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RAPID BIO-TERRORISM DETECTION AND RESPONSE

HEARING

BEFORE THE

SUBCOMMITTEE ON TERRORISM, TECHNOLOGY AND HOMELAND SECURITY

OF THE

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RAPID BIO-TERRORISM DETECTION AND RESPONSE

TUESDAY, MAY 11, 2004

UNITED STATES SENATE,
SUBCOMMITTEE ON TERRORISM, TECHNOLOGY AND HOMELAND SECURITY, COMMITTEE ON THE JUDICIARY,
Washington, D.C.

The Subcommittee met, pursuant to notice, at 9:35 a.m., in room SD–226, Dirksen Senate Office Building, Hon. Jon Kyl, Chairman of the Subcommittee, presiding.

Present: Senators Kyl and Feinstein.

OPENING STATEMENT OF HON. JON KYL, A U.S. SENATOR FROM THE STATE OF ARIZONA

Chairman KYL. This hearing of the Senate Subcommittee on Terrorism, Technology, and Homeland Security of the Senate Judiciary Committee will come to order. Let me announce at the beginning that Senator Feinstein is expected to be here momentarily, and hopefully we will have some other members of the Subcommittee as well.

I think that most of the people here are aware that despite the best-laid plans, one can't always plan and the hearing this morning in the Armed Services Committee on the events in Iraq recently has taken the TV crews and some of the other Senators who otherwise would have been joining us here. Therefore, it may deplete our ranks, but we will create a record which will be shared with all of the members of the full Committee, as well as the members of the Subcommittee.

I would also indicate that we will keep the record open for questions that members of the panel might have, and would ask that the witnesses, if possible, respond to those questions in writing. We will keep the record open until 5:00 p.m. on Tuesday, May 18.

I will begin with a brief opening statement, and then by then perhaps Senator Feinstein will be here. At an appropriate time, if she is not here, we will break for whatever opening statement she or other members of the Subcommittee might have.

Earlier this year, this Subcommittee on Terrorism, Technology, and Homeland Security examined ways to protect the Nation from cyber attacks and from attacks against our seaports. Today, we will examine a new method that would improve our ability to detect and respond to a bioterrorism attack.

In recent days, the media has noted the ever-evolving threat of bioterrorism and the catastrophic consequences of a successful large-scale bioterror attack. Earlier this year, President Bush said,

"Armed with a single vial of a biological agent, small groups of fanatics or failing states could gain the power to threaten great nations, threaten world peace. America and the entire civilized world will face this threat for decades to come. We must confront the danger with open eyes and unbending purpose."

Well, one promising way to confront this danger is a medically-based bio-attack detection and warning system which could detect and monitor infections from biological attacks and quickly communicate the results across the country.

[The prepared statement of Chairman Kyl appears as a submission for the record.]

Good morning.

Senator FEINSTEIN. Good morning.

Chairman KYL. Health providers often cannot quickly distinguish between infection caused by a bioterrorist attack and infection caused by routine causes. They must rely on a series of sequential, inefficient actions that delay a prompt response.

In a bioterrorist attack, delayed diagnosis allows contagion to spread. Health care providers need a way to determine immediately whether a person has been exposed to a bioterrorist agent or a naturally-occurring infection. One possible solution is Project Zebra. Project Zebra was developed by a consortium of some of the country's leading scientists and industrial entities to establish a diagnostic test to enable medical personnel to distinguish between infections caused by bio-threat agents from those routinely found in patients.

I should note that it is called Project Zebra because physicians in training are traditionally taught that the most common diseases occur most commonly; that when you hear hoof beats, think of horses, not zebras, is the medical terminology.

The dilemma in bio-defense is, of course, how to detect that one zebra, the rare bio-weapons pathogen, amidst the medically common germs that cause most infectious diseases. Well, Project Zebra would improve the ability to detect and respond to bioterrorist attacks. Early detection would mean faster diagnosis, and faster diagnosis would save lives, optimize the treatment selection, and enable the rapid triage of at-risk populations, which would reassure the worried and thereby reduce risk of panic.

The Subcommittee today will hear from four experts. First is Dr. Paul Keim, who is the Director of Pathogen Genomics at TGen and the Cowden Endowed Chair in Microbiology at Northern Arizona University. He has been recognized as one of our top microbiological researchers with his election to the American Academy of Microbiology. During the 2001 anthrax letter attacks, Dr. Keim served the country by diverting his laboratory and personal efforts to the DNA analysis of the anthrax strain from the letters, and his work resulted in one of the most tangible forensics leads in the anthrax investigation. Dr. Keim's laboratory has a database of 450 unique types of anthrax, based on the world's largest collection of anthrax strains that exist anywhere in the world.

Dr. Harvey Meislin is the head of the University of Arizona Department of Emergency Medicine and is a professor at the University of Arizona College of Medicine. He is president of the American Board of Medical Specialties and received his bachelor of science

degree in chemistry from Purdue and his medical degree from Indiana University.

Dr. David Relman is associate professor of medicine and microbiology and immunology at Stanford University School of Medicine, and Chief of Infectious Diseases at the Veterans Administration Palo Alto Health Care System in Palo Alto, California. He has published over 140 peer-reviewed articles, reviews, editorials and book chapters on pathogen discovery and bacterial pathogenesis.

He received the Senior Scholar Award in Global Infectious Diseases from the Ellison Medical Foundation in 2002 and the Squibb Award from the Infectious Diseases Society of America in 2001. Dr. Relman received his bachelor of science degree in biology from the Massachusetts Institute of Technology and his medical degree from Harvard Medical School.

Finally, Dr. Jeffrey Trent is president and scientific director of the recently formed Translational Genomics Research Institute, or TGen, in Phoenix, Arizona. He was formerly the scientific director of the National Human Genome Institute at the National Institutes of Health, and also served as chief of its Cancer Genetics Branch. Dr. Trent received his undergraduate degree from Indiana University and his master's of science and Ph.D. degrees in genetics from the University of Arizona.

We have a distinguished panel of witnesses before us today and I am interested in examining with them how to make the Nation safer through a medically-based bio-attack detection and warning system which could detect and monitor infections for biological attacks and quickly communicate the results across the country.

Rather than attempting at great cost to set up sensors across the Nation, which many believe would not be feasible, Project Zebra could quickly determine whether symptoms of patients presenting themselves to emergency rooms were the result of normal diseases or from biological agents.

In conclusion, the Secretary of Homeland Security, Tom Ridge, recently said the potential catastrophic consequences that the use of a biological weapon could have on our country obviously makes it a critical, vital area of homeland security concerns.

The Deputy Secretary of Defense recently said, and I am quoting here, "The American people must appreciate the magnitude of the danger that we face from possible biological terrorism. The threat is real. It is deadly serious. As horrible as it was to have thousands of innocent Americans killed on our own territory on that tragic day, that is nothing compared to what terrorists could do with biological weapons that we know they have been actively seeking. In many ways, biological weapons may be ideally suited for the methods and purposes of terrorists. A mass attack with anthrax or some other biological agent could bring about civilian casualties and catastrophic damage to our economy on a scale far beyond even that which we experienced on September 11, as devastating as that was."

Well, these comments are chilling, but they drastically point to the need for technology such as the one being developed by Project Zebra that will help the Nation detect and respond to a bioterrorism attack. I am very pleased to have the witnesses before us today.

With that, let me turn to the co-chair of our Subcommittee, Senator Dianne Feinstein.

STATEMENT OF HON. DIANNE FEINSTEIN, A U.S. SENATOR FROM THE STATE OF CALIFORNIA

Senator FEINSTEIN. Thanks very much, Mr. Chairman, and I won't take very much time. I want to thank you for the hearing and thank our witnesses. I will put my statement in the record, if that is all right with you.

I remember our earlier hearings on bioterrorism, the fact that we had about 36 deadly pathogens; that anthrax existed in 22,000 places in the United States; that we had a very lax system with respect to the handling of these deadly pathogens, if you recall, and some of our findings were placed in the bioterrorism bill. What I am really interested in today is to see whether Project Zebra would have applicability to all of the deadly pathogens or just some of them, what the time line is, and how deep and broad the project can take us in this arena.

So I look forward to hearing the witnesses and I will put my statement in the record.

[The prepared statement of Senator Feinstein appears as a submission for the record.]

Chairman KYL. Thank you. Those are great questions that I hope we can get answered.

Let's go in this order from my right: Dr. Keim, and then Dr. Meislin, Dr. Relman, and then Dr. Trent.

STATEMENT OF PAUL S. KEIM, REGENTS PROFESSOR OF BIOLOGY AND COWDEN ENDOWED CHAIR IN MICROBIOLOGY, NORTHERN ARIZONA UNIVERSITY, FLAGSTAFF, ARIZONA

Mr. KEIM. Mr. Chairman and Senator Feinstein, thank you very much for holding this hearing. It is very humbling to be here in this great institution and we really greatly appreciate your efforts for the defense of this country.

I have submitted an extensive written record, but in my oral comments today I would like to revisit some of the forensic analysis that I have performed over the last couple of years on anthrax, in particular, and try to show how we can see the threats coming out of this, as well as to see the promise for diagnostics in the health care arena and the clinical arena.

Unfortunately, bioterrorism is all too familiar to the U.S. Senate. It has now become perhaps the most notorious bio-crime ever committed in this country. Technology developed in my laboratory has played a prominent role in this investigation. But because it is an ongoing investigation and someday I hope to actually be testifying at a criminal proceeding against the perpetrator, I will be limited in what I can say about the actual case in this particular forum.

However, I can tell you that the first victim of the anthrax attack who died in Florida, in fact, died of a type of anthrax that was commonly found in laboratories around this country, and indeed around the world. This result was accomplished by using highly precise DNA fingerprinting technology developed in my laboratory.

In addition, we were able to determine the entire genetic composition of this particular type of anthrax. So it was proven beyond

a doubt that the anthrax involved in this attack was of a particular type. So, again, this is highly precise diagnostic capability which at least now is only available in the forensic arena.

Prior to 2001, this technology had been developed for other uses. For example, we analyzed the military accident that occurred in Sverdlosck, which was at that time part of the Soviet Union. Sverdlosck is a city now known as Yekaterinburg in the Ural Mountains. There was a production facility for anthrax spores that the Soviets maintained there called Compound 19.

Some time in 1979, they released a cloud of spores that wafted off across the civilian population that was adjacent to this facility. We don't know how or why this occurred, but we do know that over 60 people died in this accident. Physicians, pathologists in particular, were able to smuggle out portions of these people's necropsy samples which we analyzed and were able to demonstrate that, in fact, that cloud of spores was a mixture of anthrax types. Exactly how or why they were doing this isn't clear, but again the precision of genomic analysis allowed us to figure this out.

In 1993, the doomsday cult Aum Shinrikyo released a spray of anthrax across a suburb, Kameido, a suburb of Tokyo. If you look closely here, you can actually see a cloud of anthrax wafting out. Tokyo being one of the densest populated regions of the world, of course, was very susceptible to this type of attack. In spite of this, though, no one died.

Our analysis of the spores that were in this cloud later revealed the reason why this attack had failed and it had to do with the type of anthrax that the Aum Shinrikyo cult was using. In fact, they were using a vaccine strain that was non-lethal, and so their efforts to carry out this biological attack failed for that reason. Again, an example of our ability to precisely identify using forensic techniques.

Now, the Aum Shinrikyo doomsday cult has really set up a paradigm or a model for all sorts of terrorists around the world. We know that the Aum Shinrikyo were interested in chemical attacks. They carried out the sarin gas attack two years later in the Tokyo subway.

In addition to this anthrax attack, they have carried out several other biological attacks. And while they were a long way from creating a nuclear weapon, they were very interested in radiological and nuclear devices to carry out their terrorism.

We can't really predict what the next bioterrorism or terrorist event will be because there are so many different possibilities. But one thing we can be sure of is that they will, in fact, be trying to harm American citizens, impacting their health. My esteemed colleagues will, in fact, cover chemical, biological and radiological challenges, and the diagnostic capabilities that we hope to employ to help counter this problem.

Finally, I would just like to summarize by saying our studies of bacterial genomes has led to these highly precise methods that have been used for forensic analysis. These same types of methods are very applicable for many different pathogens. As you mentioned, there are many, many different types of germs, viruses and bacteria that can be used in biological attacks.

These same approaches are either available or very close to being available for all of them and could, in fact, move from the forensic arena, where we have put a great deal of effort in the last two years, into the clinical arena without all that much trouble.

So with that, I would yield the floor to my esteemed colleagues' testimony and I would be glad to answer any questions.

[The prepared statement of Mr. Keim appears as a submission for the record.]

Chairman KYL. Thank you, Dr. Keim.

Dr. Meislin.

STATEMENT OF HARVEY W. MEISLIN, PROFESSOR AND CHAIR, DEPARTMENT OF EMERGENCY MEDICINE, UNIVERSITY OF ARIZONA HEALTH SCIENCE CENTER, TUCSON, ARIZONA

Dr. MEISLIN. Good morning, Senator Kyl, Senator Feinstein. Thank you for the opportunity to appear before you and discuss the challenges facing our medical system in light of the potential for terrorist attacks.

My name is Harvey Meislin. I am chairman of the Department of Emergency Medicine at the University of Arizona Health Science Center. I also have the privilege of being the president of the American Board of Medical Specialties, the organization that represents all 24 medical specialty boards in the United States.

Today in the United States, the first physician point of care for acute medical injuries and illnesses 24/7 is the local ER. ER care has become an essential community service, providing front-line health care for acute trauma, medical illnesses, local disasters, and even terrorist attacks.

The ER safety net not only delivers medical care, but coordinates disaster planning, emergency medical services, poisoning and infectious disease management and public health surveillance. ERs across the country, however, are in crisis and our safety net is collapsing. Today, about one in every three U.S. citizens receives care in an emergency department annually—over 114 million visits. About 10 percent of our population accesses the 911 system and takes an ambulance ride every year.

