The New Challenges of Bioterrorism

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Serious concerns about the possible use of microbes by bioterrorists have escalated significantly over recent years (1). The havoc that could be generated by such an attack was amply illustrated by the 2001 anthrax release in the US (2). Only 22 cases occurred and few geographic areas were actually affected but fear and apprehension extended across the country and to others as well. There were realistic uncertainties as to when or if other attacks might occur and a sense of helplessness on the part of the average citizen as to how he could protect himself. The concerns generated by the anthrax epidemic experience have been intensified by all manner of speculative fictional accounts depicting disasters of untold proportion. Many of these are ludicrously exaggerated. However, the fact is that the likelihood of occurrence of a bioterrorist event is possible and increasing.

Those most knowledgeable of the threat of bioterrorism and of the underlying science believe that it is not a matter of "if" there will be a release, it is only a question of "when". Conceivably, the event could be catastrophic, if we were to remain unprepared. Last spring, Nature herself dramatically made the point that other agents like SARS, new to man, were lurking on the planet and could potentially cause as much, perhaps even more serious damage than any terrorist (3). As we have begun to examine what can and should be done, we have come to the realization that we are presently ill-prepared to deal with serious microbial challenges, whatever the source. Complacency, such as we have tolerated, is no longer an acceptable policy.

Until comparatively recently, there were three points of view which variously prevailed in national policy circles and in the academic community which served to discourage biological terrorism being considered to be more than a theoretical possibility:

1) That biological weapons have so seldom been deployed that precedent would suggest they would not be used.

2) That their use is so morally repugnant that none would deign to use them.

3) That it is technologically so difficult to produce organisms in quantity and to disperse them that the science is beyond the reach of any but the most sophisticated laboratories.

These arguments have been shown clearly to be validity.

We now know that there are nations and dissident groups who have both the motivation and access to skills to selectively cultivate some of the most dangerous pathogens and to deploy them as agents in acts of terrorism or war. Iraq was discovered after the Gulf War to have had a startlingly large biological weapons program and, in 1995, the Iraq government confirmed that it had produced, filled and deployed bombs, rockets and aircraft with spray tanks containing Bacillus anthracis and botulinum toxin (4,5). The Japanese cult, Aum Shinrikyo, in 1995, released the nerve gas Sarin in the Tokyo subway. It was later discovered to have, as well, plans

for biological terrorism (6). Included in its arsenal were large quantities of nutrient media, botulinum toxin and cultures of anthrax. Indeed, members of this group traveled to Zaire in 1992 to try to obtain samples of Ebola virus for weapons development. The cult is still intact.

A decade ago, special concerns arose regarding the bioweapons capability of the Soviet Union. Through defectors, it was learned that the Soviet bioweapons program was an enterprise far more extensive and sophisticated than any had imagined at the end of the cold war (7). Indeed, its complement of staff equaled or exceeded that which worked on its nuclear weapons program. One of the largest and most sophisticated of the facilities, called Vektor, is located in Koltsovo, Novosibirsk. Through the early 90s, this was a 4000 person, 30 building facility with ample BL-4 facilities, both for specimens and for isolation of human cases. It is the site of one of the two WHO repositories for the smallpox virus and it is where work still continues using, as well, such as Ebola, Marburg and the hemorrhagic fever viruses. However, because of economic stringencies in Russia, more than half the scientific staff have left the laboratory, dispersing to other laboratories around the world. The principal production facility for smallpox virus is located near Moscow, at Sergiev Posad. It was built to be able to produce annually at least 20 tons of smallpox virus. The laboratory is still intact and still a top secret facility operated by the Ministry of Defense.

The number of countries engaged in some form of biological weapons experimentation has grown from four in the 1960s to perhaps as many as eleven in the 1990s (8). As we now now, however, even comparatively small, non-state-supported dissident groups are entirely capable of causing serious problems.

Biological terrorism is more likely than ever before and far more greatly to be feared than either explosives or chemicals. At a congressional hearing, Colin Powell testified that of all the weapons of mass destruction, the biological weapons worried him the most. Former Senator Sam Nunn asserted that it was not a question of "if" but "when".

Civilian preparations to deal with bioterrorism have now begun in the US. Funds are being made available to strengthen the public health and medical infrastructure; smallpox vaccine, antibiotics and other products have been stockpiled; a national network of diagnostic laboratories has been created; and research programs are now underway.

