtheria toxin	0.10	62,000	Bacterium
Maitotoxin	0.10	3,400	Marine dinoflagellate
Palytoxin	0.15	2,700	Marine soft coral
Ciguatoxin	0.40	1,000	Marine dinoflagellate
Textilotoxin	0.60	80,000	Elapid snake
Clostridium perfringens toxins	0.1–5.0	35,000–40,000	Bacterium
Baltrachotoxin	2.0	539	Arrow-Poison Frog
Ricin	3.0	64,000	Plant (castor bean)
Alpha-Conotoxin	5.0	1,500	Cone snail
Taipoxin	5.0	46,000	Elapid snake
Tetrodotoxin	8.0	319	Puffer fish
Alpha-Tityustoxin	9.0	8,000	Scorpion
Saxitoxin	10.0 (Inhal 2.0)	299	Marine dinoflagellate
VX	15.0	267	Chemical agent
SEB (Rhesus/Aerosol)	27.0 (LD_{50} in pg)	28,494	Bacterium
Anatoxin-A(s)	50.0	500	Blue-green algae
Microcystin	50.0	994	Blue-green algae
Soman (GD)	64.0	182	Chemical agent
Sarin (GB)	100.0	140	Chemical agent
Aconitine	100.0	647	Plant (monkshood)
T-2 Toxin	1,210.0	466	Fungal mycotoxin

Sources: (1) Franz DR. *Defense Against Toxin Weapons*. Ft Detrick, Md: US Army Medical Research and Materiel Command; n.d: Table 2. (2) Sidell FR, Takafuji ET, Franz DR, eds. *Medical Aspects of Chemical and Biological Warfare*. In: *Textbook of Military Medicine*. Washington, DC: Borden Institute and Office of The Surgeon General, US Army; 1997: 607.

Botulinum Toxins

The botulinum toxins are a group of seven related neurotoxins produced by the bacillus *Clostridium botulinum*. These toxins, types A through G, could be delivered by aerosol to concentrations of service members. When inhaled, these toxins produce a clinical picture very similar to foodborne intoxication, although the time to onset of paralytic symptoms may actually be longer than for foodborne cases and may vary by type and dose of toxin. The clinical syndrome produced by one or more of these toxins is known as botulism. Although an aerosol attack is by far the most likely scenario for the use of botulinum toxins, theoretically the agent could be used to sabotage food supplies. Enemy special forces or terrorists might use this method in certain scenarios to produce foodborne botulism in their targets.

The botulinum toxins are among the most toxic compounds known. Table 28-4 shows the comparative lethality in laboratory mice of selected toxins and chemical agents. Botulinum toxin is the most toxic compound per weight of agent, requiring only 0.001 μg per kilogram of body weight to kill 50% of the animals challenged.[65] As a group, bacterial toxins such as botulinum tend to be the most lethal of all toxins. Note that botulinum toxin is 15,000 times more toxic than VX and 100,000 times more toxic than sarin, two of the well-known organophosphate nerve agents.

Botulinum toxins act by binding to the presynaptic nerve terminal at the neuromuscular junction and at cholinergic autonomic sites.[66] These toxins then act to prevent the release of acetylcholine presynaptically and thus block neurotransmission. This interruption of neurotransmission causes both bulbar palsies and the skeletal muscle weakness seen in clinical botulism. Unlike the situation with nerve-agent intoxication, where there is in effect too much acetylcholine because of inhibition of acetylcholinesterase, the problem in botulism is lack of the neurotransmitter in the synapse. Thus, pharmacological measures such as atropine are not helpful in botulism and could even exacerbate symptoms.

The onset of symptoms of inhalation botulism may range from 24 to 36 hours to several days following exposure.[67] Bulbar palsies are prominent early, as are eye symptoms (eg, blurred vision due to mydriasis, diplopia, ptosis, photophobia) and other bulbar signs (eg, dysarthria, dysphonia, dysphagia). Skeletal muscle paralysis follows, with a symmetrical, descending, and progressive weakness that may culminate abruptly in respiratory failure. Progression from onset of symptoms to respiratory failure has occurred in as little as 24 hours in cases of foodborne botulism.

Physical examination usually reveals an alert and oriented patient without fever. Postural hypotension may be present. Mucous membranes may be dry and crusted, and the patient may complain of dry mouth or sore throat. There may be difficulty with speaking and swallowing, the gag reflex may be absent, and the pupils may be dilated and fixed. Ptosis and extraocular muscle palsies may also be observed. Variable degrees of skeletal muscle weakness may be observed depending on the degree of progression in an individual patient. Deep tendon reflexes may be present or absent. With severe respiratory muscle paralysis, the patient may become cyanotic or exhibit narcosis from carbon dioxide retention.

The occurrence of an epidemic of cases of a descending and progressive bulbar and skeletal paralysis in afebrile patients points to the diagnosis of botulinum intoxication. Numbers of cases in a theater of operations should raise at least the possibility of a biological warfare attack with aerosolized botulinum toxin. Foodborne outbreaks are theoretically possible in service members eating meals other than the standard meals-ready-to-eat (MRE) rations.

Individual cases might be confused clinically with other neuromuscular disorders such as Guillain-Barré syndrome, myasthenia gravis, or tick paralysis. The edrophonium (Tensilon) test may be transiently positive in botulism, so it may not distinguish botulinum intoxication from myasthenia. The cerebrospinal fluid in botulism is normal, and the paralysis is generally symmetrical, which distinguishes it from enteroviral myelitis. Mental status changes generally seen in viral encephalitis should not occur with botulinum intoxication.

