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THE LOOMING THREAT OF BIOTERRORISM

P.D. Agarwal Memorial Lecture
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D.A. Henderson, M.D., M.P.H.
Distinguished Service Professor, The Johns Hopkins University

I am deeply grateful for the invitation to visit India this year and the honor to be asked to present the 2001 P.D. Agarwal Memorial Lecture. Fully 20 years have elapsed since I first became acquainted with Dr. Ashok Agarwal. This occurred during his year in graduate studies at Johns Hopkins. Soon after his return to India, the Institute for Health Management Research began to take form and today has emerged as one of the premier health management institutes in India and one now recognized internationally. This is remarkable progress in a very short time. During annual visits, I had the privilege of meeting his mother, his brothers and other members of this distinguished family whose dedication to India has been so amply expressed in their generous philanthropy. Regrettably, I did not have the opportunity to meet PD Ji but he must have been a remarkable person to have sired such a visionary family.

Once before, 16 years ago, I had the privilege of giving the P.D. Agarwal Memorial Lecture. I was Dean at Johns Hopkins University then and the topic of biological terrorism was one that never crossed my mind as a problem about which we should be concerned. As I was later to learn during my years as Science Advisor to President George Bush and later as Senior Science Advisor to the Secretary of Health and Human Services, it was likewise not a subject of serious concern within our own federal government -- that is, until 1995. And soon, thereafter, it became apparent to us that smallpox was the microbe that posed, by far, the greatest threat of all. This, to me, was a bitter blow indeed, having myself spent 11 years directing the WHO Global Eradication Program and knowing how much time and effort so many dedicated people from around the world had invested in conquering that disease. As many of you know, I came to know many parts of India very well during that period and the courageous leadership provided by Indian government health staff in the difficult program they so successfully executed. Probably the most memorable day of all for me was Indian

Independence Day, 1975, when Prime Minister Indira Ghandi proclaimed the fact that India had won freedom from smallpox for the first time in more than 3000 years. But this is getting ahead of the story.

Until the last few years, the subject of biological terrorism had 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, it is now clear that likely perpetrators already envisage every agenda one could possibly imagine.

Four points of view variously prevailed in national policy circles and in the academic community that served to discourage biological terrorism being considered as more than a theoretical possibility:(SLIDE)

- 1) That biological weapons have so seldom been employed that precedent would suggest they would never be used.
- 2) That their use is so morally repugnant that no one would ever deign to use them.
- 3) That it is technologically so difficult to produce organisms in quantity and to disperse them effectively 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 so unthinkable that it has to be dismissed.

The first three arguments, we know, are clearly without validity and we ignore at our peril the dangers posed by such weapons.

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 use them as agents in acts of terrorism or war. (SLIDE) Iraq was discovered after the Gulf War to have had a startlingly large biological weapons program. Only in 1995, when Saddam Hussein's son-in-law defected, bearing with him secret national program documents, was it known just how extensive and sophisticated the program had been. Iraq only then publicly admitted that it had produced, filled and deployed bombs, rockets and drone aircraft with spray tanks containing Bacillus anthracis and botulinum toxin (1,2). (SLIDE) The importance of this revelation was pointed out by Rolf Ekeus who directed the UNSCOM mission. To be noted is the fact that Iraq's work force and technological infrastructure are still wholly intact.

Also in 1995, the Japanese religious cult, Aum Shinrikyo, released the nerve gas, sarin, in the Tokyo subway, killing 12 persons and causing thousands to become ill (3). Only, some time later was it discovered that the group had been working with biological agents, including anthrax and botulinum toxin. It was also discovered that members of this group had also traveled to the Congo in 1992 to obtain samples of Ebola virus. They made 8 different attempts to disseminate aerosols of anthrax and botulinum toxin throughout central Tokyo with the objective of causing hundreds of thousands of deaths. Their failure to do so could be attributed to the fact that they had mistakenly used a weakened strain of anthrax that is customarily used to vaccinate animals rather than one of the more typical, naturally occurring virulent strains. Only when these efforts had failed did they resort to the use of Sarin gas. That cult, by the way, is still legal; it is still intact with thousands of followers in Japan and significant numbers in countries of the former Soviet Union.

Unquestionably, the most disturbing revelation was the discovery that since the early 1970s, the Soviet Union had been engaged in an intensive research and development program to produce biological weapons (4). This information was brought to notice when, In 1993, the Deputy Director of that program defected. In 1973 -- 20 years before -- a Biological and Toxin Weapons Convention had been agreed in which nearly all countries, including Iraq and the Soviet Union, agreed to cease bioweapons research programs and to destroy such stocks of these weapons as they then possessed. In the context of the Cold War, the Soviet Union saw the implementation of the Convention as an opportunity for it to gain an advantage over its adversaries. It then greatly expanded its existing program to the point that it eventually consisted of some 60,000 persons working in some 50 different laboratories. The decision in 1980 by the World Health Assembly that smallpox eradication had been achieved and that vaccination could be stopped everywhere spurred a special effort by the Soviet Union to weaponize smallpox virus as a strategic weapon. That effort is reported to have been successful and a manufacturing plant was built that is capable of producing between 80 and 100 tons of smallpox virus a year. That facility, by the way, is still intact; entry is forbidden to all visitors. The principal bioweapons research center for viruses and one of the largest and most sophisticated of the facilities is called Vektor. It is located in Koltsovo, Novosibirsk. Through the early 90s, this was a 4000 person, 30 building facility with ample high biological containment facilities, both for laboratory work and for isolation of human cases. Here is where research on the large scale production of smallpox virus was carried out and here is where, officially, the Russian stock of smallpox virus is kept today. At this facility, other viruses -- the fearsome Ebola,

