PRESIDENT'S ADDRESS: THINKING ABOUT THE UNTHINKABLE

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As an infectious diseases practioner for several decades, I have seen some astounding and frightening new events. They are listed below, and include:

1. New diseases such as HIV infection and AIDS.
2. The development and spread of antibiotic-resistant bacteria such as methicillin-resistant *Staphylococcus aureus* and multi-drug-resistant *Escherichia coli.*
3. The development and spread of oseltamavir (tamiflu)-resistant influenza.
4. Microbes causing conditions that no one had previously thought were infectious, such as *Helicobacter pylori* causing peptic ulcers.
5. Viruses as the cause of cancers, such as human papillomavirus and cervical cancer.
6. The event I consider most frightening of all: the threat of bioterrorism (1–3).

Our potential enemy is challenging. Through the years of the Second World War, Korea, and Vietnam, and now in the Middle East, biowarfare was possible. The Soviet Union had the ability to make and deliver massive amounts of bioweapons. It has been estimated that it had the ability to produce 20 tons of smallpox per year to use in long-range missiles. Our potential enemies, (all relatively rational countries), knew, (whether stated or implied by us), that we would respond with nuclear weapons to a major biologic attack, and in my opinion this mutually assured destruction, as with nuclear devices, probably kept these biologic weapons from being used on a large scale (4).

On April 6, 2010, the *New York Times* reported that President Obama stated that he would not authorize a nuclear response if a nation attacked us with biologic weapons.

Is this wise? I assume that we would use nuclear weapons to respond to a nuclear attack, and many experts predict that the fatalities from

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a massive biologic attack could surpass the number from a nuclear attack.

However, on April 12, 2010, US Secretary of State Hillary Clinton stated on the CBS program "Face the Nation" that if we knew that a biological attack was originated by a government, all bets would be off concerning nuclear retaliation. This makes a lot more sense to me. Of course, if it were bioterrorism from a terrorist group, and not true biowarfare from a nation, the target for our response would be vague. Most likely, we would not have an appropriate target for nuclear retaliation.

Now we are faced with a truly diabolical threat by evil elements of Islam. These people want to kill all who don't follow their fanatical religiosity. They have no qualms about killing children, women, and other non-combatants. They are not afraid to die. Many of them actually wish to die, as is evidenced by suicide bombers and pilots of planes used as missiles.

Bioterrorism weapons are ideal for these terrorists. They are cheap and relatively easy to produce (certainly as compared with nuclear devices). Biologic weapons are easy to hide and relatively easy to deliver, and they engender panic. Think of the response to a relatively benign infection such as last year's H1N1 influenza pandemic (5).

Bill Gates, who is heavily involved in issues of world disease through his foundation, told *Wall Street Journal* on November 27, 2010 that "Bioterrorism and pandemics are the only threats that I can foresee that can kill over a billion people."

I'm not going to spend much time about specific agents of bioterrorism, but will instead consider plans, dangers, and some general concepts. A detailed discussion of this topic can be found in *Principles and Practice of Infectious Diseases* (6, 7).

There is a long history of attempts to use bioterrorism. Some attacks were clearly successful, and others can't be fully evaluated.

A tome entitled *Medical Aspects of Biological Warfare* (607 pages) published by the office of the Surgeon General, US Department of the Army, discusses scores of such incidents (8, 9).

Contagion of infectious diseases has been recognized for hundreds of years, and many attempts have been made to use this as a warfare strategy (10). Bodies of patients who died from infection were used as weapons. They were deposited on the ground and dumped in water with varying degrees of success. Well-known attempts at warfare through contagion include giving blankets from patients who died of smallpox to American Indians—a group that had never been in contact

with the disease and was especially vulnerable. Their mortality was estimated to be about 70% (11).

In 1864 Dr. Luke Blackman went to Bermuda, which was in the midst of a severe yellow fever epidemic. He knew the horrible characteristics of yellow fever, including generalized bleeding, jaundice, and rapid death. Blackman, who was a compassionate and caring doctor for the citizens of Bermuda and a devout citizen of the Confederate States of America, collected many items of bedding, soiled clothing, and underwear. His plan was to ship them to Canada and then to Union soldiers fighting the Confederacy. He was caught by a Union spy and jailed. The ironic fact is that yellow fever is only spread by infected mosquitoes, and Blackman's plan failed, but how the disease was spread was not known until 37 years later.

