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I appreciate your invitation for me to speak with you on a subject which, I regret to say, the subject of bioterrorism,
is as yet little known to or discussed by more than a handful of our colleagues in the Public Health Service. My
intent today is to portray for you the realities and dimensions of that threat, and to indicate to you why
it is now critical that the Public Health Service begin to assume a proactive leadership role on behalf of the nation's public
health and medical communities. In brief, one might characterize what I have to say as a call to arms.

For me, the present threat of bioterrorism carries echoes from the past. 43 years ago, I
joined the PHS and new Alex Langmuir's EIS - created That was two wars ago - during the Korean conflict. Since WW II Alex had been
a leading scientist among a group concerned about the threat of biological weapons. That threat had
become made very real when the extensive experimental use of Japan's infamous Unit 731 with bio weapons was discovered and it was learned of
Japan's use of biological weapons in China. during the beginning of the Korean conflict. There was fear that North Korea or China might embark on a bioterrorist campaign in
this country and so, in 1951, the EIS was created - a cadre of epidemiologists, primarily assigned to
states and medical centers across the country - to be on 24 hour emergency call to investigate
epidemics so as to detect at the earliest possible time the possible use of a bioweapon. All EIS officers were
trained with regard to likely organisms to be used

From this point CDC rapidly assumed national stature as a force and an advocate for infectious disease surveillance and control and generically the rest, so they say, is history. There is thus extraordinary historical precedent for PHS leadership

Once public health and medicine were very much part of the biodefense structure. At present we are virtually out of the loop. Let me illustrate. Last September and again in February I presented at national meeting elements of what I will review today regarding the threat of bioterrorism. There followed from this a flood of invitations for conferences on bioterrorism — most were comprised of police, fire, FBI, intelligence officers, DOD and DOE staff and occasionally someone from emergency medicine. Rarely included was anyone from public health or pediatric or adult infectious disease services or from hospital management.

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. Until recently, I personally had doubts about publicly discussing 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.

Over past years, there were four points of view which variously prevailed in national policy circles and in the academic community which served to discourage biological terrorism being considered 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.

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

Each of these arguments is without 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 large biological weapons program. Iraq confirmed that it had produced, filled and deployed bombs, rockets and aircraft spray tanks containing Bacillus anthracis and botulinum toxin (1,2). Its work force and technological infrastructure are still wholly intact. The Japanese cult, Aum Shinrikyo, released the nerve gas Sarin in the Tokyo subway. Included in its arsenal were large quantities of nutrient media, botulinum toxin, cultures of anthrax 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. The cult is still intact and thousands of followers are said to be present in Russia.

Special concerns have arisen in recent years regarding Russia's bioweapons capability. Through defectors, we have learned that this was an enterprise far more extensive and far more sophisticated than any had imagined at the end of the cold war. It is almost certain that large components are still active. Special concerns have emerged over recent months regarding the status of one of the largest and most sophisticated of the facilities, called Vektor, 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 situated on an open plain 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 and the hemorrhagic fever viruses. Visits last autumn disclosed a half-empty facility and a diminished number of guards who have not been paid for months. No one can say where the scientists have gone (4) nor is there confidence now that this is the only storage site for smallpox virus outside of the CDC.

The number of countries engaged in biological weapons experimentation has grown from four in the 1960s to eleven in the 1990s (5). Meanwhile, the bombing of the World Trade Center and the Oklahoma City Federal Building has 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 (6). Four important observations deserve special note. 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". Sam Nunn asserted that it was not a question of "if" but "when".

Second is the fact that civilian preparation has scarcely begun; even the subject of bioterrorism has been little discussed publicly. Virtually no funds have yet been made available to strengthen the public health and medical infrastructure. 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 (7) and at little cost.

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. Those who are specialists in infectious diseases thus constitute the front line of defense whether or not they desire to do so. The rapidity with which they and those manning the emergency rooms 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 today few indeed who have ever seen so much as a single case of smallpox or plague or anthrax or, for that matter, would recall from the recesses of memory the characteristics of such cases. Few, if any, diagnostic laboratories would presently be prepared to confirm promptly such a diagnosis.

Most persons reviewing 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 being able to inflict sufficiently severe disease so as to paralyze a city, perhaps even a nation. In 1994, 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 (8). Smallpox headed the list followed closely by anthrax and plague. Recently, a Russian defector reported that Russia had 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 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.

Before doing so, let me recall for you the disease, 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. **(slide 1,2,3,4)** Then a rash begins with small papules developing into pustules about day 7-8 and finally changing to scabs about day 12. About 30% of all unvaccinated patients died of the disease. There was, and is, no specific treatment.

The potential for smallpox as an aerosolized agent was vividly demonstrated 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. **(slide 5)** 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 much as one would expect were smallpox to be used as a terrorist weapon. **(slide 6)** Subsequently, 19 cases occurred in the hospital, including **(slide 7)** 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 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. Three of the patients were nurses, one of whom died. And this was in a well-vaccinated population. One needs no better illustration than this to understand that smallpox virus in an aerosol

has a considerable capacity to spread over a considerable distance and to infect at low dosages.

