Testimony before the
Bioterrorism and Public Health Preparedness Subcommittee
Committee on Health, Education, Labor, and Pensions
United States Senate

"Biodefense: Building a Medical Countermeasure Capability"

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A Statement by

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Mr. Chairman and Members of the Subcommittee:

I appreciate the opportunity to appear before you to day to discuss the capacity to generate medical countermeasures against biological weapons and bioterrorism. I am currently serving as Senior Fellow in Science and Security in the Homeland Security Program at the Center for Strategic and International Studies here in Washington. I also teach a course on science, technology and homeland security in the Security Studies Program at Georgetown University's Edmund A. Walsh School of Foreign Service. I have been working in the area of science, technology, and security policy for more than twenty years and have been studying biological weapons issues and responses for nearly 15 years.

At CSIS, my colleagues and I are launching a major international effort, supported by the Carnegie Corporation of New York and the John D. and Catherine T. MacArthur Foundation, to look broadly at biological weapons threats and to identify opportunities to counter them at all stages, from influencing the intent to produce weapons, to denying access to materials and expertise, to detecting illicit programs, to managing the consequences of an attack. We are also looking at perceptions and threat reduction activities across nations and across professional communities. The activities to be addressed at today's hearing are an important part of the United States' – and the world's – response to biological weapons threats.

At CSIS I also organized a workshop to examine the global evolution of dual-use biotechnology, looking specifically at the implications of this evolution for the spread of biological weapons and bioterrorism capabilities. The report for this workshop is in press (1).

I'd like to spend some time this morning discussing aspects of the bioterrorism threat, what they imply for our ability to counter them, and some high priority actions we need to take as a result. Let me set out the following points:

1) Bioterrorism is a very serious threat, but the details of future biological weapons cannot be known today. Although certain diseases currently pose more serious terrorist threats than others, a wide variety of agents might nevertheless be used, and the exponential growth and dissemination of biotechnology will foster the creation of new ones. Since the time to develop and produce bioweapons agents is, in general, much shorter than the time to develop, license, and produce a response, we cannot rely on hard intelligence alone to direct the development of countermeasures.

2) Uncertainties about the future threat put a premium on breadth of capability and speed of response. Looking ahead, the most important medical countermeasures are new "broad spectrum" antibiotic and antiviral drugs and other post-exposure therapies. Traditional vaccines have only a limited role in civilian biodefense, because of the time they need to develop protection; we cannot vaccinate our way out of this problem.

3) Substantially increased NIH biodefense research and the new Bioshield program are necessary components of our national response, but they are insufficient. Further incentives are needed to stimulate production of post-exposure therapeutics and rapid response capabilities, for which we need new research tools and methods. We also need

to develop animal models for human disease and increased animal production and testing capacity.

4) Successful incentives that foster biodefense missions could benefit commercial enterprise as well, because many of the necessary supporting capabilities are inherently generic. Policies that attempt to ensure that government incentives or investments apply only to government biodefense missions – as the original version of the first Bioshield legislation attempted to do – are guaranteed to fail at fostering a dynamic, responsive, and flexible biodefense response capability.

5) Medical countermeasures are very important, but they are only one component of a comprehensive biodefense strategy. Countering bioterrorism also requires efforts to dissuade, frustrate, detect, and counter bioterrorism programs at every possible stage of their planning and execution, not just after an attack has been conducted.

Characteristics of the Bioterrorist Threat

Importance of Taking the Threat Seriously. As members of this subcommittee no doubt know, history is a poor guide to the bioterrorist threat. There are few areas with so great a gulf between the proven, historical capability to do grievous harm, and the relative paucity of actual attacks. We know for sure that biological weapons, when prepared for effective dissemination in large enough quantities, can kill over large areas. All the necessary capabilities to place many thousands of lives at risk were demonstrated decades ago. We know that the technology, materials, and expertise required to produce biological weapons are available to those terrorists who are sufficiently motivated and skilled to pursue them; essentially all the equipment, materials, and expertise have legitimate application or can be found without great difficulty. And we know that enemies exist who are eager to kill Americans in vast quantities. What we are not sure of is why we have not yet been attacked in this way. Maybe not enough of today's terrorists took high school biology. Tomorrow's will – and their high school biology classes will be much more potent than today's. We cannot bet our country that whatever restraints have kept terrorists from pursuing this path will persist indefinitely.

