C-10

BIOLOGICAL TERRORISM

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Until recently, the subject of biological terrorism has been little discussed or written about in the medical literature or, for that matter, in the public press. It is not a pleasant subject to contemplate and, frankly, not one I relish discussing. Until recently, I had felt it unwise to publicize the subject because of concern that it might entice some to undertake dangerous, perhaps catastrophic experiments. However, events of the past 12-18 months have made it clear that likely perpetrators already envisage every agenda one could possibly imagine.

There are three points of view which have variously prevailed in national policy circles and in the academic community which have served to discourage further discussion of biological terrorism:

1)That biological weapons have so seldom been deployed over the years and are so morally repugnant that none would deign to use them.

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

3) That, like the concept of a "nuclear winter", the potential destructiveness of bioweapons is unthinkable and so to be dismissed.

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, Iraq confirmed that it had produced, filled and deployed bombs, rockets and aircraft spray tanks containing Bacillus anthracis and botulinum toxin. Its work force and technological infrastructure are still wholly intact. 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. And,indeed, prior to the Sarin attack, the group had actually endeavored to aerosolize anthrax from the top of

later discovered to have , as well, plans for biological terrorism. And,indeed, prior to the Sarin attack, the group had actually endeavored to aerosolize anthrax from the top of an 8 story building in downtown Tokyo --fortunately without success. Included in its arsenal were large quantities of nutrient media, botulinum toxin and drone aircraft equipped with spray tanks. Notably, members of this group had traveled to Zaire in 1992 to obtain samples of Ebola virus for weapons development.

A special concern which has arisen just in the past 6 months relates to the status of Russia's largest and most sophisticated former bioweapons facility, called Vector and 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 isolated on a plain with electric fences and was protected by an elite guard. Here is where the smallpox virus is kept and here is where work has been going on using Ebola, Marburg, the hemorrhagic fever viruses such as Machupo and Crimean-Congo. Visits this autumn disclose a half-empty facility, the electric fences no longer electrified and a handful of guards who had not been paid for months. No one would say where the scientists had gone

The number of countries engaged in biological weapons experimentation has grown from four in the 1960s to eleven in the 1990s. Meanwhile, the bombing of the World Trade Center and the Oklahoma City Federal Building dramatized the serious problems which even small dissident groups could cause.

The entire August 6 issue last year of the Journal of the American Medical Association was given over to a comprehensive review and examination of the problems posed by biological terrorism and warfare. Four important observation are repeatedly noted throughout the 14 papers. (OVERHEAD) First in the fact that 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 said "Of all the weapons of mass destruction, biological weapons worry me most".

Second is the fact that significant actions on the part of our government to deal meaningfully with the threat posed to the civilian population date back less than two years and, as yet, these actions are marginally funded and minimally supported. Third is the recognition that prevention of such episodes 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

Third is the recognition that prevention of such episodes 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.

Fourth is the fact that 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 almost certainly be the appearance of cases in hospital emergency rooms. Some of you here thus constitute the front line of defense whether or not you desire it. It is those manning the emergency rooms who will have the responsibility for first suspecting and diagnosing cases of smallpox or anthrax or plague. The rapidity with which they reach the 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 seeing the patients may be at stake. I wonder how many here have ever seen so much as a single case due to one of these pathogens or, for that matter, would recall from the recesses of memory the characteristics of such cases. I wonder how many diagnostic laboratories would be prepared to confirm promptly such a diagnosis. I expect virtually none.

Most persons dealing with this subject detail a long list of potential pathogens but, in fact, only a handful share the characteristics of being reasonably easy to prepare and to disperse and are able to inflict sufficiently severe disease so as to paralyze a city, perhaps even a nation. Vorobyev, a Russian bioweapons expert presented to a working group of the National Academy, the conclusions of Russian experts as to the agents most likely to be used. Smallpox headed the list followed closely by anthrax and plague. None of these agents has so far effectively been deployed as a biological weapon and thus, no real world events exist which provide the basis for suggesting likely scenarios. However, for smallpox, we have had several well-documented importations into Europe over recent decades; two bear recounting.

