THE HASKINS LECTURESHP IN SCIENCE POLICY

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BIOTERRORISM: A CLEAR AND PRESENT DANGER

Anthony S. Fauci, M.D., introduced by James A. Thomson
The Haskins Lectureship on Science Policy was established through the generosity of Caryl and Edna Haskins, founders of Haskins Laboratories. Both Dr. Haskins and Mrs. Haskins were dedicated to improving the nation’s understanding of the relationship between scientific progress and sound public policy. Caryl Haskins was a member of RAND’s Board of Trustees for 20 years and served as an advisory trustee and member of the President’s Council.

The 2002 Haskins Lectureship on Science Policy was held on November 15, 2002, at the Bel Air Bay Club, Pacific Palisades, California.

Dr. Anthony S. Fauci received his M.D. from Cornell University Medical College in 1966 and completed an internship and residency at the New York Hospital–Cornell Medical Center. In 1968, he became a clinical associate in the Laboratory of Clinical Investigation (LCI) at the National Institute of Allergy and Infectious Diseases (NIAID). In 1972, he was appointed senior investigator and Head of the Clinical Physiology Section at LCI. In 1980, he was appointed Chief of the Laboratory of Immunoregulation, a position he still holds. Dr. Fauci has been director of NIAID since 1984.

Dr. Fauci has made significant contributions to basic and clinical research on the pathogenesis and treatment of immune-related diseases. He has pioneered in the field of human immunoregulation by making a number of basic scientific observations that serve as the basis for current understanding of the regulation of the human immune response. He has developed effective therapies for once-fatal diseases such as polyarteritis nodosa and Wegener’s granulomatosis. In addition, Dr. Fauci has made seminal contributions to the understanding of how the AIDS virus destroys the body’s defenses and has been instrumental in developing strategies for the therapy and immune reconstitution of AIDS patients. He continues to devote much of his research to identifying the nature of the immunopathogenic mechanisms of HIV infection.

Dr. Fauci is a member of the National Academy of Sciences, the American Philosophical Society, the American Academy of Arts and Sciences, and the Royal Danish Academy of Science and Letters, as well as a number of other professional societies. He serves on the editorial boards of numerous scientific journals, and has written, cowritten, and edited more than 1,000 scientific publications.
JIM THOMSON:
I want to welcome you here on a beautiful Southern California evening. With luck, the
heat engines in the room will not operate at too high a level, and we’ll be able to live in
this 1920s building, which, of course, is not air-conditioned, and have an enjoyable
evening.

This is the fifth of a series of lectures that was endowed by Caryl and Edna Haskins.

Caryl and Edna Haskins had a 40-year association with RAND, and this is the first one
of these lectures that has happened since both of them have passed on: Caryl died last
year, Edna the year before.

They were both scientists—in fact, both biologists. Caryl was a government official
during World War II, and in the period right afterwards, dealing with the policy of
science, working with Vannevar Bush. He was the leader of important scientific
institutions, in particular, the Carnegie Institution in Washington [D.C.], where his wife
Edna was a biologist. He founded an institution, the Haskins Laboratory. We’re
fortunate to have Alice Dadourian with us this evening. She was at the Haskins
Laboratory and was a longtime associate and executive assistant of the Haskins. Alice,
thanks very much for being with us this evening.

Caryl was an advisor to many corporations and nonprofit institutions—most
importantly, of course, to RAND. They [Caryl and Edna] were both devoted to RAND.
They were also devoted to science and to … public policy … It was that interest—that
combination of dedication to science and interest in public policy—that led them to
endow this lecture series.

Our speaker this evening, Dr. Tony Fauci, is very much in the mold that Caryl and Edna
had in mind when they established the lecture series.

He’ll speak tonight about bioterrorism, a topic that’s been on all of our minds since
September 11. Through the leadership of Bob Brook, we were able to establish at RAND
the Center for Domestic and International Health Security, which is now led by Dr. Ken
Shine, who we were able to recruit when he retired from the leadership of the Institute
of Medicine. Ken’s here with us this evening.

Dr. Fauci, of course, as you all know, is the director of the National Institute of Allergy
and Infectious Diseases (NIAID) at the National Institutes of Health (NIH). He’s known
as a scientist at the forefront of the efforts to understand and battle the virus that causes
AIDS and related illnesses. He’s made many contributions to the understanding of how
the virus destroys the body’s defenses and leads to susceptibility to dangerous
infections. He’s been instrumental in developing treatment strategies that now allow
many people with HIV to rebuild their immune systems and extend their lives. He
continues to devote much of his research effort to identifying the nature of the immune
response mechanisms of HIV, and the scope of the body’s immune responses to HIV.

He received his medical degree at Cornell University in 1968. He arrived at the National
Institutes of Health as a clinical investigator, and held several research leadership
positions before assuming his current post in 1984.
He’s a scientist other scientists watch. The Institute for Scientific Information found that, among the one million scientists who published works in journals from 1981 to 1994, Dr. Fauci was the fifth most cited.

Since September 11 and the subsequent anthrax attacks, many of us in this room got to know Dr. Fauci through his interviews in the press and on TV.

He’s been thinking very deeply about the matter of bioterrorism and how much it’s of potential concern to us, so it’s with great pleasure that I invite to this podium Tony Fauci.

[Applause]

DR. FAUCI:
Thank you very much, Jim. Ladies and gentlemen, it’s a great pleasure and an honor to be with you this evening. As you can see from this title slide, I’m going to talk to you about bioterrorism. I call it a “Clear and Present Danger,” because indeed it certainly is that. I’m going to talk to you a little bit about the background of understanding just what the bioterrorism threat is; and then move on to what the response of the biomedical research and public health community has been, is now, and should be over the coming years to the bioterrorism threat.

This truly has been a most unusual year for all of us. Just one year and two months ago … one of the most catastrophic events in our history … September 11, 2001.

I can’t imagine anyone who can’t tell you exactly where they were when they heard of the shooting and death of President John Kennedy. I myself was actually in a microbiology class on York Avenue and 68th Street in New York City, at Cornell Medical School. By some strange quirk of circumstance, at the time that the first plane hit the tower I was in a cab coming out of the Queens Midtown Tunnel in Manhattan, on the way to a meeting, and I didn’t notice anything except some little smoke in the sky that I thought was an air-conditioning unit on one of the buildings that had gone awry. I went into my meeting about 10 or 15 minutes later, and as I walked into the meeting itself, I saw all of the participants not where they should be but looking at television and, just as I walked in the door, this happened. We were all in shock, as I’m sure everyone in this room was—[and] had no idea how that event would not only transform this country, but would ultimately transform the biomedical research community and myself, personally, in the role that I was playing as the director for the National Institute of Allergy and Infectious Diseases. That never was even on my radar screen.