Sometimes, enemies spread infection to animals to cripple war efforts. Both anthrax and glanders (caused by *Burkholderia mallei*) were transmitted to horses in the First World War by the Germans. In the war, the Germans put anthrax spores in sugar cubes and dropped them to be eaten by horses and reindeer, which were used as pack animals in Norway. In the Second World War, the Japanese had more than 3,000 scientists working on (what was then called) germ warfare. Ten thousand Chinese prisoners died in germ-warfare experiments. Fleas infected with the plague bacillus were released from planes over population centers in China.

The Soviet Union had 60,000 workers in their biowarfare enterprise, more than were working on nuclear weapons. A leak of anthrax spores from a Russian bioweapons facility caused by faulty air filtration caused scores of deaths. The source of the spore release could be accurately determined by the pattern of deaths and wind-direction data.

To study large-scale effects of contamination with anthrax spores, an island off the coast of Scotland was seeded with spores by Great Britain. After years, it was felt that the spread of disease was likely, and the island was decontaminated with 2,000 tons of seawater and 280 tons of formaldehyde, since the spores of *Bacillus anthracis* are resistant to usual disinfectants and to radiation

In the 1950s and 1960s the US and the Soviet Union developed a large infrastructure for the production of biologic weapons. The US actually stockpiled organisms causative of anthrax, tularemia, brucellosis, Q fever, Venezuelan equine encephalitis, and botulinum toxin and staphylococcal enterotoxin B.

In 1972 the Biological Weapons Convention was held, and a declaration was signed that banned the development, production, stockpil-

ing, or acquisition of biologic weapons and their means of delivery. Although there is no formal verification of the Convention, 162 nations have now signed or ratified this declaration.

No terrorist groups have signed it!

In 1984, in the United States, the Rajinesshee religious cult utilized *Salmonella* as a weapon by putting it in salad bars in the US. This resulted in 751 cases of salmonellosis, including 45 cases of severe disease requiring hospitalization.

A frightening new developmentation is that virulence of microbes can now be increased (12). An example is the adding of genes for myelin to *Legionella pneumophila,* which converted a relatively mild cause of pneumonia into a microbe that is nearly 100% fatal in guinea pigs because of neurologic damage. Another example is adding of the gene for diphtheria toxin to the plague bacillus to create a microbe that is highly toxic to animals.

Some genomes make a person more resistant to falciparum malaria, such as those for hemoglobins S, E, C, thalasemia, sickle cell trait, and glucose-6-phosphate deficiency. Terrorists may be able to exploit those factors and develop new strategies using a reverse concept, by which, certain genotypes could enhance susceptibility to disease. Thus, another diabolical genome possibility is that microbes can be given the ability to infect humans with certain genome patterns targeting specific races and ethnic groups.

Scientists (and evolution and adaptation) have developed pathogens resistant to antimicrobial agents. Also, pathogens can be moved from one part of the world to another, encountering victims who have little or no immunity to them.

Another disturbing possibility was reported in the journal *Science* in July of 2010. A group at the Craig Venter Institute (the report had 25 co-authors) successfully synthesized a genome in one type of bacteria and transplanted it into another species of bacteria. The recipient organism, *Mycoplasma capricolum,* was controlled only by the synthetic genome, which was derived from *Mycoplasma mycoides.* (13, 14).

The US National Science Advisory Board for Biosecurity (15) is concerned with the possibility of construction of harmful genomes that can be introduced into selected microbes and used for biowarfare and bioterrorism. The advisory board wrote, that "research based on current understanding (and) that can be reasonably anticipated to provide knowledge, products, or technologies that could be directly misapplied by others to pose a threat to public health, agriculture, plants, animals, the environment, or materiel should be forbidden."

I will make a few comments about two of the diseases at the top of

everyone's list: anthrax and smallpox. These two diseases have very different epidemiologies, and each has great potential for weaponization.