In spite of this, over the last decade we have seen the closing of over 1,100 emergency departments in the country. ERs today are overcrowded, understaffed, have almost no surge capacity to handle mass casualties, yet still remain the front-line medical safety net for communities throughout this country.

The staff in emergency departments lacks the diagnostic tools, the education and the therapeutic resources to care for victims of a terrorist attack. Emergency physicians and nurses have existing training requirements that already strain the system, but contain almost nothing regarding chemical, biologic or radiologic attacks.

I can tell you that most physicians charged with caring for the acutely ill and injured in our country had little knowledge about the diagnosis and the management of anthrax before the fall of 2001. Likewise, physicians knew almost nothing about sarin and nerve gases prior to the Tokyo subway attack of 1995. And the knowledge gained from these isolated events is fading, as most physicians feel they will never have to care for patients exposed to these toxic materials.

Importantly, and why we are here today, there is a disconnect between what is happening at the basic science research level and the application of this new knowledge to the front lines of medical care. The gap between scientific discovery and what is applied at the bedside widens everyday.

As you will hear from my colleagues, techniques and skills that are currently being investigated at the basic research level have the ability to identify normal versus abnormal pathogens based upon either their genomic expression or the human response to these pathogens. Yet, few of these innovations have made their way to the front lines of medical care in the ERs or the pre-hospital care system, where critical life-and-death decisions are made every single day.

Medical aspects of an effective bio-defense system require education, prevention and intervention. In the area of education, just as we have trained our Nation's communities to respond to cardiac events through the American Heart Association's advanced cardiac life support course, and trauma events from the American College of Surgeons' advanced trauma life support course, we need to do the same to provide practitioners with the knowledge and skills to manage victims exposed to hazardous materials and toxic terrorism events.

The advantage of having one interdisciplinary program focusing on the medical management of such patients is that it has use in situations that occur in every community, every day during peace time, while preparing medical professionals for toxic terrorism and bioterrorism events.

We should promote a standard interdisciplinary program such as the Advanced Hazmat Life Support program sponsored by the American Academy of Clinical Toxicology and the Arizona Emergency Medicine Research Center that are specifically designed to teach physicians, nurses and other medical personnel in the medical management of patients exposed to hazardous material events, including toxic terrorism.

In the area of early alert and warning, we should create an emergency room surveillance system. We need to know what others are experiencing and keep a surveillance database both as an intervention and prevention strategy. Local, regional and national information should be shared to aid not only in diagnosis and treatment, but in other areas such as quarantine, public health, patient privacy and crowd control. Telemedicine capabilities across the Nation would enhance medical care on the front lines, especially in our rural areas.

In the area of rapid medical diagnosis and treatment, we need rapid, high-performance diagnosis devices throughout all major communities and risk-prone areas. Research is needed to quickly and accurately identify pathogens at the bedside. In the event of a bioattack, we cannot wait two or three days for a culture result to come back. We need diagnostic tools that rapidly and accurately identify natural and weaponized biopathogens.

Clinicians on the front line of medicine and in our local ERs must work closely with the researchers who are on the cutting edge of science and who can identify the genomic expression of a toxin and the body's response to such poison. Likewise, these researchers

need to work with the clinicians, especially in an environment as complex as an emergency room.

Diagnostic devices need to be simple to the user and specific to the pathogen. These devices must be able to identify a broad array of offending pathogens—viruses, bacterial, funguses—and differentiate the routine from the rare and alert us when pathogens are weaponized.

In summary, today the front lines of medicine simply are not prepared to diagnose and respond to a common virus while concurrently ruling out a bioterrorist event or an emerging but potentially lethal pathogen. Another vulnerability of our system is the very uniqueness of the events under consideration. We all hope that a bioterrorist attack will never happen. Yet, in some ways the very fact that it is rare makes its successful implementation more likely.

Today, we train individuals after an event occurs, and by the time that information is needed again, the training is stale and personnel often have moved on. Tomorrow, we can truly obtain a war dividend. The same tools, training and reporting systems that can be developed to diagnose the pathogen have the capability to improve the care of patients everyday, in every hospital, and in every medical office throughout the country. They can reduce patient costs, as well as time away from work and school.

Of even more importance, everyday use of such tools and reporting assures that when the unexpected does occur, the same tools and the same procedures will be available because they have become routine and of proven value to individuals in the health care system.

As you will hear from my colleagues, the science and technology necessary to accomplish this goals is within our grasp. This is not just an academic exercise. We can develop these tools and achieve a level of practicality that will be valued everyday by the individuals treated in the health care system.

Mr. Chairman, I thank you for allowing me the privilege to participate in this important hearing. I hope you will be able to develop a process whereby researchers and clinicians will work together to develop educational programs, medical devices and diagnostic tools that will help the citizens in our country in our war on terror as well as in everyday life.

Thank you.

[The prepared statement of Dr. Meislin appears as a submission for the record.]

Chairman KYL. Thank you, Dr. Meislin.

Dr. Relman.

STATEMENT OF DAVID A. RELMAN, ASSOCIATE PROFESSOR OF MICROBIOLOGY AND IMMUNOLOGY, AND OF MEDICINE, STANFORD UNIVERSITY, PALO ALTO, CALIFORNIA

Dr. RELMAN. Good morning, Chairman Kyl and Senator Feinstein. Thank you for providing me and others at this table the opportunity to address you on a new and rapidly developing area of science that may revolutionize the way we can detect and manage diseases caused by emerging and unanticipated infectious agents.

I am an infectious disease clinician and a researcher at Stanford University whose interests are in the discovery of novel disease-

causing agents and the methods that we need for that purpose. I am also a member of the board of directors of the Infectious Diseases Society of America.

In the late 19th century, we first acquired the ability to detect and identify disease-causing bacteria. It is now 100 years later and we have a surprising inability to recognize and diagnose infectious diseases. More than half of all patients who have an infectious disease remain poorly or undiagnosed at the time they come to medical care.

There are many reasons for this unsatisfactory state of affairs and we can discuss those later, if you wish. But suffice it to say that the consequences for this poor capability in the diagnosis of infectious diseases are profound. We are faced as clinicians with the unfortunate need to use antibiotics in an empiric manner without an accurate diagnosis. The consequence of this action is to promote the development and spread of antibiotic-resistant bacteria, as well as provide sub-optimal care for patients.

The best clinicians are known for their ability to listen carefully to the patient and extract useful clues. We now have a means for listening more carefully to patients than we have ever been able to do with the use of certain kinds of technology and insight that we have gained. This insight has been made possible by the deciphering of the human genome sequence.

One of the tools that has arisen from the human genome project effort is a tool that I show you here called the DNA chip or DNA microarray. On these arrays, there are many spots, each of which corresponds in some cases to each of our different 30,000 human genes.

Surprisingly, it turns out that our human genome and our genes are not static entities; they are actually alive and dynamic. And by that I mean they have the means to respond to environmental stimuli. Different stimuli promote different responses among these different genes and we can monitor that activity, that response, on a device like this.

The challenge, therefore, is to learn how to read these patterns in order to recognize what the stimulus was that provoked this particular kind of profile. This kind of analysis has begun already and is most well developed in the area of cancer, as you will hear from Dr. Trent.

In the area of human gene expression profiling for infectious diseases, the process is still in its infancy, but the results appear to be encouraging. It appears that we can glean from these patterns previously unrecognized features of different individuals both in states of health and in states of disease, such as infectious disease. In fact, we can sometimes glean features that had not been recognizable among a group of otherwise homogeneous humans. So you can see here a computer has divided a group of individuals into two classes based upon features that hadn't been recognized prior.

What is needed at this point? First of all, we need a much more extensive set of data from many different kinds of infection, naturally-occurring infection, so that we can recognize different untoward events one from another in different individuals over time. The promise is that this approach will allow us to recognize disease

at the earliest possible moment, even before an individual is aware that an untoward event has taken place.

In addition, we need standardized methods and tools. We need automated methods and miniaturized devices that might bring down the cost of this technology and make it much more affordable to implement across the board in the health care delivery system.

The future looks quite promising, but the challenges are quite large. The promise is that, as I say, we will be able to recognize infection at the earliest possible moment when we can distinguish the so-called worried well from the truly sick and allocate in appropriate fashion what might be scarce resources.

The potential coverage across the threat space for this kind of device is immense and could cover all of the different kinds of both naturally-occurring and deliberately-released agents that one can imagine. In the future, we might also imagine that individuals might be monitored on a daily basis for their state of health so that we can recognize these events at an early point in time.

In conclusion, we stand on the verge of acquiring novel capabilities. These capabilities have been brought about by technology and science that has only recently come into play. These developments need to be brought to the hands of the clinicians who have an immense challenge in front of them. We think we know how to approach this challenge today, but a great deal more work is going to be necessary both to answer unanswered questions as well as to promote maturation of this technology.

I would be pleased to answer any questions.

[The prepared statement of Dr. Relman appears as a submission for the record.]

Chairman KYL. Thank you, Dr. Relman.

Dr. Trent.

STATEMENT OF JEFFREY TRENT, PRESIDENT AND SCIENTIFIC DIRECTOR, TRANSLATIONAL GENOMICS RESEARCH INSTITUTE, PHOENIX, ARIZONA

Mr. TRENT. Thank you very much, Chairman Kyl and Senator Feinstein. My name is Jeff Trent. I am the president and scientific director of TGen, in Phoenix, Arizona. Prior to my move to Arizona 18 months ago, I served for a decade as the scientific director of the National Human Genome Research Institute at the National Institutes of Health in Bethesda. I really am delighted to have the opportunity to speak with you today.

You have heard about dangers posed by biological outbreaks and the fact that modern technology, including the technology you just heard about from Dr. Relman, could be part of a process toward addressing shortcomings in early detection and treatment capabilities. I would like to discuss very briefly two other elements for your consideration.

The first is the critical need for supporting competitively-reviewed approaches to implement comprehensive and effective end-to-end solutions. The second is to provide you with just very brief information about collaborative work that is beginning to suggest that the activities of genes, the living nature of genes that Dr. Relman just mentioned, may, in fact, help serve as a bio marker

for radiation exposure in the same way that they are also useful in being a monitor of exposure to pathogens.

While our focus must appropriately be on biological attacks that threaten our safety, the fears of possible dirty bomb detonation or similar situations have clearly spurred interest in the research community nationally and internationally in the search for bio markers that could, in fact, be useful for rapidly assessing radiation exposure and large potentially exposed populations.

So for nearly 20 years, I have worked to create and utilize tools and techniques that identify these genetic signatures for diseases, as mentioned, such as breast cancer and leukemia and melanoma and others. But while at the NIH, I also had the opportunity to work on killer viruses such as HIV, HTLV, and with investigators at Fort Detrick on the Ebola virus as well.

But it is important for this Subcommittee to be aware of similar progress, albeit preliminary, that is beginning to give us hope that radiation-associated gene response signatures could, in fact, be incorporated into a biomonitoring approach similar to that just described for bio-threat agents.

My first slide just shows an example, as Dr. Relman showed you. In this case, the stimulus is radiation, and using gamma radiation similar to that that is found in x-rays and in work that has been done in concert with investigators at the National Cancer Institute headed by Dr. Al Fornace, we have begun to look at very low doses of radiation and to look for consistent sets of genes that may be modified in response to radiation exposure.

If one could identify a set of genes by such techniques, one could incorporate these into the aforementioned rapid assays that would utilize nano technology, protein and gene expression analysis, perhaps be utilized again on easily biopsied tissue like blood, and which could become part of a profile that could be an indicator not just of exposure, but perhaps absolute dose of radiation as well.

The next slide that I have just gives you examples of preliminary information using very low doses of radiation, and the point is really just to, as Dr. Relman mentioned, begin to put in place a feeling that we need to sort this information. What this slide really tries to depict is that if one looks at even low doses of radiation—in this case, we were looking at radiation in the area of 0.2 Gray, a measurement tool for looking at radiation response.

The experience of the military that is the triage point looking to detect for 0.2 Gray or above, to give you just a feeling, a single chest x-ray would give you approximately one-ten thousandth of a Gray, or 0.0001 Gray. An upper GI, if you have had a barium enema, gives you about 0.1 percent. So what we have begun looking at is low-dose exposure, moving it up to the higher dose to be able to look at consistent changes that could be useful in this type of setting.

We have also join forces with the investigators at the DOD-funded National Functional Genomics Center at the H. Lee Moffitt Cancer Center in Tampa, Florida, to investigate protein markers for being able to look at this. Here, these investigators are looking at cancer patients being treated with radiation to oblate their bone marrow for bone marrow transplant. We are looking at those cases to be able to look at radiation response moving forward as well.

The point is just that we may be able to utilize diagnostic testing to identify, in addition to bio-threat, radiation-associated genetic signatures. I remain convinced that the most important thing I can emphasize today is the need for competitively-selected end-to-end solutions that do push forward this early detection focusing on the reality that early detection will be a key to saving lives, optimizing treatment, triaging at-risk populations—again, the worried well that you have heard about—and being able to help in many regards, and that this would include identification of these molecular signatures, diagnostic platforms, decision support systems and information architecture.

So I thank you very much for the ability to be able to put forth at least as one part of a solution the mobilization of incident activity that could be utilized in a national stockpile, as well as for a key piece in early detection.

Thank you.

[The prepared statement of Mr. Trent appears as a submission for the record.]

Chairman KYL. Thank you, Dr. Trent.

Senator Feinstein may have to attend another hearing which is already underway. Therefore, I am going to ask her to ask the first set of questions and then I will follow that.

Senator Feinstein.

Senator FEINSTEIN. Thanks very much, Mr. Chairman. Thank you all very, very much for your testimony.