It may become necessary to distinguish nerve agent or atropine poisoning from botulinum intoxication. Nerve agent poisoning produces copious respiratory secretions and miotic pupils, whereas there is, if anything, a decrease in secretions in botulinum intoxication. Atropine overdose is distinguished from botulism by its central nervous system excitation (eg, hallucinations, delirium) even though the mucous membranes are dry and mydriasis is present. The clinical differences between botulinum intoxication and nerve agent poisoning are listed in Table 28-5.

Laboratory testing is generally not helpful in the diagnosis of botulism. Survivors do not usually develop an antibody response due to the very small amount of toxin necessary to produce clinical symp-

TABLE 28-5

DIFFERENTIAL DIAGNOSIS OF CHEMICAL NERVE AGENT, BOTULINUM TOXIN, AND STAPHYLOCOCCAL ENTEROTOXIN B INTOXICATION FOLLOWING INHALATION EXPOSURE

	Chemical Nerve Agent (Organophosphate)	Botulinum Toxin	Staphylococcal Enterotoxin B
Time to symptoms	Minutes	Hours (12–48)	Hours (1–6)
Nervous system	Convulsions, muscle twitching	Progressive paralysis	Headache, muscle aches
Cardiovascular system	Slow heart rate	Normal rate	Normal or rapid heart rate
Respiratory system	Difficulty breathing, airways constriction	Normal, then progressive paralysis	Nonproductive cough, Severe cases: chest pain, difficulty breathing
Gastrointestinal system	Increased motility, pain, diarrhea	Decreased motility	Nausea, vomiting, diarrhea
Ocular	Small pupils	Droopy eyelids	May see "red eyes" (conjunctival injection)
Salivary system	Profuse, watery saliva	Normal, but swallowing difficult	May be slightly increased quantities of saliva
Death	Minutes	2–3 d	Unlikely
Responds to atropine/2PAM-Cl?	Yes	No	Atropine may reduce gastrointestinal symptoms

2PAM-Cl: pralidoxime chloride
Source: US Army Medical Research Institute of Infectious Diseases. *Medical Management of Biological Casualties Handbook*. Fort Detrick, Md: USAMRIID; 1998.

toms. Detection of toxin in serum or gastric contents is possible with a mouse neutralization assay, but it is the only test available and can be found only in specialized laboratories. If an aerosol attack with botulinum toxin is suspected, serum specimens should be drawn from suspected cases and held for testing at such a facility.

Respiratory failure secondary to paralysis of respiratory muscles is the most serious complication and usually the cause of death. Reported cases of botulism before 1950 had a mortality rate of 60%. With tracheostomy or endotracheal intubation and ventilatory assistance, fatalities should be less than 5%.[68] Intensive and prolonged nursing care may be required for recovery, which may take several weeks or even months.

Circulating toxin is present in isolated cases of foodborne botulism, perhaps due to continued absorption through the gut wall. Botulinum antitoxin (equine origin) has been used as an investigational new drug (IND) in those circumstances and is thought to be helpful. Animal experiments show that after aerosol exposure, botulinum antitoxin can be very effective if given before the onset of clinical signs.[67] Administration of antitoxin is reasonable if disease has not progressed to a stable state. A trivalent equine antitoxin has been available from the CDC for cases of foodborne botulism. This product has all the disadvantages of a horse serum product, including the risks of anaphylaxis and serum sickness. An "especiated" equine heptavalent antitoxin (against types A, B, C, D, E, F, and G) is under advanced development but is available under IND status. Its efficacy is inferred from its performance in animal studies and compassionate use in infant botulinum intoxication.[4] Disadvantages include rapid clearance by immune elimination, as well as a theoretical risk of serum sickness. Sensitivity testing must be carried out for both products before administration, as is explained in the package insert.

For preexposure prevention, a pentavalent toxoid of *C botulinum* toxin types A, B, C, D, and E is also available under an IND status. This product has been administered to several thousand volunteers and occupationally at-risk workers and induces serum antitoxin levels that correspond to

protective levels in experimental animal systems. The currently recommended schedule (ie, 0, 2, and 12 weeks, then a 1-year booster) induces protective antibody levels in greater than 90% of vaccinees after 1 year.[69] Adequate antibody levels are transiently induced after three injections, but decline before the 1-year booster. Contraindications to the vaccine include sensitivities to alum, formaldehyde, and thimerosal or hypersensitivity to a previous dose. Reactogenicity is mild, with 2% to 4% of vaccinees reporting erythema, edema, or induration at the site of injection that peaks at 24 to 48 hours, then dissipates. The frequency of such local reactions increases with each subsequent inoculation; after the second and third doses, 7% to 10% will have local reactions, with a higher incidence (up to 20%) after boosters. Severe local reactions consisting of more extensive edema or induration are rare. Up to 3% report systemic reactions, consisting of fever, malaise, headache, and myalgia. Incapacitating reactions (local or systemic) are uncommon. The vaccine should be stored at refrigerator temperatures and not frozen.

Three or more vaccine doses given by deep subcutaneous injection are recommended only to selected individuals or groups judged at high risk for exposure to botulinum toxin aerosols. There is no current indication for use of botulinum antitoxin prophylactically except under extremely specialized circumstances.