If there is such a thing as an almost ideal biologic weapon (although it lacks person-to-person spread), it is anthrax, caused by *Bacillus anthracis*. The LD_{50} for anthrax in monkeys (and presumably in humans) is 8,000 spores. There are two forms, of the organism: the vegetative form, which is a long, gram-positive rod that actually causes disease and produces potent toxins, and the spore form. Spores of *B. anthracis* have evolved to be very efficient transmitters of disease. But in order to make the spores more effective as aerosolized warfare pathogens, they have to be coated with silicon, which is difficult to do. Their normal habitat is the soil, from which infection of grazing animals such as cattle and sheep originates. Infected animals die from sepsis, often suddenly. Their corpses contain an enormous number of vegetative forms of the organism that sporulate as their nutrient supply diminishes. It is these spores that are potential of agents bioterrorism. The spores are small, powdery, and smoke-like. They are resistant to almost all disinfectants, to heat and to radiation, and can be aerosolized and cause a highly fatal syndrome of pneumonia, sepsis, and meningitis. The infamous episode in 2001 of letters containing anthrax spores indicates how lethal they can be. At least 5 letters were sent to 2 US senators and to news organizations in New York and Florida. Five people died; 17 were ill, and the attack caused a temporary closure of congressional offices, the US Supreme Court, postal facilities, and private offices. Twenty-thousand people started or completed treatment with prophylactic antibiotics for anthrax. There was fear and even panic all over the world after the attacks. The day after the attacks on September 11, 2001, crop duster airplanes, which are ideal means of transmitting airborne pathogens, were grounded

It was estimated that 100 kg of *B. anthracis* spores released over Washington, DC, would kill 1 million to 3 million people, depending on the wind speed and direction. (As an aside, the Soviet Union was thought to have prepared tons of weaponized anthrax spores.)

The prime suspect in the US anthrax attacks was Dr. Bruce Ivins, US Army biodefense expert with access to *B. anthracis* organisms. He killed himself in 2008. The FBI concluded in a 2010 report that Ivin was the culprit in the 2001 attacks and acted alone. Steven Hatfill, an early suspect, was eventually cleared. He had worked at the Fort Detrick Army Institute in Maryland, and exhibited bizarre behavior. He had forged his Ph.D. degree, wrote a novel (unpublished) (16, 17)

about an attack on Washington, and bragged about his knowledge of biowarfare agents.

Since the 2001 anthrax attacks, institutions and individuals working on potential bioterrorism organisms have to had undergo a thorough security risk assessment (18).

The only good news about anthrax is that antibiotic prophylaxis against it is effective when given immediately after contact with the spores. Ciprofloxacin is usually administered for 30 days. Treatment of the disease is also beneficial in reducing mortality. Some would add clindamycin to ciprofloxacin to reduce the activity of the *B. anthracis* toxins (19, 20).

An effective anthrax vaccine is a combination of toxins plus an adjuvant. The vaccine has to be given several times in the first months after exposure, with yearly boosters. It can cause severe local reactions with edema, tissue necrosis, and pain. At present, immunization with the vaccine is required of certain US military personnel and others who have a reasonable expectation of coming into contact with the spores and/or the toxin of *B. anthracis.* Post-exposure immunization plus the use of antibiotics has efficacy in animals and is now recommended (21, 22).

Smallpox (a disease with a mortality of 30%, and a higher mortality for certain populations, such as native Americans) is probably the only disease that has been completely eradicated from the world (we think and hope). William Jenner noted that milkmaids had smooth complexions. This was because they lacked the facial scars caused by smallpox. Jenner surmised that infection with the much milder cowpox virus resulted in immunity to smallpox. Vaccination with Vacoinia virus was so successful that smallpox was eradicated. Many of us carry the smallpox vaccination scar on our shoulders, and a few remember standing in line for vaccination after a patient with smallpox arrived in NYC from Mexico in 1947. About 4.5-million people received the vaccine at that time.

The last proven case of smallpox was in 1972, and in 1980 the World Health Organization declared the disease eradicated. This was possible because there are no other hosts than humans and there is no carrier state, for smallpox, and when herd immunity (immunity of a large portion of the population) occurs, spread of the disease stops because the only vector is a sick human being. The smallpox virus was one of the great scourges of mankind, with a frightening history of disease and outbreaks (23, 24).

The successful strategy for eliminating smallpox involved “ringing in” sporadic cases through intensive vaccination of the surrounding population.

The only known remaining stores of smallpox virus are kept by the US and Russia. When the virus is freeze-dried (lyophilized), it remains alive for an unknown period (probably many years) and retains its virulence. A great fear is that the virus can fall into the wrong hands.