No sooner had the smoke cleared on that horrible day than we were again met with something that was merely in people’s imaginations before then, and that was the bioterrorism attack with the letters—now very famous letters—that contained anthrax spores.

[New slide] These are pictures of the four letters that were addressed to two of our senators—Senators Daschle and Leahy—and to media persons and media corporations:
Tom Brokaw at NBC and the editor of the New York Post. This has now led to something in which we are all very much engaged in the biomedical research community.

[New slide] This is a scanning electron micrograph of the now infamous spores of Bacillus anthracis that were put into the letters that led to the events that occurred in Washington, D.C., Florida, New York City, and Connecticut. If you look at the actual facts of what happened, there were 18 confirmed anthrax cases, 4 probable, for a total of 22. There were 11 inhalational [cases] and five deaths, and they’re shown by their geographic location on this slide [new slide].

At that point, it became clear to us, as I wrote in this editorial [new slide] in the November 2001 issue of the Journal of the American Medical Association, that American medicine, public health and, ultimately, biomedical research was going to be faced with a challenge the likes of which we have not seen before…. The points that I made … have come to pass.

One of the first things I … had to do—and I can tell you honestly I never would have imagined in my wildest dreams, through all of what we had been through with HIV/AIDS and other challenges to the public health system—the way we had to get a handle on bioterrorism was to associate ourselves, purely because of our lack of comprehension and experience, with groups of people that I never would have thought in my wildest dreams that I would be associated with. Those were people who were responsible for the offensive bioweapons program that we had in this country up to 1969, when President Nixon—essentially by executive order—discontinued that program. Not only did I have to come into contact and learn from them—as well as our allies from the bioweapon years—but I also met people who came over to our side who were on the other side in the cold war. And what I learned—and I had to learn quickly—was [this]: … If you’re going to mount an appropriate biodefense effort that involves the biomedical research community, you have to know the difference between biowarfare, terrorism, warfare, and bioterrorism.

We know what warfare is; unfortunately our nation and others have been involved in some terrible wars over the past decades, all of which we in this room are familiar with. I just showed a cogent example of terrorism, but the critical issue is to understand the difference between biowarfare and bioterrorism, if you’re going to mount an appropriate biodefense for the civilian population. Now let me explain what I mean.

[Look at what the Army of the Department of Defense needs to deal with: They need to deal with a population that (by very definition of the fact that they’re in the service) is young and is healthy. So they have a very different population to protect than we in the civilian sector. We have to deal with infants; the elderly; pregnant women; people on immunosuppressive drugs; HIV-infected individuals; people with cancer, on or not receiving chemotherapy. So when you’re talking about vaccines and therapies, it’s an entirely different ballgame.

Second, among other points, is that biowarfare is not successful unless it is a very efficient killer in a strategic and tactical manner. In other words, you have to interrupt supply lines or kill a lot of troops. You’re not going to terrify Special Forces: You’re either going to kill them or you’re not going to kill them.
That’s not the case with the general public. You can have microbes that are not efficient killers, or might not even make people very sick for a long period of time, and you will have accomplished the goal of bioterror. So instead of a handful of microbes to worry about, you have to worry about a large array of microbes. You can prioritize them—as I’ll tell you in a moment—but you can’t just think of one or two.

With that as a background, the Centers for Disease Control and Prevention (CDC)—in collaboration with the Department of Defense and [those of us] at the NIH—have categorized agents according to A, B, and C categories. It’s really a prioritization based on impact and feasibility: Can something be easily disseminated, like anthrax spores, or transmitted from person to person, like smallpox? Does it cause a high mortality, like Ebola? Does it have the potential to cause a public panic merely by mentioning the word, like the plague? And do you require special action, like stockpiling of antibiotics and vaccines?

With that as a background, a menu of diseases and microbes were established as category A, and here they are: smallpox, anthrax, plague, botulism toxin, tularemia, and viral hemorrhagic fevers, particularly Ebola. Those are the highest priorities, but not the only ones, because there are [dangers in] categories B and C. For those of you not involved in medical fields, there’s no need at all to go through these, except to say that they cause varying degrees of illnesses. But if put in a weaponized form, [these] can be extraordinarily disruptive.

So let’s get back to anthrax…. When you’re talking about the current topic of concern, about true terrorists against us as a nation, although there were 18 confirmed [anthrax] cases, 30,000 people received antibiotics, 10,000 of whom received them for … up to 60 days. I am already taking care of people at the NIH who have rather debilitating effects of long-term ciproflaxicin, which is not a benign drug when one takes it for 60 days. But take a look at something that is even more important: With all due respect and empathy for the people who suffered and died in the anthrax attacks (there were five deaths), more people died from influenza during that period of time than died from anthrax. But if you look at the psychological impact and the societal disruption, it was enormous. It was low in terms of biological impact, but it succeeded enormously in causing fear and disruption. And that really gets to the message: If there’s one thing that you hear from me tonight, it’s that we need to take this very seriously. We need to be very prepared because, if we’re not prepared, that only fortifies the rationale for fear and panic if and when something happens.

[New slide] This was a very familiar scene in Washington, D.C. Even more familiar was this [new slide]: For those of you not getting to Washington frequently, the capital—from a legislative standpoint—was essentially shut down. We had to hold congressional hearings … I was at a hearing that Senators Frist and Kennedy called within that time frame, and they had to get permission from Secretary Thompson to use the seventh floor of the Humphrey Building to have a congressional hearing, because all of the Senate and House office buildings were closed. That is major-league disruption for a small number of deaths.
Let’s move on rapidly now to smallpox, because that is on all the networks and in all the major newspapers. [New slide] This is a sign that was tacked on a door in 1914 in San Francisco around a time—the turn of the century—when there averaged 40,000 to 50,000 cases of smallpox in this country.

[New slide] This is an electron micrograph of the Variola major, or smallpox, virus. I’m going to tell you a little bit about that, because you’re hearing a lot of things about it, some of which are conflicting, a lot of which are confusing.