Exactly how close terrorist groups are right now to the capability to conduct a major biological attack matters if we want to know how likely it is that such an attack will take place in the near future. However, looking out over the several years that our defensive preparations will take to implement, the details of today's threat are less important than the realization that the rapidly increasing capability, market penetration, and geographic dissemination of relevant biotechnical disciplines will inevitably bring weapons capabilities within the reach of those who may wish to use them for harm (see figure 1).

Difficulty in Predicting or Specifying Future Threats. Given the diversity of potential biological weapon agents and the increasing ability to modify or augment them, either through conventional techniques or genetic engineering, we will never be able to restrict our efforts to a short list of agents considered to be the most serious threats. It is true that certain agents today are considered to pose greater terrorist risks than others because of their combination of health

consequences and ease of dissemination. Moreover, a few diseases, such as smallpox and anthrax, pose such dangers that they are worth special attention (smallpox because of its lethality and contagiousness; anthrax because of its lethality and hardiness). However, a wide variety of agents could be used as weapons, and that list will grow over time as science advances, biotechnology spreads, and new capabilities become feasible.

Intelligence collection efforts will not provide a reliable guide for our biodefense activities. First, the "signatures," or observable signs, of a terrorist bioweapons development activity will be very difficult to detect, particularly amidst a large and rapidly growing background of legitimate biotechnical activities. Bioweapons programs do not require large, expensive, or distinct facilities, and we cannot have much confidence that we will spot them.

More serious is the significant mismatch in time scales between attackers and defenders. Unless we radically transform the way we do business – a scientific and technical challenge as much as a management or resource one -- our programs to design, develop, approve, and produce medical countermeasures will have lead times that are much longer than those of the terrorist weapons programs they are intended to counter. Today's defensive programs cannot be designed against today's threat but rather must anticipate the threat years in the future – posed by groups and programs that may not even exist today. Moreover, we are unlikely to be able to mount major countermeasures development programs covertly. Attackers will probably know what countermeasures we are developing and if possible, will work to evade them.

Implications for Biodefense

Role of Vaccines. Unavoidable uncertainties in the future biological threat place a premium on broad-spectrum, post-exposure therapeutics and rapid reaction capabilities. Traditional vaccines are less relevant, since they are only effective against specific diseases (and often only against specific strains), and because they generally generate immunity too slowly to be of much value if given after the fact. (Smallpox and anthrax vaccines are exceptions, because they have therapeutic value even if given after exposure.) Too many possible other disease threats exist for us to vaccinate our way out of the bioterrorism problem. And we are very unlikely as a society to decide to vaccinate large groups against potential bioterror agents in advance of any attack, since we would not be able to justify imposing the small but nonzero risk of vaccination when we have absolutely no way of knowing what harm – if any -- those vaccines will have avoided.

Novel vaccine approaches – such as so-called "DNA vaccines" – are very important because they offer the tantalizing prospect of mounting an immune response fast enough to have therapeutic value post-exposure. However, such vaccines are too speculative to be able to anticipate successful products, or to fit within the 8-year window needed to qualify for Bioshield I funding. Vaccine research might also lead to the development of antibodies to provide quick but temporary protection against a disease during the time needed for a more conventional vaccine to take effect. Even though these techniques would -- if successful – provide some "post-exposure" response capability, they would still be very specific towards particular diseases.

Need for Additional Antivirals and Antibiotics. Since traditional vaccines are of limited value in responding to an attack, we need antibiotics and antiviral drugs. However, despite their importance for dealing with natural disease outbreaks, let alone bioterror attacks, the development of such anti-infectives has been neglected by the pharmaceutical industry in favor of drugs to treat chronic conditions, such as hypertension, cancer, and heart disease. These conditions provide large and continuing markets, whereas most infectious diseases occur only sporadically, particularly in the developed world markets that can readily afford pharmaceutical products. The required course of anti-infective treatment lasts only a week or two, and if successful it clears up the problem – and eliminates the need for further business. Pharmaceutical manufacturers would rather devote their resources to drugs with larger and more lucrative markets -- and they would be punished by their investors if they didn't. (As a public policy researcher, I would love to be able to focus my attention on policy problems without considering the financial consequences -- but if I am not able to convince a funder to support my expenses and those of my institution, I'm not going to be in a position to work on that topic for long.)

