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Biological weapons have recently attracted the attention and the resources of the nation. Discerning the nature of the threat of bioweapons as well as appropriate responses to them requires greater attention to the biological characteristics of these instruments of war and terror. The dominant paradigm of a weapon as a nuclear device that explodes or a chemical cloud that is set adrift leaves us ill-equipped conceptually and practically to assess and thus to prevent the potentially devastating effects of bioterrorism. Strengthening the public health and infectious disease infrastructure is an effective step toward averting the suffering that could be wrought by a terrorist's use of a biological agent.

The past 4 years have been marked by escalating concerns in the United States about the threat of biological weapons. At first, discussions about the implications of this threat and its possible scenarios were confined primarily to those in the military, diplomatic, law enforcement, and intelligence communities and to those concerned with arms reduction issues. Only recently have the civilian medical and public health communities begun to be engaged in examining the practical challenges posed by this threat. Professional societies for the first time have begun to incorporate discussions of bioterrorism in national meetings. On the international scene, in 1998 the World Health Organization (WHO) decided to establish an expert group to review and revise its 1970 landmark document, *Health Aspects of Chemical and Biological Weapons* (*1*).

Clearly, there is growing public awareness of the threat of bioterrorism, and there is nascent concern among medical and public health professionals as well. This is important because if real progress is to be made in addressing this difficult problem, a substantially greater input of good science, medicine, and public health will be needed.

Beginnings of a National Response

The threat of bioterrorism has not been ignored. Substantial national preparedness measures were taken in June 1995 with Presidential Decision Directive 39 (PDD-39), which was further elaborated in May 1998 by PDD-62 and PDD-63, all classified documents. PDD-39 defined the broad responsibilities and coordination relationships among the federal agencies involved (*2*). PDD-62 and PDD-63 sought to define a better organizational structure. The Federal Bureau of Investigation (FBI) was assigned lead responsibility for crisis management, in implementing measures to resolve the immediate emergency and to investigate the scene with the goal of gathering evidence to support criminal prosecution of a perpetrator. The federal lead role in coordinating subsequent assistance, termed consequence management, was delegated to the Federal Emergency Management Agency. The Public Health Service's Office of Emergency Preparedness (OEP) was asked to coordinate all health and medical assistance. However, OEP was given few funds with which to do this, and the Department of Health and Human Services (HHS), in which OEP is housed, was itself provided with virtually no new resources. The dominant role and most of the funds were assigned to the Department of Defense (DOD) under the 1997 Defense Against Weapons of Mass Destruction Act. The act directed DOD to develop and implement a domestic preparedness program to improve the ability of local, state, and federal agencies to cope with chemical, biological, and nuclear threats and to conduct exercises and preparedness tests.

Metropolitan Medical Response Teams, funded by OEP, are now being trained in a program that will eventually reach 120 major cities (*3*). These teams are to be composed of first responders (fire fighting, law enforcement, and emergency medical personnel) that are already employed by their municipal governments. Limited funds are available for training and for the cities to lease equipment but not for operating costs. Meanwhile, 10 National Guard units of 22 full-time people each, called Rapid Assessment and Initial Detection Teams, are being trained. One unit is planned for each federal region. Under consideration is the possibility of providing one or more such units for each state. The units will be on a standby basis, able to be mobilized quickly should a chemical or biological substance be released. Two other specialized units, each consisting of several hundred people, have been established—the Marine Corps' Chemical and Biological Incident Response Force and the Army's Technical Escort Unit. Additional resources have also been provided to the FBI to permit additional agents to be hired, intelligence efforts are being augmented, and DOD and the Department of Energy have mounted greatly expanded research programs. Research areas include the development of environmental detection devices for chemical agents and some for biological agents, plus the development of equipment such as masks and suits for working in chemically contaminated areas.

The Challenge of Biological Agents

Of the weapons of mass destruction (nuclear, chemical, and biological), the biological ones are the most greatly feared (*4*), but the country is least well prepared to deal with them. Virtually all federal efforts in strategic planning and training have so far been directed toward crisis management after a chemical release or an explosion. Should such an event occur, fire, police, and emergency rescue workers would proceed to the scene and, with the FBI assuming lead responsibility, stabilize the situation, deal with casualties, decontaminate, and collect evidence for identification of a perpetrator. This exercise is not unfamiliar. Spills of hazardous materials, explosions, fires, and other civil emergencies are not uncommon events.