Marburg and other hemorrhagic fever viruses are being studied. However, because of economic problems, salaries have been cut and are erratically paid and as many as half of the scientific personnel have left the lab. No one can say where the scientists have gone but several countries, known to be interested in developing biological weapons, have been actively recruiting in Russia even as we speak. Has the smallpox virus migrated to other countries along with expertise for producing it as a weapon? We don't know.

We do know, however, that 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, the Oklahoma City Federal Building and the American embassies in Kenya and Tanzania have recently dramatized the serious problems which even small groups can cause and their intent to inflict large numbers of casualties.

In 1999, an entire issue 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. (SLIDE)

- First is the fact that biological terrorism is more likely than ever before and far more greatly to be feared than either explosives or chemicals. (SLIDE) At a congressional hearing, now Secretary of State Colin Powell said "Of all the weapons of mass destruction, biological weapons worry me most".
- (SLIDE) Second is the fact that civilian preparation to cope with the problem has scarcely begun and even the subject of bioterrorism has been little discussed publicly.
- 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 extremely difficult. Thus, the first evidence of intent to use such weapons will almost certainly be the appearance of cases in doctors' offices and hospital emergency rooms. Those who are specialists in infectious diseases will also be part of the front line of defense whether or not they so desire. 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 hundreds and perhaps tens of thousands of casualties. Indeed, the survival of the physicians and health care staff who are caring for the patients may be at stake. However, there are today few 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 are presently prepared to confirm promptly such a diagnosis.

Most persons reviewing this subject detail a long list of possible pathogens that might possibly be used as a weapon and, in fact, almost any infectious agent could be considered a candidate. In fact, however, only a handful share the characteristics of being reasonably easy to prepare and to disperse and being able to both generate panic and to inflict sufficient number of casualties so as to paralyze a city, perhaps even a nation. In 1994, Vorobyev, a Russian bioweapons expert presented to a working group of the United States National Academy of Science, the conclusions of Russian experts as to the agents most likely to be used (8). (SLIDE) Smallpox headed the list followed closely by anthrax and plague. This analysis was reflected in priorities given to production. A Russian defector reported that, at least into the 1990s, Russia had stockpiled 30 metric tons of dried anthrax spores and 20 tons each of smallpox, plague and tularemia -- all of which had been weaponized (4). In a study undertaken by a Working Group meeting at Hopkins but including expertise from throughout government and the country, 5 agents and a diagnostic group were identified as being those of greatest concern, the release of which could result in a catastrophe. 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 should they be used. However, for smallpox, we have had several well-documented importations into Europe over recent decades; two bear recounting as portents of what we might experience today were a biological attack to be conducted.

Before doing so, let me recall for you the disease, smallpox. Many of you, I know, have seen cases of the disease at sometime in your lives but it is now almost 25 years since there was a case in India. It is helpful to renew memories for this was the most feared of all the contagious diseases of recent centuries. (SLIDES--CLINICAL SERIES) The disease 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, sub-clinical 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 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. No other disease has killed more individuals than has smallpox.

How concerned were the countries of the world about smallpox? Until 1980, essentially all endemic areas conducted vaccination programs of some sort whether or not they had endemic disease (9). To do otherwise was unacceptable both politically and from a public health standpoint. Until 1972, the United States mandated smallpox vaccination for all children at school entry despite the fact that the country's last smallpox 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 isolation hospitals were constructed in the 1960s specifically for the isolation of smallpox cases should they occur.

The potential for smallpox as an aerosolized agent was vividly demonstrated in an outbreak in Germany in 1970 (10). 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) 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. After the diagnosis of smallpox was made, hospital patients and staff were quarantined and remained so for four weeks. Patients and staff were vaccinated. However, the patient had had a cough, an unusual symptom except with the most severe forms of the disease. Coughing produces a large volume, small particle aerosol much as one would expect were smallpox to be used as a terrorist weapon. (SLIDE) Subsequently, 19 cases occurred in the hospital, (SLIDE) 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 opened a corridor door, easily 30 feet from the patient's room, to ask directions and left immediately when he was told he was in the wrong building. 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 form has an enormous 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 in an area long free of smallpox(9). 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 religious 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 the others were ill and physicians who saw the patients failed to make a correct diagnosis. Few had ever seen a case of smallpox.

(SLIDE) 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. 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) 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 others 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. It was, in fact, a small outbreak.