A 2004 paper by UCLA researchers finds that, out of 506 new drug candidates that have been disclosed in the development programs of the largest pharmaceutical and biotechnology firms, only 31 represented anti-infectives: 6 antibiotics; 12 antiviral drugs to combat HIV; 5 other antivirals; 5 drugs to combat parasites; 5 to combat fungi; and 1 other. (2) This dearth of new anti-infectives in the pipeline is especially troubling given the rate at which naturally occurring pathogens are evolving resistance to existing antibiotics and antiviral drugs.

The Infectious Disease Society of America points out that infections that were once easily treatable are becoming "difficult, even impossible, to treat" today. More than 70 percent of the bacteria causing hospital-acquired infections are resistant to at least one of the drugs typically used to combat them. Resistance to multiple drugs is increasing, including resistance to vancomycin, a drug of "last resort." Only two new classes of antibiotic have been developed in the last 30 years, where a class represents those drugs that all utilize the same mechanism to kill bacteria or viruses -- and that are all subject to losing their effectiveness as soon as pathogens evolve the ability to evade that mechanism (3). A 1998 United Kingdom House of Lords report concluded that "antibiotic resistance threatens mankind with the prospect of a return to the pre-antibiotic era." (4) Clearly there is a critical need for new antibiotics and antiviral drugs not only for biodefense, but also to combat naturally occurring infectious disease.

Need for Research Tools, Methods, and Infrastructure. In the long run, we need a vibrant, flexible, and responsive biodefense system that can adapt to threats as they materialize. We cannot mount decade-length; billion-dollar scale vaccine or drug development programs to combat every potential threat agent. Therefore, we must develop research tools that can make a much more responsive system possible. Building such a system will be a tremendous challenge, and there are fundamental scientific questions that will need to be resolved. However, there will certainly be need for tools such as assays for rapidly screening drug candidates; improved methods for determining chemical and biological properties of drug candidates that can accelerate and/or replace certain stages of preclinical testing; bioinformatics approaches to identify promising drug targets; and a wealth of other approaches, including many that are undoubtedly yet to be envisioned.

A major component of this research infrastructure will be improved animal facilities and understanding. Given that many diseases of bioterror concern occur too rarely in humans to permit clinical trials, the Food and Drug Administration has specified that efficacy testing of drugs can be conducted in two different species of animals, rather than humans. However, the "animal models" utilized in these tests must be sufficiently well understood so that the drug's effect on the disease in those animals can be reliably related to how that drug would work against human disease. Development of these animal models; as well as the construction of animal facilities in which these animals can be bred and these tests can be conducted, is a critical biodefense need. Right now, shortages of animals, animal facilities, and animal models threaten to limit constrain research.

Existing Government R&D Programs and Incentives for Industry Are Necessary, but Not Sufficient

The Role of the National Institutes of Health. Substantially increased NIH biodefense research funding and the Bioshield program that was enacted last year are necessary components of our national response, but they are not sufficient to generate these post-exposure therapeutics and other essential components of a response to bioterrorism. Important parts of the problem remain unaddressed, such as the research tools and animal model issues described above.

Scientific investments made by NIH have driven the growth of the biotechnology industry over the last few decades, and the very substantial ($1.7 billion) increase in the level of annual NIH funding for biodefense research will improve our basic understanding of disease pathogenesis as well as lay the groundwork for the development of drug and vaccine countermeasures. These investments are also funding substantial increases in "high-containment" research facilities that allow scientists to work with dangerous organisms safely. In its traditional role of pursuing the most exciting and productive biomedical science, leaving industry to pick up and run with what it wants, NIH has been tremendously productive. However, this largely "bottom-up" approach is less well suited for a more mission-oriented, product-focused program to filling specific biodefense needs that involve product design and development, clinical trials, FDA approval, scaleup, and manufacturing. Industry's involvement in this process is critical.