Staphylococcal Enterotoxins

Staphylococcus aureus produces a number of exotoxins, one of which (SEB) was weaponized and tested by the United States as part of its offensive program. SEB is very stable and causes illness with minute amounts of toxin exposure and therefore makes a good biological weapon. Other staphylococcal toxins, such as SEC, could also be weaponized.

SEB is a common cause of food poisoning in humans after ingestion of improperly handled food that has allowed production of toxin by the bacteria. Gastrointestinal manifestations, predominantly nausea and vomiting with occasional diarrhea, are the hallmark of intoxication after ingestion. After inhalation, SEB produces a markedly different clinical syndrome, but either method of intoxication causes significant morbidity. The incapacitating dose is several logarithms lower than the lethal dose and can cause illness and inability to perform the mission for 1 to 2 weeks.

The effects of staphylococcal enterotoxins are mediated by interactions with the host's own immune system. Toxins bind directly to the major histocompatibility complex and stimulate the proliferation of large numbers of T cell lymphocytes.[70] These so-called superantigens stimulate the secretion of various cytokines from immune system cells.[71] These cytokines mediate many of the toxic effects of SEB.

Symptoms of intoxication with SEB begin 3 to 12 hours after inhalation. The sudden onset of fever, chills, headache, myalgia, and nonproductive cough can be followed by dyspnea and retrosternal chest pain in more severe cases. If toxin has been ingested, nausea, vomiting, and diarrhea can occur and may produce significant fluid loss. High fever (39°C to 41°C) with chills and prostration can be present for up to 5 days. The cough can persist for up to 4 weeks, and patients may be incapacitated for 2 weeks.[53]

The diagnosis of SEB intoxication requires clinical and epidemiologic skill. Symptoms can be similar to other respiratory pathogens, such as influenza, adenovirus, and mycoplasma, and they must be included in the differential diagnosis. The physical exam is usually unremarkable, with possible conjunctival injection and postural hypotension if fluid losses have been significant. The chest radiograph is usually normal, but in severe cases may show pulmonary edema or an acute respiratory disease picture. Laboratory findings are not helpful with SEB intoxication. Typical signs of illness, such as a neutrophilic leukocytosis and elevated erythrocyte sedimentation rate, may be seen. While toxin is difficult to detect in serum, a specimen should be drawn for future analysis. Urine samples should also be tested, as toxin metabolites may accumulate in the urine. The toxin can be detected for 24 hours in nasal swabs after an aerosol exposure, and antibody can also be detected in convalescent serum.[53]

Treatment is currently limited to supportive care. Oxygenation and hydration must be monitored, and, in severe cases of pulmonary edema, positive end-expiratory pressure ventilation and diuretics may be needed. Most patients will recover fully in 1 to 2 weeks, although the cough may persist longer. There is no presently available vaccine, although a toxoid and several recombinant vaccines have potential for the future.[72]

Ricin

Ricin is a potent protein toxin derived from the beans of the castor plant (*Ricinus communis*). Its significance as a potential biological warfare toxin relates in part to its wide availability. Worldwide, 1

million tons of castor beans are processed annually in the production of castor oil; the waste mash from this process is approximately 5% ricin by weight. The toxin is quite stable and extremely toxic by several routes of exposure, including the respiratory route.

Ricin can be produced relatively easily and inexpensively in large quantities with fairly simple technology. It is of marginal toxicity in comparison with toxins such as botulinum, so an enemy would have to produce it in larger quantities to cover a significant area on the battlefield. This might limit large-scale use of ricin by an adversary. Ricin can be prepared in liquid or crystalline form, or it can be lyophilized to make it a dry powder. It could be disseminated by an enemy as an aerosol or used by saboteurs, assassins, or terrorists.

Ricin is very toxic to cells. It acts by inhibiting protein synthesis.[4] The clinical picture in intoxicated victims depends on the route of exposure. After aerosol exposure, signs and symptoms depend on the dose inhaled. Accidental sublethal aerosol exposures that occurred in humans in the 1940s were characterized by onset of the following symptoms in 4 to 8 hours: fever, chest tightness, cough, dyspnea, nausea, and arthralgias.[73] The onset of profuse sweating some hours later was commonly the sign of termination of most of the symptoms. Although lethal human aerosol exposures have not been described, the severe pathophysiological changes seen in the animal respiratory tract, including necrosis and severe alveolar flooding, are probably sufficient to cause death if enough toxin is inhaled. Time to death in experimental animals is dose dependent, occurring 36 to 72 hours after inhalation.[74] Humans would be expected to develop severe lung inflammation with progressive cough, dyspnea, cyanosis, and pulmonary edema.

By other routes of exposure, ricin is not a direct lung irritant, but intravascular injection can cause minimal pulmonary perivascular edema due to vascular endothelial injury. Ingestion causes gastrointestinal hemorrhage with hepatic, splenic, and renal necrosis. Intramuscular administration causes severe local necrosis of muscle and regional lymph nodes with moderate visceral organ involvement.[4]

An attack with aerosolized ricin would be diagnosed, as with many biological warfare agents, primarily by the clinical and epidemiologic setting. Acute lung injury affecting a large number of cases in a war zone where an attack could occur should raise suspicion of an attack with a pulmonary irritant such as ricin, although other pulmonary pathogens could present with similar signs and symptoms. Additional supportive clinical or diagnostic features after aerosol exposure to ricin may include the following: bilateral infiltrates on chest radiographs, arterial hypoxemia, neutrophilic leukocytosis, and a bronchial aspirate rich in protein compared to plasma, which is characteristic of high permeability pulmonary edema. Specific enzyme-linked immunosorbent assay testing on serum or immunohistochemical techniques for direct tissue analysis may be used where available to confirm the diagnosis. Ricin is an extremely immunogenic toxin, and acute and convalescent sera should be obtained from survivors for measurement of antibody response.[4]

Management of ricin-intoxicated patients depends on the route of exposure. Patients with pulmonary intoxication are given appropriate treatment for pulmonary edema and respiratory support as indicated. Gastrointestinal intoxication is best managed by vigorous gastric decontamination with lavage and superactivated charcoal, followed by use of cathartics such as magnesium citrate. Volume replacement of gastrointestinal fluid losses is important. In percutaneous exposures, treatment is primarily supportive.