Historically, smallpox is one of the most—if not the most—important diseases known to mankind. It has actually shaped civilizations. Hundreds of millions of people have died of smallpox over the years. The earliest known case—certainly not the earliest real case—was in Pharaoh Ramses V, who died in 1157 B.C. [We know] only because we had a mummy to do DNA testing on to demonstrate smallpox.

Also, smallpox is important historically because it was the prototype of what you can do with vaccines. In fact, the use of Vaccinia, which is a relative of the cowpox that was used by Edward Jenner in vaccinating James Phipps, was such an impressive feat that now we call everything a vaccine; whether it’s for Haemophilus, hepatitis, polio, we call it a vaccine. But the name “vaccine” really comes from vaccinia, which was really the first vaccination against smallpox. (Parenthetically, that is also one of the most famous unethical experiments that was ever performed—never having got an informed consent and challenging somebody with a lethal disease—but we won’t go into that right now!)

Smallpox was used as a bioterror weapon centuries ago. It was used by the British in the French and Indian War, and I just put up—for your consideration—the quote of General Geoffrey Amherst, when he approved the plan to spread smallpox. [New slide] A bit politically incorrect: “You would do well by trying to inoculate Indians by means of blankets, as well as to try every other method that can serve to extricate this execrable race.” Good guy! In any event, it wasn’t particularly successful but, nonetheless, Native Americans died from it.

What about smallpox? When I was in medical school, smallpox had not yet been eradicated, so we had to learn a lot about the disease. We had to learn how to distinguish it from chickenpox, that was the big thing. Centrifugal lesions versus centripetal lesions. Lesions all in the same phase, lesions in different crops. That was always on the exam at the end of the year. No one ever saw a case of smallpox, but it was always on the exam.

Its most severe form is caused by Variola major. It’s what we call an orthopox virus. It’s transmitted by the aerosolized route, but you can also transmit it by contaminated clothing, bed linens—which was the reason why they used the blankets on the Indians. The incubation period is important. It’s about 7–17 days, and I’m telling you this—maybe you think I’m getting a little too clinical—because you’re going to start reading about this in the paper a lot…. The incubation period is about 12 days, on average. It is not communicable from the moment you get infected: It only becomes communicable once you develop the oral lesions and the beginning of maculopapular rash, which then goes into pustules. So you have to be essentially symptomatic to spread the virus. You can’t be well, walking around infected with smallpox but feeling
fine, and infect someone else. That’s something that people don’t understand when they
think about what the ultimate impact may be. It is a very serious disease. Thirty percent
of the people who get infected die, and there’s no treatment….

Now I’m going to show you some slides that are a little bit disturbing. [New slide] This
is a child who is evolving from day 3 through day 7 of a typical pustular rash of
smallpox. This child survived. [New slide] This adult did not survive, and it’s pictures
like this that are part of the terror of bioterror. It’s the thought that this might happen if
someone were to deliberately release smallpox in this country.

The timeline of smallpox is interesting. I already mentioned to you that, at the turn of
the 20th century, there were about 40,000 to 50,000 cases. The last reported case of
smallpox in this country was in 1949. We stopped routine vaccinations in 1972. As I’m
going to show you in a moment or two, for every million people that you vaccinate,
there are one or two deaths—something that would be unacceptable with any other
vaccine today—and there are about 15 life-threatening complications. We accepted that
without blinking an eye when there was smallpox in the world, because the
consequence of not being vaccinated was horrible: There were epidemics around the
world, and people would be coming into the United States … there was always the
threat. But from ’49 to ’72—23 years—each year there was a cohort of about 10 million
to 14 million people vaccinated. So if you’re talking one to two deaths per million over
23 years, that’s up to 40 deaths per year. So 40 deaths per year times 23 years, you’re
talking a very serious number of people who die when there’s no smallpox in the
country. So the public health officials rightly decided, “We’re going to discontinue
routine smallpox [vaccinations].”

The last case of endemic smallpox was in 1977; two additional cases occurred in a
laboratory accident in England in 1978, and—as I’m going to mention in a moment—in
1980, the World Health Assembly declared smallpox eradicated.

[New slide] This is a picture of the last naturally occurring case of Variola major in 1975,
in a young child in Bangladesh, who is now alive and well. Actually, one of our
investigators went to visit her.

[New slide] This is the last case, period, of Variola minor in Somalia in 1977 and, believe
it or not, just last month we celebrated the 25th anniversary of the last case of naturally
occurring, naturally acquired smallpox.

[New slide] And this is the cover of the World Health Assembly’s magazine, which
pronounced smallpox eradicated. That was one of the greatest public health triumphs in
history but, unfortunately now, that’s one of our biggest problems: That is, … we have
an immunologically naïve population. No one in the general population was vaccinated
after 1972, and those of us who were vaccinated as children—and also later, some of us
were—likely have what we call “waning immunity”; not absent, but waning….

[S]upposedly there were two stores of smallpox that were allowed by the WHO.
Everything else was asked to be destroyed. (For the scientists in the room, if someone
tells you to throw all your specimens out of your freezer, what are the chances that
you’re going to do that?) In any event, the two stores are one in the Soviet Union (now
the Russian Federation) and one in Atlanta—at the CDC—under lock and key and guard.

So, if that’s the case, why am I wasting your time this evening, talking about the threat of smallpox? It comes from some rather compelling and corroborated intelligence.

[New slide] This is a picture of Dr. Kanatjan Alibekov—Lieutenant Colonel Alibekov—shown in 1982 getting two medals. One was for developing an aerosolized form of tularemia, and one was for perfecting a weaponized form of anthrax. At the time, he was the deputy director of Biopreparat, which was the covert Soviet bioweapons program…. That was in 1982. That was actually two years before I became director of NIAID.

Now, in 2002, Kanatjan Alibekov is Ken Alibek, and he resides in northern Virginia, is an M.D.-physician-scientist, and is working on a biodefense program. He wrote a book, when he came to the United States, called Biohazard that I really recommend you read—it’s a very well written book. What he says in the book—and this has been corroborated by intelligence—is that, from 1972, when the Soviets signed the Biological Weapons and Toxin Convention treaty, “the Soviet Union built the largest and most advanced biological warfare establishment in the world…. through our covert program, we stockpiled hundreds of tons of anthrax and dozens of tons of plague and smallpox near Moscow and other Russian cities, for use against the United States and its Western allies.” Now I’ve gotten to know Ken very well over the last year and a half, and I asked him, “How could you possibly have done that? You swore the Hippocratic Oath! You’re an M.D.” He said he did it because he was absolutely convinced that we were doing the same thing at Fort Detrick in Frederick, Maryland—which we actually had been doing—before 1969. President Nixon stopped it, but they didn’t believe that we had stopped, and it was only when he came over to inspect Fort Detrick that he actually realized that we had stopped, and then he came over to our side and gave us an enormous amount of information.