I wanted to ask you a question about Project Zebra. I have a difficult time understanding it because assuming you have these 36-or-so deadly pathogens, and assuming that once these pathogens hit someone the likelihood is that they will die, and assuming that once one hits they hit any number—hundreds, thousands, tens of thousands—of people to be effective, I don't understand how a clinical response in terms of a clinical diagnosis is very helpful because it seems to me it is too late.

It seems to me that the sniffer technique of trying to detect the chemical before it emerges, if you can—and that may not be possible either—is the most realistic in terms of being able to evacuate an area and actually save lives.

Could you comment, please?

Mr. KEIM. Perhaps one of the clinicians should respond first and then I will follow.

Senator FEINSTEIN. This is directed toward Project Zebra, whoever is the advocate for that.

Dr. RELMAN. I would be happy to provide a short response, Senator Feinstein. We, I think, would propose that this generic kind of effort be seen as a complement to other efforts, as well. But it remains true that for a number of these threat agents, if one were able to detect exposure at an early time it might be possible to intervene and save lives with certain kinds of therapies and preventative measures.

Senator FEINSTEIN. For all of the deadly pathogens? I mean, anthrax, yes, but others?

Dr. RELMAN. We believe that for at least a good number of others, there either are now or will be some means of intervening. That is our hope.

Senator FEINSTEIN. How many others and which others?

Dr. RELMAN. Currently, I would say it is about half we have something we can do for now. The other aspect of this is that whether or not we can save all those who have been exposed, we could certainly at the same time distinguish those who have been exposed from those who haven't and direct these limited resources toward an attempt to help and ameliorate disease in the small number that have actually been exposed.

Senator FEINSTEIN. I would like to ask this question. For those of you who work with deadly pathogens, have you noticed a change in the procedures for handling those pathogens, a tightening up, and if so, what are they?

Mr. KEIM. I am probably the best qualified to answer that question.

Senator FEINSTEIN. Senator Kyl mentioned that you have large amounts of anthrax.

Mr. KEIM. Let me say right from the beginning that, in fact, we have very good security before September 11. But after September 11, we voluntarily increased our security tremendously. And, again, I won't go into details about that security in this forum, but I can tell you that we increased our security perhaps five-fold.

Senator FEINSTEIN. Have you heard from the Department of Health and Human Services?

Mr. KEIM. Definitely. People who work in this field live in our backyard now, and so I would say that at least in my personal experience the Centers for Disease Control, the Department of Agriculture and the Department of Transportation have stepped up their monitoring. Certainly, they have required compliance. And it has been, again, my experience that the laboratories have again voluntarily complied and met these standards.

Senator FEINSTEIN. Just one point. The Department of Health and Human Services on March 25 presented what is called a summary report on select agent security at universities, and let me just quote it. "In general, our reports disclose serious weaknesses that compromise the security of select agents at all universities we reviewed. Physical security weaknesses at all 11 universities left select agents vulnerable to theft or loss, thus elevating the risk of public exposure," and it goes on.

Mr. KEIM. I am familiar with that report. I will assure you that one of those eleven was not in Arizona. That was disheartening, actually, to hear that report. Our personal experience is, and the reaction of the inspectors who have visited our laboratory have agreed that we, in fact, have excellent security.

Senator FEINSTEIN. I am really concerned about this because it was brought to my attention. Someone walked into a university, took a letterhead, went and filled it out, sent it to a mail order house and bought plague. That kind of thing has to stop, and we thought that by really activating HHS to move in and set the rules and regulations for the position, for the transfer and for the movement of these pathogens that we wouldn't have a report like this. So it is very disappointing to me.

Did somebody else want to comment? Yes, Dr. Relman.

Dr. RELMAN. I would just add that I think we all share your concern equally. We can tell you that the level of sensitivity within the

academic community has risen immensely. We all now live and breathe this kind of concern, and I think it is only with that kind of sensitivity that we will be able to recognize perhaps those among us or those who seek to collaborate with us that aim to do harm.

One other brief comment. I have been involved in work with the CDC on the use of smallpox virus in monkeys at CDC and I can tell you that the security there and the sensitivity to security surrounding that particular agent is now quite overwhelming and quite impressive.

Senator FEINSTEIN. I guess that is it for me, Mr. Chairman. Thank you very much.

Chairman KYL. Okay, thank you, Senator Feinstein.

Let me get right to the heart of one of the points Senator Feinstein had raised earlier, both the breadth of the potential here for detection of pathogens and also the time within which this might be accomplished. I think at least one of you talked about the breadth being almost pervasive.

The question is how close would we be to developing a technique by which this could actually be implemented. I know that may depend to some extent on how much support there is in the community generally and perhaps with NIH, and so on. But can you give us some idea of how soon this might be expected to evolve?

Mr. KEIM. There are different degrees of implementation, of course, and it is my belief that devices that could, in fact, be monitoring the host response could be available within a couple of years. How discerning they will be we don't know at this point, but I think that a device that provides the best available science to clinicians needs to be developed and put into the clinical setting so that as the science becomes better, we can adapt those devices to provide whatever the best science is.

Again, that means that we have to be able to have people working on the devices. We have to have people working on the science, the host response, as well as getting clinicians engaged with the basic scientists in a fashion that is going to make it effective.

Our hope and what we believe will happen down the road is very grand, but we need to start modestly and get something in place so that we can start to build upon that. And, again, a device that can deliver the best science that is available is what we need to be striving for.

Chairman KYL. Now, Dr. Relman, you testified that perhaps on the order of about half of the pathogens out there we could deal with, if we detected them early enough, in a way that may help patients if we could prioritize our treatment.

So part of this, as I understand it, is to differentiate and appreciate that we don't have to deal with everybody that presents themselves to an emergency room to identify those that really specifically do need care and then focus our treatment on them; that that would maximize our ability to respond to a crisis.

One of the ways that we are trying to do this already is through something called Bioshield, which is to create stockpiles of certain kinds of medicines to deal with outbreaks or potentially a bio-terror attack, and I gather to not only develop those but also to have them stockpiled for response.

In what way would the kind of detection techniques that you are talking about here enhance the ability to prioritize and to develop treatments that could be quickly available anyplace in the country?

Let me ask it another way. I am presuming that it wouldn't be possible to have every single antidote or treatment for every single potential pathogen in every emergency room in the country; that there has got to be some regionalization and quick response to get the material to the right place, or else it would simply be cost-prohibitive.

How would the kind of work that you are talking about here this morning enable us to better do that prioritization and therefore have a reasonable way of dealing with a potential attack rather than simply having to have everything in every location?

Dr. Meislin.

Dr. MEISLIN. Senator, I think you need to look at these pathogens as a myriad of things. Some are very quick. Nerve gases are quick; they are a matter of minutes to hours. Bio-pathogens often are a matter of hours to days, and then there are others such as radiologic effects which are months to years.

I think if you want to prioritize, you really need to look at the life-and-death threats of pathogens. You also have to realize that many times the presentations of these are not unique. Headache, sore throat, stiff neck, ill feelings are common every single day in every single emergency department. How would one physician differentiate the walking wounded from the severely attacked? We need to have those skills.

The diagnostic devices have the ability to give us the day-to-day information. Is this a virus, is this a bacteria, is this a bad one, is this the routine one, versus are you exposed, is this a pathogen? You relate that to the stockpiling. You have to know what it is you are treating, what the speed of it is and then get the antidotes and get medication. So it is a whole process.

The reality of just having stockpiling will only serve you well if you know what you are dealing with and you know the numbers you are dealing with, and you are kind of dealing with the end result, not the front end of it. At least my premise here is that we need to know the front end. We need from the presentation either as a community health disaster or as individual by individual what is going on. We need the diagnostic tools. They have the ability for routine care, they have the ability in the event of a bioterrorist attack.

Chairman KYL. And you said in your testimony that we can't wait two or three days in the case of a bio-attack. What is the prospect, then, for having a diagnostic capability in every emergency room in the country so that we wouldn't be waiting two or three days for the lab results to come back?

Dr. MEISLIN. I believe you heard from Dr. Keim, Dr. Trent and Dr. Relman here that we have technology and research that is probably a few years away. I think once there is a device, the device can be anywhere. I think the device can be miniaturized, that devices can be able to put either in communities or in local emergency departments, if indeed they are specific enough to work.

I don't think the issue of having it in every emergency department is a problem. Every emergency department has diagnostic

tools, laboratories, x-rays. We have all of these devices now. If there is such a diagnostic tool that can be developed and implemented, I don't think the problem is getting it to local emergency departments. I believe the problem is really getting a device that has the sensitivity and the specificity to tell us what we need to know.

Chairman KYL. Does anybody else want to comment on that?

Dr. Trent.

Dr. TRENT. I echo your earlier comment that one of the ways that this will permeate the infrastructure and be able to participate in the incident management is for the Government to aggressively champion this as indeed one of the important elements, as Dr. Relman mentioned, of a comprehensive approach that includes, of course, fixed-point sensoring, but also recognizes that history tells us that in the case of bio-threat agents such as the ones Dr. Keim mentioned, it may not be possible to detect in every feasible instance every example of attack and that there could be the presentation of sick and dying people that we have to deal with and we have to triage.

But I would also agree that there is a pre-symptomatic value to these types of aspects as well; that this is part of the important component for developing tools that would perhaps give us that canary-in-the-coal-mine sentinel approach for being able to look at that. And Dr. Relman's work, I think, is an example of that and trying to recognize that the harboring of some of these signatures can be maintained in our biologic system and can be recognized over time.

Chairman KYL. One of the things that I think would help the Congress direct resources would be a better appreciation of the potential for an attack of this kind. If it is a very rare or a longshot kind of thing, then that might give us time, we would think. But if it is much more likely that terrorists are actually working on these kinds of agents, then that might cause us to accelerate our efforts.

Dr. Keim, let me ask you in a general way—I don't want to get into anything classified here, but in a general way do you have any experience that suggests that terrorists are indeed working on, in your case, different strains of anthrax that could be used? Put that into perspective for us.

Mr. KEIM. I think the best way to put it in perspective is to look at what has happened historically. We have had biological attacks in this country before the September-October 2001. There was a bioterrorism attack in Oregon by a radical cult. There have been disgruntled workers who have poisoned their coworkers. Indeed, we probably experience what I would call bio-crimes almost on a weekly basis in this country involving intentional infection by HIV.

So it isn't like it hasn't happened. It has been very present. Unfortunately, the anthrax letters show how effective it can be, and so I think that there is no doubt that this is going to happen again. Putting a probability or a date on it would be impossible.

It is important, I think, to follow up with what Dr. Meislin mentioned that time is of essence here, and also that the personnel that are involved in doing this have to be doing it on a regular basis. In the case of a medical diagnostic device, this will offer such a div-

idend to physicians and to health care that it will be used and utilized on a daily, hourly, probably moment-by-moment basis in emergency rooms and in clinics across the country. Physicians will know how to use it. If we can engineer a value-added or a war dividend into these devices at the same time that we are monitoring for these exotic diseases like anthrax, it will be used and it will be ready to go when the event occurs.

Chairman KYL. Dr. Relman.

Dr. RELMAN. I would just add a few comments in support or what Dr. Keim has just said. In December of this past year, Dr. Ben Pietro from the Defense Intelligence Agency and I published a paper in the journal Science describing and providing direct evidence that Al Qaeda has, in fact, been interested in trying to acquire B. anthracis, a virulent anthrax bacteria, as well as other agents. This is public information and further documents associated with this article are available through the Freedom of Information Act. So I would be happy to make that available to you and others as you see fit.

But I think you would have to say that if you were a betting person, the most likely event we face in the near future of a major probable impact is avian flu, and what we are talking about today would be equally useful to the clinician trying to sort avian flu from those with many other identically-appearing infectious and non-infectious problems.

Chairman KYL. And just for the uninitiated here, what is so bad about avian flu?

Dr. RELMAN. Avian flu is a new variant of influenza that has already emerged into the animal populations of Southeast Asia and may, in fact, represent the next world pandemic, worldwide epidemic, of flu to hit human beings on the scale of 1918, so a potentially catastrophic event.

Chairman KYL. In other words, it can kill you?

Dr. RELMAN. This kills about two-thirds of the humans it has infected so far. It has simply failed to acquire the ability to transmit from person to person easily, but everyone believes it will acquire that ability quite soon.

Chairman KYL. So having this kind of diagnostic capability would be important for both naturally-occurring as well as man-inducted pathogens?

Dr. RELMAN. Absolutely.

Chairman KYL. One of the questions deals with this complementary relationship between sensors and this kind of diagnostic technique. I would like to have any of you who could discuss that in a little bit more detail. I think there is a sense that sensors might be an efficient way to test in a particular confined area at a particular point, maybe not so much all over the United States. But also could you comment on what the technology is with respect to what it could sense and how important that is, versus the kind of technique that you are talking about here?

Dr. Keim.

Mr. KEIM. I think the point that we made before that these are not mutually exclusive technologies is very important. Decisions that will have to be made by the U.S. Government and public health officials will be how much coverage do you want and you are

willing to pay for when it comes to environmental detectors. Do you want to just protect large events in Washington, D.C., and major cities? Are you going to try to protect the western plains of Kansas, the Sonoran Desert? I think the answer is no to many of those questions, because the price tag will be exorbitant.

The one thing we do know is that when people get sick, they show up in emergency rooms and that type of diagnostic technology will be complementary and will be used on a regular basis. If there is an event or if there is not an event, it will be helping out this country.

Chairman KYL. Yes, Dr. Relman.

Dr. RELMAN. The other thing to add is that we now know from the routine use of these environmental detectors that there are occasional positives during times when we don't believe we are under deliberate attack. One of the complementary advantages and values of a human diagnostic chip is its ability to help us interpret the results of the biosensors.