When worn correctly, the military's protective mask is effective in preventing aerosol exposure. Although a vaccine is not currently available, candidate vaccines are under development that are immunogenic and confer protection against lethal aerosol exposures in animals.[4] Prophylaxis with such a vaccine is the most promising defense against a biological warfare attack with ricin.

EPIDEMIOLOGY AS A DETECTION TOOL

The understanding of agent characteristics, diagnosis, and treatment is important in effectively responding to a biological attack. However, the health care provider must also think like an epidemiologist to achieve an advantage over an intentional, or even naturally occurring, outbreak of disease. Through the knowledge and application of basic epidemiologic principles, a biological warfare or terrorist attack can be quickly detected and effective preventive and treatment measures instituted to save lives.

A biological attack can be overt (with an announcement of the release of an agent) or covert (with no notice that an agent has been released). The overt attack, which includes hoaxes, will cause profound, immediate psychological manifestations and raise the questions of how to verify the attack

EXHIBIT 28-1

EPIDEMIOLOGIC CLUES FOR A BIOLOGIC WARFARE OR TERRORIST ATTACK

- The presence of a large epidemic with a similar disease or syndrome, especially in a discrete population
- Many cases of unexplained diseases or deaths
- More severe disease than is usually expected for a specific pathogen or failure to respond to usual therapy
- Unusual routes of exposure for a pathogen, such as inhalation anthrax
- A disease that is unusual for a given geographic area or transmission season
- Disease normally transmitted by a vector that is not present in that area
- Multiple simultaneous epidemics of different diseases in the same population
- A single case of disease by an uncommon agent (smallpox, some viral hemorrhagic fevers)
- A disease that is unusual for an age group
- Unusual strains or variants of organisms or antimicrobial resistance patterns differ from those circulating
- Similar genetic type among agents isolated from distinct sources at different times or locations
- Higher attack rates in those exposed in certain areas, such as inside a building if released indoors, or lower rates in those inside a sealed building if released outside
- Disease outbreaks of the same illness occurring in noncontiguous areas
- A disease outbreak with zoonotic impact
- Intelligence of a potential attack, claims by a terrorist or aggressor of a release, and findings of munitions or tampering

and what preventive measures to take, such as decontamination, quarantine, vaccination, and prophylaxis. The covert attack presents more difficulties, both in recognizing an attack and in rapidly and effectively responding to it. The covert attack is where the epidemiologic clues are most important. These clues are listed in Exhibit 28-1.

Because the medical effects of biological warfare and terrorism may mimic many endemic diseases, medical personnel will have to be extremely alert to differentiate the initial cases resulting from natural disease. The range of causes of an outbreak needs to be considered. The possibilities include a spontaneous outbreak of a known endemic disease, a spontaneous outbreak of a new or reemerging disease, a laboratory accident, or an intentional attack with a biological agent. Use of the epidemiologic clues can assist in this differentiation.

Once a biological attack or any outbreak of disease is suspected, the epidemiologic investigation should begin. The first step is to confirm that a disease outbreak has occurred. A case definition should be constructed to determine the number of cases and the attack rate. The case definition allows investigators who are separated geographically to use the same criteria when evaluating the outbreak. The use of objective criteria in the development of a case definition is very important in determining an accurate case number, as additional cases may be found and some cases may be excluded, especially as the potential exists for hysteria to be confused with actual disease. The estimated rate of illness should be compared with rates during previous years to determine if the rate constitutes a deviation from the norm.

Once the attack rate has been determined, the outbreak can be described by time, place, and person. These data will provide crucial information in determining the potential source of the outbreak. The epidemic curve is calculated based on cases over time. In a point-source outbreak, which is most likely in a biological attack or terrorism situation, the early parts of the epidemic curve will tend to be compressed compared with propagated outbreaks. The peak may be in a matter of days or even hours. Later phases of the curve may also help determine if the disease appears to spread from person to person, which can be extremely important in instituting effective disease control measures.

Early recognition of a disease outbreak through prior knowledge of disease rates, a good surveillance system, and a quick epidemiologic investigation can allow prompt institution of prophylactic antibiotic therapy (eg, for anthrax, plague) or vaccination (eg,

for smallpox), which could save thousands who are still incubating infections and prevent the spread of contagious organisms. It can also help allocate scarce military and public sector resources and enable military and political leaders to reduce panic through disseminating accurate information.

PUBLIC HEALTH PREPAREDNESS

Especially in civilian settings, it will be the physician and the medical facility, probably not the emergency responders, who will face the initial shock of a biological attack. Medical personnel must be prepared for this possibility, just as with any other public health disaster or disease outbreak.

First of all, medical personnel need to be trained to recognize and treat casualties of biological warfare or terrorism. They must be able to apply appropriate preventive measures rationally and without unnecessary panic or alarm. All members of the hospital team need to be trained, including engineering personnel, to establish improvised containment if necessary.