First, the disease of smallpox. It is caused by a virus which is 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, much like one has with a severe case of influenza. Then a rash begins to

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How concerned were the countries of the world about smallpox? Until 1980,essentially all conducted vaccination programs of some sort whether or not they had endemic disease. 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. International travelers were obliged to carry an official vaccination card attesting to the fact that they had been successfully vaccinated within the preceding three years. 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 isolation hospitals were constructed in the 1960s specifically for the isolation of smallpox cases should they occur. In fact, for the 1976 Innsbruck Olympics, a special 8 bed ward was constructed for use of possible smallpox cases. occur. For no other disease was there any where near the international concern evoked by smallpox.

In 1962, the United States faced the question as to steps which should be taken in the face of an importation. That year, a young Canadian boy returned from Brazil, traveling by air to New York and by train to Toronto by way of Albany and Buffalo. He developed a rash shortly after arrival and was quickly isolated in hospital. As Chief of the Epidemic Intelligence Service, I had immediately gone to Toronto to see the case and to review the situation with Canadian authorities when I received an emergency call to come to Washington immediately to decide on measures to be taken. I was astonished on arrival to be ushered into a meeting with many of our most senior Public Health Service officials and to be informed that the course of action they were seriously contemplating at that moment called for closure of the border with Canada, a mass

emergency call to come to Washington immediately to decide on measures to be taken. I was astonished on arrival to be ushered into a meeting with many of our most senior Public Health Service officials and to be informed that the course of action they were seriously contemplating at that moment called for closure of the border with Canada, a mass vaccination campaign to be launched in all cities along a route extending from New York through Albany, Syracuse, Rochester and Buffalo, and the issuance of a public announcement asking all who had been in Grand Central Station on the day that the boy had taken the train to come forward and be vaccinated. After considerable discussion, they were reluctantly persuaded that watchful waiting would suffice for the present given the fact that smallpox is not normally contagious prior to eruption of the rash. It is instructive, however, to note that there were many fully prepared to take heroic action involving the vaccination of hundreds of thousands of people threatened by spread of disease from a single patient. It is clear that smallpox terrified as no other disease.

The potential for smallpox as an aerosolized agent was vividly demonstrated in an outbreak in Germany in 1970. That year, a German electrician returning from Pakistan became desperately ill with high fever and diarrhea. (SLIDE 6) 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. The hospital had been closed to visitors for several days prior to admission of the patient because of an influenza outbreak. After the diagnosis of smallpox was made, hospital patients and staff were quarantined and remained so for four weeks. Patients and staff were vaccinated, very ill patients receiving VIG first. However, the patient had had a cough, a symptom seldom seen with smallpox and, as you know, coughing can produce a large volume. small particle aerosol (SLIDE 7) Subsequently, 19 cases occurred in the hospital, (OVERHEAD) including four in other rooms on the patient's floor of the hospital; eight on the floor above; and nine on the third floor. Two were contact cases. One on 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. Three of the patients were

third floor. Two were contact cases. One on 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. Three of the patients were nurses, one of whom died. And this was in a well-vaccinated population. (OVERHEAD) How well vaccinia - and presumably smallpox virus- survives as an aerosol, especially in conditions of lower temperature and humidity was well illustrated in studies conducted during the 1960s. Note that at a temperature of 50° F. and a relative humidity of 20%, most of the virus particles persist for 24 hours but even at higher temperatures and higher humidities, one finds remarkable persistence of the virus for at least 6 hours.