You detect an anthrax spore in a room here in the Senate office building and the human response element can tell you whether, in fact, there are any humans here who are telling you that they have been exposed to something serious and untoward and are about to become ill.

Chairman KYL. Dr. Meislin.

Dr. MEISLIN. Sensors have the ability to detect the environment, or devices. Take it down to the individual. Again, let me take it into my world. It is three in the morning, and I gave you an example in my testimony, but a young college student who has just returned home from Hong Kong on an educational experience comes into the emergency department with some headache and neck stiffness and a little bit of fever and some nausea and some vomiting.

The physician there says, well, it looks like meningitis. Typically, today, there is a viral meningitis and there is a bacterial meningitis. But you know SARS is coming back this year into Hong Kong and maybe it is something there, and perhaps the environmental monitoring detected something in the air. Something was going on. Maybe it is the evolution of the avian virus coming in here.

So what is a clinician to do at three in the morning? Do I quarantine the individual? Do I quarantine her dormitory? Do I put her in isolation? Do I do what we call the shotgun approach? I treat her with anti-virals, I treat her with vaccines, I treat her with antibiotics. I don't know what is going on. I isolate her, with a cost probably in the hundreds of thousands of dollars and thousands of man-hours and disruptions of everybody, versus a device that can say, well, she probably has hoof beats, not zebras, because we have the ability to test what is going on at the human level, at the individual level, and I can take a specimen from a bodily fluid and I can test it and I can say it looks like it is the normal.

Perhaps the end result of this case is I treat her and I send her home in a couple of hours, and her hospital bill is a couple hundred dollars instead of a couple of hundred thousand dollars and we don't have to worry about a community crisis. So I think you need to take the environmental sensors from kind of a 3,000-foot down to the device which is at the local emergency department treating

the human beings that are coming in day in and day out with potential exposures.

Chairman KYL. Let me ask Dr. Trent, in point of fact if you have sensors at, let's say, something like the Super Bowl and it detects something, obviously you still have to figure out who has been infected and exactly what it is that they have been infected with in order to know how to treat them.

So how does the sensor help with that latter point, and isn't therefore this kind of what we mean by the complementary nature of these two things—and in view of the fact that there is very little time, a point that a couple of you have made, in the case of some of these agents, obviously you want to get to it as quickly as you can. How would something like Project Zebra assist in that element of this?

Mr. TRENT. Well, I think again the triaging of what we continue to say is the worried well or those that may have been exposed but are yet pre-symptomatic is an area in which we have great hope, but again, as Dr. Relman mentioned, little data.

But without any question, as I mentioned, whether it is radiation exposure or work from Dr. Relman and others in terms of pathogen exposure, there are early signatures from the host, from an easily biopsied tissue like blood that could at least, we believe, be part of a triaging process for those that are pre-symptomatic.

There are going to have to be areas put in place to triage individuals so that if a sensor does come up, as you said, with exposure at a mass event, how one triages that within the normal community setting of the emergency room is very difficult. One could imagine that this type of approach could at least be one measurement tool that would be useful in the armamentarium that the physician would use in concert with their own good judgment and the other abilities they have to make these assessments.

Chairman KYL. So let me just hypothesize for a minute. Dr. Keim, you talked about some different kinds of anthrax strains, some of which were really dangerous and some of which were not that dangerous. So you have got a sensor at, let's say, the Super Bowl and it picks up the fact that there is something in the air and maybe it is sophisticated enough to say it looks like anthrax. I am not sure that they are that sophisticated or not, but let's say they are.

Now, to have any effect at all, the news immediately has to go out to everybody in, let's say, the Phoenix area, where we are going to have a Super Bowl in a couple of years, that sensors have just detected something really bad in the air. What is the likely effect on all of the emergency rooms in the entire three-million population area around Phoenix, and what happens if you don't have the kind of capability we are talking about here?

You have got the sensors and everybody worries that they have been infected, obviously, because you don't have any idea how far it has spread. You can't withhold the information. The whole point of the sensors is to let people know that they had better see whether there is something wrong with them. Everybody that has got a sniffle is going to be panicked to death, and even those who don't are going to worry. So now you have got three million people trying to get into an emergency room.

What is the advantage of having the kind of thing we are talking about here, over what physicians currently do to try to differentiate and diagnose and triage?

Dr. MEISLIN. Senator, I am sure you probably know the condition of the emergency departments in Phoenix, Arizona. They are overcrowded. Ambulances go on divert for hours, sometimes days at a time. People wait long periods of time, and yet the volume still is increasing. Let's add on to that another few hundred thousand people wanting to seek care in the emergency department. The system is overwhelmed.

Let's assume that there is a bad pathogen that has been detected, and what happens is the normal human response is they will go to the hospital emergency department. They are not going to wait for an ambulance to take them, they are not going to wait for crowd control. They are worried about themselves and their family and they respond.

The potential to contaminate the hospital is very real, thereby literally taking that hospital off line because it is now a contaminated environment. The ability to have something like Dr. Trent was talking about in the triage, in the sorting of the patient prior to entry into the medical system, just as we are now doing with the Federal response level, which is decontamination—we are learning how to decontaminate people before they get into the facility in large numbers.

If you add this type of device to that triage process, so there is a decontamination and there is a testing for exposure, then at that point you are kind of narrowing into the funnel in here and out would shoot the people who really have been exposed. And those that need the hospital services now would be decontaminated and now they can enter the health care facility and now they can be treated. So not only on line diagnosis, but part of the triage for a mass casualty event of a biopathogen.

Chairman KYL. Well, is the advantage here that, A, you could do it very quickly, and, B, you could it much more precisely and therefore target whatever relief is appropriate in each case? That is kind of what I am hearing, that some kind of device that quickly tests would be far quicker and therefore more efficient to triaging hundreds of thousands of people than current techniques. Is that correct?

Dr. MEISLIN. Yes. We really have no current techniques. I mean, we have nothing down at the level of the hospital at this point in time. But you are absolutely right on both counts. It has the ability on the one-to-one level; it has the ability in a mass casualty event to triage multiple people. So you don't overwhelm health care facilities. You are allowed to be selective with respect to who is contaminated.

Chairman KYL. So this is not a matter of either/or; that is to say either sensors or a quick and efficient and comprehensive way of triaging and diagnosing. This truly is complementary.

Would that be a fair statement, Dr. Keim?

Mr. KEIM. Yes. If I could just add that the forensic analysis and the highly precise identification methods that we have been developing are obviously going to be very important for this diagnostic device. Likewise, those same techniques are moving into the detec-

tor arena and providing a type of specificity as things are being detected. There is no doubt that the detector devices can recognize anthrax. In fact, in the future they will be able to detect exactly what type of anthrax and whether they are virulent or not.

Chairman KYL. Let me, if I could, just walk through a hypothetical attack with anthrax. And before I do that, let me ask you this: There have been a lot of strains of anthrax collected around the world, including some from sources that may have something to do with terrorism. Let's say you are an organization that has produced an anthrax strain and you have had to move on.

How difficult is it to reconstitute that strain and produce it for some possible terrorist kind of attack, number one? And, number two, walk through the process by which you would deal with that after it is first detected today and then with the kind of diagnostic capability that we are talking about developing here.

Mr. KEIM. Well, the good news is I don't actually know how to make anthrax into a weapon. It is not something that we studied in graduate school. So, in fact, that expertise is not commonly available in U.S. laboratories now, given that the U.S. stopped doing this type of production back in the 1960s.

It is a little bit tough for me to answer that question, in fact, since I don't work in public health.

Harvey, would you—

Chairman KYL. Let me just go back to the question of—I wasn't really referring to you making anthrax as much as I was a terrorist who might have had the capability. Do you need a big laboratory to do this? Do you need special vacuum chambers or something like that?

Mr. KEIM. I can talk about it in general. Anthrax, in fact, is a surprisingly safe organism to work with in the laboratory. There have been very few cases of laboratory infection with this pathogen. In fact, historically it was an important pathogen for developing the scientific theory of infectious diseases partially because scientists could work with it safely. The vaccines are pretty effective and there is antibiotic treatment. So it is only considered what we would call a Class II pathogen on a scale from I to IV.

Likewise, terrorists would have that same advantage in being able to work with it without killing themselves. Smallpox and some other things might be more dangerous, in fact. Anthrax is available in many, many parts of the world, especially in the developing world where it is a common disease. Even in this country, we have scores of cases of animals dying of anthrax every year. So you have to think that as a source it would be possible for terrorists to get a hold of it. Again, then the routine handling would be relatively safe. Scaling up and turning it into a weapon is more difficult for me to say since, again, it is not something that I know very much about.

Chairman KYL. But the way that you would ordinarily deal with it—if it came into an emergency room, what would the process be?

Dr. RELMAN. I am an infectious disease clinician, so I too deal with this kind of scenario. If someone comes into the room right now with this as a possibility, after a routine history and physical the kinds of things you would do today are draw blood and send it off for a culture, which would take probably 24 to 48 hours to

give you a result. You would send off additional blood for antibody detection, which would again take days to detect and after exposure might not even be present—that is, the antibodies—until weeks later.

You might do a chest x-ray looking for the tell-tale signs of inhalational anthrax, but those signs only show up days into the clinical illness at a time point when there is very little you can do. So all of these routine, currently available approaches give you interesting information, but in general well past the point when you can intervene and help the person.

Chairman KYL. Dr. Meislin.

Dr. MEISLIN. I think the core answer to your question is unless we thought about it, we wouldn't do anything; we wouldn't know. Has any physician seen anthrax other than in these situations where there is an attack or a lab event? Anthrax pneumonia looks like other pneumonias. The presentation of signs and symptoms of these pathogens look like other common things. We don't think about it.

This gets back to the zebra thing. You know, when you hear hoof beats, you think of horses and you don't think of zebras because common things occur commonly. So the reality is we would probably not do anything; in many cases, probably just send the patient back into the environment.

So one of the other advantages of these medical devices is that they become passive to the user. In other words, you put in your specimen and your specimen looks for things that you aren't thinking about. It looks for the common, it looks for the rare, it looks for the weaponized, and it gives you the answer without you even thinking about it, because I can guarantee you there is nobody in an emergency department today in this country, if someone comes in with pneumonia, that is thinking of anthrax. It just isn't happening.

Chairman KYL. I haven't let you talk enough about the benefits to the development of these diagnostic capabilities here with respect to non-terrorist incidents. I mean, obviously, if you have got this kind of capability, it is just enormously helpful—and I presume there are great cost savings associated with the ability to detect with a great deal of certainty precisely what is going on in somebody's body when they are not feeling well. Maybe we should spend just a second talking about that aspect of this.

And then the last question I am going to ask you really is what do you think we need to do and what can the Government do to assist in the research and development here. This is basic research that we are doing that we hope to be able to apply at some point, but what can we do?

But first of all, I think we would be remiss if we didn't focus just a little bit on the broader public health benefits to the development of this kind of technique. Whoever would like to speak to that, please do.

Dr. Meislin.

Dr. MEISLIN. Well, let me address it, and this probably goes into Dr. Relman's world, but the simple ability to tell a virus versus a bacteria. Think of the thousands of times a day across the country people go to their physician's office or to an emergency department

with a sore throat or with "I have got a little fever and I have got some aches," or "I have a little nausea and vomiting," thousands and thousands of times a day.

The ability of the physician to understand what is going on—is it just a virus versus a bacteria, knowing that if it is a virus, I am not going to give you antibiotics? Think of the effect, then, of the amount of antibiotic usage, the lack of resistance to the antibiotics we have today, which is a huge problem we have where we are trying to develop more antibiotics at a huge cost to our society.

The ability to reassure patients of what is going on and the length of their illness and what they should expect is huge. The advantage to day-to-day medicine is just phenomenal. I think it would be a huge cost saving. I think it would advantage emergency departments everywhere because probably 30 to 40 percent of these types of patients present to emergency departments. This would be a huge benefit to American medicine just on an everyday, routine thing. And then if you want to be more specific, the ability to tell which virus or which bacteria, to know which sensitivities to which drugs, is just a phenomenal benefit to everybody.

Chairman KYL. So in one sense, the tremendous burden that the emergency rooms have now, the challenge that is presented to us from a public health standpoint of figuring out how to better deal with this, could actually be alleviated to some extent by having this kind of technique available to more efficiently do the job that emergency rooms today are not as well equipped to handle.

Would that be a fair statement, Dr. Meislin?

Dr. MEISLIN. Senator, I think you are talking probably 30 percent, maybe even more of emergency department visits would be aided with devices like this, of people who either don't have to come or people who could come and be treated very quickly and then go home.

Chairman KYL. Dr. Relman.

Dr. RELMAN. Even if the only thing that such a device could do would be to distinguish those who feel terrible and have a low-grade fever but who can go home, because we know that 48 hours from now they are not going to be sick, from those who feel identically and cannot be distinguished from the former by any physician but who need to be in a hospital and stay, that ability to distinguish between those two groups of people who today we cannot distinguish between—that ability alone would provide incredible savings in terms of our health care resources.

Chairman KYL. In this sense, then, is it not true that the human body itself is a sensor and if you have this technique, you can much more efficiently and quickly and with better results, then, use that sensor to determine what the appropriate course of action is?

Dr. RELMAN. Exactly, and I think as I was saying, the best old-time doctors are those that know how to look at somebody and somehow intuit what is going on, whether it is serious or not. We are always taught you can look at a patient and sometimes tell if they are sick or not. Well, the truly gifted might be able to do that, but the average doc can't quite do that, and this is what we are hoping this device could do.

Chairman KYL. Dr. Trent, did you have something on that?

Mr. TRENT. Well, just that again I believe absolutely that the Government can play a major role, and has done so very effectively in the past through the competitive process, and that is the area that we strongly support. But the end-to-end solutions of combing molecular signatures that we have talked about with the diagnostic platform technologies that we have talked about with a national information architecture and decision support system and looking at that as a unified program is really a critical component for trying to have this be effectively introduced and effectively bring value.