We also know from the actual weapons inspection that took place following the Persian Gulf War that the Iraqis actually had stockpiled botulism toxin, anthrax, camelpox, and other microbes that could be used in biowarfare or bioterror. This is a fact, this is not surmising. They were actually documented and, as a matter of fact, what they did [uncover]—when [former UN weapons inspector Richard] Sperzel and others went over there—were bombs that were labeled to have contained botulism toxin that were never used in the Gulf War but are now clearly known to have been ready to be used. [New slide] Just last month, the CIA came out with a report [about nuclear and biological weapons of mass destruction]. [New slide] In fact, these are the sites that will be inspected over the next couple of months—you’re all aware of it, from reading it and seeing it in the media, of the teams that will go over … These are the declared bioweapons sites that will be looked at. I’m not going to get into the implications of that, because that’s not the subject of the talk, but there has obviously been a lot of skepticism as to whether or not we’re really going to be able to look at those sites.

I’m going to leave that for a second and come now to some of the other microbes that we need to deal with. Viral hemorrhagic fevers, particularly Ebola, are very important. [New slide] This is, again, an electron micrograph of Ebola and Marberg viruses. For
any of you who read *The Hot Zone* by Robert Preston—that was an interesting book. As the CDC people like to joke around, Dustin Hoffman—who played the lead in the movie version of that—got more for that movie than the entire CDC got for bioterrorism that year [audience laughter]. But things have changed.

[New slide] This is a picture of an eyelid of an individual who has a hemorrhagic fever. Ebola is one of the most frightening diseases, merely because of the *modus exodus* of individuals, who tend to just ooze out and bleed from their capillaries. [New slide] This is a picture of an epidemic in 1976, of a patient being evacuated from Zaire to Johannesburg, South Africa. As you can see, this is what’s called a modified BSL [Bio-Safety Level]-3 transport facility—it’s a BSL-3 on wheels. I show you this picture [new slide], showing the funeral—the people involved with the pallbearing as well as the health officials—dressed this way.

It is not a very well appreciated fact that, when you say Ebola, there’s panic. If there’s a case of Ebola in Seattle, the people in Los Angeles are going to get very, very frightened, I can assure you. But Ebola is not an efficiently spread virus. It spreads to the health care workers who take care of you. The reason is that people will not be infectious until they’re very, very sick, so it’s unlikely that somebody is going to be mingling in an elevator with you and give you Ebola. But when you mention Ebola, there’s really a lot of panic. There’s been a most recent outbreak in the Congo. The thing about Ebola is that it’s not under lock and key: If the terrorists want to get it, they could get it and they could grow it.

The thing that many of us are as worried about—or maybe more worried about—than smallpox, is the threat of botulinum toxin, because botulinum toxin causes severe paralysis and the mortality is 60 percent or greater. It requires the administration of antitoxin and, if there were a massive attack right now, we wouldn’t have enough antitoxin. If there are a few people who get [exposed], we can handle it, but if there really were a massive attack of something like that, this is what the result would be. [New slide] This is a child with naturally occurring infant botulism, requiring a respirator. If there were large numbers of people who got this, we really don’t have enough respirators. So right now there’s a crash program under way trying to develop antitoxin for botulism. In fact, probably the way to go is to develop monoclonal antibodies against certain epitopes and store an unlimited amount.

Okay, that’s the background. Let me just spend the rest of the time talking to you about the federal government’s response to the threat of bioterrorism after September 11.... The CDC and NIH and the FDA had actually been preparing, based on reasonably good (and now proven) intelligence about the possibility of bioterrorism. We had been working on this since 1998–99 as part of our “emerging microbes” program. The Office of Homeland Security—soon to be the Department of Homeland Security—was established in the fall and early winter, and we worked very closely with them. As part of their program, they put together an outline of what it would look like were they to have a comprehensive effort. It was a $37 billion effort and, [new slide] as you can see here, it includes a lot of things: aviation security, border security, non–Department of Defense homeland security. And about 16 percent of it is biological terrorism security—defending the homeland against biological terrorism. That task has fallen predominantly—not exclusively, but predominantly—on the Department of Health and
Human Services, with the CDC being the first responder: surveillance and detection, tracking whatever outbreak occurs. The NIH has been called upon to do what we do well—and have done traditionally—which is basic research, but also to develop medical interventions.

The FDA is going to have a very interesting role. They’re looked upon fundamentally as a regulatory agency. However, we’re going to have to approve drugs and vaccines for diseases that don’t exist in society, and the FDA approves a vaccine or a drug if it’s safe and if it’s effective. We can prove safety, but how do you prove efficacy if the disease doesn’t exist? How do you prove something’s an effective antiviral against smallpox? This has pushed them in the right direction, to develop what’s called a “two-animal rule,” which means if you show safety in humans and efficacy in two animals, you can actually approve a drug. That’s groundbreaking for the FDA.

In addition, another important element—maybe as important as all the science that we do—is to prepare the state and local public health officials for bioterrorism, because you can have all the interventions in the world but, if you can’t get it to the people who need it, you’re in very serious trouble. It’s much better now than it was a year ago, but it still has a long way to go.

Someone outside asked me about whether we’ve gotten a significant amount of money. [New slide] As you see, in the year 2000, we had about $40 million to $50 million, which, at the time, was a lot of money. People were wondering why we were spending so much money on biodefense in 2000–01. Well, at the time of the anthrax attack, we got about a $100 million supplement. In the 2003 President’s budget ... [there] is an increase of $1.5 billion, which, if you put it into perspective, is the largest single increase for any disease, for any institute in the history of the NIH, including the war on cancer, and far outstripping the acceleration that we witnessed in the early years of HIV, when we would struggle for $100 million or $75 million. Now the HIV budget is $2.77 billion for the NIH, but, in the early years, it was not accelerated.