The expected scenario after release of an aerosol cloud of a biological agent is entirely different (Table 1). The release could be silent and would almost certainly be undetected. The cloud would be invisible, odorless, and tasteless. It would behave much like a gas in penetrating interior areas. No one would know until days or weeks later that anyone had been infected (depending on the microbe). Then patients would begin appearing in emergency rooms and physicians' offices with symptoms of a strange disease that few physicians had ever seen. Special measures would be needed for patient care and hospitalization, obtaining laboratory confirmation regarding the identity of microbes unknown to most laboratories, providing vaccine or antibiotics to large portions of the population, and identifying and possibly quarantining patients. Trained epidemiologists would be needed to identify where and when infection had occurred, so as to identify how and by whom it may have been spread. Public health administrators would be challenged to undertake emergency management of a problem alien to their experience and in a public environment where pestilential disease, let

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alone in epidemic form, has been unknown.

The implicit assumption has frequently been that chemical and biological threats and the responses to them are so generically similar that they can be readily handled by a single "chembio" expert, usually a chemist. This is a serious misapprehension (Table 1).

First responders to a biological weapons incident (in contrast to an explosion or chemical release) would be emergency room physicians and nurses, family physicians, infectious disease specialists, infection control practitioners, epidemiologists, hospital and public health administrators, and laboratory experts. Surprisingly, to date there has been little involvement of any of these groups in planning for appropriate responses or in training. One recent measure to address this deficit is the convening, by the Hopkins Center, of a national Working Group on Civilian Biodefense, which is composed of government and nongovernment experts. The principal goal of this group has been to identify which biological agents require priority attention and what should be the most appropriate response to each.

Emergence of the Bioweapons Threat

Bioweapons programs began to receive substantial attention during World War II. An infamous Japanese program ceased with the end of the war, but programs in the United States, Canada, the Soviet Union, and the United Kingdom expanded steadily until 1972 (*5*). At that time, the Biological and Toxin Weapons Convention (BWC) was opened for signature and was eventually ratified by 140 nations, including the Soviet Union and Iraq (*6*). It called for the termination of all research on offensive bioweapons and the destruction of existing stocks of agents. The Western countries complied but, as time passed, other countries took an interest in developing their own capacities. There was no mechanism for verification of this. In the United States during the 1970s and 1980s, there was a mood of complacency about bioterrorism; funds for defensive activities all but evaporated, and a highly regarded research program and team were partially dismantled.

That complacency has been shattered in recent years by events in Iraq and Japan, by revelations from Soviet defectors that documented the extent of the program in Russia, and by the disclosure that at least 10 nations now have a biological weapons capacity (*7*). Discoveries during and after the 1990 Gulf War brought new concerns about bioweapons (*8*). Iraq used chemical weapons in the Iran-Iraq war; it was known to be developing a nuclear capability; and there were signs that it had been engaged in developing anthrax as a weapon. Concerns about anthrax arose too late, however, for enough vaccine to be produced to vaccinate more than a small proportion of the allied forces. After the war, it was learned that Iraq's bioweapons program was substantially larger and more advanced than had been appreciated. In 1995, with the defection of the President's son-in-law Hussein Karnel Hassan, Iraqi documents were obtained that portrayed an operation of previously unknown scope and sophistication. The acknowledged production included 20,000 liters of botulinum toxin and 8000 liters of anthrax spore suspension. SCUD missiles with a range of 300 to 600 km and carrying 400-lb bombs had been outfitted with botulinum toxin and anthrax warheads, and drone aircraft had been equipped with aerosol dispersal systems. Iraq's bioweapons capability remains intact.

In 1995, the sarin gas attack on metropolitan Tokyo by the Japanese religious cult Aum Shinrikyo came as an unexpected surprise. This little known cult foresaw the coming of an apocalyptic war from which its followers would emerge to assume control first of Japan and then the world (*9*). To speed this process, they sought to use weapons of mass destruction to kill hundreds of thousands, if not millions, and to spread panic. Only in 1998 was it learned that the cult had actually sought to aerosolize anthrax and botulinum toxin throughout metropolitan Tokyo on eight occasions between 1990 and 1995. Although its leader has been imprisoned, the cult remains intact and legal today; it operates electronic, computer, and other stores with a net revenue of $30 million annually. It is said to have about 5000 adherents in Japan and to have branches in Russia, Ukraine, Belarus, and Kazakhstan (*10*).