So I strongly believe that the addition of, as you said, the body as a sensor should be part of the competitive platform that is considered by the Government in trying to initiate our ability to hopefully result in a critical needs and biodefense, but also, as you have heard, improve public health and safety.

Chairman KYL. If we just look at this in terms of cost and forget for a moment the wellness that results from this, but just looking at the cost, is there a way to quantify the cost of our current system and the kinds of cost savings that could result if we could develop and use this technology? Maybe that is a question that you could think about it and maybe if you could supply an answer for the record after you think about it a little bit, that would be very helpful, or to even give us a way of trying to calculate that cost it would be very helpful.

Let me conclude with this. It is clear to me that all the way from the huge burden that we have in running a Government Medicare system—I mean, that is something that the Federal Government is directly responsible for—to our veterans care programs, our support for the States in their Medicaid programs and our general research through NIH and others that attempt to help with public health all over the country—you combine that with the benefits from an antiterrorism standpoint and you have got a potential here that clearly should attract the attention of the United States Government in terms of what it can do to promote this kind of research.

So my last question is—and you were actually getting to this in a couple of the answers, Dr. Trent—what are the best ways for us to look at this as members of the Senate to be able to support this kind of activity, again appreciating that it is not a substitute for anything else, but could be very complementary to other things that are already being supported?

Mr. TRENT. Well, again, I think you just said it extremely well. I think that the unification of interests across the various elements of the Government is, I think, being focused appropriately on this type of effort. So on this panel are individuals that work with CDC, that work with NIH, that work with the defense community and a number others.

I think that the type of coordinated programs that again rely on competitive winnowing of responses to ensure the excellence in science and opportunities is critical across this entire spectrum of response that we need to put into place. So I believe that it can't be as simple as saying that the body as a sensor belongs to NIH and the sensor technology belongs to CDC.

I think that really those integrated components that bring all of those together and focus on that are really very essential. And having lived within one small element for a decade of the Federal Gov-

ernment, I think those opportunities you have to broaden the discourse between groups is important in many regards, and I think that is one area that you could play a role.

Chairman KYL. Thank you.

Dr. Keim.

Mr. KEIM. I would just add that this is an enormous task to put together a large program like this and it is going to require components from different types of entities. On the one hand, we are going to need large science, and that is where agencies bring together—you know, this is like NASA putting somebody on the moon. You bring together people who can put together a nationwide program.

At the same time, we can't ignore the fact that a lot of the innovation is going to come from small, what we call principal investigator-driven laboratories, where you will see innovative science going on, where you are getting graduate students trained. So we have to have kind of a union with that.

On top of all of that, we have to have some type of a commercial engine involved with this, companies that can actually power the implementation of this, because ultimately it is going to be delivered not by the Government; it is going to be delivered by some U.S. or international consortium of companies. So the problem is multi-faceted and we can't ignore any of these. Otherwise, it won't work.

Chairman KYL. Does anybody else have anything to add?

Again, we will keep the record open for a week for questions, and there probably will be some. And anything else you would like to supplement the record with we would be happy to get.

I might just say one thing. Senator Feinstein was addressing a question that had come up in hearings that we had held many, many months ago about the vulnerability of our system. I realize that none of you are in a position to answer those questions and I would just indicate that one way or another we will try to address that question probably with people at the Department of Homeland Security. I am sure you will be interested in the results of that, as well, and we will get that information back to you. If you have anything else you can add to that, fine, but I know that is not your area of responsibility.

We are literally five minutes ahead of schedule here and I want to thank all of you for keeping to the time constraints that we set out and for very concisely but clearly and, in my view, in a very helpful way not only bringing attention to the problem and the challenges, but offering a very constructive and potentially very beneficial way of addressing not just the public health problem, but the problem of a potential terrorist attack.

We will certainly share the results of this hearing with my colleagues. We will write up a summary and get it to everyone. Anything else over the course of time that you would like to present to us that would help us to continue to appreciate how this is evolving I would invite you to submit to us. So thank you again very much for testimony.

If there is nothing else, I will declare this hearing adjourned.

[Whereupon, at 10:57 a.m., the Subcommittee was adjourned.]

[Submissions for the record follow.]

SUBMISSIONS FOR THE RECORD

Statement
Hearings before the Subcommittee on Terrorism, Technology and Homeland Security

"Rapid Bio-Terrorism Detection and Response"
[Project Zebra]

Dianne Feinstein
United States Senator

Today the subcommittee will address one of the most frightening aspects of the threat posed by terrorists – biological terrorism. I want to thank the Chairman, Senator Kyl of Arizona, for holding this hearing, and for focusing our attention on this issue.

Bioterrorism is not an easy subject to discuss or study. It is difficult to conceive of the devastation that could be brought about by a successful biological attack. Those of us who lived, and worked, through the anthrax attack of 2001 in these buildings know the fear that can be engendered by a biological attack – silent, invisible and deadly. But we must be honest and realize that the anthrax attacks, luckily, were just a small taste of what could happen, and should serve as a warning to our nation.

Bioterrorism is also a difficult subject because it is depended on cutting edge science, often of breathtaking complexity. Thus it is critical that the Congress draw upon the scientific expertise of experts, such as will testify today, to help us craft policy. This part of the war on terrorism will be won where **science meets policy**, and we can start today on that effort.

Today's hearing will focus on Project Zebra, an innovative, creative and important concept, as we build our national toolset to respond to potential bioterrorism.

I want to thank our witnesses today, **Dr. Paul Keim,** of Northern Arizona University, **Dr. Harvey W. Meislin**, of the Arizona Emergency Medicine Research Center, **Dr. David A. Relman,** Associate Professor of Medicine **at** Stanford University, and **Dr. Jeffrey Trent,** President of the Translational Genomics Research Institute.

I am confident that they will explain the complex science, and cutting-edge thinking, that is behind Project Zebra.

I would like to make a few observations before we hear from our witnesses.

First, I agree with the Chairman – **it is critical that our nation's biodefense be founded on a spectrum of defensive mechanisms.** We cannot put all of our eggs in one basket, and simply rely on sensors.

What is needed is "defense in depth," drawing on the creativity and knowledge of our scientific community. We can then develop technologies which can allow us to:

- Search out biological weapons abroad,
- Detect them at our borders and ports
- Sense them at our critical points of vulnerability, and
- Identify, using concepts like Project Zebra, a bioattack after it happens based on its clinical signature in the affected population.

Second, I remain concerned that I do not see the Department of Homeland Security stepping up to the plate and taking the lead in this, and other, issues. The Department of Homeland Security has yet to fulfill its promise as the central place in our

government where threat information is mapped against vulnerability information, thus driving homeland defense policy.

Third, I want to emphasize my belief that one of our nation's **great strengths is its scientific and medical community**, which encompasses **government agencies, academia and private industry**.

That community works best, and will be most effective, when it combines its three components. I hope that Project Zebra can serve as an example of this proposition, drawing upon government, industry and our great universities.

I look forward to our witnesses testimony, and working with my colleague, Chairman Kyl, on this promising concept.

STATEMENT OF PAUL S. KEIM
REGENTS PROFESSOR OF BIOLOGY,
THE COWDEN ENDOWED CHAIR IN MICROBIOLOGY,
NORTHERN ARIZONA UNIVERSITY
FLAGSTAFF, ARIZONA

AND,

THE DIRECTOR OF PATHOGEN GENOMICS,
TRANSLATIONAL GENOMICS RESEARCH INSTITUTE
PHOENIX ARIZONA

BEFORE THE

COMMITTEE ON THE JUDICIARY
SUBCOMMITTEE ON TERRORISM, TECHNOLOGY & HOMELAND SECURITY
UNITED STATES SENATE

CONCERNING

THE USE OF PATHOGEN GENOMIC ANALYSIS FOR DETECTING AND EVALUATING ACTS OF BIOTERRORISM

PRESENTED ON

MAY 11, 2004

My experience in biothreat analysis. In early October 2001, a photo editor for a Florida, USA, tabloid newspaper contracted anthrax and died. In the initial days of his infection, we weren't sure that this was indeed a bioterrorism event. An anthrax case in the southeastern United States was unusual, but perhaps it was a natural case? The inhalational diagnosis was doubted by at least one national expert, who questioned the ability of the naïve medical team to make the correct diagnosis. A primary "anthrax" culture from the victim's cerebral spinal fluid was jetted by courier to our relatively remote Northern Arizona University laboratory on Thursday October 7th, while the Centers of Disease Control experts did parallel studies. Early on Friday morning, a conference call between the Keim Genetics Lab and Drs. Alex Hoffmaster and Tanja Popovic at the CDC concluded that the initial anthrax-letter victim had been infected with the Ames strain. Our work has shown that this strain is very rare in nature. But we also knew that it was a highly virulent and commonly used in laboratory experiments and vaccine challenge trials. The first anthrax-letter victim died later that day turning this from just an epidemiological investigation, into a forensic investigation of murder.

My testimony on the anthrax-letter attack will be limited today because of our involvement in this ongoing criminal investigation. Though, I can provide this one insight into the investigation: one of our most valuable services to the FBI and this country has been our ability to exclude natural cases of anthrax from the criminal investigation. For example, in November 2001 a herd of cattle died of anthrax near San Jose California. Our rapid analysis quickly identified the strain as a naturally occurring one and diffused a potential regional crisis. Like in human forensic analysis, conclusions about "exclusion" are very powerful and important.

The well known "anthrax letter attacks were preceded by several other anthrax investigations that pushed our DNA-based technology along and the status necessary to identify the Ames strain in 2001.

Anthrax's use as a biological weapon by many countries' weapons programs (e.g., USSR, Britain and the USA) doubtlessly contributed to the wide spread knowledge of its weapon potential. The technology to produce large amounts of "anthrax" spores, weaponize them, and deliver the agent was well developed by several different countries. In 1979, there was an accident at an anthrax spore production facility in Sverdlosck (Yekaterinburg) USSR. A spore plume stretched downwind across the city, infecting individuals and, ultimately, killing at least 64 individuals from anthrax.

Along with my colleague Dr. Paul Jackson at Los Alamos National Laboratory, we have investigated the 1979 Sverdlosck military accident where a spore cloud was releases across this eastern Russian community killing at least 65 people. Strain analysis of victims' necropsy tissues suggested that the plume was a composite of multiple genotypes. The multiple types of "anthrax" suggested that the Soviet bioweaponeers were mixing types during their weaponization program. Alternatively, they may have just accidentally released multiple types.

How or why an industrial accident of this scale would have spores from multiple strains is not known and details from the accident were never officially revealed by the Soviets. Thus, the strain identity work is still one of the few publicly known insights into what happened in this tragedy.

A second example our pre 2001 efforts involved the Aum Shinrikyo dooms day cult in Japan. Indeed it was in early 2001 that we had completed strain analysis on "anthrax" culture isolated at the site of an attempted bioterrorism event in the Tokyo, Japan, suburb of Kameido. The Aum Shinrikyo cult was striving for social chaos, in order to overturn established political institutions for their own benefit. In late June 1993, culture members sprayed liquid *B. anthracis* cultures over this densely populated suburb for several days. The spray resulted in a stench and caused the local population discomfort, but no one contracted anthrax. After the cult's deadly sarin gas attack on the Tokyo subway, interest was renewed in the earlier Kameido incident. We analyzed the single remaining environmental sample from 1993 and discovered *B. anthracis* spores that were still viable. Strain analysis identified these spores as Sterne, a common veterinary vaccine strain. The cult would have had easy access to this strain, as 100,000's doses of the Sterne vaccine are produced, distributed and utilized every year in Japan. This easily explains the cult's failure to kill, as the Sterne vaccine is highly attenuated and cannot cause anthrax in humans. This investigation had an eerie parallel to the anthrax letter attacks, in that our technology identified the type of "anthrax" and lead to reasonable explanation for what had happened.

Genomic based diagnostic analysis. The key to strain identification is the genomic technology developed in my Arizona laboratory. Even before the first victim died in the anthrax-letter attacks, the U.S. government knew that this threat started in a laboratory setting and was not a natural infection. As it turned out, as a country we were better prepared for a forensic investigation of anthrax than just about any other bioweapons. (Because this is an ongoing criminal investigation, I will go into no further details on this particular case.) We had

Lessons learned. From a decade of experience in bioweapons research and from my investigative role in these bioweapons incidents, i have learned several things.

First, you have to be broadly prepared for crises involving bioweapons. While the threat is extremely real, it represents a very diffuse target. It is hard to anticipate what the next biothreat agent will be and harder yet to predict what scenario will play out. While specific preparation for a particular scenario and a particular agent, for example anthrax in letters, may or may not help in the next bioweapons event. Highly skilled personnel can adapt to just about any crisis situation. Building a broad infrastructure in infectious disease and public health will be valuable in any biothreat scenario. Maintaining stocks of suitable reagents, diagnostic devices and capabilities to respond are crucial once a crisis occurs. Point-of-care diagnostic devices are badly needed and not yet developed sufficiently.

Secondly, I have found that it is impossible to prepare everything. We were surprisingly well prepared in the forensic arena for an anthrax attack. My lab had tools, we had databases and we even had recent experience in tackling a bioterrorist event. But, when I got the call from the FBI that a clinical samples was in route from an anthrax victim – I shuttered and thought "Oh God, give me another six months to prepare!" I got six hours. So, again I would urge for building infrastructure that is adaptable. This needs to include both well equipped laboratories and a trained work force that can fill in the gaps and expand out knowledge as needed. It is impossible to exactly predict the next event arguing for broad healthcare based efforts.