A Bioterrorism Readiness Plan should be prepared for all military and civilian medical facilities similar to the Federal Response Plan for disasters, with details for management of both overt and covert attacks and with phone numbers of both internal and external contacts.[75] Important contacts include the hospital infection control activity, the preventive medicine office, the local and state health departments, the CDC, and the Federal Bureau of Investigation. A plan should also be prepared for field and overseas military situations.

Well before any event, public health authorities must implement surveillance systems so they can recognize patterns of nonspecific syndromes that could indicate the early manifestations of a biological warfare attack. The system must be timely, sensitive, specific, and practical. But it is difficult for medical advisors to know if a disease outbreak is consistent with a biological warfare or terrorism attack or an endemic disease outbreak unless background rates of disease for an area are known. A theater, installation, or municipal epidemiologic surveillance program therefore must be specifically tailored to both the mission and the geographical area and must allow for specific, diagnosable disease entities and syndromes (eg, influenza-like syndromes). Regular and rapid analysis of syndromic epidemiologic surveillance data may provide the first clue that an attack has occurred. These data may be based on standard disease rates or more nontraditional sources such as laboratory test requests, pharmaceutical sales, or emergency services calls (Exhibit 28-2). As medical systems and records become more automated, extraction and rapid analysis of these data should become more routine. Such information can provide invaluable data to focus response activities, allocate scarce resources, and contain panic.

The possibility of psychological consequences and the need for mental health preparedness should not be overlooked. Following a biological attack, potential psychological responses include anger, panic, fear, paranoia, demoralization, and a loss of faith in social organizations.[76] If quarantine or rationing of medical supplies is needed, even more disruption of usual social supports can occur. As medical personnel are not immune to these psychological reactions, they must be prepared. This emphasizes the importance of realistic training. Training of medical responders will need to include rec-

EXHIBIT 28-2

POSSIBLE SURVEILLANCE DATA TO DETECT AN EMERGING DISEASE OR BIOLOGICAL WARFARE OR TERRORISM

- Traditional reportable diseases from clinicians
- Unexplained deaths
- Intensive care unit admissions
- Syndromic groupings of diseases not based on specific diagnoses (eg, respiratory, gastrointestinal, neurological, fever)
- 911 or emergency calls for conditions such as respiratory distress
- Pharmaceutical usage rates and use of prescription, over-the-counter, and investigational new drugs
- Laboratory test ordering (eg, stool cultures)
- Laboratory results for specific diseases
- Radiological test ordering (eg, chest radiographs)
- Veterinary surveillance
- School absenteeism
- Billing and insurance data
- Internet access of health websites

ognizing the symptoms of anxiety, depression, and dissociation. Plans should be in place to prevent or mitigate stress for both the affected population and the responders.[76] One important way to decrease fear and panic is effective risk communication, and every hospital should be prepared to provide accurate and timely information to the public. Protocols should be developed covering a broad range of scenarios to prevent panic in the community or the military units affected. Through careful planning and preparation, some of the terror involved in a biological attack can be diminished.

Diagnostic capacities should be determined for each hospital or field location. Most standard hospital laboratories can provide a significant amount of support, especially for bacteriology, with traditional culture, staining, and sensitivity capabilities. However, there are many agents that cannot be identified in routine laboratories. It is important to know where the closest reference laboratory is located, whether it is civilian or military, and how to request its assistance if necessary. Many state health departments have the capability to diagnose many biological threat agents. Specialized laboratories, such as at the CDC and at the US Army Medical Research Institute of Infectious Diseases, Fort Detrick, Md, can also provide confirmatory and reference laboratory services. There has been an increase in handheld and rapid detection and diagnostic devices, but the sensitivity and specificity of these diagnostic tools are still in question, and a sample must be sent to an appropriate laboratory. Any clinical information that can be obtained will assist the laboratory in making a rapid and accurate diagnosis. Advance planning to identify appropriate packaging materials and how to coordinate specimen transport should also be done (see Chapter 34, Laboratory Support for Infectious Disease Investigations in the Field).

Infection control practices in the hospital must be planned before a biological attack occurs. Most traditional agents are not transmitted from person to person, with the two major exceptions being smallpox and pneumonic plague. Both of these diseases will require that the patient be isolated until he or she is no longer infectious. Persons affected by most other traditional agents can be managed by health care providers using standard precautions, to include handwashing, wearing gloves when touching blood or any body fluids, and wearing masks, eye protection, and gowns if splashes may occur.[75]

Decontamination of persons after exposure depends on the suspected agent and in most cases is not necessary. The goal of decontamination is to reduce the contamination and to prevent further spread of the agent. Most biological agents are not dermally active and do not form secondary aerosols so are not likely to be a hazard to the patient or the medical staff once the original aerosol has dispersed. Decisions regarding decontamination of persons should be made in consultation with public health personnel. Depending on the intensity of contamination, clothing of the patient may need to be removed and placed in a sealed biohazard bag. Patients should then shower with soap and water, including washing their hair, to remove any residual agent. Bathing patients with bleach solutions can be harmful and is not necessary. Bleach is an excellent way to decontaminate any grossly contaminated equipment and material or any areas known to have come in contact with the agent.

It is important to remember that preparation for a biological attack is similar to that for any disease outbreak, but the surveillance, response, and other demands on resources would likely be of an unparalleled intensity. A strong public health infrastructure is truly a dual-use way to control diseases from either source, whether they are naturally occurring or otherwise.