We have considered what might happen if smallpox were to be released today in a U.S. city. The experience were it to occur in India would differ somewhat but, in broad outline, the consequences would not be so different. First, it is important to recall that in the U.S. routine vaccination stopped in 1972, nearly 30 years ago; in India, 20 years ago. Thus, there are large numbers who have never been vaccinated and, for all others, vaccine immunity has steadily waned. We would guess that 80% or more of our population would be fully susceptible. Suppose that some modest volume of virus were to be released in a small lecture hall with perhaps 60 to 80 persons in attendance. 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 50 persons had been infected and would require hospitalization. As soon as smallpox was suspected, this number would soon be submerged among a larger group of patients, perhaps as many as 100 persons, all with illnesses with fever and rash but whose diagnosis was uncertain. Some would be reported from other cities. Where would all of these patients be housed so as to prevent further transmission of disease? There are fewer than 100 hospital beds in the entire Baltimore-Washington area which can provide the needed negative pressure isolation to prevent further spread. 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 who 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 one thousand or more. 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 in our country.

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. 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.

But this would be only the beginning of the problem. Based on the experience when smallpox was introduced into European countries in the 1950-70 period, we might expect each of the 50 cases to produce, on average, at least 20 new cases, all of whom would have been exposed before control measures could even begin. Thus, the second wave of cases would be at least 1000 persons and, what with the mobility of people today, one would expect such cases to be widely dispersed across the country with some cases in other countries. Meanwhile, we would expect to have exhausted our supply of vaccine within 4 to 5 weeks and, today, there are no vaccine production facilities anywhere. And, bear in mind, there is no therapy for the disease

It is apparent that even a modest-sized outbreak offers an alarming 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 goat hides (12) What was clear was that inhalation anthrax was highly lethal. Just how lethal became evident during an epidemic that occurred in April 1979 in the city of Sverdlovsk, Russia (13).

In all, 77 cases were identified with certainty of whom 66 died. It is suspected that, in fact, there were upwards of 300 cases with at least 100 deaths. (SLIDE) 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 early one morning 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) 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.

The group that 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 anthrax spore solution. Note also that Russia had in storage a reported 30 tons of dried anthrax spores (4).

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 5 to 7 days would elapse before a definitive diagnosis could be made.

Once the diagnosis was made, one would be faced with the prospect of what to do over the succeeding 6 to 8 weeks. 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 an 8 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 totally impossible in many settings.

The specter of biological weapons use is an ugly one, every bit as grim and foreboding as the picture which has been painted of the results of a nuclear explosion. As was done in response to the nuclear threat, I believe that the medical and public health communities 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 have already been made. In a broader sense, there is the need to build a strong moral consensus utterly condemning biological weapons. An important step in that process

would be for the World Health Assembly to reaffirm its demand that all countries destroy their existing stocks of smallpox virus by the end of the year 2002 and to agree that any country, any laboratory, any scientist in possession of the virus after that date would be guilty of a serious crime against humanity. I would note parenthetically that it was the Government of India that led the initiative by the 1999 Assembly to demand destruction of the virus by the end of 2002. I salute India for its stand and would hope it might continue its efforts.

But this is not enough. In the near term, we need to be as prepared to detect and diagnose and to respond appropriately not only to epidemics caused by biological weapons but the increasing challenges posed by new and emerging infections. (SLIDE) And, we are now seeing many more such infections than we did in earlier years -- HIV/AIDS, mad cow disease, a new influenza strain in Hong Kong that killed 6 of the 18 people infected. There are many more. Organisms are constantly mutating and every so often, we can expect that variants that are lethal to man will occur. AIDS is serious enough but others, far more serious, can be imagined. This itself calls for the strengthening of our public health structure, for alerting and educating those concerned with infectious diseases, for developing our laboratory diagnostic capabilities. The needs are the same whether the outbreak is naturally occurring or man-made. If we fail to respond, we can experience serious consequences. In the US, there were a number of instances two years ago in which envelopes were sent to different offices with the indication that they contained anthrax. Our health departments didn't know what steps to take; CDC was asleep at the switch. The proper approach was to place the envelope in a plastic bag, call police authorities to take it to a laboratory and wash one's hands. Instead, whole buildings were evacuated, individuals were asked to strip to their underwear so that they could be decontaminated by hosing them down and often, they were given antibiotics. The result -- all sorts of press coverage and many, many more hoaxes, many of them still improperly handled. In India, you, too, have had outbreaks recently, such as in Surat, in which panic took over when the public health and medical response was inadequate.

Thus, at all levels, international, state and local, there is an urgent need for a far greater capacity for surveillance; for a far better network of laboratories and better diagnostic instruments; and a far larger cadre of trained epidemiologists, clinicians and researchers. The problems are not uniquely American -- or Indian -- or British. In this ever more populated world with ever more extensive travel an outbreak of disease anywhere is potentially a problem for everyone everywhere. There is thus a compelling need to enhance international cooperation in coping with the challenges of the

infectious diseases. Dr. Josh Lederberg, Nobel Laureate said it best, and I paraphrase, "Man's only real competitor for dominion of this planet are the viruses -- and the ultimate outcome, the ultimate victor, is not foreordained. "