Thirdly, we need to have established communication mechanisms. In a crisis you gravitate towards what you know. In our case, we had long-established personal contacts at the FBI and the CDC. These were far from the upper echelon folks, but rather with the skilled technical personnel in each agency. Years of scientific interaction this these folks had established our area and specific expertise with them. They knew and trusted our work. Following September 11th, our country's communication and transportation infrastructure was greatly impacted. We need to have established networks of experts and communication channels in order to react effectively in a crisis situation.

Fourthly, flexible contracting and mechanisms for moving funds need to be available. Even in crisis situations payrolls have to be met and supplies have to be purchased. In days following September 11th, basic economics still applied. In our cases, we temporarily stopped all other government contracts and moved these people and resources on the investigation. The government needs contracting mechanisms to quickly respond to a crisis. This sounds easy to the folks high in the chain of command, but it has to be implemented at the level of accounts and contract officers who try really hard to obey the government rules. While this topic lacks all the pizzazz of hazmat suits and genetic engineered germs, but it was a real problem and distraction in the investigation of this case, which began in a crisis situation.

Finally, our nation has such great scientific and technical expertise and this gives us a distinct advantage in the fight against terrorism. In the future, we will be able to monitor infectious disease pre symptomatically and this will minimize the impact of future bioterrorism events. It is important that the US government is forward thinking and moving in this direction. Clearly, this is not a solution for what happens next weeks or even next year, but it will not happen at all if we are not planning for 5 to 10 years now.

The great potential of genomic research. Forensic investigations are driving diagnostic analysis to the absolute limit of specificity. In the area of bioterrorism defense, you will hear a lot of talk about specificity levels. Can we tell one bacterium from another? In forensics we are required to "precisely" identify the biological agent involved in an event. Now that forensics has become so important, we are benefiting the whole field by providing exquisitely precise and specific identification. This specificity will greatly benefit both environmental and medical diagnostics assays.

One of the sad realities associated with forensic work is that our technical capacity is only realized when crimes have been committed and as they are investigated. Thus, forensics is focused on post event characterization in order to prevent and deter future terrorist efforts. However, our work and technological advancements can be important in environmental detectors and healthcare that are important before and during a terrorist event.

We don't know what the next bioterrorism event will be, let alone the next terrorism event will be. However, it is easy to predict that terrorists will be striving to hurt American citizens. While there are many non exclusive strategies for protecting our citizens, ultimately the point-of-care is where all of the different terrorist scenarios coalesce. A terrorist attacks have and will create confusion and chaos. It is easy to envision the potential for a panicked population to overcome our healthcare's capacity to effectively treat and manage the influx of "worried well" and truly sick citizens. Comprehensive, sophisticated and highly specific diagnostic resources are needed to avoid or mitigate this scenario.

Thank you, Mr. Chairman for holding this hearing on this important topic. Our efforts today and those that will follow in the future weeks will have pronounced affect upon biodefense and healthcare in general. I will gladly answer any questions you may have.

STATEMENT SENATOR JON KYL
CHAIRMAN
SENATE SUBCOMMITTEE ON TERRORISM, TECHNOLOGY, AND HOMELAND SECURITY
SENATE JUDICIARY COMMITTEE

"RAPID BIO-TERRORISM DETECTION AND MANAGEMENT"

11 MAY 2004

Overview

Earlier this year, the Subcommittee on Terrorism, Technology, and Homeland Security examined ways to protect the nation from cyber attacks and from attacks against our seaports. Today, we will examine a new method that would improve our ability to detect and respond to a bio-terrorist attack.

In recent days, the media has noted the "ever-evolving threat of bioterrorism" and "the catastrophic consequences of a successful large-scale bioterror attack."[1] And earlier this year, President Bush said, "Armed with a single vial of a biological agent . . . small groups of fanatics, or failing states, could gain the power to threaten great nations, threaten the world peace. America, and the entire civilized world, will face this threat for decades to come. We must confront the danger with open eyes, and unbending purpose."[2]

One promising way to confront this danger is a medically based bio-attack detection and warning system, which could detect and monitor infections from biological attacks and quickly communicate the results across the country.

Background & Project Zebra

Health providers often cannot quickly distinguish between infection caused by a bio-terrorist attack and infection caused by routine causes. They must rely on a series of sequential, inefficient actions that delay a prompt response. In a bio-terrorist attack, delayed diagnosis allows contagion to spread. Healthcare providers need a way to determine immediately whether a person has been exposed to a bio-terrorist agent or a naturally occurring infection. Project Zebra is a solution.

Project Zebra was developed by a consortium of some of the country's leading scientists and industrial entities to establish a diagnostic test to enable medical personnel distinguish between infections caused by bio-threat agents from those routinely found in patients. I should note that it is called Project Zebra because physicians in training are traditionally taught that the most common diseases occur most commonly — that "When you hear hoof beats, think of horses, not zebras." The dilemma in bio-defense is, of course, how to detect "the Zebra" — the

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[1] *Offensive against Bioterrorism*, WASH. TIMES, April 30, 2004, at A22.
[2] President George W. Bush, February 11, 2004, quoted in *Biodefense for the 21st Century*, at 1.

rare bio-weapons pathogen amidst the medically common germs that cause most infectious diseases.

Project Zebra would improve the ability to detect and respond to bio-terrorist attacks. Early detection would mean faster diagnosis — and faster diagnosis would (1) save lives, (2) optimize the treatment selection, and (3) enable the rapid triage of at-risk populations, which would reassure the worried, thereby reducing the risk of public panic.

Witnesses

The subcommittee will hear from four experts.

Dr. Paul Keim

Dr. Paul Keim is the Director of Pathogen Genomics at TGen and the Cowden Endowed Chair in Microbiology at Northern Arizona University. He has been recognized as one of our top microbiological researchers with his election to the American Academy of Microbiology. During the 2001 anthrax letter attacks, Dr. Keim served the country by diverting his laboratory and personal efforts to the DNA analysis of the anthrax strain from the letters, and his work resulted in one of the most tangible forensic leads in the Amerithrax investigation. Dr. Keim's laboratory has a database of 450 unique types of anthrax, based on the world's largest collection of anthrax strains that exist anywhere in the world.

Dr. Harvey Meislin

Dr. Harvey Meislin is the head of the University of Arizona Department of Emergency Medicine, and is a professor at the University of Arizona College of Medicine. He is the President of the American Board of Medical Specialties. Dr. Meislin received his bachelor of science degree in chemistry from Purdue University, and his medical degree from Indiana University.

Dr. David Relman

Dr. David Relman is the Associate Professor of Medicine and of Microbiology & Immunology at Stanford University School of Medicine; and Chief of Infectious Diseases at the Veterans Affairs Palo Alto Health Care System, Palo Alto, California. He has published over 140 peer-reviewed articles, reviews, editorials and book chapters on pathogen discovery and bacterial pathogenesis. He received the Senior Scholar Award in Global Infectious Diseases from the Ellison Medical Foundation in 2002, and the Squibb Award from the Infectious Diseases Society of America in 2001. Dr. Relman received his bachelor of science degree in biology from the Massachusetts Institute of Technology, and his medical degree from Harvard Medical School.

Dr. Jeffrey Trent

Dr. Jeffrey Trent is President and Scientific Director of the recently formed Translational Genomics Research Institute (TGen) in Phoenix, Arizona. He was formerly the Scientific Director of the National Human Genome Research Institute (NHGRI) at the National Institutes of Health (NIH), and also served as Chief of its Cancer Genetics Branch. Dr. Trent has received his undergraduate degree from Indiana University, and received his masters of science and Ph.D. degrees in genetics from the University of Arizona.

Conclusion

We have a distinguished panel of witnesses before us today. I am interested in examining with them how to make the nation safer through a medically based bio-attack detection and warning system, which could detect and monitor infections from biological attacks and quickly communicate the results across the country. Rather than attempting, at great cost, to set up sensors across the nation, which many believe would not be feasible, Project Zebra would quickly determine whether symptoms of patients presenting themselves to emergency rooms were the result of normal diseases or from biological agents.

The Secretary of Homeland Security, Tom Ridge, recently said that the "potential catastrophic consequences that the use of a biological weapon could have on our country obviously makes it a critical vital area of . . . homeland security concerns."[3] And the Deputy Secretary of Defense recently said:

> [T]he American people must appreciate the magnitude of the danger that we face from possible biological terrorism. The threat is real. It is deadly serious. As horrible as it was to have thousands of innocent Americans killed on our own territory on that tragic day, that is nothing compared to what terrorists could do with the biological weapons that we know they have been actively seeking. In many ways, biological weapons may be ideally suited for the methods and purposes of terrorists. A mass attack with anthrax or some other biological agents could bring about civilian casualties and catastrophic damage to our economy on a scale far beyond even that which we experienced on September 11th, as devastating as that was.[4]

These comments are chilling — but they drastically point to the need for technology, such as the one being developed by Project Zebra, that will help the nation detect and respond to a bio-terrorist attack.

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[3] Tom Ridge, April 28, 2004, at http://www.defenselink.mil/transcripts/2004/tr20040428-depsecdef1383.html.
[4] Paul Wolfowitz, April 28, 2004, at http://www.defenselink.mil/transcripts/2004/tr20040428-depsecdef1383.html.

Statement
United States Senate Committee on the Judiciary
Project Zebra: Rapid Bio-Terrorism Detection and Response.
May 11, 2004

The Honorable Patrick Leahy
United States Senator , Vermont

Statement of Senator Patrick Leahy
Hearing Before the Subcommittee on
Terrorism, Technology & Homeland Security
"Rapid Bio-Terrorism Detection and Response"
May 11, 2004

Today's hearing focuses on the continued threat of bio-terrorism and the need for rapid detection and response. I remember holding what may have been the Senate's first hearings on these types of issues back in 1988, as Chairman of the Subcommittee on Technology and the Law. I said then that we cannot be complacent and assume that bio-terrorism and other sorts of techno-terrorism are never going to happen here. Now more than ever, we should assume just the opposite, and prepare ourselves accordingly.

This subcommittee last addressed this issue in November 2001, after a frightening experience here in our own Senate office buildings. Anthrax-laced letters were mailed to Senator Daschle and me, and to various news media personnel, leading to the first cases of infection, illness and death of Americans from the deployment of a biological weapon. Twenty-two Americans ranging in age from seven months to 94 years were stricken; five of our fellow Americans died. These were innocent victims, some just at work on the wrong day at the wrong time – reminiscent of so many others who fell victim to the September 11 attacks.

We in the Senate are still adjusting to the aftermath of the attacks. Just this past February, a ricin scare announced by Senator Frist shut down some congressional offices for as much as four business days. We then learned that there had been other ricin attacks at the White House and elsewhere. Though we continue to learn and to implement increased security measures in our workplaces, we sometimes feel as vulnerable as ever.

As we continue our struggle to be safe and free from threats of terrorism, it is important that we not allow these victims to become forgotten casualties of terror. This past October, I introduced the Anthrax Victims Fund Fairness Act of 2003, with my good friends Senators Daschle, Lautenberg, Nelson of Florida, Feingold, Corzine, Mikulski, and Sarbanes. The bill would allow the victims of the anthrax attacks in 2001 to seek help through the September 11th Victims Compensation Fund to pay for medical expenses and to provide for themselves and their families if they have been unable to return to work. The perpetrator or perpetrators of these acts of terrorism remain at large, as the FBI continues its investigation. Though justice will have to wait for these victims, they should not have to wait for Congress to act.

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STATEMENT OF:

HARVEY W. MEISLIN, MD FACEP
PROFESSOR AND CHAIR, DEPARTMENT OF EMERGENCY MEDICINE
UNIVERSITY OF ARIZONA HEALTH SCIENCE CENTER

BEFORE THE:

COMMITTEE ON THE JUDICIARY
UNITED STATES SENATE US SENATE

CONCERNING

TERRORISM, TECHNOLOGY AND HOMELAND SECURITY

PRESENTED ON:

May 11, 2004

STATEMENT OF:

HARVEY W. MEISLIN, MD FACEP
PROFESSOR AND CHAIR, DEPARTMENT OF EMERGENCY MEDICINE
UNIVERSITY OF ARIZONA
BEFORE THE COMMITTEE ON THE JUDICIARY
UNITED STATES SENATE

MAY 11, 2004

Good morning Chairman Kyl, Senator Feinstein and Members of the Committee. Thank you for the opportunity to appear before you to discuss challenges facing the United States medical system in light of the new potential for terrorist attacks at home.

CURRENT STATUS

Today, in the United States, the first physician point of contact for acute medical crises, 24/7, is the local Emergency Room (ER). ER care has become an essential community service providing front-line health care for injury, illness, local disasters, and even terrorist attacks. The ER safety net not only delivers medical care but coordinates disaster planning, medical direction of pre-hospital emergency medical services (EMS), poisoning and infectious disease management, and public health surveillance.

ERs across our country are in crisis and this safety net is collapsing. Over 1/3 of our population seeks care at an ER (114 million visits annually). Over 10% of our

population accesses the 911 system annually. In spite of this, from 1988 – 1998 over 1,128 ERs have closed. ERs today are over-crowded, understaffed, have almost no surge capacity to handle mass casualties, are lacking in diagnostic tools and medical training, and yet remain the front-line medical safety net for communities throughout this country.

To prepare for terrorist threats, we have put considerable resources into the federal response and the public health system. However, little effort has been paid to the place where victims will actually be cared for, the local ER. During times of medical crisis, as in the Tokyo subway sarin attack in 1995, victims went to the local hospital ERs well before local emergency medical systems could bring them. In the United States the public health system is better prepared to identify victims of disaster and terrorism; yet ERs lack the capacity to care for them. Likewise, realistic simulations have demonstrated that in the event of a bioincident, local capabilities are ill-informed and lack the tools necessary to coordinate with the federal response system.

Hospital-based ERs lack the education, diagnostic tools and therapeutic resources to care for victims of a terrorist attack. Emergency physicians and nurses have existing training requirements that already strain the system, yet contain almost nothing regarding chemical, radiological, or biological attacks. Even today, there is no approved or standardized body of educational content in this area.