It is clear, however, that preventing the use of biological weapons or countering them will be extremely difficult. Recipes for making biological weapons are now available on the Internet and even groups with modest finances and basic training in biology and engineering could develop, should they wish, an effective weapon (8) and at little cost. Detection or interdiction of those intending to use biological weapons is next to impossible. Thus, the first evidence of intent to use such weapons will very likely be the appearance of cases in hospital emergency rooms. The rapidity with which those manning the emergency rooms and the specialists in infectious diseases reach a proper diagnosis and the speed with which preventative or therapeutic measure are applied could well spell the difference between 1000s and perhaps tens of thousands of casualties. Indeed, the survival of those physicians and health care staff who are caring for the patients may be at stake. However, there are few indeed who have ever seen patients with

diseases caused by those agents most likely to be employed – as, for example, smallpox or plague or anthrax.

Most persons reviewing this subject detail a long list of potential pathogens that might be employed but, in fact, only a handful share the characteristics of being reasonably easy to prepare and to disperse and being able to inflict sufficiently severe disease so as to paralyze a city, perhaps even a nation. In 1994, Vorobyev, a Soviet bioweapons expert presented to a working group of the US National Academy, the conclusions of Soviet experts as to the agents most likely to be used (9). Smallpox headed the list followed closely by anthrax and plague. Indeed, a Russian defector was to report that the Soviet Union had regularly stockpiled 30 metric tons of dried anthrax spores and 20 tons each of smallpox, plague and tularemia -- all of which have been weaponized. None of these agents has so far been deployed effectively as a biological weapon in significant quantities and thus, no real world events exist which provide the basis for suggesting likely scenarios. However, for smallpox, we had in the 1970s, two importations into Europe that bear recounting for what they illustrate about the threat posed by that agent.

Recall that smallpox is a virus disease, spread from person to person, each infected person, in turn, experiencing the characteristic fever and rash. Infection caused by the virus invariably results in symptomatic disease. There are no mild, subclinical infections among unvaccinated persons. After an incubation period of about 10 to 12 days, the patient experiences high fever and aching pains. Then a rash begins with small papules developing into pustules about day 4-5 and finally changing to scabs about day 12. Some 30% of all unvaccinated patients died of the disease. There was, and is, no specific treatment.

Many have forgotten as to how concerned the countries of the world were about smallpox. Until 1980, essentially all conducted vaccination programs of some sort whether or not they had endemic disease (10). Until 1972, the United States mandated smallpox vaccination for all children at school entry despite the fact that the last cases had occurred in 1949, 23 years before. In the United Kingdom, there were four standby hospitals to be opened only in case of smallpox cases being imported and, in Germany, two state-of-the-art smallpox isolation hospitals were constructed in the 1960s. Tourists everywhere carried yellow vaccination books attesting to the fact that they had been successfully vaccinated within the preceding three years.

The potential for smallpox as an aerosolized agent was vividly illustrated in an outbreak in Germany in 1970 (11). That year, a German electrician returning from Pakistan became desperately ill with high fever and diarrhea. On January 11, he was admitted to a local hospital and isolated in a separate single room on the ground floor because it was feared he might have typhoid fever. He had contact with only two nurses over the next three days. On January 14, a rash developed and on 16 January, the diagnosis of smallpox was confirmed. He was immediately transported to one of Germany's special isolation hospitals and more than 100 000 persons were promptly vaccinated. Hospital patients and staff were vaccinated and quarantined. However, the patient had had a cough, a symptom seldom seen with smallpox. Coughing, as is well-known can produce a large volume, small particle aerosol much as one would expect were smallpox to be used as a terrorist weapon. Subsequently, 19 cases occurred in the hospital, including four in other rooms on the patient's floor of the hospital; eight on the floor above; and nine on the third floor. One of those afflicted was a visitor who had spent less than 15 minutes in

the hospital and had only briefly opened a corridor door, easily 30 feet from the patient's room, to ask directions. One needs no better illustration to understand that smallpox virus in an aerosol form has a considerable capacity to spread over a great distance and to infect at very low dosages.

The experience of Yugoslavia in February 1972 is also instructive in comprehending the havoc created even by a small outbreak (10). Yugoslavia's last previous case of smallpox had occurred 45 years before, in 1927. Nevertheless, Yugoslavia, like most countries throughout the world had continued population-wide vaccination to protect itself should an importation occur. In 1972, a pilgrim returning from a pilgrimage became ill with an undiagnosed febrile disease. Friends and relatives visited from a number of different areas and two weeks later, 11 of them developed high fever and rash. None were aware that others were ill and physicians who saw the patients failed to make a correct diagnosis. Few had ever seen a case of smallpox.

