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The Ominous Shadow of Infectious Agents

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Generals, as they say, prepare to fight the last war, a war in which enemies and technology are best known and understood--not a hypothetical war employing novel weapons wielded by poorly understood adversaries. Analogously, such may be said to apply to nuclear and chemical weapons as contrasted to biological agents. Nuclear and chemical weapons are now comparatively familiar--well understood in terms of their potential destructiveness, of methods for their production and delivery as well as plausible defensive counter measures which might be taken. Much has been gleaned from practical experience as well as from the substantial investments which have been made in experimental studies.

In contrast, we have had little to no practical experience with the potential destructiveness of biological agents either on the battlefield or as terrorist weapons. Relevant research budgets for biological defense have been small and steadily diminishing. ~~This problem is~~ a handicap compounded by the fact that research support pertinent to infectious diseases of all types has, until recently, eroded steadily as antibiotics, vaccines, better food and improved housing sharply reduced or eliminated many microbial diseases in the industrialized world. This lack of support hardly seems justified given the fact that ~~the~~ infectious diseases even today remain the most important problems for most ~~the world's~~ peoples, and given the fact that biological weapons have been publicly labeled as being potentially the poor man's atomic weapon.

I believe that the apathy of concern regarding biological agents reflects, in part, the fact that most policy makers have themselves no personal knowledge of the destructiveness and chaos implicit in the occurrence of epidemic infectious disease. The intelligent weighing of priorities is made even more difficult by the fact that so many identified experts in biological weapons systems are, in fact, chemists, who have some knowledge of biological toxins but little or no direct experience with human disease. Thus, over the years, microbial agents, as a threat, have been increasingly relegated to a minor status, undoubtedly taken more seriously than the threat posed

by alien spaceships but not much. In my own country, I have watched with dismay as budgets have eroded, as misguided threat definitions have closed down some of our most informative research and as many of our best scientists have departed for more productive fields. The status of progress which relates to biological weapons limitation and verification measures you know well.

You should know, however, that over the past five years or so, the biological community's complacency about microbial infections has undergone a profound transformation. The AIDS pandemic shattered an unwarranted confidence that modern science and public health could satisfactorily cope with whatever microbial challenges arose, at least in temperate climate countries. Clearly, we are not coping well with AIDS. Twelve years after characterizing the human immunodeficiency virus and with research budgets exceeding one thousand million dollars annually, there is still no vaccine in large-scale human trials and such drugs as seem to be proving effective, at least in the short term, are beyond reach of more than 98% of all victims of the disease. Meanwhile, the disease spreads inexorably across the world.

Other hitherto unknown diseases have emerged--including such as the so-called mad cow disease, Ebola and Hanta fever epidemics; dengue and cholera have spread globally. The question has been raised as to whether we might expect other new or hitherto unknown agents with a lethality comparable to AIDS but which are more infectious, perhaps with the capability of spreading rapidly and widely worldwide, like pandemic influenza. Given what we know about microbes and microbial genetics, the answer is "yes". The last few years have been marked by sobering introspection. Our views and policies with respect to biological weapons warrant similar serious reflection.

For candidate agents of biological terrorism, we don't need to conjure up visions of the exotic to be concerned. The intrinsic potential destructiveness of known microbial agents is far more substantial than is commonly recognized. It has been estimated that during this century, between 100 and 150 million persons will have died, either directly or indirectly, as a result of armed conflict. An impressive number but far fewer than died from smallpox alone prior to its extinction in 1980, and despite the fact that throughout this century, a large proportion of the population was protected by vaccine.

For most of you in this room the implications, the fear, the panic induced by life-threatening epidemic disease is unknown or at best, a distant memory. However, for those of us who have been deeply involved with such events, the memories remain all too vivid and all too persuasive of the need for us to deal seriously and urgently with possible BW agents.

The villain for my reflection tonight is the smallpox virus which has not been found in nature since 1978. However, it is at the very top of some lists as the organism of choice for terrorism. The death rate for smallpox is in the range of 20 to 25% among the unprotected--and most persons today are unprotected because vaccination stopped world-wide 16 years ago. This is a death rate far higher than for any other epidemic disease with the exception perhaps of Ebola virus disease.

The time is February 1972, the setting Yugoslavia, a country whose last case of smallpox had occurred 45 years before (in 1927). Nevertheless, like most countries throughout the world, population-wide vaccination had continued in order to deter smallpox should it be imported. 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. Most were unaware that the others were sick and physicians who saw the patients failed to make a diagnosis. Few had ever seen a case of smallpox.