I can tell you that most physicians charged with caring for the acutely ill and injured had little knowledge about the diagnosis and management of anthrax before the fall of 2001. Likewise, physicians knew almost nothing about sarin before the Tokyo subway attack in 1995. The knowledge gained from these isolated events is fading as most physicians believe they will never care for patients exposed to these toxic materials.

There is a disconnect from what is happening in the basic sciences and research, and the application of this new knowledge on the front lines of medical care. The gap between scientific discovery and what is applied at the bedside widens everyday. As you will hear today, techniques and skills that currently exist at the bench research level have the ability to identify normal versus abnormal pathogens based upon either their genomic expression or the human response to that pathogen. Yet few of these innovations have made their way to the front line of patient care, in the ER and EMS systems, where critical life and death decisions are constantly made.

CHALLENGES:

Medical aspects of an effective biodefense require:

- *Education and Training:* Physicians and first-line medical responders must receive training in the medical management of victims exposed to hazardous materials and toxic terrorism events including:

- *Toxicodynamics*: the study of the cellular and molecular mechanisms of action of a poison, *"What the poison does to the body."*
- *Toxicokinetics*: the study of the absorption, distribution, metabolism and elimination of a poison, *"What the body does to the poison."*
- *Identification and Medical Management of Hazmat and Toxic Terrorism Victims:* using the standardized Poisoning Treatment Paradigm.

➢ *Prevention*: identifying and removing perpetrators and bioweapons before an incident

➢ *Intervention*:

- *Early alert and warning:* This must occur at the local, regional and national level. Faster diagnosis of the cause of a bioattack saves lives.
- *Rapid medical diagnosis and treatment:* Diagnostic tools that identify pathogens, normal, abnormal and weaponized, are within our grasp. These diagnostic tools have an immense value for our citizens in peace time and at war. Faster diagnosis helps contain the event and accelerates treatment. Who will make the diagnosis of a smallpox victim at 3:30 AM? It will be an Emergency Physician.
- *Availability of vaccines and suitable drugs:* We need these therapeutic agents, as well as the training, to know who to treat,

who not to treat, how to treat, and how to identify appropriate responses and complications to therapy.

FUTURE DIRECTIONS:

- *Education and Training*: The likelihood that many of our front-line medical personnel will face a terrorist event is small. The chance that they will face a local hazardous materials event is very likely. Just as we have trained our nation's medical community to respond to sudden cardiac events via the American Heart Association's *Advanced Cardiac Life Support (ACLS) program* and respond to traumatic injuries with the American College of Surgeon's *Advanced Trauma Life Support (ATLS) program*, we should do the same to provide for the medical management of victims exposed to hazardous materials events including toxic terrorism. These life support programs, such as ACLS and ATLS, have to be retaken or refreshed every few years so medical personnel stay current with state-of-the-art diagnoses and treatment. Similarly, the advantage of having one interdisciplinary training program focusing on the medical management of patients exposed to hazardous materials and toxic terrorism incidents is that it has use in situations that occur regularly in every community (e.g. chemical spills, pesticide exposures) during peacetime yet also prepares medical professionals for toxic terrorism and bioterrorist attacks.
- *Intervention:*
    - *Early alert and warning:*

- On the front line of medical care, we must create an ER surveillance and communication System. We need to know what others are experiencing and keep a surveillance database both as an interventional and preventative strategy.
- Local, regional and national information should be shared to aid in the diagnosis and treatment of victims including issues such as quarantine, public health, patient privacy concerns, public information, and crowd control.
- Telemedicine capabilities across the nations could enhance medical care on the front lines, especially in rural areas.

➢ *Rapid medical diagnosis and treatment:*

- Rapid high-performance diagnostic tests must exist throughout all major communities and risk-prone areas.
- Research is needed to quickly and accurately identify pathogens at the bedside. In the event of a bioattack, we cannot wait 2-3 days for a culture result to come back. We need diagnostic tools that rapidly identify natural and weaponized biopathogens. Clinicians on the front lines of medicine need to work closely with the researchers on the cutting edge of science who can identify the genomic expression of a toxin and the body's response to such a poison. Likewise researchers need to understand the clinician's environment, especially one as

complex as the ER, so researchers can rapidly develop front-line applications of their research.

- Diagnostic tools need to be simple for the user and specific for the pathogen. These devices must be able to identify a broad array of offending pathogens (e.g. viruses, bacteria, fungi), differentiate the routine from the rare (chickenpox vs. smallpox), and alert us when pathogens are weaponized.

➢ *Availability of vaccines and suitable drugs*

- Identification of appropriate vaccines, antibiotics and other treatment modalities and their sensitivities to the offending pathogen must be swift and accurate.
- Vaccines and suitable drug stockpiles needs to be available and easily obtained at the local ER and EMS system.

POLICY RECOMMENDATIONS:

1. Promote a standardized interdisciplinary training program, such as the Advanced Hazmat Life Support program (AHLS), sponsored by the American Academy of Clinical Toxicology and the Arizona Emergency Medicine Research Center, that are specifically designed to teach physicians, nurses and other medical personnel the medical management of patients exposed to hazardous materials incidents, including toxic terrorism.

2. Develop a national telemedicine communication system among the country's ERs to coordinate surveillance, communication and medical care and link that system to relevant Federal and State agencies.
2. Fund specific programs that will develop diagnostic tools for the rapid identification of routine, rare, and weaponized pathogens.
3. Create funding programs to improve collaborations between clinicians and basic science researchers to enhance epidemiological data collection and accelerate development of diagnostic tools to use on the front line of medical care.

CLINICAL SCENARIO:

Today:

It's February in the height of flu season and a young college student walks into the ER complaining of a severe headache, stiff neck, fever and the inability to keep down food since her return from the Far East. The treating physician suspects meningitis and does a spinal tap and submits the fluid obtained to the lab for a culture that will take 2-3 days for results.

The physician knows that there are two types of meningitis, viral and bacterial but is also concerned because the newspaper reported West Nile virus in his state, SARS in the Far East, and concern of a bioweapon similar to equine encephalitis. The course and threat of each is very different, but the ability to distinguish between them is outside his immediate capability. The physician has no choice but to assume the worst, quarantine the patient, her dormitory, and the

ER. He then initiates a shotgun approach of expensive antiviral and antibiotic agents, notifies local, state, and federal public health authorities, and initiates a series of decisions that imposes significant additional burdens both on the healthcare system and on the individual, her family, and close contacts. A nationwide investigation occurs to identify a potential bioweapon and/or rare or emerging pathogen. After several days, the patient recovers uneventfully with a diagnosis of viral meningitis and is discharged. The cost, in direct and indirect resources, is close to a million dollars and thousands of man-hours.

Tomorrow:

It's February in the height of flu season and a young college student walks into the ER complaining of a severe headache, stiff neck, fever and the inability to keep down food since her return from the Far East. The treating physician suspects meningitis and does a spinal tap and submits the fluid obtained. The physician knows that there are two types of meningitis, viral and bacterial but is also concerned because the newspaper reported West Nile virus in his state, SARS in the Far East and there has been some concern of a bioweapon similar to equine encephalitis. A micro array genomic analysis of the spinal fluid is performed and the offending pathogen is quickly identified as this year's adenovirus, an agent commonly seen among college-age students. Knowing it is viral meningitis; he treats her with fluids and anti-emetics and discharges her from the ER three hours later. He communicates on the national ER

communication system that he has seen another case of viral meningitis. Her hospital bill is a few hundred dollars.

SUMMARY:

ERs today are over-crowded, understaffed, have almost no surge capacity to handle mass casualties, are lacking in diagnostic tools and medical training, and yet remain the front-line medical safety net for communities throughout this country.

Today the medical systems in this country simply are not prepared to diagnosis and respond to a common pathogen, while concurrently ruling out a bioterrorist pathogen or a rare, emerging natural but potentially lethal pathogen. Another vulnerability in our system is the very uniqueness of the events under consideration. We all hope that a bioterrorist attack will never happen. Yet, in some ways, the very fact that it is rare makes its successful implementation more likely. Today we train individuals after an event occurs; and by the time the information is needed again, the training is stale and often the personnel have moved on to another environment.

Tomorrow, we can obtain a true war dividend. The same tools, training and reporting systems that can be developed to diagnosis the biopathogen or rare, emerging natural pathogen have the capacity to improve the care of patients every day, in every hospital and medical office in this country. They can truly

reduce patient costs as well as patient time away from work and school. Of even more importance is that the everyday use of such tools and reporting assures that when the unexpected does occur, the same tools and procedures will be used because they have also become routine and have a proven importance to individuals and the healthcare system.

As you have and will hear from my colleagues, the science and technology necessary to accomplish these goals is within our grasp. This is not an academic exercise. We can develop these tools and achieve a level of practicality that will be valued everyday by the individuals treated in the healthcare system.

Mr. Chairman, thank you for allowing me to participate in this important hearing. I hope that we will be able to develop a process where researchers and clinicians work together to create and deliver educational programs, medical devices and diagnostic tools and a communication system that will help the citizens of our country in our war on terror as well as in everyday life.

I would be pleased to answer any questions you may have. Thank you

STATEMENT OF DAVID A. RELMAN
ASSOCIATE PROFESSOR, STANFORD UNIVERSITY

BEFORE THE

COMMITTEE ON THE JUDICIARY
SUBCOMMITTEE ON TERRORISM, TECHNOLOGY & HOMELAND SECURITY
UNITED STATES SENATE

CONCERNING

EARLY RECOGNITION AND MANAGEMENT OF INFECTIOUS DISEASES: HARNESSING THE HUMAN GENOME IN AN ERA OF NEW AND EMERGING BIOLOGICAL THREATS

PRESENTED ON

MAY 11, 2004

STATEMENT OF DAVID A. RELMAN, MD
ASSOCIATE PROFESSOR OF MICROBIOLOGY & IMMUNOLOGY,
AND OF MEDICINE
STANFORD UNIVERSITY
BEFORE THE
COMMITTEE ON THE JUDICIARY
UNITED STATES SENATE

May 11, 2004

Good morning Chairman Kyl and Members of the Committee. Thank you for providing me, and others at this table, the opportunity to appear before you today and discuss a new and rapidly developing area of science that may revolutionize the way we detect and manage disease caused by emerging and unanticipated infectious agents. I am an infectious diseases clinician and a researcher based at an academic medical center whose interests are in the discovery of novel pathogens, the study of human microbial ecology and the use of genomic techniques for these purposes. I am also a member of the Board of Directors of the Infectious Diseases Society of America.

Introduction: Persistent difficulties in the diagnosis of infectious diseases

Disease-causing microorganisms were recognized and identified more than one hundred years ago. Methods for cultivating bacteria and viruses have been available since the early or mid twentieth century, and are widely established in clinical settings. These statements would therefore understandably lead one to believe that in today's clinical work-place the ability to diagnose human disease caused by microbial agents is well-established and reliable. However, this is not the case. Carefully-performed studies of various clinical syndromes suggestive of an infectious etiology fail to identify a possible microbial causal agent in more than 50% of cases. An investigation by CDC and academic scientists of unexplained critical illnesses and deaths with features strongly suggestive of infection found that all of the cases subsequently diagnosed using state-of-the-art laboratory methods were caused by well-known microbial agents which failed to be detected with routinely-available tests. Furthermore, even when infectious disease agents are successfully identified, the answer often arrives late in the course of the illness, after the patient has either recovered or succumbed.

There are multiple reasons for this unsatisfactory state of affairs, including a heavy reliance on cultivation techniques (these techniques are often insensitive), difficulties in obtaining clinical specimens from an appropriate patient site and at an appropriate time (such that one can expect the agent to be present in the specimen), and the inherent delays and lack of specificity in many of today's

diagnostic approaches. It is important to emphasize that the clinical features of different serious systemic infections often look identical to both the health care provider and the patient in the earliest phases of the disease. The consequences of this poor diagnostic capability in infectious diseases are profound. Clinicians are often compelled to institute antibiotic treatment in a broad, empiric manner without a definitive diagnosis, despite the fact that in many cases, a different or more specific drug would have indicated had the infectious agent been known. In addition, for many cases, antibiotics are inappropriate altogether because the causative agent is a virus, or the condition is not caused by an infectious agent at all. As a result, patients suffer from delayed or sub-optimal treatment, and the prevalence of antibiotic-resistant bacteria grows inexorably.

How the unraveling of the human genome sequence has presented a set of unprecedented opportunities

The best clinicians are known for their ability to listen carefully to the patient and extract subtle clues as to the correct diagnosis. We are now in a position to be able to "listen" to patients in a manner that is far more sensitive and comprehensive than any method has previously available. This capability has been enabled by the deciphering of the human genome sequence. One new approach that I wish to describe to you is based on highly-parallel measurements of human gene expression and the analysis of these patterns of expression, using a tool called a DNA microarray.

Although we all share the same set of genes, there is a great deal of variability over time within any individual, and between individuals, in how we use our genes. Each gene provides the blueprint for production of a protein. At times when a protein is needed, the corresponding gene is "activated" to make (express) copies of its own specific messenger RNA (mRNA), which then serves as the template for protein synthesis. When the protein is no longer needed, the gene is "repressed", its specific mRNA is no longer made, and the abundance of this mRNA decreases. DNA microarrays are high density arrays of DNA probes that are each specific for a different gene and its mRNA. These probes capture their target mRNA in a specific and reliable manner. If the starting pool of mRNA in a specimen is labeled with a fluorescent dye, the captured mRNA molecules can be detected bound to their matching probe on the microarray using a laser. By scanning a DNA microarray with this laser one can quickly measure the abundance of mRNA bound to each probe, and hence the amount of mRNA present in the specimen for each human gene. Thus, a human DNA microarray can be used to monitor the degree to which each and every human gene was active (being expressed) within any given patient specimen at the moment the specimen was obtained. Genes are activated and repressed on a minute-to-minute basis in response to environmental cues. Each gene responds in a unique manner to different stimuli. One can view the human genome (our complete collection of genes) as a living, dynamic entity! If we could learn to recognize the various patterns of gene expression associated with specific kinds

of stimuli, such as disease caused by different microbial disease-causing agents, we might be able to "read" this form of host response and diagnose infectious diseases at the earliest stages of development.