ENVIRONMENTAL OR ATMOSPHERIC DETECTION OF BIOLOGICAL WARFARE AGENTS

Adequate and accurate intelligence is required to develop an effective defense against biological warfare. Once an agent has been dispersed, detection of the biological aerosol before its arrival over the target in time for personnel to don protective equipment would be an important way to minimize or prevent casualties. However, not until the late 1990s were interim systems of detecting biological agents fielded in limited numbers. Until reliable detectors are available in sufficient numbers, the first indication of a biological attack in unprotected service members may well be the ill individual. This is even more likely in a civilian setting.

Detector systems are evolving and represent an area of intense interest with the highest priorities within the military research and development community. One of the first systems fielded was the Biological Integrated Detection System. This is vehicle-mounted and can test environmental air samples by concentrating appropriate aerosol particle sizes in the air samples, then subjecting the sample to both generic and antibody-based detection for selected agents. The Long-Range Standoff Detection System is being developed to provide a

biological standoff detection capability and, it is hoped, early warning. It employs an infrared laser to detect aerosol clouds at a distance of up to 30 km, with plans to extend the range to 100 km. This system will be available for fixed-site applications or inserted into various transport platforms, such as fixed-wing or rotary aircraft. The other standoff detection system that is currently in the research and development phase is the Short-Range Biological Standoff Detection System. It will employ an ultraviolet- and laser-induced fluorescence to detect biological aerosol clouds at distances of up to 5 km. The information will be used to provide early warning, enhance contamination avoidance efforts, and cue other detection assets.[77]

The principal difficulties in detecting biological agent aerosols are timeliness, false positives, and differentiating the artificially generated biological warfare cloud from the background of organic matter normally present in the atmosphere. Therefore, the aforementioned detection methods must be used in conjunction with medical protection (eg, surveillance, vaccines, other prophylactic measures), intelligence, and physical protection to provide service members layered primary defenses against a biological attack.

SUMMARY

The threat of a battlefield or terrorist attack with a biological agent is real. It is known that several potential adversaries of the United States have worked on or are continuing to explore the offensive use of biological weapons. All military medical personnel should have a solid understanding of the biological threat, how to recognize an attack, and the medical options for defending against that attack. The potential for devastating casualties is high for certain biological agents. With appropriate use of medical countermeasures either already developed or under development, however, many casualties can be prevented or minimized.

REFERENCES

1. Stockholm International Peace Research Institute. *The Rise of CB Weapons*. Vol 1. In: *The Problem of Chemical and Biological Warfare*. New York: Humanities Press; 1971.

2. Christopher GW, Cieslak TJ, Pavlin JA, Eitzen EM. Biological warfare: A historical perspective. *JAMA*. 1997;278:412–417.

3. Rothschild JH. *Tomorrow's Weapons*. New York: McGraw-Hill; 1964.

4. Franz DR, Zajtchuk R. Biological terrorism: Understanding the threat, preparation and medical response. *Dis Mon*. 2000;46(2):125–190.

5. Robertson AG, Robertson LJ. From asps to allegations: biological warfare in history. *Mil Med*. 1995;160:369–373.

6. Geissler E, ed. *Biological and Toxin Weapons Today*. Oxford, England: Oxford University Press, Stockholm International Peace Research Institute; 1986.

7. Williams P, Wallace D. *Unit 731: Japan's Secret Biological Warfare in World War II*. New York: The Free Press (Macmillan, Inc.); 1998.

8. Hersh SM. *Chemical and Biological Warfare: America's Hidden Arsenal*. Indianapolis, Ind: Bobbs-Merrill; 1968.

9. Harris SH. *Factories of Death*. New York: Routledge; 1994.

10. Tomilin VV, Berezhnoi RV. Exposure of criminal activity of the Japanese military authorities regarding preparation for bacteriological warfare [in Russian]. *Voen Med Zh*. 1985;8:26–29.

11. Cole LA. *Clouds of Secrecy: The Army's Germ Warfare Tests Over Populated Areas*. Totowa, NJ: Rowman and Littlefield; 1988.

12. Manchee R, Stewart W. The decontamination of Gruinard Island. *Chem Br*. 1988;July:690–691.

13. World Health Organization Group of Consultants. *Health Aspects of Chemical and Biological Weapons.* Geneva: WHO; 1970. Report.

14. Bailey KC. *Doomsday Weapons in the Hands of Many: The Arms Control Challenge of the 90's.* Chicago: University of Illinois Press; 1991.

15. Carus WS. *Bioterrorism and Biocrimes: The Illicit Use of Biological Agents in the 20th Century*. Washington, DC: Center for Counterproliferation Research, National Defense University; November 1998 revision. Working Paper.

16. Defense Intelligence Agency. *Soviet Biological Warfare Threat*. Washington, DC: Department of Defense, DIA; 1986. DST-1610F-057–86.

17. Smith JR. Yeltsin blames '79 anthrax on germ warfare efforts. *Washington Post*. June 16, 1992: A1.

18. Meselson M, Guillemin J, Hugh-Jones M, et al. The Sverdlovsk anthrax outbreak of 1979, *Science*. 1994;266:1202–1208.

19. Alibek K. *Biohazard: The Chilling True Story of the Largest Covert Biological Weapons Program in the World: Told from the Inside by the Man Who Ran It.* New York: Random House; 1999.

20. Carus WS. *Bioterrorism and Biocrimes: The Illicit Use of Biological Agents in the 20th Century*. Washington, DC: Center for Counterproliferation Research, National Defense University: July 1999 (revision). Working Paper.