Perhaps of greatest concern is the status of Russia's bioweapons establishment. The scope of the Soviet program and details of its operation have become increasingly available during the 1990s as a result of defections by senior officials of its bioweapons program. The signing of the BWC in 1972 is reported to have been seen by the Soviet Union as an opportunity to gain an advantage over its Cold War adversaries. Accordingly, a massive expansion of its bioweapons program was begun (*11*). The eradication of smallpox and the cessation of vaccination in 1980 were considered another opportunity to be exploited. A program was begun to produce smallpox virus on a very large scale and to weaponize it. By 1989, this had been achieved with a production capacity of dozens of tons of smallpox virus annually. Ken Alibek, a former first deputy chief of research and production for the Russian biological weapons program, has reported that smallpox virus had been mounted in intercontinental ballistic missiles and in bombs for strategic use.

The biological weapons R&D programs in the former Soviet Union were funded and managed by at least two different entities: the first, called Biopreparat, was in the Ministry of Medical and Microbiological Industry; the second was in the Ministry of Defense. Still operative is a significant proportion of a multilaboratory complex (the vestiges of Biopreparat) extending across at least eight different cities, which once employed 60,000 workers. One of these laboratories, the Russia State Research Center of Virology and Biotechnology, is located in Koltsovo, Novosibirsk Region (*12*). It houses one of the two WHO-sanctioned repositories of small-

Table 1. Important distinctions between chemical and biological terrorism.

Chemical terrorism	Biological terrorism
Speed at which attack results in illness	
Rapid—usually minutes to hours after attack	Delayed—usually days to weeks after attack
Distribution of affected patients	
Downwind area near point of release	Widely spread through city or region; major international epidemic in worst-case scenario
First responders	
Paramedics, firefighters, police, emergency rescue workers, and law enforcement	Emergency department physicians and nurses, infectious disease physicians, infection control practitioners, epidemiologists, public health officials, hospital administrators, and laboratory experts
Release site of weapon	
Quickly discovered; possible and useful to cordon off area of attack	Difficult to identify; probably not possible or useful to cordon off area of attack
Decontamination of patients and environment	
Critically important in most cases	Not necessary in most cases
Medical interventions	
Chemical antidotes	Vaccines and/or antibiotics
Patient isolation/quarantine	
After decontamination there is no need	Crucial if easily communicable disease is involved (such as smallpox); advance hospital planning for isolating large numbers of patients is critical

pox virus [the other being the U.S. Centers for Disease Control (CDC)]. It has extensive biosafety level 4 containment facilities, permitting it to work with the most virulent pathogens, and is currently utilizing smallpox, Marburg, and hemorrhagic fever viruses in recombinant research studies. Like other laboratories in Russia, it is experiencing financial difficulties; substantial numbers of scientists have departed and security is more lax. Where the scientists have gone is unknown, but Libya, Iran, Syria, Iraq, and North Korea have actively been recruiting such expertise (*13*). Relative to Biopreparat, far less is known about the activities of the biological weapons programs centered in the Ministry of Defense (*14*).

A mixture of rogue states and well-financed religious cults with scientists desperately seeking funds creates a volatile situation with potentially serious consequences.

Probable Agents

Any one of thousands of biological agents that are capable of causing human infection could be considered a potential biological weapon. Realistically, only a few pose serious problems. The NATO handbook dealing with potential biological warfare agents lists 31 infectious agents (*15*). Only a very small number of these, however, can be cultivated and dispersed effectively so as to cause cases and deaths in numbers that would threaten the functioning of a large community. Other factors also determine which microbes are of priority concern: specifically, the possibility of further human-to-human spread, the environmental stability of the organism, the size of the infectious dose, and the availability of prophylactic or therapeutic measures.

A Russian panel of bioweapons experts reviewed the microbial agents and concluded that there were 11 that were "very likely to be used." The top four were smallpox, plague, anthrax, and botulism (*16*). Lower on their list were tularemia, glanders, typhus, Q fever, Venezuelan equine encephalitis, and Marburg and influenza viruses. Each of the four top-rated agents is associated with high case fatality rates when dispersed as an aerosol. The rates range upward from 30% for smallpox to more than 80% for anthrax. Smallpox and anthrax have other advantages in that they can be grown reasonably easily and in large quantities and are sturdy organisms that are resistant to destruction. They are thus especially suited to aerosol dissemination to reach large areas and numbers of people.

Plague and botulinum toxin are less likely prospects. From experience in the now defunct U.S. bioweapons development program, producing and dispensing substantial quantities of plague organisms or botulinum toxin (*17*) pose virtually insurmountable problems. Thus, smallpox and anthrax are effectively alone at the top of the list among potential agents.