We can also look to the experience of Yugoslavia in February 1972. Its last previous case of smallpox had occurred 45 years before, in 1927. Nevertheless, Yugoslavia, like most countries throughout the world at that time, had continued population-wide vaccination to protect itself should an importation occur. In 1972, a pilgrim returning from Mecca 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. (SLIDE 8) Most were unaware that the 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, pictured here (SLIDE 9) in a Pakistani girl who died 48 hours later, is not readily diagnosed even by experts. The Yugoslav teacher was first given penicillin at a local clinic but as he became increasingly ill he 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 going in to 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, including two physicians, two nurses and four other hospital staff. The cases occurred in widely separated areas of the country. By the time of diagnosis, the 150 secondary cases had already begun to expose yet another generation and, inevitably, questions arose as to how many other yet undetected cases

were infected by the young teacher, including two physicians, two nurses and four other hospital staff. The cases occurred in widely separated areas of the country. By the time of diagnosis, the 150 secondary cases had already begun to expose yet another generation and, inevitably, questions arose as to how many other yet undetected cases there might be. The country was in panic.

Government health authorities saw no alternative but to launch a nation-wide vaccination campaign. Mass vaccination clinics were held (SLIDE 10) check points along roads were established where vaccination certificates were examined. Hotels and residential apartments were taken over, cordoned off by the military and all known contact of cases forcibly moved into these centers under military guard. Some 10 000 persons spent two weeks or more in such isolation. Meanwhile, each of the neighboring countries closed its borders to all traffic. 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 and it was, in fact, a small outbreak.

How difficult would it be to prepare a smallpox weapon? Smallpox virus is readily grown on the chorioallantoic membrane of embryonated hens' eggs. It is a large virus and a stable one. It is so stable, in fact, that in the early 19th century, smallpox vaccine virus (a cousin of smallpox, if you will) was simply dried on small pieces of glass or on cotton threads and shipped from place to place on journeys of days to weeks.

What might happen if smallpox were to be released today in a U.S. city? First, it is important to recognize that routine vaccination stopped in the U.S. in 1972, 25 years ago. Some travelers were vaccinated over the following 8 years and many military recruits as well as a handful of laboratory workers. Overall, however, it is doubtful that more than 10 to 15% of the population have significant residual smallpox immunity at this time. Suppose that some modest volume of virus were to be released perhaps by exploding a light bulb containing virus in the Washington subway and perhaps in a departure lounge at Dulles Airport.. The event would almost certainly go unnoticed until the first cases with rash began to appear perhaps 9 or 10 days later. With patients being seen by different physicians in different clinics, most likely in a number of different cities, and by individuals who almost certainly had never before seen a smallpox case, it is probable that several days would elapse before suspicions of smallpox would arise

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Assume that perhaps 100 persons have 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, all with illnesses with fever and rash but whose diagnosis was uncertain. Some would be reported from other cities and other states. Where would all of these patients be admitted? It is doubtful that there are more than perhaps 50 to 75 hospital beds in the metropolitan D.C. area which provide adequate isolation. And who would care for the patients? Few hospital staff have any 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, perhaps with few isolation precautions because an infectious disease was not suspected.

What of contacts? Based on experience in other outbreaks, the number of contacts of confirmed or suspected cases would number in the thousands, if not tens of thousands, depending on how wide the net for possible contacts was extended. What measures should or would be taken to deal with them. Would they be isolated as in Yugoslavia and if so, where? Or would they simply be subjected to daily checks to determine if they had become ill? Where would one find the manpower to do this?

Logistics could be simplified if rapid, easily used laboratory tests could confirm or rule out smallpox among suspected cases. At present, however, such tests are known only to scientists in two government laboratories

Predictably, there would be an immediate clamor for mass vaccination such as occurred in the cited outbreaks in Germany and Yugoslavia. Present U.S. stocks of smallpox vaccine are nominally listed at 15 million doses but, as it is packaged, the useful number of doses is perhaps half that number. How widely does one apply this vaccine and how quickly? 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 would almost certainly preclude such a cautious, measured vaccination effort. Present reserves of vaccine would disappear

able to be limited strictly to close contacts of confirmed cases. However, the realities of dealing with even a modest-sized epidemic would almost certainly preclude such a cautious, measured vaccination effort. Present reserves of vaccine would disappear within days and there is, at present, no manufacturing capacity anywhere to produce additional vaccine. If an emergency effort were made to produce new stocks of smallpox vaccine, many months to a year or more would be required.