21. Crompton R, Gall D. Georgi Markov: Death in a pellet. *Med Leg J*. 1980;48:51–62.

22. Livingstone NC, Douglass JD. *CBW: The Poor Man's Atomic Bomb*. Cambridge, Mass: Institute for Foreign Policy Analysis, Inc.; 1984.

23. Seeley TD, Nowicke JW, Meselson M, Guilleman J, Akratanakkul P. Yellow rain. *Sci Am*. 1985;253(3):128–137.

24. United Nations Security Council. *Report of the Secretary General on the Status of the Implementation of the Special Commission's Plan for the Ongoing Monitoring and Verification of Iraq's Compliance with Relevant Parts of Section C of Security Council Resolution 687 (1991).* New York: United Nations; October 11, 1995. Publication S/1995/864.

25. Zilinskas RA. Iraq's biological weapons: the past as future? *JAMA*. 1997;278:418–424.

26. US Government White Paper. *Iraqi Weapons of Mass Destruction Programs*. February 13, 1998.

27. Block SM. Living nightmares: Biological threats enabled by molecular biology. In: Drell SD, Sofaer AD, Wilson GD, eds. *The New Terror: Facing the Threat of Biological and Chemical Weapons*. Stanford, Calif: Hoover Institution Press, Stanford University; 1999.

28. Statement by Director of Central Intelligence George J. Tenet Before the Senate Foreign Relations Committee on the Worldwide Threat in 2000: Global Realities of Our National Security. 21 March 2000. As prepared for delivery.

29. Bozheyeva G, Kunakbayev Y, Yeleukenov D. *Former Soviet Biological Weapons Facilities in Kazakhstan: Past, Present, and Future.* Monterey, Calif: Monterey Institute of International Studies, Center for Nonproliferation Studies; June 1999. Occasional Paper No. 1.

30. US General Accounting Office, National Security and International Affairs Division. Biological Weapons: *Effort to Reduce Former Soviet Threat Offers Benefits, Poses New Risks*. Washington, DC: GAO/NSIAD: 2000. GAO/NSIAD-00-138.

31. Henderson DA. The looming threat of bioterrorism. *Science.* 1999;283:1279–1282.

32. Miller J. U.S. helps Russia turn germ center to peace uses. *New York Times*. January 8, 2000: A3.

33. Alibek K. Statement before the Joint Economic Committee. United States Congress. May 20, 1998.

34. Committee on Armed Services, House of Representatives. *Special Inquiry into the Chemical and Biological Threat: Countering the Chemical and Biological Weapons Threat in the Post-Soviet World.* Washington, DC: US Government Printing Office; 23 February 1993. Report to the Congress.

35. Chemical and bacteriological weapons in the 1980s. *Lancet*. 1984;2:141–143.

36. Takafuji ET, Johnson-Winegar A, Zajtchuk R. Medical challenges in chemical and biological defense for the 21st century. In: Sidell FR, Takafuji ET, Franz DR, eds. *Medical Aspects of Chemical and Biological Warfare*. Part 1, Vol 5. In: *Textbook of Military Medicine*. Washington, DC: Office of the Surgeon General, US Department of the Army, and the Borden Institute; 1997.

37. Spertzel RO, Wannemacher RW, Linden CD. *Biological Weapons Proliferation*. Fort Detrick, Md: US Army Medical Research Institute of Infectious Diseases; 1993. Defense Nuclear Agency Report DNA-TR-92–116.

38. Roberts B. *Biological Weapons: Weapons of the Future?* Washington, DC: The Center for Strategic and International Studies; 1993.

39. Huxsoll DL. The nature and scope of the BW threat. In: Bailey KC, ed. *Director's Series on Proliferation*. Livermore, Calif: Lawrence Livermore National Laboratory; 1994. UCRL-LR-114070-4.

40. Leskov S; Kovan V, trans. Military bacteriological programs in Russia and USA are strictly secretive and represent terrible threat to the world. *Izvestiya*. June 26, 1993: 15.

41. Douglass JD Jr, Livingston NC. *America the Vulnerable: The Threat of Chemical and Biological Warfare.* Lexington, Mass: Lexington Books; 1987.

42. Iraq's growing threat. *Boston Globe*. Feb 13, 2000; E6. Editorial.

43. Bermudez JS. Asia, exposing the North Korean BW arsenal. *Jane's Intelligence Rev*. 1998;10(8):28.

44. Fialka JJ. CIA says North Korea appears active in biological, nuclear arms. *Wall Street Journal*. February 25, 1993: A10.

45. Tucker JB. Historical trends related to bioterrorism: An empirical analysis. *Emerg Inf Dis.* 1999;5:498–504.

46. Torok TJ, Tauxe RV, Wise RP, et al. A large community outbreak of salmonellosis caused by intentional contamination of restaurant salad bars. *JAMA*. 1997;278:389–395.

47. Perlman D. Russia accused of violating pact with secrecy on its germ weapons: Major nations, not terrorists or loonies, called biggest threat. *San Francisco Chronicle*. February 19, 2000: A14.

48. Patrick WC 3d. Biological Warfare: An overview. In: Bailey KC, ed. *Director's Series on Proliferation*. Livermore, Calif: Lawrence Livermore National Laboratory; 1994. UCRL-LR-114070-4.

49. Department of the Army. *NATO Handbook on the Medical Aspects of NBC Defensive Operations: Biological*. Washington, DC: DA; 1996. Field Manual 8-9.