Likely Perpetrators

Some argue that almost anyone with intent can produce and dispense a biological weapon. It is unlikely, however, that more than a few would be successful in obtaining any of the top-rated agents in a form suitable to be dispensed as an aerosol. Naturally occurring cases of plague, anthrax, and botulism do occur on almost every continent and so provide a potential source for strains. However, there is considerable variation in the virulence of different strains, and a high level of expertise, which is much less obtainable than the agents themselves, is needed to identify an especially pathogenic one. Moreover, producing these particular organisms in large quantity and in the ultra-small particle form needed for aerosolization is beyond the average laboratory.

Soviet laboratories had the sophistication and capacity to produce all of the most pathogenic organisms in large quantities. It is assumed that a number of other countries now also possess this capacity because the costs of equipping and staffing a bioweapons laboratory are modest when compared to those required for a nuclear or chemical facility. Any group with sufficient resources could purchase prepared supplies of aerosolizable organisms and could transport them easily, because only small quantities are needed to inflict casualties over a very wide area. No mechanisms currently exist for screening to intercept such materials at state or national borders.

Discrete outbreaks of less virulent organisms could certainly be propagated by dissident groups with less access to resources and sophisticated laboratories. One such outbreak occurred in 1984, when members of the Rajneeshi religious sect introduced *Salmonella typhimurium* into salad bars in Dallas, Oregon (*18*). In all, some 750 people became ill; none died or were hospitalized. Other episodes of this type could occur but would be unlikely to panic or cripple a city as would an outbreak of smallpox or anthrax.

Greatest Threats: Smallpox and Anthrax

Of the potential biological weapons, smallpox and anthrax pose by far the greatest threats, albeit because of different clinical and epidemiological properties. So far there have been no examples of the potential devastation of biological weapons like those provided by nuclear weapons during World War II. Epidemics of smallpox in Yugoslavia (1972) (*19*) and of anthrax in the Soviet Union (1979) (*20*) after an accidental release from the Sverdlosk bioweapons production facility provide some sense of the magnitude and nature of the problems posed (*21*).

Comprehensive reviews of these two diseases and consensus views as to appropriate medical and public health responses have already been completed by the working group convened by the Hopkins Center (*22*).

Smallpox poses an unusually serious threat; in part, because virtually everyone is now susceptible, vaccination having stopped worldwide 20 or more years ago as a result of the eradication of the disease. Because of waning immunity, it is probable that no more than 20% of the population is protected. Among the unprotected, case fatality rates after infection with smallpox are 30%. There is no treatment. Virus, in aerosol form, can survive for 24 hours or more and is highly infectious even at low dosages (*23*).

An outbreak in which as few as 100 people were infected would quickly tax the resources of any community. There would be both actual cases and people with a fever and rash for whom the diagnosis was uncertain. In all, 200 or more patients would probably have to be treated in the first wave of cases. Most of the patients would be extremely ill with severe aching pains and high fever and would normally be hospitalized. Hospitalization poses problems, however. Because of the risk of widespread transmission of the virus, patients would have to be confined to rooms under negative pressure that were equipped with special filters to prevent the escape of the virus. Hospitals have few rooms so ventilated; there would, for example, probably be less than 100 in the Washington, D.C., metropolitan area.

A vaccination program would have to be undertaken rapidly to protect as many as possible of those who had been in contact with the patients. Vaccination given within 3 to 4 days after exposure can protect most people against a fatal outcome and may prevent the disease entirely. It is unlikely, however, that smallpox would be diagnosed early enough and vaccination programs launched rapidly enough to prevent infection of many of the people exposed during the first wave. Few physicians have ever seen smallpox and few, if any, have ever received training in its diagnosis. Moreover, mounting a vaccination campaign requires time unless there has been advance planning, and no city has yet done such planning. The human immunodeficiency virus epidemic and the more general issue of vaccine complications among immunosuppressed populations introduce added complexity to decision-making regarding smallpox vaccination administration.

A second wave of cases would be almost inevitable. From experiences with smallpox imported into Europe over the past 40 years, it is estimated that there would be at least 10 secondary cases for every case in the first wave (*21*), or 1000 cases in all, appearing some 14 days after the first wave. Vaccination would initially be needed for health workers, essential service personnel, and contacts of patients at home and at work. With mounting numbers of cases, contacts, and involved areas, mass vaccination would soon be the only practical approach. That would not be possible, however, because present vaccine supplies are too limited, there being approximately 5 to 7 million doses currently available. To put this number in perspective, in New York City in 1947, 6 million people were vaccinated over approximately 1 week in response to a total of eight cases of smallpox. Moreover, there are no longer any manufacturers of smallpox vaccine. Best estimates indicate that substantial additional supplies could not be ensured sooner than 36 months from the initial outbreak.