NIH research investments will also be essential for bolstering the scientific underpinnings for improved research tools and methods. NIH has developed guidelines that are intended to ensure that research tools, materials, and other resources developed in the course of NIH-sponsored research become available to other investigators. However, it is not clear that these Guidelines are optimally designed to achieve that end, particularly on the scale that will be needed to support a robust, responsive biodefense capability. The working group that developed those guidelines found that "intellectual property restrictions can stifle the broad dissemination of new discoveries and limit future avenues of research and product development." (5) Although the group also found that "reasonable restrictions on the dissemination of research tools are sometimes necessary to protect legitimate proprietary interests and to preserve incentives for commercial development," (6) the resulting guidelines do not appear to give sufficient emphasis to the role that commercial firms play in improving,

standardizing, distributing, and marketing these tools – and to the corresponding ability that these firm must have to control the distribution of the resulting materials and recoup their investment. I hope that other witnesses at this hearing can provide further information on incentives that NIH and others can offer that will best facilitate the development and dissemination of research tools.

The Role of the Pharmaceutical/Biotech Industry. Pharmaceutical and biotech firms, on the other hand, have not in the past had much incentive to develop products for what are essentially government biodefense markets. Debate leading up to the passage of the original Bioshield legislation last year recognized the importance of engaging these firms, the barriers that had prevented them from participating, and the need to develop new incentives to engage them. Indeed, Congress has appropriated $5.6 billion dollars as of Fiscal Year 2004 to fund Bioshield purchases, and procurements using these new authorities are now underway. However, it is not clear that these existing incentives will be sufficient, for example, to motivate firms to increase their development of anti-infectives. Given how important it is to augment our existing antibiotic and antiviral arsenal for public health purposes as well as for biodefense, government incentives to stimulate their development – even ones that are not immediately applicable to biodefense -- would be appropriate.

The original Bioshield legislation also left gaps, such as the failure to provide liability protection for firms that develop medical countermeasures in good faith. The best available scientific and technical understanding notwithstanding, no vendor preparing products to mitigate the consequences of a terrorist attack can ever fully predict the circumstances under which those products would be used, let alone conduct fully realistic tests or evaluations. It will therefore be important to assure firms who are otherwise willing and able to produce medical countermeasures that the threat of product liability lawsuits will not put their survival at risk. An Institute of Medicine Committee that examined DoD's program to develop medical countermeasures against biological warfare agents concluded that "it is important for the government to address industry concerns about product liability risks as part of efforts to accelerate the development of medical biodefense countermeasures." (7) The SAFETY Act (part of the Homeland Security Act, Public Law 107-296) does provide some liability protection to manufacturers of products to counter terrorist attack, but it does not apply to products used in anticipation of such an attack, as many medical products might be. Nor does it provide compensation for those who may have been harmed by an antiterrorism product. Therefore, if liability protection is to be provided to shield vendors from unwarranted liability claims, some mechanism going beyond the SAFETY Act – and preferably one that provides compensation for legitimate claims -- must be provided.

Inadvisability of Drawing Strict Boundaries between Biodefense and Commercial Missions

At an earlier stage of my career, I directed a study that examined the relationship between military and commercial technologies, looking in particular at the effects and implications of government policies to stimulate one or the other (8).

It was clear at the time -- and it remains true today -- that government policies that have the intent – or the effect – of stimulating commercial technology development can be quite controversial. Legitimate objections would be raised to policies that would put government in the position of "Picking Winners and Losers," with the argument being made that the marketplace was much more appropriate than the government in making such a determination. Interestingly, I think that "picking winners" was often a bigger problem than "picking losers." The latter merely wasted money, whereby the former took resources from all of us and had the effect of applying them to the benefit of just a few. Even when such actions were well justified on the basis of their public benefit, the fact that there were private beneficiaries raised issues of equity and fairness.