50. Zilinskas RA. Terrorism and biological weapons: Inevitable alliance? *Perspect Biol Med*. 1990;34(1):44–72.

51. Arita I. Virological evidence for the success of the smallpox eradication programme. *Nature*. 1979;279:293–298.

52. Fenner F, Henderson DA, Arita I, Jezek Z, Ladnyi ID. *Smallpox and Its Eradication.* Geneva: World Health Organization; 1988.

53. Franz DR, Jahrling PB, Friedlander AM, et al. Clinical recognition and management of patients exposed to biological warfare agents. *JAMA*. 1997;278:399–411.

54. Downie AW, St Vincent L, Meiklejohn G, et al. Studies on the virus content of mouth washings in the acute phase of smallpox. *Bull World Health Organ.* 1961;25:49–53.

55. Sarkar JK, Mitra AC, Mukherjee MK, De SK, Mazumdar DG. Virus excretion in smallpox. *Bull World Health Organ.* 1973;48:517–522.

56. Mitra AC, Sarkar JK, Mukherjee MK. Virus content of smallpox scabs. *Bull World Health Organ.* 1974;51:106–107.

57. Zdenek J. *Human Monkeypox.* Basel, Switzerland: S Karger; 1988.

58. Jezek A, Fenner F. Human monkeypox. *Virol Monogr.* 1988;17:93–95.

59. Human monkeypox—Kasai Oriental, Zaire 1996–1997. *MMWR.* 1997;46:304–307.

60. Sarkar JK, Mitra AC, Mukherjee MK, De SK. Virus excretion in smallpox, 2: Excretion in the throats of household contacts. *Bull World Health Organ.* 1973;48:523–527.

61. Kato S, Takahashi M, Kameyama S, Kamehora J. A study on the morphological and cyto-immunological relationship between the inclusions of variola, cowpox, rabbitpox, vaccinia (variola origin) and vaccinia IHD and consideration of the term "Guarneri body." *Biken J.* 1959;2:353–363.

62. Ibrahim MS, Esposito JJ, Jahrling PB, Lofts RS. The potential of 5' nuclease PCR for detecting a single-base polymorphism in orthopoxvirus. *Mol Cell Probes*. 1997;11:143–147.

63. Wehrle PF, Posch J, Richter KH, Henderson DA. An airborne oubreak of smallpox in a German hospital and its significance with respect to other recent outbreaks in Europe. *Bull World Health Organ.* 1970;43:669–679.

64. Henderson DA, Moss B. Smallpox and vaccinia. In: Plotkin SA, Orenstein WA, eds. *Vaccines.* 3rd ed. Philadelphia: WB Saunders; 1999: 74–97.

65. Gill DM. Bacterial toxins: a table of lethal amounts. *Microbiol Rev.* 1982;46:86–94.

66. Simpson LL. Peripheral actions of the botulinum toxins. In: Simpson LL, ed. *Botulinum Neurotoxin and Tetanus Toxin.* New York: Academic Press Inc; 1989: 153–178.

67. Franz DR, Pitt LM, Clayton MA, Hanes MA, Rose KJ. Efficacy of prophylactic and therapeutic administration of antitoxin for inhalation botulism. In: Das Gupta B, ed. *Botulinum and Tetanus Neurotoxins and Biomedical Aspects.* New York: Plenum Press; 1993: 473–476.

68. Chin J, ed. *Control of Communicable Diseases Manual.* 17th ed. Washington, DC: American Public Health Association; 2000: 70–75.

69. Middlebrook JL. Contributions of the U.S. Army to botulinum toxin research. In: Das Gupta B, ed. *Botulinum and Tetanus Neurotoxins and Biomedical Aspects.* New York: Plenum Press; 1993: 515–519.

70. Kappler J, Kotzin B, Herron L, et al. V beta-specific stimulation of human T cells by staphylococcal toxins. *Science.* 1989;244:811–813.

71. Stiles BG, Bavari S, Krakauer T, Ulrich RG. Toxicity of staphylococcal enterotoxins potentiated by lipopolysaccharide. *Infect Immun.* 1993;61:5333–5338.

72. Bavari S, Olson MA, Ulrich RG. Engineered bacterial superantigen vaccines. In: Brown F, Norrby E, Burton D, Mekalonos J. *Vaccines 96.* Cold Spring Harbor, NY: Cold Spring Harbor Laboratory Press; 1996:135–141.

73. Brugsch HG. Toxic hazards: The castor bean. *Mass Med Soc.* 1960;262:1039–1040.

74. Wilhelmsen C, Pitt L. Lesions of acute inhaled lethal ricin intoxication in rhesus monkeys. *Vet Pathol.* 1996;33:296–302.

75. Association for Professionals in Infection Control and Epidemiology (APIC) Bioterrorism Task Force, CDC Hospital Infections Program Bioterrorism Working Group. *Bioterrorism Readiness Plan: A Template for Healthcare Facilities*. APIC: 1999. Available at www.apic.org/html/educ/readinow.html.

76. Holloway HC, Norwood AE, Fullerton CS, Engel CC, Ursano RJ. The threat of biological weapons: prophylaxis and mitigation of psychological and social consequences. *JAMA*. 1997;278:428–430.

77. Ezzell J. Acting Chief, Special Pathogens Branch, Diagnostics Systems Division, US Army Medical Research Institute of Infectious Diseases, Fort Detrick, Md. Personal communication, November 1995.