One of the 11 patients who acquired smallpox was a 30-year-old teacher who quickly became critically ill with the hemorrhagic form. This form of smallpox is not readily diagnosed even by experts. He was first given penicillin at a local clinic but as he became increasingly ill be was transferred to a dermatology ward in a city hospital, then to a similar ward in the capitol city and finally, to a critical care unit because he was bleeding profusely and in shock. He died without a definitive diagnosis being made. He was buried two days before the first case of smallpox was recognized. The first cases were correctly diagnosed four weeks after the first patient became ill but, by then 150 persons were already infected. Among them were 38 who were infected by the young teacher in the hospital. The cases occurred in widely separated areas of the country and by the time of diagnosis, they had already begun to expose yet another generation. Each of the neighboring countries closed its borders to all traffic. The country was in panic.

Government health authorities saw no alternative but to launch a nation-wide vaccination campaign. Mass vaccination clinics were held and check points along roads were established where vaccination certificates were examined. Twenty million persons were vaccinated. Hotels and residential apartments were taken over, cordoned off by the military and all known contacts of cases forcibly moved into these centers under military guard. Some 10 000 persons spent two weeks or more in such isolation. Nine weeks after the first patient became ill, the outbreak was stopped -- 175 patients had developed small pox and 35 had died -- and this was in a generally well-vaccinated population. It was, in fact, a small outbreak.

What might happen if smallpox were to be released today in a modern city? First, it is important to recall that routine vaccination stopped more than 30 years ago. Thus, there are large numbers who have never been vaccinated and, for virtually all others, vaccine immunity has been waning for more than 30 years. It is unlikely that more than 25% would have significant residual protection. Suppose that some modest volume of virus were to be released perhaps by exploding a light bulb containing the virus in a subway in a powder form. The event would go unnoticed until the first cases with rash began to appear perhaps 7 to 10 days later. With patients being seen by different physicians in different clinics and by individuals who almost certainly had never before seen a smallpox case, it is probable that a few days would elapse before the diagnosis of smallpox could be confirmed and an alarm sounded.

Assume that perhaps 100 persons had been infected and would require hospitalization. As soon as smallpox was suspected, this number would soon be submerged among a group of patients many times larger, perhaps 200 or 300 persons, all with illnesses with fever and rash but whose diagnosis was uncertain. Some would be reported from other cities and other countries. Where would all of these patients be admitted? Most hospitals have no more than a handful of beds which can assure isolation under negative pressure and few communities have developed plans to accommodate large numbers of contagious patients. Who would care for the patients? Few hospital staff have smallpox immunity. Couple this with the problems posed by the one or two severe hemorrhagic cases which typically have very short incubation periods and would have already been admitted to hospital before smallpox was suspected. They would have been cared for by a large, unprotected intensive care team.

Predictably, there would be an immediate clamor for vaccination such as occurred in the cited outbreaks in Germany and Yugoslavia. In most countries, present stocks of smallpox vaccine are limited. How widely should this vaccine be distributed? Comparatively few doses might be needed were vaccine able to be limited strictly to close contacts of confirmed cases. However, the realities of dealing with even a modest-sized epidemic coupled with anxiety, if not panic, in the civilian population would almost certainly preclude a cautious, measured vaccination effort. In most countries, present reserves of vaccine would rapidly disappear and there is, at present, only a limited manufacturing capacity to produce additional vaccine.

What of anthrax which had been so enthusiastically embraced by both the Soviet Union as well as Iraq and the Aum Shinrikyo? The interest, in part, stems from the fact that the organism is so easy to produce in large quantity and so extremely stable in its dried form. What the effect of aerosolized anthrax might be on humans once had to be inferred from animal experiments and the occasional human infection among workers in factories processing sheep and goat hides (12) What was clear was that inhalation anthrax is highly lethal. Just how lethal became evident in the 1979 Sverdlovsk epidemic (13) when an accident occurred at a Soviet bioweapons factory that was producing anthrax.

In all, 77 cases were identified with certainty of whom 66 died. It is suspected that the actual total was at least 300 patients with 100 or more deaths. The cases lived or worked somewhere within a narrow zone extending some four kilometers south and east of the facility. An accidental airborne release of anthrax spores occurred during a single day and may well have lasted no more than minutes. Anthrax deaths among sheep and cows occurred in six different villages ranging up to 50 kilometers southeast of the military compound along the same axis as the human cases.

Of the 58 cases with known dates of onset, only nine experienced symptoms within a week after exposure; some experienced the onset of disease as late as six weeks after exposure. Whether the onset of illness occurred sooner or later, death almost always followed within one to four days after onset of symptoms.