A scenario for an inhalation anthrax epidemic is of no less concern. Like smallpox, the aerosol would almost certainly be unobtrusively released and would drift throughout a building or even a city without being noticed. After 2 to 3 days, infected individuals would appear in emergency rooms and doctors' offices with a variety of nonspecific symptoms such as fever, cough, and headache. Within a day or two, patients would become critically ill and then die within 24 to 72 hours. It is doubtful that antibiotic therapy given after symptoms develop would be of benefit. The case fatality rate is 80% or greater.

Although anthrax does not spread from person to person, it has another dangerous attribute. Individuals who are exposed to an aerosol may abruptly develop illness up to 8 weeks after the initial exposure. Cases can be prevented by the administration of antibiotics, but such treatment would have to be continued daily for at least 60 days. This period might be shortened by the prompt administration of vaccine. Experimental studies suggest that two doses of vaccine given 15 days apart may provide protection beginning 30 days after the initial inoculation. At this time, however, there is no vaccine available for civilian use; building of stockpiles of antibiotics is still in the planning stage, and no city at present has a plan for distributing antibiotics so as to ensure that drugs are given over a 60-day period.

A Look at the Future

Biologists, especially those in medicine and public health, are as critical to confronting the problems posed by biological weapons as are physicists in dealing with nuclear threats and chemists with chemical weapons. During 1998, steps were taken to facilitate such involvement. Nonetheless, the need to discuss bioterrorism in national forums remains. One first step was the National Symposium on Medical and Public Health Response to Bioterrorism convened by the HHS, the Hopkins Center, and 12 other sponsoring organizations on 16 and 17 February 1998.

In May, Assistant Secretary Margaret Hamburg was assigned responsibility for developing a strategic plan for HHS. Formerly New York City Commissioner of Health, she guided the nation's most advanced counterterrorist planning effort from the perspective of public health and medical consequence management. At the request of the president and with bipartisan support from Congress, $133 million was appropriated to HHS for fiscal 1999 for countering biological and chemical threats, $51 million of which is for an emergency stockpile of antibiotics and vaccines. Most of the funds are allocated to the CDC, primarily for the strengthening of the infectious disease surveillance network and for enhancing the capacity of federal and state laboratories. This is not a large sum of money, considering the needs of a fragile public health infrastructure extending over 50 states and at least 120 major cities, but it is a beginning.

The provision of funds to HHS is consonant with the general belief that the most effective step now is to strengthen the public health and infectious disease infrastructure. An augmented full-time cadre of professionals at the state and local level would represent, for biological weapons, a counterpart to the National Guard Rapid Assessment and Initial Detection Teams for chemical weapons. Rather than being on a standby basis, however, the biological cadre would also serve to strengthen efforts directed toward dealing with new and emerging infections and food-borne diseases.

Developing these experts, however, requires a considerable training effort, given the variety of specialists that are needed for preparation and response. First, there is a need to train primary care doctors in early recognition of the most important disease threats and to intensify the training of emergency room physicians and nurses. Infectious disease specialists and hospital epidemiologists must also become versed in case recognition and in steps to take if a suspicious case is detected. There is a need to train laboratory directors and key staff in laboratories with designated responsibilities for lab diagnosis. Moreover, state and local health officers and epidemiologists require training in, among other things, detection, surveillance, and management of epidemic disease.

National Institutes of Health– and CDC-administered research agendas are needed to attract both university and private sector talents to address a host of constraints and problems. Among the most critical needs now are improved vaccines, available in large supply, for both smallpox and anthrax. Areas for vaccine improvement include increasing overall efficacy; in the case of smallpox, reducing complications and in the case of anthrax, reducing the number of inoculations. Feasibility studies suggest that substantially improved second-generation vaccines can be developed quickly.

Finally, there is a need both now and in the longer term to pursue measures that will prevent acts of terrorism. Whatever can be done to strengthen the provisions of the BWC deserves all possible support. The strengthening of our intelligence capabilities so as to anticipate and perhaps interdict terrorists is of the highest priority. The fostering of international cooperative research programs to encourage openness and dialogue as is now being done with Russian laboratories is also important.

Once the medical community rallied to support Lown and Chazov (*24*) in educating peoples and policymakers everywhere about the dread realities of a nuclear winter. Perhaps the same should now be done with respect to the realities of biological weapons, which are now considered to be a more serious threat than the nuclear ones.

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