Now that’s a lot of money. So what we had to do—and this became a twenty-four/seven job in November and December, when we were negotiating with Governor Ridge in the White House, with the President himself, with Vice President Cheney, with the Office of Management and Budget (OMB), about the responsibility of so much money going to an organization—was put together, in a crash time, a strategic plan for biodefense research that’s now transparent and available on our Web site, as well as a biodefense research agenda for category A agents. We called in the best and the brightest to come and massage it with us, to go over it and see if, in fact, we were on the right track. We have an incredible amount of enthusiasm on the part of the biomedical research community to get involved in this. This schematically diagrams the fact that we have to develop expanded research facilities, as well as basic research, to get to the end points of deliverables.

[New slide] I put this slide up to remind myself to tell you a story of the early months of this, when there was some concern [about giving] money to a bunch of scientists: Are they just going to do what scientists do and learn things, which might not necessarily get any results? I think it could be sort of condensed into a statement … that was the result of a discussion between myself and Governor Ridge, as well as Tommy
Thompson and President Bush, on Air Force One as we were going up to site-visit a facility in Pittsburgh that actually was a first-surveillance facility.... We were on the plane talking about it and he [Governor Ridge] was joking, saying, “So what are you going to do with $1.748 billion? I tell you one thing, the right answer is not going to be, ‘We learned a lot.’” The right answer is ‘We’ve learned a lot, [and] have things at the end of that— … vaccines, diagnostics, or what have you.’ [He said this] knowing full well … that we’re not going to get things that are really substantial right away, but we need to go in that direction. But we did do some things immediately, which I’ll tell you about in a moment.

[New slide] This is a picture of what we call a BSL-4 Highest Containment Facility. We’re going to have to expand our capabilities: We’re not going to build a whole bunch of these, but we need to at least allow researchers to handle safely—for themselves and for the community—microbes that they were not used to dealing with before. We’re going to put one up at the Rocky Mountain Lab in Hamilton, Montana—which is an NIAID facility—and one up in Fort Detrick, but we’re also going to construct facilities with lower levels of containment—one in Bethesda and one in Rockville. And we have a regional program of about seven to ten centers that may or may not have BSL-4 facilities, depending on the proposals that are put forth by the investigators.

I know that many people in the audience are not scientific or medical people, so I’ll very quickly go over these slides and leave you with the concepts. You don’t need to know every single detail of what I’m saying. One of the big targets of what we’re doing are the microbes themselves. In this era of being able to sequence the genome of any microbe you want—so rapidly that you can do it essentially in days, where it took years before—is going to offer unprecedented opportunities to discover targets for diagnostics, therapeutics, and vaccines. Let me give you some examples of what has happened in the arena of getting basic scientists to really apply themselves to going in the direction of therapeutics.

[New slide] This is one example of many. There’s a group up at Harvard, led by John Collier and John Mekalanos, who have—over a period of a year and a half—identified, isolated, and crystallized the three major toxins of anthrax: the lethal factor, edema factor, and recombinant protective antigen. Again, for those of you not familiar with that, it might not mean much, but what it tells us is [this]: Anthrax toxins are what actually kill a patient … we now know exactly how you can inhibit toxins by designing molecules that will actually block their effects. We already have prototypic models. That’s what I meant when I told the President and Governor Ridge that we actually can do this in the scientific community … we can translate basic science into real results.

[New slide] This is just a partial list of some of the microbes whose genomes have been completely sequenced or are in the process of completion. You can see the diseases that they cause, all of which are on one of the three lists that I showed you.

Another issue is understanding the host response. You can’t possibly vaccinate everybody against every microbe, so you have to understand how to boost the immune system and how to make therapeutics. [New slide] There’s an interesting association between innate and adaptive immunity, which is shown on this slide. As we evolved as a species, the ancient predecessors of the human race had an innate immunity that was
very nonspecific, which protected them against toxic affronts against them. Amoebas have it. If you look at adaptive immunity, that’s an evolution that we, and some of the higher animals, have that can actually specifically recognize microbes. We are now beginning to understand the extraordinary interaction between innate and adaptive immunity, which can actually nonspecifically boost up the ability of the body to respond. There’s an enormous amount of work going on in that arena now. It was kind of a sleepy field before.

Vaccines are clearly at the forefront of what we do. Getting back to what I said on an earlier slide, the critical issue is that you’ve got to protect all groups of citizens, not just 18- to 35-year-old young men and women in uniform. It’s everyone. Also, you’ve got to improve vaccines. Some vaccines have checkered histories, like [the one for ] anthrax. Whether … the toxicities are real or not, the public perceives it as a problematic vaccine. We also need new vaccines for things that we don’t have vaccines against.

We have put out a contract for developing a new anthrax vaccine that is not made of typical tissue culture but is made from recombinant proteins. One of the real major advances that has occurred, very rapidly and quietly on the NIH campus, was done by Gary Nabel, in which he developed an Ebola vaccine that proved to be effective in a monkey-model challenge, and is now going into Phase I trials in humans in calendar year 2003.

But the thing that’s on everyone’s mind and has now captured everyone’s attention … is the question of a smallpox vaccine…. One of the questions that the President asked when we were on that trip was, “How many doses of smallpox vaccine do we have in our national stockpile?” The answer was 15 million doses. We have 288 million people in the country. Anticipating that question, about eight months earlier we started a dilutional study to take those doses and see if we could inject people with 1:5, or 1:10, and actually expand those 15 million doses to a much larger number of doses, in case we got hit tomorrow (tomorrow being June 2001, antedating September 11). The results were striking. This is relatively low-tech science, but look at the results: [New slide] The success, or “take rate,” of the diluted material was identical to the undiluted. So, now, based on these results, instead of having 15 million doses, we have 75 million doses. In fact, the FDA just last week relicensed the smallpox vaccine. It had gone into hibernation, as it were. It was formerly licensed and now it’s relicensed for use.

This is a very crude vaccine. I don’t even want to tell you how the vaccine is made, but I will. What you do is you inject, under the skin of a calf, vaccinia, and you wait until a lot of virus gets produced and there’s a lot of puss there. You scrape it off, you spin it down, you take the crude material, and you inject it. This was what was being done in the 1960s, not very different from what was done in the 1800s. That’s the vaccine that we all got vaccinated with. It was pure virus, but it started off in a very crude way. Because of that, we have now led a contract to produce smallpox vaccine from a much less crude tissue culture preparation. That will ultimately head on to a critical path to licensure, but it’s not going to be overnight.