What do smallpox patients look like? Some 10 to 12 days after a person is infected via the respiratory tract, he develops a high fever, aching pains like severe influenza and two to three days late, small vesicles begin to erupt over the face **(S)**; after a further four to five days, they progress to pustules **(S)**; and later, if the patient survives, scabs form which later fall off (S), leaving deeply pitted disfiguring scars. (There is no treatment whatsoever for the disease.) A more typical severe case **(S)** which occurred in a European man shows densely packed pustules and facial swelling which eventually resolved with extensive facial scarring **(S)**. A number of patients were permanently blinded (S) and, in about 10% of the cases, even more severe forms of the disease occurred which you would not wish me to depict. Some patients had such extensive lesions that the entire skin surface separated as the patient lay dying, while others bled extensively into the skin, the lungs, the intestinal tract and died within three to five days. It is a disease guaranteed to cause alarm.

One of the 11 patients in Yugoslavia who acquired smallpox from the pilgrim was a 30-year-old teacher who quickly became critically ill with the hemorrhagic form, a form not readily diagnosed even by experts. He 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 capital city and finally, to a surgical clinic because he was bleeding severely and going into shock. He died without a definitive diagnosis. He was buried two days before the first cast of smallpox was diagnosed in Yugoslavia.

The first cases were correctly diagnosed just 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 and these cases occurred in widely separated areas in different parts of the country.

It was impossible for government authorities to gauge the potential magnitude of the epidemic but it was clear that the infection was widespread. Accordingly, the government immediately launched a nation-wide vaccination campaign; check points along roads were established **(S)** where vaccination certificates were examined. 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(S). 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 finally stopped--175 patients had developed smallpox and 35 had died.

That there weren't many more cases than this reflects the fact that most Yugoslavs were already partially protected by an ongoing vaccination program. Moreover, smallpox is usually spread by droplet infection from the mouth and nose. Such droplets don't normally travel great distances and so most patients tend to infect not more than two to five others.

In contrast, a fine aerosol containing smallpox virus has a remarkable potential for spread as we were to learn in a 1969 outbreak in Meschede, Germany. That year, a German electrician returning from Pakistan became desperately ill with high fever and cough **(S)**. He was admitted to the local hospital and isolated in a separate single room because of concern that he might have a

communicable infection. Three days later a rash developed, the diagnosis of smallpox was quickly made, the patient was immediately transported to a special smallpox hospital and more than 100 000 persons were vaccinated. Coughing invariably produces a large volume, small particle aerosol. Fortunately, cough seldom accompanied a smallpox infection. This case proved to be the exception **(S)**. Seventeen subsequent cases occurred including four in other rooms on the patient's floor of the hospital; seven on the floor above; and eight 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 a question. In all there were 20 cases of whom four died. And this, too, was in a well-vaccinated population.

Need we today fear the possible release of smallpox amongst a civilian population? We would like to believe that the smallpox virus is confined to just two laboratories--one in Russia and one in the United States. Certainly the World Health Organization made heroic efforts to try to assure that all other stocks were destroyed and it is possible that WHO obtained full compliance. As a practical matter, however, there is no certain way to verify that no other laboratory holds the virus because strains of virus can be readily retained for decades in small vials in an ordinary deep-freeze. Over recent years, many governments and scientists have argued the desirability of at least destroying the two known virus stocks. It is an initiative, however, that has so far been blocked by a few governments, at least until 1999.

It is fact that smallpox is easily grown in the laboratory in embryonated eggs; it is a hardy virus, not readily destroyed; and it can be readily aerosolized and remain suspended and fully viable for hours. A release in any of a thousand different settings in any city would generate hundreds to thousands of cases; diagnosis would have to wait at least two weeks until those who were exposed developed illness and, by the time of diagnosis, each would have exposed many others. Recall that in the Yugoslavian epidemic, despite the prevalence of substantial population-wide vaccine protection, 11 patients successfully transmitted infection to 139 others in a number of different cities. Not knowing where infection might occur next brought ordinary commerce virtually to a standstill.

Should we today be routinely vaccinating our civilian populations? Both cost and the frequency of adverse reaction following smallpox vaccination argue against such a policy. A

more serious concern is the fact that the only remaining stocks of smallpox vaccine are limited in quantity and there is today no laboratory capable of producing more should it be needed.

How likely is it that smallpox might be employed as a terrorist weapon? Who knows? In terms of difficulty of production and use, both nuclear and chemical weapons are infinitely more complex but, in terms of cost and weight, far less destructive. But such can also be said about other microbial agents such as anthrax and brucella and Q fever, each of which bears with it, its own scenario of death and destruction.

For myself, I continue to be astonished that there has been so little concern focussed on smallpox and other biological agents. I would hope we would not have to await an actual event to occur before beginning to take this threat seriously.

Reference: Fenner F, Henderson DA, Arita I, Jezek Z, Ladnyi ID (1988). Smallpox and Its Eradication, Geneva, World Health Organization.