It is apparent that even a modest-sized outbreak offers an agenda replete with problems.

What of anthrax which has been so enthusiastically embraced by both Iraq and the Aum Shinrikyo? Their interest, in part, stems from the fact that the organism is so easy to produce in large quantity. In its dire form it is extremely stable. 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. What was clear is that inhalation anthrax is highly lethal. Just how lethal became evident in the 1979 Sverdlovsk epidemic (SLIDE 11)

In all, 77 cases were identified with certainty of whom 66 died. It is suspected that the actual total was more than 100. The cases lived or worked somewhere within a narrow zone extending some four kilometers south and east of a military bioweapons facility. An accidental airborne release of anthrax spores occurred during a single day and may well have lasted no more than a few minutes. Further investigations revealed anthrax deaths among sheep and cows 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 and some experienced the onset of disease as late as six weeks after exposure. (SLIDE 12) Whether the onset of illness occurred sooner or later, death almost always followed within one to four days after onset. However, there did appear to be a somewhat higher proportion of survivors after the fourth week. This almost certainly resulted from the widespread application of penicillin prophylaxis and anthrax vaccine both of which were distributed in mid-April throughout a population of 59 000 persons.

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Meselson and his colleagues who have so well 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". Note that Iraq acknowledged producing at least 8000 Liters of solution with an anthrax spore and cell count of 10^9/ml.

Speculate upon the ramifications of even a modest-sized release of anthrax spores in a city of perhaps 1 000 000 persons. Emergency rooms would begin seeing a few patients with high fever and some difficulty breathing after perhaps 3 to 4 days following exposure. Although essentially all would be dead within 24 to 48 hours, it is probable that a delay of at least 3 to 5 days would elapse before a definitive diagnosis were made. No emergency room physicians or infectious disease specialists have ever seen a case of inhalation anthrax and would probably not suspect this diagnosis unless they had been forewarned of this possibility-- and none so far have been warned. Medical laboratories have had virtually no experience in diagnosing anthrax.

Once the diagnosis was made, one would be faced with the prospect of what to do over the succeeding six weeks. Should vaccine be administered to those who might have been exposed? Unfortunately, there is at present, little vaccine available and no plan to produce any for civilian use. Should antibiotics be administered prophylactically? If so, which antibiotics and what should be the criteria for exposure? What quantity would be required to treat an exposed population of perhaps 500 000 persons over a 6 week period? Should one be concerned about additional infections occurring as a result of anthrax spores being subsequently resuspended and inhaled by others? Does one request everyone who has been anywhere near the city to report to his or her local physician for treatment should fever or cough, however mild, occur? Undoubtedly, there would be many persons with such symptoms, especially in winter, but how does one distinguish these from the premonitory symptoms of anthrax which may proceed to death within 24 to 48 hours? Can one imagine the reaction of a large population confronted with this array of problems?

To say that we are today ill-prepared to deal with a terrorist attack which employs biological weapons is to state the case optimistically. To date, the focus of concern for civilian populations has been on chemical weapons and a response which is, at most, a modest extension of existing hazmat capabilities. A chemical release or a major explosion is far more manageable than the biological challenges posed by smallpox or

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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, I believe that we, as a medical community, bear a responsibility to educate the public and policy makers. There is a need to build on the 1972 Biological and Toxin Weapons Convention to strengthen measures prohibiting the development and production of biological weapons and to assure compliance with agreements which are made. In a broader sense, there is the need to build a strong moral consensus utterly condemning biological weapons and to give preventive measure needed sustainability and priority.

But this is not enough. We need to be as prepared to detect and diagnose, to characterize epidemiologically and to respond appropriately to biological weapons use as we are to respond to the threat of new and emerging infections. In fact, the needs are convergent. We need at international, state 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 clinician-researchers broadly versed in diseases of both temperate and tropical areas.

Surely, if we can and are willing to spend tens of billions to deal with the threat of nuclear weapons, as is now the case, we should be more than prepared to devote hundreds of millions to cope with the greater threat of new and emergent infections, whether naturally occurring or induced by man.