Getting back to the President’s question: What happens if we get hit tomorrow? We had a lucky thing happen to us: Aventis Pasteur Inc. found … that they had between 75 million and 80 million doses of a similar vaccine in their freezer. They gave it to the
federal government for a pittance, and we started a new dilutional study and rapidly showed that you can easily dilute it 1:5. So, now, today, November 15—five times about 80 million—we have more smallpox vaccine than we need to vaccinate every man, woman, and child in this country.

That has led to a discussion of the formulation of a smallpox vaccine policy, which is imminent, as it were. It was so imminent, it scared me, as I mentioned to Ken [Shine] and Jim [Thomson] … I was told on Wednesday evening … we were getting close to making a decision of the policy that you’re all reading about: “What are we going to do with the military? What are we going to do with the general population, the first responders, the police, etc.” We were back and forth to the White House multiple times and we were told that there may be a decision Friday so, “anybody that has any plans on going out of town, forget about it.” So I was deciding to myself, “Maybe I should call Ken and Jim and tell them that maybe I can’t come.” But, at the advice of my very prudent wife, I decided not to do that and cause them anxiety. As it turned out, he didn’t [decide]: the President is going to NATO on Tuesday, so there probably will not be a decision at least for the next couple of weeks.

What do we mean by this policy decision? First of all, the question is: Do those of us in this room who’ve been vaccinated have any degree of immunity? The answer is: We don’t have perfect immunity, but we certainly have some. If you do laboratory tests, we can prove it, but we don’t know if the laboratory test is a correlate of immunity that’s protective. We do know that, if you go back retrospectively and look at some introductions of smallpox naturally in Europe—from 1950 to 1971—and you look at smallpox cases among people who were never vaccinated (young people, children), the fatality rate was 52 percent, whereas people who were vaccinated more than 20 years prior to that had a mortality of 11 percent. Clearly there is some degree of protection, at least against dying. You can’t do a statistical analysis of whether it protects against infection, but at least against dying.

So now we’re faced with a policy decision: Do we vaccinate the 500,000 smallpox response people and the 10 million people who are health workers and firemen and police? And what about making it available to the general public? I don’t know about the editorials in Los Angeles, but the editorials in New York and Washington are saying, “In our libertarian society, we need to make vaccine available to people who want it,” which is not an unreasonable thing to say, or even to execute. But if one does that, what we need to understand are the complications of the smallpox vaccine. They’re rare, but they’re serious, and that is the reason why the administration and the Congress and others—particularly the administration, because it’s their decision—is being very deliberative about that decision, because it’s not a decision you take lightly.

The best data on the complications of smallpox comes from the last big cohort in 1968. [New slide] This is a typical primary vaccine site reaction. This is what happens if I were to vaccinate a very healthy person, day 4, then day 7. By day 14 you get a scab that falls off, and that’s it. You get a little ache, you may get some swelling of your lymph nodes, and then you’re protected. However, for every million people you vaccinate, there will be one to two deaths, and about 14 to 15 life-threatening events, and about 60 less serious events. Of the life-threatening events, there’s encephalitis, which occurs predominantly in children. If you’re going to vaccinate first responders, you’re not
going to be vaccinating children, so already one of the major cohorts most susceptible to a major complication is taken out of the equation. But, if you let the vaccine be available to the general public, and a mother or a father says, “I want to vaccinate my child,” and the vaccine is made available, there may be a very rare—but nonetheless serious—complications, like encephalitis.

There are also some other types of complications that I’m going to show you. I apologize for this, but I feel I’ve got to show them to you because I know there are people in the audience who are thinking, “Well, if the vaccine becomes available, maybe I will be vaccinated.” I can tell you that, at a Senate hearing, Arlen Specter pointed his finger at me and said, “I’m going to get the vaccine as soon as we get it out, because I want to get it for myself and my family.” I keep trying to show these slides, but I haven’t had the chance to show him yet.

[New slide] This is a baby who has what’s called generalized vaccinia. This is not life-threatening. You put the vaccine on the arm and, for some reason that we don’t understand, the child can’t contain the virus that’s in the vaccine, so it just spreads. The child got well and was okay.…

[New slide] This is a child who accidentally inoculated himself: The child scratched the vaccination site and then rubbed his eye, and this is what happened. Again, this is very rare. You’re talking about a couple cases out of a million vaccinations, but, when people make that decision, they better understand that.

[New slide] This is what happens when a child can’t contain the vaccine virus locally: This is called vaccinia necrosum. [New slide] Then this is what happens when that gets bad.

Again, all these adverse reactions were seen in the ‘50s and ‘60s, when we were routinely getting vaccinated against smallpox, but we didn’t have all-night CNN and we didn’t have 24-hour news. They happened, but were accepted. Why? Because there was a real threat of smallpox in the world.…

[New slide] The next picture I’m going to show you—and that’s the last of the bad ones—is of a child who developed eczema vaccinatum, not because the child was vaccinated, but because of contact with a child who was vaccinated. So I vaccinate little Janey, and she goes and plays with Helen, and the child who’s unvaccinated could get it. But, again, if you’re in the middle of a smallpox problem, the complications are so rare that there’s no doubt you absolutely should get vaccinated if you have an attack.

But how do you do a risk–benefit ratio analysis when you know the risk of the vaccine but you don’t really know what the risk of an attack is, except that it’s not zero? That’s a very tough calculation that we are facing now.

Having said that, one of the answers is to develop a completely safe vaccine, and we can do that. There are some vaccines—particularly one called modified vaccinia Ankara, which is very safe and has been used on more than 100,000 people. We can’t prove its efficacy absent a smallpox outbreak, so we will have to go with the two-animal model, because it has never been used in the setting of a smallpox epidemic.
I’m going to close up with the next few slides, and talk a little bit about therapeutics very, very quickly. Obviously, that’s the way to go: stockpile therapeutics. As I mentioned, you’re not going to vaccinate everybody.

An antiviral drug called Cidofovir was developed for cytomegalovirus (CMV) in HIV-infected individuals, and it was very effective against CMV, but we found—by accident—that it’s also very effective against orthopox viruses, and is now being tested in monkeys for monkeypox, as well as against variola. So we may have the first antiviral against smallpox. That’s moving pretty rapidly.