I revisit this debate because I fear that similar concerns could cripple our efforts to generate a vibrant, responsive, and effective biodefense capability. Some of the most important requirements we face – improved research infrastructure; new tools and methods; new antiviral and antibiotic products; new animal models and facilities – are not specific to biodefense; they apply to biodefense and to commercial missions alike. If we are too concerned about "picking winners" – if we avoid taking actions that might benefit commercial firms, even as they support the biodefense mission – we are guaranteed to fail at developing the capabilities we need. The original Bioshield legislation attempted to do just that, making any product that had a non-biodefense application ineligible for Bioshield support. Congress wisely eliminated that prohibition before enacting that legislation.

Future actions to support our biodefense capability are similarly bound to raise this same question. Given how generically applicable the necessary capabilities are, we must embrace, rather than avoid, these "dual-use" benefits. Clearly, careful attention will have to be paid to the details in any such incentive scheme to ensure that they are not abused by firms that are not contributing to the biodefense mission, or that are taking advantage of loopholes in the procedures to enrich themselves at the public's expense. But if firms acting in good faith to support the nation's biodefense mission are unable to benefit in their commercial activities, we are not doing what we need to be doing.

Need for a Comprehensive Approach

Finally, although my comments today have been directed primarily at medical countermeasures to bioterrorist attack, it is important to recognize that we cannot rely solely on after-the-fact responses in dealing with the threat of bioterrorism. As important as they are, medical countermeasures are only one component of a comprehensive biodefense strategy. We must put programs in place to dissuade, frustrate, detect, and counter bioterrorism programs at every possible stage, not just after an attack has already taken place.

One of the chief difficulties in fighting bioterrorism is that none of the measures we can imagine, by itself, can offer high confidence in successfully countering this threat. But by putting a combination of measures in place, or a layered defense – recognizing that each measure or layer has limitations and weaknesses – we can maximize our chances of success.

Endnotes

(1) Gerald L. Epstein, *Global Evolution of Dual-Use Biotechnology: A Report of the Project on Technology Futures and Global Power, Wealth, and Conflict* (Washington, DC: Center for Strategic and International Studies, in press)

(2) Brad Spellberg, John H. Powers, Eric P. Brass, Loren G. Miller, and John E. Edwards, Jr., "Trends in Antimicrobial Drug Development: Implications for the Future," *Clinical Infectious Disease* 2004:38: 1279-86

(3) Quotations and statistics in this paragraph from The Infectious Disease Society of America, *Bad Bugs, No Drugs: As Antibiotic Discovery Stagnates … A Public Health Crisis Brews*, July 2004 (available online at http://www.idsociety.org/pa/IDSA_Paper4_final_web.pdf, accessed February 6, 2005); pp. 9, 10

(4) United Kingdom Parliament, House of Lords, Science and Technology Committee, "Resistance To Antibiotics and Other Antimicrobial Agents," Seventh Report, 17 March 1998, available online at http://www.parliament.the-stationery-office.co.uk/pa/ld199798/ldselect/ldsctech/081vii/st0703.htm (accessed February 6, 2005); section 1.19

(5) *Federal Register*, vol. 64, no. 100 (May 25, 1999), p. 28206

(6) *Ibid.*

(7) Committee on Accelerating the Research, Development, and Acquisition of Medical Countermeasures Against Biological Warfare Agents, *Giving Full Measure to Countermeasures: Addressing Problems in the DoD Program to Develop Medical Countermeasures Against Biological Warfare Agents*, Lois M. Joellenbeck, Jane S. Durch, Leslie Z. Benet, eds., (Washington, DC: National Academies Press, 2004), p. 80 (available online at http://books.nap.edu/books/0309091535/html/80.html#pagetop, accessed February 6, 2005)