Routine vaccination against smallpox was discontinued in the 1970s. At present, only government personnel and military and pharmaceutical personnel who are at some risk through working on various bioterrorism projects are vaccinated. When the question of smallpox vaccination of all US armed forces personnel came up, it was decided that the risk of adverse reactions was greater than the even smaller risk of exposure to the virus. Approximately 500,000 high-risk people have been vaccinated.

Defense against bioterrorism is difficult (25). Early detection of disease is essential. Development of chips that can identify large numbers of possible pathogens is proceeding rapidly. A chip has just been devised at the University of Virginia that can identify thousands of organisms almost immediately.

Immunization is a potent defensive tool against bioterrorism. However, there are several major problems with this. Manufacture of vaccine for many organisms may be difficult, and immune responses may be too slow. It also can be anticipated that there will be many adverse reactions, as has occurred in many mass immunization programs.

Another strategy would be to have enough chemotherapy available for the prevention and treatment of bioterrosist infections. Problems with this are stability of stored drug, resistance development and chance of adverse reactions, which represent a risk that may not be tolerated by the public if an attack does not pan out.

Additionally, the attackers may develop or locate organisms that are resistant to chemotherapy. Over 200-million doses of tamiflu (oseltamivir) have been stored around the world in anticipation of an outbreak of influenza, either natural or as a result of bioterrorism. However, a vigorous, resistant strain of the influenza virus has been identified, and there is a possibility that this will be the dominant strain, leaving the world with 200-million ineffective doses of an antiviral drug.

In early 2010, The US Commission on the Prevention of Weapons of Mass Destruction Proliferation and Terrorism presented its report. Senator Bob Graham of Florida was chair and Senator Jim Talent of Missouri was vice chair of the commission (26). They wrote that “The lack of US capability to rapidly recognize, respond, and recover from a biological attack is the most significant failure indentified in this

report card. Deterrence of bioterrorism rests upon the ability of the nation to mitigate the effects of an attack. Unfortunately, there is no national plan to coordinate federal, state, and local efforts following a bioterrorism attack, and the United States lacks the technical and operational capabilities required for an adequate response. These technical and operational capabilities are each links in a chain critical to the strength of the attack response. Weakness in any capability leads to a diminished response, and diminished effectiveness in deterring an attack."

Graham and Talent said that rapid detection and diagnotic capabilities are the first links in the chain of response, followed by providing actionable information to federal, state, and local leaders and the general public; having adequate supplies of appropriate medical countermeasures; quickly distributing those countermeasures; treating and isolating the sick in medical facilities; protecting the well through vaccines and prophylactic medications; and in certain cases, such as that of anthrax, providing environmental cleanup (27).

The United States is seriously lacking in each of these vital capabilities. Especially troubling is the lack of priority given to the development of medical countermeasures—the vaccines and medicines that would be required to mitigate the consequences of a bioterrorrist attack. Congress created the Biomedical Advanced Research and Development Authority Advanced Development Fund to promote the development of new vaccines, drugs, and production processes required to meet the modern threats from man- made and naturally occurring epidemics of infectious disease. The estimated cost of developing the medical countermeasures required to meet the threats identified by the Department of Homeland Security is $3.4 billion a year for the next 5 years. The appropriation for the Fiscal year 2010 is less than one-tenth of that. In addition, there have been several attempts by the Administration and Congress to "raid" the BioShield Strategic Reserve Fund for other programs.

Some significant recommendations for protecting against bioterrorism have included tightening government oversight of high-containment laboratories, conducting a comprehensive review of the domestic program to secure dangerous pathogens, strengthening domestic and global disease surveillance networks, and developing global and national strategies for advancing bioforensic capabilities.

There are currently two tracking systems for infectious diseases: one in animals and one in humans. It has been proposed that these be combined as a One Health Initiative that will use human and animal sentinels to determine shared health risks.

The committee predicted a serious bioterrorism event in the US by 2013 (26). That is an official expert government group predicting a serious bioterrorism event in the US within a relatively short time.

Screening and monitoring of laboratories that have the capability of producing bioterrorism weapons will be a difficult challenge (28). Searching for known or potential terrorists who have the knowledge to make bioweapons must include US and foreign nationals. Suspicion of an attack should occur when there is an unusual pattern or severity of disease in humans or animals (29). Important containment strategies after an attack include the large-scale quarantine of populations that have been exposed to an agent that can spread from person to person and the isolation of ill persons (30).

I wish I could end this talk on a positive note, but I cannot.

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