[New slide] This is great science. I couldn’t help but show you this. This is an example of the beauty of basic science. This is a fundamental observation, made by an investigator, Vince Fischetti, who’s spending all his time looking at phages, which are particular viruses that specifically attack a bacteria. He found that *Bacillus anthracis* has a phage that specifically attacks it, and has a lysin in that phage, which tends to lyse and kill the bacteria. What he did is, he isolated it … and he put it in a petri dish with anthrax. Why is he doing this if we have antibiotics? We’re doing it because we know, from Ken Alibek and others, that anthrax was being genetically modified to be resistant to the antibiotics we have, so you have to be one step ahead to stay ahead. So if you can get a specific antimicrobial … [New slide] I’m going to show you a video that’s going to last for eight seconds: It’s what happens when you throw the lysin into the test tube, and—you see this?—these are all anthrax bacilli; they’re going to implode and explode with a relatively harmless lysin. This approach is now being pursued with the goal of developing a drug. This is going to take the whole field of bacteria phages a giant step forward.

Also important to the biodefense effort is research in genomics. We know the genomic sequence of smallpox. One of our investigators has mined that genome and produced a recombinant protein, which turns out to be similar to a growth factor protein and, actually, is the way that smallpox binds to the cells of the body. He’s making a monoclonal antibody in the mouse and, hopefully, we’ll be able to develop stores of antibodies for the first time in history that actually can block a smallpox infection. Again, another example of the power of science.

Finally, diagnostics. We’re going to certainly use all the genomic technology of being able to rapidly identify the expression of genes of a microbe, or of the host, that would give us rapid diagnosis. What’s going to happen when the chickenpox season comes? The CDC is going to get overwhelmed with samples of people who think it’s smallpox. What we need is a rapid test in the office, where you could immediately determine the correct diagnosis.

So let me close by tying the loop for you. We’ve been talking about bioterrorism; people are fixated on bioterrorism. There’s been a lot going on through the past centuries and decades that is *really* bioterrorism, and that is *Nature*…. The worst bioterrorism might actually be nature itself, if you look at the constant assault of emerging and reemerging diseases that we have had to deal with.
This map is just a partial listing of diseases that have either emerged new, like HIV; or reemerged in a new place, like West Nile Virus in the United States; or in a strange manner, like multiple drug-resistant malaria, tuberculosis, enterococcus, and staphylococcus. We’re constantly being besieged. Let me just take three examples for you in this last minute or so: There’s the flu pandemic of 1918, there’s the AIDS epidemic, and—most recently—there’s West Nile. There are no terrorists involved in this. This is the natural evolution of microbes.

Let’s talk about influenza. Every year there’s a little bit of a drift in the antigenicity of influenza. Every once in a while, there’s a big shift and it changes and, when it changes, all of us in the room are relatively naïve (immunologically), unless scientists can anticipate what the change is and get the right vaccine. That didn’t happen in 1918 and 1919, when a brand-new, big-time shift occurred, and 20 million to 40 million people worldwide died in one spring, fall, and winter from influenza—more than a half a million in this country. That is “bioterrorism” that occurs naturally. It will likely happen again. In fact, if you look ahead from 1918, we had a bad flu in ’57; the sickest I’ve ever been in my life was in 1968, when I had this flu—and maybe some of you did also; and, in 1976, remember the swine flu? That was no pandemic, but it certainly created a lot of ruckus around the country. And in 1997, there was the famous Hong Kong “Bird Flu,” and it’s a good thing they killed all the chickens in Hong Kong, because it might very well have spread. Just this past summer there was a major epidemic in Madagascar that was highly lethal.

What about HIV/AIDS? I remember this: I was sitting in my office at the NIH in the summer of 1981 [during] the first cluster of cases of HIV—which was not yet recognized as a virus. It evolved naturally as a zoonotic infection: It jumped from a chimpanzee to a human. Now we have 23 million deaths and 40 million people living with HIV. If ever there was something that’s a biological terror, it’s HIV, that’s naturally occurring. The National Intelligence Council projects that, from now until 2010, there will be an additional 40 million cases.

Finally, West Nile, a virus that jumped from Africa and the Middle East to New York City in 1999. And, over a period of four years, it went from 62 cases in New York to, now in 2002, more than 3,500 cases, as of yesterday, November 14. As predicted, the virus has spread all the way to the West Coast.

As Richard Krause—my predecessor as the director of NIAID—said in a very nice little book that he wrote years ago, one must look upon the emerging and reemerging diseases as a restless tide: a tide of microbes that continually, back and forth, assaults our human species. We’re not going to succumb to them, and we’re not going to get rid of them, but they will always be with us.

Unfortunately, now we have a different kind of emerging and reemerging disease—bioterrorism—but we need to think of it in the context of the broad emergence of microbes and their interaction with mankind. So what I hope—as a biomedical researcher and a public health official—is that the amount of resources and effort and focus that we’re devoting to biological terrorism—and the defense against biological terrorism—might ultimately, if looked upon in the context of all emerging and
reemerging diseases, be an important and positive boon for public health, now and in future years.

Thank you.

APPLAUSE

JIM THOMSON:
Tony, we’ve got some time for a few questions, and I hope you’ll be willing to take them.

DR. FAUCI:
I’d be happy to.

AUDIENCE MEMBER:
My understanding was that you could still give the smallpox vaccine after infection, and, if that was the case, would a strategy be—with the proper diagnostics—to wait until infection actually occurred before people got vaccinated?

DR. FAUCI:
The answer is “yes” to your first point, and then there’s a caveat with your second point. It has been shown in some studies in Bangladesh—not overwhelmingly definitive, but strongly suggestive—that you have about three or four days to get vaccinated from the time you … come into contact and get exposed to somebody with smallpox. If I get vaccinated within those three or four days, there is a good chance that I would be protected. So you can, postexposure, vaccinate against smallpox. That’s not the usual situation with microbes, but it’s true with smallpox. That works okay for a cluster or so of smallpox cases. But it wouldn’t work that well for a massive attack. So the answer to your question is, “You’re absolutely right: You have a leeway of four or five days.” What that underscores is the point that I made, that we need a better public health delivery system, because the better the system is, the easier it’s going to be to vaccinate people who come into contact with someone, and save them from actually getting infected.

AUDIENCE MEMBER:
Do you see a role for protease inhibitors?

DR. FAUCI:
For what?

AUDIENCE MEMBER:
For some of the viruses.