The analysis of human gene expression patterns in clinical specimens ("gene expression profiling") began about 5-7 years ago. The vast majority of these analyses, so far, have focussed on the study of human cancers, and the results have been impressive. To summarize a growing body of published data, expression profiling has been used successfully to diagnose various forms of cancer that could not be otherwise diagnosed, and to predict patient clinical outcome (favorable or unfavorable course, response to therapy, etc) when these predictions could not have otherwise be made. In addition, novel, critical mechanisms of cancer have been deduced from these expression patterns, which in turn have led to the development of novel effective therapies. It should be mentioned that the same kinds of new insights have been gleaned from a different type of genomic analysis: instead of analyzing patterns of mRNA abundance, patterns of protein expression have been measured directly. Additional details of this work will be presented by the next discussant in this session.

The application of gene expression profiling to infectious diseases, and to related diseases caused by biological agents (e.g., toxins), is still in an early stage of exploration. However, early findings are encouraging. It appears that these profiles differ in the blood of different sick patients as a function of the specific disease-causing agent, thus, indicating that humans do discriminate between different infectious agents at the level of gene expression patterns. Gene expression profiles in the blood of healthy persons also differ between individual but much less so than in disease; however, these lesser degrees of variation may be sufficient to reveal important physiological differences between individuals. At the same time, there are inadequate data with which to determine the level of resolution offered by these patterns in the identification of a causal infectious agent. And while we expect that patient outcome might well be predicted one day based on these patterns, we do not yet have enough experience to identify and recognize prognostic "signatures" in a wide spectrum of different humans.

What is needed?

One of the most important needs for advancing this technology application is a much more extensive, well-annotated set of expression profile data from diverse individuals at varying stages of different infectious diseases, and after exposure to a wide variety of different biological agents. While it may not be possible to collect many (or any) specimens from humans after exposure to agents that are important bio-threats in the context of malevolent use, but uncommon causes of disease in a natural setting, it may be possible to collect relevant data from surrogate non-human hosts in an experimental laboratory setting. Furthermore, it

will be critical to collect a large amount of additional data from humans exposed to agents that cause clinical syndromes close to, or indistinguishable from those caused by bio-threat agents, both before and after onset of clinical findings. One goal will be to recognize critical disease processes during the incubation period, prior to signs and symptoms, or else during an early clinical stage when the patient has mild, nonspecific signs and symptoms, and is not yet debilitated. In order to acquire these large, new sets of data, coordinated multi-center clinical studies will be needed. Standardized methods and tools will be needed in order that the resulting data from different subjects at different geographic sites and at different times, are comparable.

From these expanded clinical studies we will learn how and where gene expression profiles can be applied for early detection and prognosis of infectious diseases. Candidate signatures will be identified, and will then need to be validated with independent sets of clinical specimens and patients. This effort should ideally be an international venture, with the goal of identifying signatures that are useful for human populations of diverse origins. Other needs include the development of more automated methods and miniaturized devices for measuring gene expression patterns and other genomic patterns that reflect human response to disease. Blood may not be the most appropriate type of specimen for large scale monitoring of human populations; thus, the utility of other specimens types, such as saliva and urine, should be explored. Finally, it is expected, but necessary that this technology become less expensive.

Future prospects for the use of gene expression profiling in defense against the threats of biological agents to human health

The impact of gene expression profiling on our management of individuals with possible exposure to a bio-threat agent, who might be in the earliest phase of a potentially serious illness, may be enormous. The potential value of this approach includes early indication of an imminent important illness, such as a serious infectious disease of either natural or malevolent origin. This indication may be provided before the onset of significant signs and symptoms, and might contain specific information about etiology and the likely future clinical course for that individual. Microbial agents with disease-causing capabilities often colonize humans without inducing disease. By examining the response pattern of the host (i.e., is the host "perturbed?") one can establish whether the presence of the microbial agent is clinically significant. Thus, in the setting of a large disease outbreak, a diagnostic gene expression signature might distinguish the many-fold greater numbers of "worried-well", from the otherwise indistinguishable people with incipient serious infectious disease. The latter would then be able to receive early, specific treatment, thereby directing what might be scarce health care resources to those in true need. These early diagnostic patterns would also provide valuable information to those responsible for coordinating and planning emergency medical care on a regional or national level.

Gene expression profiling and other genome-wide measurements of human response to disease should be viewed as complementary to more traditional approaches based on direct detection of the infectious agent. We may discover that human gene expression patterns lack the degree of microbiological specificity provided by direct microbial detection approaches. This weakness will probably be most evident when the goal is a forensic one and focussed on establishing attribution. Concerns about maintaining privacy that are raised by genomic approaches such as this must also be addressed. On the other hand, one advantage to host expression profiling that has not been mentioned so far is its ability in theory to identify hosts who have been affected by novel, genetically-engineered microbial agents. This broad degree of "coverage" across the biological "threat space" is a strong relative advantage for the host response approach. Other potential uses of this approach might include the discovery of novel early markers of host protective immunity following immunization. By using a host expression pattern as a surrogate indicator of protection, new vaccines against bio-threat agents might be developed and tested much more effectively.

At some point in the future, one might imagine a system that would permit minimally-invasive routine monitoring of each person's genome-wide response pattern, perhaps on a daily basis. The establishment of a individual-specific baseline would maximize our ability to recognize significant events at a pre-clinical stage, and alert the individual to seek medical attention, as well as alert the health care system to early signs of a more widely-distributed problem.

Conclusion

We stand on the verge of acquiring novel capabilities for recognizing and characterizing disease caused by a wide variety of biological agents at an early phase of the illness. These capabilities are brought about by discoveries and advances in the field of genomics. Clinicians and other point-of-care providers desperately need these kinds of capabilities. In order to bring to fruition the promises raised by these advances, we will need to address important, as yet unanswered scientific questions, conduct carefully-designed large-scale clinical studies, and promote further maturation of the associated technology. I would be pleased to answer any questions you may have.

Statement of Dr. Jeffrey Trent
President and Scientific Director
Translational Genomics Research Institute
Before the
U.S. Senate Committee on the Judiciary
Subcommittee on Terrorism, Technology and Homeland Security
Concerning
Rapid Bio-Terrorism Detection and Response

May 11, 2004

Good morning, Chairman Kyl, and Members of this Subcommittee. My name is Dr. Jeffrey Trent, and I am the President and Scientific Director of the Translational Genomics Research Institute in Phoenix, Arizona. Prior to my move to Arizona 18 months ago, I served for nearly a decade as the Scientific Director of the Division of Intramural Research of the National Human Genome Research Institute of the National Institutes of Health in Bethesda, Maryland. I wish to thank the members of the Subcommittee and particularly Chairman Jon Kyl for inviting me to testify at this hearing today.

Today's panel of speakers has clearly outlined the dangers posed by a biological outbreak and the ability of modern technology to work toward addressing shortcomings of our early detection and treatment capabilities. In my brief comments I will discuss how one can examine the "injury response" to radiation in much the same way that one examines a response generated by an infectious agent. I commend the Subcommittee for your willingness to hear from representatives of the medical and scientific community about this serious and important issue. All of us at the table, as well as research scientists across the country, stand ready to work toward addressing solutions of our early detection and treatment capabilities.

I would like to address two additional key points for your consideration. The first is the critical need for supporting approaches to implement a comprehensive and effective end-to-end solution. Second, I will provide a brief description of work [a collaborative partnership between my laboratory and the National Cancer Institute (headed by Dr. Albert Fornace) and his former assistant, Dr. Sally Admundson (now of Columbia University] that when joined to other work from scientists in the US and elsewhere, is beginning to suggest that the activity of the genes of an individual may serve as biomarkers for radiation exposure. Our cooperative studies indicate that genomics-based measurement of injury responses to specific toxic agents, like ionizing radiation, can be used to develop signatures for exposure.

History tells us that for the case of a biothreat agent, pre-exposure detection is not likely to be feasible in every instance. As described by Dr. Meislin, we will likely be presented at the time of a bio-threat crisis with sick and dying people or animals. For this situation the answer will lie in how quickly we can detect and identify these early cases.

Also, as you have also heard today from both Dr. Keim and Dr. Relman, the answer will also lie in new approaches to develop cost-effective diagnostic tests that can reliably separate bio-threats from the background of "noise," thus distinguishing "genetic signatures" of the common cold/flu that may cause similar initial clinical symptoms to those of a weaponized bio-agent.

While our focus must appropriately be on biologic attacks that threaten our safety, fears of a possible "dirty bomb" detonation or similar situation have spurred interest in the search for biomarkers that could be used to rapidly assess radiation exposure status in large, potentially exposed, populations. With the September 11 terrorist attack and subsequent anthrax attacks, it seems more than a topic popularized for science fiction that a radiation-threat could result in a chilling scenario for the US or other nations who may be targeted.

Mr. Chairman, for nearly 20 years, I have worked to create and utilize tools and techniques to identify the genetic signature of killers. I have worked on reading the fingerprints of such killers as breast cancer, leukemia and malignant melanoma. While at the NIH, I also worked on identifying the genetic signatures, or what is known as the molecular fingerprint, of killer viruses such as HIV, human T-lymphotropic virus type 1 (HTLV-1), human herpesvirus 8 (Kaposi's sarcoma-associated herpesvirus) and, in collaboration with investigators at Ft. Dietrich, the dreaded Ebola virus. Also outlined by this panel today is the progress in surveying the response of the individual infected (the host) to provide a recognizable "molecular fingerprint" separating a naturally infecting virus, as an example, from bioweaponized strain of anthrax.

It is also important for this Subcommittee to be aware of similar progress, albeit preliminary in nature, of emerging work that is beginning to recognize that a "radiation-associated" gene response signature could be incorporated into a biomonitoring approach similar in design to that just described for biothreat-agents. Picturing the near-future, one can see the identification of sets of genes which once proven informative, could be incorporated into rapid assays (utilizing such techniques as nanotechnology and protein and gene expression analysis) performed on an easily biopsied tissue such as blood, and which could become part of a gene induction profile that could serve as an indicator of both an individuals' rate of exposure as well as their absolute dose of radiation (part of the collaboration between my laboratory at the NIH and the National Cancer Institute).

Recently my laboratory at TGen also joined forces with investigators at the DOD funded "National Functional Genomics Center" at the H. Lee Moffitt Cancer Center in Tampa, Florida to investigate protein markers of radiation response as well. By performing molecular signatures of patients undergoing cancer treatments with radiation therapy, we can establish a diagnostic profile using both genomics and proteomics that will be characteristic of someone exposed to radiation.

While there is hope that we may be able to utilize diagnostic testing to identify a biothreat or radiation-associated genetic signature, I remain convinced that the most important

thing I can emphasize today is the need for an end-to-end solution that pushes forward early detection, focusing on the reality that early detection is the key to faster diagnosis.

This faster diagnosis will:

•Save lives;

•Optimize treatment selection; and,

•Enable the rapid triage of at risk populations which will provide the vital goal of reassurance to the (potentially exposed) "worried well" (thereby reducing the risk of public panic).

To achieve this goal of early detection, several critical elements must be in place, and a "systems-based" approach is essential to addressing the problem. The failure to develop any one of the four will not address the critical needs in biodefense or result in improved public health and safety. These elements include:

- **Molecular Signatures:** Gene and protein sequencing of selected pathogens; detection of genomic, proteomic, and phenotypic signatures of the host immune response; and the creation of unique markers radiologic as well as a broad range of biothreat agents.

- **Diagnostic Platform:** Incorporating the signatures into a low-cost diagnostic platform suitable for routine patient testing in a variety of clinical settings.

- **National Information Architecture:** An integrated collection of data, syndromic surveillance, reliable anomaly detection, and real-time alerting of local and national decision-makers that a bioincident has occurred and permit real-time assessment of incident progression and the effectiveness of containment actions. And,

- **Decision Support Systems:** – An infrastructure linking key decision-makers with relevant medical and public health authorities to ensure rapid launch of optimum treatment protocols, rational allocation of drugs and vaccines, and comprehensive incident containment actions.

Chairman Kyl and Members of the Subcommittee, as stated today by this panel of scientists and physicians, currently health providers do not have all of the necessary tools to distinguish between an infection caused by a bio attack and that caused by the average cold. They must rely on a series of sequential and intuitive actions that in some cases could delay mobilization of prompt responses.

Further, in the case of a "dirty bomb," to aid in the triage of patients, biologic tests could help provide information on an individuals' radiation dosage. The requirement that I

personally believe could be of great benefit would be the pursuit of a purposeful end-to-end solution of the aforementioned system elements, something that will require an obligate demand for public/private partnerships.

These factors and more have compelled me to join my colleagues, including Dr. George Poste, Director of the Arizona BioDesign Institute at Arizona State University, and Dr. Paul Keim, in a consortium involving Arizona State University and Northern Arizona University, linked with Dr. Michael Tracy and his team at the Stanford Research Institute, International in Menlo Park, California, in the development of a project called the "Project Zebra," which can be part of the solution for this complex problem, allowing faster mobilization of all relevant incident management actions as the key piece in early detection.

In closing, I would like to thank Chairman Kyl for convening this hearing on an extremely critical subject matter and offering me the opportunity to testify before your distinguished Subcommittee. I would be pleased to answer any questions you may have. Thank you.

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