Meselson and his colleagues who documented this outbreak calculate that the weight of spores released as an aerosol could have been as little as a few milligrams or as much as "nearly

a gram". Alibek, the former deputy director of the Soviet program estimated that as much as 100 grams had been released (7). Recall that the Soviet Union had a reported 30 tons of dried anthrax spores. In the US anthrax attack, it is estimated that the envelopes contained, all told, no more than 10 grams of anthrax powder.

The ramifications of even a modest-sized release of anthrax spores in a city are profound. Emergency rooms would begin seeing a few patients with high fever and difficulty breathing perhaps 2 to 3 days following exposure. Because of the often rapid clinical deterioration, it would already be too late for some to receive antibiotic therapy. Few physicians have ever seen a case of inhalation anthrax and most medical laboratories have had little experience in its diagnosis. Thus, it is probable that a delay of at least another 2 to 3 days would elapse before a definitive diagnosis.

Once the diagnosis was made, one would be faced with the prospect of what to do for others who might have been exposed and could be incubating the disease for as long as 6 to 8 weeks. Vaccine use would be out of the question simply because there is virtually none available. Antibiotics could serve to protect, provided that the organisms were sensitive but the logistics of procuring and distributing antibiotics to perhaps several hundred thousand would be a formidable undertaking and to assure the availability of the antibiotic for 8 weeks would tax resources. When does one permit access to the affected area? This is a serious concern given the fact that anthrax spores may persist in the environment for 40 years or more and methods for decontamination are extremely costly and conceivably impossible for many settings.

The realities of dealing with a comparatively straightforward release of a modest quantity of either smallpox or anthrax are staggering, let alone the problems that would be faced were genetically modified organisms employed. We are today ill-prepared to deal with a terrorist attack which employs biological weapons. Indeed, prior experience of the emergency services has primarily related to events in which explosives have been used or to accidental spills or leaks of chemicals. An explosion, even a fairly major one, or a chemical release is more manageable than the biological challenges posed by smallpox or anthrax. Following an explosion or a chemical attack, the worst effects are quickly over; the dimensions of the catastrophe can be defined; the toll of injuries and deaths can be ascertained; and efforts can be directed to stabilization and recovery. Not so following use of smallpox or anthrax. Day after relentless day, additional cases could be expected -- and in new areas.

The specter of biological weapons use is an ugly one, every bit as grim and foreboding as the picture which has been painted of a nuclear winter. As was done in response to the nuclear threat, there is a need to educate fully both the public and the policy makers as to the nature of that threat. There is a need to build on the 1972 Biological and Toxin Weapons Convention to strengthen measures that deter the development and production of biological weapons. In a broader sense, there is the need to build a strong moral consensus severely condemning the possible use of biological weapons.

Whatever is done, however, it is difficult to imagine a future devoid of the threat of biological weapons. There is no room in today's world for the complacency once felt by many in the industrialized world in the 1970s that the problems posed by infectious agents were

history. Since that time, we have experienced a rude awakening with the discovery and spread of HIV/AIDs with cases still growing in numbers and neither a curative drug or vaccine in sight. This has been but the harbinger of a number of new and emergent organisms culminating with SARS this past Spring. Will SARS vanish or will it return with a vengeance as did the new strains of influenza in 1918 and 1957. How near might we be to developing an effective vaccine or antiviral compound? The realities of drug and vaccine development, whatever the priority, indicate that time line is not weeks, nor months but several years, absent remarkable breakthroughs. The threat of biological weapons, coupled now with the realization that Nature itself may pose an even more serious threat to an unprepared world, dictates a new look at the infectious agents.

In the near term, we need to be as prepared to detect and diagnose, to characterize epidemiologically and to respond appropriately to biological weapons use as we need to be prepared to respond to the threat of new or emergent infections. The needs, in fact, are convergent. We need at international, national and local levels, a greater capacity for surveillance; we need a far better network of laboratories and better diagnostic instruments; we need a more adequate cadre of trained epidemiologists, clinicians and researchers; and we need infinitely better communication and coordination.

Perhaps, most of all, this is the time to give serious thought as to how we might organize, fund and undertake emergency research and development programs to cope with any new and dangerous threat. We need to look carefully at a basic research agenda directed to unraveling important mysteries of pathogenesis and immunity. Most of all, we need to look at the relationships between industry, academia and government, especially the regulatory agencies, as all are needed in a new kind of partnership if we expect to adequately cope with the inevitable challenges ahead.

Josh Lederberg has reminded us, more than once, that man's only competition for dominion of the planet are the viruses and the ultimate outcome is not foreordained.

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