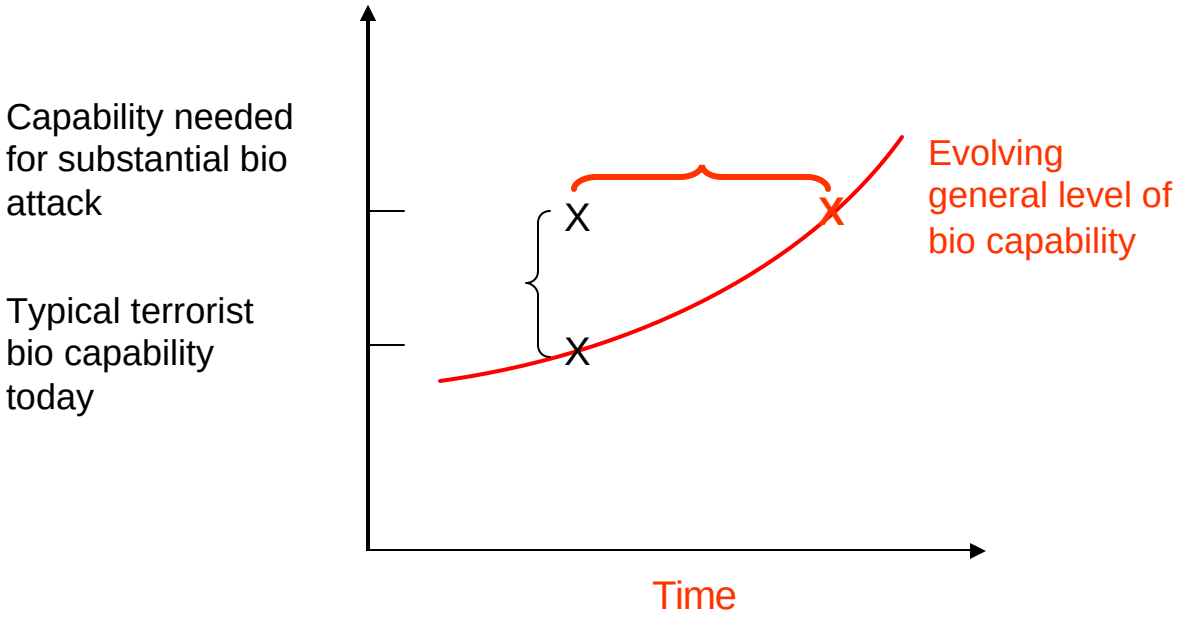
(8) Alic, John A.; Branscomb, Lewis M.; Brooks, Harvey; Carter, Ashton B., and Epstein, Gerald L.; *Beyond Spinoff: Military and Commercial Technologies in a Changing World* (Boston, MA: Harvard Business School Press, 1992)

Other Useful References

Bradley T. Smith, Thomas V. Inglesby, Tara O'Toole, "Biodefense R&D: Anticipating Future Threats, Establishing a Strategic Environment," *Biosecurity and Bioterrorism*, Vol. 1, No. 3: September 2003, pp. 193-202

Lynne Gilfillan, Bradley T. Smith, Thomas V. Inglesby, Krishna Kodukula, Ari Schuler, Mark Lister, and Tara O'Toole, "Taking the Measure of Countermeasures: Leaders' Views on the Nation's Capacity to Develop Biodefense Countermeasures," *Biosecurity and Bioterrorism*, Vol. 2, No. 4: September 2003, pp. 320-327

FIGURE 1: Implications of Technology Advance for Bioterrorism



No matter what the actual gap is today between a terrorist group's level of capability in biological weapons and the level needed to do substantial harm, that gap will disappear over time.

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ONE-PAGE SUMMARY

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3) Substantially increased NIH biodefense research and the new Bioshield program are necessary components of our national response, but they are insufficient. Further incentives are needed to stimulate production of post-exposure therapeutics and rapid response capabilities, for which we need new research tools and methods. We also need to develop animal models for human disease and increased animal production and testing capacity.

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@article{Smith2009DevelopingMC, title={Developing medical countermeasures for biodefense.}, author={Bradley T. Smith and Michael Mair and Gigi Kwik Gronvall and Jason Matheny}, journal={Biosecurity and bioterrorism : biodefense strategy, practice, and science}, year={2009}, volume={7 1}, pages={. 42-3 } }. Gerald L. Epstein, Senior Fellow for Science and Security, Homeland Security Program: Testimony before the Bioterrorism and Public Health Preparedness Subcommittee, Committee on Health, Education, Labor, and Pensions, United States Senate on Biodefense: Building a Medical Countermeasure Capability. Downloads.