The experience of Yugoslavia in February 1972 is also instructive in comprehending the havoc created even by a small outbreak. 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 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. 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. **(slide 8)** This form of smallpox 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 in shock. He died without a definitive diagnosis being made. He was buried two days before the first case of smallpox was recognized.

(slide 9) 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 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 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. 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.

What might happen if smallpox were to be released today in a U.S. city? First, it is important to recall that routine vaccination stopped in the U.S. in 1972, 25 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 25 years. Based on what

we know, it is unlikely that more than 25% or so would have any residual protection. Suppose that some modest volume of virus were to be released, perhaps by exploding a light bulb containing virus in a Washington subway. The event would 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 and by individuals who almost certainly had never before seen a smallpox case, it is probable that several days would elapse before the diagnosis of smallpox would 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 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 negative pressure 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.

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. What measures should or would be taken to deal with them. Would they be isolated as in Yugoslavia and if so, where?

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 rapidly disappear 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, at least 30 to 36 months would elapse before significant stocks became available.

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 dried 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 (13) What was clear is that inhalation anthrax is highly lethal. Just how lethal became evident in the 1979 Sverdlovsk epidemic (14).

(slide 10) In all, 77 cases were identified with certainty of whom 66 died. It is suspected that the actual total was considerably 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 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.

(slide 11) 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. 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.

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". Note that Iraq acknowledged producing at least 8000 Liters of solution with an anthrax spore and cell count of 10^9/ml. Recall also that Russia has a reported 30 tons of dried anthrax spores.

The ramifications of even a modest-sized release of anthrax spores in a city are profound. Bear in mind that the small particle aerosol penetrates interior spaces such that the risk is roughly equivalent whether an individual is inside or outside. Emergency rooms would begin seeing a few patients with high fever and some difficulty breathing perhaps 3 to 4 days following exposure. By the time they were seen, it would be too late for antibiotic therapy. Essentially all would be dead within 24 to 48 hours. No emergency room physicians or infectious disease specialists have ever seen a case of inhalation anthrax; medical laboratories have had virtually no experience in its diagnosis. Thus, it is probable that a delay of at least 3 to 5 days would elapse before a definitive diagnosis.

Once the diagnosis was made, one would be faced with the prospect of what to do over the succeeding 6 to 8 weeks. Should vaccine be administered to those who might have been exposed? Unfortunately, there is at present, little vaccine available

and no plan at present 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 week period? Should one be concerned about additional infections occurring as a result of anthrax spores being subsequently resuspended and inhaled by others? Finally, when does one permit any in the population to return 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.

We are today ill-prepared to deal with a terrorist attack which employs biological weapons. To date, the focus of concern with respect to countering civilian terrorism has been almost wholly on chemical and explosive weapons and a response which is, at most, a modest extension of existing protocols to deal with a hazardous materials incident. A chemical release or a major explosion is far 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, I believe that we, as a medical community, bear a responsibility to educate 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 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.

But this is not enough. 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 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 trained epidemiologists, clinicians and researchers.

On the immediate horizon, as well you know, we face heightened risks associated with the crises in the Middle East. We cannot delay in the development and implementation of strategic plans for coping with civilian bioterrorism. The needed stocking of vaccines and drugs as well as the training and mobilization of health workers, both public and private, at state, city and local levels will require time. Knowing well what little has been done to date, I can only say that a mammoth task

A flavor

What is being done? The National Guard has been given $300 million for the training and deployment of 50+ 22 man (1100 persons) Special Chem-Bio Units. (Standby) What role they might play in epidemic control is far from clear. The Navy & Marine Corps has established a 350 man Chem/Bio Incident Response Force at Camp LaJeune NC, and the DOD is developing a 500 man Chem/Bio Quick Response Force in Aberdeen MD. The FBI has added 150 new agents.

But the essential personnel who will be dealing with such as anthrax, plague or smallpox are our understaffed state and local health departments and emergency and infectious disease staff at medical centers with back-up support primarily from CDC. No funds whatsoever have been made available for strengthening this infrastructure. No funds have been made available for desperately needed research. In fact, as state and local health officials testified last week at a Senate Appropriations Committee hearing, they feel totally unprepared, the more so because, in fact, no one has even met as yet with them to discuss plans and needs.

The GAO, in a December 1997 report, documented that approximately $7 billion per year is being spent for counter terrorism (nb. biological most dangerous) of which HHS spends $17 million.

We face a grave threat.

If ever there was an opportunity for the Public Health Service to step forward and to demonstrate national and advocacy leadership in behalf of the nation's public health, the time is it.

If the nation is prepared to spend $ 300 million for stand by National Guard Units, surely it should be more than prepared to spend $1 billion in support of the infrastructure which is expected to bear the burden of response to bioterrorism and to other new and emergent infections from whatever source.

From our vantage point at Johns Hopkins, we see the situation as extremely serious and urgent and so the decision to formally establish a Center for Civilian Biodefense Studies, a Center which will endeavor to galvanize the medical and public health community. We look forward to working closely with the Public Health Service in meeting the challenges of bioterrorism.