DR. FAUCI:
It depends on what virus you’re talking about. If you look at the top group there are two viruses: Ebola and smallpox. Protease inhibitors are not good against either of them. The rest of the class A agents are bacteria. Among some of the hepatitides, they have a sensitivity perhaps to a protease inhibitor, but it’s not going to be a universal drug that’s going to be used for biodefense.
AUDIENCE MEMBER:
We always want our results fast, so my question is: In what way do you expect our defense against bioterrorism would be improved in, say, five years?

DR. FAUCI:
What we’re doing now—pursuing basic research and developing new diagnostics, therapeutics, and vaccines—is one way to do it. We’re not going to be where we want to be in five years—science just doesn’t work that way—but we’ll be much closer than we are now. Probably the thing that can be done most rapidly is an overhauling—a serious overhauling—of the state and local public health system, to allow responsiveness to be adequate, swift, and efficient.

AUDIENCE MEMBER:
Do we know what has happened to the stores of dangerous materials in Russia? Are they in Russia itself, or in some of the breakaway states?

DR. FAUCI:
The official version of what happened is that it was all destroyed. Let’s say that’s true: The thing that is worrying the intelligence community is that, with the dissolution of the Soviet Union, there were many, many knowledgeable, skilled bioweaponers, in the thousands, who were economically deprived because, although democracy came, economic instability came with it. It is likely—at least there’s some evidence—that these individuals—some of them, not all, by any means, but just some of them—may have gone over to the side of people who would use microbes in a nefarious way. So, although they supposedly were destroyed, that’s the same group that said they never made it to begin with, so you have to take it with a grain of salt. We can’t account for all of it, is the answer.

AUDIENCE MEMBER:
What are we doing to make a better smallpox vaccine?

DR. FAUCI:
There are two approaches. When we put our smallpox program together, there were three limbs: immediate, intermediate, long-range. Immediate was the dilutional studies. Intermediate was to develop and test an attenuated MVA (modified vaccinia Ankara). MVA—we can’t say it works effectively, but we need to find that out rapidly—is incredibly safe. It’s been used in hundreds, if not thousands, of cancer patients as a vehicle for inserting genes of cancer proteins and, even though they’re immunosuppressed, even though they’re on chemotherapy, they don’t get into any trouble. The Germans vaccinated 120,000 people in the 1970s with almost no toxicities. But it wasn’t in the middle of a smallpox epidemic. So what we’re doing to get a safer one now is really trying to push the system. The system is going to have to be “re-looked at,” and a lot of very important people in government are very interested in shortening the length of time it takes to push something through the process. The ultimate goal is to develop a recombinant product that’s not a live virus. With regard to our intermediate goal … we’re not too far from it. If we can show MVA protects a
mouse from lethal vaccinia challenge, it is highly likely it will protect a human against smallpox.

AUDIENCE MEMBER:
From a public policy point of view, how do we tell patients not to ask for antibiotics when they don’t need them? The example—the best one, of course—is the anthrax, where in Los Angeles we had a lot of people asking for Cipro when there was no anthrax at all on the West Coast, but people were demanding this.

DR. FAUCI:
I can answer you with a stock answer I’ve given for so many, many years, and it’s just we have to keep trying to educate the public; we need to make them sophisticated with regard to health and science. One of the most egregiously unreasonable things to do—and I hope I’m not insulting anybody in the audience—is, if you’re nowhere near the Hart Building, if you’re in some canyon in Los Angeles, and you want Cipro, it makes absolutely no sense at all. It just doesn’t.

AUDIENCE MEMBER:
You’ve mentioned that we might develop antibodies to some of these pathogens and store large quantities, and, of course, there have been technologies developed recently to humanize myriad antibodies, generate fully human antibodies in genetic mice, and so on. Would you elaborate a little more on that strategy, and how you see it working?

DR. FAUCI:
The strategy that’s being referred to is [this]: It is possible, with the technology we have today, to pick out a particular protein on a smallpox or on an Ebola, make an antibody against it, [and thereby] actually block the ability of that microbe to infect someone. The trouble is that the general approach is to infect people, then draw their blood and to purify it to get gamma globulin. That’s a very tedious procedure that isn’t volume-friendly. It just takes a lot of work. There’s a technology of making what are called monoclonal antibodies in the mouse, by fusing a specific cell with a tumor cell. And you can make completely unlimited quantities of antibody. You can humanize it by genetically manipulating it so that it has the appearance—to the immune system—of being a human antibody, even though it was originally derived from a mouse. Personally, I happen to think that this is an important approach: to stockpile monoclonal antibodies against botulism, against smallpox, and against other pathogens, because you can always use them like a gamma globulin shot. If there were an attack, you could get anybody who was exposed and just hit them with the appropriate, specific antibody. That’s much easier than vaccinating people a priori against 15 microbes.

AUDIENCE MEMBER:
You showed Mike Lane’s data, with regard to complications, which is ’68 data. And, as you pointed out, since that time there’s been an enormous increase of immuno-compromised people. Should there be a decision made to recruit, to vaccinate x hundred thousand people, do you anticipate that might be done in such an incremental way that one could look at the secondary complication rates and find out if those numbers really are relevant to the 21st century?
DR. FAUCI:
Almost certainly it will be done in an incremental way—I can’t give you a 100 percent guarantee—but the complications from 1968 are a certain known number. There are those who, appropriately, argue—not argue, but put forth the fact—that, in the year 2002, there are many more immunosuppressed people. We have transplant people, we have HIV-infected people, we have people on steroids. We didn’t have that many people with these conditions back in 1968. So that tips it this way. What tips it the other way is (a) we’re going to be very exclusive in our criteria for whether or not somebody can get a vaccine, in the absence of an attack. So, if you have a history of eczema (atopic dermatitis), if you’re on steroids, if you have any suspicion that you’re HIV-infected (you should get tested) … we’re likely going to screen out a lot of the people who potentially are at increased risk today. Also, when you’re vaccinating first responders, you’re not going to be vaccinating children, and the majority of the serious problems are in the children, which I think the parents need to understand when they feel that they want to voluntarily get smallpox vaccine for their family. That doesn’t mean they shouldn’t get it, but they need to know there is a heightened risk in children.

JIM THOMSON:
Thanks to all of you for attending this fifth Haskins Lecture, and thanks to the Haskins for making these kinds of events possible.